

# Chemical Current-Conveyor: a new approach in biochemical computation

by

**Panavy Pookaiyaudom**

A thesis submitted for the  
Doctor of Philosophy of Imperial College London  
and the  
Diploma of Imperial College London

Department of Electrical and Electronic Engineering, Imperial College London

18 March 2011

*Dedicated to my wonderful parents,*

*Prof. Sitthichai and Pornpan Pookaiyaudom*

*and,*

*the Kingdom of Thailand*

# Abstract

Biochemical sensors that are low cost, small in size and compatible with integrated circuit technology play an essential part in the drive towards personalised healthcare and the research described in this thesis is concerned with this area of medical instrumentation. A new biochemical measurement system able to sense key properties of biochemical fluids is presented. This new integrated circuit biochemical sensor, called the Chemical Current-Conveyor, uses the ion sensitive field effect transistor as the input sensor combined with the current-conveyor, an analog building-block, to produce a range of measurement systems.

The concept of the Chemical Current-Conveyor is presented together with the design and subsequent fabrication of a demonstrator integrated circuit built on conventional  $0.35\mu\text{m}$  CMOS silicon technology. The silicon area of the Chemical Current-Conveyor is ( $92\mu\text{m} \times 172\mu\text{m}$ ) for the N-channel version and ( $99\mu\text{m} \times 165\mu\text{m}$ ) for the P-channel version. Power consumption for the N-channel version is  $30\mu\text{W}$  and  $43\mu\text{W}$  for the P-channel version with a full load of  $1\text{M}\Omega$ . The maximum sensitivity achieved for pH measurement was  $46\text{mV}$  per pH.

The potential of the Chemical Current Conveyor as a versatile biochemical integrated circuit, able to produce output information in an appropriate form for direct clinical use has been confirmed by applications including measurement of (i) pH, (ii) buffer index ( $\beta$ ), (iii) urea, (iv) creatinine and (v) urea:creatinine ratio. In all five cases the device has been demonstrated successfully, confirming the validity of the original aim of this research project, namely to produce a versatile and flexible analog circuit for many biochemical measurement applications. Finally, the thesis closes with discussion of another potential application area for the Chemical Current Conveyor and the main contributions can be summarised by the design and development of the first:

- ISFET based current-conveyor biochemical sensor, called ‘Chemical Current Conveyor, CCCII+’ has been designed and developed. It is a general purpose biochemical analog building-block for several biochemical measurements.
- Real-time buffer capacity measurement system, based on the CCCII+, which exploits the imbedded analog computation capability of the CCCII+.

- Real-time enzyme based CCCII+ namely, Creatinine-CCCI+ and Urea-CCCI+ for real-time monitoring system of renal system. The system can provide outputs of 3 important parameters of the renal system, namely (i) urea concentration, (ii) creatinine concentration, and (iii) urea to creatinine ratio.

# Acknowledgements

First and foremost, I would like to express my deepest gratitude to my supervisor, Professor Chris Toumazou, for his suggestion, motivation and guidance not only throughout my PhD but also since 2003, when we met in Bangkok. Without his support, belief, vision and encouragement, I would not be here today. It is such an honour to be his student and to be able to work a long side his team at the Centre for Bio-Inspired Technology, CBIT.

I would also like to give a very special thank to my co-supervisor, Professor John Lidgey and his family (Jill Lidgey), for their continual friendship, support, and motivation since I have started my study in the UK. I am fortunate to have his feedbacks, countless discussions, helps and advices not only throughout my PhD but also toward life in the UK. I will be forever grateful.

I thank my colleagues and friends in ‘the CBIT, Imperial College, London’, ‘MMRC, Mahanakorn University of Technology, Thailand’ and ‘Electronics and Communications group, Oxford Brookes University’ for their outstanding supports, useful information and discussions during the course of my PhD: Dr. Timothy Constandinou, Dr. Pantelakis Georgiou, Dr. Amir Eftekhari, Dr. Themis Prodromakis, Wai Pan Chan, Yan Lui, Surachoke Thanapitak, Parinya Seelanan, Tassanai Parittotokkaporn, Orada Chumphukam, Dr. Apisak Worapishet, Dr. Ittipat Roopkom and Dr. Khaled Hayatleh. A special mention must also go to Thanaporn Kongprapunt who always there when I needed. I thank her for her understanding, support and love through all my darkest and gloomy time during this long journey.

I would also like to give special thanks to Maria Khaleeq from the department of physics at Imperial College for doing the encapsulation and wire-bonding of the chip and, Dr. Themis Prodromakis from CBIT for taking the micro photographs of my chip. Last but not least, I would also like to thank Wiesia Hsissen for her kindness and warmth while looking after me during my PhD.

And most of all, I thank my wonderful parents, Prof. Sitthichai Pookaiyaudom and Pornpan Pookaiyaudom, for all their love and support, for their understanding and

sacrifices they have made, they are the best parents any son could ask for and I am grateful for that. Lastly, I dedicated this thesis to my family (Dad, Mum, King and Kaew).

# Contents

|                                                                                                                |            |
|----------------------------------------------------------------------------------------------------------------|------------|
| <b>List of figures</b>                                                                                         | <b>ix</b>  |
| <b>List of tables</b>                                                                                          | <b>xiv</b> |
| <b>List of companies</b>                                                                                       | <b>xv</b>  |
| <b>List of publications</b>                                                                                    | <b>xvi</b> |
| <b>Chapter 1: Introduction</b>                                                                                 | <b>1</b>   |
| 1.1 Motivation and achievements.....                                                                           | 1          |
| 1.2 Overview and structure of the thesis.....                                                                  | 3          |
| 1.3 References.....                                                                                            | 5          |
| <b>Chapter 2: Using Ion Sensitive Field Effect Transistors (ISFETs) in Biochemical Instrumentation</b>         | <b>7</b>   |
| 2.1 Introduction.....                                                                                          | 7          |
| 2.2 Operation of the ISFET.....                                                                                | 9          |
| 2.2.1 ISFETs in an unmodified CMOS process.....                                                                | 20         |
| 2.3 Reference Electrode.....                                                                                   | 24         |
| 2.4 Drift, hysteresis and lifetime in ISFETs.....                                                              | 28         |
| 2.5 Temperature sensitivity in ISFETs.....                                                                     | 30         |
| 2.6 Trapped charges in CMOS ISFETs.....                                                                        | 32         |
| 2.7 Noise in CMOS ISFETs.....                                                                                  | 35         |
| 2.8 ISFET interfacing techniques.....                                                                          | 37         |
| 2.9 Summary of Chapter 2.....                                                                                  | 50         |
| 2.10 References.....                                                                                           | 50         |
| <b>Chapter 3: Current-Conveyor: The Current Mode Approach</b>                                                  | <b>57</b>  |
| 3.1 Introduction.....                                                                                          | 57         |
| 3.2 Background.....                                                                                            | 58         |
| 3.3 Current-Conveyor implementation.....                                                                       | 62         |
| 3.4 Current-Conveyor (CCII) applications.....                                                                  | 65         |
| 3.4.1 Voltage and current readout amplifiers using the CCII.....                                               | 66         |
| 3.4.2 Analog computation using the CCII.....                                                                   | 69         |
| 3.4.3 Impedance conversion using the CCII.....                                                                 | 70         |
| 3.4.4 Filters.....                                                                                             | 73         |
| 3.4.5 The relationship between the ideal transistor and current-conveyor.....                                  | 76         |
| 3.4.6 The relationship between the current-conveyor and the current-feedback operational amplifier (CFOA)..... | 79         |
| 3.5 Summary of Chapter 3.....                                                                                  | 81         |

|                                                                                                                            |            |
|----------------------------------------------------------------------------------------------------------------------------|------------|
| 3.6 References.....                                                                                                        | 81         |
| <b>Chapter 4: Chemical Current-Conveyor for Biochemical Computation</b>                                                    | <b>83</b>  |
| 4.1 Introduction.....                                                                                                      | 83         |
| 4.2 Concept of the CCCII+: Topology and analysis.....                                                                      | 84         |
| 4.3 Design and implementation of Chemical Current-Conveyor.....                                                            | 86         |
| 4.3.1 The basic initial design of the Chemical Current-Conveyor.....                                                       | 88         |
| 4.3.2 Full implementation of the Chemical Current-Conveyor.....                                                            | 96         |
| 4.4 Simulation results.....                                                                                                | 99         |
| 4.5 Design fabrication.....                                                                                                | 108        |
| 4.5.1 Matching of transistors, common-centroid layout and dummy transistors.....                                           | 109        |
| 4.5.2 Full layout of N-channel and P-channel ISFET CCCII+ Devices.....                                                     | 113        |
| 4.5.3 Electrostatic discharge (ESD) protection.....                                                                        | 115        |
| 4.6 Measured results.....                                                                                                  | 117        |
| 4.6.1 Wire bonding the CCCII+ chips.....                                                                                   | 118        |
| 4.6.2 Test board preparation.....                                                                                          | 120        |
| 4.6.3 Measured results on N-channel ISFET CCCII+ in comparison with fixed $V_{ds}$ and $I_d$<br>ISFET readout circuit..... | 123        |
| 4.6.4 Measured results on P-channel ISFET CCCII+.....                                                                      | 129        |
| 4.7 Applications of Chemical Current-Conveyor for biochemical computation.....                                             | 131        |
| 4.7.1 Basic readout: Voltage-mode and current-mode amplifiers built with the Chemical<br>Current-Conveyor.....             | 132        |
| 4.7.2 Analog biochemical computation.....                                                                                  | 138        |
| 4.7.3 Current-feedback Chemical Current-Conveyor.....                                                                      | 142        |
| 4.7.4 ‘Super’ ISFET.....                                                                                                   | 148        |
| 4.8 Summary of Chapter 4.....                                                                                              | 149        |
| 4.9 References.....                                                                                                        | 149        |
| <b>Chapter 5: Real-Time Buffer Capacity and Buffer Index Measurement using Chemical<br/>Current-Conveyor (CCCI+)</b>       | <b>152</b> |
| 5.1 Introduction.....                                                                                                      | 152        |
| 5.2 Buffer the fundamental acid/base concepts.....                                                                         | 153        |
| 5.2.1 Acid/base buffer operation.....                                                                                      | 154        |
| 5.2.2 Buffer index/capacity and pH.....                                                                                    | 156        |
| 5.2.3 Buffer capability of blood.....                                                                                      | 157        |
| 5.3 Chemical Current-Conveyor for buffer index/capacity ( $\beta$ ) measurement.....                                       | 160        |
| 5.4 Operation of the Chemical Current-Conveyor for buffer index/capacity measurement.....                                  | 165        |
| 5.5 Measured results and discussion.....                                                                                   | 167        |
| 5.6 Measurement of ISFET response time.....                                                                                | 170        |

|                                                                                                                                                |            |
|------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| 5.6.1 Circuit operation and description.....                                                                                                   | 171        |
| 5.6.2 Result and discussion.....                                                                                                               | 173        |
| 5.7 Summary of Chapter 5.....                                                                                                                  | 175        |
| 5.8 Reference.....                                                                                                                             | 175        |
| <b>Chapter 6: Real-Time Measurement of Urea, Creatinine and Urea to Creatinine Ratio using Enzyme Based Chemical Current-Conveyor (CCCII+)</b> | <b>177</b> |
| 6.1 Introduction.....                                                                                                                          | 177        |
| 6.2 Renal disorders.....                                                                                                                       | 179        |
| 6.3 ISFET as a versatile biosensor.....                                                                                                        | 180        |
| 6.3.1 Procedure of EnFET fabrication.....                                                                                                      | 182        |
| 6.4 Chemical Current-Conveyor for urea and creatinine measurement.....                                                                         | 183        |
| 6.5 Chemical Current-Conveyor for urea to creatinine ratio measurement.....                                                                    | 185        |
| 6.6 Measured results and discussion.....                                                                                                       | 188        |
| 6.6.1 Possible anti-logarithm approach at the output.....                                                                                      | 195        |
| 6.7 Output to the $N^{\text{th}}$ -power circuit.....                                                                                          | 199        |
| 6.8 Summary of Chapter 6.....                                                                                                                  | 200        |
| 6.9 References.....                                                                                                                            | 201        |
| <b>Chapter 7: Conclusion and Future Work</b>                                                                                                   | <b>204</b> |
| 7.1 Conclusion.....                                                                                                                            | 204        |
| 7.2 Future work: Determination and monitoring of cells culture using array CCCII+ platform.....                                                | 207        |
| 7.3 References.....                                                                                                                            | 209        |
| <b>Appendix A: Matching of Transistors, Common-Centroid Layout and Dummy Transistors for CCCII+ .....</b>                                      | <b>210</b> |
| <b>Appendix B: The Full Circuit Schematic of the CCCII+ Test and Application Board.....</b>                                                    | <b>215</b> |
| <b>Appendix C: CCCII+: Voltage Input/Output Transfer and Titration Test.....</b>                                                               | <b>220</b> |

# List of figures

|                                                                                                                                                                                                                                        |    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| <b>Figure 2-1.</b> [1] Comparison of (a) MOSFET and (b) ISFET cross section .....                                                                                                                                                      | 10 |
| <b>Figure 2-2.</b> Measured (a) $I_D \sim V_{GS}$ characteristic for pH = 7 using commercial $Al_2O_3$ ISFET<br>obtained from Sentron Europe (Roden, The Netherlands, part no, OEM-679) and<br>(b) leakage on reference electrode..... | 11 |
| <b>Figure 2-3.</b> Surface sites available on insulator silicon dioxide membrane when immersed in<br>solution .....                                                                                                                    | 14 |
| <b>Figure 2-4.</b> Charge and potential distribution across the electrical double layer.....                                                                                                                                           | 16 |
| <b>Figure 2-5.</b> ISFET Behavioural Macromodel.....                                                                                                                                                                                   | 19 |
| <b>Figure 2-6.</b> Comparison between (a) original ISFET design and (b) extended gate ISFET<br>approach for CMOS .....                                                                                                                 | 21 |
| <b>Figure 2-7.</b> Schematic of the reference electrode and photo of a practical reference electrode .....                                                                                                                             | 24 |
| <b>Figure 2-8.</b> Pseudo-reference electrode with differential circuit configuration.....                                                                                                                                             | 26 |
| <b>Figure 2-9.</b> Trapped charge removal using UV radiation .....                                                                                                                                                                     | 33 |
| <b>Figure 2-10.</b> Programmable gate ISFET (PG-ISFET) device.....                                                                                                                                                                     | 34 |
| <b>Figure 2-11.</b> Instrumentation amplifier ISFET readout circuit.....                                                                                                                                                               | 40 |
| <b>Figure 2-12.</b> Fixed $V_{DS}$ and $I_D$ ISFET readout circuit .....                                                                                                                                                               | 41 |
| <b>Figure 2-13.</b> differential pair ISFET readout circuit.....                                                                                                                                                                       | 44 |
| <b>Figure 2-14.</b> Operational amplifier ISFET readout circuit .....                                                                                                                                                                  | 45 |
| <b>Figure 2-15.</b> (a) Current feedback op-amp ISFET readout circuit and (b) its macromodel .....                                                                                                                                     | 46 |
| <b>Figure 2-16.</b> Feedback through reference electrode ISFET readout circuit, (a) where $V_{Bias} =$<br>$V_{DS(ISFET)}$ of ISFET and (b) where $V_{Bias} = V_{S(ISFET)}$ .....                                                       | 48 |
| <b>Figure 3-1.</b> First generation current-conveyor (CCII) (a) system diagram and (b) hybrid matrix .....                                                                                                                             | 59 |
| <b>Figure 3-2.</b> Second generation current-conveyor (CCII) (a) system diagram and (b) hybrid matrix ..                                                                                                                               | 59 |
| <b>Figure 3-3.</b> Current-conveyor applications.....                                                                                                                                                                                  | 61 |
| <b>Figure 3-4.</b> Negative current-conveyor.....                                                                                                                                                                                      | 62 |
| <b>Figure 3-5.</b> Negative current-conveyor implementation.....                                                                                                                                                                       | 63 |
| <b>Figure 3-6.</b> Positive current-conveyor .....                                                                                                                                                                                     | 64 |
| <b>Figure 3-7.</b> Positive current-conveyor implementation .....                                                                                                                                                                      | 65 |
| <b>Figure 3-8.</b> Grounded negative impedance converters (NIC).....                                                                                                                                                                   | 71 |
| <b>Figure 3-9.</b> Current-controlled NIC .....                                                                                                                                                                                        | 71 |
| <b>Figure 3-10.</b> Voltage-controlled NIC .....                                                                                                                                                                                       | 71 |
| <b>Figure 3-11.</b> Generalised impedance converter (GIC).....                                                                                                                                                                         | 72 |
| <b>Figure 3-12.</b> (a) Voltage-mode SAB (b) Current-Mode SAB .....                                                                                                                                                                    | 74 |
| <b>Figure 3-13.</b> Butterworth low-pass filter using CCII+ .....                                                                                                                                                                      | 75 |

|                                                                                                                     |     |
|---------------------------------------------------------------------------------------------------------------------|-----|
| <b>Figure 3-14.</b> Comparison of (a) single NMOS transistor, (b) CCII- and (c) single BJT .....                    | 78  |
| <b>Figure 3-15.</b> Current-feedback (a) macromodel and (b) op-amp structure.....                                   | 80  |
| <b>Figure 4-1.</b> System overview of CCCII+.....                                                                   | 84  |
| <b>Figure 4-2.</b> Describing $pH \sim V \sim I$ matrix of CCCII+ .....                                             | 85  |
| <b>Figure 4-3.</b> CCCII+ macromodel.....                                                                           | 87  |
| <b>Figure 4-4.</b> Common-Drain or Source follower amplifier.....                                                   | 88  |
| <b>Figure 4-5.</b> Initial implementation of the voltage-buffer stage.....                                          | 90  |
| <b>Figure 4-6.</b> Small signal equivalent circuit of the voltage-buffer stage.....                                 | 91  |
| <b>Figure 4-7.</b> Transistor schematic of the initial integrated CCCII+ .....                                      | 95  |
| <b>Figure 4-8.</b> Full transistor implementation of the N-channel ISFET CCCII+ .....                               | 97  |
| <b>Figure 4-9.</b> Full transistor implementation of the P-channel ISFET CCCII+ .....                               | 98  |
| <b>Figure 4-10.</b> Operation range of N-channel ISFET CCCII+ .....                                                 | 100 |
| <b>Figure 4-11.</b> Operation range of P-channel ISFET CCCII+ .....                                                 | 101 |
| <b>Figure 4-12.</b> Test circuit to determine the signal operating characteristics .....                            | 102 |
| <b>Figure 4-13.</b> Voltage transfer of N-channel ISFET CCCII+ .....                                                | 102 |
| <b>Figure 4-14.</b> Voltage transfer of P-channel ISFET CCCII+ .....                                                | 103 |
| <b>Figure 4-15.</b> Frequency response of N-channel ISFET CCCII+ .....                                              | 104 |
| <b>Figure 4-16.</b> Phase response of N-channel ISFET CCCII+ .....                                                  | 105 |
| <b>Figure 4-17.</b> Frequency response of P-channel ISFET CCCII+ .....                                              | 105 |
| <b>Figure 4-18.</b> Phase response of P-channel ISFET CCCII+ .....                                                  | 106 |
| <b>Figure 4-19.</b> CCCII+ connector diagrams .....                                                                 | 109 |
| <b>Figure 4-20.</b> One dimensional common-centroid arrays .....                                                    | 111 |
| <b>Figure 4-21.</b> Interdigitated MOS transistors with connected dummy.....                                        | 112 |
| <b>Figure 4-22.</b> Sample of common-centroid with connected dummy used in N-channel ISFET<br>CCCI+ .....           | 113 |
| <b>Figure 4-23.</b> Full layout of N-channel ISFET CCCII+ .....                                                     | 114 |
| <b>Figure 4-24.</b> Full layout of P-channel ISFET CCCII+ .....                                                     | 115 |
| <b>Figure 4-25.</b> ESD pad Schematic of CCCII+ .....                                                               | 116 |
| <b>Figure 4-26.</b> Full layout of CCCII+ including ESD pads protection.....                                        | 116 |
| <b>Figure 4-27.</b> Microphotograph of CCCII+ chip: (a) N-channel ISFET CCCII+, (b) P-channel<br>ISFET CCCII+ ..... | 117 |
| <b>Figure 4-28.</b> Bond wiring schematic of CCCII+ .....                                                           | 119 |
| <b>Figure 4-29.</b> Bond wiring microphotograph of CCCII+ .....                                                     | 120 |
| <b>Figure 4-30.</b> Readout portion of the test and application board schematic .....                               | 121 |
| <b>Figure 4-31.</b> The photograph of CCCII+ test and application board.....                                        | 122 |
| <b>Figure 4-32.</b> Potential trim-able circuit for Z-node outputs.....                                             | 123 |
| <b>Figure 4-33.</b> Source-follower bench mark ISFET readout circuit .....                                          | 124 |

|                                                                                                                                                                                                                     |     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| <b>Figure 4-34.</b> CCCII+ testing diagram for voltage transfer test.....                                                                                                                                           | 125 |
| <b>Figure 4-35.</b> Measured voltage transfer input and outputs of Sentron N-channel ISFET CCCII+<br>(no. D2_5) .....                                                                                               | 126 |
| <b>Figure 4-36.</b> Measured voltage transfer input and outputs of source-follower bench mark circuit<br>(Sentron ISFET N-channel, no. D2_5).....                                                                   | 126 |
| <b>Figure 4-37.</b> CCCII+ testing diagram for titration test .....                                                                                                                                                 | 127 |
| <b>Figure 4-38.</b> Measured titration curve of N-channel CCCII+ (no. N_D2) with Sentron ISFET N-<br>channel (no. D2_1).....                                                                                        | 128 |
| <b>Figure 4-39.</b> Measured titration curve of source-follower bench mark circuit with Sentron ISFET<br>N-channel (no. D2_1).....                                                                                  | 129 |
| <b>Figure 4-40.</b> Measured voltage transfer input and outputs of P-channel ISFET CCCII+ (DNA-E<br>ISFET P-channel, no. D1_1) .....                                                                                | 130 |
| <b>Figure 4-41.</b> Measured titration curve of P-channel CCCII+ (no. P_D2) with DNA-E ISFET P-<br>channel (no. D1_1).....                                                                                          | 131 |
| <b>Figure 4-42.</b> pH to I converter (pHCCS).....                                                                                                                                                                  | 132 |
| <b>Figure 4-43.</b> pH to V converter (pHCVS) .....                                                                                                                                                                 | 133 |
| <b>Figure 4-44.</b> pH to Voltage amplifier .....                                                                                                                                                                   | 134 |
| <b>Figure 4-45.</b> Differential pH to I converter .....                                                                                                                                                            | 136 |
| <b>Figure 4-46.</b> pH Instrumentation amplifier.....                                                                                                                                                               | 137 |
| <b>Figure 4-47.</b> pH to I output summing .....                                                                                                                                                                    | 138 |
| <b>Figure 4-48.</b> pH integrator .....                                                                                                                                                                             | 139 |
| <b>Figure 4-49.</b> pH differentiator .....                                                                                                                                                                         | 141 |
| <b>Figure 4-50.</b> Comparison of (a) CCII+ and (b) CCCII+ Current-feedback Op-amp structures .....                                                                                                                 | 143 |
| <b>Figure 4-51.</b> CCCII+ CFOA closed loop non-inverting pH amplifier .....                                                                                                                                        | 143 |
| <b>Figure 4-52.</b> Analysis diagrams of CCCII+ CFOA: (a) Small signal analysis and (b) Thevenin<br>theory analysis.....                                                                                            | 144 |
| <b>Figure 4-53.</b> pH-CCCI+ Non-inverting feed-back pH amplifier.....                                                                                                                                              | 146 |
| <b>Figure 4-54.</b> (a) single N-channel ISFET, (b) CCCII- and (c) Dual CCCII .....                                                                                                                                 | 148 |
| <b>Figure 5-1.</b> The ratio of the conjugate acid-base pair .....                                                                                                                                                  | 155 |
| <b>Figure 5-2.</b> pH-differentiator using CCCII+ .....                                                                                                                                                             | 160 |
| <b>Figure 5-3. (a)</b> System diagram to determine the capacity of buffer solution and, <b>(b)</b> discrete<br>implementation of CCCII+ to obtain the voltage output at Z-node as the time<br>derivative of pH..... | 162 |
| <b>Figure 5-4.</b> HEPES concentration at 5.0mM (10 times diluted). (a) Voltage $\propto$ pH at X-node (see<br>Figure 5-3 (b)), (b) $dpHdt$ at Z-node (see Figure 5-3 (b)).....                                     | 167 |
| <b>Figure 5-5.</b> HEPES concentration at 1.0mM (50 times diluted). (a) Voltage $\propto$ pH at X-node (see<br>Figure 5-3 (b)), (b) $dpHdt$ at Z-node (see Figure 5-3 (b)).....                                     | 168 |

|                                                                                                                                                                                                                                            |     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| <b>Figure 5-6.</b> HEPES concentration at 0.5mM (100 times diluted). (a) Voltage $\propto$ pH at X-node (see Figure 5-3 (b)), (b) $dpHdt$ at Z-node (see Figure 5-3 (b)).....                                                              | 168 |
| <b>Figure 5-7.</b> Measurement system for determination the response time of the ISFET .....                                                                                                                                               | 171 |
| <b>Figure 5-8.</b> Measured result of three different injected periods at 1 $\mu$ m distance between micropipette tip and ISFET surface (insert is a ‘Zoom in’ of the measured result included).....                                       | 173 |
| <b>Figure 5-9.</b> Measured result of three different current amplitudes at a fixed injected period of 1ms and 1 $\mu$ m distance between micropipette tip and ISFET surface (insert is a ‘Zoom in’ of the measured result included) ..... | 174 |
| <b>Figure 6-1.</b> (a) Urea-CCCII+ system diagram and its (b) hybrid matrix.....                                                                                                                                                           | 184 |
| <b>Figure 6-2.</b> Creatinine-CCCII+ (a) system diagram and (b) hybrid matrix.....                                                                                                                                                         | 184 |
| <b>Figure 6-3.</b> Initial system configuration for urea-to-creatinine ratio measurement.....                                                                                                                                              | 186 |
| <b>Figure 6-4.</b> Plot of the ratio of Ref. Electrode “A” to Ref. Electrode “B” versus Ref. Electrode “A” .....                                                                                                                           | 189 |
| <b>Figure 6-5.</b> Plot of the ratio of $pHY_1$ to $pHY_2$ versus $pHY_1$ .....                                                                                                                                                            | 190 |
| <b>Figure 6-6.</b> Urea calibration curve.....                                                                                                                                                                                             | 191 |
| <b>Figure 6-7.</b> Urea-to-creatinine ratio (urea titration, creatinine fixed at 80 $\mu$ M) .....                                                                                                                                         | 191 |
| <b>Figure 6-8.</b> Inverting op-amp configuration used to invert the output signal of Urea-CCCII+ .....                                                                                                                                    | 192 |
| <b>Figure 6-9.</b> The adapted practical system configurations for urea-to-creatinine ratio measurement .....                                                                                                                              | 193 |
| <b>Figure 6-10.</b> Creatinine calibration curve.....                                                                                                                                                                                      | 194 |
| <b>Figure 6-11.</b> Urea-to-creatinine (creatinine titration, urea fixed at 8mM).....                                                                                                                                                      | 195 |
| <b>Figure 6-12.</b> Diode (D3) added anti-log practical system configurations .....                                                                                                                                                        | 196 |
| <b>Figure 6-13.</b> Proposed additional current-mode signal processing circuit .....                                                                                                                                                       | 199 |
| <b>Figure 7-1.</b> Monitoring cell culture using CCCII+ array-based micro-system.....                                                                                                                                                      | 208 |
| <b>Figure B-1.</b> Readout circuit schematic for CCCII+ Chip_D1 .....                                                                                                                                                                      | 215 |
| <b>Figure B-2.</b> Readout circuit schematic for CCCII+ Chip_D2 .....                                                                                                                                                                      | 216 |
| <b>Figure B-3.</b> Power supplies schematic for all the test and application circuits in the board .....                                                                                                                                   | 216 |
| <b>Figure B-4.</b> Division circuit schematic for urea-to-creatinine ratio using CCCII+ .....                                                                                                                                              | 217 |
| <b>Figure B-5.</b> Voltage to current converter circuit schematic used in buffer capacity measurement ...                                                                                                                                  | 217 |
| <b>Figure B-6.</b> Instrumentation amplifier circuit schematic using CCCII+ .....                                                                                                                                                          | 218 |
| <b>Figure B-7.</b> Top overlay layout .....                                                                                                                                                                                                | 218 |
| <b>Figure B-8.</b> Top layer layout .....                                                                                                                                                                                                  | 219 |
| <b>Figure B-9.</b> Bottom layer layout.....                                                                                                                                                                                                | 219 |
| <b>Figure C-1.</b> Parameters for voltage transfer test of CCCII+ (N_D2) and Sentron ISFET N-Chanel (D2_5) .....                                                                                                                           | 220 |
| <b>Figure C-2.</b> Parameters for voltage transfer test of CCCII+ (N_D2) and Sentron ISFET N-Chanel (D2_3) .....                                                                                                                           | 223 |

|                                                                                                                               |     |
|-------------------------------------------------------------------------------------------------------------------------------|-----|
| <b>Figure C-3.</b> Parameters for voltage transfer test of CCCII+ (N_D2) and Sentron ISFET N-Chanel<br>(D2_4) .....           | 225 |
| <b>Figure C-4.</b> Parameters for voltage transfer test of CCCII+ (P_D2) and DNA-E ISFET P-Chanel<br>(D1_1) .....             | 227 |
| <b>Figure C-5.</b> Parameters for titration test of CCCII+ (N_D2) and Sentron ISFET N-Channels<br>(D2_1, D2_3, D2_4).....     | 228 |
| <b>Figure C-6.</b> Measured titration curve of N-channel CCCII+ (N_D2) with Sentron ISFET N-<br>Chanel (D2_1) .....           | 228 |
| <b>Figure C-7.</b> Measured titration curve of N-channel CCCII+ (N_D2) with Sentron ISFET N-<br>Chanel (D2_3) .....           | 229 |
| <b>Figure C-8.</b> Measured titration curve of N-channel CCCII+ (N_D2) with Sentron ISFET N-<br>Chanel (D2_4) .....           | 229 |
| <b>Figure C-9.</b> Parameters of source-follower bench mark circuit and Sentron ISFET N-Channels<br>(D2_1) .....              | 230 |
| <b>Figure C-10.</b> Measured titration curve of source-follower bench mark circuit with Sentron ISFET<br>N-Chanel (D2_1)..... | 230 |
| <b>Figure C-11.</b> Parameters for titration test of CCCII+ (P_D2) and DNA-E ISFET P-Channels<br>(D2_1) .....                 | 231 |
| <b>Figure C-12.</b> Measured titration curve of P-channel CCCII+ (P_D2) with DNA-E ISFET P-<br>Chanel (D1_1) .....            | 231 |

# List of tables

|                                                                                                                                                        |     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| <b>Table 2-1.</b> Sensing characteristic of ion-sensing membranes of pH ISFETs.....                                                                    | 8   |
| <b>Table 2-2.</b> ISFETs in commercial CMOS technologies .....                                                                                         | 23  |
| <b>Table 3-1.</b> Impedance and $I \sim V$ operation of the ideal CCII.....                                                                            | 66  |
| <b>Table 3-2.</b> Applications of current conveyors to amplifier .....                                                                                 | 67  |
| <b>Table 3-3.</b> Applications of current conveyors to differential and instrumentation amplifier .....                                                | 68  |
| <b>Table 3-4.</b> Applications of current conveyors to analog computation.....                                                                         | 69  |
| <b>Table 4-1.</b> N-channel ISFET CCCII+ Simulation parameters.....                                                                                    | 99  |
| <b>Table 4-2.</b> P-channel ISFET CCCII+ Simulation parameters.....                                                                                    | 100 |
| <b>Table 4-3.</b> Frequency response errors.....                                                                                                       | 107 |
| <b>Table 4-4.</b> Characteristics of N-channel CCCII+ with loading at $R_X = R_Z = 1M\Omega$ .....                                                     | 108 |
| <b>Table 4-5.</b> Characteristics of P-channel CCCII+ with loading at $R_X = R_Z = 1M\Omega$ .....                                                     | 108 |
| <b>Table 4-6.</b> Interdigitation patterns for arrays having one axis of symmetry .....                                                                | 110 |
| <b>Table 5-1.</b> The parameters of the buffer capacity/index measurement system.....                                                                  | 164 |
| <b>Table 5-2.</b> Parameters and results of buffer capacity/index $\beta$ measurement.....                                                             | 169 |
| <b>Table 6-1.</b> Urea to Creatinine ratio ranges and implication.....                                                                                 | 178 |
| <b>Table A-1.</b> Schematic and layout of N-CCCI+ .....                                                                                                | 210 |
| <b>Table A-2.</b> Schematic and layout of N-CCCI+ .....                                                                                                | 213 |
| <b>Table C-1.</b> Measured results of Sentron ISFET N-Chanel (D2_5), Test (ac1-1), using CCCII+ and<br>source-follower benchmark readout circuit ..... | 221 |
| <b>Table C-2.</b> Measured results of Sentron ISFET N-Chanel (D2_5), Test (ac1-2), using CCCII+ and<br>source-follower benchmark readout circuit ..... | 222 |
| <b>Table C-3.</b> Measured results of Sentron ISFET N-Chanel (D2_3), Test (ac1-1), using CCCII+ and<br>source-follower benchmark readout circuit ..... | 223 |
| <b>Table C-4.</b> Measured results of Sentron ISFET N-Chanel (D2_3), Test (ac1-2), using CCCII+ and<br>source-follower benchmark readout circuit ..... | 224 |
| <b>Table C-5.</b> Measured results of Sentron ISFET N-Chanel (D2_4), Test (ac1-1), using CCCII+ and<br>source-follower benchmark readout circuit ..... | 225 |
| <b>Table C-6.</b> Measured results of Sentron ISFET N-Chanel (D2_4), Test (ac1-2), using CCCII+ and<br>source-follower benchmark readout circuit ..... | 226 |
| <b>Table C-7.</b> Measured results of DNA-E ISFET P-Chanel (D1_1) .....                                                                                | 227 |

# List of companies

## **DNA-E:**

DNA Electronics Ltd

Bessemer Building, Imperial College

London, SW7 2AZ UK

## **Sentron:**

Sentron Europe BV

Aan de Vaart 3, 9301 ZH Roden

The Netherlands

## **LTP Electronics:**

15 Gover Close, Wareham

Dorset BH20 5BU

UK

## **Elantec Inc:**

675 Trade Zone Boulevard

Milpitas, CA 95035

USA

## List of publications

1. Pookaiyaudom, P., C. Toumazou, and F.J. Lidgey. *The chemical current-conveyor: a new microchip biosensor*. in *Circuits and Systems, 2008. ISCAS 2008. IEEE International Symposium on*. 2008.
2. Pookaiyaudom, P., C. Toumazou, and F.J. Lidgey, *Measurement of buffer index using the Chemical Current Conveyor (CCCII+)*, in *ANALOG SIGNAL PROCESSING*. 2008: Oxford Brookes University. p. 15.1-15.6.
3. Pookaiyaudom, P., et al., *Chemical current conveyor (CCCII+): System design and verification for buffer index/capacity measurement*. *Sensors and Actuators B: Chemical*, 2010. **147**(1): p. 228-233.
4. Pookaiyaudom, P., et al., *Measurement of urea, creatinine and urea to creatinine ratio using enzyme based chemical current conveyor (CCCII+)*. *Sensors and Actuators B: Chemical*, 2011. **153**(2): p. 453-459.
5. Thanapitak, S., et al., *Verification of ISFET response time for millisecond range ion stimulus using electronic technique*. *Electronics Letters*, 2011. **47**(10): p. 586-588. (2<sup>nd</sup> author)

## Chapter 1

### Introduction

#### 1.1 Motivation and achievements

The continuing trend towards personalised healthcare coupled with the parallel development of low-cost, small-sized and disposable biomedical sensors have focused research effort in recent years on the development of electronic integrated circuit sensors. The research described in this thesis is the application of the very versatile current-conveyor to the design and development of a new biochemical measurement system able to sense key properties of biochemical fluids and presenting output information in a meaningful and useful form for clinical use. There are several drivers/enablers for this work, namely (i) the recognition of the value to society of a healthy population with increasing standard of living and life expectancy, (ii) the move towards personalised healthcare, which reflects the shift towards a greater emphasis for disease prevention and healthcare (iii) the development of a reliable integrated circuit biochemical electronic sensor, and the availability of mature semiconductor technology, which can produce high

quality, miniature, low-cost, and potentially low-power signal processing and signal computational hardware.

The two main electronic elements brought together in this research work are (i) the Ion Sensitive Field Effect Transistor (ISFET) and (ii) the current-conveyor type II. They are combined to form the basis of a new biochemical sensing system, which the author has called the ‘Chemical Current-Conveyor’, (CCCII+). The motivation of combining these two elements was to produce a low complexity, and hence potentially low-cost, integrated measurement system that builds on the analog computational capability of the versatile current-conveyor.

There has been extensive research in recent years on the design and development of the ISFET, and in particular the fully integrate-able CMOS ISFET, towards improving the sensitive and stability of the device. The initial concept of the chemical current-conveyor is described, developed into a practical integrated circuit design and applied to the measurement of several biochemical fluid parameters, the first being measurement of pH [1]. Because of the in-built analogue capability within the CCCII+ consideration was then given to measurement of related biochemical fluid parameters, such as buffer capacity. Being able to produce a ‘real-time’ value for buffer capacity together with pH is significantly more useful for clinical diagnosis than simply pH alone. This prompted the second application development of the CCCII+ which leads to the first reported ‘real-time’ buffer index/capacity measurement device [2].

The next area to be considered as a contender for exploitation of the CCCII+ was the renal system. The value of urea, creatinine and urea to creatinine ratio are the key parameters in a renal measurement system. Again because of the inherent computational capability the CCCII+ was considered potentially suitable as the basis for the

development of a monolithic off-the-shelf device to obtain these parameters. Research in this application of the CCCII+ leads to the development of a successful measurement system providing these three parameters [3]. Further exploration of the CCCII+ leads to the final application reported in this thesis, namely a verification system to confirm that capability of the ISFET for rapid DNA sequencing and chemical synapse measurement [Paper submitted for publication, see list of publications].

## 1.2 Overview and structure of the thesis

The ISFET is the first key element in the design and development of the CCCII+. The ISFET is an extremely effective biomedical sensor and has been the subject of extensive development over more than 40 years [4]. Recent research work has focussed on development of integrated circuit sensors with an ISFET to form a biosensor microchip, generally with an on-chip operational amplifier to give the required analog system gain [5-10]. The structure, operation, performance and limitations of the ISFET, in particular the CMOS ISFET is essential to the design of the CCCII+ and reviewed in Chapter 2 together with published read-out circuits.

The second key element in the CCCII+ is the current-conveyor type II, CCII [11]. It is an essential element in the CCCII+, particularly because the CCII+ has inherent and versatile analogue computational ability which is exploited in the application of the CCCII+ to a range of biochemical parameter measurements described in the latter part of the thesis. To appreciate the evolution of the CCCII+ in Chapter 3, the author reviews the current-conveyor concept and operation and its versatility as an analog building block capable of being configured to provide many analog circuit functions, including amplifiers, analog computation, impedance conversion and filters. In addition a range of application CCII circuits are examined, including the relationship between the current-feedback op-amp

and the ‘ideal transistor’, the majority of which are exploited in CCCII+ applications. Also this chapter may be a useful review of the CCII for bio-chemists and any future potential applications of the CCCII+ where the versatility of the CCII may be exploited to advantage. Thus Chapters 2 and 3 provide background, understanding and limitations of both the ISFET and the CCII and therefore underpin the next stage of the research which is the design and development of the first CCCII+.

The concept, design and development of the first CCCII+ for pH measurement is described in Chapter 4 together with the development of an integrated circuit implementation using CMOS technology. Also included in Chapter 4 are the initial circuit design and simulation, the development of a design suitable for practical implementation, circuit layout and silicon fabrication, integrated circuit test and evaluation, and subsequent testing in a range of application scenarios. The results of this CCCII+ for pH measurement were first presented by the author at IEEE ISCAS-2008 [1]. Also presented in Chapter 4 is the concept of a composite or ‘super-ISFET’, which stems from the ‘ideal transistor’ based on the current-conveyor [12].

The second application area of the CCCII+ is measurement of ‘real-time’ buffer capacity,  $\beta$ , [2, 13], which is the subject of Chapter 5. This is a novel application which confirms the potential for using the CCCII+ for continuous in-vivo measurement of both pH and  $\beta$ . Also included in Chapter 5 is the third application of the CCCII+ for verification of the capability of the ISFET for fast response measurement of ‘local’ biochemical fluid parameter measurements for synapse and rapid DNA sequencing.

Renal dysfunction leads to an increase in the urea concentration. Thus the measurement of urea and creatinine, together with the ratio of urea to creatinine are very useful indicators for diagnostic purposes. In Chapter 6, the fourth application of the CCCII+ to

be explored is for ‘real-time’ measurement of these three parameters [3]. Obtaining all three parameters is made possible by exploitation of the analog computational capabilities of the CCII+ that is imbedded within the CCCII+, thus drawing on the underpinning review of the CCII contained in Chapter 3.

The thesis closes with a discussion of the achievements of the research on the CCCII+ and its various applications, together with the author’s thoughts and reflections on related areas of interest for future exploration of the CCCII+.

### 1.3 References

- [1] P. Pookaiyaudom, *et al.*, "The chemical current-conveyor: a new microchip biosensor," in *Circuits and Systems, 2008. ISCAS 2008. IEEE International Symposium on*, 2008, pp. 3166-3169.
- [2] P. Pookaiyaudom, *et al.*, "Chemical current conveyor (CCCI+): System design and verification for buffer index/capacity measurement," *Sensors and Actuators B: Chemical*, vol. 147, pp. 228-233, 2010.
- [3] P. Pookaiyaudom, *et al.*, "Measurement of urea, creatinine and urea to creatinine ratio using enzyme based chemical current conveyor (CCCI+)," *Sensors and Actuators B: Chemical*, vol. In Press, Corrected Proof.
- [4] P. Bergveld, "Development of an Ion-Sensitive Solid-State Device for Neurophysiological Measurements," *Biomedical Engineering, IEEE Transactions on*, vol. BME-17, pp. 70-71, 1970.
- [5] B. Premanode, *et al.*, "Ultra-low power precision ISFET readout using global current feedback," *Electronics Letters*, vol. 42, pp. 1264-1265, 2006.
- [6] C. Wen-Yaw, *et al.*, "Temperature compensation electronics for ISFET readout applications," in *Biomedical Circuits and Systems, 2004 IEEE International Workshop on*, 2004, pp. S1/6-S5-8.
- [7] A. Morgenshtein, *et al.*, "Wheatstone-Bridge readout interface for ISFET/REFET applications," *Sensors and Actuators B: Chemical*, vol. 98, pp. 18-27, 2004.
- [8] A. Morgenshtein, *et al.*, "CMOS readout circuitry for ISFET microsystems," *Sensors and Actuators B: Chemical*, vol. 97, pp. 122-131, 2004.

- [9] R. A. Rani and O. Sidek, "ISFET pH sensor characterization: towards biosensor microchip application," in *TENCON 2004. 2004 IEEE Region 10 Conference*, 2004, pp. 660-663 Vol. 4.
- [10] L. Shepherd, *et al.*, "A novel voltage-clamped CMOS ISFET sensor interface," in *Circuits and Systems, 2007. ISCAS 2007. IEEE International Symposium on*, 2007, pp. 3331-3334.
- [11] K. C. Smith and A. Sedra, "The current conveyor: A new circuit building block," *Proceedings of the IEEE*, vol. 56, pp. 1368-1369, 1968.
- [12] C. Toumazou, *et al.*, *Analogue IC design: the current-mode approach*: Institution of Engineering and Technology 1993.
- [13] P. Pookaiyaudom, *et al.*, "Measurement of buffer index using the Chemical Current Conveyor (CCCII+)," presented at the ANALOG SIGNAL PROCESSING, Oxford Brookes University, 2008.

## Chapter 2

# Using Ion Sensitive Field Effect Transistors (ISFETs) in Biochemical Instrumentation

### 2.1 Introduction

One of the key physiological parameters is pH and ISFET based sensors have been exploited for pH measurement since their invention almost 40 years ago by Bergveld [1]. In 1970, Bergveld [2] introduced the new solid-state chemical sensors which has an exposed membrane which can chemically react with the hydrogen ions in a chemical solution. As a result, it forms the pH-dependent interfacial potential between the membrane and the solution. This device is fabricated in silicon technology and called an Ion Sensitive Field Effect Transistor (ISFET).

Despite inherent problems with the ISFET, in particular drift, threshold variation [3] and temperature dependence [4], this sensing-transistor is particularly well suited for exploitation in development of CMOS integrated circuit pH sensing. In recent

publications [5-6] the ISFET has been incorporated into CMOS technology to produce successful monolithic pH sensors.

**Table 2-1.** Sensing characteristic of ion-sensing membranes of pH ISFETs [7]

| Characteristics     | $SiO_2$ | $Si_3N_4$ | $Al_2O_3$ | $Ta_2O_5$ |
|---------------------|---------|-----------|-----------|-----------|
| Range of pH         | 4-10    | 1-13      | 1-13      | 2.5-13    |
| Sensitivity (mV/pH) | 25-46   | 46-56     | 53-56     | 55-57     |
| Response time       | < 1 min | < 1s      | < 1s      | < 1s      |

Van Der Wal et al [8] and Abe et al [9] explored different types of materials in producing the ISFET ion sensitive membranes. Their findings are summarised in Table 2-1 from which it can be seen that tantalum pentoxide ( $Ta_2O_5$ ) can achieve the sensitivity closest to a Nernstain sensitive of 59mV/pH. Whereas silicon dioxide  $SiO_2$ , which is the common dielectric in standard CMOS technology has the poorest sensitivity of 25mV/pH. Furthermore, it had been shown that such ISFETs can be used with more selective membranes, such as those with immobilised enzymes, allowing a wide variety of applications. By choosing the right and appropriate inorganic or organic insulator, ISFETs can be sensitive to different ions [10-11].

This chapter begins with the operating of the traditional ISFET is reviewed, as well as the CMOS-based ISFET sensors where passivation layer is used as the ion sensitive membrane. Then the choice of selecting the reference electrode will be discussed, followed by the nonidealities of the ISFET, including drift, hysteresis and lifetime. The temperature sensitivity, trapped charge and noise effects in ISFETs will also be reviewed

This chapter concludes with the analysis of existing ISFET readout circuits, some of which have a topology that is better suited to integrated circuit fabrication than others.

## 2.2 Operation of the ISFET

The structure of the ISFET is shown in Figure 2-1 and it can be seen to be almost identical to the MOSFET. Both devices have gate, source, drain and body terminals. The gate of a MOSFET is insulated from the channel by a silicon dioxide insulator covered with a polysilicon conducting gate layer, metalised and connected to the external gate lead. In the traditional ISFET, first reported by Bergveld [2], the polysilicon gate and metal are removed from the body and replaced with a chemically sensitive insulating membrane,  $G'$ , and a reference electrode,  $G$ , which is immersed in an electrolyte aqueous solution, as shown in Figure 2-1 (b). Any field effects from ionic charge interaction at the insulator membrane surface the value of the threshold voltage of the ISFET changes [1]. Thus the value of the threshold voltage of the ISFET is now proportional to the pH value of the aqueous solution, and a direct means of pH sensing has been obtained [1]. The change of  $I_D \sim V_{GS}$  characteristics of the ISFET device is shown in Figure 2-2.

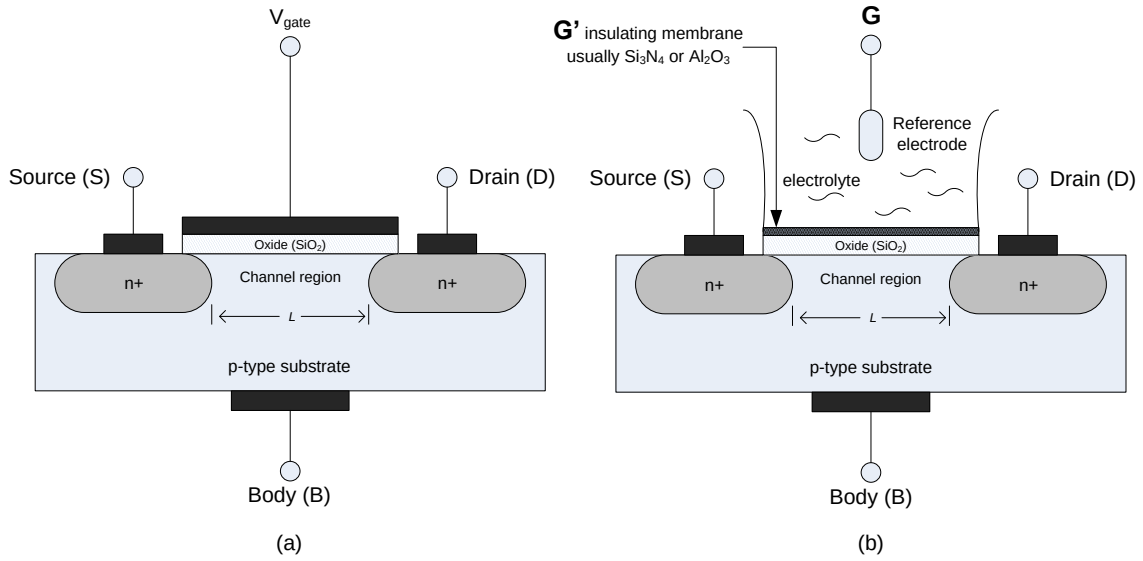


**Figure 2-1.** [1] Comparison of (a) MOSFET and (b) ISFET cross section

It should be noted that the ISFET can be regarded as a ‘floating-gate MOS transistor’ where the insulating membrane is the floating gate and the reference electrode is the control gate. Furthermore, this insulator membrane is chosen according to its chemical properties and sensitivity to a particular ion and for pH sensing, silicon nitride ( $Si_3N_4$ ) and aluminium oxide ( $Al_2O_3$ ) membranes are commonly used due to their wide ranging sensitivity to pH and low drift [8-9]. Matsuo and Esashi [12] show experimental results from different gate materials from which it can be concluded that tantalum oxide ( $Ta_2O_5$ ) and aluminium oxide ( $Al_2O_3$ ) give the closest to bench-mark Nernstian pH-sensitivity. On the other hand, silicon nitride ( $Si_3N_4$ ) and silicon oxynitride ( $SiO_xN_y$ ) are also used because these materials are readily availability in semiconductor device fabrication facilities.

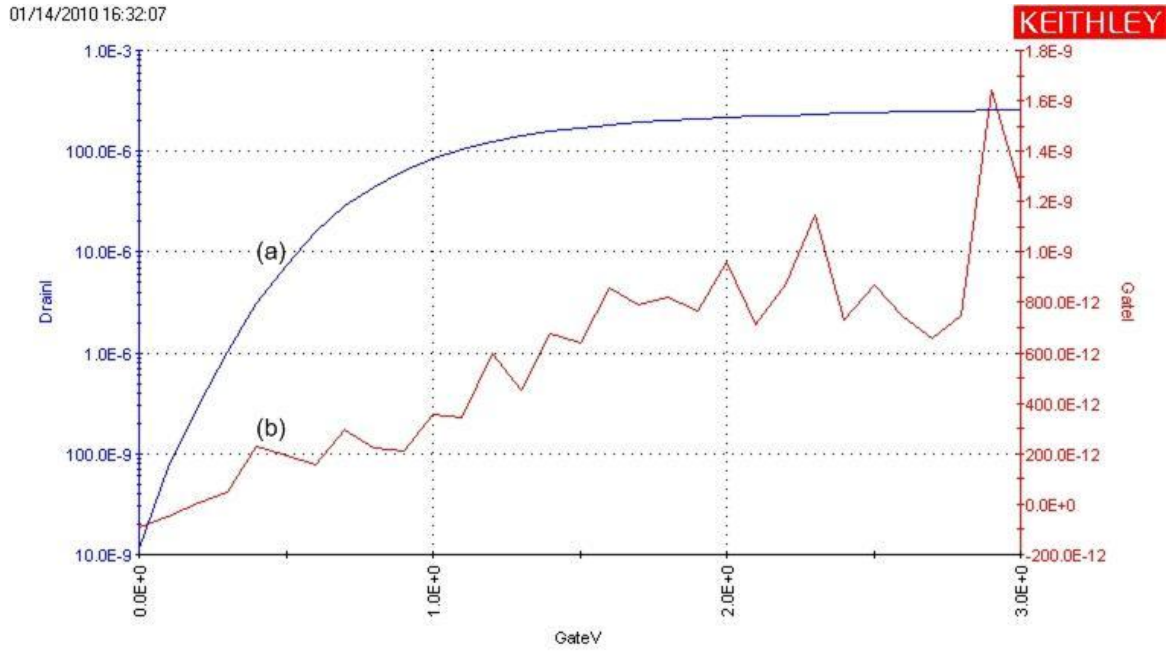


**Figure 2-2.** Measured (a)  $I_D \sim V_{GS}$  characteristic for pH = 7 using commercial  $Al_2O_3$  ISFET obtained from Sentron Europe (Roden, The Netherlands, part no, OEM-679) and (b) leakage on reference electrode

As in the MOSFET, with no bias voltage applied to the gate of the ISFET, two back-to-back diodes exist in series between the drain and source terminals. These back-to-back diodes prevent current flow from drain to source when a voltage  $V_{DS}$  is applied [13]. However, when the proper voltage bias,  $V_{ref}$ , is applied between the gate and the source such that the applied gate source voltage exceeds the threshold of the ISFET device, a channel is formed enabling current flow between drain and source and hence the drain current depends on the voltage between gate and source ( $V_{GS}$ ) [13]. The threshold equation for a typical MOSFET is shown in Equation 2-1

$$V_{th(MOSFET)} = \frac{\phi_m - \phi_{si}}{q} - \frac{Q_{ox} + Q_{ss} + Q_B}{C_{ox}} + 2\phi_f$$

**Equation 2-1**

where its parameters consist of three potential terms, namely (i) the difference in work-function between the gate metal contact ( $\phi_m$ ) and the silicon surface ( $\phi_{si}$ ), (ii) the accumulated charge in the oxide ( $Q_{ox}$ ), at the oxide-silicon interface ( $Q_{ss}$ ) and the depletion in silicon ( $Q_B$ ) per unit area  $C_{OX}$  as well as (iii) the Fermi potential of the semiconductor ( $\phi_f$ ).

In case of the ISFET, the same fabrication process is used, resulting in the same constant physical part of the threshold voltage [1], as shown in Equation 2-2. It should be noted that the gate metal work-function,  $\phi_m$ , is replaced by the constant potential of the reference electrode,  $E_{ref}$ , and the interfacial potential,  $\psi_0 + x_{sol}$ , at the solution/oxide interface of which  $x_{sol}$  is the potential due to the existence of dipole molecules in the solution. Also note that  $\psi_0$  is the only chemical potential term related to pH, and hence the expression of ISFET threshold voltage becomes

$$V_{th(ISFET)} = E_{ref} - \psi_0 + x_{sol} - \frac{\phi_{si}}{q} - \frac{Q_{ox} + Q_{ss} + Q_B}{C_{OX}} + 2\phi_f$$

**Equation 2-2**

which can be expressed as

$$V_{th(ISFET)} = V_{chem} + V_{th(MOSFET)}$$

**Equation 2-3**

where  $V_{chem}$  is a grouping of the chemical potentials of which  $\psi_0$  is the only pH-dependent term. This term is given by

$$V_{chem} = E_{ref} - \psi_0 + x_{sol} - \frac{\phi_m}{q}$$

**Equation 2-4**

Notably, that the metal work function,  $\phi_m/q$ , is also included in the  $V_{chem}$  expression to be subtracted from  $V_{th(MOSFET)}$  because of the absence of gate metal on the ISFET.

The Nernstian equation defines the potential generated due to ion activity on either side of a semi-permeable membrane and is always used as benchmark for pH sensitivity achieved by any pH measurement systems. The Nernstian equation is given below

$$E_{mem} = \frac{RT}{nF} \ln \frac{a_{i,sample}}{a_{i,int}}$$

**Equation 2-5**

where  $a_{i,sample}$  is the activity of the sample solution,  $a_{i,int}$  is the activity of the reference solution,  $R$  is the universal gas constant,  $T$  is the temperature in degrees Kelvin,  $F$  is the Faraday constant and  $n$  is the charge of ion  $i$ . Therefore, when the activity of the reference is constant the following relationship exists which is defined as the Nernstian sensitivity for pH sensors

$$\frac{\partial E_{mem}}{\partial pH} = \frac{2.303RT}{nF} = 2.303U_t = 59mV$$

**Equation 2-6**

Furthermore electrode potentiometric systems, which consist of metal references in contact with ionic solutions giving stable potentials, are easily defined in terms of Nernst potentials. For a glass pH electrode, the measurement signal of 59mV per unit change in pH is expected. However, in the ISFET there are more complex mechanisms which occur on the surface that give a potential related to pH. There is an electrolyte in contact with an insulator on semiconductor (EIS)<sup>1</sup> [14], therefore dependence of the electrolyte-insulator interface potential on pH is modelled using two phenomena, (i) the site binding of ions at

---

<sup>1</sup> EIS: Electrolyte Insulator Semiconductor boundary

the insulator surface [15], and (ii) the Gouy-Chapman-Helmholtz capacitive double layer formed [16].

According to the site binding model when the ISFET surface is immersed in the chemical solution, the insulating membrane of the device interacts with the ions present in the solution. As a result the membrane can be hydrolysed and contains discrete surface sites which are neutral, positive or negative allowing binding of ions from the solution. These discrete surface sites are defined as the amphoteric, and the basic sites [17-19] are as shown in Figure 2-3.

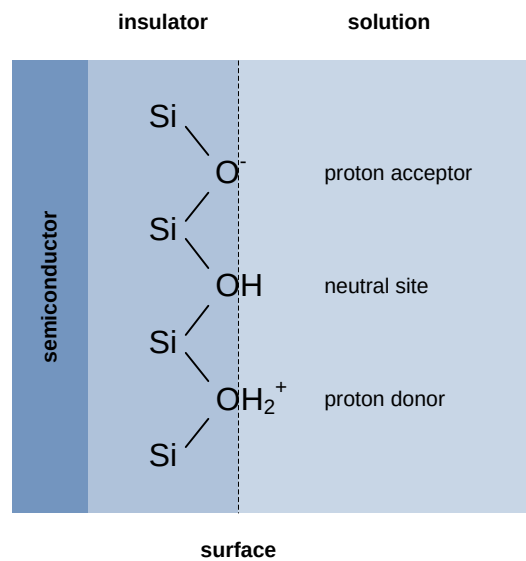


**Figure 2-3.** Surface sites available on insulator silicon dioxide membrane when immersed in solution

In the case of Figure 2-3, the amphoteric site of the  $SiO_2$  insulating membrane would be  $SiOH$  which would either accept or donate hydrogen ions, whereas  $SiNH_2$  would be the basic site as it can only accept hydrogen ions from its surrounding solution. Hence, the surface of the insulating membrane can be positively or negatively charged, depending on

whether the hydrogen ions are leaving or entering the membrane. By the law of conservation of charge, the insulator surface charge build-up at the insulating membrane is matched by an equal amount but of opposite charge ions which accumulated over the electrolyte. These two groups of opposite charges form a double layer capacitor [1, 16] on the surface of the ISFET as a result of the presence of ions creating a Helmholtz plane and a Gouy-Chapman layer, show in Figure 2-4. The Helmholtz plane is a compact layer of tightly-packed charge closest to the insulator surface and consisting of two planes. Firstly, there is the inner Helmholtz plane (IHP), defined as the line of charge attracted to the surface site of the insulator membrane, and secondly, the outer Helmholtz plane (OHP) is defined as the line through the centres of the hydrated ions which are at their distance of closest approach to the solid due to the water molecules bound to them not allowing them to get very close. The combination of these two planes results in the almost linear voltage drop of the potential in the solution and is modelled with the linear Helmholtz capacitor,  $C_{Helm}$ , which is given as [20]

$$C_{Helm} = \frac{A\epsilon_0\epsilon_r}{d_{OHP}}$$

**Equation 2-7**

where  $A$  is the surface area of the insulator,  $\epsilon_0$  is the permittivity of free space,  $\epsilon_r$  is the relative permittivity of the electrolyte and finally,  $d_{OHP}$  is the distance of the OHP from the insulator surface.

To the right of the OHP in Figure 2-4 is the diffuse layer, also referred to as Gouy-Chapman layer, which consists of diffuse charge falling-off exponentially from OHP to the electrolyte bulk. This charge follows a Boltzmann distribution before an even distribution of charge is reached at the imaginary boundary of the double layer. The non-

linear charge distribution in this region is represented in the Gouy-Chapman theory [16] by a capacitor,  $C_{Gouy}$ , described by Equation 2-8 below

$$C_{Gouy} = \frac{d\sigma_{dl}}{d\psi_1} = -\sqrt{8kT\epsilon_r\epsilon_0n^0} \sinh\left(\frac{q\psi_1}{2kT}\right)$$

**Equation 2-8**

where  $\psi_1$  is the potential across the diffuse layer and  $n^0$  is the bulk number concentration of ions in the electrolyte.

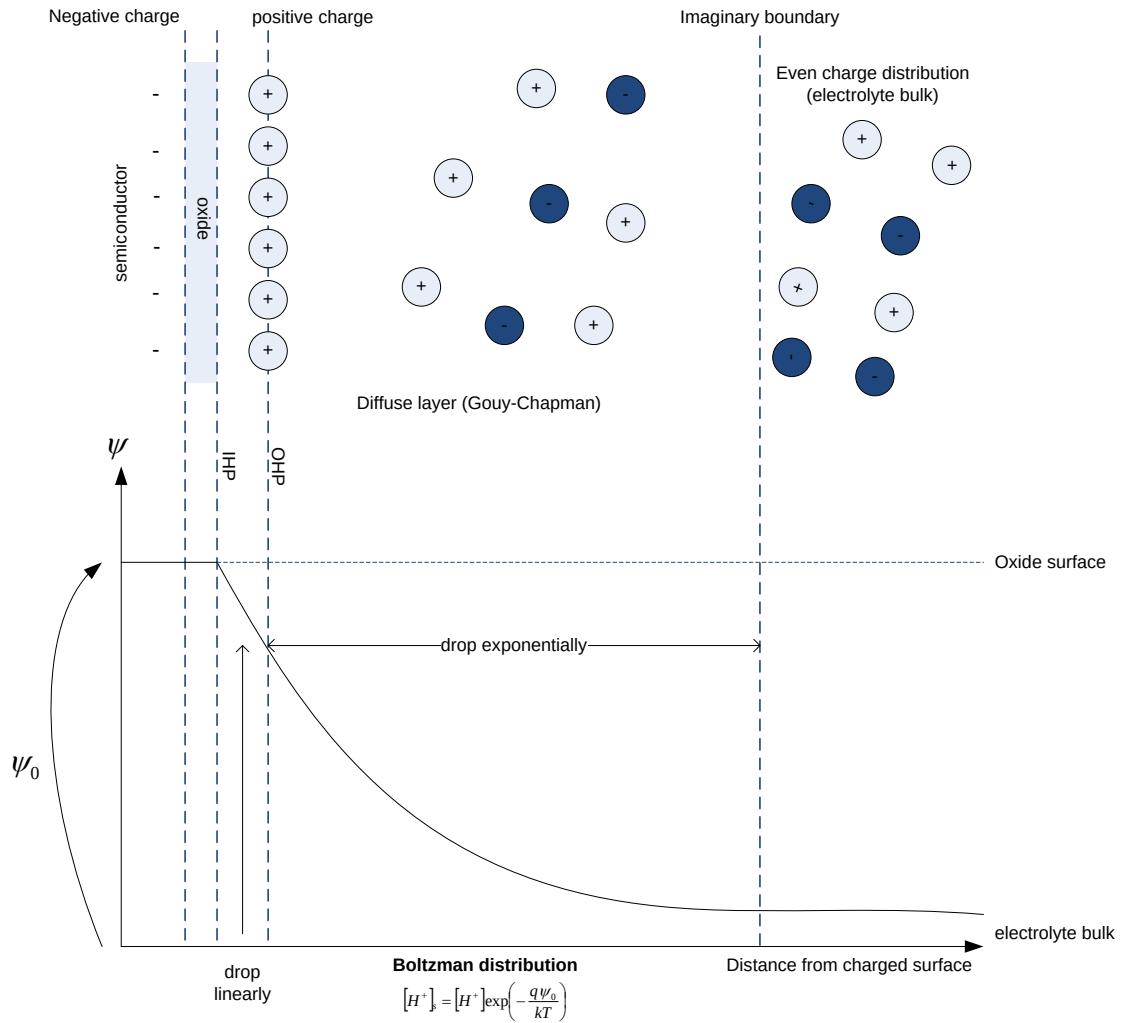


**Figure 2-4.** Charge and potential distribution across the electrical double layer [21]

According to the Boltzmann distribution in the Gouy-Chapman layer, the hydrogen ion concentration at the surface of the insulator,  $[H^+]_s$ , is related to the bulk hydrogen ion concentration,  $[H^+]_{bulk}$ , [22] by

$$[H^+]_s = [H^+]_{bulk} \exp\left(-\frac{q\psi_s}{kT}\right)$$

**Equation 2-9**

Converting Equation 2-9 to a pH-scale, where  $pH = -\log_{10}[H^+]$  and rearranging this gives a Nernstian potential response shown below in Equation 2-10

$$S_N = \frac{d\psi_s}{dpH_{bulk}} = -2.3 \frac{kT}{q}$$

**Equation 2-10**

However, ISFET pH-sensitivity is non-Nernstian, but as proposed in [23] the site binding and double layer models can be used to modified Equation 2-10 to derive the ISFET pH-sensitivity expression [23], which is

$$S_{ISFET} = \frac{d\psi_0}{dpH_{bulk}} = -2.3\alpha \frac{kT}{q}$$

**Equation 2-11**

and,

$$\alpha = \left(\frac{2.3kTC_{dl}}{q^2\beta_{int}} + 1\right)^{-1}$$

**Equation 2-12**

where  $\alpha$  is a dimensionless sensitivity reflecting the,  $\beta_{int}^2$ , as the intrinsic buffer capacity of the oxide surface from the site binding model and the total capacitance,  $C_{dl}^3$ , in the electrical double layer capacitor model as defined in [22-23]. It should be noted that  $\alpha$  is a Nernstian response and varies between 0 and 1. Nernstian sensitivity where  $\alpha = 1$ , is equal to 59mV/pH at room temperature [1] which can be realized in the materials of the insulating membrane having a large buffer capacity,  $\beta_{int}$ , while the double layer capacitance,  $C_{dl}$ , value is small. In addition [1], with a large buffer capacity material, such as tantalum pentoxide ( $Ta_2O_5$ ), a Nernstian response of 59mV is obtained over a unit pH change whilst a smaller buffer capacity material like silicon nitride ( $Si_3N_4$ ) only achieves a sensitivity of 45 to 46 mV/pH.

Finally, Equation 2-11 can be substituted into Equation 2-4, resulting in a simpler expression for  $V_{chem}$  as

$$V_{chem} = \gamma + 2.3\alpha U_T pH$$

**Equation 2-13**

where  $\gamma$  is a group of non-pH related variables and  $U_T$  is the thermal voltage and equal to  $kT/q$  or  $RT/F$ . Note that in obtaining this expression, the assumption is made that the pH of the chemical solution is larger than the point-of-zero charge ( $pH_{pzc}$ ) at the insulating membrane [1]. The final Equation 2-13 can only be used therefore when the insulating membrane is negatively charged. A silicon nitride insulating membrane, for example, consists of a  $pH_{pzc}$  at approximately 2.2 [24], so Equation 2-13 is only valid when the pH of the solution is larger than 2.2.

---

<sup>2</sup>  $\beta_{int} = \frac{d([SiO^-] + [SiOH_2^+])}{dpH_s}$  and defines as the change in number of surface sites available for a given change in pH  
<sup>3</sup>  $\frac{1}{C_{dl}} = \frac{1}{C_{Gouy}} + \frac{1}{C_{Helm}}$

The operation of ISFET can be represented with a behavioural macromodel such that described by Martinoia et al [25], in which a standard MOSFET model is modified to include the various chemical related components as shown in Figure 2-5. This modelling approach is used as a ‘standard’ ISFET macromodel for different MOSFET technologies.

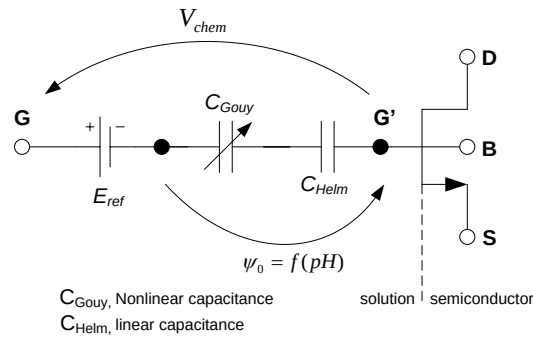


**Figure 2-5.** ISFET Behavioural Macromodel [25]

By comparing the ISFET behavioural macromodel to a standard MOSFET, some distinctions between them can be identified. Firstly, the gate bias is transferred into the solution via reference electrode at the G-node in the term of  $E_{ref}$ , which is in series with the pH-dependent voltage source,  $\psi_0 = f(pH)$ . Secondly, this  $\psi_0$  is not only dependent on pH concentration but it is also temperature dependent and exhibits drift. Thirdly, the double layer capacitor is connected in series with the insulating membrane at the G'-node. These double layer capacitors consist of linear capacitor  $C_{Helm}$  and non-linear capacitor,  $C_{Gouey}$ .

### 2.2.1 ISFETs in an unmodified CMOS process

The fabrication of ISFETs in an unmodified CMOS process has been pursued over the last decade in an effort to merge the advantages of miniaturised solid-state sensors with those of a CMOS process, resulting in ‘Smart Chemical Systems-On-Chip’ [18, 24, 26-27].

The original ISFET introduced by Bergveld [2] required the addition of a dedicated customised step to etch away the passivation layer, intra-metals, intra-dielectrics and polysilicon gate, to a precise shape [28]. As a result of these requirements this made the custom fabrication of the ISFET incompatible with the standard CMOS processes, due to the absence of polysilicon gate for alignment of the source and drain diffusions. Therefore, the separation of the  $n^+$  implantation regions for the source and the drain had to be done using lithographic methods, thus making the deposition of a pH insulating membrane directly on the substrate possible.

The method of the deposition of the insulating layer is achieved using Low Pressure Chemical Vapour Deposition (LPCVD) at high temperature on a thinner re-growth silicon dioxide layer on the substrate [29-30]. The metallisation layers are made silicon rich with tungsten silicide rather than aluminium, which provides source and drain contacts capable of withstanding the high temperatures required for the LPCVD deposition of the nitride.

These original ISFET extra post processes are able to produce reliable ISFET devices with pH sensitivities around the Nernstian value of 59mV/pH, achieved with a single ( $Ta_2O_5/SiO_2$ ) gate ISFET [29]. However, these methods added technical complexity and added extra cost making the early ISFET process less attractive than building ISFETs with full (unmodified) CMOS process.

Cane et al [26] proposed using an unmodified CMOS process for ISFET production. Later Bausells et al [27], adopted this method of using the extended gate approach to develop the floating electrode CMOS ISFETs, as shown in Figure 2-6 (b). The polysilicon gate is left intact to provide and hence enable registration of the source and drain regions. The top passivation material, typically,  $Si_3N_4$  or  $SiO_xN_y$  used in standard CMOS processes, forms the pH insulator membrane. This top passivation layer is added by Plasma Enhanced Chemical Vapour Deposition (PECVD) at low temperature and the formation of the floating gate is achieved by extending the polysilicon gate to the passivation layer through the intra-metal layers using metal via-connected layers shown in Figure 2-6 (b). Therefore, charges built up at the passivation layer will be coupled to the polysilicon through the metal layers.

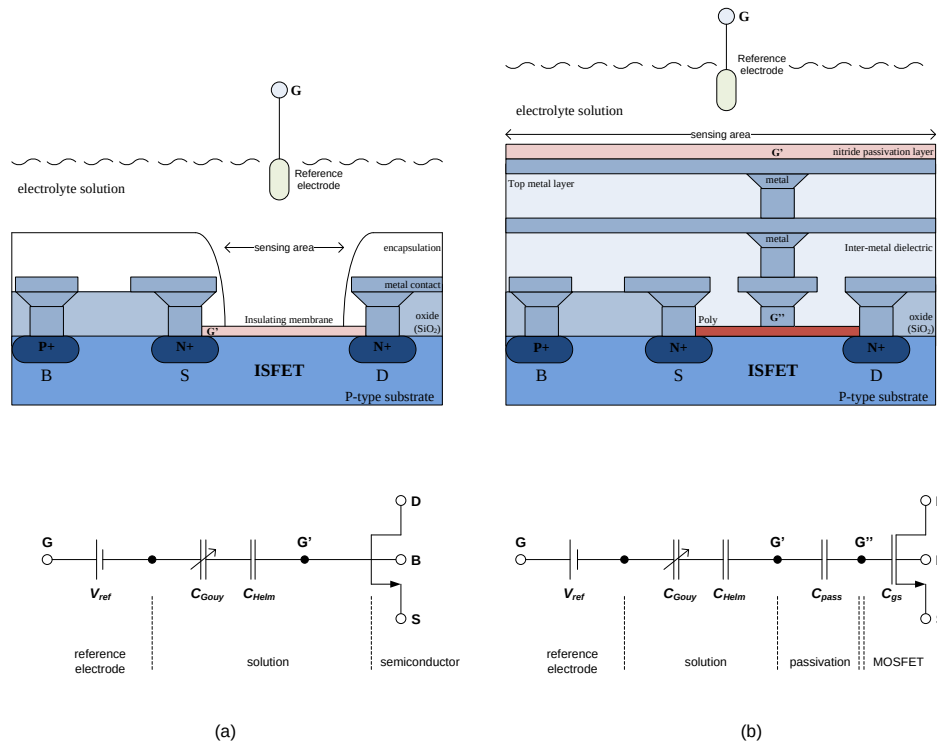


**Figure 2-6.** Comparison between (a) original ISFET design [1] and (b) extended gate ISFET approach for CMOS [31]

The main differences between the original ISFET design and the extended gate ISFET can also be seen clearly from their macromodels by comparing, Figure 2-6 (a) and Figure 2-6 (b). It can be seen that there are two more capacitors connected in series with  $C_{Helm}$  and  $C_{Gouy}$ . These two additional capacitors are the passivation capacitor,  $C_{pass}$ , and gate oxide capacitor,  $C_{gs}$ . Furthermore, the polysilicon gate does not affect the basic operation of the ISFET [27]. Also, the polysilicon gate conveniently shields the channel of the ISFET from any external light source which is essential as an unshielded ISFET would be light sensitive [27].

One particular disadvantage of using an unmodified CMOS process for ISFET fabrication is that the threshold voltage obtained is considerably higher in comparison with the traditional ‘Bergveld ISFET’ fabrication method. This is thought to be due to (i) the extra thick passivation layer and (ii) the trapped charge occurring during the fabrication process. The trapped charge phenomena will be discussed in greater detail later in Section 2.6 together with a possible way to ameliorate this problem.

A comparison published key parameters of unmodified ISFETs is shown in Table 2-2, progressing from 1996 through to 2010, using a range of different semiconductor technologies and including both P-channel as well as N-channel. None reported the Nernstian response of 59mV/pH. The sensitivities are all in the range 25mV to 47mV with the notable exception of one at 0.22mV/pH, this poor performance may well be due to an unstable passivation layer. It is interesting to observe that the sensitivity does not degrade significantly with shorter channel devices, suggesting that high frequency or rapid changes in pH measurements with the ISFET are feasible.

**Table 2-2.** ISFETs in commercial CMOS technologies

| Year | Type   | Passivation thickness<br>( $\mu\text{m}$ )              | Threshold<br>voltage (V) | Sensitivity<br>(mV/pH) | Technology                     | Ref  |
|------|--------|---------------------------------------------------------|--------------------------|------------------------|--------------------------------|------|
| 1996 | n-type | 1.5                                                     | 3.5                      | 41                     | Atmel 1 $\mu\text{m}$ 1P2M     | [4]  |
| 1999 | n-type | 1.5                                                     | -7 to 6.5                | 47                     | Atmel 1 $\mu\text{m}$ 1P2M     | [5]  |
| 2000 | n-type | 0.75- $\text{SiO}_2/\text{Si}_3\text{N}_4$              | 8.5                      | 25                     | AMS 0.6 $\mu\text{m}$<br>2P3M  | [9]  |
| 2002 | p-type | 0.4- $\text{Si}_3\text{N}_4/0.6\text{-SiO}_x\text{N}_y$ | -8 to -33                | 42                     | AMS 0.6 $\mu\text{m}$<br>1P2M  | [10] |
| 2004 | n-type | 1- $\text{Al}_2\text{O}_3$                              | <0.4                     | 0.22                   | AMS 1.6 $\mu\text{m}$<br>1P2M  | [11] |
| 2004 | p-type | 0.4- $\text{Si}_3\text{N}_4/0.6\text{-SiO}_x\text{N}_y$ | -5                       | 42                     | AMS 0.6 $\mu\text{m}$<br>2P3M  | [12] |
| 2005 | n-type | -                                                       | -                        | 31, 51                 | AMS 1.5 $\mu\text{m}$<br>1P2M  | [13] |
| 2008 | p-type | 1.03- $\text{SiO}_2/\text{Si}_3\text{N}_4$              | -4 to -1                 | 46                     | AMS 0.35 $\mu\text{m}$<br>2P3M | [14] |
| 2008 | n-type | 0.5- $\text{SiO}_2/0.7\text{-Si}_3\text{N}_4$           | -1.03 to 4.17            | 33.2                   | UMC 0.18 $\mu\text{m}$<br>1P6M | [15] |
| 2008 | n-type | 0.6- $\text{SiO}_2/0.7\text{-Si}_3\text{N}_4$           | -10 to -0.03             | 33.6                   | UMC 0.25 $\mu\text{m}$<br>1P5M | [15] |
| 2008 | n-type | 1.03- $\text{SiO}_2/\text{Si}_3\text{N}_4$              | 0.97 to 1.73             | 31.7                   | AMS 0.35 $\mu\text{m}$<br>2P4M | [15] |
| 2010 | p-type | 0.5- $\text{SiO}_2/0.7\text{-Si}_3\text{N}_4$           | 0.8                      | 37                     | UMC 0.18 $\mu\text{m}$<br>1P6M | [32] |

## 2.3 Reference Electrode

One of the very important factors influencing ISFET sensor design is the reference electrode. The initial assumption was that the ISFET would successfully measure ion activity without applying a reference electrode in the solution [1]. However, several experiments performed in a later stage of the development of the ISFET demonstrated that for correct operation and accurate measurement of changes in ion concentration, a constant well-defined electrical potential (voltage bias) is needed in a chemical solution [7]. Normally, the standard method used to set-up this potential is with a silver/silver chloride,  $Ag/AgCl$ , reference electrode. The standard macroscopic  $Ag/AgCl$  electrode consists of three parts, namely (i) a silver wire providing a contact for the applied reference voltage,  $V_{ref}$ , (ii) a solid coating of silver chloride, and (iii) a concentrated chloride solution, normally saturated potassium chloride (KCl) electrolyte, as shown in Figure 2-7.

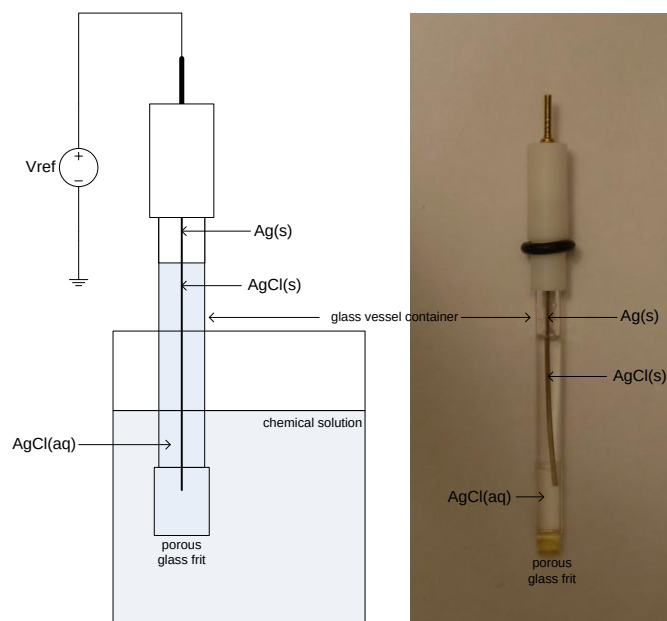
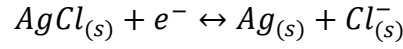


**Figure 2-7.** Schematic of the reference electrode and photo of a practical reference electrode

As shown in [33] the following chemical reaction will take place in the silver chloride electrode



**Equation 2-14**

When a transfer of electrons between the silver chloride electrode and the aqueous solution happens, a small electrical potential is set-up at the interface between the silver-chloride electrode and the surrounding chloride solution such that the liquid junction potential of the chloride solution is very near the potential of the silver chloride electrode. Furthermore, this potential of the chloride is coupled to the external chemical solution via the porous glass frit fitted at the end of glass vessel container as shown in Figure 2-7. In addition, this porous glass frit allows electrical conduction between the chemical solution and the internal chloride solution, while preventing convective mixing of the two solutions.

The miniaturisation process is mostly applied to the ISFET sensor, whereas standard macroscopic reference electrodes are still used. In order to take the full advantage of the micro size of the overall system, there is a need for miniaturising the reference electrode. Generally speaking, there are two approaches adopted. First, the miniaturisation of a conventional reference electrode on-chip using micromachining as shown by Huang et al [34] and Suzuki et al [35]. This process is incompatible with the standard CMOS process as it requires photolithography and chemical etching in order to fabricate a micro-chamber with a silver chloride electrode in a concentrated chloride electrolyte solution. The complexity of the fabrication is the realisation of the liquid junction membrane of the micro-chamber between the inner chloride electrolyte, KCl, and the sample solution. A further drawback of this approach is the uncertainty in maintaining the significantly small

amount of the electrolyte solution in the chamber, as leakage may occur and cause the potential between the electrode and the electrolyte to drift as reported by [34] and [35].

The second approach is the development of an integrated pseudo-reference electrode on chip. This electrode is a noble metal electrode such as platinum [36] and gold [37], instead of relying on the fact that the inner chemical fluids contain a constant and relatively high concentration of chloride ions [38-39]. However, this pseudo-reference electrode is intended to be used with a differential measurement device, one consisting of an input ISFET and the other one consisting of an input REFET, or an ion-insensitive reference FET, as shown in Figure 2-8. In addition, the use of a differential mode can help improve common mode noise, which originates from the interfacial potential between the electrode and the chemical solution [33]. Moreover, any differences between the sensitivity of the ISFET and the REFET will stimulate the output of the differential readout to respond to the pH change in the chemical solution.

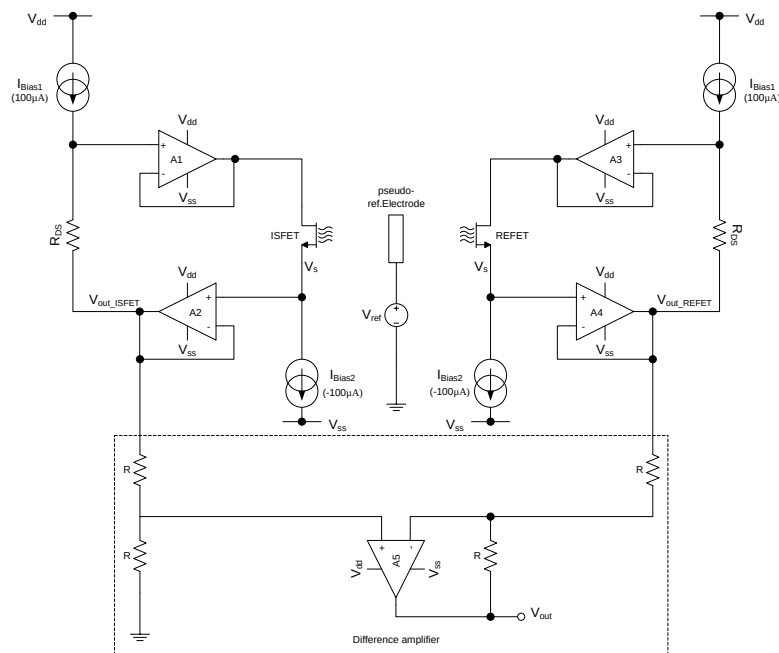


**Figure 2-8.** Pseudo-reference electrode with differential circuit configuration [24]

Both ISFET and REFET, in Figure 2-8, are biased with a fixed drain current,  $I_D$ , by the current sink  $I_{Bias2}$ . While the drain-source voltage,  $V_{DS}$ , of both ISFET and REFET are kept constant by the bootstrap technique via the two voltage-follower configured op-amps, A1/A2 for the ISFET sensor and A3/A4 for the REFET sensor, where  $V_{DS} = I_{Bias1}R_{DS}$ . The outputs of both sensors are taken as voltages from the source of the sensors, namely  $V_{out\_ISFET}$  and  $V_{out\_REFET}$  for ISFET and REFET, respectively. Finally,  $V_{out\_ISFET}$  and  $V_{out\_REFET}$  are fed into the difference amplifier A5 with voltage output of  $V_{out} = V_{out\_ISFET} - V_{out\_REFET}$  [40]. However, it should be noted that this ISFET/REFET differential configuration can only be successfully used when the electrical characteristics of both devices are well matched [41].

Ideally, the REFET should respond identically to the ISFET in the term of drift and noise but the RFET needs to be insensitive to pH, as first proposed by Janata and Comte in 1978 [42]. However, one drawback of the REFET is that making a chemically inert REFET is difficult. Some approaches used in making an REFET are to cover an ISFET insulating membrane with a pH-insensitive layer, as such a blocking polymer layer of teflon, parylene [43] or polyvinyl chloride (PVC) [44]. Unfortunately, this additional surface layer applied in creating REFET, results in an extra capacitance and different insulating membrane properties, which then leads to a different response between ISFET and RFET in terms of DC bias and drift and thus the output signal may be inaccurate.

Nonetheless, a totally new approach of implementing an on-chip reference electrode is reported in [45] by Kim et al. In their work, the solid-state reference electrode now has a Nernstian response of pH and the pH sensor is now REFET. The chosen material for a pH-sensitive electrode is iridium oxide as it exhibits good chemical stability, insolubility in solution, is stable and has a fast response time over a wide pH range [46]. Furthermore,

iridium oxide can be simply prepared by using an electroplating method as shown in [47]. The advantages of the reported configuration are not only its integrated-ability but also the complicated circuitry and well-matched device requirements for the ISFET and REFET in the differential measurement system are no longer required. The new approach to the design and incorporation of the reference electrode taken by [45] shows considerable promise, but more work is still needed, especially to achieve the ultimate goal of providing a fully integrated miniaturised monolithic ISFET pH sensing device.

## 2.4 Drift, hysteresis and lifetime in ISFETs

The drift means the temporal shift of the output voltage under constant conditions like temperature, pH value and concentration of the chemical solution [48]. In addition to drift, hysteresis also exists in the ISFET [49]. Both these non-ideal effects degrade the ISFET and need to be considered when using the ISFET as a sensor in medical applications. The long term accuracy required for biomedical pH sensors is very high. As reported in [50], ISFET sensors which have a pH membrane made of  $Si_3N_4$  appears to have a long term drift in accuracy of typically 0.02-0.06 pH per hour, but the initial drift or short term drift is often far higher and may even reach 0.1-0.2 pH per hour during the first hour of testing. Typically, a pH sensor should be capable of measuring to an accuracy of better than 0.03 pH over a period of one hour [51]. The origin of drift has yet to be fully understood, however there are many theories proposed to explain the cause and behaviour of drift, which include the following (i) enhanced ion migration within the gate insulating membrane, (ii) ejection of electrons from the chemical solution, (iii) slow surface effects and (iv) hydration of the insulating surface [52].

Jamasb et al proposed that ISFET transient response both in the terms of drift and hysteresis are dependant on the material used for the gate insulating membrane as well as

the gate deposition method and reported that  $Si_3N_4$ -gate ISFETs exhibited a higher drift and hysteresis than those with an insulating membrane are made of  $Al_2O_3$  and  $Ta_2O_5$  [51-53]. Usually, in practice the ISFET is immersed in solution and burnt-in for several hours in order to minimise the effect of short term drift. Furthermore, mathematical models are also being proposed for these transient properties of the ISFET, with the objective of then being able to compensate for these effects [52, 54-58]. As such an empirical model can be realised using a stretched-exponential time dependence which is given in [52] as

$$M(t) = M(\infty) \left( 1 - \exp \left( - \left( \frac{t}{\tau} \right)^\beta \right) \right)$$

**Equation 2-15**

where  $M(t)$  represents the molecule numbers of the gate insulator membrane undergoing the hydration at the time  $t$ ,  $M(\infty)$  is the total number molecules allow for hydration transformation,  $\tau$  is the time constant of the model and finally the dispersion parameter is presented by  $\beta$ . It should be noted that the equation describes the rate of growth of the hydrated ion-sensitive layer, from which it can be seen that this change in chemical property of the insulating membrane layer is a slow and monotonic process. Moreover, most of the post-process drift corrections [51, 59] were based on the assumption that the drift is insignificant during the relatively short time that measurements are taken. In other words as long as the rate of pH change in the sample solution is much larger than 0.1 pH per hour, the consecutive measurements taken between short intervals are reasonably free of drift [51].

Finally, a lifetime or ageing effect, described by Palan [7], showed a degradation in the terms of the ISFET response time from a few seconds to several tens of seconds. On the other hand, the lifetime of the ISFETs is often limited due to encapsulation breakdown,

insulating membrane degradation or bond-wire corrosion, all of which result in loss of sensitivity in ISFETs.

## 2.5 Temperature sensitivity in ISFETs

The standard MOSFET theory and the site-binding theory, together with pH temperature characteristics of the electrolyte itself, can be used to explain the temperature dependence of ISFETs [60]. The factors most affected by temperature in MOSFETs and ISFETs are the threshold voltage and the carrier mobility,  $\mu$ , within the channel of the transistor [61]. The mobility is an inverse function of the absolute temperature,  $T$ , according to the empirical expression [62]

$$\mu(T) = \mu(300K)(300/T)^\alpha$$

**Equation 2-16**

where the exponent  $\alpha$  is between 1.0 and 1.5 and this term depends on the impurity concentration in the channel of the transistor. However, the temperature dependence of threshold voltage is mainly in the Fermi potential,  $(\phi_F)$ , given by

$$\phi_F = \frac{kT}{q} \ln \frac{N_{SUB}}{n_i}$$

**Equation 2-17**

where  $N_{SUB}$  is the substrate doping and  $kT/q$  is the thermal voltage. Note that the intrinsic carrier  $n_i$ , is also temperature dependent and assumed to be giving by

$$n_i = BT^{1.5} \exp\left(\frac{-qE_g(0)}{2kT}\right)$$

**Equation 2-18**

where  $B$  is a constant dependent on  $T$ , and  $E_g(0)$  is the energy gap at 0°K. In addition, the temperature influence on site-binding and the electrolyte is reflected in the expression of pH sensitivity of the ISFET in Equation 2-11 and rewritten again as

$$\frac{\partial \psi_0}{\partial pH} = -2.3 \frac{kT}{q} \alpha$$

**Equation 2-19**

where  $\alpha$  is the sensitivity coefficient and the equation suggests that the sensitivity is linearly proportion to the thermal voltage. As can be seen, the temperature dependencies are complex and involved multiple sources. Therefore many of the commercial devices use some kind of temperature compensation method to minimise temperature effects.

Shown here are two different approaches to compensate the temperature dependency of ISFETs. The first implementation is based on a compensation software approach [63-64] reported by Chung et al. In this approach, two analog input stages are included. The first input stage is a  $V_T$  extractor temperature sensor which measures the temperature of the circuits as  $V_T$  comprises  $\phi_F$  which is directly proportion to the thermal voltage and therefore the absolute temperature [65]. The second input is a bridge-type floating-source ion sensing circuit, first report in [66], which shows a linear response for pH of the solution [64]. A data acquisition card is used in order to register the two inputs. Furthermore, the second input is processed using compensation software which has been developed by using LabVIEW<sup>®</sup> to correct any temperature variation in the output [64].

The second implementation proposed by Shepherd and Toumazou, is based on an analog approach using weak-inversion bias for the ISFET and translinear current-mode circuit techniques then applied [5, 67]. The ISFET sensor in the circuit when operated in weak-inversion results in significantly lower current and voltage operation. Furthermore, the

drain current of the ISFET in weak-inversion is exponentially related to its threshold voltage, which is proportional to pH, and since pH is logarithmically related to hydrogen ion concentration. A direct relationship between ISFET drain current and hydrogen ion concentration can be obtained as [5], shown as a function of ISFET drain current expression below

$$I_D(V_{T0} + \Delta V_{chem}) = I_{DQ} \Delta[H^+]^{\alpha/n}$$

**Equation 2-20**

where  $\alpha$  is the sensitivity coefficient,  $V_{T0}$  is the threshold voltage for  $V_{BS} = 0$ ,  $\Delta V_{chem}$  is a grouping of chemical potentials at the ISFET insulator surface,  $n$  is the sub-threshold slop factor and  $I_{DQ}$  is a constant. Finally, Equation 2-20 suggested that the drain current of the ISFET in weak-inversion is scaled by a known change in hydrogen ion concentration and more importantly it is temperature insensitive [67].

## 2.6 Trapped charges in CMOS ISFETs

In CMOS ISFETs, trapped charges left by fabrication can exist either in the passivation layer or on the floating gate. As the polysilicon gate is only connected to the floating metal where the path to ground is eliminated, any charge in the gate oxide will remain trapped. In addition, this is also true for the passivation layer which forms a stack with no path to ground where charge can also remain trapped for a long period. Furthermore, this trapped charge has been proposed to be the main reason for a large variation in the threshold voltage of the ISFET [68]. For instance, in [27] Bausells et al reported a threshold voltage deviation of -7V to 6V in their N-channel ISFET and Hammond et al [24] reported the threshold voltage variation as wide as -33V to -8V with their P-channel ISFETs.

Several different approaches were proposed to minimise the affect of the trapped charges in CMOS ISFETs. The first approach used UV radiation to remove the excess electrons either by tunnelling out of the polysilicon gate to the floating metal where the electrons will later be discharged via the metal contact, or by tunnelling out of the passivation layer as shown in Figure 2-9. This technique works because the UV radiation gives the electrons enough energy to excite, or tunnel out from, these layers to their surrounding [69-70]. Furthermore, this technique shows satisfactory results in improving the threshold voltage of the device as reported in [24], where the P-channel threshold voltage was changed from -22V to -2V.

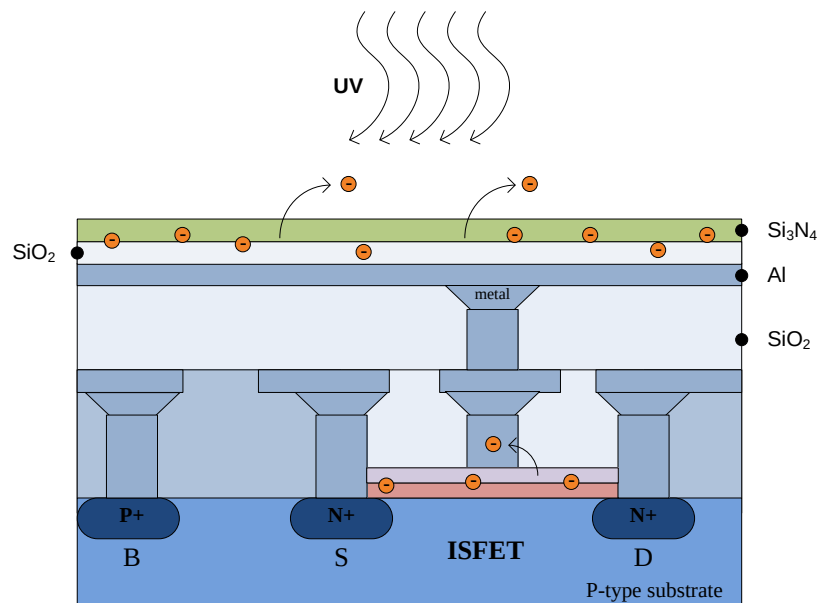


**Figure 2-9.** Trapped charge removal using UV radiation [24]

The second approach was proposed by Georgiou and Toumazou [71]. They used hot-electron injection as a non-volatile method to modulate the charge on the floating gate of the P-channel ISFET. Hot-electron injection can arise in the device when the drain to

source potential is sufficiently high to create a large lateral electric field in the transistor. This results in electrons within the substrate being injected into the floating gate such that they counteract the effect of trapped positive charges and thus lower the threshold voltage of the ISFET. Georgiou and Toumazou achieved threshold voltage shifts of up to 2.8V in a standard pH 7 buffer solution.

The third and final technique is also from the same two authors, Georgiou and Toumazou [72]. In this work, they proposed a new approach referred to as a programmable gate ISFET (PG-ISFET). The new device is based on the CMOS ISFET shown in Figure 2-6 (b) with an additional control-gate capacitor,  $C_{CG}$ , attached to the floating gate of the device as shown in Figure 2-10 where  $V_{G'}$  is the effective gate voltage given by the combination of the voltage applied to the reference electrode, the input referred trapped charge and the pH dependent potential.

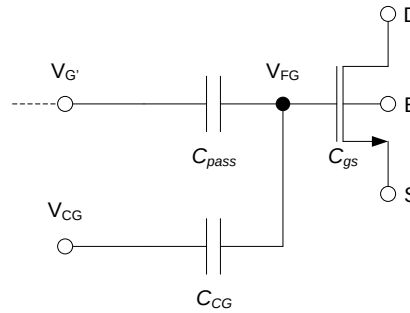


**Figure 2-10.** Programmable gate ISFET (PG-ISFET) device [72]

By doing so, a reduction in large threshold voltages is achieved. The compensation of trapped charge follows the expression below

$$C_{pass}V_{tc} = -C_{CG}V_{CG}$$

Equation 2-21

where  $V_{tc}$  is the equivalent voltage modelled of the trapped charges of the device,  $C_{pass}$  is the capacitance due to the passivation. Therefore, by biasing the control-gate with

$$V_{CG} = -\frac{C_{pass}}{C_{CG}}V_{tc}$$

Equation 2-22

the large threshold voltage of the device due to trapped charge can be reduced.

## 2.7 Noise in CMOS ISFETs

This section deals with the effects of electrical noise in ISFETs particularly at low frequencies. The two main noise sources are (i) thermal noise and (ii) flicker noise, also known as 1/f noise. Noise phenomena are inherent within all physical devices. They may be reduced but never eliminated completely [73]. Thermal noise is generated by the thermal excitation of the charge carriers in a conducting material and consequently proportional to the absolute temperature and consistent over the frequency spectrum. As in a MOSFET, the thermal noise of an ISFET can be expressed in terms of the drain current of the device, as given in the follow expression [74]

$$I_d^2(f) = 4kT\left(\frac{2}{3}\right)g_m$$

Equation 2-23

where  $k$  and  $T$  are Boltzmann's constant and absolute temperature, respectively, and  $g_m$  is the transconductance of the ISFET.

Flicker noise is found in all active devices. The origin of flicker noise varies, but in FETs, both MOSFETs and ISFETs, it is mainly caused by energy-band traps within the conducting channel where charge carriers are captured and released in a random fashion. Furthermore, it is known that a P-channel device has a lower flicker noise than a N-channel device. The flicker noise can be represented as the gate voltage within the device, given by [74]

$$V_g^2(f) = \frac{K}{WLC_{ox}f}$$

**Equation 2-24**

where  $K$  is a constant for a particular FET,  $W$  and  $L$  is the width and length of the device gate,  $C_{ox}$  is the gate oxide capacitance and  $f$  is the frequency. Moreover, the above expression also suggests that for a good design practice the gate width,  $W$  and length,  $L$  and gate oxide capacitance  $C_{ox}$  of the device should be maximised in order to achieve the minimum flicker noise.

Correlated double sampling, or chopper stabilization circuit techniques, are used to reduce noise in active devices [75]. Both techniques are particularly effective in dealing with low frequency flicker noise, however, both can result in an increase in in-band noise of the system. An alternative approach has been proposed by Chan et al [32], which exploits the principle of averaging the ISFET front-end interface to reduce noise in general. Chan's new concept uses 64 ISFET sensors in a CMOS array configuration with global current feedback. Not only is the reduction of overall noise achieved but also the improvement in long-term drift and linearity owing to averaging and negative feedback is also obtained.

## 2.8 ISFET interfacing techniques

This section covers a review of existing ISFET readout circuits some of which have a topology that is better suited to integrated circuit fabrication than others. Before considering specific interface circuit designs, the operating regions of the ISFET will be reviewed with reference to the large signal equations applicable for each region.

As stated already in this thesis, the underpinning parameter of interest in development of a biochemical sensor using an ISFET is the device threshold voltage,  $V_T$ , [74, 76] where  $V_T$  is the threshold voltage of the ISFET and  $V_T = V_{chem} + V_{th(MOSFET)}$ . The other ISFET parameters are (i)  $\mu_n$  which is surface mobility of electrons under the gate, (ii)  $C_{ox}$  which is the gate oxide capacitance per unit area, (iii)  $W$  and  $L$  are the gate width and length respectively, (iv)  $\gamma$  is the body effect coefficient, (v)  $\phi_F$  is the Fermi level of the semiconductor, and finally, (vi) the term  $\lambda$  represents channel-length modulation between the drain source terminals of the transistor.

There are four regions of operation in an ISFET, as there are in any field effect transistor, namely (i) Cut-Off, (ii) Weak Inversion or Sub-Threshold, (iii) Triode, and (iv) Saturation. The key features of each region of operation are described below.

**Cut-off region:** This is where  $V_{G'S} < V_T$  and the surface potential,  $\phi_s$  is less than Fermi level,  $\phi_s < \phi_F$ , and essentially no source to drain electron flow takes place, hence

$$I_D = 0$$

**Equation 2-25**

**Weak inversion (or sub-threshold) region:** This is where  $V_{G'S} < V_T$ ,  $\phi_F < \phi_s < 2\phi_F$  and  $V_{DS} \gg 100mV$ , then the drain current of the ISFET is given

$$I_D = I_t \frac{W}{L} \exp\left(\frac{V_{GS} - V_T}{nU_T}\right)$$

Equation 2-26

where  $I_t$  is a pre-exponential multiplier,  $n$  is the subthreshold slope factor and  $U_T = KT/q$  is the thermal voltage, where  $K$  is the Boltzmann constant,  $T$  is the absolute temperature and  $q$  is the electronic charge.

**Triode (or linear) region:** This is where  $V_{GS} > V_T$  and  $0 < V_{DS} < V_{GS} - V_T$  and the drain current is given by

$$I_D = \frac{1}{2} \frac{W}{L} \mu_n C_{ox} [2(V_{GS} - V_T) - V_{DS}] V_{DS}$$

Equation 2-27

**Saturation region:** this is where  $V_{GS} > V_T$  and  $0 < V_{GS} - V_T < V_{DS}$  and the drain current is given by

$$I_D = \frac{1}{2} \frac{W}{L} \mu_n C_{ox} (V_{GS} - V_T)^2 (1 + \lambda V_{DS})$$

Equation 2-28

$V_T$  is the parameter of the ISFET sensitive to and directly proportional to the biochemical fluid input. Consequently, ISFET sensors are used either in the triode region or in the saturation region as in both regions  $V_T$  is readily accessed. The weak-inversion region could be used for very low power biochemical sensing. In this region, as seen from Equation 2-26,  $V_T$  is in the exponent of the exponential  $I_D$  term.

In this thesis the ISFET is used primarily for sensing pH, Urea and Creatinine, and so ‘linear’ access to  $V_T$  is required. Therefore, operation of the ISFET will be confined to the Triode and Saturation regions.

The first ISFET interface circuit to be reviewed, is shown in Figure 2-11 was proposed by [77]. The circuit is an ISFET source and drain follower design connected with an instrumentation amplifier (IA) realized with op-amps A1, A2 and A3. The ISFET is placed at the IA terminals where the gain determining resistor would normally be connected. As a result the voltage,  $V_{DS}$ , of the ISFET is kept at a constant value of  $V_{DS} = I_{Bias}R_1$ . Thus, any change in the ion concentration will cause a change in the output voltage of the instrumentation amplifier,  $V_{out(A3)} = V_{is}$ . The difference between this output and a fixed reference voltage,  $V_{ref}$ , will be amplified by op-amp A4, and acts as a feedback signal that adjust the common mode level of  $V_{DS}$  to continuously keep a constant drain current running through ISFET. Analysis of the circuit, see [77], concludes that the voltage output is

$$V_{out} = \frac{R_6}{R_2} V_T$$

**Equation 2-29**

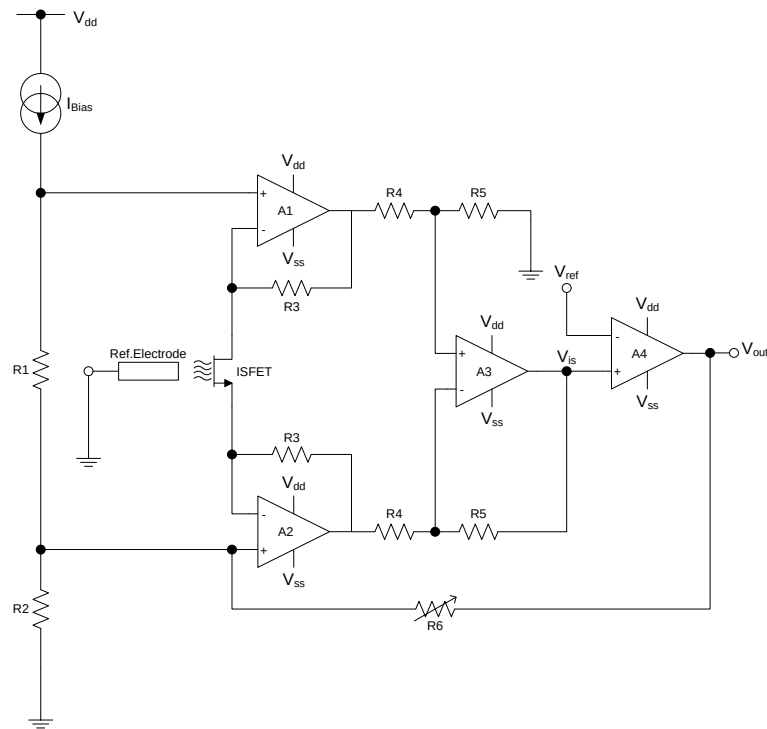


**Figure 2-11.** Instrumentation amplifier ISFET readout circuit [77]

This design is claimed to work well and is used widely in discrete implementations. Another good feature of the design, as identified earlier, is that the reference electrode is grounded and not used as a feedback terminal. This has the advantage that multiple ISFETs could be used with the same reference electrode. However, the fact that four op-amps are required together with nine resistors and one current source makes it an unattractive circuit from the view point of total component count. In particular, in biomedical micro-system where only limited silicon area is available for implementing an interface circuit, this design has limited value.

The second ISFET interface circuit to be considered is shown in Figure 2-12. It was proposed in [78] is a very interesting and an elegant alternative. It operates in a similar way to the Figure 2-11 design in that the feedback from source to drain maintains a

constant  $V_{DS} = I_{Bias1} \cdot 5k1$  and the drain current,  $I_D$ , of the ISFET is fixed by the current sink,  $I_{Bias2}$ .

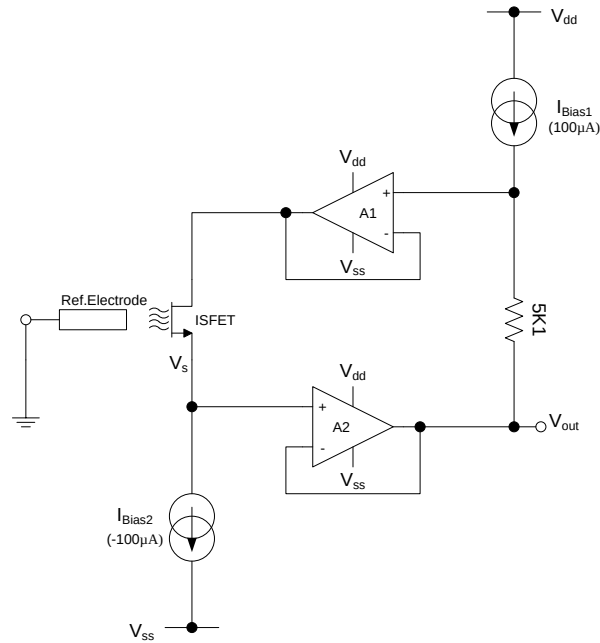


**Figure 2-12.** Fixed  $V_{DS}$  and  $I_D$  ISFET readout circuit [78]

Again the design has the advantage of not applying feed-back to the reference electrode which is held at ground potential. This circuit requires two op-amps, however as they are simply unit-gain voltage followers, in a monolithic realisation of the complete circuit their design could be much simpler than a full op-amp. The output voltage is the inverse of the gate-source voltage thus the closed-loop voltage gain of the circuit with respect to the gate to source voltage is  $A_{VCL} = -1$ .

A change in ion concentration will result in a change of common mode level of  $V_S$  therefore when the ISFET is working in the linear (triode) region of strong inversion, the

voltage output will track the modulation of threshold voltage or  $V_{chem}$  linearly as shown in the analysis below

$$V_{GS} = -V_S = -V_{out}$$

**Equation 2-30**

The drain current of the ISFET in the triode region as given in Equation 2-27 can be rewritten as

$$I_D = \beta \left[ (-V_{out} - V_T)V_{DS} - \frac{V_{DS}^2}{2} \right]$$

**Equation 2-31**

where

$$\beta = \frac{W}{L} \mu_n C_{ox}$$

**Equation 2-32**

Finally,  $V_{out}$  can be obtain from Equation 2-31 and reference to Figure 2-12 as

$$V_{out} = -V_T - \frac{I_{Bias2}}{\beta I_{Bias1} 5K1} - \frac{I_{Bias1} 5K1}{2}$$

**Equation 2-33**

where  $I_{Bias1}$ ,  $I_{Bias1}$  and  $\beta$  are constants, making

$$V_{out} \propto V_T$$

**Equation 2-34**

In addition, as a direct consequence of using negative feed-back to force the output voltage to be linearly proportional to  $V_T$ , then  $V_{out}$  is also proportion to pH in the weak-

inversion, the triode and the saturation operating regions. It should be noted that this circuit is easily modified for P-channel ISFET, all that is needed is to reverse the current source and sink. So far neither of the circuits described offer any temperature compensation beyond biasing of the ISFET as close as possible to its isothermal point. Furthermore, these circuits were originally intended for discrete components implementation in which case any potential advantages of the ISFET being an integrated sensor with the potential to integrate the entire readout circuit is lost. Incidentally in an integrated implementation, unless triple well technology is used, the body effect will affect the operation degrading the linearity of the output signal.

The third ISFET interface circuit, shown in Figure 2-13, exploits the ability to monolithically integrate the ISFET and MOSFET in a differential pair topology which has the advantage of inherent temperature compensation [60, 79]. The ISFET and MOSFET are best created on the same substrate to achieve a matched pair of devices, particular in the term of geometry, structure and temperature. The drain current of both FETs will be almost equal and therefore virtually constant,  $I_{DS} = I_{Bias}/2$  as a result of a high amplification of op-amp A1 and negative feedback to the gate of the MOSFET.

Any changes in ion concentration of the solution, result in a change in the threshold voltage,  $V_T$ , of the ISFET. Because the high output impedance of the  $I_{Bias}$  current sink together with the close-loop feedback from the output of op-amp A1 to the gate of transistor M1, this forces an equal change in the gate voltage of M1, in order to keep  $V_{DS}$  and  $I_{DS}$  of both devices the same. Therefore, the gate voltage of M1 is used as a circuit signal output due to its ability to perfectly duplicate the threshold voltage,  $V_T$ , of the ISFET. Furthermore, with well matched transistors, the temperature effect and body effect tend to cancel.

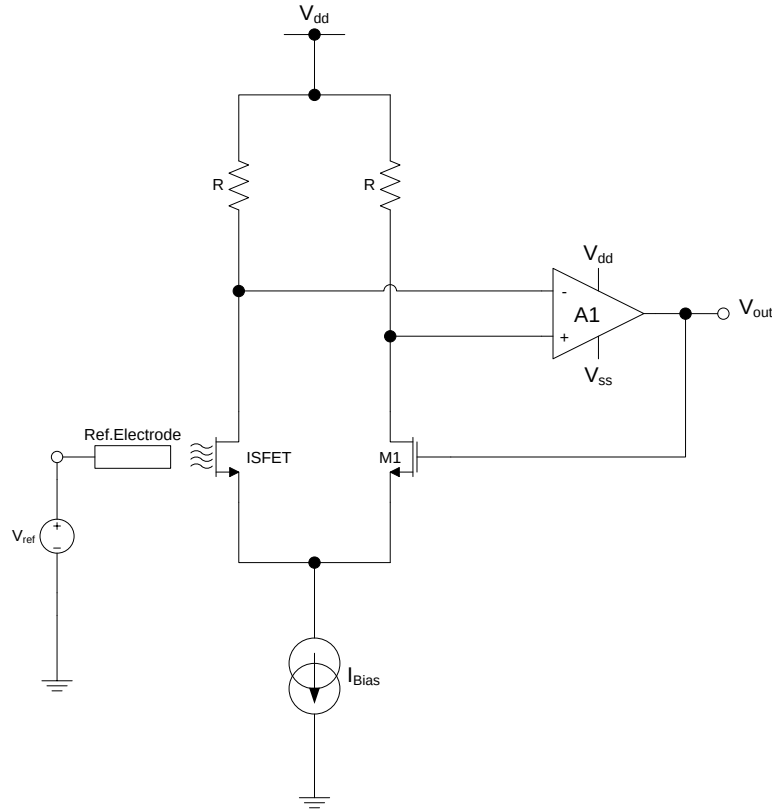


**Figure 2-13.** differential pair ISFET readout circuit [79]

Again an op-amp is required for the circuit of Figure 2-13, but this time only one.

Assuming that the  $V_{th(MOS)}$  of both devices is the same, then output voltage will be

$$V_{out} \propto V_{chem}$$

**Equation 2-35**

However, this will only be true if both the electrical characteristics of the two FETs are the same and they also need to be at the same temperature. In practice, the circuit can only offer a reasonable degree of temperature compensation [77] and would exhibit a relatively large input offset voltage due to the difference in threshold voltage between the ISFET and the MOSFET as a result of the chemical potential across the electrolyte solution [77] and any trapped charge in the ISFET.

The fourth ISFET interface circuit, shown in Figure 2-14 also exploits the advantage of integrating the ISFET within a CMOS environment, but this time as part of the voltage buffer operational amplifier [37, 80]. In fact the circuit is functionally the same as the third example above, but the op-amp function is now realised at transistor level. The input stage is differential and consists of the ISFET/MOSFET M1 long-tail pair, where the ISFET is the non-inverting input transistor. The output of this differential stage drives the second stage common-source amplifier M6. By connecting the output of the common-source amplifier to the gate of the inverting transistor input M1, the amplifier now operated as a voltage buffer and thus the close-loop gain obtained is unity.

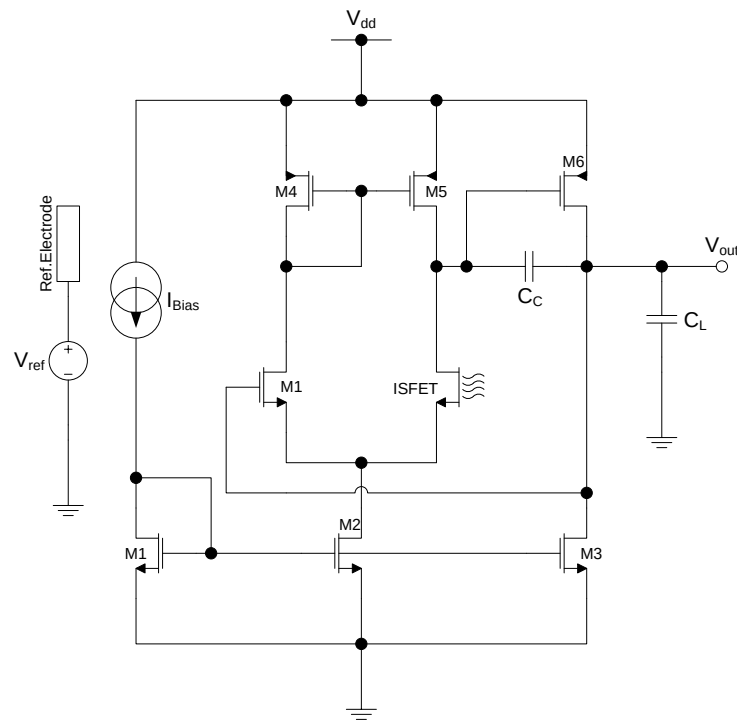


**Figure 2-14.** Operational amplifier ISFET readout circuit [37]

Any differences in the threshold voltages between the ISFET/MOSFET differential pair at the input stage will appear at the output. As a result, the output voltage expression,  $V_{out}$ , can be approximated as [37]

$$V_{out} = V_{os} + V_{chem}$$

**Equation 2-36**

where  $V_{os}$  is the input referred offset voltage, which is temperature and light sensitive but chemically insensitive.

The fifth ISFET interface circuit is shown in Figure 2-15. This circuit is an alternative current-feedback approach to the voltage-mode feedback system of Figure 2-13 and Figure 2-14. The operation can be seen most easily from the small-signal equivalent circuit of Figure 2-15 (a), which is shown in Figure 2-15 (b).

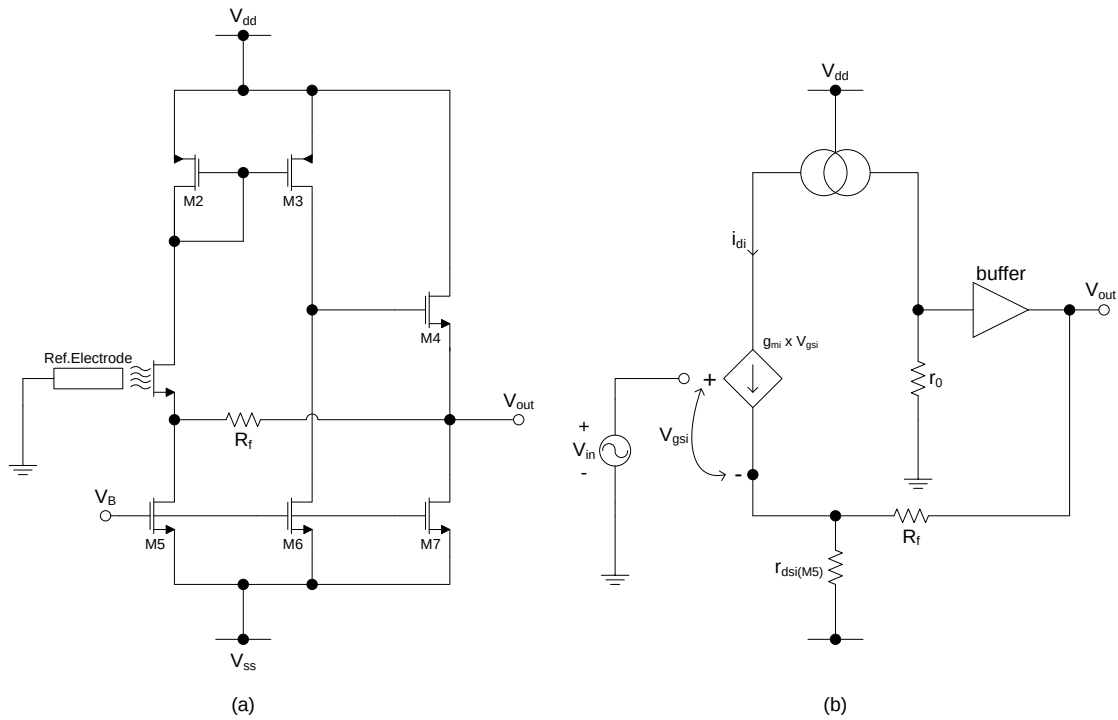


**Figure 2-15.** [81] (a) Current feedback op-amp ISFET readout circuit and (b) its macromodel

There are parallels in this design with the circuit in Figure 2-13 and Figure 2-14 which use the ISFET as one half of the long-tail pair input stage of a voltage op-amp, with the significant problem of requiring close matching between the ISFET and its MOSFET input pair. However, the circuit of Figure 2-15 uses a current feedback type of op-amp topology with the ISFET at the input stage. Comparing the current feedback op-amp with a voltage op-amp, the most significant difference is that it does not use long-tail pair at the input, which means that there is no requirement in this circuit for matching between the ISFET and a counterpart MOSFET. The circuit is closed-loop in structure with current feed-back applied to the low impedance source of the ISFET, with the reference electrode, as for all the previous designs, is connected to ground. From the feedback topology, using small signal analysis, the closed-loop gain,  $A_{close}$ , is given by [81]

$$A_{close} = \frac{\partial V_{out}}{\partial V_{in}} = \frac{A_{open}}{1 + \beta A_{open}}$$

**Equation 2-37**

where,

$$A_{open} = \frac{g_{mi}}{1 + g_{mi}R_f} r_o$$

**Equation 2-38**

and since  $r_{ds(M5)} \gg R_f$ ,

$$\beta = \frac{r_{ds(M5)}}{r_{ds(M5)} + R_f} \approx 1$$

**Equation 2-39**

Finally, by substituting Equation 2-39 into Equation 2-37 the close-loop gain of the circuit obtained is unity, thus the output expression is given as

$$\frac{\partial V_{out}}{\partial pH} = -2.3 \frac{kT}{q} \alpha$$

Equation 2-40

The sixth and final ISFET interface circuit, shown in Figure 2-16, uses a reference electrode feedback configuration [82]. In both Figure 2-16 (a) and (b), the source voltage is held at zero which means that  $V_{BS}$  can be made zero by grounding the bulk, thus removing the body effect. It was demonstrated in [77] that changes in the ion concentration of the solution are compensated by an equal and opposite change of reference electrode potential. Thus the drain current,  $I_d$ , of the ISFET is kept constant and the reference electrode voltage,  $V_{ref}$  can be taken as the output signal, proportional to the pH of the solution.

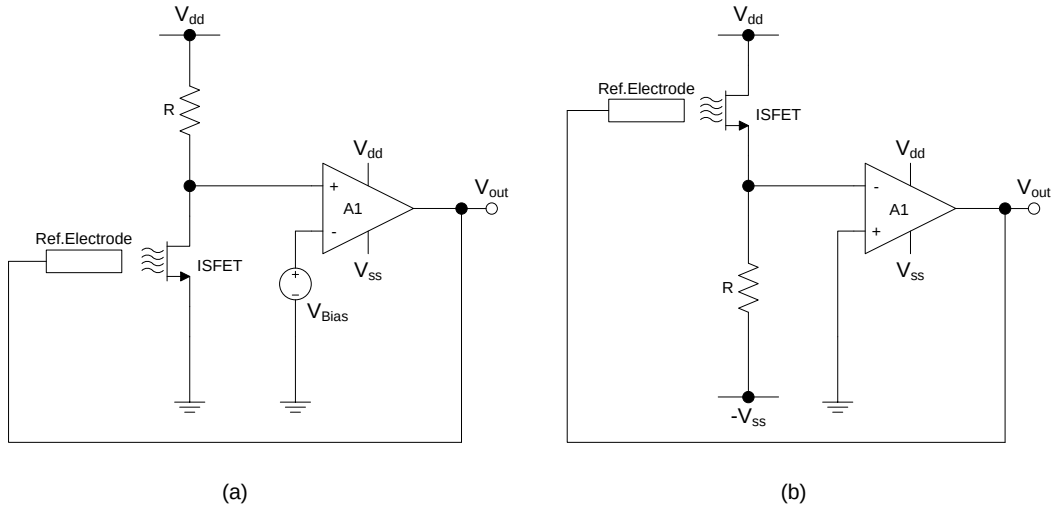


**Figure 2-16.** [82] Feedback through reference electrode ISFET readout circuit, (a) where  $V_{Bias} = V_{DS(ISFET)}$  of ISFET and (b) where  $V_{Bias} = V_{S(ISFET)}$

In the circuit of Figure 2-16 (a) the net operation is similar to that of Figure 2-16 (b), the main difference is that the op-amp feedback connections are reversed because the ISFET in the Figure 2-16 (a) circuit introduces an additional phase inversion in the feedback path. The output voltage for Figure 2-16 (a) and Figure 2-16 (b) is

$$V_{out} = V_T$$

**Equation 2-41**

Both Figure 2-16 (a) and Figure 2-16 (b) are relatively simple topologies but the fact that the reference electrodes cannot be held at constant voltage, ideally or ground is a disadvantage. The feed-back signal in both cases is applied to the reference electrode and as such the reference electrode is closing the loop. This is highly undesirable because in a practical application the feedback loop will be broken if (i) bubbles form in the cells or (ii) when dipping the electrode into different solution that are being analysed. When such a break occurs, the feed-back potential becomes large and positive. As soon as the feedback is re-established, a high voltage transients may cause the temporarily polarisation of the reference electrode or the intrinsic gate resulting in an offset potential and sometimes this can cause the breakdown of the ISFET encapsulation [79]. Furthermore, the use of the reference electrode as a control signal terminal means that this design is not suitable for applications with many ISFET sensors where the individual control of each ISFET is now required. Moreover, this design certainly cannot be used for a differential configuration, since two reference electrodes are then needed in the same solution and thus cannot be separately controlled. Lastly, a circuit configuration with non-ground potential reference electrodes may cause undesired ions to be produced in the chemical solution [81] leading to an inaccurate reading of pH.

## 2.9 Summary of Chapter 2

This chapter has focused on the biochemical sensing element of the CCCII+, namely the ISFET. The origins, structure, evolution and operation of the ISFET have been described in some detail to serve as a knowledge base for the input part of the CCCII+. Both the traditional ISFET and the unmodified CMOS ISFET have been reviewed including appropriate macromodels. Like all sensors, the ISFET is not ideal and issues of nonideality have been considered, including drift, temperature sensitivity, trapped charge effects and noise. The chapter closes with a review of several interface, or read-out circuits, that are potential contenders for a fully integrated biochemical ISFET instrument. The next key element of the CCCII+, namely the CCII+, is the subject of the next chapter of this thesis, Chapter 3.

## 2.10 References

- [1] P. Bergveld, "Thirty years of ISFETOLOGY: What happened in the past 30 years and what may happen in the next 30 years," *Sensors and Actuators B: Chemical*, vol. 88, pp. 1-20, 2003.
- [2] P. Bergveld, "Development of an Ion-Sensitive Solid-State Device for Neurophysiological Measurements," *Biomedical Engineering, IEEE Transactions on*, vol. BME-17, pp. 70-71, 1970.
- [3] T. Prodromakis, *et al.*, "Effect of mobile ionic-charge on CMOS based ion-sensitive field-effect transistors (ISFETs)," in *Circuits and Systems, 2009. ISCAS 2009. IEEE International Symposium on*, 2009, pp. 2165-2168.
- [4] M. JANICKI, *et al.*, "Temperature dependent model of ion selective transistor for multidomain simulations," presented at the 10th Conf. THERMINIC Sophia Antipolis, France, 2004.
- [5] L. Shepherd and C. Toumazou, "Weak Inversion ISFETs for ultra-low power biochemical sensing and real-time analysis," *Sensors and Actuators B: Chemical*, vol. 107, pp. 468-473, 2005.

- [6] P. Georgiou and C. Toumazou, "An adaptive ISFET chemical imager chip," in *Circuits and Systems, 2008. ISCAS 2008. IEEE International Symposium on*, 2008, pp. 2078-2081.
- [7] B. Pallan, "Design of low noise pH-ISFET Microsystems and Integrated Inductors with Increased Quality Factor Q," PhD, Institut National Polytechnique De Grenoble, 2002.
- [8] P. D. van der Wal, *et al.*, "High-k dielectrics for use as ISFET gate oxides," in *Sensors, 2004. Proceedings of IEEE*, 2004, pp. 677-680 vol.2.
- [9] H. Abe, *et al.*, "ISFET's using inorganic gate thin films," *Electron Devices, IEEE Transactions on*, vol. 26, pp. 1939-1944, 1979.
- [10] Y. Ohta, *et al.*, "Prototype sodium and potassium sensitive micro ISFETS," *Sensors and Actuators*, vol. 2, pp. 387-397, 1981.
- [11] R. Hintsche, *et al.*, "Integrated differential enzyme sensors using hydrogen and fluoride ion sensitive multigate FETs," *Biosensors and Bioelectronics*, vol. 5, pp. 327-334, 1990.
- [12] T. Matsuo and M. Esashi, "Methods of isfet fabrication," *Sensors and Actuators*, vol. 1, pp. 77-96, 1981.
- [13] B. Streetman and S. Banerjee, *Soild State Electronic Devices*: Prentice Hall, 2000.
- [14] C. D. Fung, *et al.*, "A generalized theory of an electrolyte-insulator-semiconductor field-effect transistor," *Electron Devices, IEEE Transactions on*, vol. 33, pp. 8-18, 1986.
- [15] D. Chan, *et al.*, "Electrical double layer interactions under regulation by surface ionization equilibria-dissimilar amphoteric surfaces," *Journal of the Chemical Society, Faraday Transactions 1: Physical Chemistry in Condensed Phases*, vol. 72, pp. 2844-2865, 1976.
- [16] A. J. Bard and L. Faulkner, *Electrochemical Methods: Fundamentals and Applications*: John Wiley and Sons, 2001.
- [17] P. A. Hammond, *et al.*, "Design of a single-chip pH sensor using a conventional 0.6- $\mu$ m CMOS process," *Sensors Journal, IEEE*, vol. 4, pp. 706-712, 2004.
- [18] B. Palan, *et al.*, "CMOS ISFET-based structures for biomedical applications," in *Microtechnologies in Medicine and Biology, 1st Annual International, Conference On. 2000*, 2000, pp. 502-506.

- [19] D. L. Hareme, *et al.*, "Ion-sensing devices with silicon nitride and borosilicate glass insulators," *Electron Devices, IEEE Transactions on*, vol. 34, pp. 1700-1707, 1987.
- [20] D. A. Borkholder, "Cell based biosensors using microelectrodes," PhD, Stanford University, 1998.
- [21] L. M. Shepherd, "Low-Power Computational Interfacing with CMOS ISFETs," PhD, Electrical and Electronic Engineering, Imperial College, 2008.
- [22] P. Bergveld, *et al.*, "The remarkable similarity between the acid-base properties of ISFETs and proteins and the consequences for the design of ISFET biosensors," *Biosensors and Bioelectronics*, vol. 10, pp. 405-414, 1995.
- [23] R. E. G. Hal van, *et al.*, "A novel description of ISFET sensitivity with the buffer capacity and double-layer capacitance as key parameters," *Sensors and Actuators B: Chemical*, vol. 24-25, pp. 201-205, 1995.
- [24] P. A. Hammond, *et al.*, "A single-chip pH sensor fabricated by a conventional CMOS process," in *Sensors, 2002. Proceedings of IEEE*, 2002, pp. 350-355 vol.1.
- [25] S. Martinoia, *et al.*, "Development of ISFET array-based microsystems for bioelectrochemical measurements of cell populations," *Biosensors and Bioelectronics*, vol. 16, pp. 1043-1050, 2001.
- [26] C. Cané, *et al.*, "Multilayer ISFET membranes for microsystems applications," *Sensors and Actuators B: Chemical*, vol. 35, pp. 136-140, 1996.
- [27] J. Bausells, *et al.*, "Ion-sensitive field-effect transistors fabricated in a commercial CMOS technology," *Sensors and Actuators B: Chemical*, vol. 57, pp. 56-62, 1999.
- [28] T. Tong Boon, *et al.*, "Toward a miniature wireless integrated multisensor microsystem for industrial and biomedical applications," *Sensors Journal, IEEE*, vol. 2, pp. 628-635, 2002.
- [29] W. Hon-Sum and M. H. White, "A self-contained CMOS integrated pH sensor," in *Electron Devices Meeting, 1988. IEDM '88. Technical Digest., International*, 1988, pp. 658-661.
- [30] L. Bousse, *et al.*, "A process for the combined fabrication of ion sensors and CMOS circuits," *Electron Device Letters, IEEE*, vol. 9, pp. 44-46, 1988.
- [31] P. Georgiou, "Chemical Bionics - A novel design approach using Ion Sensitive Field Effect Transistors," PhD, Electrical and Electronic Engineering, Imperial College, 2008.

- [32] W. P. Chan, *et al.*, "64 pH-ISFET averaging array employing global negative current feedback," *Electronics Letters*, vol. 45, pp. 536-537, 2009.
- [33] R. Catrall, *Chemical Sensors*: Oxford Uni. Press, 1997.
- [34] I. Y. Huang, *et al.*, "Improvement of integrated Ag/AgCl thin-film electrodes by KCl-gel coating for ISFET applications," *Sensors and Actuators B: Chemical*, vol. 94, pp. 53-64, 2003.
- [35] H. Suzuki, *et al.*, "Micromachined liquid-junction Ag/AgCl reference electrode," *Sensors and Actuators B: Chemical*, vol. 46, pp. 146-154, 1998.
- [36] Y. Haigang, "A pH-ISFET Based Micro Sensor System on Chip Using Standard CMOS Technology," 2005, pp. 180-183.
- [37] H. S. Wong and M. H. White, "A CMOS-integrated 'ISFET-operational amplifier' chemical sensor employing differential sensing," *Electron Devices, IEEE Transactions on*, vol. 36, pp. 479-487, 1989.
- [38] W. Sansen, *et al.*, "A smart sensor for the voltammetric measurement of oxygen or glucose concentrations," *Sensors and Actuators B: Chemical*, vol. 1, pp. 298-302, 1990.
- [39] Z. Jichun, *et al.*, "Electrochemical array microsystem with integrated potentiostat," in *Sensors, 2005 IEEE*, 2005, p. 4 pp.
- [40] L. Ravezzi and P. Conci, "ISFET sensor coupled with CMOS read-out circuit microsystem," *Electronics Letters*, vol. 34, pp. 2234-2235, 1998.
- [41] P. Bergveld, *et al.*, "How electrical and chemical requirements for refets may coincide," *Sensors and Actuators*, vol. 18, pp. 309-327, 1989.
- [42] P. A. Comte and J. Janata, "A field effect transistor as a solid-state reference electrode," *Analytica Chimica Acta*, vol. 101, pp. 247-252, 1978.
- [43] T. Matsuo and H. Nakajima, "Characteristics of reference electrodes using a polymer gate ISFET," *Sensors and Actuators*, vol. 5, pp. 293-305, 1984.
- [44] S. Zhao-Xia and Z. Da-Zhong, "0.6/spl mu/m CMOS pH sensor IC with Si/sub 3/N/sub 4/ island structure," in *Solid-State and Integrated Circuit Technology, 2006. ICSICT '06. 8th International Conference on*, 2006, pp. 646-648.
- [45] Y. J. Kim, *et al.*, "Configuration for micro pH sensor," *Electronics Letters*, vol. 39, pp. 1515-1516, 2003.
- [46] S. Yao, *et al.*, "A pH Electrode Based on Melt-Oxidized Iridium Oxide," *Journal of The Electrochemical Society*, vol. 148, pp. H29-H36, 2001.

- [47] S. A. M. Marzouk, *et al.*, "Electrodeposited Iridium Oxide pH Electrode for Measurement of Extracellular Myocardial Acidosis during Acute Ischemia," *Analytical Chemistry*, vol. 70, pp. 5054-5061, 1998.
- [48] P. Hein and P. Egger, "Drift behaviour of ISFETs with Si<sub>3</sub>N<sub>4</sub>-SiO<sub>2</sub> gate insulator," *Sensors and Actuators B: Chemical*, vol. 14, pp. 655-656, 1993.
- [49] A. Garde, *et al.*, "Improving the drift and hysteresis of Si<sub>3</sub>N<sub>4</sub> pH response using RTP technique," *Sensor Materials*, vol. 9, pp. 15-23, 1997.
- [50] C. G. Jakobson and Y. Nemirovsky, "1/f noise in ion sensitive field effect transistors from subthreshold to saturation," *Electron Devices, IEEE Transactions on*, vol. 46, pp. 259-261, 1999.
- [51] S. Jamasb, *et al.*, "Correction of instability in ion-selective field effect transistors (ISFETs) for accurate continuous monitoring of pH," in *Engineering in Medicine and Biology Society, 1997. Proceedings of the 19th Annual International Conference of the IEEE*, 1997, pp. 2337-2340 vol.5.
- [52] S. Jamasb, *et al.*, "A physical model for threshold voltage instability in Si<sub>3</sub>N<sub>4</sub>-gate H<sup>+</sup>-sensitive FET's (pH ISFET's)," *Electron Devices, IEEE Transactions on*, vol. 45, pp. 1239-1245, 1998.
- [53] S. Jamasb, *et al.*, "A physically-based model for drift in Al<sub>2</sub>O<sub>3</sub>-gate pH ISFET's," in *Solid State Sensors and Actuators, 1997. TRANSDUCERS '97 Chicago, 1997 International Conference on*, 1997, pp. 1379-1382 vol.2.
- [54] S. Martinoia, *et al.*, "Modelling non-ideal behaviours in H<sup>+</sup>-sensitive FETs with SPICE," *Sensors and Actuators B: Chemical*, vol. 7, pp. 561-564, 1992.
- [55] L. Bousse, *et al.*, "Comparison of the hysteresis of Ta<sub>2</sub>O<sub>5</sub> and Si<sub>3</sub>N<sub>4</sub> pH-sensing insulators," *Sensors and Actuators B: Chemical*, vol. 17, pp. 157-164, 1994.
- [56] S. Jamasb, *et al.*, "A physical model for drift in pH ISFETs," *Sensors and Actuators B: Chemical*, vol. 49, pp. 146-155, 1998.
- [57] P. Woias, *et al.*, "Slow pH response effects of silicon nitride ISFET sensors," *Sensors and Actuators B: Chemical*, vol. 48, pp. 501-504, 1998.
- [58] J. C. Chou, *et al.*, "Simulation of time-dependent effects of pH-ISFETs," *Sensors and Actuators B: Chemical*, vol. 62, pp. 88-91, 2000.
- [59] B. Premanode, *et al.*, "Drift reduction in ion-sensitive FETs using correlated double sampling," *Electronics Letters*, vol. 43, pp. 857-859, 2007.

- [60] P. Bergveld and A. Sibbalb, *Analytical and biomedical applications of ion-selective field-effect transistors* vol. 12: Elsevier edition, 1988.
- [61] P. R. Barabash, *et al.*, "Analysis of the threshold voltage and its temperature dependence in electrolyte-insulator-semiconductor field-effect transistors (EISFET's)," *Electron Devices, IEEE Transactions on*, vol. 34, pp. 1271-1282, 1987.
- [62] L. J. Sevin, *Field-Effect Transistors*. New York: McGraw-Hill, 1965.
- [63] C. Wen-Yaw, *et al.*, "Temperature compensation electronics for ISFET readout applications," in *Biomedical Circuits and Systems, 2004 IEEE International Workshop on*, 2004, pp. S1/6-S5-8.
- [64] W.-Y. Chung, *et al.*, "New ISFET interface circuit design with temperature compensation," *Microelectronics Journal*, vol. 37, pp. 1105-1114, 2006.
- [65] B. Streetman and S. Banerjee, *Soild State Electronic Devices* Prentice Hall, 2000.
- [66] W. Y. Chung, *et al.*, "ISFET interface circuit embedded with noise rejection capability," *Electronics Letters*, vol. 40, pp. 1115-1116, 2004.
- [67] C. Toumazou and L. Shepherd, "Using transistors to linearise biochemistry," *Electronics Letters*, vol. 43, pp. 65-67, 2007.
- [68] M. J. Milgrew and D. R. S. Cumming, "Matching the Transconductance Characteristics of CMOS ISFET Arrays by Removing Trapped Charge," *Electron Devices, IEEE Transactions on*, vol. 55, pp. 1074-1079, 2008.
- [69] M. Levin, *et al.*, "X-ray or UV adjustment of MOS threshold voltage: Analytical and numerical modeling," *Russian Microelectronics*, vol. 35, pp. 329-336, 2006.
- [70] P. A. Hammond and D. R. S. Cumming, "Encapsulation of a liquid-sensing microchip using SU-8 photoresist," *Microelectronic Engineering*, vol. 73-74, pp. 893-897, 2004.
- [71] P. Georgiou and C. Toumazou, "ISFET threshold voltage programming in CMOS using hot-electron injection," *Electronics Letters*, vol. 45, pp. 1112-1113, 2009.
- [72] P. Georgiou and C. Toumazou, "CMOS-based programmable gate ISFET," *Electronics Letters*, vol. 44, pp. 1289-1290, 2008.
- [73] A. S. Sedra and K. C. Smith, *Microelectronic Circuits*. New York: Oxford University Press, 2004.
- [74] D. John and K. Martin, *Analog Integrated Circuit Design*. New York: Wiley, 1997.

- [75] C. C. Enz and G. C. Temes, "Circuit techniques for reducing the effects of op-amp imperfections: autozeroing, correlated double sampling, and chopper stabilization," *Proceedings of the IEEE*, vol. 84, pp. 1584-1614, 1996.
- [76] P. Allen, *CMOS Analog Integrated Circuit Design*. UK: Short Course Presentation at Imperial College London, 2006.
- [77] P. Bergveld, "The operation of an ISFET as an electronic device," *Sensors and Actuators*, vol. 1, pp. 17-29, 1981.
- [78] B. Palán, *et al.*, "New ISFET sensor interface circuit for biomedical applications," *Sensors and Actuators B: Chemical*, vol. 57, pp. 63-68, 1999.
- [79] A. Sibbald, "A chemical-sensitive integrated-circuit: the operational transducer," *Sensors and Actuators*, vol. 7, pp. 23-38, 1985.
- [80] E. Lauwers, *et al.*, "A CMOS multiparameter biochemical microsensor with temperature control and signal interfacing," *Solid-State Circuits, IEEE Journal of*, vol. 36, pp. 2030-2038, 2001.
- [81] B. Premanode, *et al.*, "A composite ISFET readout circuit employing current feedback," *Sensors and Actuators B: Chemical*, vol. 127, pp. 486-490, 2007.
- [82] A. Morgenshtein, *et al.*, "CMOS readout circuitry for ISFET microsystems," *Sensors and Actuators B: Chemical*, vol. 97, pp. 122-131, 2004.

## Chapter 3

# Current-Conveyor: The Current Mode Approach

### 3.1 Introduction

The focus of the last chapter is on the first key element in the CCCII+, namely the ISFET. In this chapter, the focus moves to the second key element of the CCCII+, namely the CCII. This device is a versatile analog building-block which was originally designed to be used with other circuit components to perform a wide variety of analog signal processing functions. The current-conveyor may be considered as an analog circuit building-block rather like a voltage op-amp (VOA), operating in a different way to achieve a range of analog systems which classically have been based on VOAs. The different approach leads to new methods of realising analog transfer functions, and in several cases the conveyor-based implementation provides improved performance over the VOA based designs in accuracy, bandwidth and also convenience. Circuits based on VOAs are generally simple to design because the behaviour of a VOA can be described with a few straightforward design rules. In much the same way, the current-conveyor can be described with a few

simple design rules and having appreciated their operation, current-conveyor-based circuits be designed just as easily.

The current-conveyor was first proposed by Sedra and Smith in 1968 [1], however mainly for technology reasons it took almost 20 years for the current-conveyor to reach maturity with the first single-chip designed by LTP Electronics and produced by Elantec Inc. The realisation of the current-conveyor as a monolithic device with good performance has stimulated a resurgence of research resulting in a better understanding of the operation and applications of device and its potential for analog signal processing.

The current-conveyor is one of the key parts of the chemical current-conveyor and in this chapter the operation of the current-conveyor and analysis of various application circuits and systems will be presented. The main purpose of this section of the thesis is to obtain a full understanding of the current-conveyor and its versatility in preparation for the Chapter 4 which focuses on the design and development of the first chemical current-conveyor realisation.

## 3.2 Background

After the first generation current-conveyor or CCI, shown in Figure 3-1 was introduced, the more versatile second generation current-conveyor, or CCII, shown in Figure 3-2 was proposed by the same two authors, Sedra and Smith, in 1970 [2], as an extension of their first generation conveyor.

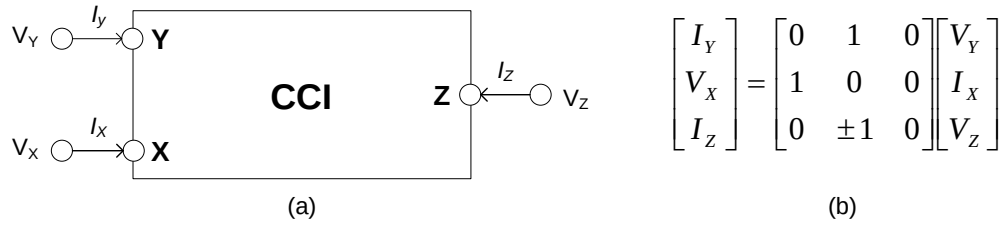


**Figure 3-1.** First generation [1] current-conveyor (CCI) (a) system diagram and (b) hybrid matrix

Figure 3-1 (a) shows the schematic normally used for the CCI without the power supply connections and Figure 3-1 (b) the  $I \sim V$ , describing matrix for the CCI is shown. The input current at X-node,  $I_X$ , was reflected to input Y-node, that is, the two inputs had equal currents. Furthermore, the sign ‘ $\pm$ ’ with number ‘1’ indicates ‘polarity’ and the ‘current gain’, respectively between output current Z-node,  $I_Z$ , with respect to  $I_X$  of either +1 or -1. Although the devices aroused considerable interest, it was not until the much more versatile second generation current-conveyor, CCII, that the circuits’ community world-wide took the current-conveyor concept really seriously.

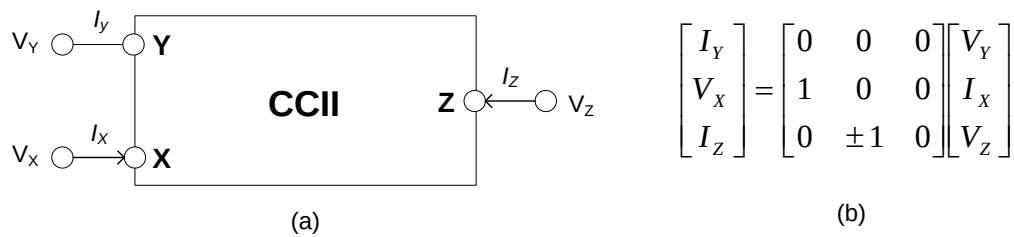


**Figure 3-2.** Second generation [2] current-conveyor (CCII) (a) system diagram and (b) hybrid matrix

The CCII, shown schematically in Figure 3-2 (a), is described by the  $I \sim V$  matrix in Figure 3-2 (b). Again two possible implementations can be constructed with current gain

between  $I_X$  and  $I_Z$  of either +1 or -1. As will be shown below the more useful CCII is so called CCII+ which has +1 current gain  $I_X$  and  $I_Z$  with respect to the current directions shown in Figure 3-2 (b). The relationship between the terminal voltages and currents of CCII can be described by the three equations below, rather than a matrix description.

$$I_Y = 0$$

**Equation 3-1**

$$V_X = V_Y$$

**Equation 3-2**

$$I_Z = I_X$$

**Equation 3-3**

By inspection of Equation 3-1 to Equation 3-3, it is clear that the CCII is the combination of a voltage-follower, between input voltage,  $V_Y$ , and output voltage,  $V_X$ , and a current-follower between  $I_X$  and  $I_Z$ , either negative unity gain for CCII- or positive for the CCII+. Furthermore, since the input Y-node draws no current hence,  $I_Y = 0$ , this implies that ideally  $Z_{INY} = \infty$ . Similarly, because the X-node has two functional uses either for voltage output or current input, then ideally  $Z_X = 0$ , and to obtain  $I_Z = I_X$  implies that  $Z_{OUTZ} = \infty$ .

Note that while Y-node is clearly a voltage input terminal and Z-node is a current output terminal. The X-node has dual function, that is, input for current and output for voltage. At the first sight this may seem unusual. Nevertheless, because of the combined voltage and current following properties, the CCII has proved to be much more adaptable and versatile than its first generation predecessor (CCI) and can be used to produce a wide-

range of analog circuit functions as shown in Figure 3-3, some of which are not easily realised using conventional VOA.

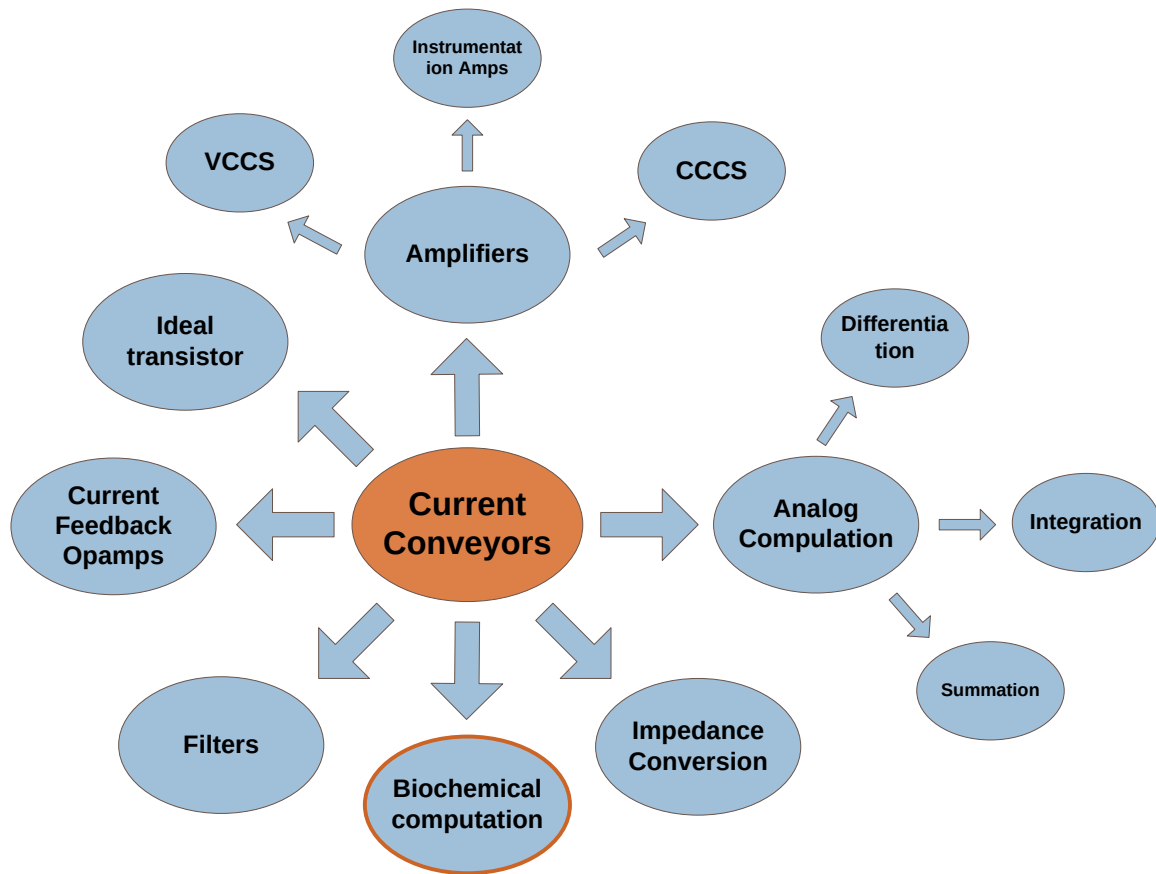


**Figure 3-3.** Current-conveyor applications

The applications of the current-conveyor shown in Figure 3-3 excited considerable interest from the analog circuit community and resulting in many publications in this general area, many of which can be found in [3], and subsequent IEEE publications throughout the 1990's. To date, the potential of the current-conveyor for biomedical uses has received little attention. The 'new' application area in Figure 3-3 is 'Biochemical computation' which is the focus of the research programme described in this thesis. To

obtain an appreciation of the full versatility of the CCII+, a number of application circuits will now be described.

### 3.3 Current-Conveyor implementation

As mentioned above practical implementations of the CCII took a long time to appear following the initial proposal of the concept. The op-amp based realisation below was first proposed by Toumazou and Lidgey [4] using the technique of accessing the output current from an op-amp by sensing the supply currents using current-mirrors in the power supply leads of a VOA and coupling them together to provide a high output impedance Z-node, shown in Figure 3-4.

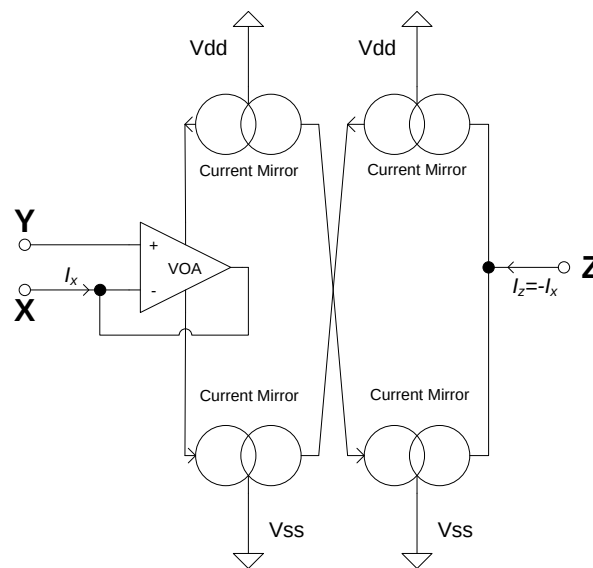


**Figure 3-4.** Negative current-conveyor [3-4]

The VOA is connected as a voltage-follower and the non-inverting terminal forms the high input impedance Y-node, and the inverting terminal the low impedance X-node.

Since the current flowing into the Y-node is almost zero, any current flowing out of the X-node will be copied and at the current-mirror connection which forms the Z-node and will be drawn into the Z-node. The net effect is that a CCII- has been produced. One transistor implementation of this CCII- is shown in Figure 3-4, where the output current has been taken more directly from the output terminal of the VOA, and copied to the Z-node using two cross-coupled current mirrors.

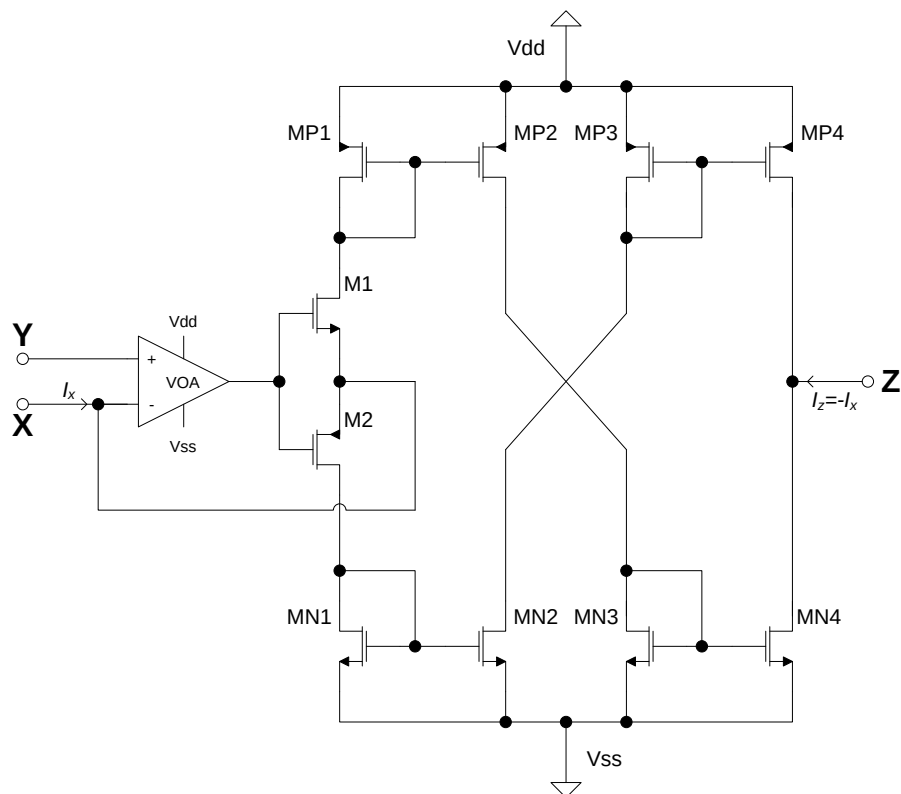


**Figure 3-5.** Negative current-conveyor implementation [3-4]

As already mentioned the CCII+ is in fact more useful than the CCII- and the same technique of sensing the power supply current from a VOA can be used, as shown in Figure 3-6, with one practical realisation being shown in Figure 3-7. Comparing Figure

3-5 and Figure 3-7, it can be seen that the only difference is the removal from Figure 3-5 of the second cross-coupled current mirrors pair, and the versatile CCII+ is formed. It should be noted that both Figure 3-5 and Figure 3-7 are not optimal designs. They have been included here simply to illustrate the approach used in creating a transistor level CCII.

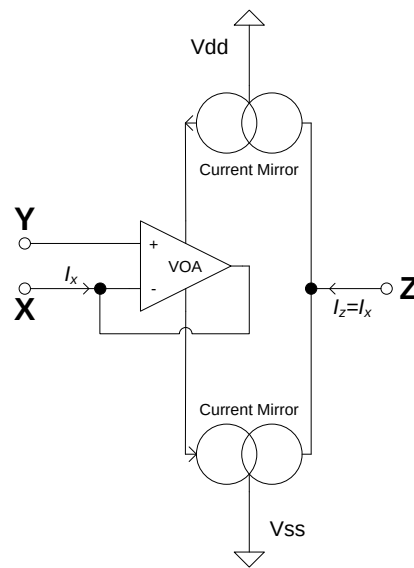


**Figure 3-6.** Positive current-conveyor [3-4]

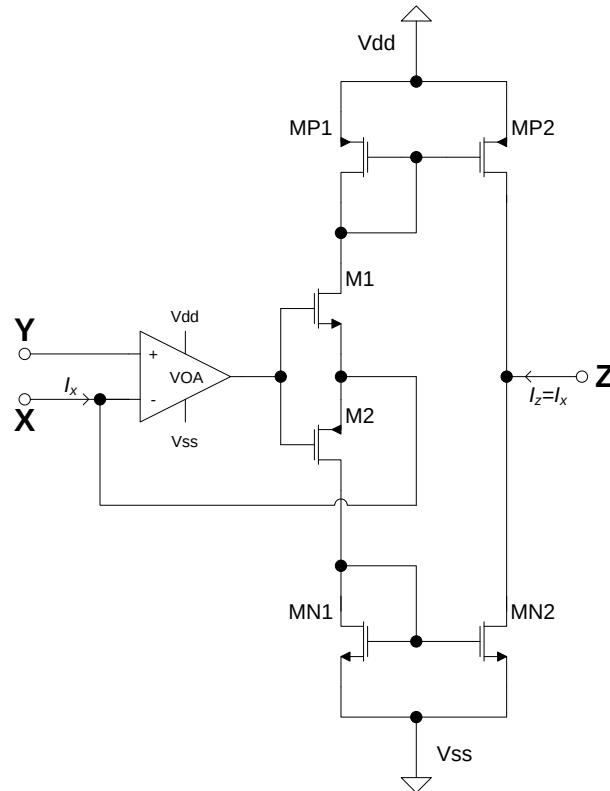


**Figure 3-7.** Positive current-conveyor implementation [3-4]

### 3.4 Current-Conveyor (CCII) applications

To assist the reader in understanding the operation of a range of CCII application circuits presented below, Table 3-1 which shows the impedance and  $I \sim V$  operation of the ideal CCII has been included.

**Table 3-1.** Impedance and  $I\sim V$  operation of the ideal CCII

| Impedance and $I\sim V$ operation of the ideal CCII |           |
|-----------------------------------------------------|-----------|
| $Z_{INY}$                                           | $\infty$  |
| $Z_X$                                               | 0         |
| $Z_{OUTZ}$                                          | $\infty$  |
| $I_Y$                                               | 0         |
| $V_X$                                               | $V_Y$     |
| $I_Z$                                               | $\pm I_X$ |

### 3.4.1 Voltage and current readout amplifiers using the CCII

The Table 3-2 shows 5 different readout amplifiers. Circuit (a) is a unity gain voltage controlled voltage source (VCVS) or voltage-follower. The Z-node is grounded to provide reference of zero voltage and thus ensure that the output transistors remain active. Circuit (b) is a unity gain current controlled current source (CCCS) or current-follower. Grounding the Y-node ensures that the X-node is a virtual ground input. The next circuit (c) is a voltage controlled current source (VCVS) with transconductance gain  $1/R_X$ . Input voltage applied to the Y-node results in the same voltage appearing at the X-node and hence  $I_X = V_{in}/R_X$  and because  $I_X = I_Z$ , then  $I_Z = I_{out} = V_{in}/R_X$ . The next circuit shown in Circuit (d) which is a voltage controlled voltage source (VCVS) with gain determined by the resistor ratio  $R_Z/R_X$ . In fact the circuit is simply circuit (c) with an output voltage-follower, and the resistor at the Z-node is used to convert  $I_Z$  into an output voltage  $V_Z = V_{out} = I_Z R_Z = R_Z/R_X V_{in}$ . The circuit (e) is a current controlled current source with gain  $R_Y/R_X$ . The role of  $R_Y$  is to convert the input current into a voltage  $V_Y = I_{in} R_Y$ , which results in  $I_X = I_{out} = R_Y/R_X I_{in}$ .

**Table 3-2.** Applications of current conveyors to amplifier [3]

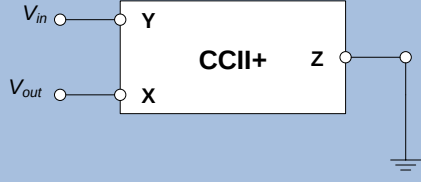
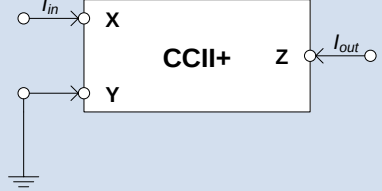
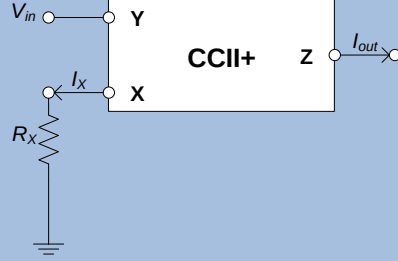
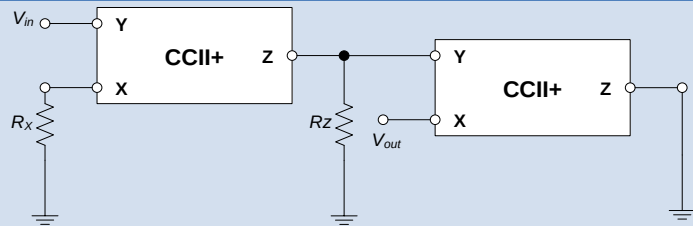
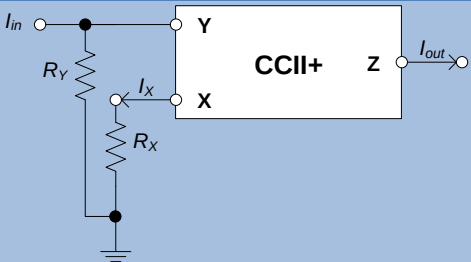
| Functional Element                                      | Function                           | Realization using Current-Conveyor                                                   |
|---------------------------------------------------------|------------------------------------|--------------------------------------------------------------------------------------|
| (a) Voltage Controlled Voltage Source (VCVS unity gain) | $V_{out} = V_{in}$                 |    |
| (b) Current controlled current source (CCCS unity gain) | $I_{out} = I_{in}$                 |    |
| (c) Voltage Controlled Current Source (VCCS with gain)  | $I_{out} = \frac{V_{in}}{R_x}$     |   |
| (d) Voltage Controlled Voltage Source (VCVS gain)       | $V_{out} = \frac{R_z}{R_x} V_{in}$ |  |
| (e) Current Controlled Current Source (CCCS with gain)  | $I_{out} = \frac{R_y}{R_x} I_{in}$ |  |

Table 3-3 shows two differential amplifiers based on the VCCS of Table 3-2, circuit (c) by coupling two CCI+ devices, the input becomes differential as only a voltage difference between the upper and lower Y-nodes results in any current flow through  $R_x$ . The current

is conveyed to the output Z-nodes differentially. The resultant differential transconductance is  $1/R_X$ . The second circuit (b) of Table 3-3 is an extension of circuit (a) using the same addition of a grounded resistor  $R_Z$  and output voltage-follower as in Table 3-2 circuit (d). This provides a single ended output voltage  $V_{out} = (R_Z/R_X)V_{in}$  or instrumentation amplifier.

**Table 3-3.** Applications of current conveyors to differential and instrumentation amplifier [3]

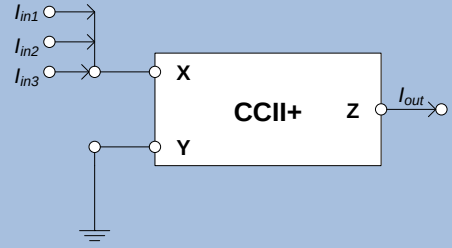
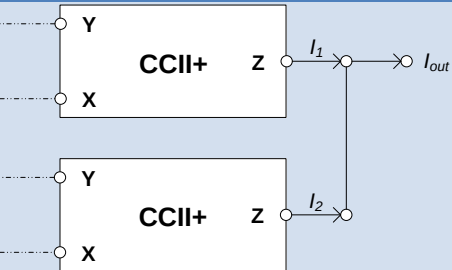
| Functional Element                | Function                           | Realization using Current-Conveyor |
|-----------------------------------|------------------------------------|------------------------------------|
| (a) Differential V to I converter | $I_{out} = \frac{V_{in}}{R_X}$     |                                    |
| (b) Instrumentation amplifier     | $V_{out} = \frac{R_Z}{R_X} V_{in}$ |                                    |

It is worth noting that in all of the above circuits in both Table 3-2 and Table 3-3 that the function of the resistors is to convert voltage to current and vice-a-versa. They are not feedback components and as such have no direct influence on the bandwidth.

### 3.4.2 Analog computation using the CCII

The CCII can be used for analog computation, and Table 3-4 shows several application circuits. The first two, circuits (a) and (b) provide input current summing and output current summing, respectively. Input current summing is readily achieved in circuit (a) because of the low input impedance into the X-node. Similarly output current summing is achieved by connecting the outputs on two or more CCII's together, the output currents simply add because of the high output impedances from each Z-node. The remaining circuits in Table 3-4 are voltage and current differentiation and integration circuits. Using similar analysis as above, the input/output transfer functions given in Table 3-4 can be obtained.

**Table 3-4.** Applications of current conveyors to analog computation [3]

| Functional Element         | Function                                   | Realization using Current-Conveyor                                                   |
|----------------------------|--------------------------------------------|--------------------------------------------------------------------------------------|
| (a) Input current summing  | $I_{out} = -(I_{in1} + I_{in2} + I_{in3})$ |  |
| (b) Output current summing | $I_{out} = (I_1 + I_2)$                    |  |

|                            |                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|----------------------------|--------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (c) Current integrator     | $I_{out}(t) = \frac{1}{C_Y R_X} \int_0^t I_{in}(t) dt$ | <p>The circuit diagram shows a CCII+ block with terminals Y, X, and Z. The input current <math>I_{in}</math> is connected to terminal Y. A capacitor <math>C_Y</math> is connected between terminal Y and terminal X. A resistor <math>R_X</math> is connected between terminal X and ground. The output current <math>I_{out}</math> is taken from terminal Z.</p>                                                                                                                                     |
| (d) Current differentiator | $I_{out}(t) = C_X R_Y \frac{dI_{in}(t)}{dt}$           | <p>The circuit diagram shows a CCII+ block with terminals Y, X, and Z. The input current <math>I_{in}</math> is connected to terminal Y. A resistor <math>R_Y</math> is connected between terminal Y and terminal X. A capacitor <math>C_X</math> is connected between terminal X and ground. The output current <math>I_{out}</math> is taken from terminal Z.</p>                                                                                                                                     |
| (e) Voltage integrator     | $V_{out}(t) = \frac{1}{C_Z R_X} \int_0^t V_{in}(t) dt$ | <p>The circuit diagram shows two CCII+ blocks. The first block has terminals Y, X, and Z. The input voltage <math>V_{in}</math> is connected to terminal Y. A resistor <math>R_X</math> is connected between terminal Y and ground. The output of the first block is connected to terminal Y of the second block. A capacitor <math>C_Z</math> is connected between the output of the first block and ground. The output voltage <math>V_{out}</math> is taken from terminal X of the second block.</p> |
| (f) Voltage differentiator | $V_{out}(t) = C_X R_Z \frac{dV_{in}(t)}{dt}$           | <p>The circuit diagram shows two CCII+ blocks. The first block has terminals Y, X, and Z. The input voltage <math>V_{in}</math> is connected to terminal Y. A capacitor <math>C_X</math> is connected between terminal Y and ground. The output of the first block is connected to terminal Y of the second block. A resistor <math>R_Z</math> is connected between the output of the first block and ground. The output voltage <math>V_{out}</math> is taken from terminal X of the second block.</p> |

### 3.4.3 Impedance conversion using the CCII

Much of the research in the area of the current-conveyors has focused on the implementation of impedance converters and filters. Many VOA-based impedance converters required complicated circuitry and tight component matching requirements. With its combined voltage and current following properties, the CCII is a more flexible alternative to implement these functions.

Impedance converters are found to be useful in many of active circuit designs, for example in active filters and inductance simulation. Also, negative resistors that are

frequency dependent, the so called FDNR, can be obtained and used in place of inductors to achieve high order filter functions. In addition negative resistance and capacitance can be created and used to cancel losses in capacitance to improve filter Q values [5-6].

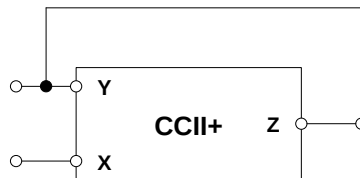


**Figure 3-8.** Grounded negative impedance converters (NIC) [2, 7-8]

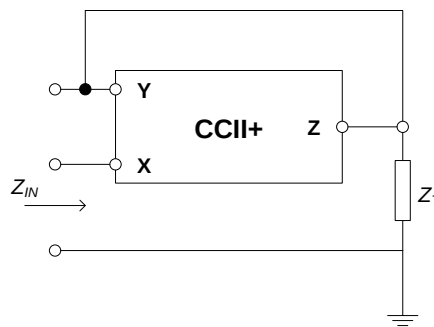


**Figure 3-9.** Current-controlled NIC [7-8]

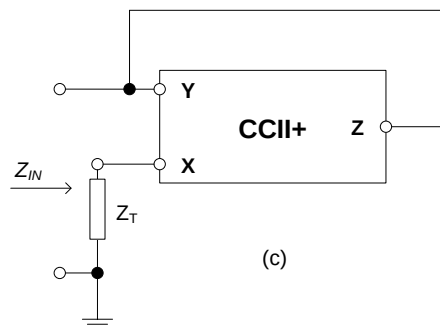


**Figure 3-10.** Voltage-controlled NIC [7-8]

Sedra and Smith [2] presented the negative impedance converter shown in Figure 3-8. If the Z-node of Figure 3-8 is connected to a grounded impedance,  $Z_T$ , as shown in Figure 3-9, the net effect is an input impedance into the circuit of  $-Z_T$ . Alternatively, if the impedance  $Z_T$  is connected to the X-node, as shown in Figure 3-10, then again the net result is an input impedance of  $-Z_T$ . The circuit of Figure 3-9 is a current-controlled negative impedance converter (NIC) whereas the circuit of Figure 3-10 is a voltage controlled NIC.

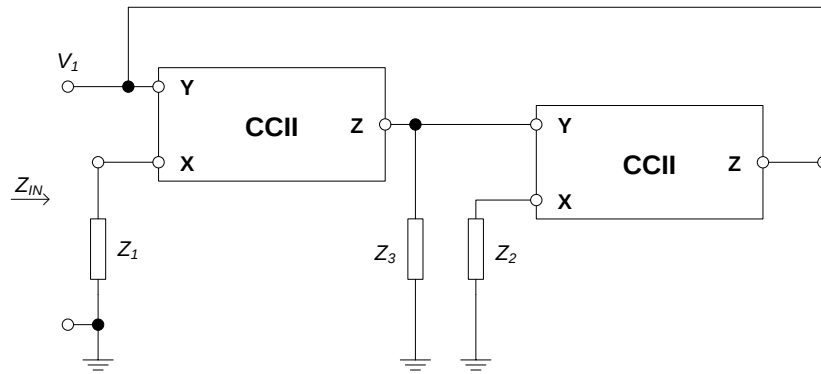


**Figure 3-11.** Generalised impedance converter (GIC) [2, 7-8]

Using two CCII as shown in Figure 3-11, more general impedance conversion (GIC) can be implemented, depending on the nature of the circuit components chosen. In addition, if both conveyors are of equal polarity, that is both CCII+ or both CCII-, then a negative GIC is obtained. The resulting input impedance at  $V_1$ , is  $Z_{IN} = -(Z_1 Z_2 / Z_3)$ . Conversely, if the two conveyors are of opposite polarity, then a positive GIC is obtained.

### 3.4.4 Filters

Circuit designers concerned with the implementation of active filters have paid considerable attention to current-conveyor implementations, since voltage op-amp based filters suffer from bandwidth limited by the voltage op-amps themselves. Many of the earlier CCII- based filter designs required floating capacitors but these filters have inherently poor sensitivity and were only able to realise one particular filter type [9-10]. The emergence of GICs described in the previous section allowed for a wider range of filters to be implemented, based on simulated inductors, for example, various types of Butterworth filters as well as elliptic ladder filters.

To illustrate the field of CCII filter design, two circuits will be described, the first being an approach based on converting a classical second-order voltage mode circuit into a current-mode equivalent and the second being a third-order filter that uses grounded capacitors,; the latter being particularly attractive for monolithic implementation.

Many voltage mode active RC-filters use VOAs configured as a unity gain VCVS, or voltage-follower, to maximise the useable bandwidth of the circuit. Current-mode filters can be derived from these voltage buffer-based filters using the adjoint circuit method. To find the adjoint circuit of any network, a replica of the original circuit must be constructed first. All elements in this replica circuit are then replaced by their adjoint elements. Passive components such as resistors and capacitors remain the same, while unity gain voltage buffers are replaced by the unity gain current buffers, or current-conveyors. Voltage input and output signals are replaced by current output and input signals, hence the two adjoint circuits are exactly equivalent in the voltage-mode and current-mode. The new current-mode circuit will have the same component sensitivities as the voltage-mode original, so low sensitivity current-mode circuits can be obtained from low sensitivity

voltage-mode circuits which have already been developed. The Sallen-key active biquad (SAB) [11] of Figure 3-12 (a) would be, therefore transformed to the CCII-based circuit of Figure 3-12 (b) by the adjoint circuit method.

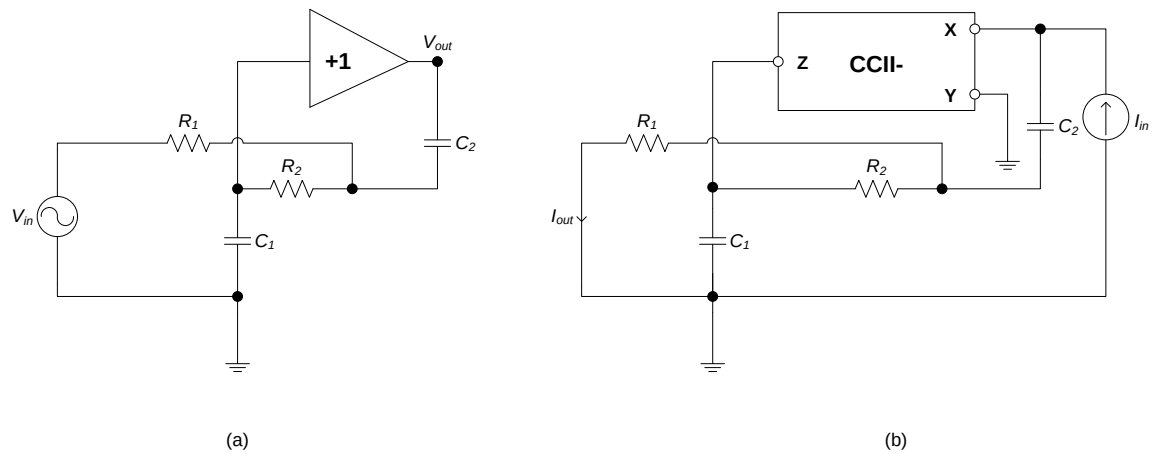


**Figure 3-12.** [11] (a) Voltage-mode SAB (b) Current-Mode SAB

A third-order low-pass Butterworth filter reported by Nandi [12] which is particularly attractive, due to its use of grounded capacitors and equal valued components, is shown in Figure 3-13.

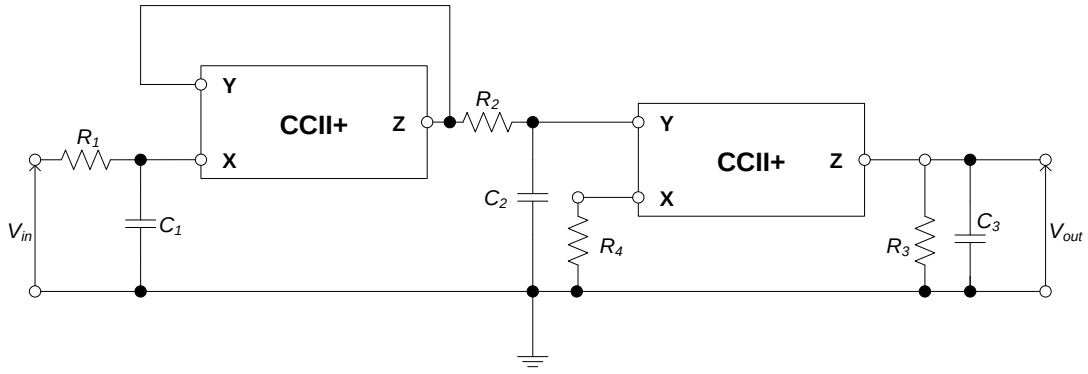


**Figure 3-13.** Butterworth low-pass filter using CCII+ [12]

As reported in [12] the voltage transfer function of the filter can be obtained as

$$\frac{V_{out}}{V_{in}} = \frac{R_3/R_4}{a_3s^3 + a_2s^2 + a_1s + 1}$$

**Equation 3-4**

where,

$$a_3 = R_1C_1R_2C_2R_3C_3$$

$$a_2 = R_1C_1R_2C_2 + R_2C_2R_3C_3 + R_1R_3C_3(C_1 - C_2)$$

and

$$a_1 = R_1(C_1 - C_2) + R_2C_2 + R_3C_3$$

Using the standard filter design approach of normalising the resistors to  $1\Omega$  and capacitors to  $1F$ , then since equal valued components are used, and letting ( $R_1 = R_2 = R_3 = 1\Omega$ ) and ( $C_1 = C_2 = C_3 = 1F$ ), then the above equations simplify to a third-order low-pass voltage transfer function, given by

$$\frac{V_{out}}{V_{in}} = \frac{1}{s^3 + 2s^2 + 2s + 1}$$

**Equation 3-5**

Furthermore, the resulting filter has low sensitivity to component values. There are many more active filter CCII-based designs, but the two examples above are more than adequate to show that filter functions can be created using the CCII with no more complexity, indeed often with less complexity, than conventional VOA-based designs, confirming again the universality of the CCII.

It should be noted that in practice an input DC current path must be provided for all active devices employed. As for all analog circuits and in the circuits described in the impedance converter and filter sections above, any such additional DC bias components have not been included in the circuit diagrams.

### 3.4.5 The relationship between the ideal transistor and current-conveyor

An alternative and useful perspective of designing with CCIIs is to consider the relationship between the CCII and an ideal transistor. As a reminder, the  $I \sim V$  transfer relationship for the CCII given in Table 3-1 is given here again as

$$V_X = V_Y$$

$$I_Y = 0$$

$$I_Z = I_X$$

As mention before, these equations show that there is a simple voltage-follower or voltage buffer action between the input Y-node and the voltage output X-node. Also, there is a simple current-follower or current buffer action between current input X-node

and current output Z-node. In addition, these equations imply that the ideal impedance relationships for the CCII are

$$Z_{INY} = \infty$$

$$Z_X = 0$$

$$Z_{OUTZ} = \infty$$

Consequently, the current-conveyor can be considered to behave as an ideal transistor, either in BJT or MOSFET as illustrated in Figure 3-14. If the transistors were ideal, as shown in Figure 3-14 (a), the  $V_{GS}$  would approach zero. As a result when driving into the gate of an MOSFET, it would give exactly unity voltage gain from input gate to output source. Hence the gate terminal of the MOSFET, which is close to an open circuit, is equivalent to the Y-node of a CCII. In the case of an ideal MOSFET, the source terminal would exhibit zero impedance, just as the X-node of an ideal CCII should. Consider now the current gain between source and drain of a MOSFET. Driving current into the source gives almost exactly unity current-gain from source input to drain output where the impedance level would ideally be infinite, just as the Z-node of an ideal CCII. In addition, the direction of the current flow from drain to source follows that an ideal MOSFET behaves as a negative current-conveyor (CCII-), as shown in Figure 3-14 (b).

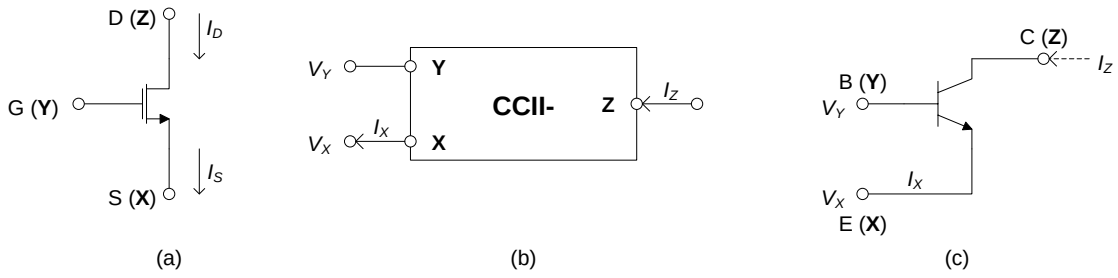


**Figure 3-14.** [3, 7-8] Comparison of (a) single NMOS transistor, (b) CCII- and (c) single BJT

Figure 3-14 (c) shows a BJT representation of a CCII- and on reflection it is clear that the current-conveyor can be considered as effectively an ideal BJT as shown in the voltage-gain and current-gain equations below, where the current gain,  $\beta$ , and the transconductance,  $g_m$ , are ideally infinite. The voltage output at X-node can be obtained

$$V_X = \frac{V_Y}{\left[1 + \left(\frac{1}{g_m R_X}\right)\right]}$$

**Equation 3-6**

since,  $g_m R_X \gg 1$ , therefore

$$V_X \approx V_Y$$

**Equation 3-7**

and the current output at the Z-node can be obtained as

$$I_Z = -\frac{\beta}{(\beta + 1)} I_X$$

**Equation 3-8**

and since  $\beta \gg 1$ , therefore

$$I_Z = -I_X$$

**Equation 3-9**

Undoubtedly, a single transistor cannot function alone as a complete current-conveyor as only unipolar signals can be handled by an unbiased single transistor. Also, the high accuracy unity voltage gain together with unity current gain required for a high performance current-conveyor cannot be achieved. However, the generic relationship between either a MOSFET or BJT and the current-conveyor is valid. Furthermore, it does provide valuable insight into the operation and development of monolithic current-conveyors [7].

### 3.4.6 The relationship between the current-conveyor and the current-feedback operational amplifier (CFOA)

The CFOA architecture is basically a transimpedance amplifier, or a current-controlled voltage source, while the classical voltage-feedback operational amplifier (VFOA) is a voltage-controlled voltage source. There are two major advantages of the CFOA compared with its voltage-feedback counter part. Firstly, the closed-loop bandwidth of the CFOA is larger than that of classical voltage-feedback design for comparable open-loop voltage gain. Secondly, the CFOA is able to provide a constant closed-loop bandwidth for close-loop voltage gains up to about 10. A further advantage of the current-feedback architecture is an almost unlimited slew-rate due to the class-AB input stage, which does not limit the amount of current available to charge up the internal compensation capacitor, unlike the conventional VFOA. This high speed performance of the CFOA is extremely useful for analog signal processing applications within video and telecommunication systems [13]. As a result, the monolithic CFOA became commercially available as an alternative to the VOA.

The CFOA and CCII were conceived independently. The research and development of these two devices progressed through to the early 1990s before the close relationship was recognised. Simple circuit level macromodels of the conventional VOA are useful in analysis and give the applications engineer valuable insight into the operation of the VOA, and the same is true for the CFOA [8] as shown in Figure 3-15 (a).

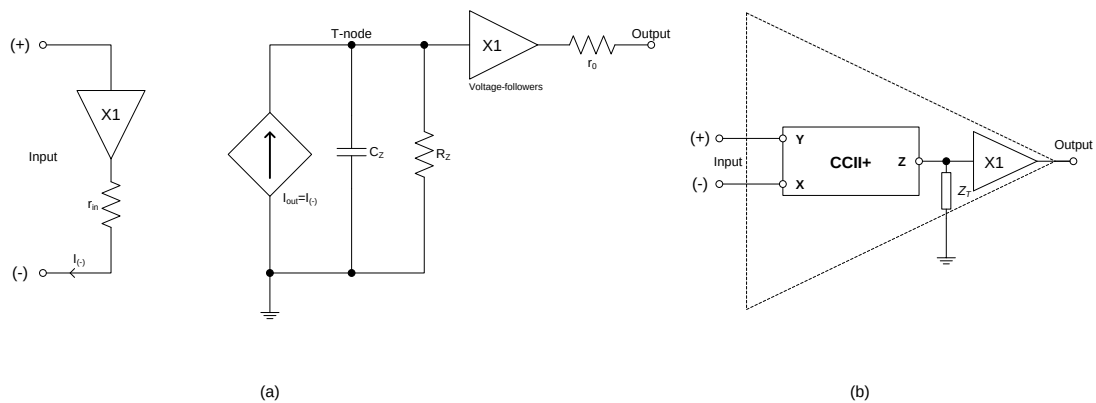


**Figure 3-15.** Current-feedback (a) macromodel [13] and (b) op-amp structure [7-8]

Having constructed the macromodel of the CFOA, shown in Figure 3-15, the generic relationship between the CCII+ and the CFOA is evident; in fact it is extremely close and several of the features offered by the CCII are also present in the CFOA. The basic structure of the CFOA is essentially that of a CCII+ with the now internal Z-node connected directly to the input stage of an output voltage-follower, as shown in Figure 3-15 (b). Any current flowing into the low impedance inverting input is conveyed to the internal gain node,  $Z_T$ , and the resulting voltage is then buffered to the output.  $Z_T$  is, thus, the open-loop transimpedance gain of the CFOA, which in practice is equal to the parallel combination of the output impedance of the CCII+, the final stage voltage buffer input impedance and any additional compensation capacitance at that internal gain Z-node. In

most CFOAs gain node is not connected to an external pin, and so the internal CCII+ within the CFOA is not available. However, there are some commercially produced CFOAs that do provide access to the internal Z-node, so it is possible to obtain a CCII+ function by using one of these devices.

### 3.5 Summary of Chapter 3

In this chapter, the CCII has been examined together with a wide range of possible application circuits. Undoubtedly the CCII is both versatile and convenient for many applications. Those described here demonstrate the ease with which complex analog functions can be realised using CCIIs. Often fewer parts are needed than its op-amp counter part, due to the very attractive combined voltage/current capability of the device. There are many applications where op-amp realisations are significantly less practical than the equivalent CCII realisation, such as voltage controlled current sources or transconductance amplifiers. Furthermore, the CCII can provide high performance operation as a result of the inherent local feedback of the follower-based structure of the device.

The main point that has been shown in this chapter is the very versatile capability of the CCII, which is the second key element in the CCCII+. Indeed, if we applied only a small fraction of this versatility to the CCCII+, many useful biochemical computations may be possible. The remainder of this thesis will be devoted to the development of the CCCII+ and several biochemical sensing applications.

### 3.6 References

- [1] K. C. Smith and A. Sedra, "The current conveyor - A new circuit building block," *Proceedings of the IEEE*, vol. 56, pp. 1368-1369, 1968.

- [2] A. Sedra and K. Smith, "A second-generation current conveyor and its applications," *Circuit Theory, IEEE Transactions on*, vol. 17, pp. 132-134, 1970.
- [3] C. Toumazou, *et al.*, *Analogue IC Design: The Current-Mode Approach*: Institution of Engineering and Technology, september 1993.
- [4] C. Toumazou, "Universal Current-Mode Analogue Amplifiers," PhD, Department of Engineering, Oxford Brookes University, 1968.
- [5] C. Toumazou and F. J. Lidgey, "Floating Impedance Convertors Using Current-Conveyors," *Electron. Lett.*, vol. 21, pp. 640-642, 1985.
- [6] C. Toumazou, *et al.*, "Extending voltage-mode op amps to current-mode performance," *Circuits, Devices and Systems, IEE Proceedings G*, vol. 137, pp. 116-130, 1990.
- [7] J. Lidgey and K. Hayatleh. (2000, March) Are current conveyors finally coming of age part I. *Electronics World*.
- [8] J. Lidgey and K. Hayatleh. (2000, April) Are current conveyors finally coming of age part II. *Electronics World*.
- [9] U. Kumar, "Current-Conveyors : A Review of the State of the Art," *IEEE Circuits and Syst. Mag.*, pp. 10-14, 1981.
- [10] B. Wilson, "Recent developments in current conveyors and current-mode circuits," *Circuits, Devices and Systems, IEE Proceedings G*, vol. 137, pp. 63-77, 1990.
- [11] G. W. Roberts and A. S. Sedra, "All current-mode frequency selective circuits," *Electronics Letters*, vol. 25, pp. 759-761, 1989.
- [12] R. Nandi, "Equal-valued earthed-capacitor realisation of a third-order lowpass Butterworth characteristic using current conveyors," *Electronics Letters*, vol. 14, pp. 699-700, 1978.
- [13] F. J. Lidgey and K. Hayatleh, "Current-feedback operational amplifiers and applications," *Electronics & Communication Engineering Journal*, vol. 9, pp. 176-182, 1997.

## Chapter 4

# Chemical Current-Conveyor for Biochemical Computation

### 4.1 Introduction

In this chapter the ISFET sensor, that was covered in Chapter 2, and the CCII+ that was covered in Chapter 3 are brought together to form a new biochemical microchip, the Chemical Current-Conveyor or CCCII+. In developing this device, a new approach to the design of an ISFET pH biosensor microchip has been taken, in that it incorporates an integrated current-conveyor type two, CCII+, [1-2], rather than an operational amplifier. One of the major advantages offered with this circuit topology is that the reference electrode can be at constant potential and feedback readily applied to the source of the ISFET, unlike other operational amplifier reported techniques where the ISFET forms part of the differential pair input stage and so feedback cannot be applied directly to the ISFETs source or gate [3-6]. Further advantages arise from using the CCII+ as the primary basis for the design, namely [7] (i) it is a relatively simple circuit with a lower parts count than an operational amplifier, (ii) it does not require frequency compensation

and is therefore inherently stable, and (iii) finally, not only it can readily be configured to provide an output directly proportional pH and with the choice of gain but also a multitude of linear and non-linear computational functions can be produced and so the concept can be used for excellent real-time process biochemistry. In addition, extending the design by adding an output voltage buffer creates the potential to produce a current-feedback operational amplifier (CFOA) architecture to enable overall feedback to be applied, thus producing an accurate closed-loop gain.

In this chapter, the initial CCCII+ concept is described followed by the design, simulation layout and evaluation of a monolithic device implemented using conventional  $0.35\mu\text{m}$  CMOS technology. The final part of the chapter discusses evaluation of the practical CCCII+ as a pH measuring instrument and its direct computational capability is presented.

## 4.2 Concept of the CCCII+: Topology and analysis

The diagram shown in Figure 4-1 is a system diagram of the chemical current-conveyor, having their outputs related to pH. The device incorporates an input ISFET pH sensor/transistor in the Y-node circuitry of a current-conveyor type II, commonly referred to as a CCII+. Figure 4-2 is the ideal performance hybrid matrix for the CCCII+.

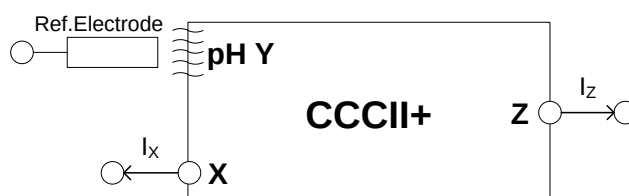


**Figure 4-1.** System overview of CCCII+ [8]

It can be seen that the voltage,  $V_X$ , at the low impedance X-node follows that at the high impedance input ISFET sensor node ' $pHY$ ' ( $V_{pH}$ ), while the input current at the X-node is mirrored or conveyed to the high impedance output node ' $Z$ '. The sign '+' indicates the polarity of the output current with respect to the input current. In this case the CCCII+ indicates that both the input and output currents simultaneously flow into, or out of, the device.

$$\begin{bmatrix} I_{pHY} \\ V_X \\ I_Z \end{bmatrix} = \begin{bmatrix} 0 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & \pm 1 & 0 \end{bmatrix} \begin{bmatrix} V_{pHY} \\ I_X \\ V_Z \end{bmatrix}$$

**Figure 4-2.** Describing pH~V~I matrix of CCCII+ [8]

In practice, the ISFET sensor at pHY-node is biased with an appropriate reference electrode, typically silver/silver-chloride ( $Ag/AgCl$ ) which defines the potential of the electrolyte solution. Ions in solution bind to the exposed insulating membrane causing an accumulation of charge, which in turn modulates the threshold voltage of the ISFET device.  $V_{pHY}$  is equal to the X-node voltage as can be seen from the matrix in Figure 4-2. Therefore, the output voltage taken at the X-node is directly proportional to the sensed pH value at pHY-node making,

$$V_X = V_{pHY}$$

**Equation 4-1**

thus,

$$V_{pHY} = I_{ISFET\_source} \times r_{ISFET\_source}$$

Equation 4-2

where  $I_{ISFET\_source}$  is the source current and  $r_{ISFET\_source}$  is the equivalent source resistance of the input ISFET sensor and as illustrated in Chapter 2,  $I_{ISFET\_source}$  expression can be written as

$$I_{ISFET\_source} = C_{OX}\mu \frac{W}{L} \left[ (V_{gs} - (V_{th(MOSFET)} + V_{chem})) V_{ds} - \frac{1}{2} V_{ds}^2 \right]$$

Equation 4-3

where  $V_{th(MOSFET)}$  is the grouping of conventional MOSFET parameters,  $V_{chem}$  is the grouping of chemical potentials at the surface of ISFET sensor insulating membrane,  $C_{OX}$  is the oxide capacity per unit area,  $W$  and  $L$  are the width and the length of the channel, respectively, and  $\mu$  is the electron mobility in the channel, [9]. And finally, the currents which flow into, or out of, X-node and Z-node are given in general by

$$I_X = \frac{V_X}{Z_X} = -I_Z$$

Equation 4-4

where  $Z_X$  is the impedance connected between the X-node and ground. The output can be taken either as voltage from the low output impedance X-node, or alternatively as current  $I_Z$  from the high output impedance Z-node.

### 4.3 Design and implementation of Chemical Current-Conveyor

The next step in development of the CCCII+ is to take the above concept and construct a macro/behavioural model that matches the hybrid matrix shown in Figure 4-2. What is

required is essentially a voltage-follower (voltage-buffer) between the pHY-node and the voltage output X-node, and a current-follower (current-buffer) between the X-node and the current output Z-node, as shown in Figure 4-3.

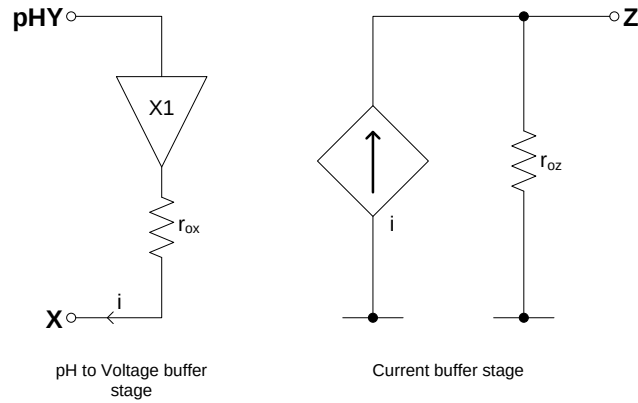


**Figure 4-3.** CCCII+ macromodel

Referring again to the ideal hybrid matrix of Figure 4-2, the primary voltage and current equations can be obtained, namely

$$I_{pHY} = 0$$

$$V_X = V_{pHY}$$

$$I_X = I_Z$$

Clearly, the input/output impedance from the X-node ( $r_{ox}$ ) should be as low as possible (ideally zero) and the gain between  $V_{pHY}$  and  $V_X$  should be unity, and the output impedance from the Z-node ( $r_{oz}$ ) should be very high (ideally infinite) and the gain between  $I_X$  and  $I_Z$  should be unity. The next step is realisation of Figure 4-3 at transistor level.

### 4.3.1 The basic initial design of the Chemical Current-Conveyor

Clearly, there are two essential circuit building blocks require, namely a voltage-follower and a current-follower. Figure 4-4 shows two typical single transistor source-followers or common-drain configurations. In both cases, the bias currents are provided by current source  $I_{BIAS}$ . On the left is the NMOS configuration and on the right is the PMOS configuration operating as voltage buffers with both inputs at the gate of M1 and outputs at the source of M1. In both cases, the ‘unity-gain’ performance can be approached by maximising the transconductance of the MOS device utilized, confirmed below by small signal analysis.

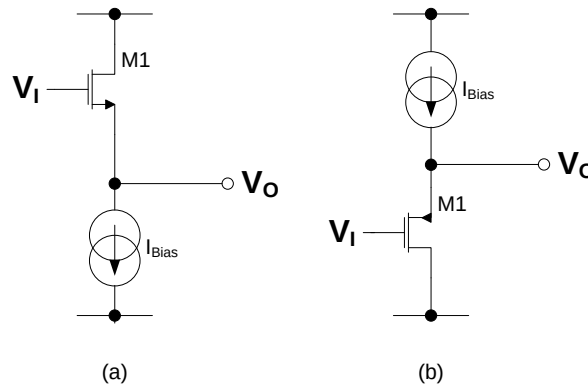


**Figure 4-4.** Common-Drain or Source follower amplifier

In the case of NMOS or PMOS common-drain (or source-follower) configuration, small signal analysis reveals

$$y_{22} = g_m + g_{ds}$$

$$y_{21} = g_m$$

$$\frac{v_{out}}{v_{in}} = \frac{g_m}{g_m + g_{ds}}$$

**Equation 4-5**

where  $g_m$ ,  $g_{ds}$  are the small signal transconductance and the drain-source conductance of M1 respectively and normally  $g_{ds} \ll g_m$ , causing the output impedance looking into the source of M1 which is given by the inverse of  $y_{22}$  parameter to become [10]

$$r_{out} \cong \frac{1}{g_m}$$

**Equation 4-6**

From the above Equation 4-5 and Equation 4-6, it is clear that the higher the transconductance of the transistor will achieve better unity gain and lower output impedance. Since  $g_m = \sqrt{2\mu_n C_{ox}} \sqrt{W/L} \sqrt{I_B}$ , it is necessary to increase the bias current  $I_{BIAS}$  in order to increase the transconductance of M1. This results in increased power dissipation. Alternatively, the dimensions ( $W/L$ ) of M1 can be increased. This, however, increases the size of the transistor and results in additional parasitic capacitances, and thus inferior frequency performance. An improved circuit replacing Figure 4-4 (a), which achieves higher transconductance than the single transistor source-follower configuration for the same bias current, is shown in Figure 4-5.

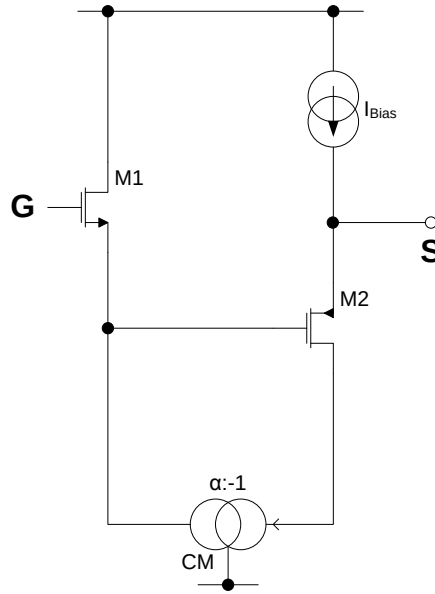


**Figure 4-5.** Initial implementation of the voltage-buffer stage [11]

The design is based on the CMOS voltage output buffer first proposed by Manetakis and Toumazou [11]. It comprises two source-followers, one implemented with a NMOS transistor M1 and the other implemented with a PMOS transistor M2. The source of M1 is biased with the current-feedback loop from the drain of M2 via the current-mirror (CM) which has a unity gain current transfer ratio. This configuration can be viewed as a compound transistor, with the gate of M1 and the compound source, is the source of M2. A drain terminal can be obtained by duplicating the current of M2. A consequence of using two source-followers, the first being NMOS followed by a second PMOS device is that the DC voltage step-down of  $V_{gs}(M1)$  is compensated by the step-up  $V_{gs}(M2)$ , which reduces the bias offset voltage. The second and very positive reason the circuit was chosen because the current-feedback loop preformed by CM results in a significant reduction in the output node impedance, which is confirmed below by small signal analysis of the circuit.

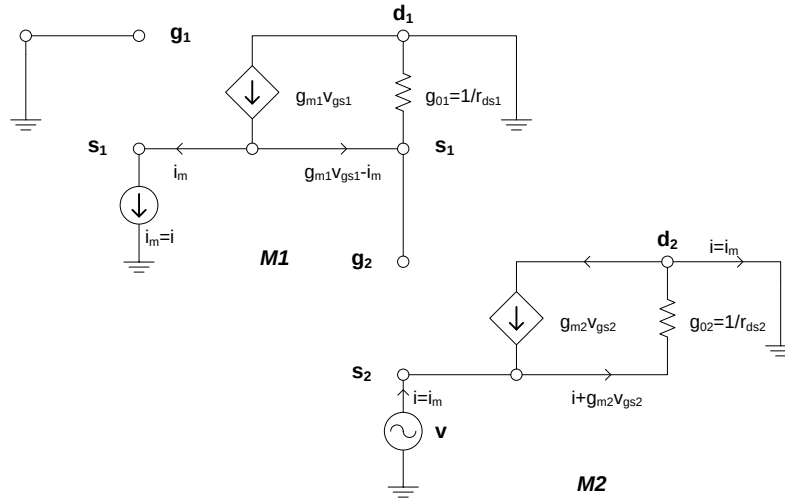


**Figure 4-6.** Small signal equivalent circuit of the voltage-buffer stage

A first order small signal equivalent circuit, assuming a simple model for each transistor and ignoring the small signal capacitors for determining the output impedance, is shown in Figure 4-6. Note that, the transistors and their corresponding parameters are numbered according to Figure 4-5. The input node at the gate of M1 is grounded and a voltage source ( $v$ ) is now connected to the output node at the source of M2.

To proceed with the analysis, the current-mirror is assumed to be ideal, that is, it has the following properties

$$r_{in} = 0$$

$$r_{out} = \infty$$

$$\text{gain } \alpha = -1$$

The voltage across the gate and source terminals of M1 and M2 are

$$v_{gs1} = v_{g1} - v_{s1}$$

$$v_{gs2} = v_{g2} - v_{s2}$$

respectively, thus the gate ( $v_{g1}$ ) of M1 is grounded and equal to zero making

$$v_{gs1} = 0 - v_{s1}$$

**Equation 4-7**

and the source ( $v_{s1}$ ) of M1 is connected to the gate ( $v_{g2}$ ) of M2 and the source ( $v_{s2}$ ) of M2 is connected to voltage source ( $v$ ) resulting in

$$v_{gs2} = v_{s1} - v$$

**Equation 4-8**

Furthermore, from inspection of the equivalent-circuit of M1, the source voltage ( $v_{s1}$ ) can be defined as

$$v_{s1} = (g_{m1}v_{gs1} - i)\frac{1}{g_{01}}$$

which can be simplified as

$$v_{s1} = \frac{-i}{(g_{01} + g_{m1})}$$

**Equation 4-9**

and thus from M2, the source voltage ( $v_{s2}$ ) or output voltage ( $v_{out}$ ) is given as

$$v_{s2} = v_{out} = v = (i + g_{m2}v_{gs2})\frac{1}{g_{02}}$$

**Equation 4-10**

but since  $v_{gs2} = (v_{s1} - v)$  from Equation 4-8 and substituting  $(v_{s1})$  from Equation 4-9 then the voltage across gate and source of M2 is obtained by

$$v_{gs2} = \frac{-i}{(g_{01} + g_{m1})} - v$$

Equation 4-11

In addition, substituting  $(v_{gs2})$  from Equation 4-11 into Equation 4-10 we can compute the output as follows

$$v = \frac{i}{g_{02}} + \left(\frac{g_{m2}}{g_{02}}\right) \left(\frac{-i}{(g_{01} + g_{m1})}\right) - v \left(\frac{g_{m2}}{g_{02}}\right)$$

Equation 4-12

resulting in

$$v \left(1 + \frac{g_{m2}}{g_{02}}\right) = \frac{i}{g_{02}} \left(1 - \frac{g_{m2}}{(g_{01} + g_{m1})}\right)$$

Equation 4-13

Finally, using Equation 4-13 the output impedance of the voltage-buffer stage can be found as

$$\frac{v}{i} = r_{out} = \left(1 - \frac{g_{m2}}{(g_{01} + g_{m1})}\right) \frac{1}{(g_{02} + g_{m2})}$$

$$r_{out} = \frac{(g_{01} + g_{m1} - g_{m2})}{(g_{01} + g_{m1})(g_{02} + g_{m2})}$$

Equation 4-14

however, the voltage-buffer transconductance is given by the inverse of  $r_{out}$  then

$$g_{m\_out} = \frac{1}{r_{out}} = \frac{(g_{01} + g_{m1})(g_{02} + g_{m2})}{(g_{01} + g_{m1} - g_{m2})}$$

**Equation 4-15**

Normally  $g_{01} \ll g_{m1}$  and  $g_{02} \ll g_{m2}$ , which enables Equation 4-15 to be approximated by

$$g_{m\_out} \cong \frac{g_{m1}g_{m2}}{g_{m1} - g_{m2}}$$

**Equation 4-16**

The final Equation 4-16 emphasizes the fact that by having a unity gain current-mirror transfer ratio and by matching the transconductance of M1 with M2, then the output impedance looking into the source of M2 becomes very small indeed. At the same time, the transconductance becomes very large. A simpler technique has been reported in [12] for reducing the impedance at the voltage-buffer stage of the current-conveyors implemented with bipolar transistors (BJTs). However, current-feedback with BJTs reduces not only the output impedance but also the input impedance as well. Since MOS devices will only be used, the input impedance will remain high, which is a major advantage over the bipolar case.

The device implementation of the system level chemical current-conveyor (CCCII+) described in section 4.2 is shown in Figure 4-7. This was used in simulation as the initial circuit for the CCCII+ to verify the concept and explore its potential applications. Notably, the circuit only used a signal rail power supply due to the primary potential application of sensing pH that will never go below zero, thus, removing the need of negative power supply and reducing the power consumption of the device.

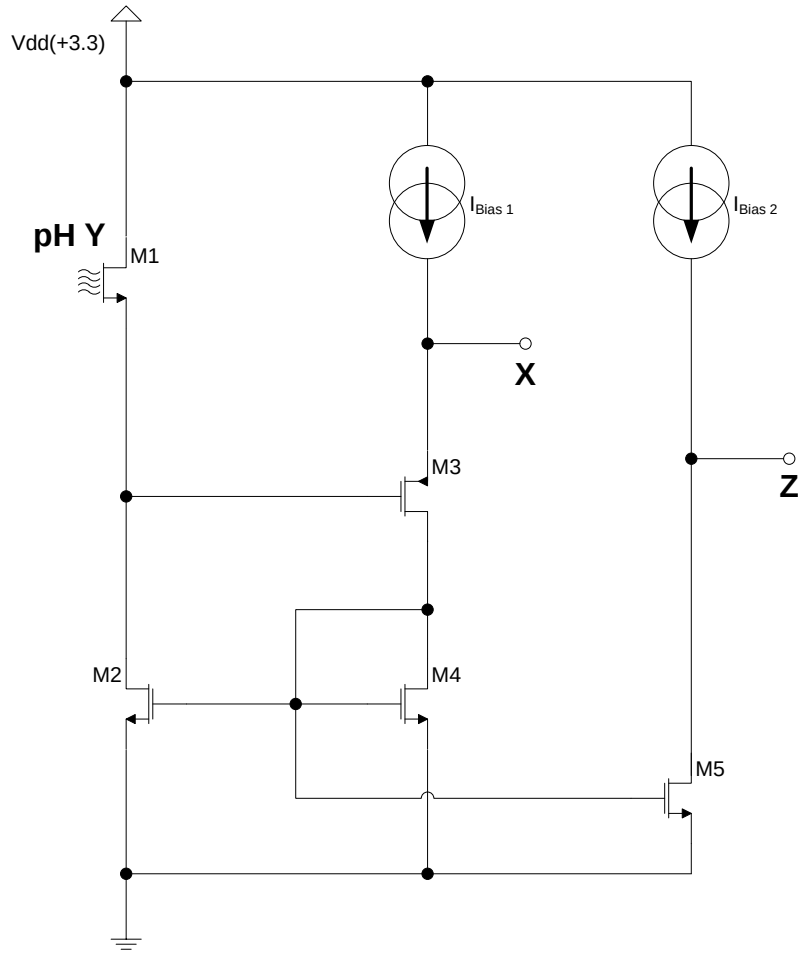


**Figure 4-7.** Transistor schematic of the initial integrated CCCII+ [13]

The design shown in Figure 4-7 is based on the voltage-buffer previously described in Figure 4-5 and benefits from the improved features namely having a very high input resistance, a relatively low output resistance at X-node and low power dissipation, a voltage gain that is close to unity. It can be seen that the current-mirror in Figure 4-5 has been implemented with the M2 diode connected transistor and M4 (the classic Widlar current-mirror) and further more transistor M1 is now replaced with an ISFET sensor. In addition, transistor M5 and the current source bias,  $I_{BIAS2}$ , have been introduced to form the current output Z-node of the CCCII+. This circuit was simulated and functionally

behaved as expected. The next phase of development of the CCCII+ is the design of a full transistor level circuit.

#### 4.3.2 Full implementation of the Chemical Current-Conveyor

The circuit diagram of the full CCCII+, based on Figure 4-7, is shown below in Figure 4-8. It can be seen that, in the full implementation diagram, the current output transistor M11 has been cascoded with M9 and M10 to achieve higher output impedance at the Z-node. Diode connected transistors M15 and M16 bias the gates of M9 and M10 respectively. Also the equal bias currents,  $I_{BIAS1}$  and  $I_{BIAS2}$ , have now been implemented at transistor level with cascode current-mirror, M12/M13 and M5/M6 for  $I_{BIAS1}$ , and M12/M13 and M7/M8 for  $I_{BIAS2}$ . Both are derived from the DC current-mirror M14/M17 and equal to the current flowing through  $R_{POT}$ .

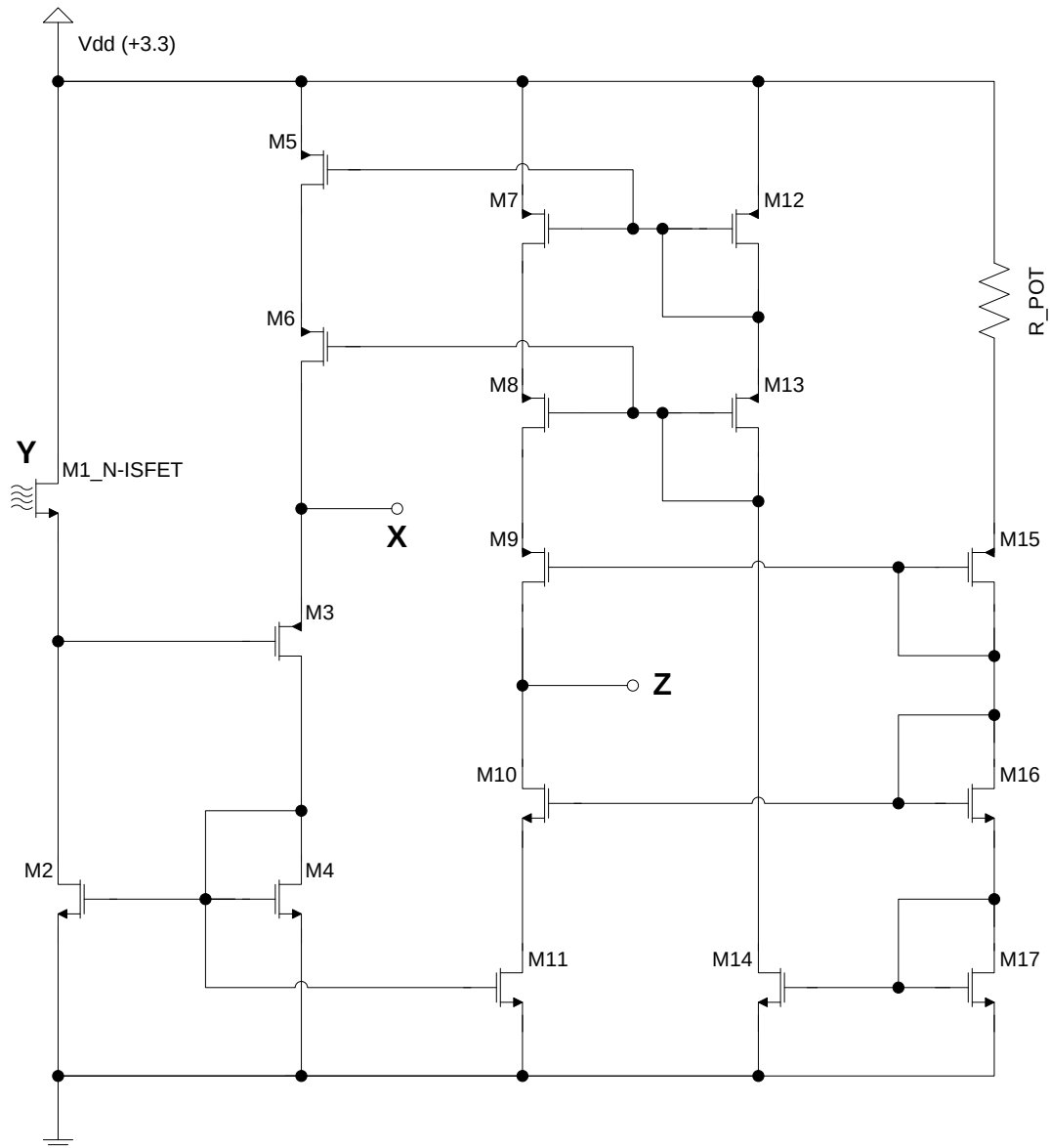


**Figure 4-8.** Full transistor implementation of the N-channel ISFET CCCII+ [13]

Although the NMOS ISFET is generally more prevalent in industrial application circuits because of better NMOS performance compared with PMOS, due largely to the higher electron mobility in silicon compared with hole mobility, it was considered worthwhile simulating and fabricating a P-channel ISFET CCCII+ for comparison purposes. Figure 4-9 shows this alternative topology version of the CCCII+, where the input now is an



## 4.4 Simulation results

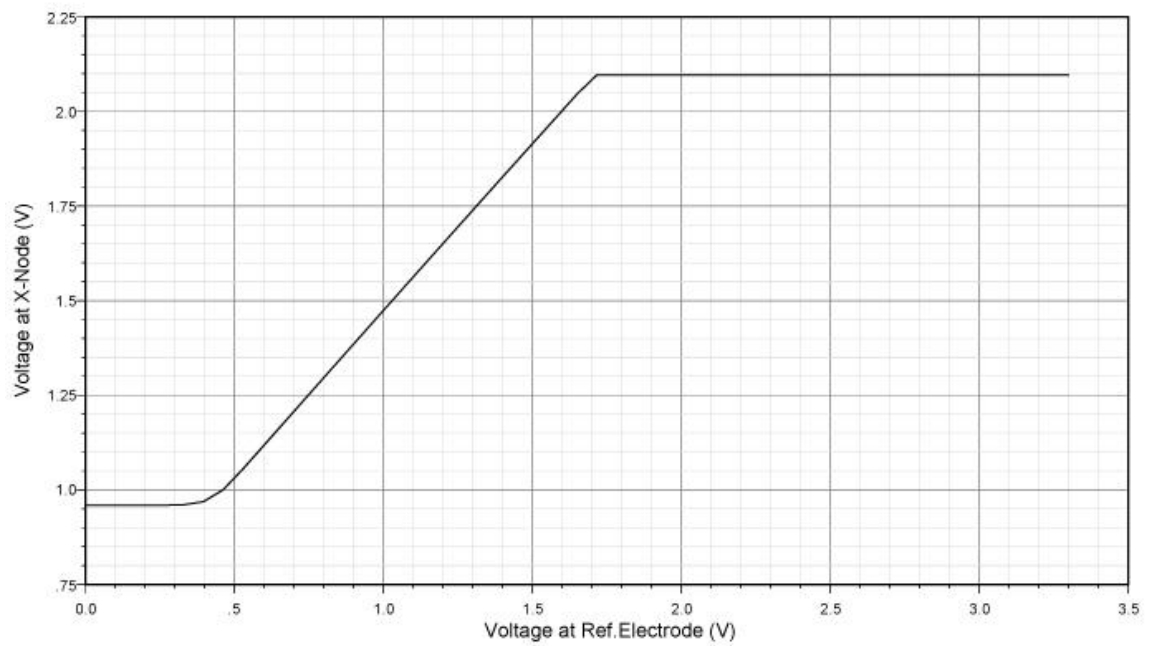
Both N-channel and P-channel ISFET CCCII+ designs shown above were simulated using Cadence. The designs were based on the AMS technology pack below, in readiness for the next stage of taking the CCCII+ to silicon implementation. This technology pack was chosen because it is readily available for prototype production and evaluation. Operating speed is not a major concern for all the envisaged applications, so the 0.35µm minimum gate length of this technology is considered more than adequate. The simulation parameters of the designs are shown in Table 4-1 and Table 4-2, followed by the simulation results showing key characteristics of both N-channel and P-channel ISFET CCCII+ devices.

**Table 4-1.** N-channel ISFET CCCII+ Simulation parameters

| N-channel ISFET CCCII+ Simulation parameters |                                    |
|----------------------------------------------|------------------------------------|
| <b>Technology</b>                            | Cadence AMS 0.35µm (CMOS, 3-metal) |
| <b>Power Supply</b>                          | 3.3V                               |
| <b>I<sub>BIAS</sub></b>                      | 2µA                                |
| <b>W/L of M1 (ISFET)</b>                     | 200µ/1µ                            |
| <b>M3</b>                                    | 600µ/1µ                            |
| <b>M10, M16</b>                              | 30µ/2µ                             |
| <b>M2, M4, M5-9, M11-15, M17</b>             | 50µ/2µ                             |

**Table 4-2.** P-channel ISFET CCCII+ Simulation parameters

| <b>P-channel ISFET CCCII+ Simulation parameters</b> |                                          |
|-----------------------------------------------------|------------------------------------------|
| <b>Technology</b>                                   | Cadence AMS 0.35 $\mu$ m (CMOS, 3-metal) |
| <b>Power Supply</b>                                 | 3.3V                                     |
| <b>I<sub>BIAS</sub></b>                             | 2 $\mu$ A                                |
| <b>W/L of M1 (ISFET)</b>                            | 200 $\mu$ /1 $\mu$                       |
| <b>M3</b>                                           | 65 $\mu$ /1 $\mu$                        |
| <b>M10, M16</b>                                     | 30 $\mu$ /2 $\mu$                        |
| <b>M2, M4, M5-9, M11-15, M17</b>                    | 50 $\mu$ /2 $\mu$                        |

**Figure 4-10.** Operation range of N-channel ISFET CCCII+

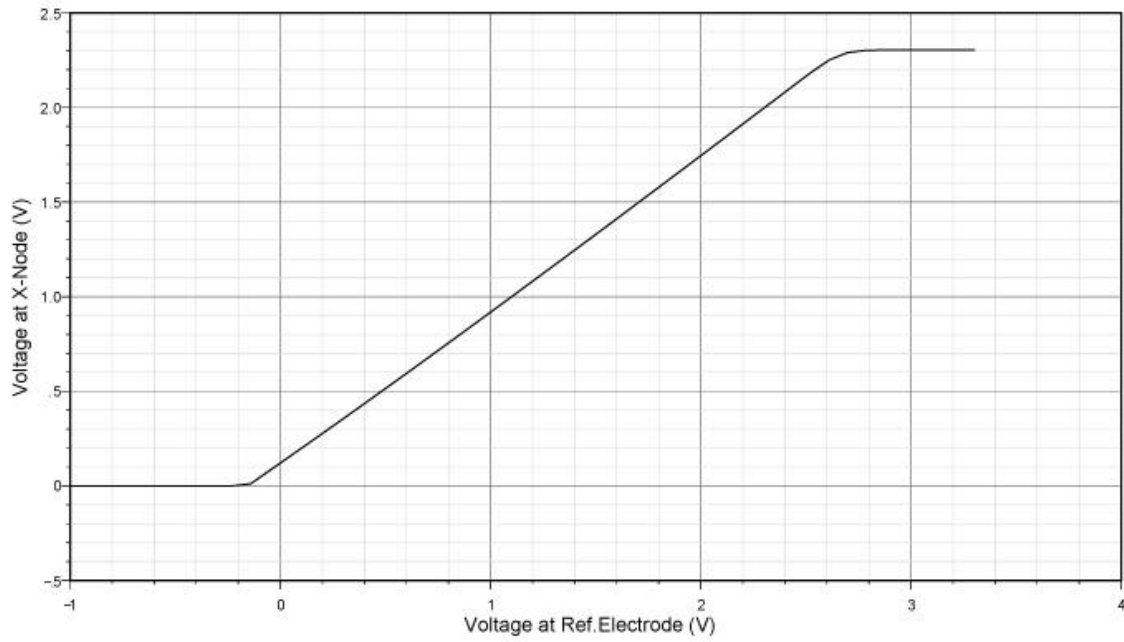


**Figure 4-11.** Operation range of P-channel ISFET CCCII+

The above two figures are the DC transfer characteristics obtained by sweeping the reference electrode as the input and by plotting the corresponding X-node ( $V_x$ ) voltage across  $1\text{M}\Omega$  load. As can be seen, the N-channel ISFET device has an operating range in the region of 0.96V to 2.10V, whereas the P-channel ISFET device has an operating range from 0.0V to 2.3V. As discussed in Chapter 2, the maximum silicon ISFET pH sensor sensitivity will not exceed the Nernstian value of 59mV/pH, which means that the operating range for both CCCII+ devices simulated will cover the required pH range of 1 to 14. One advantage of the P-channel ISFET device is that it can operate from zero input because of the lower threshold voltage,  $V_T$ , value.

The next results presented are the signal operating characteristics of both CCCII+ devices for the test circuit shown in Figure 4-12. The test load used for both X-node and Z-node

are at  $1\text{M}\Omega$ . Note that in practical measurements of the fabricated silicon devices, these resistors will be the internal oscilloscope probe input resistance.

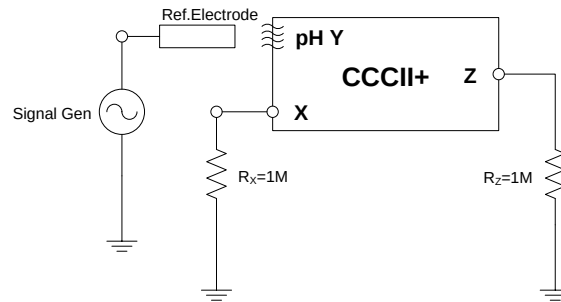


**Figure 4-12.** Test circuit to determine the signal operating characteristics

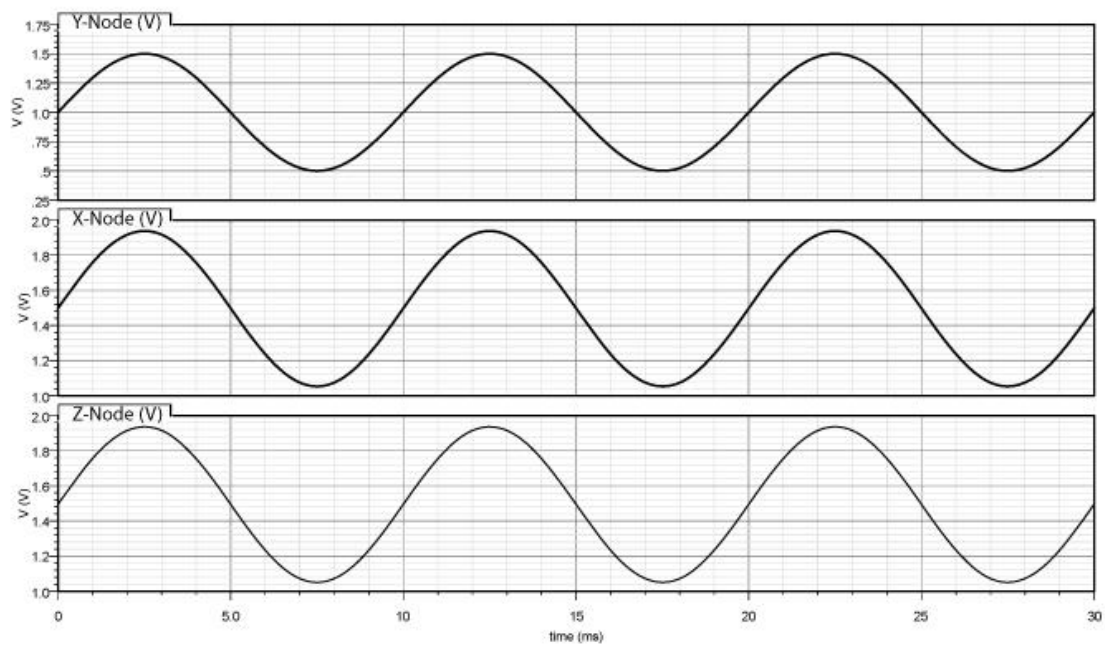


**Figure 4-13.** Voltage transfer of N-channel ISFET CCCII+

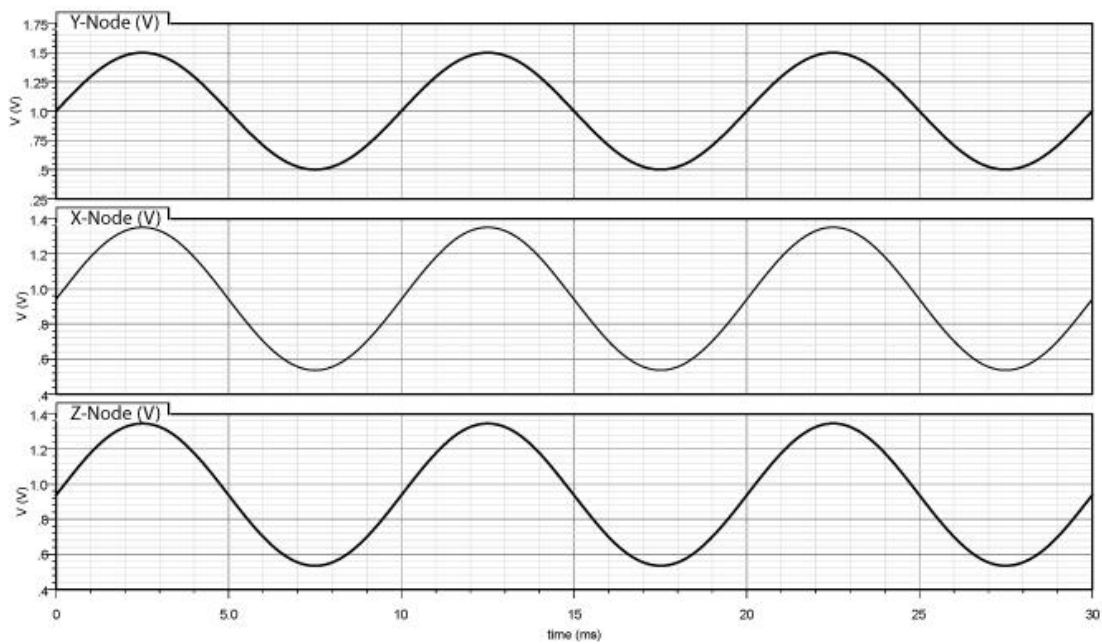


**Figure 4-14.** Voltage transfer of P-channel ISFET CCCII+

As can be seen from the above graphs, the input signal is a sinusoidal voltage of  $1.0V_{pp}$  with an applied DC offset of  $+1.0V$  to bias the ISFET in the centre of its operating region and a frequency of  $100Hz$  for both devices. The X-node output for the N-channel ISFET device is  $0.89V_{pp}$ , with an additional  $+0.49V$  offset voltage and the Z-node is virtually identical. The X-node output for the P-channel ISFET device is  $0.81V_{pp}$ , with an additional  $-0.06V$  offset voltage and the Z-node is almost the same. It should be noted that no attempt at this stage has been made to trim out the DC offset voltage for either device. However this offset voltage is mainly caused by the mismatch in threshold voltages,  $V_T$ , of the ISFET and the output transistor, M3. The major reason that the signal to voltage gain is below unity (between 80% to 90%) is because of body effects. This could be eliminated if the body were connected to the source, but this cannot be done with the semiconductor technology used.

The output impedance was measured at the X-node of each device, giving  $88.5\Omega$  for the N-channel ISFET devices and  $809.5\Omega$  for the P-channel ISFET devices. The body effect is again the cause of the differences in X-node output impedances. Finally, the measured Z-node output impedance was  $28.43\text{G}\Omega$  for the N-channel ISFET devices and  $10.24\text{G}\Omega$  for the P-channel ISFET devices. This is a consequence of the superiority of the NMOS devices in the cascoded Z-node output stage of the N-channel ISFET CCCII+ compared with the P-channel ISFET CCCII+ where  $r_{dsN} > r_{dsP}$ . The last result presented here is the frequency and phase responses of both N-channel and P-channel ISFET devices.

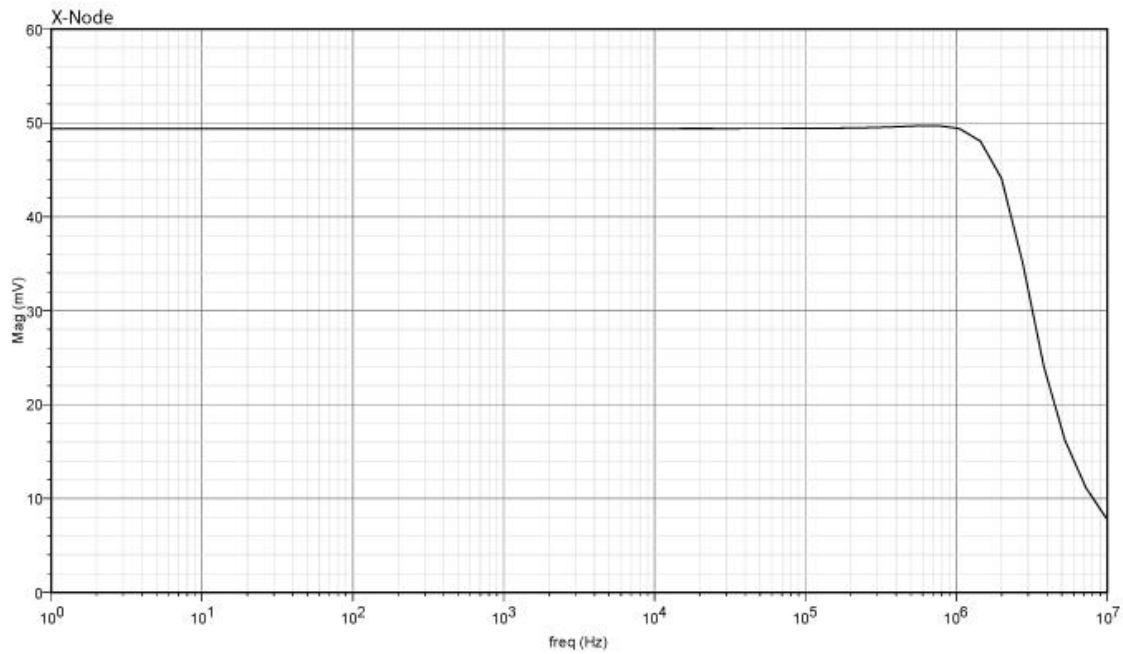


**Figure 4-15.** Frequency response of N-channel ISFET CCCII+

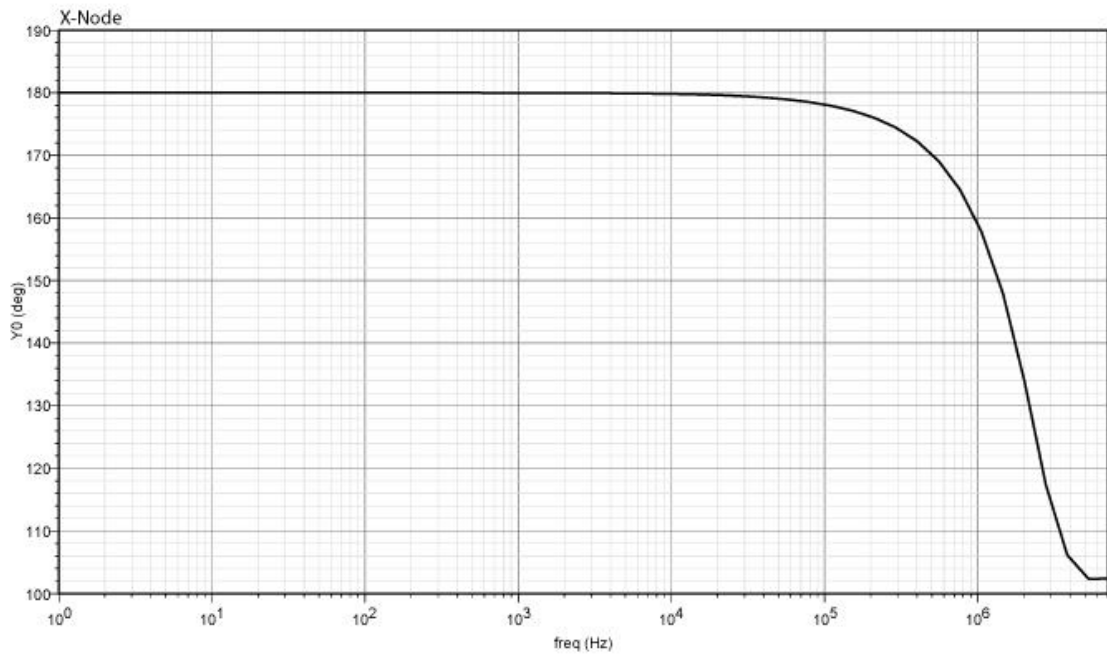


**Figure 4-16.** Phase response of N-channel ISFET CCCII+

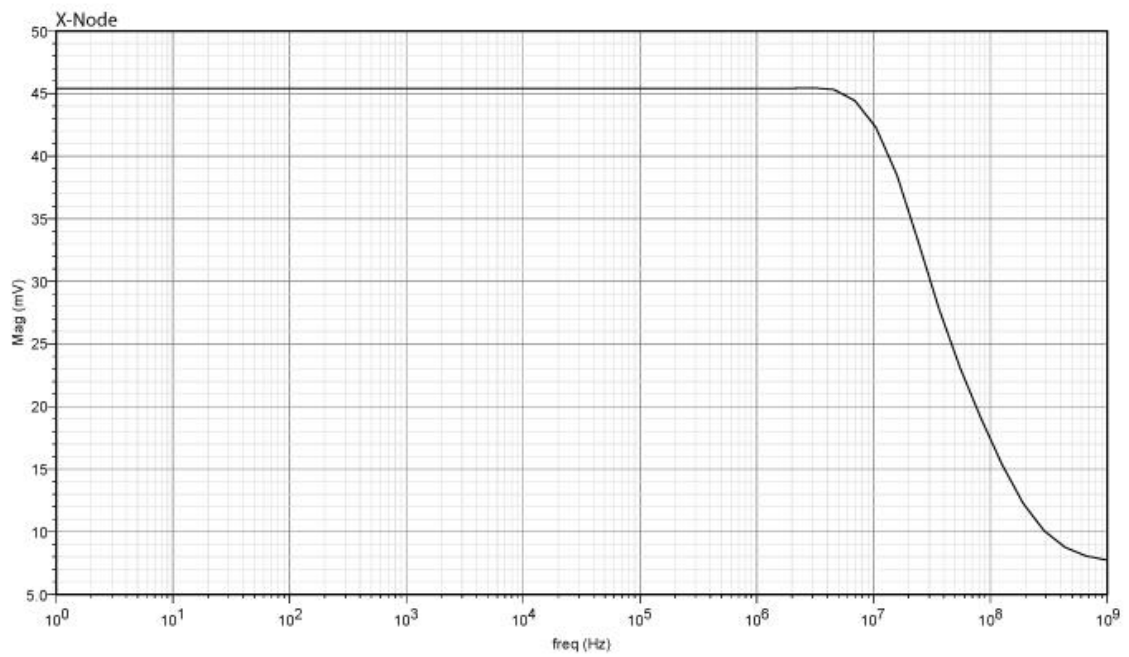


**Figure 4-17.** Frequency response of P-channel ISFET CCCII+

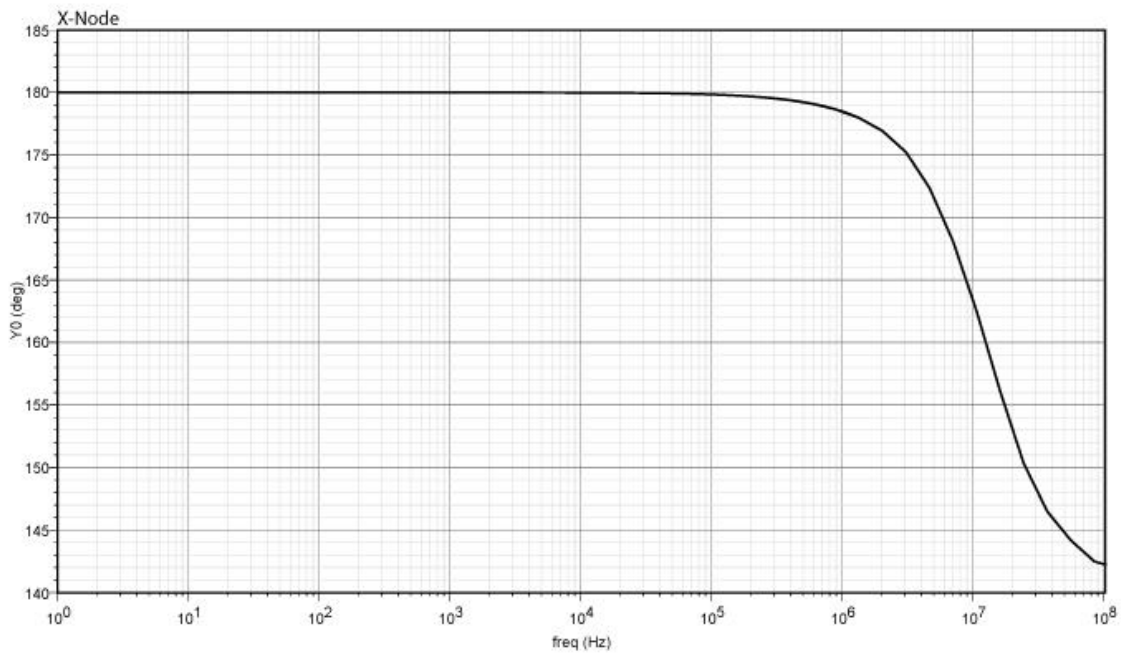


**Figure 4-18.** Phase response of P-channel ISFET CCCII+

The frequency and phase responses are shown above in Figure 4-15 to Figure 4-18. Referring back to the full transistor implementation of the N-channel and P-channel ISFET CCCII+ devices, it should be noted that each of the X-node output transistor namely, PMOS M3 of N-channel ISFET device and NMOS M3 of P-channel ISFET devices are significant different in size. In fact PMOS M3 of N-channel ISFET device are about 10 times larger than NMOS of P-channel ISFET device and as a result the N-channel ISFET CCCII+ device exhibits an upper operating maximum frequency of around 0.2MHz, compared with 2.5MHz for the P-channel ISFET CCCII+ device. This is also the case for the phase responses of both CCCII+ devices where operating maximum phase response of device is around 10KHz and around 0.1MHz for N-channel ISFET and P-channel ISFET CCCII+, respectively.

The frequency responses obtained show that the operating frequency can be quite high, up to several MHz, far beyond the normal requirements in most biochemical application areas. Although the -3dB cut-off frequency is as high as several MHz, to obtain good accuracy, say 0.5%, this requires operation well below the -3dB cut-off frequency. Indeed, if the frequency response is dominant pole, then 0.5% equates to operation up to but not beyond  $f_0/10$ . This is confirmed by the dominant pole frequency response error figures shown in Table 4-3.

**Table 4-3.** Frequency response errors

| $f/f_0$  | $ A $       |
|----------|-------------|
| 0.01     | $\approx 1$ |
| 0.1      | 0.995       |
| 0.5      | 0.894       |
| 1 (-3dB) | 0.707       |
| 1.5      | 0.555       |

In summary, the two tables namely, Table 4-4 and Table 4-5 below contain the key characteristics of the N-channel and P-channel ISFET CCCII+ devices. Note that both have low fully loaded power supply current consumption which is an advantage for a device that could potentially be portable and battery powered.

**Table 4-4.** Characteristics of N-channel CCCII+ with loading at  $R_X = R_Z = 1M\Omega$ 

| Characteristics of N-channel CCCII+             |                           |                            |
|-------------------------------------------------|---------------------------|----------------------------|
|                                                 | X-node (Voltage-follower) | Z-node (Current-follower)  |
| Gain                                            | 0.885                     | 0.999                      |
| Operation range                                 | 0.96V to 2.1V             | 956.63nA to 2.0957 $\mu$ A |
| Impedance                                       | 88.47 $\Omega$            | 28.43G $\Omega$            |
| Output offset                                   | 0.498V                    | -1.03nA                    |
| Power consumption                               | 29.34 $\mu$ W             |                            |
| X-node -3dB Bandwidth (Loading at 1M $\Omega$ ) | 2.76MHz                   |                            |

**Table 4-5.** Characteristics of P-channel CCCII+ with loading at  $R_X = R_Z = 1M\Omega$ 

| Characteristics of P-channel CCCII+             |                           |                           |
|-------------------------------------------------|---------------------------|---------------------------|
|                                                 | X-node (Voltage-follower) | Z-node (Current-follower) |
| Gain                                            | 0.815                     | 0.995                     |
| Operation range                                 | 0V to 2.3V                | 0A to 2.287 $\mu$ A       |
| Impedance                                       | 809.53 $\Omega$           | 10.24G $\Omega$           |
| Output offset                                   | -58.33mV                  | -2.53nA                   |
| Power consumption                               | 43.27 $\mu$ W             |                           |
| X-node -3dB Bandwidth (Loading at 1M $\Omega$ ) | 26.40MHz                  |                           |

The final phase of development of the CCCII+ is the implementation and evaluation of the fabricated devices. Both N-channel and P-channel ISFET CCCII+ devices will be fabricated and this work is described in the next section.

## 4.5 Design fabrication

The circuits of Figure 4-8 and Figure 4-9 were laid out for fabrication using the AMS 0.35 $\mu$ m CMOS 3-metal layer technology. To provide flexibility, two additional features

were included in the layout. Firstly, ESD protection was integrated into the connection pads to make the devices more electrically robust. Secondly, to facilitate the use of an external ISFET as well as the on-chip ISFET, the ISFET in the fabricated CCCII+ was not connected on-chip but provided with external pad to enable off-chip jumper connections, as shown below in Figure 4-19. During test, an external NMOS ISFETs from Sentron Europe (Roden, The Netherlands, part no, OEM-679) and PMOS from DNA-E were used in addition to the on-chip ISFETs.

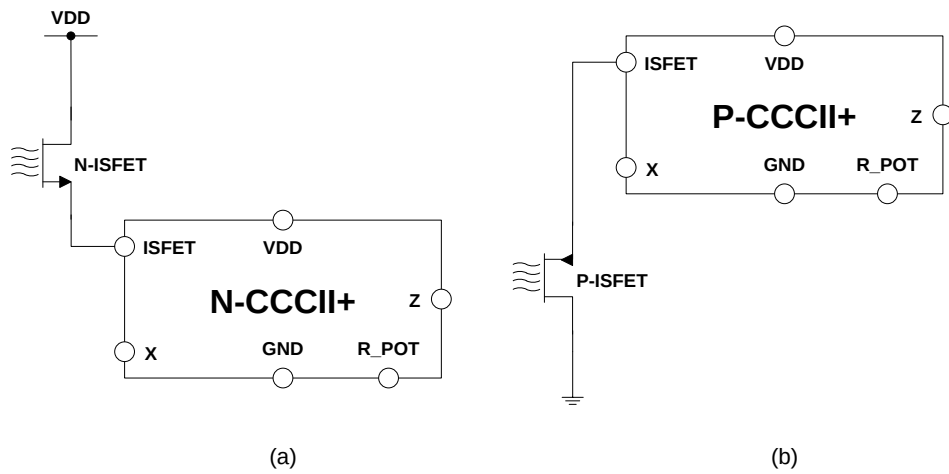


**Figure 4-19.** CCCII+ connector diagrams

#### 4.5.1 Matching of transistors, common-Centroid layout and dummy transistors

Most integrated components such as resistors, capacitors and transistors have tolerances of  $\pm 20$  to  $30\%$  [14]. These tolerances are much poorer than those compared with discrete devices, mainly due to all of the devices in an integrated circuit occupying the same piece of silicon, so they all experience similar manufacturing conditions. For example, if the

value of one component increases by 10%, then all similar components experience similar increases. However, this does not prevent integrated circuit from achieving a high degree of precision matching.

Analog integrated circuit, like the CCCII+, usually depend on matching to obtain much of their precision and performance, in particular the ratio between two similar components on the same integrated circuit can be controlled to better than  $\pm 1\%$ , and, in many cases, to better than  $\pm 0.1\%$ . Many mechanisms, such as random variation, process biases, interconnection parasitics, photolithographic effects, diffusion interactions, hydrogenation and stress gradients [14-15] all can interfere with the matching, but most of these are known, and layout designers have to devise ways to minimize their impact. Furthermore, the layout designer needs to determine which components ought to match, and with what degree of precision.

**Table 4-6.** Interdigitation patterns for arrays having one axis of symmetry [14]

|      |          |              |                  |
|------|----------|--------------|------------------|
| A    | AA       | AAA          | AAAA             |
| AB   | ABBA     | ABBAAB       | ABABBABA         |
| ABC  | ABCCBA   | ABCBACBCA    | ABCABCCBACBA     |
| ABCD | ABCDDCBA | ABCDBCADBCDA | ABCDDCBAABCDDCBA |

The main matching technique applied on the layouts of the CCCII+ devices is known as ‘one dimensional common-centroid arrays’ which uses an interdigitation pattern, shown in Table 4-6, to complete the layout for each device. Suppose that a matched device is divided into sections or fingers. If these sections are all identical, and if they are arranged

to form a symmetrical pattern, then the centroid of the device will lie at the intersection of the axes of symmetry passing through the array, as shown schematically in Figure 4-20.

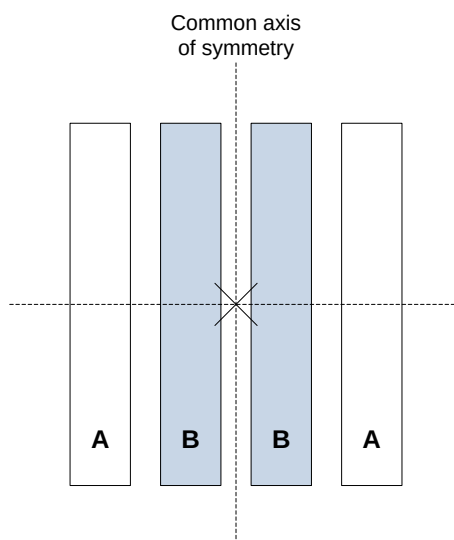


**Figure 4-20.** One dimensional common-centroid arrays [14]

Figure 4-20 shown the example of such a common-centroid layout. The two devices are marked A and B, their axes of symmetry are shown as dotted lines, and their centroid is marked by 'X' where the two axes of symmetry intersect. This pattern has an axis of symmetry that divides it into two mirror-image halves (AB and BA), however, the array that used the interdigitated patterns requires dummy transistors because the segments of the device occupy both ends of the array making the segments on the ends of the array face whatever geometries happen to reside nearby. The geometries adjacent to one end of the array are likely to differ from those next to the other. If this happens, then mismatches will result if dummies are omitted. As a result, all the transistors used in the CCCII+ layout were carefully grouped into segments according to their role of operation and

dummy transistors were added to both ends of each array as shown in Figure 4-21 and Figure 4-22.

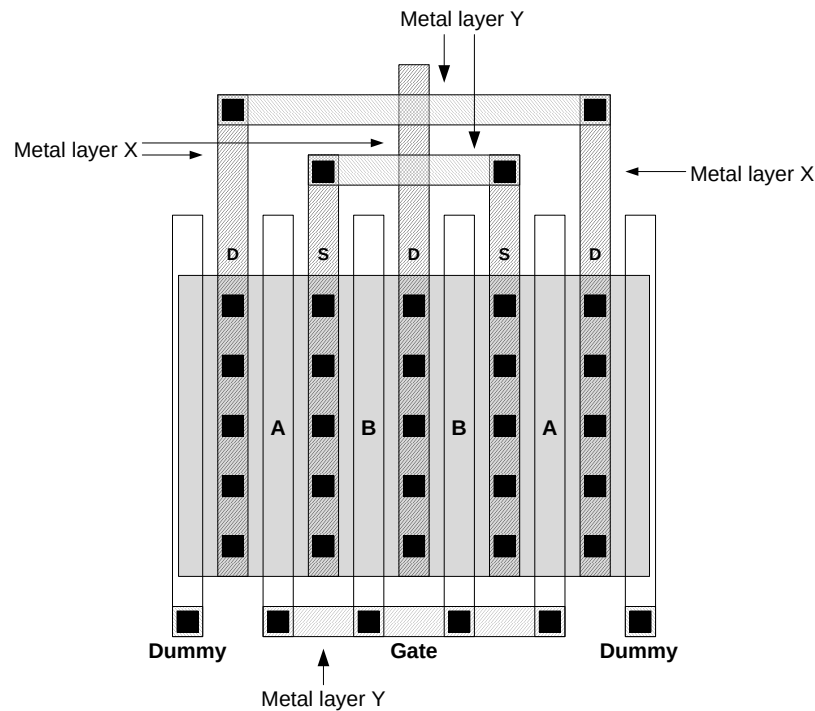


**Figure 4-21.** Interdigitated MOS transistors with connected dummy

The Figure 4-21, not only shows the use of an interdigitation pattern ABBA to ensure exact alignment of the centroids but the source and drain fingers, connected dummy, and metal connections are also included. If source and drain fingers are denoted by source (S) and drain (D) subscripts, then the pattern becomes  $_D A_S B_D B_S A_D$ . Notice that the A and B segments share the drain and source, the A-segment on the right has its drain on the right, while the A-segment on the left has its drain on the left. Similarly, the B-segment on the right has its source on the right, while the B-segment on the left has its source on the left. As a result each transistor contains one segment oriented in either direction. The reason

for this precaution is rather subtle. Suppose the first transistor consists entirely of segments with drains on the left, while the drain of the entire segments of second transistor is on the right. If left-oriented and right-oriented segments differ in any way, the effect of orientation will not cancel each other, and then the two transistors will not be well matched.

Figure 4-22 shows a part of the CCCII+ (a) with the dummy transistor present, and the layout of this part of the CCCII+ is shown in (b). Matching in this part of the circuit is essential and adopting the common-centroid approach achieves this. The rest of the layout details can be found in the Appendix A.

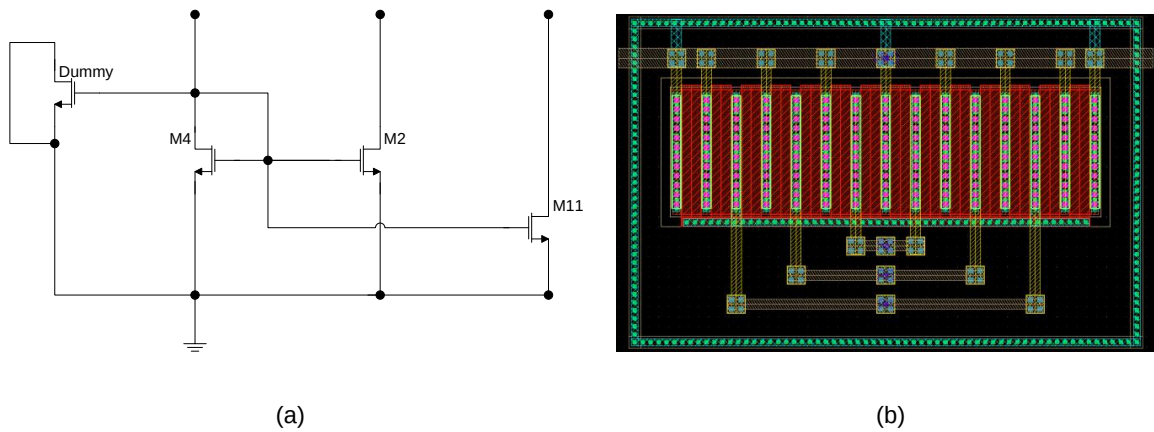


**Figure 4-22.** Sample of common-centroid with connected dummy used in N-channel ISFET CCCII+

#### 4.5.2 Full layout of N-channel and P-channel ISFET CCCII+ Devices

The full layout is shown in Figure 4-23 and Figure 4-24 for the N-channel and P-channel CCCII+ devices, respectively. Each part of the circuit is identified on the layout and can be related back to the original circuit designs in Figure 4-8 and Figure 4-9. The process is

a 3-metal layer technology, and so the vertical metal connections used one-metal layer and the horizontal connections used another to avoid unwanted short circuits occurring.

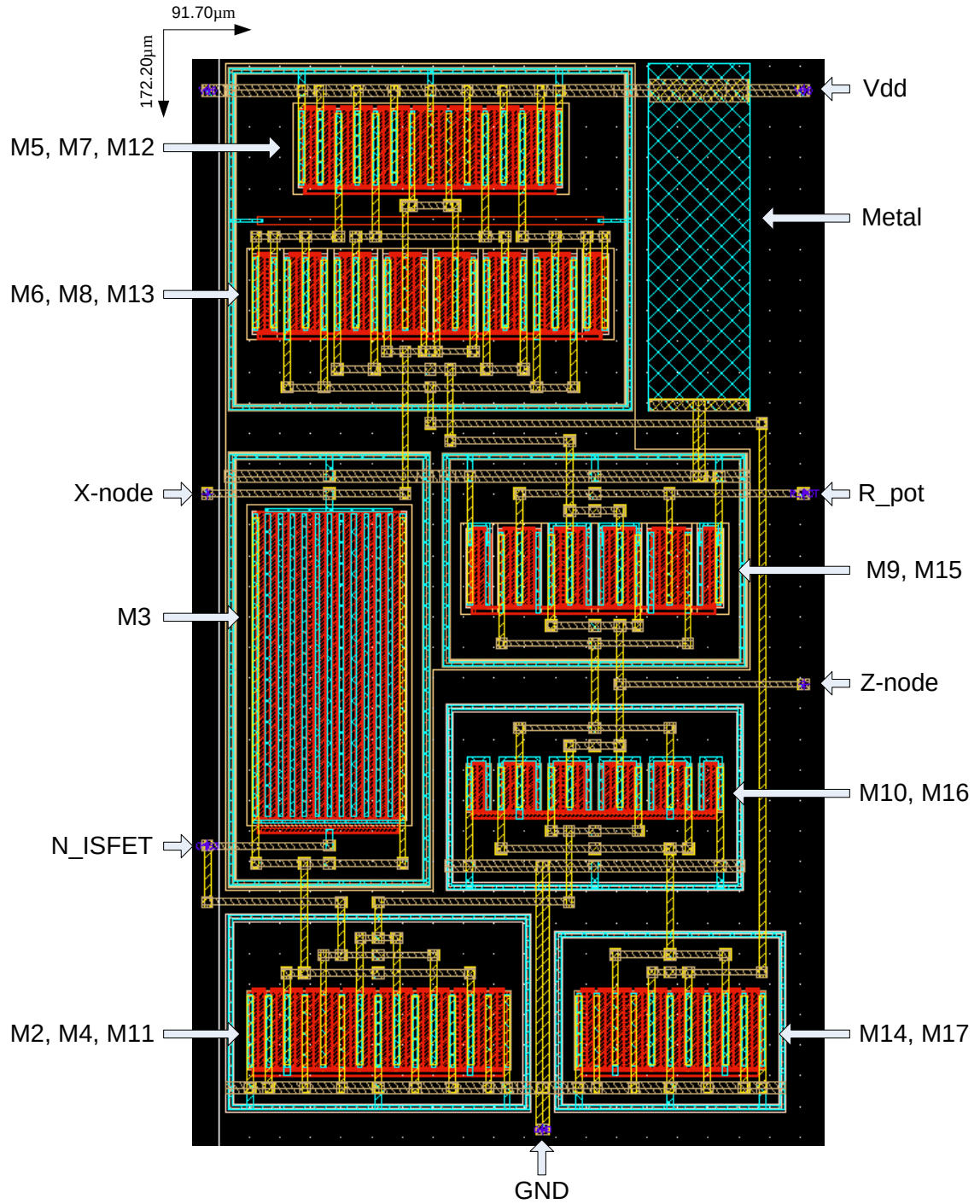


**Figure 4-23.** Full layout of N-channel ISFET CCCII+

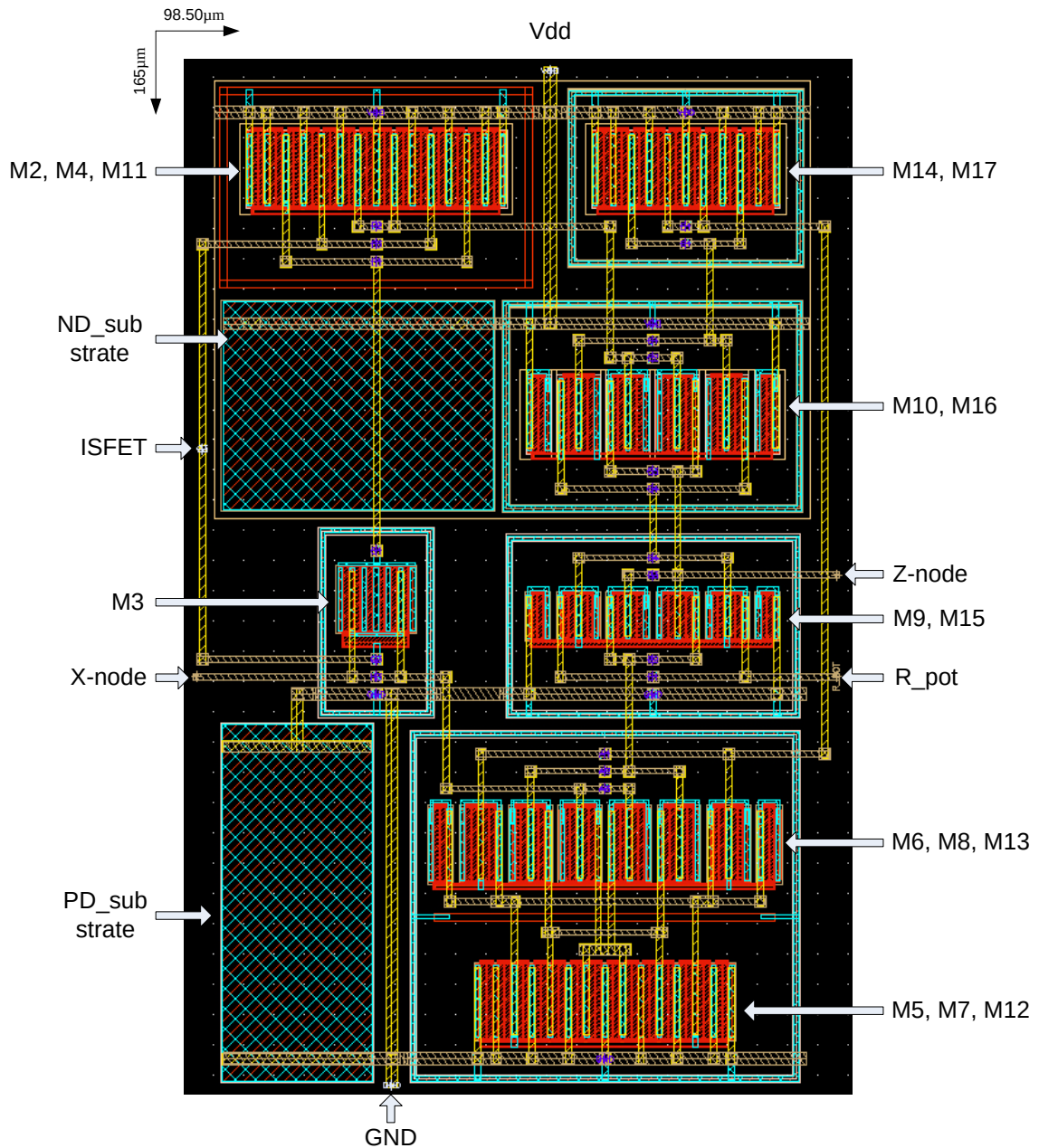


**Figure 4-24.** Full layout of P-channel ISFET CCCII+

#### 4.5.3 Electrostatic discharge (ESD) protection

The connection pads to the design are shown in the schematic of Figure 4-25. The series resistors were added to provide current limiting in the event of ESD.  $200\Omega$  was used in the current connection lines and  $500\Omega$  in the voltage connection lines. The final layout,

including pad and ESD, is shown in Figure 4-26. It is interesting to note the significantly larger area needed for the pads and ESD than the CCCII+ devices themselves.

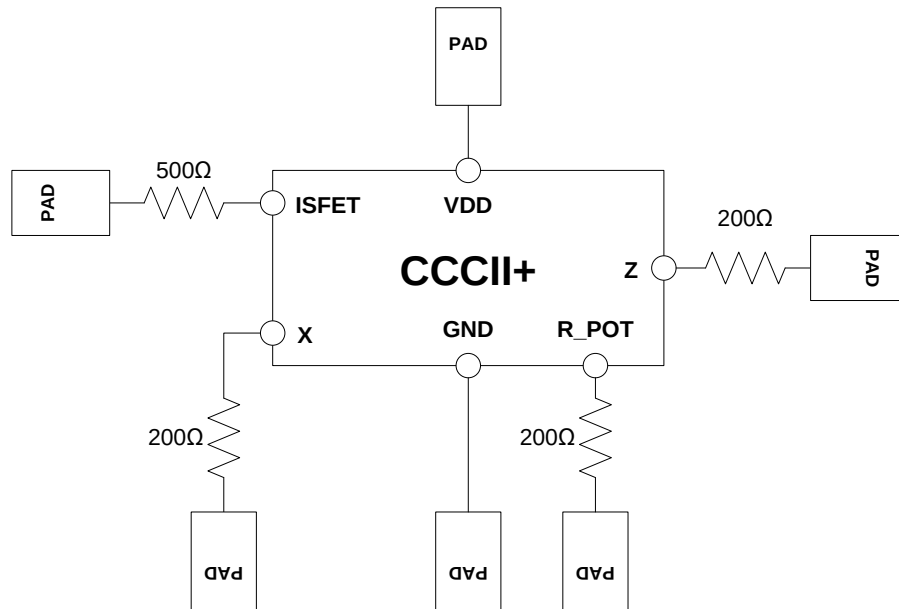


**Figure 4-25.** ESD pad Schematic of CCCII+

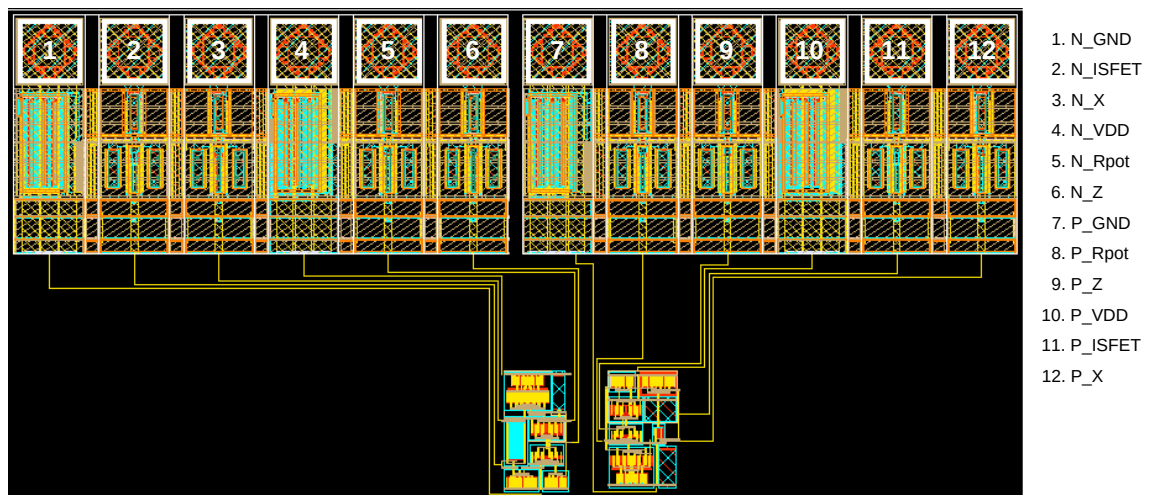


**Figure 4-26.** Full layout of CCCII+ including ESD pads protection

## 4.6 Measured results

This section is concerned with the evaluation of the fabricated CCCII+ chip, as shown in the microphotograph in Figure 4-27. Measurements were taken and are presented showing the performance of the CCCII+ devices for both N-channel and P-channel CCCII+ designs. By way of benchmarking the performance of the N-channel CCCII+ device, a standard discrete ISFET read-out circuit was prepared and tested at the same time under the same conditions.

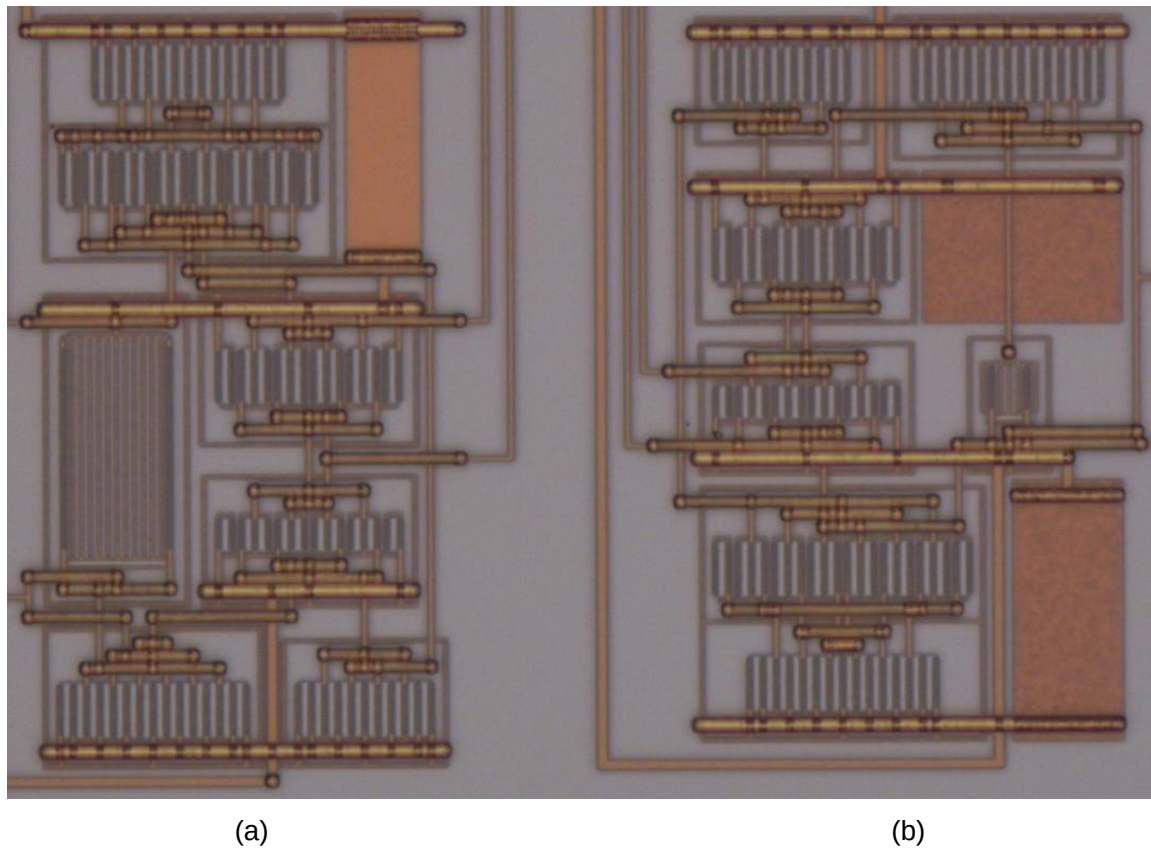


**Figure 4-27.** Microphotograph of CCCII+ chip: (a) N-channel ISFET CCCII+, (b) P-channel ISFET CCCII+

#### 4.6.1 Wire bonding the CCCII+ chips

The CCCII+ device was produced using the AMS 0.35 $\mu$ m CMOS technology as described above. The integrated circuit is shared between several other research projects and so contains several designs from different researchers, the CCCII+ is one of these. The schematic of the IC is shown in Figure 4-28 with the bond wire connections for the CCCII+ device which used leads 1 to 12 inclusive. Note that the other devices on the chip and their interconnections are omitted for clarity. 40 fabricated chips were returned for testing, but only two were available for this and one other researcher's work, and these two chips were bonded to enable the CCCII+ measurements to be obtained. Figure 4-29 is a microphotograph of the chip which includes the two CCCII+ device connections together with one other research circuit and its bond wire connections. The reverse side of the whole chip is bonded using conductive adhesive connected to ground leads to ensure correct ground referencing.

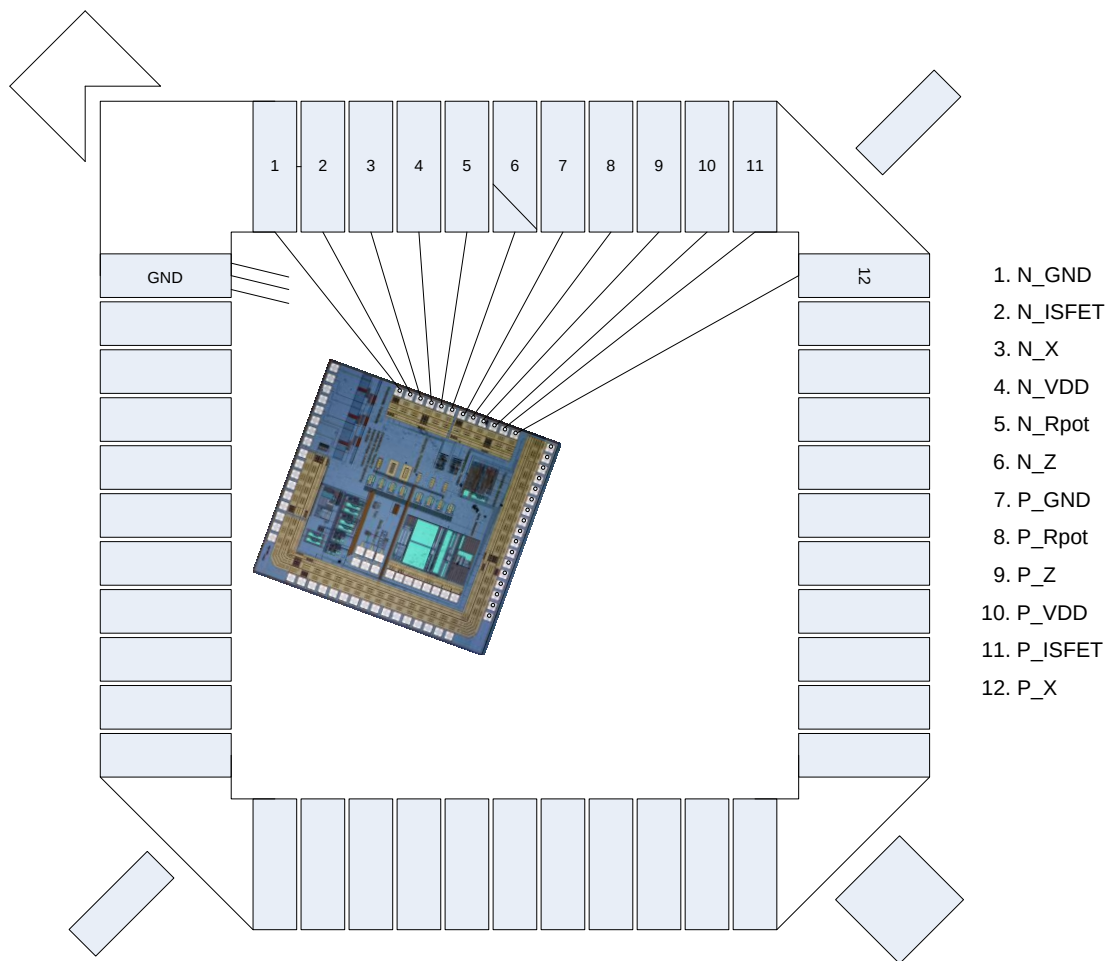


**Figure 4-28.** Bond wiring schematic of CCCII+

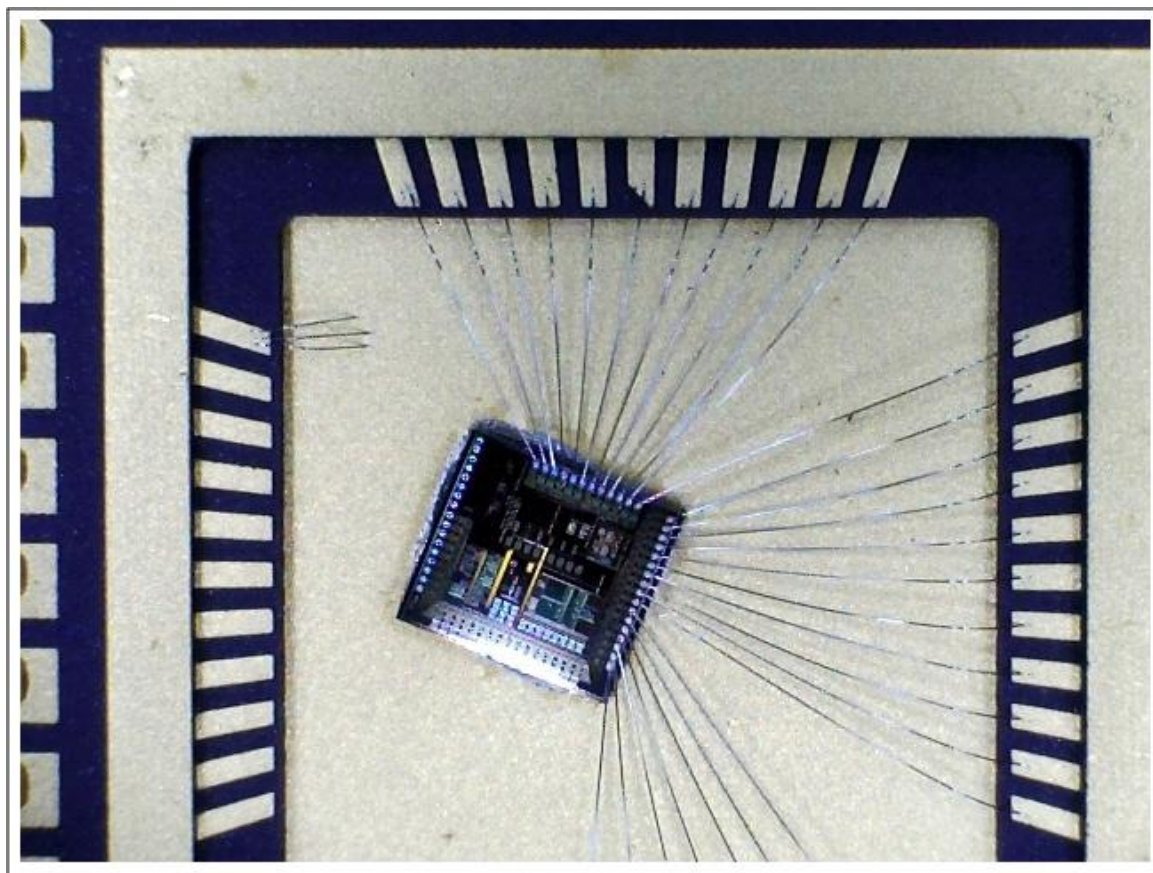


**Figure 4-29.** Bond wiring microphotograph of CCCII+

#### 4.6.2 Test board preparation

A test and application board was designed to provide the correct environment for the chip during test and is also configured to enable two applications to be assessed, namely measurement of (i) buffer capacity/index and (ii) urea to creatinine ratio. The readout portion of the test board circuit is shown in Figure 4-30. The full board schematic can be found in Appendix B. The board has been designed with maximum flexibility, for example, on board DC power regulators have been included in the board design so that power supplies are available on the board, or alternatively they can be provided via external connections if required. This is also the same for provision of the CCCII+ bias current which is available on chip but can also be provided externally if required. In

addition BNC and SMA connectors are included on the board to provide ease of connectivity to external instruments.

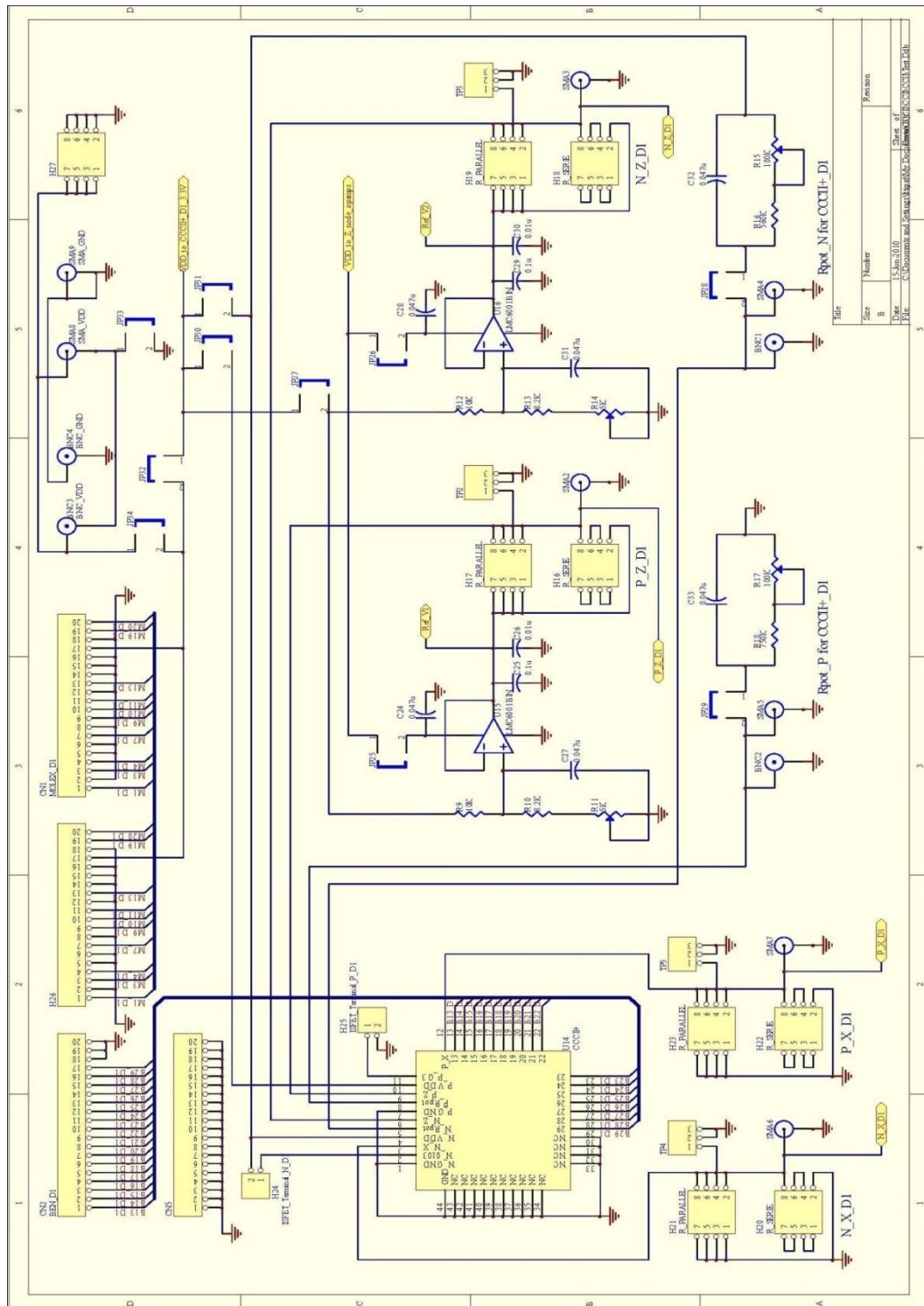


**Figure 4-30.** Readout portion of the test and application board schematic

The overall test and application board external dimensions are approximately 281mm by 200mm. A photo of the board, Figure 4-31, shows that it has two chip sockets which is necessary for the second application (urea-to-creatinine ratio). The board is a double sided PCB designed using ‘Altium designer<sup>4</sup>’ software. Care was taken in the board layout to provide good ground shielding and appropriate power supply decoupling.

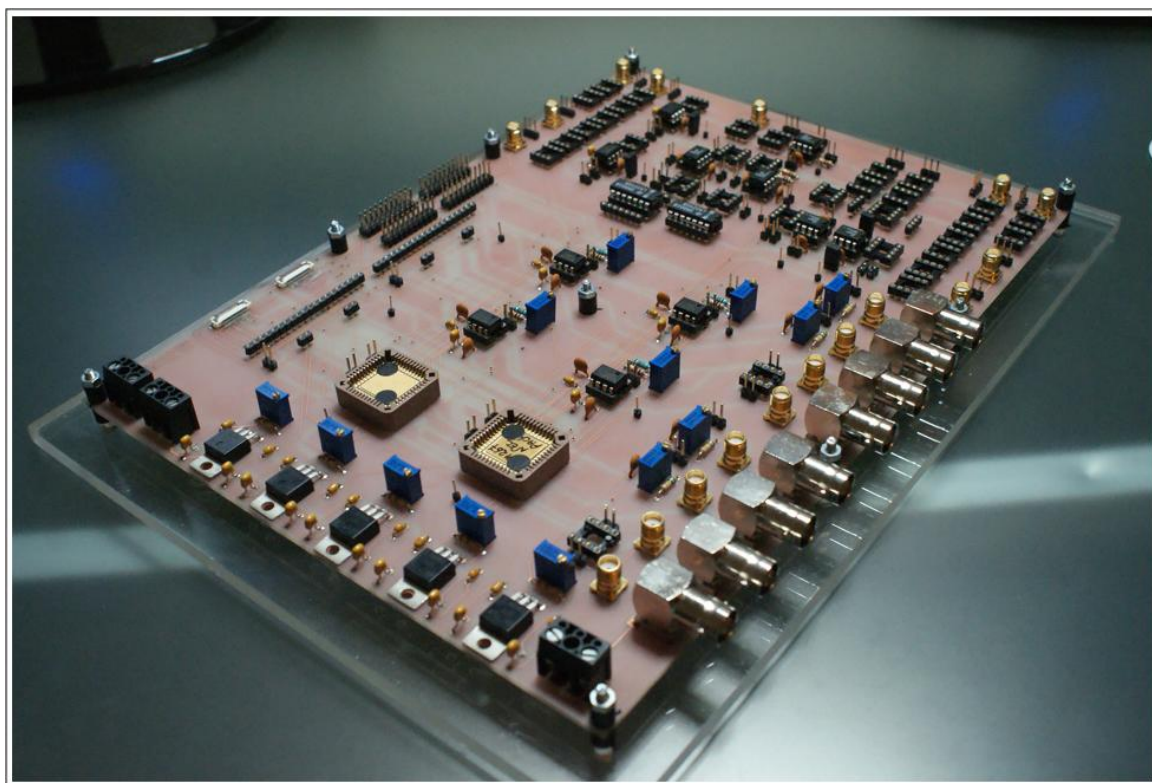


**Figure 4-31.** The photograph of CCCII+ test and application board

One aspect of the high output impedance Z-node of the CCCII+ is that its potential must remain within the power supply voltage range for correct operation. The ancillary voltage reference circuitry, which is adjusted to about  $V_{dd}/2$ , is shown in the circuit diagram of

---

<sup>4</sup> The next version of Protel 99 SE

Figure 4-32. These circuits are available on the board for each Z-node output with ‘jumper’ connections to each Z-node should they be required.

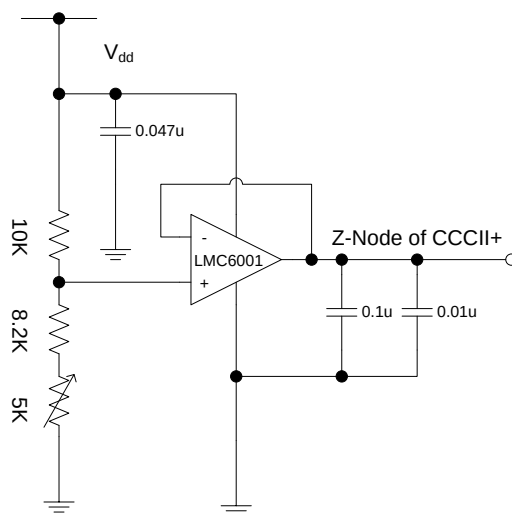


**Figure 4-32.** Potential trim-able circuit for Z-node outputs

#### 4.6.3 Measured results on N-channel ISFET CCCII+ in comparison with fixed $V_{ds}$ and $I_d$ ISFET readout circuit

In this section, the results of the CCCII+ will be described and compared with a conventional discrete fixed  $V_{ds}$  and  $I_d$  ISFET readout circuit. The latter was described earlier in Chapter 2 and shown again here as Figure 4-33. Note in the previous section, the possibility of using either external ISFET devices or internal was discussed. The results reported here all use external Sentron ISFETs so that a true comparison can be made between the discrete and integrated pH measurement systems of Figure 4-33 and Figure 4-34, respectively.

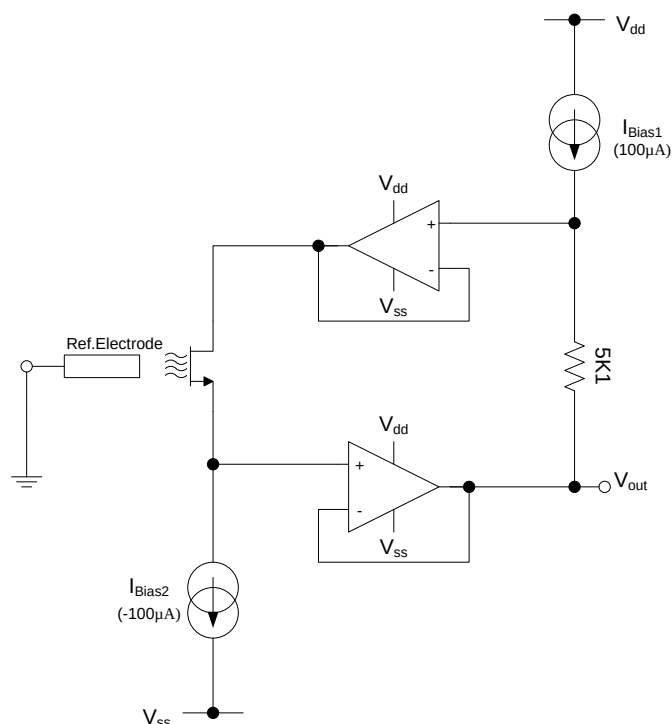


**Figure 4-33.** Source-follower bench mark ISFET readout circuit [16]

The CCCII+ configured as a pH sensor is shown in Figure 4-34, and the results are shown in Figure 4-35. A triangular waveform of 100mV peak to peak and 100Hz is supplied through the,  $A_g/A_gCl$ , reference electrode as the effective input and the output voltages obtained at the X-node and Z-node. A triangular waveform was used as this enables a visual assessment of any non-linearity to be readily seen at the outputs. These waveforms are direct oscilloscope outputs captured and presented. The voltage transfer between input and X-node is closer to unity than obtained via simulation because the measured results presented in Figure 4-35 uses an external ISFETs, whereas the simulation use the slightly inferior integrated ISFET and all the external ISFETs have their body connections tied to their respective sources, hence eliminated all body effects. It should be noted that a range of 3 different ISFETs were used to examine the dependence of the circuit on the

particular characteristic of an ISFET, see Appendix C, where the slight differences in results are described.

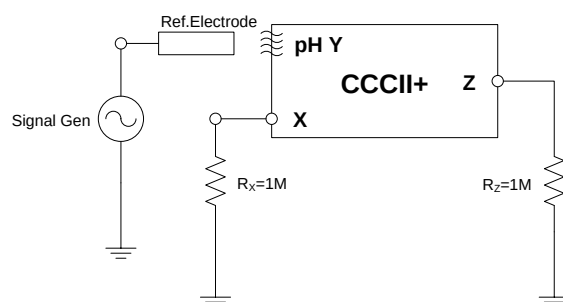


**Figure 4-34.** CCCII+ testing diagram for voltage transfer test

The output of CCCII+ can be taken either as voltage at the X-node or as current at the Z-node. In Figure 4-34, the Z-node has been terminated with a grounded  $1\text{M}\Omega$  resistor allowing comparison between the X-node and Z-node to be made. Inspection of Figure 4-35 shows that the voltages at the X and Z-nodes are very close (better than 1%), from which two facts can be inferred (i) the output can be taken either as voltage from the X-node or as current from the Z-node, and (ii) because the load on each is a  $1\text{M}\Omega$  resistor, the output impedance at the voltage output X-node must be very much lower than  $1\text{M}\Omega$  and the output impedance from the current output Z-node is very much higher than  $1\text{M}\Omega$ .

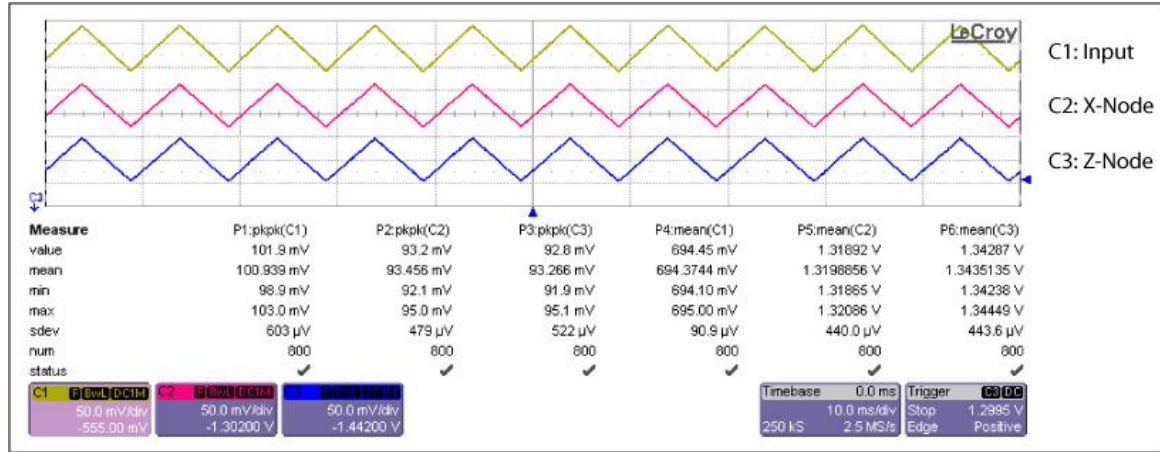


**Figure 4-35.** Measured voltage transfer input and outputs of Sentron N-channel ISFET CCCII+ (no. D2\_5)

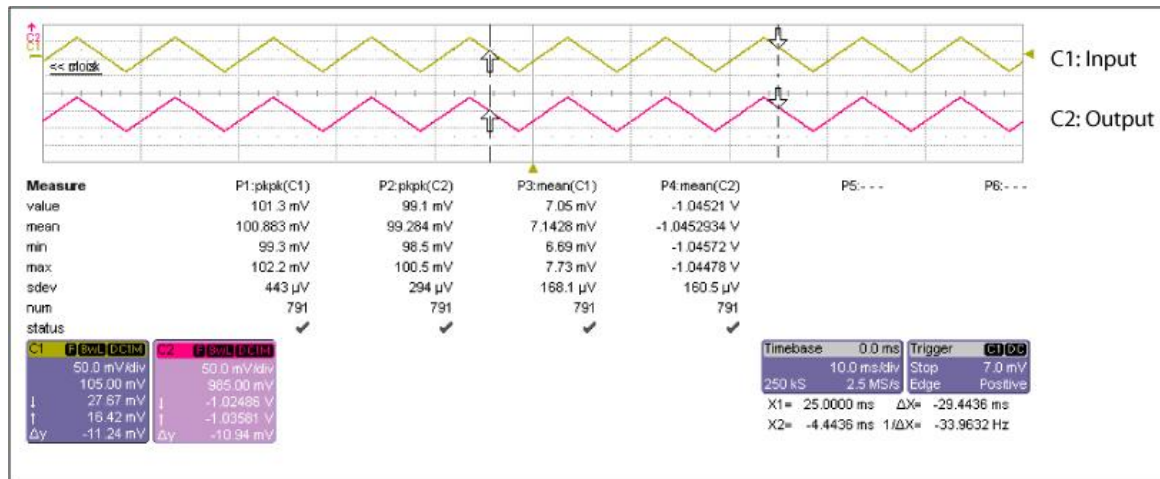


**Figure 4-36.** Measured voltage transfer input and outputs of source-follower bench mark circuit (Sentron ISFET N-channel, no. D2\_5)

The resultant waveform for comparison purpose for the discrete pH sensor circuit of Figure 4-33 is shown in Figure 4-36. The input signal was again 100mV peak to peak at 100Hz and the load at the output was set to  $1M\Omega$ , the same as for the CCCII+ circuit. The waveform of Figure 4-36 shows that the gain is closer to unity 98.4% compared with the CCCII+ circuit with 92.6%. The difference is small and considering the CCCII+ design

only comprises 16 transistors, whereas the discrete design with two op-amps configured as voltage-followers and two current sources have considerably more transistors, perhaps in the region of 3 to 4 times as many. Note that this discrete design is a voltage input and voltage output circuit which is less versatile than the CCCII+ design with its dual current and/or voltage output facility.

The next sets of results to be presented are the titration curve which gives the sensitivity of the circuit to pH as well as the linearity of the circuit to pH. The CCCII+ design was configured as shown in Figure 4-37. Note the Z-node is grounded and the output will be taken from the voltage output X-node only.

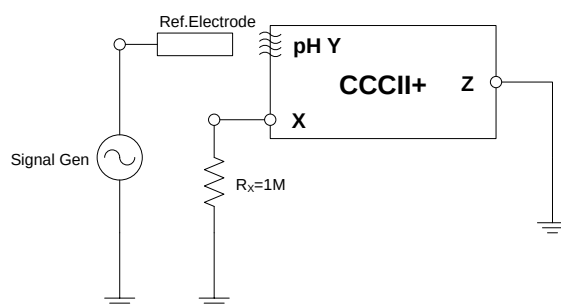


**Figure 4-37.** CCCII+ testing diagram for titration test

The titration results of Figure 4-37 are shown in Figure 4-38. These were obtained using 4 different pH values, 4, 5.1, 7 and 10. The sensitivity value is 46.4mV/pH and the linearity factor  $R^2 = 0.9982$ . Turning now to the benchmark comparator circuit of Figure 4-33, the titration results are shown in Figure 4-39 for the same ISFET sensor. The sensitivity is slightly higher at 50mV/pH and the linearity is virtually the same at  $R^2 = 0.9983$ . It is interesting that the CCCII+ performance is really quite close to the discrete design despite the fact that (i) the discrete design uses many more active devices, and (ii) the bias current

for the ISFET is less than  $2\mu\text{A}$  for the CCCII+ yet the benchmark discrete circuit is about 50 times more. As before it should be noted that a range of 3 different ISFETs were used to examine the dependence of the titration performance on the particular characteristic of an ISFET, see Appendix C, where the minor differences in results are shown.

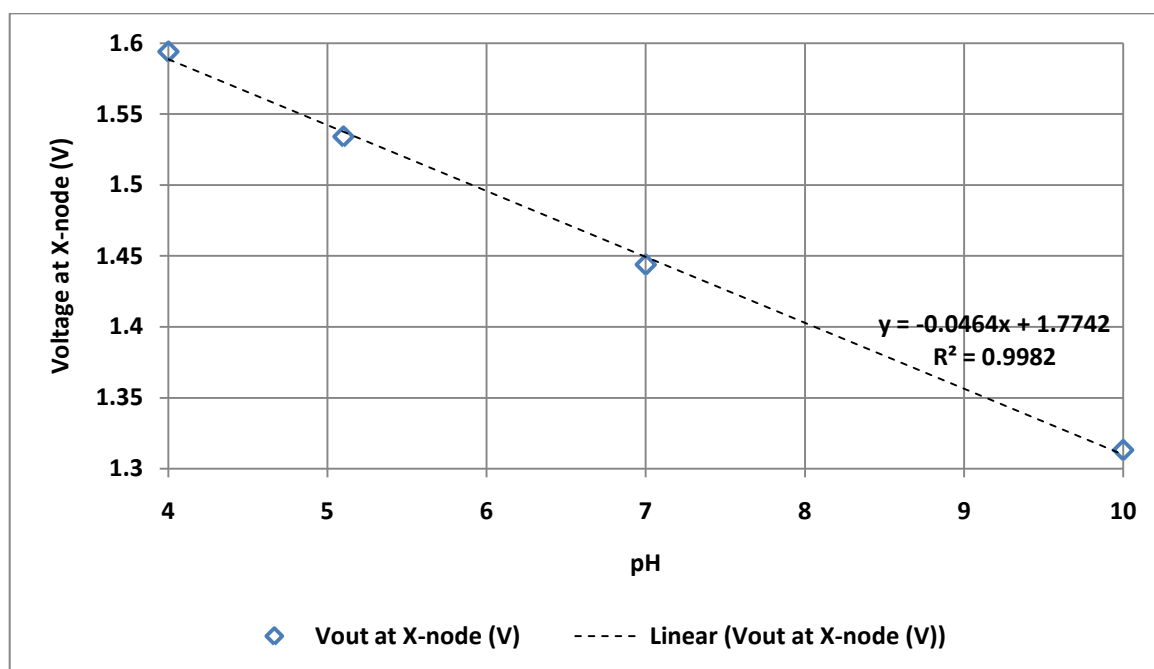


**Figure 4-38.** Measured titration curve of N-channel CCCII+ (no. N\_D2) with Sentron ISFET N-channel (no. D2\_1)

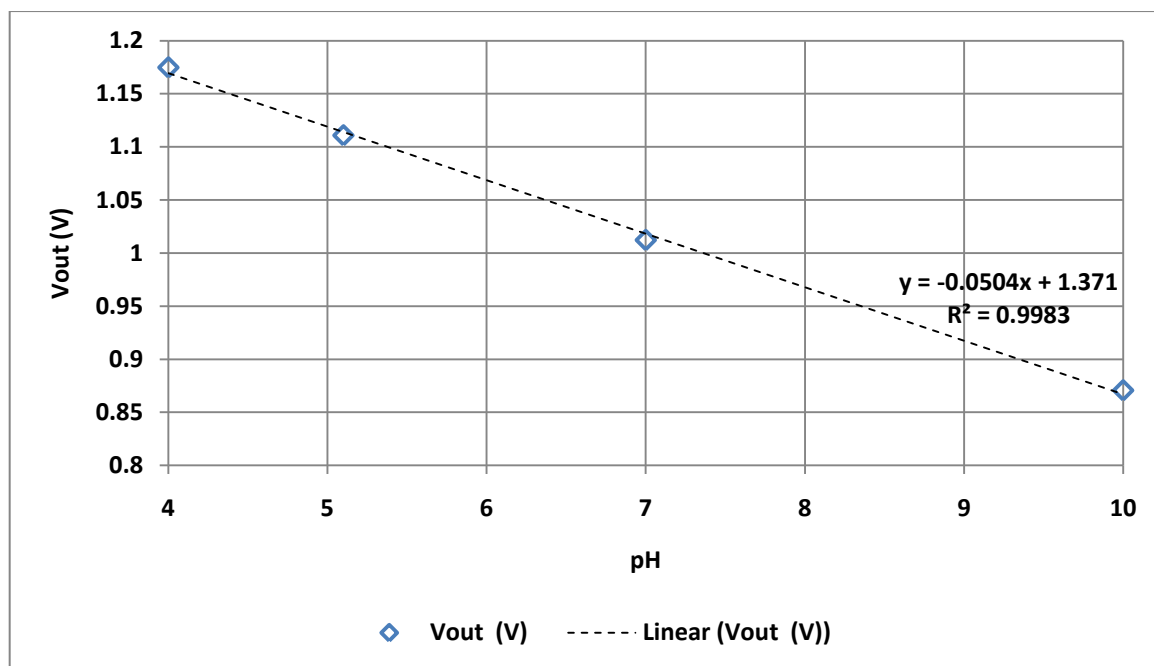


**Figure 4-39.** Measured titration curve of source-follower bench mark circuit with Sentron ISFET N-channel (no. D2\_1)

#### 4.6.4 Measured results on P-channel ISFET CCCII+

The CCCII+ devices fabricated has one N-channel and one P-channel ISFET, thus a similar set of results can be taken for the P-channel CCII+ device. However, as will be shown, the titration sensitivity is of the order of 50% for the P-channel CCCII+ device compared with the N-channel rendering the P-channel CCCII+ device significantly less useful.

Figure 4-40 shows the input~output waveforms as above for the P-channel CCCII+ device using an external ISFET sensor supplied by DNA-E. The input was a triangular waveform of amplitude 200mV peak to peak at 100Hz. The resultant output from both X and Z-nodes is around one half the input amplitude. It should be noted that the outputs at the X and Z-nodes were in close agreement, suggesting that the reduction in gain is due to

the P-channel ISFET. It should be noted that the discrete ISFET readout bench-mark comparisons performed above for the N-channel CCCII+ were not undertaken for the P-channel ISFET as it was clear that the N-channel significantly outperformed the P-channel CCCII+ device.

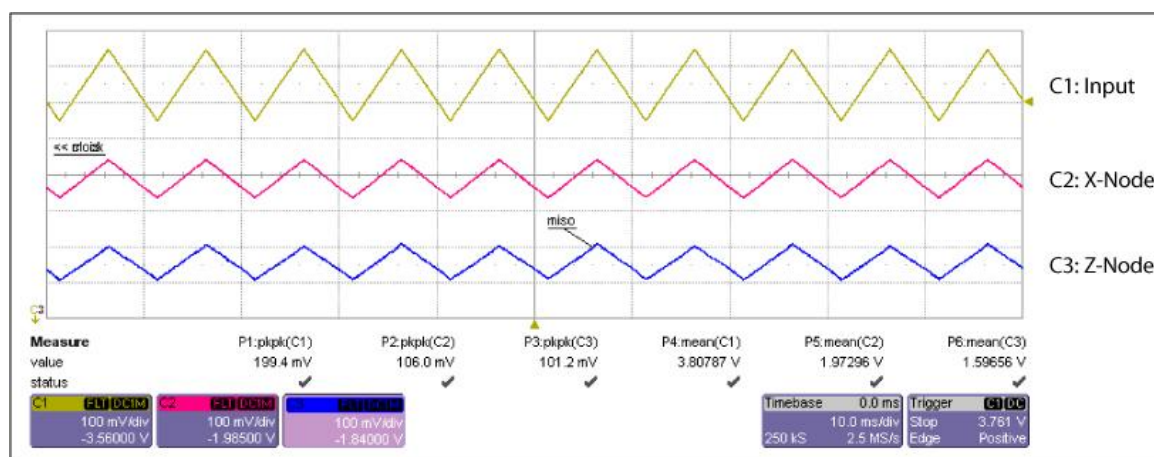


**Figure 4-40.** Measured voltage transfer input and outputs of P-channel ISFET CCCII+ (DNA-E ISFET P-channel, no. D1\_1)

The titration curve shown in Figure 4-41 exhibits a significantly lower sensitivity of 23.5mV/pH once more confirming that the superior performance of the N-channel CCCII+

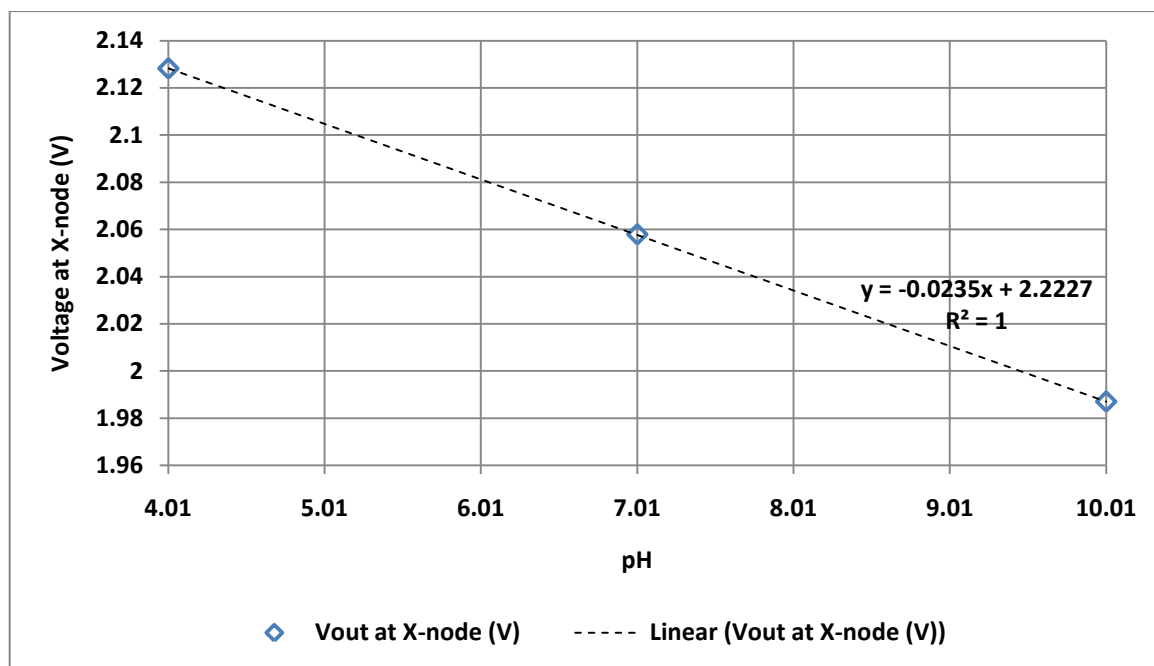


**Figure 4-41.** Measured titration curve of P-channel CCCII+ (no. P\_D2) with DNA-E ISFET P-channel (no. D1\_1)

## 4.7 Applications of Chemical Current-Conveyor for biochemical computation

The CCCII+ has two parts, the ISFET sensor followed by the current-conveyor section [1-2]. It is the latter that gives the CCCII+ the capability of performing useful analog computation on the value of the biochemical input signal. In this section of the chapter both the direct input signal readout aspects of the CCCII+ and its computational capability are presented.

### 4.7.1 Basic readout: Voltage-mode and current-mode amplifiers built with the Chemical Current-Conveyor

The CCCII+ has precise inverting unity current gain between Z and X-node, rather than the high ill-defined open-loop gain of the voltage op-amp, therefore in amplifier applications the CCCII+ is often used without any overall negative feedback, as shown in Figure 4-42 and Figure 4-43. Note that in these two figures and the majority throughout Section 4.7.1, the reference electrode part is not shown thereby making the diagrams clearer. The advantage of this approach over the traditional closed-loop gain is that the bandwidth conflict of the negative feedback voltage op-amp circuit is avoided. Of course, the benefits of global negative feedback, for example noise reduction, improvement in input and output impedance levels, can no longer be exploited, but the absence of overall negative feedback generally results in wider bandwidths at higher levels of gain. Although high bandwidth does not appear to be an essential requirement in many biochemical instrumentation applications, it must be remembered that for good accuracy, the operational -3dB frequency should be substantially higher than the maximum input signal frequency. However, in order to maintain a high level of accuracy without the use of negative feedback, a high quality CCCII integrated circuit realisation is required.

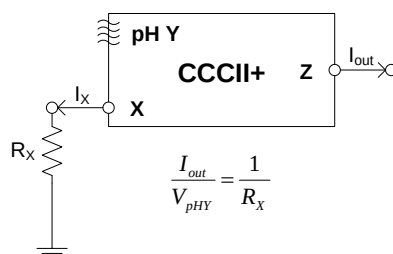


**Figure 4-42.** pH to I converter (pHCCS)

As shown in Figure 4-42, the CCCII+ can easily be used to configure into a current output amplifier in this case pH input to current output, or as a pH transconductance amplifier. The voltage across load  $R_X$  is given as

$$V_X = I_X R_X$$

Since the operation of CCCII+ gives  $V_{pHY} = V_X$ , the above equation can be rewritten as

$$V_{pHY} = I_X R_X$$

Furthermore, the X-node is a low impedance point and the X-node current is conveyed to the high output impedance Z-node, and as a result  $I_X = I_Z = I_{out}$ . The current output of the circuit is given by

$$I_{out} = \frac{V_{pHY}}{R_X}$$

**Equation 4-17**

However, it is important to note that  $R_X$  will form a pole with parasitic capacitance to ground at the X-Node, therefore ideally the value of this resistor should be kept sufficiently low to ensure that this parasitic pole does not adversely affect the frequency response.

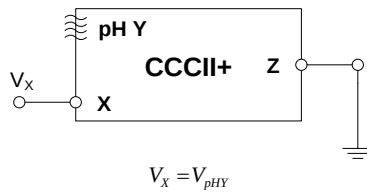


**Figure 4-43.** pH to V converter (pHCVS)

Figure 4-43 shows the direct configuration of the CCCII+ as a voltage readout circuit. The high output impedance Z-node is not required. It is connected to ground to ensure that the Z-node is held at 0V, thus keeping the transistors in their normal active region of operation. The circuit can be regarded as a pH voltage follower, and the output of the circuit expressed as

$$V_x = V_{pHY}$$

**Equation 4-18**

Note that because the output is taken from the low impedance X-node, it is effectively a voltage output circuit.

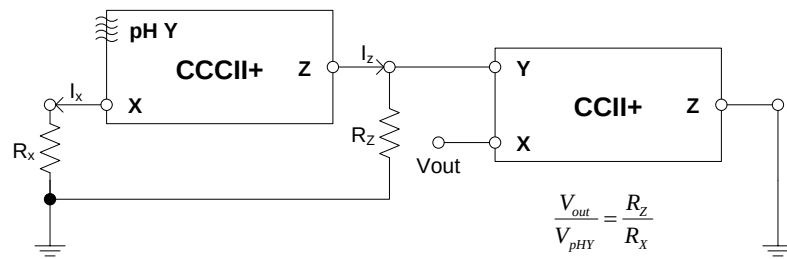


**Figure 4-44.** pH to Voltage amplifier

Voltage amplification can be obtained by modifying the circuit to that shown in Figure 4-44. By taking the output from the CCCII+ Z-node which has an additional grounded resistor  $R_z$  this provides voltage gain by converting the Z-node current into a Z-node voltage. The CCII+ in Figure 4-44 is configured as a voltage-buffer to provide a low final output impedance point. The output gain is determined by the ratio of  $R_z/R_x$ , as a result of the current that flowed into  $R_x$ , which is given by

$$I_X = \frac{V_X}{R_X}$$

since  $V_{pHY} = V_X$  then

$$I_X = \frac{V_{pHY}}{R_X}$$

Once again the X-node has a low input impedance and conveys the X-node current  $I_X$  through to the high output impedance Z-node of the CCCII+ forcing

$$I_Z = \frac{V_{pHY}}{R_X}$$

The Z-node of the CCCII+ is connected to high input impedance Y-node of CCII+ and so the current  $I_Z$  from the CCCII+ can only flow into resistor  $R_Z$  to ground, making the voltage across  $R_Z$

$$V_Z = \frac{V_{pHY}}{R_X} R_Z$$

Since the voltage output of the circuit is taken from the low input impedance X-node of CCII+ then

$$V_{out} = \frac{R_Z}{R_X} V_{pHY}$$

**Equation 4-19**

Using two CCII+, Toumazou and Lidgey described a differential voltage to current converter as shown in [17]. In Figure 4-45 the same implementation is presented but with two CCCII+ devices, the lower one of which has a reference FET, referred to as an ReFET, rather than an ISFET. This ReFET is ideally an ISFET with zero pH sensitivity and is used simply to balance the differential input of the circuit.

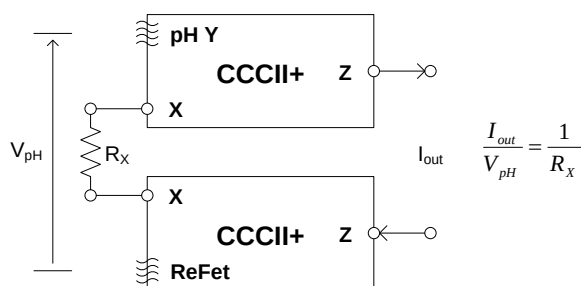


**Figure 4-45.** Differential pH to I converter

Any difference in sensed input pH-voltage appears across resistor  $R_X$  and thereby generates an X-node current which is then conveyed to the two output Z-nodes making the output current

$$I_{out} = \frac{V_{pH}}{R_X}$$

**Equation 4-20**

where  $V_{pH}$  is the difference in pH between pH-CCCII+ and ReFET-CCCII+.

This configuration of two matched CCCII+ devices is essentially a differential amplifier with very low common-mode gain and differential gain settable with two resistors. It should be noted that the high CMRR does not rely on any precise resistor matching unlike conventional operational amplifier instrumentation amplifiers. However, the CMRR does roll off at higher frequencies primarily due to the parasitic capacitance to ground at the X-nodes, which will then give rise to common-mode currents. Because the common-mode gain of the circuit is so low, then if the ISFET and ReFET are well matched so any offset, noise or drift in these two devices will tend to cancel. This is a particularly attractive feature of this readout double CCCII+ circuit.

The high performance pH instrumentation amplifier, shown in Figure 4-46 [18-19], is obtained by adding a CCII+ configured as a voltage-buffer to the outputs of Figure 4-45, in order to convert the output current back to a single-ended voltage. Note, the lower CCCII+ output Z-node is connected to ground as it is unwanted and this also ensures that the transistors within this CCCII+ are kept in the active region. Again this instrumentation amplifier has a high CMRR, requires no precisely matched resistor network. Also this type of instrumentation amplifier built with two interconnected CCII+ devices exhibits a bandwidth independent of gain. The same attractive features of offset and drift cancellation that were described for the circuit in Figure 4-44 also apply to this circuit.

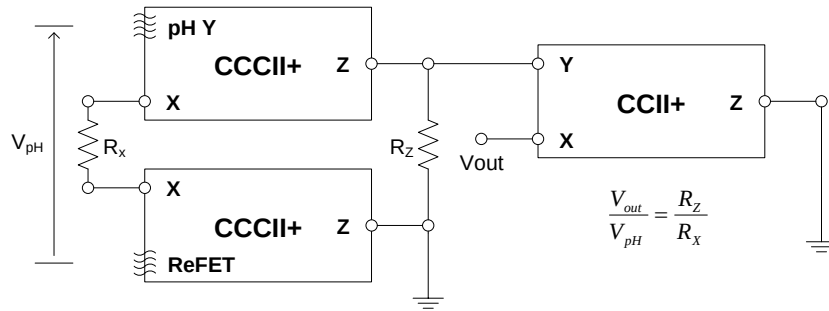


**Figure 4-46.** pH Instrumentation amplifier

To work out the voltage output expression of this instrumentation amplifier, first consider the current which being push into resister  $R_z$  which can be obtained from Equation 4-20 and rewritten here as the term of  $I_z$

$$I_z = \frac{V_{pH}}{R_x}$$

Making the voltage across resistor,  $R_z$ , equals to

$$V_Z = \frac{V_{pH}}{R_X} R_Z$$

The Z-node of upper CCCII+ is connected to the high input impedance Y-node of the CCII+. This device is configured as a voltage follower and so the voltage output of the circuit is

$$V_{out} = \frac{R_Z}{R_X} V_{pH}$$

**Equation 4-21**

where  $V_{pH}$  is the difference in pH between pH-CCCII+ and ReFET-CCCII+.

#### 4.7.2 Analog biochemical computation

As already mentioned, the CCCII+ has an inherent capability of providing analog computation. This useful feature of the CCCII+ device will be explored in detail within this section.

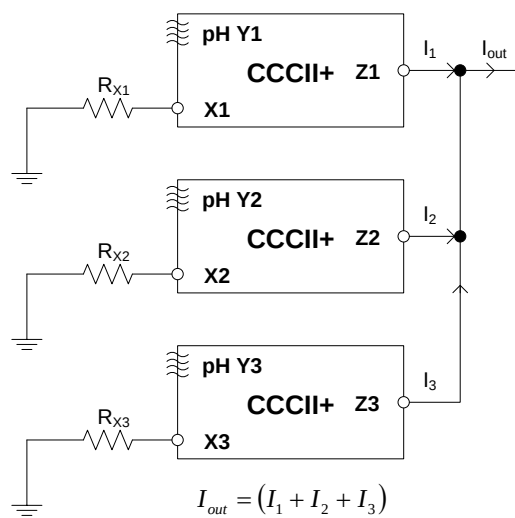


**Figure 4-47.** pH to I output summing

pH to current summation is readily achieved with CCCII+ by connecting the high output impedance Z-nodes as shown in Figure 4-47. The output current summing is possible because each Z-node is a high output impedance current source, so simply connecting them together sums the respective current outputs. Note that each CCCII+ device has a grounded resistor connected the X-node which effectively converts  $V_{pH}$  to  $I_{pH}$ . The current output expression is obtained as

$$I_{out} = (I_1 + I_2 + I_3)$$

Equation 4-22

In their original papers presenting the current-conveyor, Sedra & Smith [1-2] outlined a number of other current-mode analog computational elements, ranging from integrators and differentiators to more complex function generators. This advantage is inherited by the CCCII+ thus a pH integrator and a pH differentiator are relatively easily implemented, as shown in Figure 4-48 and Figure 4-49.

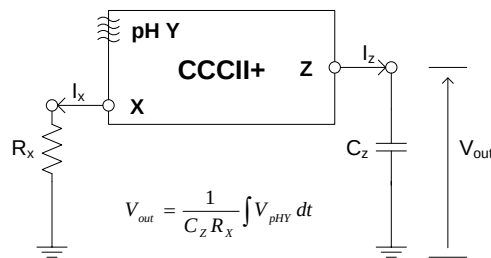


Figure 4-48. pH integrator

By placing a capacitor at the high output impedance Z-node and a resistor at the low output X-node to ground, a pH integrator circuit is created. This circuit is shown in Figure

4-48 provides an output voltage proportional to the time-integral of pH. The current  $I_X$  that flows through the resistor  $R_X$  is

$$I_X = \frac{V_X}{R_X}$$

where,

$$V_X = V_{pHY}$$

making

$$I_X = \frac{V_{pHY}}{R_X} = I_Z$$

Thus the CCCII+ is used here to convey the same current to the high impedance Z-node. This current  $I_Z$  flows through the capacitor  $C_Z$ , causing charge to accumulate on  $C_Z$ . And finally the capacitor voltage is denoted as an output  $V_{out}(t)$  of the circuit, thus

$$V_{out}(t) = \frac{1}{C_Z R_X} \int V_{pHY}(t) dt$$

**Equation 4-23**

Note that in this integrator, unlike the conventional op-amp Miller integrator, this circuit is not inverting.

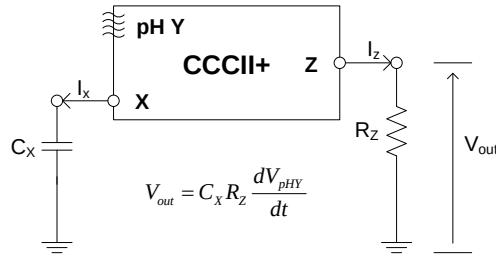


**Figure 4-49.** pH differentiator

Interchanging the location of the capacitor and the resistor of the pH integrator circuit results in the circuit shown in Figure 4-49, which performs the mathematical computation of differentiation. To see how this comes about, the analysis will start with the current  $I_X$  that through the capacitor  $C_X$  which is given by

$$I_X(t) = C_X \frac{dV_X(t)}{dt}$$

where

$$V_X = V_{pHY}$$

results in

$$I_X(t) = C_X \frac{dV_{pHY}(t)}{dt} = I_Z(t)$$

Because, same current also appears at the high impedance output Z-node due to the characteristic of CCCII+. Finally, the voltage across resistor  $R_Z$  is  $I_Z R_Z$  and the output voltage of the circuit is

$$V_{out}(t) = C_X R_Z \frac{dV_{pHY}(t)}{dt}$$

In voltage op-amp circuits with capacitor as part of the feedback network, the circuit may be unstable because the capacitor contributes phase lag. However, because of the absence of global negative feedback, these CCCII-based integrator and differentiator circuits do not experience the same potential instability problems. The circuits of Figure 4-48 and Figure 4-49 also utilise grounded rather than floating capacitors, which is an advantage for integrated circuit realisations.

### 4.7.3 Current-feedback Chemical Current-Conveyor

Monolithic current-feedback op-amps have relatively recently become commercially available as alternatives to voltage op-amps [20]. Examination of the internal structure of the current-feedback op-amp or CFOA is revealing as the device is essentially a CCII+ with the internal high impedance Z-node connected to an output voltage-follower, as shown in Figure 4-50 (a). The CCCII+, like the ‘parent’ CCII+, is an extremely versatile analog building block and can easily be configured as a CFOA, as shown in Figure 4-50 (b). Any current flowing into the low impedance inverting input is conveyed to the gain node ( $Z_T$ ) via the Z-node of the CCCII+. The resulting Z-node voltage is buffered to the output.  $Z_T$  is thus the open-loop transimpedance gain of the current-feedback op-amp, which in practice is equal to the parallel combination of the CCCII+ Z-node output impedance and the input impedance of the voltage buffer and any additional compensation capacitance at the gain, or  $Z_T$ , node.

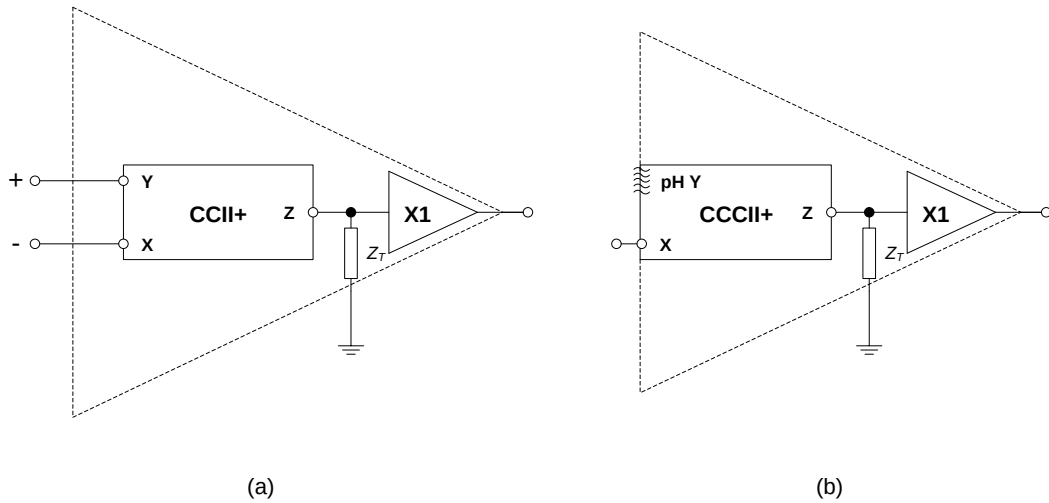


**Figure 4-50.** Comparison of (a) CCII+ [21] and (b) CCCII+ Current-feedback Op-amp structures

The circuit implementation of the CCCII+ based CFOA, Figure 4-50 (b), configured as a non-inverting closed-loop amplifier, is shown in Figure 4-51. The voltage follower of Figure 4-50 (b) is implemented by a CCII+ device and resistors  $R_f$  and  $R_g$  are the gain defining feedback components.

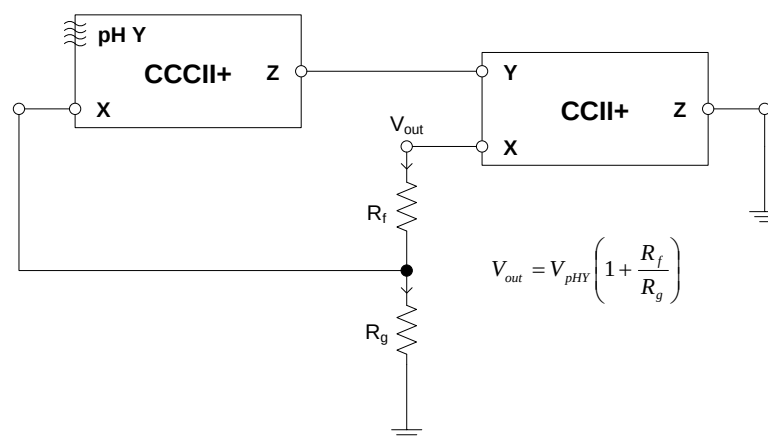


**Figure 4-51.** CCCII+ CFOA closed loop non-inverting pH amplifier

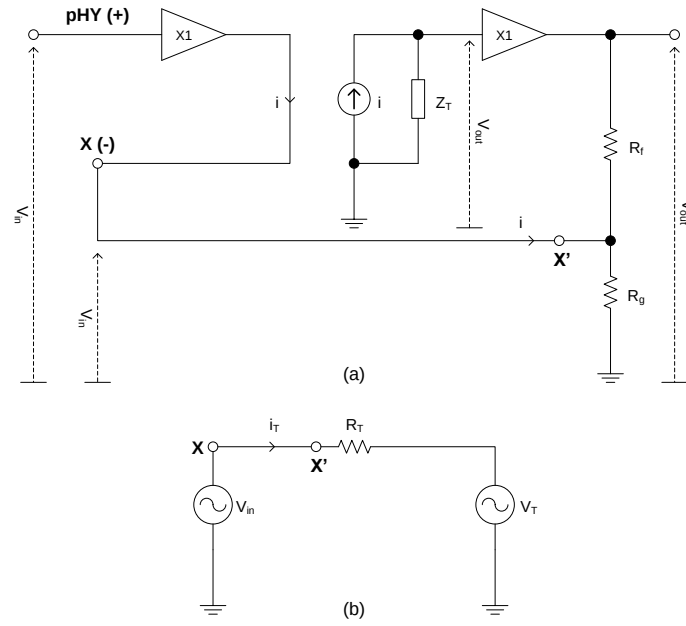


**Figure 4-52.** Analysis diagrams of CCCII+ CFOA: (a) Small signal analysis and (b) Thevenin theory analysis

The small signal analysis circuit diagram of the CCCII+ CFOA in Figure 4-51 is shown in Figure 4-52 (a). Thevenin theory can be applied at the X-node of Figure 4-51 and used to obtain the voltage output of the CCCII+ CFOA where the ‘Thevenin equivalent current’,  $i_T$ , is the same current  $i$  from Figure 4-52 (a) which is given as

$$i_T = \frac{V_{out}}{Z_T}$$

**Equation 4-25**

and the ‘Thevenin equivalent resistor’ is  $R_g$  and  $R_f$  in parallel, given as

$$R_T = \frac{R_g R_f}{R_g + R_f}$$

**Equation 4-26**

and the ‘Thevenin voltage’,  $V_T$ , is

$$V_T = \frac{R_g}{R_f + R_g} V_{out}$$

**Equation 4-27**

which is also equal to

$$V_T = V_{in} - i_T R_T$$

**Equation 4-28**

Substituting Equation 4-25, Equation 4-26 and Equation 4-27 into Equation 4-28 gives

$$\frac{R_g}{R_f + R_g} V_{out} = V_{in} - \frac{V_{out}}{Z_T} \frac{R_g R_f}{R_g + R_f}$$

**Equation 4-29**

and multiply both sides by  $(1/R_f R_g)$  gives

$$V_{out} \left( 1 + \frac{R_f}{Z_T} \right) = V_{in} \frac{R_f + R_g}{R_g}$$

**Equation 4-30**

which can be simplified to

$$\frac{V_{out}}{V_{in}} \frac{Z_T + R_f}{Z_T} = \frac{R_f + R_g}{R_g}$$

**Equation 4-31**

which can be rewritten as gain expression as

$$\frac{V_{out}}{V_{in}} = \left(1 + \frac{R_f}{R_g}\right) \left(\frac{Z_T}{Z_T + R_f}\right)$$

Equation 4-32

and usually  $Z_T$  is much larger than  $R_f$ , making the final output voltage of the CCCII+ CFOA as

$$V_{out} = V_{pHY} \left(1 + \frac{R_f}{R_g}\right)$$

Equation 4-33

where  $V_{pHY}$  is the input signal of the circuit which is proportional to pH.

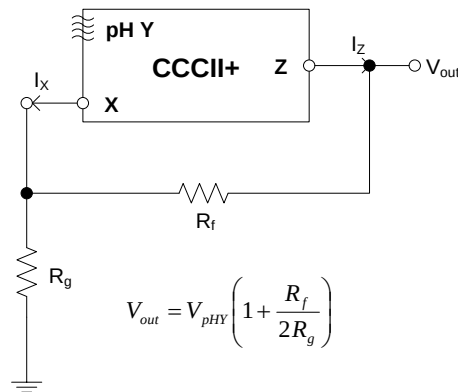


Figure 4-53. pH-CCCI+ Non-inverting feed-back pH amplifier

Feedback can be applied directly to the CCCII+ device as shown in Figure 4-51. The circuit is simpler than the Figure 4-51 amplifier in that no CCII+ or voltage buffer is required. However, the output impedance will not be particularly low because although the negative feedback does reduce the output impedance in closed-loop relative to the open-loop, it will not be as low as the voltage CCCII+ CFOA based design.

The analysis of the Figure 4-51 circuit is as follows. The current flowing into resistor  $R_g$  is the summation of X-node current and Z-node current, that is

$$I_{Rg} = I_X + I_Z$$

and since

$$I_X = I_Z = I$$

then,

$$I_{Rg} = 2I$$

Forcing the voltage at the X-node to be

$$V_X = 2IR_g$$

and since

$$V_X = V_{pHY}$$

Therefore,

$$V_{pHY} = 2IR_g$$

and

$$I = \frac{V_{pHY}}{2R_g}$$

Finally, the output voltage of the circuit shown in Figure 4-53 is obtained by adding the voltage across  $R_g$  and  $R_f$  together, which can be expressed as

$$V_{out} = V_{pHY} + \frac{V_{pHY}}{2R_g} R_f$$

which can be simplified and given as

$$V_{out} = V_{pHY} \left( 1 + \frac{R_f}{2R_g} \right)$$

**Equation 4-34**

#### 4.7.4 ‘Super’ ISFET

The background leading to the proposed the ‘super’ ISFET draws on the thinking behind the ‘ideal’ transistor described in Chapter 3. As can be identified by considering the source and drain impedances the ISFET, in common with any single transistor, is not ideal [7]. The concept described in this section is to create a functionally ideal ISFET using a modified CCCII+, shown schematically in Figure 4-54.

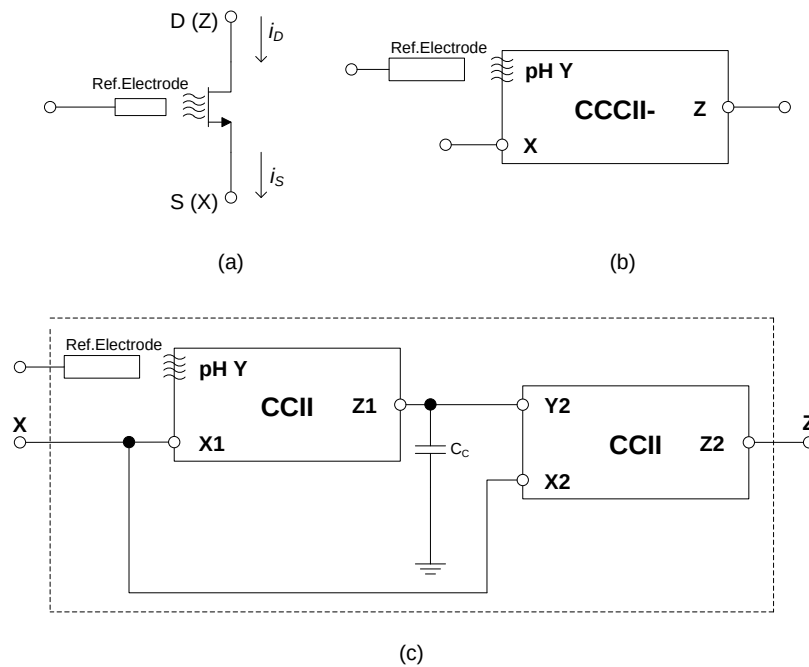


**Figure 4-54.** (a) single N-channel ISFET, (b) CCCII- and (c) Dual CCCII

The first step in realising the ‘ideal’ or ‘super’ ISFET of Figure 4-54 (a) is to consider the CCCII- as shown in Figure 4-54 (b). The net result is a reduction of equivalent source impedance which is now the X-node of the CCCII- and an increase of equivalent drain impedance which is now the Z-node. Also as the bias circuitry of the CCCII- must be in place, the created ‘ideal’ ISFET does not need any additional bias circuitry. This concept can be extended further by addition of a CCII as shown in Figure 4-54 (c). This CCII reduces the effective source impedance at X-node still further and the overall effective ISFET is even closer to the ‘ideal’ ISFET.

## 4.8 Summary of Chapter 4

In this chapter the CCCII+ has been taken from concept through design, simulation, layout to a monolithic biochemical measuring system. The technology platform used for practical implementation was a standard 0.35 $\mu\text{m}$  CMOS technology. Layout techniques to obtain good device matching using common-centroid methods were used. A multi-purpose test board was designed, built and used for practical device evaluation. This new device has been tested and its performance compared with the benchmark fixed  $V_{DS}$  and  $I_D$  readout circuit; the CCCII+ performing well in these tests. At the end of the chapter the inherent analogue computational capability of the chip is explored in preparation for use in Chapters 5 and 6, which will be devoted to two new areas of biochemical measurement, namely buffer index and urea to creatinine ratio.

## 4.9 References

- [1] K. C. Smith and A. Sedra, "The current conveyor - A new circuit building block," *Proceedings of the IEEE*, vol. 56, pp. 1368-1369, 1968.
- [2] A. Sedra and K. Smith, "A second-generation current conveyor and its applications," *Circuit Theory, IEEE Transactions on*, vol. 17, pp. 132-134, 1970.

- [3] C. F. Chan and M. H. White, "Characterization of surface and buried channel ion sensitive field effect transistors (ISFET's)," in *Electron Devices Meeting, 1983 International*, 1983, pp. 651-653.
- [4] R. A. Rani and O. Sidek, "ISFET pH sensor characterization: towards biosensor microchip application," in *TENCON 2004. 2004 IEEE Region 10 Conference*, 2004, pp. 660-663 Vol. 4.
- [5] A. Sibbald, "A chemical-sensitive integrated-circuit: the operational transducer," *Sensors and Actuators*, vol. 7, pp. 23-38, 1985.
- [6] H. S. Wong and M. H. White, "A CMOS-integrated 'ISFET-operational amplifier' chemical sensor employing differential sensing," *Electron Devices, IEEE Transactions on*, vol. 36, pp. 479-487, 1989.
- [7] C. Toumazou, *et al.*, *Analogue IC design: The current-mode approach*: Institution of Engineering and Technology, 1993.
- [8] P. Pookaiyaudom, *et al.*, "The chemical current-conveyor: a new microchip biosensor," in *Circuits and Systems, 2008. ISCAS 2008. IEEE International Symposium on*, 2008, pp. 3166-3169.
- [9] P. Bergveld, "Thirty years of ISFETOLOGY: What happened in the past 30 years and what may happen in the next 30 years," *Sensors and Actuators B: Chemical*, vol. 88, pp. 1-20, 2003.
- [10] A. S. Sedra and K. C. Smith, *Microelectronic Circuits*. New York: Oxford University Press, 2004.
- [11] K. Manetakis and C. Toumazou, "A new high-frequency very low output-impedance CMOS buffer," in *Circuits and Systems, 1996. ISCAS '96., 'Connecting the World'. 1996 IEEE International Symposium on*, 1996, pp. 485-488 vol.1.
- [12] C. Toumazou, *et al.*, "Emerging techniques for high frequency BJT amplifier design, a current-mode perspective," presented at the First International Conference on Electronics Circuits and Systems Cairo, Egypt, 1994.
- [13] P. Pookaiyaudom, *et al.*, "Measurement of urea, creatinine and urea to creatinine ratio using enzyme based chemical current conveyor (CCCII+)," *Sensors and Actuators B: Chemical*, vol. 153, pp. 453-459, 2011.
- [14] A. Hastings, *The Art of Analog Layout*, 2 ed.: Pearson Education, 2005.
- [15] E. Sicard and S. D. Bendhia, *Basics of CMOS Cell Design*: Tata McGRAW HILL 2006.

- [16] B. Palán, *et al.*, "New ISFET sensor interface circuit for biomedical applications," *Sensors and Actuators B: Chemical*, vol. 57, pp. 63-68, 1999.
- [17] C. Toumazou and F. J. Lidgey, "floating impedance converters using current conveyors," *Electron. Lett.*, vol. 21, pp. 640-642, 1985.
- [18] C. Toumazou, *et al.*, "Extending voltage-mode op amps to current-mode performance," *Circuits, Devices and Systems, IEE Proceedings G*, vol. 137, pp. 116-130, 1990.
- [19] C. Toumazou and F. J. Lidgey, "Novel current-mode instrumentation amplifier," *Electronics Letters*, vol. 25, pp. 228-230, 1989.
- [20] D. F. Bowers, "A precision dual 'current feedback' operational amplifier," in *Bipolar Circuits and Technology Meeting, 1988., Proceedings of the 1988*, 1988, pp. 68-70.
- [21] F. J. Lidgey and K. Hayatleh, "Current-feedback operational amplifiers and applications," *Electronics & Communication Engineering Journal*, vol. 9, pp. 176-182, 1997.

## Chapter 5

# Real-Time Buffer Capacity and Buffer Index Measurement using Chemical Current-Conveyor (CCCII+)

### 5.1 Introduction

The concept and development of the CCCII+ were described in the last chapter and successfully used to design a pH measurement system. The work described in this chapter uses the CCCII+ for a more advanced pH related measurement system, namely for measurement of buffer index/capacity [1]. A key part of the system design is exploitation of the CCCII+ which is capable of providing both pH and ‘real-time’ buffer capacity measurement, the latter being achieved by exploiting the inherent analogue computational capability of the imbedded CCII+ device within the CCCII+.

Being able to produce a ‘real-time’ value for buffer capacity is significantly more useful for clinical diagnosis than the classical static buffer capacity measurement systems employing a glass electrode, pH meter and subsequent computation to determine the

value of buffer capacity. The sensor system described here is capable of being produced as a monolithic integrated circuit and hence will be a very small dimension device by comparison. Furthermore, because the system exploits integrated circuit technology, it has the potential of being low cost, low power, reliable and versatile.

The penultimate section of this chapter describes a system, again exploiting the CCCII+, for verifying the capability of using an ISFET for millisecond time ion sensing. This confirms that the ISFET can be used not only for the more commonly encountered low speed applications, but also for relatively fast chemical synapse applications and rapid DNA sequencing techniques.

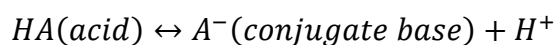
## 5.2 Buffer the fundamental acid/base concepts

Buffered solutions are increasingly important and are used in many applications in the laboratory and in medicine. In most biological and chemical processes, they are often necessary to maintain a constant pH value during the course of a reaction in which hydrogen ions  $H^+$  or hydroxide ions  $OH^-$  may be produced. Under these circumstances, the reaction is carried out in a buffer solution. Therefore, buffers provide resistance to change in pH of a solution when  $H^+$  or  $OH^-$  are added or removed. It is not possible for any buffer to resist these changes fully, but the buffer solution may reduce changes in pH [2]. Much of the chemical behaviour of seawater is determined by its pH and buffered at about 8.1 to 8.3 near the surface. However, the most important practical example of buffered solution is human blood, which can absorb the acids and bases produced in biological reactions without significant changes in pH. A 'constant' pH for blood is vital because cells can survive only within a very narrow pH range [3].

### 5.2.1 Acid/base buffer operation

The physical chemistry underlying the way that a buffer solution works is important and the following section is based on very clear discussions given in [1, 3-4]. In acid/base system, any buffer can resist changes in pH because the equilibrium between a form that has hydrogen ions bound,  $HA$  (acid, proton donor) and a form that has lost its hydrogen ions,  $A^-$  (base, proton acceptor).

The buffer contains both an acidic species to neutralize  $OH^-$  ions and a basic one to neutralize  $H^+$  ions. The acidic and basic species that make up the buffer must not consume each other through a neutralization reaction. These requirements can be fulfilled by a weak acid-base conjugate pair. Thus, buffers are often prepared by mixing a weak-acid with a salt (its conjugate base) or a weak-base with a salt (its conjugate acid).



**Equation 5-1**

The equation above shows a symbolic example of weak-acid and its conjugate base, where  $HA$  and  $A^-$  are generic symbols for an acid and its deprotonated form, the conjugate base, respectively. The acid-dissociation equilibrium in this buffered solution involves both the acid and its conjugate base and can be expressed as

$$K_a = \frac{[H^+][A^-]}{[HA]}$$

**Equation 5-2**

and solving for  $[H^+]$  the expression can be written as

$$[H^+] = K_a \frac{[HA]}{[A^-]}$$

Equation 5-3

It can be seen from the expressions above that  $[H^+]$ , and thus the pH, is determined by the value of  $K_a$  for the weak-acid component of the buffer and the ratio of the concentrations of the conjugate acid-base pair,  $[HA]/[A^-]$ . If a base is added to the buffered solution, the added  $OH^-$  will react with the acid component of the buffer to produce water and the base component,  $A^-$ . This reaction causes  $[HA]$  to decrease and  $[A^-]$  to increase. As long as the amounts of  $HA$  and  $A^-$  in the buffer are large compared with the amount of  $OH^-$  added, however, the ratio  $[HA]/[A^-]$  will not change much, and thus the change in pH will be small.

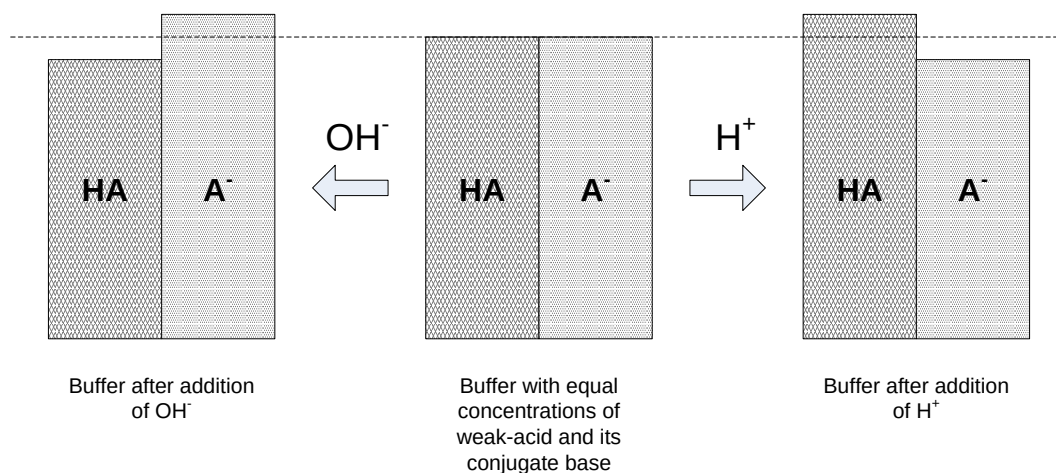


Figure 5-1. The ratio of the conjugate acid-base pair [3-4]

If an acid were added, the added  $H^+$  would react with the base component of the buffer as shown in the right of Figure 5-1. The reaction causes  $[A^-]$  to decrease and  $[HA]$  to

increase, however as long as the change in ratio  $[HA]/[A^-]$  is small, the change in pH will be small.

It should be note that by choosing the appropriate components, a solution can be buffered at virtually any pH value. However, buffers work most effectively in either direction when the concentrations of weak acid and conjugate base are about the same. From Equation 5-3 it can be seen that when the concentrations of weak acid and conjugate base are equal, that is  $[H^+] = K_a$ , therefore  $pH = pK_a$ . For this reason, it is desirable to select a buffer is  $pK_a$  close to the desired pH value. For any buffer system, the ability to maintain its pH value is generally defined as buffer capacity which will be described in the following section.

### 5.2.2 Buffer index/capacity and pH

Two important characteristics of a buffer are its capacity and its pH values. Buffer capacity, also referred to as a scale of buffer index,  $\beta$ , is the amount of acid or base the buffer can defuse before the pH begins to change [3] which depends on the amount of acid and base from which the buffer is made. According to Van Slyke [1, 5] this ability can be measured by the amount of strong-acid, or strong-base, required to produce a given change in pH. The Van Slyke buffer index,  $\beta$ , is given in the equation below,

$$\beta = -\frac{dC_a}{dpH} = \frac{dC_b}{dpH}$$

**Equation 5-4**

where  $C_a$  is the added amount of protons,  $H^+$ , and  $C_b$  is the added amount of hydroxide,  $OH^-$ , ions (or, equivalently, protons are removed from the solution) per litre of buffer

solution used to exert a measured shift in pH. The negative sign indicates the polarity of the added acid or base.

The pH of the buffer depends on the  $K_a$  for the acid and on the relative concentrations of the acid and base that comprise the buffer as shown in the *Henderson-Hasselbalch* Equation 5-7 which can be derived by first taking the negative log of both side of Equation 5-3. The expression obtained is

$$-\log_{10}[H^+] = -\log_{10}\left(K_a \frac{[HA]}{[A^-]}\right) = -\log_{10} K_a - \log_{10} \frac{[HA]}{[A^-]}$$

**Equation 5-5**

since  $-\log_{10}[H^+] = pH$  and  $-\log_{10} K_a = pK_a$ , the above equations simplify to

$$pH = pK_a - \log_{10} \frac{[HA]}{[A^-]} = pK_a + \log_{10} \frac{[A^-]}{[HA]}$$

**Equation 5-6**

In general pH can be written as,

$$pH = pK_a + \log_{10} \frac{[base]}{[acid]}$$

**Equation 5-7**

where  $[acid]$  and  $[base]$  refer to the equilibrium concentrations of the conjugate acid-base pair. Note that when  $[base] = [acid]$ ,  $pH = pK_a$ .

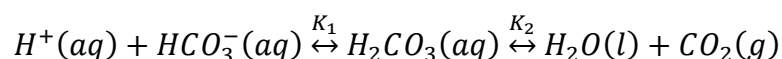
### 5.2.3 Buffer capability of blood

The physical chemistry underlying the behaviour of blood as a buffer solution is important and the following section is based on the discussion given in [3]. Many of the

chemical and biochemical reactions that occur in the human body are extremely sensitive to pH, which only varies within a narrow range. For this reason the human body maintains a complex system of buffers, both within tissue and in the fluids that transport cells. Blood is the fluid that transports oxygen to different parts of the body, and its ability to maintain an almost constant pH value is vital.

Human blood performs many important tasks within the body. One of which is to exchange chemicals in cells and tissues such as nutrients, waste products, and ions. These chemical changes, unless offset by other physiological functions, cause blood pH to drop and if the value of pH becomes too low, a condition known as acidosis may occur. On the other hand, if the pH rises too high, the condition is called 'alkalosis'. Acidosis is the more common tendency and can be very serious because many of the chemical reactions within the body, especially those involving proteins, are pH dependent. Ideally, the pH of the blood should be maintained around 7.4 and if pH drops below 6.8 or rises above 7.8, this may be fatal. Fortunately, human blood has a capacity to resist large change in pH, thereby keeping the variation to a minimum. This is referred to as the buffer capacity of blood.

The *carbonic acid-bicarbonate* buffer system is the major buffer system within blood that controls the pH. Carbonic acid,  $H_2CO_3$ , and bicarbonate ion,  $HCO_3^-$ , are a conjugate acid-base pair. In addition, carbonic acid can change and decompose into carbon dioxide gas and water. The important equilibria in this buffer system are shown below in Equation 5-8 [3].



**Equation 5-8**

Several aspects of these equilibria are notable. Firstly, the equilibrium on the left is an acid-base reaction with carbonic acid,  $H_2CO_3$  is the acid and bicarbonate ion,  $HCO_3^-$  as its conjugate base. Secondly, although carbonic acid is a diprotic acid, the carbonate ion ( $CO_3^{2-}$ ) is not important in this system [3]. Thirdly, the equilibrium on the right of the equation is not an acid-base reaction. The gas  $CO_2$  is one of the components of this equilibrium which provides a mechanism for the body to adjust the equilibria. Removal of  $CO_2$  via exhalation shifts the equilibria to the right, consuming  $H^+$  ions. Fourthly, the buffer system in the blood operates at a pH of 7.4, which is far from the  $pK_{a1}$  value of  $H_2CO_3$  which is pH of 6.1 at physiological temperature. In order for the buffer to have a pH of 7.4, the value of about 20 in the ratio of  $[base]/[acid]$  is required. In normal blood plasma the concentration of  $HCO_3^-$  and  $H_2CO_3$  are 0.024M and 0.0012M, respectively [3]. As a consequence, the buffer has a high capacity to neutralize additional acid, but low capacity to neutralize additional base.

The principal organs that help regulate the pH of the *carbonic acid-bicarbonate* buffer system when the addition of protons to the blood due to heavily metabolic processes perhaps by strenuous exercise, which maybe too great for the buffer alone to effectively control the pH of the blood, are the lungs and kidneys [6]. When this happens, some of the receptors in the brain that are sensitive to the concentrations of  $H^+$  and  $CO_2$  in the body fluids are triggered causing faster and deeper breathing. The result is an increase in the rate of elimination of  $CO_2$  from the lungs hence, which helps to raise the pH level via shifts in the equilibria in Equation 5-8, and the kidneys remove excess  $HCO_3^-$  from the body helping to lower the pH.

### 5.3 Chemical Current-Conveyor for buffer index/capacity ( $\beta$ ) measurement

The discussion above confirms that an instrumentation system that is capable of providing both the pH value together with the  $\beta$  would be significantly more useful for clinical analysis than a system that provides the pH value alone. Using Equation 5-4 an alternative representation of the buffer index value,  $\beta$ , is given by the ratio of time derivatives of  $C_a$  and pH, that is

$$\beta = \frac{dC_a}{dt} \div \frac{dpH}{dt}$$

**Equation 5-9**

The analogue computing capability of the CCCII+ can be used to obtain the time derivative of pH as shown below in Figure 5-2. If the time derivative of  $C_a$  is a known value, then the value of  $\beta$  can be readily obtained [7].

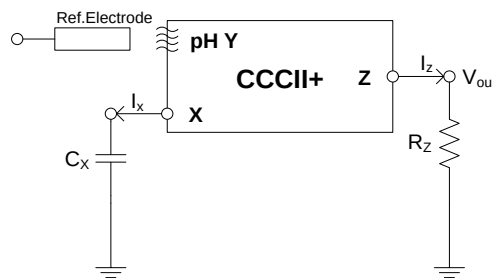


**Figure 5-2.** pH-differentiator using CCCII+ [7]

A CCCII+ system configuration to achieve this  $\beta$  evaluation is shown in Figure 5-3 (a). An alternative approach in the implementation of CCCII+ is also demonstrated in Figure

5-3 (b), in which the CCCII+ functional behaviour is realised by a circuit comprised only of ‘off-the-shelf’ components. Note that, OA2 and OA3 are conventional voltage-mode op-amps, and the current-feedback, OA4, is again a conventional device.

Referring initially to Figure 5-3 (a), the buffer solution is fed with an AC current source provided by OA1 and its associated circuitry, which is configured as a transconductance or voltage to current converter. This AC current flows between ‘reference electrode 2’, and the ‘platinum working electrode’ and it modulates the protons in the buffer solution, and hence sets  $(dC_a/dt)$  to a fixed value. As shown in Figure 5-3 (b) the ISFET, which is immersed in the buffer solution, is biased by the DC current sink  $I_{Bias2}$ . The CCCII+ is configured as a differentiator, and the output obtained is the time derivative of pH.

In Figure 5-3 (b), OA2 and OA3 are both connected as voltage followers, the latter providing  $V_{pHY}$  input to the non-inverting terminal of OA4. The DC current source,

$I_{Bias1}$ , ensures that the voltage across the 5K1 resistor is constant, and equal  $V = (I_{Bias1} \times 5k1)$ . This voltage is the value of  $V_{DS}$  for the ISFET which ensures that it is in the right region of operation for pH measurement. The final part of the circuit is a current conveyor type +II, or CCII+ realised by the current-feedback op-amp, OA4, with the output taken from the transimpedance terminal- $Z_T$  of OA4. As a result the output voltage,  $V_{out}$ , which is taken from Z-node of the CCCII+ pH-differentiator, will be proportional to the time derivative of pH and therefore proportional to  $(-\beta^{-1})$ . As shown in Chapter 4 the output is given by

$$V_{out}(t) = C_X R_Z \left( \frac{dV_{pH}(t)}{dt} \right)$$

Equation 5-10

which can be simplified to

$$\frac{dV_{pH}(t)}{dt} = \frac{V_{out}(t)}{C_X R_Z}$$

Equation 5-11

and by substituting Equation 5-11 for the pH-divertive term in Equation 5-9,  $\beta$  can be expressed as

$$\beta = \frac{dC_a}{dt} \div \frac{V_{out}(t)}{C_X R_Z}$$

and

$$\beta = \frac{dC_a}{dt} \times \frac{C_X R_Z}{V_{out}(t)}$$

Equation 5-12

Since  $C_X R_Z$  is the differentiator time-constant and the time derivative of  $C_a$  is a known constant, then the relationship between the voltage output of the circuit is inversely related to  $\beta$  and can be written as

$$V_{out}(t) = \alpha \beta^{-1}$$

**Equation 5-13**

where  $\alpha$  is all of the constant terms grouped together. It should be noted that in practice, it is important to choose values for  $C_X$  and  $R_Z$ , and hence the time-constant of the differentiator  $\tau = C_X R_Z$  such that  $\tau$  is appropriate for the given input frequency. Table 5-1 shows the parameters of the system in Figure 5-3 that were used for an input signal test frequency of 100mHz.

**Table 5-1.** The parameters of the buffer capacity/index measurement system

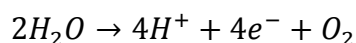
| Component          | Value                           |
|--------------------|---------------------------------|
| Ref. Electrode 1   | Ag/AgCl                         |
| Ref. Electrode 2   | Ag/AgCl                         |
| Working Electrode  | Platinum                        |
| Supply (Vdd1&Vss1) | ±6V                             |
| Supply (Vdd2&Vss2) | ±6V                             |
| ISFET              | NMOS ISFET by sentron (OEM-679) |
| $R_{IN}$           | 1kΩ                             |
| $C_X$              | 2200uF                          |
| $R_Z$              | 680Ω                            |

## 5.4 Operation of the Chemical Current-Conveyor for buffer index/capacity measurement

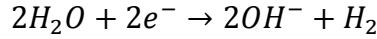
The physical geometry of ‘reference electrode 2’ and the ‘platinum working electrode’, shown in Figure 5-3 (a), does not matter as long as the solution is stirred continuously ensuring that the solution is homogeneous. Clearly, this system will measure global pH/buffer capacity, not local pH/Buffer capacity. However, the system could be developed further by miniaturisation so that all the electrodes and the ISFET are in close proximity, thus obviating the need to stir the fluid. Such miniaturisation is feasible if the full system, including the CCCII+, is realised as a monolithic integrated circuit device.

The electrochemical acid/base titration method is used to modulate ions such as protons,  $H^+$  in the buffer solution with high accuracy [8], and hence  $dC_a/dt$  may be set to a fixed and known value. This is achieved by driving the ‘reference electrode 2’ and the ‘platinum working electrode’ with a square waveform alternating current of  $\pm 0.6\text{mA}$  with the frequency of  $100\text{Hz}$ . This current value is set by  $(V_{IN}/R_{IN})$  because OA1 is configured as a voltage to current converter. Acid or base concentrations can be determined by performing an acid/base titration with coulometrically generated  $OH^-$  or  $H^+$  ions at an actuator electrode. The titrant can be generated by the electrolysis of water at a noble metal actuator electrode. When a current is applied to the electrodes, water molecules in the solution will undergo the electrochemical reaction at the electrodes, depending on the direction of the current [8-10].

At the anode, oxidation of water occurs as



and at the cathode, reduction of the water occurs as



**Equation 5-15**

Now consider a voltage to current converter system such as OA1 in Figure 5-3 (a) is being placed in a HEPES buffer solution. At  $t = 0$  the alternating current ( $V_{IN}/R_{IN}$ ) will start to flow through ‘reference electrode 2’ and the ‘platinum working electrode’ to the low-output impedance terminal of OA1, causing the generation of  $H^+$  and  $OH^-$  ions, according to Equation 5-14 and Equation 5-15. In this case, the ‘platinum working electrode’ shown in Figure 5-3 (a), acts as an anode and  $H^+$  ions will be generated when the applied current is in the negative half-cycle. The opposite occurs in the positive half-cycle during which time  $OH^-$  ions will be generated as the ‘platinum working electrode’ is now becomes the cathode. Both electrochemical reactions caused a change in the pH of the solution. It should be noted that ‘reference electrode 2’ which is placed in the HEPES buffer solution is packed in the glass vessel containing 3M-KCl with a porous glass frit at the end. The porous glass frit allows electrical conductivity between the HEPES buffer solution and the internal filling solution, while preventing convective mixing of the two solutions. Hence, the effect of the chemical reaction from ‘reference electrode 2’ is negligible [7], where the current flow through the reference electrode is not significant. As a result, a change in the source voltage of the ISFET due to the global pH change can be achieved and therefore the buffer capacity of tested HEPES buffers can be obtained using the CCCII+.

## 5.5 Measured results and discussion

The circuit of Figure 5-3 was constructed using conventional commercial discrete components on a prototype board and its performance evaluated. The LMC6001 op-amp was selected for OA1, OA2 and OA3 as suitable for this application in terms of ultra-low input current and noise. In fact the LMC6001 can provide almost noiseless amplification from a high resistance signal source. Even though the gain-bandwidth product of this op-amp is at 1.3MHz, it is more than enough for most biochemical applications where fast biochemical sensing, such as chemical synapse and rapid DNA sequencing, only required the response time in the order of millisecond or 1kHz [11-12]. The current-feedback op-amp (CFOA) chosen for OA4 was the AD844 as this device conveniently provides a pin connected to the  $Z_T$ -node of the CFOA that enables it to be used as a CCII+ device [7].

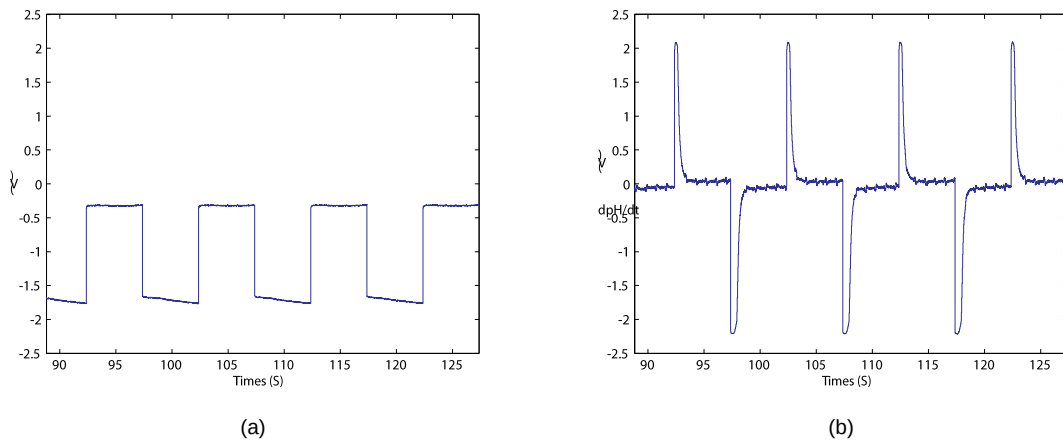


**Figure 5-4.** [7] HEPES concentration at 5.0mM (10 times diluted). (a) Voltage  $\propto$  pH at X-node (see Figure 5-3 (b)), (b)  $dpH/dt$  at Z-node (see Figure 5-3 (b))

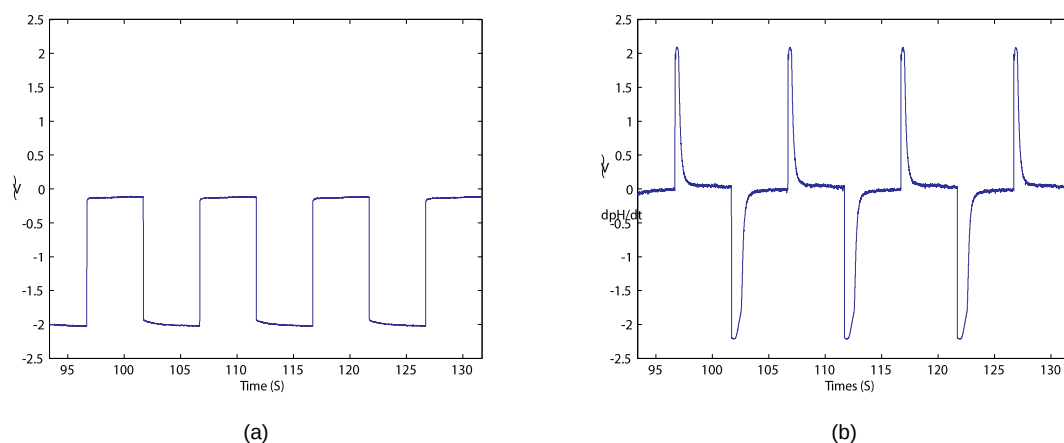


**Figure 5-5.** [7] HEPES concentration at 1.0mM (50 times diluted). (a) Voltage  $\propto$  pH at X-node (see Figure 5-3 (b)), (b)  $dpH/dt$  at Z-node (see Figure 5-3 (b))

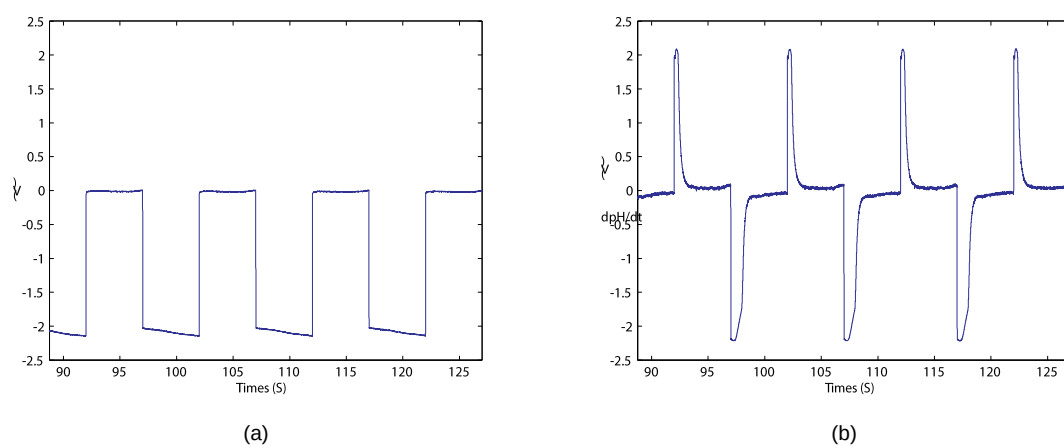


**Figure 5-6.** [7] HEPES concentration at 0.5mM (100 times diluted). (a) Voltage  $\propto$  pH at X-node (see Figure 5-3 (b)), (b)  $dpH/dt$  at Z-node (see Figure 5-3 (b))

Verification of the buffer index measurement system based of Figure 5-3 (a) is shown in the oscilloscope (voltage~time) plots of Figure 5-4 through to Figure 5-6. The plots are all for the same value of pH 6.84 and sample volume of 10mL, but with different solution

concentrations as shown in Table 5-2. The three figures, Figure 5-4 (a), Figure 5-5 (a) and Figure 5-6 (a) show the graphs of the voltage proportional to pH which is taken from X-node shown in the system diagram of Figure 5-3 (a).

The next set of plots, namely Figure 5-4 (b), Figure 5-5 (b) and Figure 5-6 (b) show the graphs of the rate of change of pH with time, ( $dpH/dt$ ), which is taken from Z-node shown in the system diagram of Figure 5-3 (a). It can be seen that the DC voltage at the X-node is negative due to the bias on the ISFET. This could be changed with the addition of a DC level shift circuit to the system shown in Figure 5-3 (a) should this be required.

**Table 5-2.** Parameters and results of buffer capacity/index ( $\beta$ ) measurement [7]

| Solution | pH   | HEPES concentration | Mean of ( $dpH/dt$ ) |
|----------|------|---------------------|----------------------|
| (a)      | 6.84 | 5.0mM               | 0.0321               |
| (b)      | 6.84 | 1.0mM               | 0.0532               |
| (c)      | 6.84 | 0.5mM               | 0.0732               |

The final column in Table 5-2 is the mean value of  $dpH/dt$ , and as can be seen from the results, the pH of the dilute solution will be affected most for the same amount of generated  $H^+$ , and so on, from which we can conclude, as expected, that the more concentrated solution has a higher buffer capacity than the weaker solution. The absolute value of  $\beta$  has not been obtained as this will require further computational circuitry to provide inversion and multiplication to obtain  $\beta$ . Alternatively, a ‘look-up-table’ approach could be developed to provide the final  $\beta$  figure. However, the main purpose of this work has been to verify the feasibility of using the CCCII+ to measure both pH and

$\beta$ . This has been achieved and the principle of the measurement system has been confirmed.

## 5.6 Measurement of ISFET response time

The majority of applications of the ISFET to date are for static or long term pH measurements. However, there are applications in biomedical electronics that require fast sensing of ion activity, such as chemical synapse and rapid DNA sequencing [11-12]. The objective of this research is to demonstrate that the ISFET can be adapted for successful operation to measure millisecond ion stimulation. Woias et al [13] used a complex flow-injection system with a solenoid valve as the mechanism to introduce millisecond pH perturbations in an ISFET pH measurement test rig. However, Van der Schoot et al [8] proposed a less complex method to create pH perturbation using electrochemical generation but with slower time responses in order of seconds.

In this section, the author reports an alternative electronic technique which verifies that the ISFET is able to detect fast proton ( $H^+$ ) changes in the order of a few milliseconds. With this technique, a circuit is used to create an input pH signal for the ISFET in the millisecond range, as in [8], but using a simpler and more practical method of proton ( $H^+$ ) introduction, known as iontophoresis. The results obtained are used to determine the factors that affect the high speed chemical sensing with an ISFET and how it is influenced by the time period of the injected ion signal.

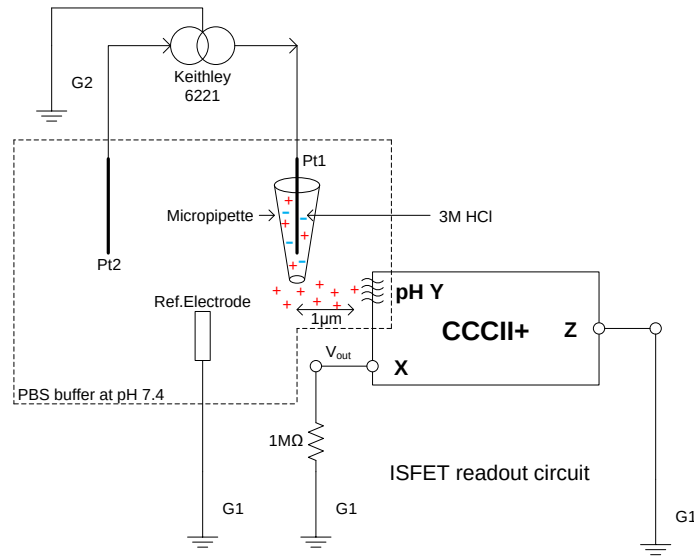


**Figure 5-7.** Measurement system for determination the response time of the ISFET [14]

### 5.6.1 Circuit operation and description

The proposed circuit is shown in Figure 5-7. It consists of three main parts, namely (i) the iontophoresis system, formed by a current-source (Keithley 6221) and two platinum wires (Pt1 and Pt2) where one of which is in the micropipette, (ii) the phosphate buffer saline (PBS) solution, and (iii) the ISFET readout circuit, which is based on the Chemical Current-Conveyor (CCCII+) [15]. The Keithley 6221 current source is simply used to supply a small signal current (in the microampere range), to perform iontophoresis. This signal current is fed through ‘Pt1’ to ‘Pt2’. Furthermore, a high concentration of hydrochloric acid ( $HCl$ ) was placed in a glass micropipette in which ‘Pt1’ is submerged. To monitor the local pH change, the micropipette was placed vertically on top of the ISFET surface and controlled by the micromanipulator to be approximately one micron from the surface of the ISFET. When a positive current is applied to ‘Pt1’, the anions ( $Cl^-$ ) are maintained inside the chamber whereas the cations ( $H^+$ ) are repelled and injected into the PBS solution. The amount of injected  $H^+$  depends on the applied signal

current and injection period. In this case, the detected  $H^+$  can be related to the diffusion equation as shown in Equation 5-16. With constant applied signal current ( $i$ ), the amount of  $H^+$  added to the solution will be proportional to the applied period [16] as shown in Equation 5-16.

$$H^+ = \frac{it}{F4\pi Dr} \operatorname{erfc}\left(\frac{r}{2\sqrt{Dt'}}\right)$$

**Equation 5-16**

where  $D$  is the diffusion coefficient of  $H^+$ ,  $F$  is Faraday's constant,  $r$  is the distance between micropipette tip and ISFET surface,  $t'$  is time and  $t$  is the transport number. Longer injected period will provide higher transport number,  $t$ , resulting in larger change of local pH.

It should be noted that all experiments were done in a PBS solution with a pH 7.4 which matched pH within the human body. The ISFET that was used is manufactured by Sentron Europe (Roden, The Netherlands, part no, OEM-679) and was connected and monitored versus a silver/silver chloride reference electrode ( $Ag/AgCl$ ) for all experiments.

As reported in [15] the operation of CCCII+ can be seen as follows. The voltage at the low input impedance X-node follows that at the high input impedance pH\_Y-node, while the input current at the X-node is mirrored or 'conveyed' to the high output impedance Z-node. In Figure 5-7 the output signal,  $V_X$ , is taken from the X-node of the CCCII+ which is directly proportional to pH stimulus and is given by

$$V_X = V_{pH} = I_{ds}R_s = C_{ox}\mu \frac{W}{L} \left[ (V_{gs} - V_{th(ISFET)})V_{ds} - \frac{1}{2}V_{ds}^2 \right] R_s$$

**Equation 5-17**

where  $C_{ox}\mu(W/L)$  is the semiconductor parameter of the ISFET and  $R_s$  is the equivalent source resistance of the ISFET.

### 5.6.2 Result and discussion

The circuit of Figure 5-7 was constructed and tested. Practical results are shown in Figure 5-8 to Figure 5-9. In order to verify that the ISFET can sense the change of protons released in a fast response time, injected periods in the order of millisecond were applied and shown in Figure 5-8. It can be seen that the ISFET responds within 1ms but 0.1ms changes were not detected. With longer injection times, larger response was obtained which agrees with Equation 5-16. Satisfactory repeatability of response was achieved by successive proton injections.

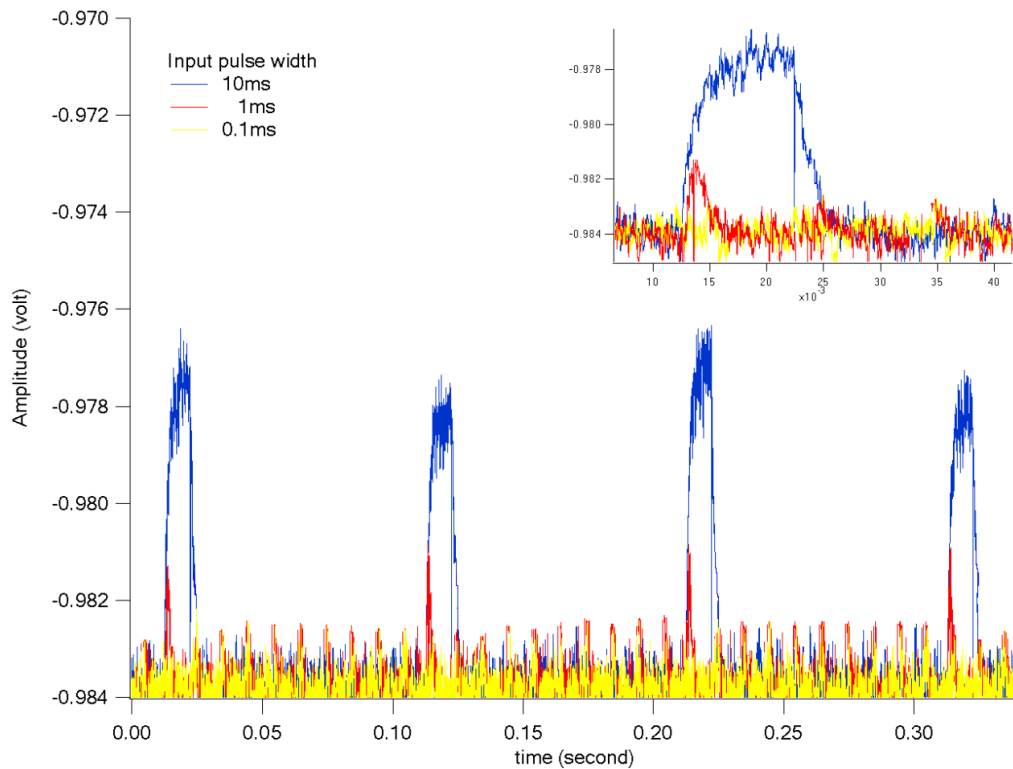


**Figure 5-8.** Measured result of three different injected periods at 1  $\mu\text{m}$  distance between micropipette tip and ISFET surface (insert is a ‘Zoom in’ of the measured result included) [14]

The pH response at a 1ms injection period was further investigated by changing the applied current of proton injection as shown in Figure 5-9. The amplitude of current signal was varied from  $0.6\mu\text{A}$  to  $1.0\mu\text{A}$  whilst the pulse duration was kept at 1ms. As a result, the greater the amplitude of current injected, the larger delta pH ( $\Delta\text{pH}$ ) signal sensed from the ISFET which is consistent with Equation 5-16. Therefore, this again confirms that the ISFET is able to detect a change of pH perturbing beyond a millisecond. The final test used a negative amplitude,  $-1\mu\text{A}$ , of injection current and as expected the ISFET did not respond, which is correct as it is only sensitive to proton changes.

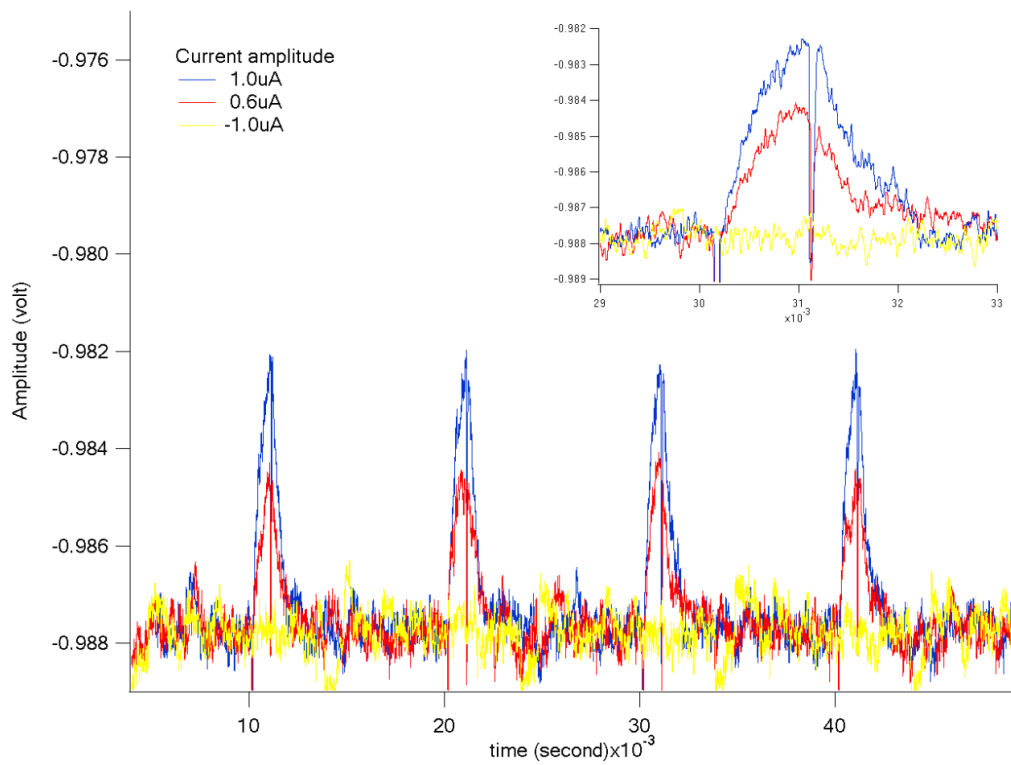


**Figure 5-9.** Measured result of three different current amplitudes at a fixed injected period of 1ms and  $1\mu\text{m}$  distance between micropipette tip and ISFET surface (insert is a 'Zoom in' of the measured result included)

## 5.7 Summary of Chapter 5

In this chapter, the versatility of the CCCII+ has been utilised for use in buffer index ( $\beta$ ) measurement. Preliminary results show that the system in Figure 5-3 is capable of producing a useful clinical instrument providing simultaneous outputs of both pH and  $\beta$ . Both method and the practical realisation of obtaining pH and  $\beta$  are to the author's knowledge novel. It should be noted that the system is able to produce an output proportional to  $\beta$  but not yet able to provide the absolute value of  $\beta$ . In addition, a system has been developed to verify that the ISFET is capable of being used for fast ion sensing applications, in the order of millisecond response time. In the next chapter, the CCCII+ will be applied to development of a measuring system to assist renal diagnosis, namely measurement of urea and creatinine.

## 5.8 Reference

- [1] M. F. C. L. H. Lee, *Modern physical chemistry: an introduction*: The Penguin library of physical sciences: Chemistry, 1969.
- [2] R. J. Beynon and J. S. Easterby, *Buffer Solutions: The Basics*: IRL Press Oxford University, 1996.
- [3] T. L. Brown, *et al.*, *Chemistry: The Central Science*. U. S. A.: Prentice Hall, 2000.
- [4] S. S. Zumdahal and S. A. Zumdahl, *Chemistry*, 5 ed. New York: Houghton Mifflin, 2000.
- [5] C. Sorokin, "Van Slyke's buffer values for cell secretions," *Protoplasma*, vol. 60, pp. 79-85, 1965.
- [6] A. Vander, *et al.*, "Haman Physiology," ed. Boston: WCB McGraw-Hill, 1994.
- [7] P. Pookaiyaudom, *et al.*, "Chemical current conveyor (CCCI+): System design and verification for buffer index/capacity measurement," *Sensors and Actuators B: Chemical*, vol. 147, pp. 228-233, 2010.

- [8] B. van der Schoot and P. Bergveld, "An ISFET-based microlitre titrator: integration of a chemical sensor--actuator system," *Sensors and Actuators*, vol. 8, pp. 11-22, 1985.
- [9] W. Olthuis and P. Bergveld, "Simplified design of the coulometric sensor--actuator system by the application of a time-dependent actuator current," *Sensors and Actuators B: Chemical*, vol. 7, pp. 479-483, 1992.
- [10] W. Olthuis, *et al.*, "A dipstick sensor for coulometric acid-base titrations," *Sensors and Actuators*, vol. 17, pp. 279-283, 1989.
- [11] S. Thanapitak and C. Toumazou, "Towards a bionic chemical synapse," in *Circuits and Systems, 2009. ISCAS 2009. IEEE International Symposium on*, 2009, pp. 677-680.
- [12] S. Purushothaman, *et al.*, "Towards fast solid state DNA sequencing," in *Circuits and Systems, 2002. ISCAS 2002. IEEE International Symposium on*, 2002, pp. IV-169-IV-172 vol.4.
- [13] P. Woias, *et al.*, "Modelling the short-time response of ISFET sensors," *Sensors and Actuators B: Chemical*, vol. 24, pp. 211-217, 1995.
- [14] S. Thanapitak, *et al.*, "Verification of ISFET response time for millisecond range ion stimulus using electronic technique," *Electronics Letters*, vol. 47, pp. 586-588, 2011.
- [15] P. Pookaiyaudom, *et al.*, "The chemical current-conveyor: a new microchip biosensor," in *Circuits and Systems, 2008. ISCAS 2008. IEEE International Symposium on*, 2008, pp. 3166-3169.
- [16] E. Neher and H. D. Lux, "Rapid Changes of Potassium Concentration at the Outer Surface of Exposed Single Neurons during Membrane Current Flow," *The Journal of General Physiology*, vol. 61, pp. 385-399, 1973.

## Chapter 6

# Real-Time Measurement of Urea, Creatinine and Urea to Creatinine Ratio using Enzyme Based Chemical Current-Conveyor (CCCII+)

### 6.1 Introduction

The trend towards personalised healthcare requires early detection and diagnosis of any adverse medical condition [1]. One of the key indicators of renal dysfunction is an increase of urea concentration in the blood. Thus, measurement of the concentration of urea in blood is extremely useful for diagnostic purpose. However, a rise in urea may not always be a correct indicator of renal failure [2-4]. A more precise picture to be distinguished and predicted is obtained with a combination of urea and creatinine measurements, including the ratio of urea-to-creatinine [5] as shown in Table 6-1. These ratios indicated the type of renal disease and what medical intervention is required.

**Table 6-1.** Urea to Creatinine ratio ranges and implication [3, 6]

| Urea: Creatinine ratio | Location of renal disorder                   |
|------------------------|----------------------------------------------|
| >100:1                 | Pre-Renal Disease (before glomeruli)         |
| 100:1 to 40:1          | Normal or Post-Renal Disease (within ureter) |
| <40:1                  | Intra-Renal Disease (within kidneys)         |

A proposed novel ISFET based biosensor for real time monitoring of creatinine and urea was reported in 2007 [7]. However, the system is relatively complex and provides output of creatinine and urea, but not the ratio of urea to creatinine. Also the design cannot easily be implemented in single chip form. Following on from this work, Juffali et al [3] proposed a novel ISFET based Urea to Creatinine sensor working in the sub-threshold region that employs the translinear circuit principle [8] as the key analog computational part of the system to perform the ratio function. However, the system will only produce the ratio, not the values of urea and creatinine separately and has not yet been implemented in practice. In addition, the author of this thesis believes that further work is required to ensure that in practice the uses of a single reference electrode in a balance two ISFET circuit can operate successfully.

In the previous chapter, the versatile CCCII+ was used very effectively in the development of a novel measurement system for  $\beta$  determination. Using a similar approach in this chapter the CCCII+ is exploited as an ‘off-the-shelf’ component to the development of a continuous-time biochemical measurement system. The design objective is for it to be able to deliver the three important parameters for predication of renal condition, namely (i) urea concentration, (ii) creatinine concentration and (iii) urea-to-creatinine ratio. The system that has been developed is based on two enzyme modified chemical current-conveyors, one for sensing the urea and the other for sensing the

creatinine. The ratio of these two parameters is also provided by direct analogue signal processing to give the third output above.

## 6.2 Renal disorders

Renal failure might happen quickly, resulting in the set of symptoms of acute renal failure (ARF). If the patient survives, the condition may be reversible and normal renal function may resume. This is not the case in chronic renal failure (CRF) which generally develops over many years and cannot be reversed, leading to ‘end stage renal failure’. Patients suffering from such a condition will need either dialysis or transplant if survival is to be achieved. The renal system ceases to operate correctly when ARF occurs, resulting in retention of creatinine, urea, hydrogen ions etc. Although potentially reversible, the condition is potentially life threatening if not reversed, which may not be achievable with patients who are already very ill.

ARF can be divided into 3 categories of disfunction: (i) decrease in renal blood flow, referred to as ‘pre-renal’, (ii) intrinsic damage to the kidneys, referred to as ‘intrinsic’, and (ii) obstruction to the urinary tract, referred to as ‘post-renal’. If any of the above occur for a patient with a pre-existing renal condition, the consequences are less favourable.

Irreversible renal failure or CRF may be caused by many diseases which can lead to an irreversible decline in renal function. For example, diabetes mellitus, glomerulonephritis, pyelonephritis, hypertension, polycystic kidneys and renovascular disease are the most common causes that can readily be identified. All of these lead to a reduction in the number of functioning nephrons, and the consequences are serious with significant medical intervention, such as dialysis or transplantation, no longer an option. The time

from the onset of CRF to end-stage renal failure may be a matter of weeks to several years, depending on several factors including appropriate control of blood pressure.

### 6.3 ISFET as a versatile biosensor

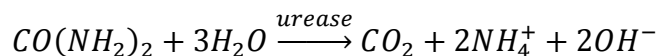
Not long after the ion sensitive field effect transistor (ISFET) had been introduced by Bergveld [9], many biosensors based on the ISFET were created after that. In 1980, Caras and Janata described the first pH-ISFET based enzyme modified biosensor sensitive to penicillin and the name EnFET was introduced for this sensor [10]. The term EnFET refers to the ability of the modified ISFET to respond to other enzymes. In comparison with other types of biosensors, the ISFET has several well-known advantages such as integrate-ability, scalability, high sensitivity, low cost and multi-detection potential. With all its advantages, no doubt ISFET biosensors are becoming increasingly popular for use in integrated biochemical processing platforms used for the early detection and diagnosis of medical conditions. However, the ISFET is not without some less desirable features, including drift, temperature sensitivity, and long-term stability, as discussed in Chapter 2.

The ISFET biosensors were adapted for different purposes. One of which is the determination of urea and creatinine in blood and urine specimens [11-15] with the idea of further use in clinical analyses. It can be very important to have such biosensors in many clinical cases dealing with kidney and liver diseases, when fast urea measurement is valuable [4, 16].

The stability and life-time of many biosensors depend on the enzyme immobilization method used. There are main methods, namely [17] (i) physical (including: adsorption on a matrix, encapsulation between dialysis membrane, entrapment within polymeric network), (ii) chemical (including: cross linking of enzyme molecules to each other with a multi-functional cross linking reagent covalent bond to a water insoluble matrix) and (iii)

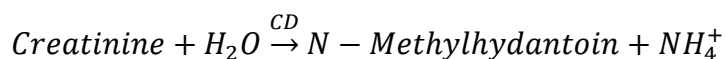
mixed physico-chemical (including: entrapment and cross linking). The biosensors with chemically immobilized enzymes in comparison to those with physical immobilization are better offering greater stability.

The general principle of the ISFET biosensor is based on the use of catalytic properties of chemical immobilised enzyme onto a semiconductor structure which is preceded by the silanization procedure [13, 18-22]. This procedure allows chemically reactive groups to be introduced. In the case of silanization performed with aminosilanes, the reactive groups are of the amine type and used to form covalent bonds between enzyme amino group and glutaraldehyde at the ISFET surface. For a urea and creatinine ISFET biosensor, enzyme urease and creatinine deiminase (CD) are applied, respectively. The substrate will be hydrolysed and detected at the gate insulating membrane of the ISFET, according to the following reactions of urea, Equation 6-1 and creatinine, Equation 6-2.



**Equation 6-1**

From Equation 6-1, it can be seen that not only the detection of ammonium, carbonate or bicarbonate ions but also carbon dioxide and ammonia may be used for the urea determination. However, the change in pH resulting from the end-metabolic products of the acid/base reaction allows pH-based detection to be used for the indirect determination of the urea concentration [17]. This is also true for the reaction in Equation 6-2 [23].



**Equation 6-2**

### 6.3.1 Procedure of EnFET fabrication

The procedure of EnFETs fabrication adopted for this research project is based on very straightforward method described in [24]. The chemicals which are used in the procedure were creatinine deiminase (CD) microbial (EC 3.5.4.21), urease from *Canavalia ensiformis* (Jack bean, EC 3.5.1.5) and standard powders of creatinine monohydrate and urea were purchased from Sigma-Aldrich (St. Louis, MO). Bovine serum albumin (BSA), glutaraldehyde (GA), glycerol, DEAE–dextrane, lactitol, were of analytical grade or purer and also obtained from the same source, Sigma-Aldrich. The alcohol based additives were used to increase the stability of the biosensor developed, it has been previously shown that such alcohols favour a non-polar environment protecting the protein [25]. All stock solutions were prepared in a 10mM phosphate buffer pH 7.4, unless otherwise stated.

To improve stability, the immobilisation of CD and urease was carried out using the classical cross-linking with bovine serum albumin (BSA) [26] in a glutaraldehyde (GA) vapour. Also Glycerol was used as a plasticiser to avoid the formation of cracks in the enzymatic immobilisation membrane during storage. Furthermore, glycerol also results in an improved homogeneity of the membrane and better adhesion to the insulating surface of the ISFET [2]. Prior to enzyme immobilization, all ISFETs were cleaned with ethanol and deionised water using an ultrasonication bath then dried with a dry nitrogen purge. For a creatinine sensitive EnFET, the solution of 4% w/v CD containing 4% w/v BSA, 8% v/v glycerol, 0.2% w/v DEAE–dextrane and 2% w/v lactitol as stabilizers was prepared. Only 10µl of the solution was carefully dropped onto ISFET gate surface from a pipette. To enhance the protein cross-linking formation, the ISFET was placed in the saturated GA vapour for 30 minutes and then dried at room temperature for 15 minutes. The urea sensitive EnFET was prepared in a similar way with 4% w/v urease, instead of

CD. All of the ISFETs used were  $Al_2O_3$ -ISFETs fabricated by Sentron Europe (Roden, The Netherlands, part no, OEM-679). Having prepared the EnFETs, they are now ready for use in the chemical current-conveyor to obtain the value for the urea-to-creatinine ratio of a biochemical liquid.

## 6.4 Chemical Current-Conveyor for urea and creatinine measurement

The diagrams shown in Figure 6-1 and Figure 6-2 are (a) system diagram and (b) the hybrid matrix of the ISFET based urea and creatinine or Urea and Creatinine-CCCII+, having their output related to urea and creatinine, respectively. From which it can be seen that the voltage at X-node,  $V_X$ , follows the high impedance input EnFET sensor nodes ‘*EnFET (Urea) Y*’ and ‘*EnFET (Creatinine) Y*’, making the voltage at X-nodes proportional to the sensed urea and creatinine value at Y-nodes then, for the Urea-CCCII+

$$V_{urea\_Y} = I_S \times R_S = V_X$$

**Equation 6-3**

and for the Creatinine-CCCII+

$$V_{creatinine\_Y} = I_S \times R_S = V_X$$

**Equation 6-4**

where  $I_S$  is the source current and  $R_S$  is the equivalent source resistance of the input EnFET.

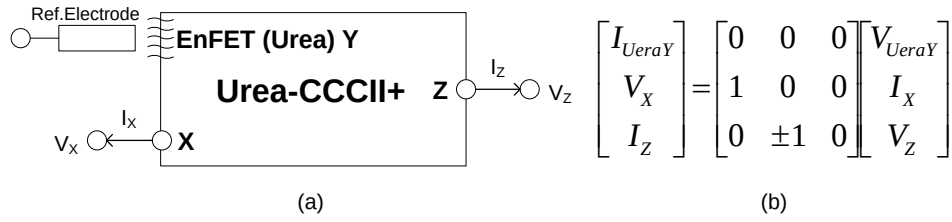


**Figure 6-1.** [6] (a) Urea-CCCII+ system diagram and its (b) hybrid matrix

Thus, the X-node exhibits low input impedance. The current supplied to the X-node is conveyed to the high impedance output node 'Z' where it is supplied with either positive polarity (in EnFET-CCCII+) or negative polarity (in EnFET-CCCII-). It should be noted that the sign '+' indicates that both 'Urea-CCCII+' and 'Creatinine-CCCII+' input and output currents simultaneously flow into, or out of, the device.

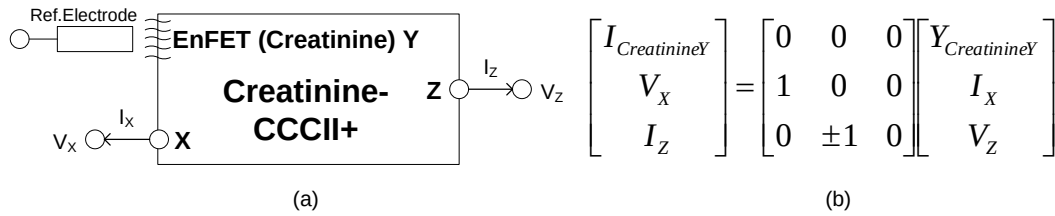


**Figure 6-2.** [6] Creatinine-CCCII+ (a) system diagram and (b) hybrid matrix

Like in the CCCII+, both EnFETs are biased with an appropriate reference electrode, typically silver/silver-chloride ( $Ag/AgCl$ ) which defines the potential of the electrolyte solution. The build up of charge at the exposed insulating membrane is related to the concentration of urea and creatinine in the aqueous solution. This changes the EnFETs channel, and in particular the value of threshold voltage for the EnFET alters resulting in

a shift in the  $I_D \sim V_{GS}$  characteristic and the drain current of the EnFET sensors given by [6]

$$I_{D\_urea} = C_{OX}\mu \frac{W}{L} \left[ (V_{gs} - (V_{th(mos)} + V_{urea})) V_{ds} - \frac{1}{2} V_{ds}^2 \right]$$

Equation 6-5

$$I_{D\_creatinine} = C_{OX}\mu \frac{W}{L} \left[ (V_{gs} - (V_{th(mos)} + V_{creatinine})) V_{ds} - \frac{1}{2} V_{ds}^2 \right]$$

Equation 6-6

where  $V_{urea}$  and  $V_{creatinine}$  are the grouping of chemical potentials at the surface of the insulating membrane of the EnFET,  $C_{OX}$  is the oxide capacity per unit area,  $W$  and  $L$  are the width and the length of the channel, respectively, and  $\mu$  is the electron mobility in the N-channel device [6]. And finally, the  $I_X$  and  $I_Z$  currents are given by

$$I_X = \frac{V_X}{Z_X} = -I_Z$$

Equation 6-7

where  $Z_X$  is the impedance connected between the X-node and ground. The output can be taken either as voltage,  $V_X$ , from the low output impedance X-node, or alternatively as current,  $I_Z$ , from the high output impedance Z-node.

## 6.5 Chemical Current-Conveyor for urea to creatinine ratio measurement

The CCCII+, like the original current-conveyor or CCII+, is an extremely versatile analog building-block, capable of processing either in the voltage or in current domains, as such it can easily be configured to provide amplification and time domain differentiation. The

previous chapter has used the CCCII+ to provide both pH and ‘real-time’ buffer capacity measurements, and here is another example showing the adaptability of the CCCII+. A practical system to achieve (i) urea concentrations, (ii) creatinine concentrations and (iii) urea-to-creatinine ratio measurement is shown in Figure 6-3.

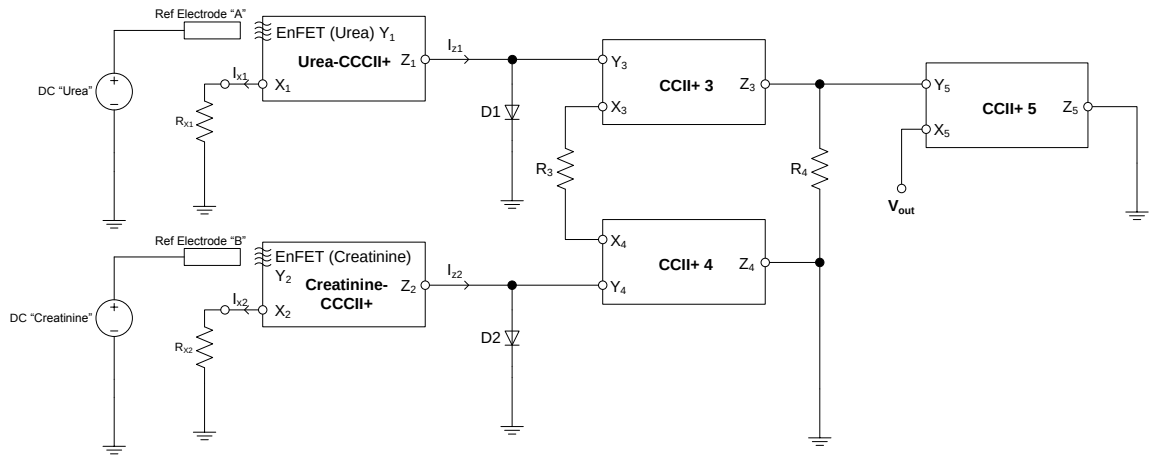


**Figure 6-3.** Initial system configuration for urea-to-creatinine ratio measurement [6]

As shown before in Equation 6-5 and Equation 6-6 the currents that flow out of node  $Z_1$ , ( $I_{Z1}$ ) and  $Z_2$ , ( $I_{Z2}$ ) are related to urea and creatinine concentration in the sample solution, respectively. The diodes D1 and D2 are constructed from two transistors in an integrated circuit BJT array with collector connected to base. This ensures that the diodes are well matched and at the same temperature. The voltages across the diode D1 and D2 are  $V_{Z1}$  and  $V_{Z2}$ , respectively, and given by

$$V_{Z1} = V_T \ln \left( \frac{I_{Z1}}{I_{S1}} \right)$$

**Equation 6-8**

and

$$V_{Z2} = V_T \ln \left( \frac{I_{Z2}}{I_{S2}} \right)$$

**Equation 6-9**

where  $I_S$  is the forward saturation current of the diode connected BJTs and  $V_T = KT/q$  is the thermal voltage (26mV@300K). Thus the diode currents are

$$I_{Z1} = \frac{V_{urea\_Y1}}{R_{X1}}$$

**Equation 6-10**

and

$$I_{Z2} = \frac{V_{creatinine\_Y2}}{R_{X2}}$$

**Equation 6-11**

Using the instrumentation amplifier CCII+ principle formed by CCII+3 and CCII+4, described in Chapter 3, the output voltage of the system,  $V_{out}$  is given by

$$V_{out} = \frac{R_4}{R_3} (V_{Z1} - V_{Z2})$$

**Equation 6-12**

In addition, by substituting Equation 6-8 and Equation 6-9 into Equation 6-12 and using the basic relation of natural logarithms, the output can be computed as follows

$$V_{out} = \frac{R_4}{R_3} \left( V_T \ln \left( \frac{I_{Z1}}{I_{S1}} \right) - V_T \ln \left( \frac{I_{Z2}}{I_{S2}} \right) \right)$$

**Equation 6-13**

since  $R_3 = R_4$  and  $I_{S1} = I_{S2}$ , then the output can be simplified to

$$V_{out} = V_T \ln \frac{I_{Z1}}{I_{Z2}}$$

**Equation 6-14**

Furthermore, by substituting Equation 6-10 and Equation 6-11 into Equation 6-14 and letting  $R_{X1} = R_{X2}$  the output voltage of the system is proportional to the urea-to-creatinine ratio and is given by

$$V_{out} = V_T \ln \left( \frac{V_{urea\_Y1}}{V_{creatinine\_Y2}} \right)$$

**Equation 6-15**

where  $V_{urea\_Y1}$  is proportional to the urea concentration and equal to the voltage at node  $X_1$ , while  $V_{creatinine\_Y2}$  is proportional to the creatinine and equal to the voltage at node  $X_2$ . It should be noted that the unused Z-node of CCII+4 is grounded, this is to ensure the transistors within the CCII+ are kept in the active region.

## 6.6 Measured results and discussion

To ensure that the output voltage of the system shown in Figure 6-3 is sufficiently linear and well-characterised, two experiments using pH-ISFETs as sensors for both CCCII+ were undertaken: (i) the DC sweep of reference electrode 'A' while reference electrode 'B' is kept at a constant DC value and (ii) the pH titration at  $Y_1$ -node while  $Y_2$  is kept at a constant pH value. The results are shown in Figure 6-4 and Figure 6-5 which confirmed the expected linearity between inputs node- $Y_1$  and  $Y_2$  with the output node as the ratio of  $Y_1$  over  $Y_2$ , neglecting the natural logarithm term in the Equation 6-14 and Equation 6-15. The coefficients of determination value,  $R^2$ , achieved more than 0.99 on both

experiments, representing good agreement for output voltage ( $V_{out}$ ). This in part is due to the relatively low input dynamic range used.

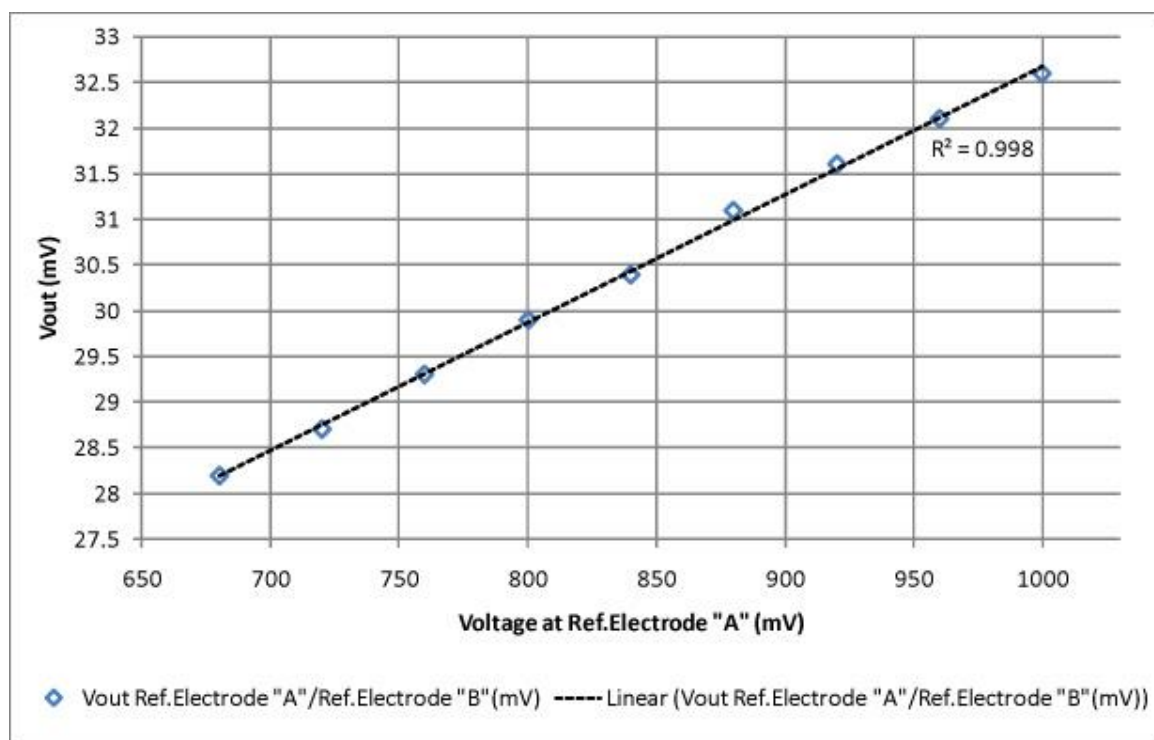


**Figure 6-4.** Plot of the ratio of Ref. Electrode "A" to Ref. Electrode "B" versus Ref. Electrode "A" [6]

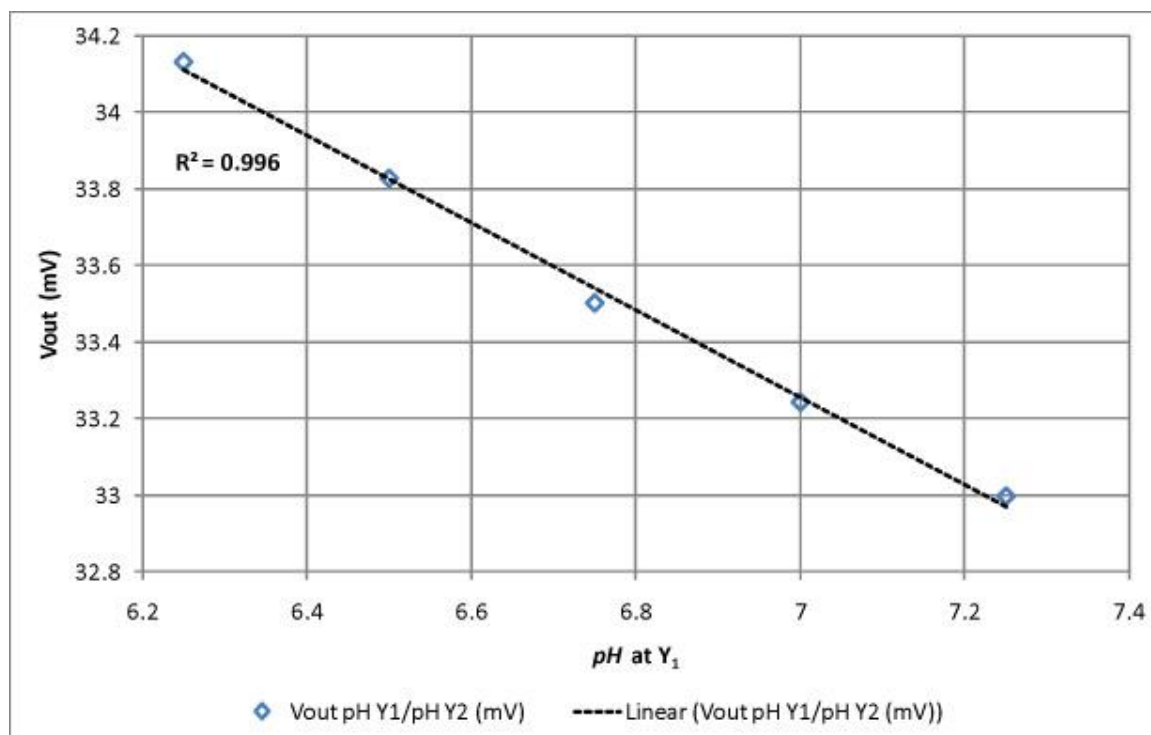


**Figure 6-5.** Plot of the ratio of pHY<sub>1</sub> to pHY<sub>2</sub> versus pHY<sub>1</sub> [6]

Prior to all experiments, the sensors were soaked in a vessel filled with 10mM phosphate buffer solution at pH 7.4 and conditioned for at least 30 minutes in order to equilibrate the enzyme membrane. After each consecutive calibration, the sensors were rinsed and then soaked with a phosphate buffer ready for the next test. At the end of the experiment, the sensors were flushed with large amounts of phosphate buffer and kept dry overnight in a dark environment at 4°C. As previously mentioned, both urea and creatinine standards were prepared using the same buffer to maintain the level of background signal. Consequently, the observed response will be related only to the concentration of urea and creatinine in the solution.

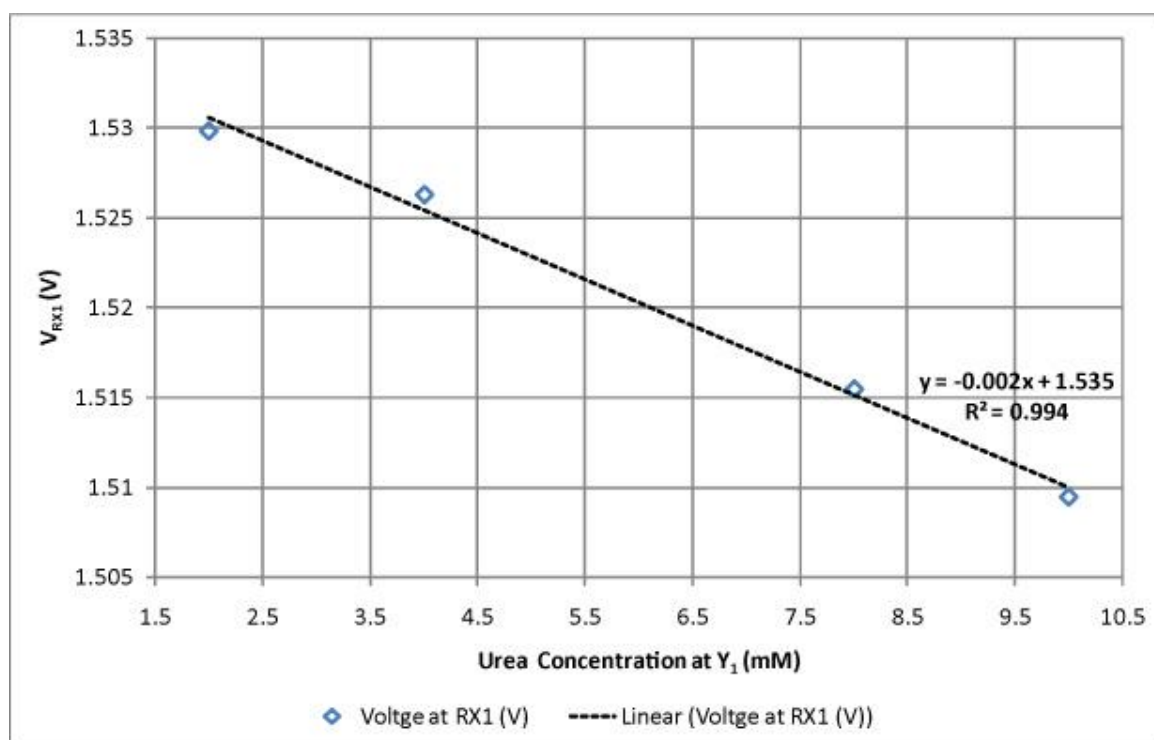


Figure 6-6. Urea calibration curve [6]

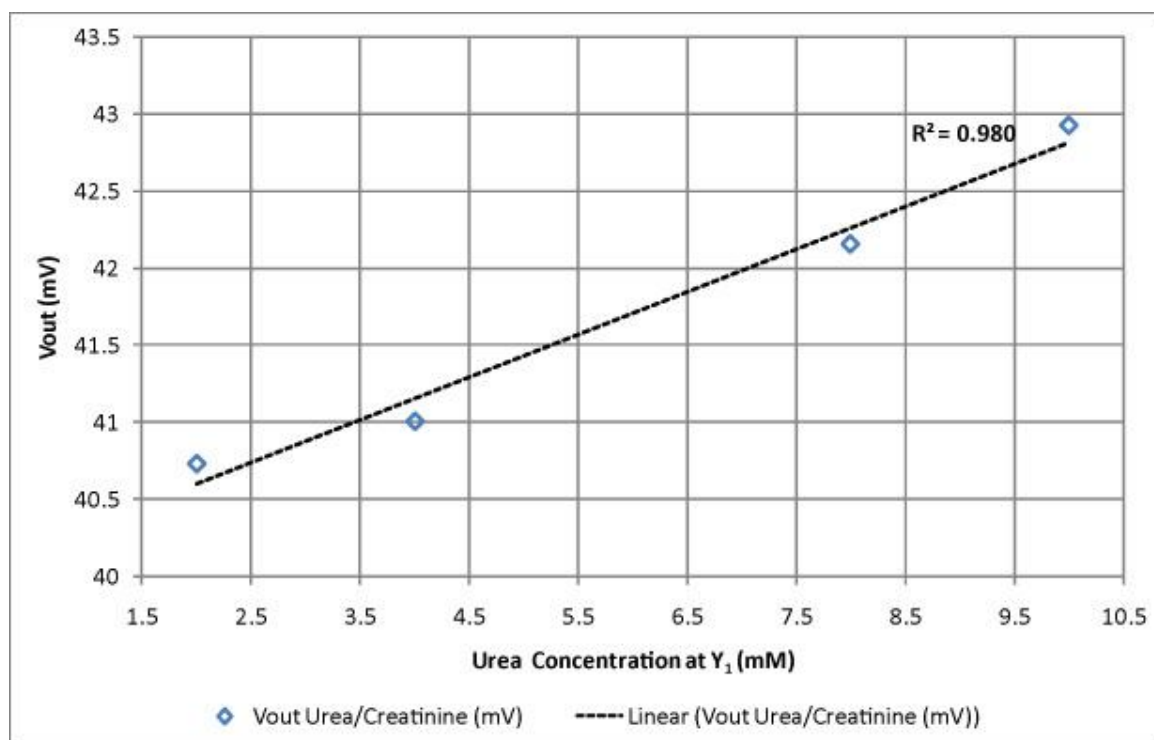


Figure 6-7. Urea-to-creatinine ratio (urea titration, creatinine fixed at  $80\mu\text{M}$ ) [6]

The ability of the system to deliver multiple outputs linearly proportional to urea, creatinine, and the ratio of urea-to-creatinine, which are important markers for the prediction of renal failure, is confirmed by Figure 6-6, Figure 6-7, Figure 6-10 and Figure 6-11. The figures, Figure 6-6 and Figure 6-10, show the calibration curves for the Urea and the Creatinine-CCCII+, respectively. It should be pointed out that the curve representing the urea calibration of Figure 6-6 shows the output voltage decreasing linearly as the urea concentration increases [17, 27-28]. The fact that the response is not curved, as it would be if the enzyme were controlling, suggests that urea diffusion is controlling and limiting the reaction, hence a linear response is obtained.

As drawn, the system in Figure 6-9 will provide the required output because of the inverted signal gain from the urea-CCCII+. In order to obtain the correct signal trend for the logarithmic and instrumentation amplifier stage, additional circuitry was added between diode, D1 and Y<sub>3</sub>-node of the CCII+3 to invert the output signal of the Urea-CCCII+. The additional circuitry consists of a simple high input impedance voltage follower and an inverting amplifier as shown in Figure 6-8.

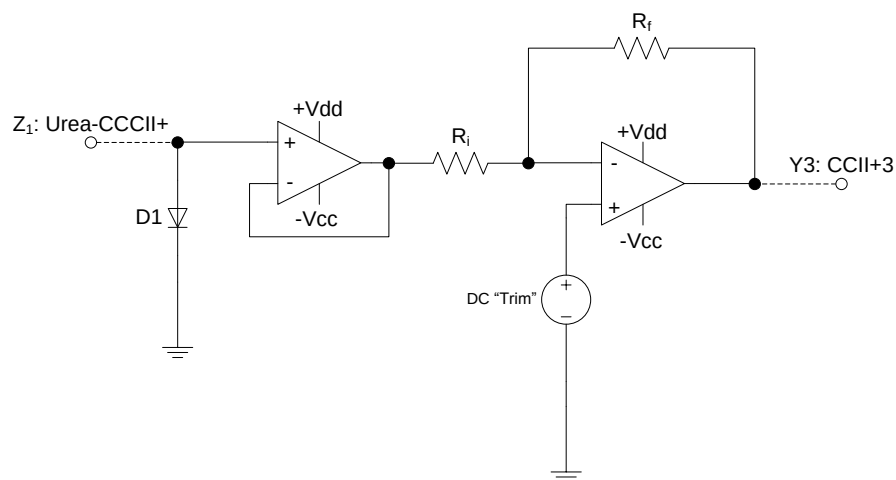


**Figure 6-8.** Inverting op-amp configuration used to invert the output signal of Urea-CCCII+

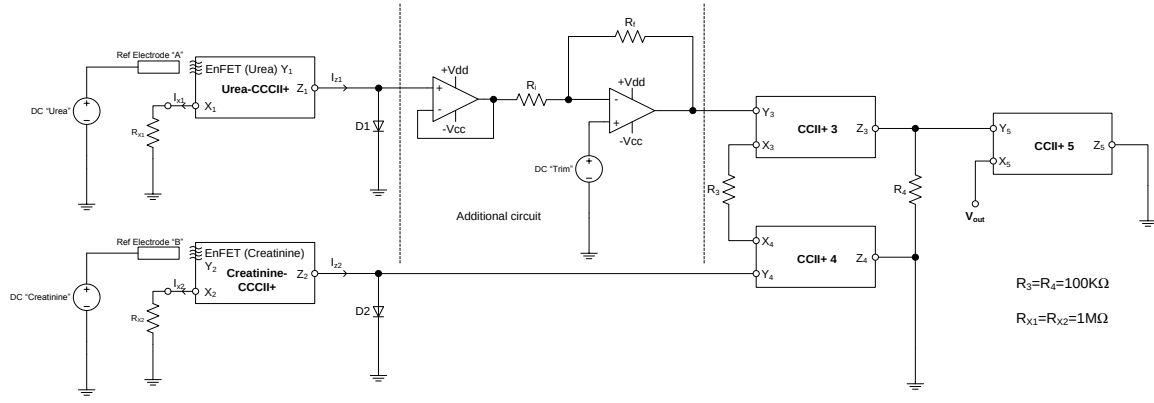


**Figure 6-9.** The adapted practical system configurations for urea-to-creatinine ratio measurement

The circuit shown in Figure 6-9 is a combination of the initial system shown in Figure 6-3 with the addition of the inverting stage shown in Figure 6-8 and the system of Figure 6-9 now provides the required output. This system was constructed on the full system test board described in Chapter 4. As one of the primary objectives of this research was to explore the fully integrated CCCII+, the integrated circuit device versions of the CCCII+ designed by the author were used. The next step taken was to verify the performance of the system. Titrated concentrations of both urea and creatinine were prepared covering values in the normal physiological range [3-4, 6, 16] for the system evaluation to be undertaken. The concentration value used for urea were 2mM, 4mM, 8mM and 10mM, while the concentration for creatinine were 40 $\mu$ M, 80 $\mu$ M, 100 $\mu$ M and 150 $\mu$ M. Fixed concentrations were selected and applied to two tests (i) urea titration while the concentration of creatinine is fixed at 80 $\mu$ M and vice versa (ii) creatinine titration while urea is fixed at 8mM.

As a result, the output signals of the system which holds the vital information for diagnosis and prediction of renal failure were achieved. The coefficients of determination values,  $R^2$ , were obtained and these were more than 0.97 for both urea Figure 6-7 and

creatinine titration Figure 6-11. It should be noted that the sensitivity of urea and creatinine sensors are not particularly high. However, they are typical of these types of EnFET sensors, which in general give relatively low output signal changes corresponding to input concentration changes. Notably, low sensitivity [2, 17, 24, 28] together with drift [1, 29-31] are the two inherent aspects of this particular EnFETs which has been adapted from an integrated ISFET. These issues will need to be addressed in order to take the results of the research work presented here into development of a commercially viable clinical instrument.

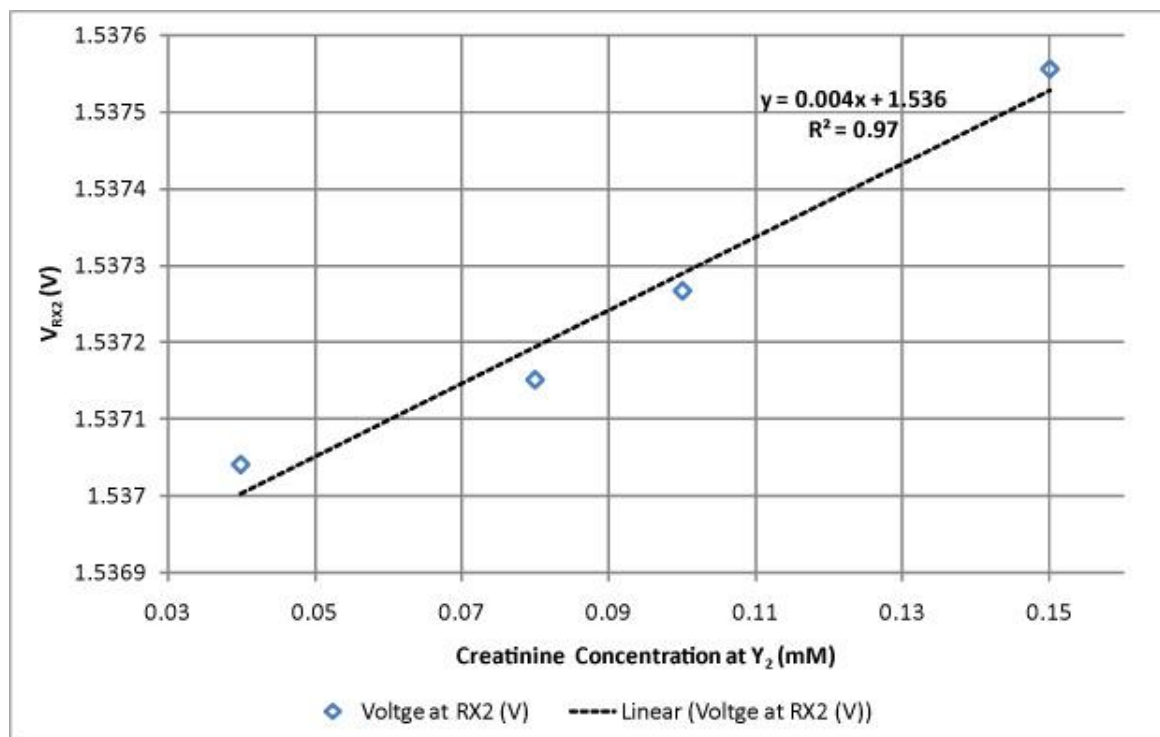


**Figure 6-10.** Creatinine calibration curve [6]

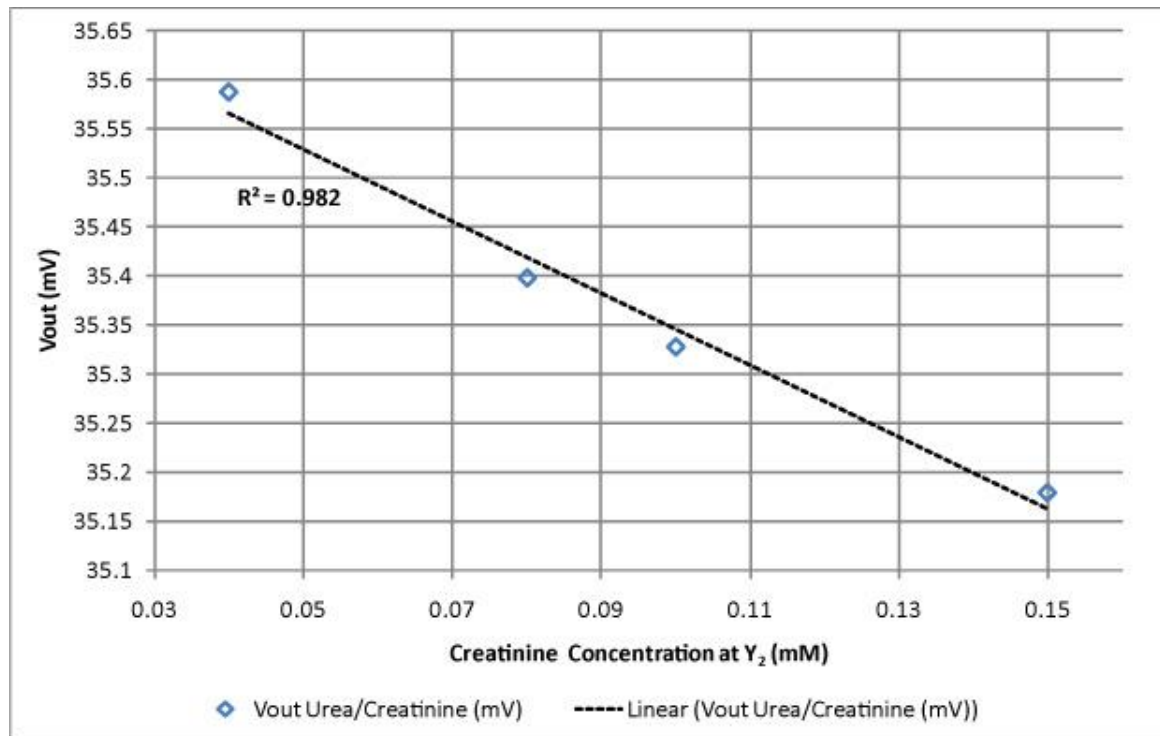


Figure 6-11. Urea-to-creatinine (creatinine titration, urea fixed at 8mM) [6]

### 6.6.1 Possible anti-logarithm approach at the output

The output obtained from the system of Figure 6-3 is proportional to the logarithm of the urea-to-creatinine ratio. In order to provide just the urea-creatinine ratio, an anti-log or exponential operation on the output signal is needed. The modified system shown in **Error! Reference source not found.** is one way to obtain that required output, achieved by adding the third diode, D3, together with the output resistor  $R_{Load}$ .

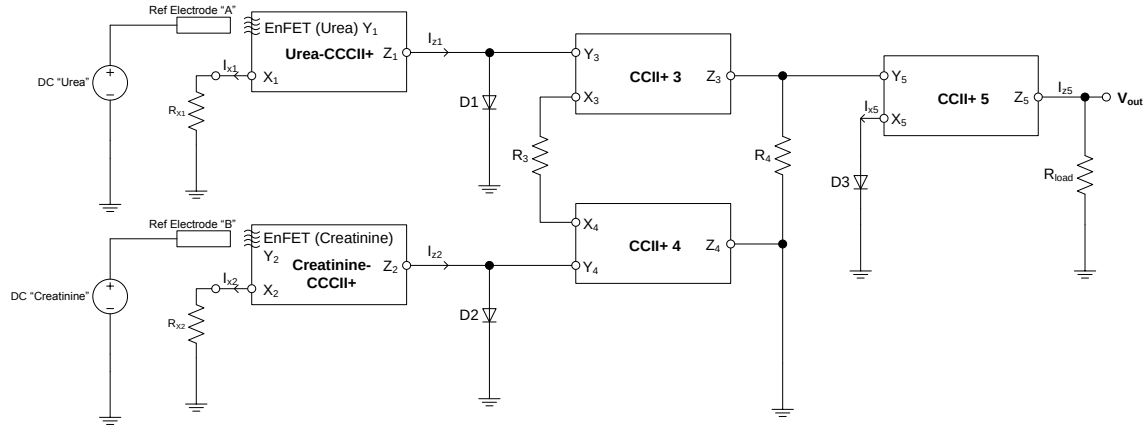


**Figure 6-12.** Diode (D3) added anti-log practical system configurations

The current at X<sub>5</sub>-node of ‘CCII+ 5’ which flows into the diode D3 can be expressed as

$$I_{X5} = I_S e^{\frac{V_{X5}}{V_T}}$$

**Equation 6-16**

and since the voltage at X-node follows the voltage input at Y-node by the characteristics of the CCII+, this results in

$$V_{X5} = V_{Y5} = V_{Z3}$$

**Equation 6-17**

where  $V_{Z3}$  can be obtained from Equation 6-14 where  $R_3 = R_4$  and  $I_{S1} = I_{S2}$ , and leading to

$$V_{X5} = V_T \ln \left( \frac{I_{Y1}}{I_{Y2}} \right)$$

**Equation 6-18**

Substituting Equation 6-18 into Equation 6-16, gives

$$I_{X5} = I_S e^{\frac{V_T \ln\left(\frac{I_{Y1}}{I_{Y2}}\right)}{V_T}}$$

Equation 6-19

which can be simplified as

$$I_{X5} = I_S \left( \frac{I_{Y1}}{I_{Y2}} \right)$$

Equation 6-20

This same current will be conveyed to the high impedance Z-node of CCII+5, thus the output voltage at this node can be obtained as

$$V_{out} = R_{Load} I_S \left( \frac{I_{Y1}}{I_{Y2}} \right)$$

Equation 6-21

where  $R_{Load}$  and  $I_S$  can be constant terms,  $I_{Y1}$  and  $I_{Y2}$  related to urea and creatinine concentration, respectively. It can be seen in Equation 6-21 that there is no longer a natural logarithm. It should be noted that resistor matching and diode matching, including temperature matching are essential to achieve the required output response.

Removing the logarithm function can be achieved in other ways and a second proposal will now be considered. Equation 6-22 hold for values of  $x \ll 1$  and this fact can be exploited to remove the log function in the output.

$$\ln(1 + x) \cong x$$

Equation 6-22

Let

$$I_Y = I_{Y2} + I_{Y1}$$

**Equation 6-23**

Therefore by dividing both sides by  $I_{Y2}$  the expression above can be expressed as

$$\frac{I_Y}{I_{Y2}} = 1 + \frac{I_{Y1}}{I_{Y2}}$$

**Equation 6-24**

and by applying the same principle from Equation 6-22 to Equation 6-24 will result in

$$\ln\left(\frac{I_Y}{I_{Y2}}\right) \cong \frac{I_{Y1}}{I_{Y2}}$$

**Equation 6-25**

The additional circuitry shown in Figure 6-13 provides the correct signal processing to achieve the final result shown in Equation 6-25. The circuit is a current-mode based on current-mirrors and does not require any matched resistor network. Operation, however, is contingent on precision well match monolithic transistors in an array or some form of integrated circuit.  $I_{Z1}$  flows through D1 to ground. T1 is connected as a current mirror with D1 and hence  $I_{C1}$  will equal  $I_{Z1}$ . This current, in turn, draws current from  $+V_{CC}$  through T2. T2 is the input of a current-mirror source, the output of which flows from the collector of T4. The current-mirror T2, T3, T4 is a Wilson current-mirror [32] providing a high output impedance current drive of  $I_{Z1}$  down into D2.  $I_{Z2}$  is connected to the current output node from the creatinine-CCCII+ and this current too flows through D2 adding to  $I_{Z1}$ . Note that the anodes of both D1 and D2 are connected as in Figure 6-9, to complete the circuit modification.

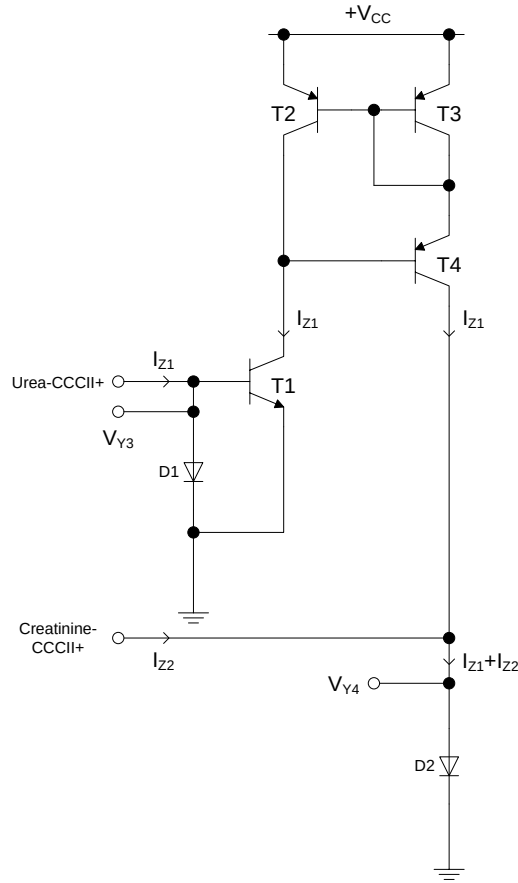


**Figure 6-13.** Proposed additional current-mode signal processing circuit

## 6.7 Output to the $N^{\text{th}}$ -power circuit

The system shown in **Error! Reference source not found.** is easily adapted to provide different output functions depending on the particular application requirements primarily because the system uses logarithmic and exponential functions. This is readily seen by referring back to Equation 6-13. Re-writing this equation again below as Equation 6-26 with the output taken as  $V_{X5}$ , the equation becomes

$$V_{X5} = \frac{R_4}{R_3} \left( V_T \ln \left( \frac{I_{Z1}}{I_{S1}} \right) - V_T \ln \left( \frac{I_{Z2}}{I_{S2}} \right) \right)$$

**Equation 6-26**

By keeping  $R_4/R_3$  as variables and remembering that the diodes will be formed from a BJT array, making the  $V_T$  terms equal and  $I_{S1} = I_{S2}$ , then the voltage  $V_{X5}$  can be simplified to

$$V_{X5} = \frac{R_4}{R_3} \left( V_T \ln \left( \frac{I_{Y1}}{I_{Y2}} \right) \right)$$

**Equation 6-27**

Therefore, the current which flows into the X-node and Z-node of ‘CCII+ 5’ will be

$$I_{X5} = I_S \left( \frac{I_{Y1}}{I_{Y2}} \right)^{\frac{R_4}{R_3}} = I_{Z5}$$

**Equation 6-28**

and the voltage across  $R_{Load}$  will be

$$V_{out} = R_{Load} I_S \left( \frac{I_{Y1}}{I_{Y2}} \right)^{\frac{R_4}{R_3}}$$

**Equation 6-29**

where the ratio  $(R_4/R_3) = N$  is the  $N^{\text{th}}$ -power of the output, the load  $R_{Load}$  and the forward saturation current  $I_S$  can be regarded as constant terms. This  $n^{\text{th}}$ -power output function may be useful, although at the time of writing the author is not aware of any specific biochemical application.

## 6.8 Summary of Chapter 6

In this chapter, a system has been presented that is capable of providing continuous outputs of urea concentration, creatinine concentration and urea-to-creatinine ratio. These three parameters are useful indicators for clinical assessment of renal condition. The

system utilises two CCCII+ and three CCII+ devices. Both of these current-mode building-blocks are extremely versatile not only providing the sensor signal conditioning input stage of the system but also the analogue signal processing to generate the output proportional to the ratio of urea-to-creatinine, thus demonstrating the flexibility of the CCCII+/CCII+ combination for biochemistry and electrical signal manipulation.

This is the last application area for the CCCII+ to be reported in this thesis, although the author is confident that there are more yet to be explored. The next and final chapter in this thesis is Chapter 7 ‘conclusions and future work’ where the overall achievements of the research are summarised and reviewed together with possible areas for further development and applications of the CCCII+.

## 6.9 References

- [1] S. Casans, *et al.*, "ISFET drawbacks minimization using a novel electronic compensation," *Sensors and Actuators B: Chemical*, vol. 99, pp. 42-49, 2004.
- [2] M. L. Hamlaoui, *et al.*, "Development of a urea biosensor based on a polymeric membrane including zeolite," *Analytica Chimica Acta*, vol. 466, pp. 39-45, 2002.
- [3] W. Juffali, *et al.*, "ISFET based urea:creatinine translinear sensor," *Electronics Letters*, vol. 46, pp. 746-748, 2010.
- [4] W. J. Marshall and S. K. Bangert, *Clinical Chemistry*: MOSBY Elsevier, 2008.
- [5] D. B. Morgan, *et al.*, "Plasma creatinine and urea: creatinine ratio in patients with raised plasma urea," *British Medical Journal*, pp. 929-932, 1977.
- [6] P. Pookaiyaudom, *et al.*, "Measurement of urea, creatinine and urea to creatinine ratio using enzyme based chemical current conveyor (CCCI+)," *Sensors and Actuators B: Chemical*, vol. In Press, Corrected Proof.
- [7] B. Premanode and C. Toumazou, "A novel, low power biosensor for real time monitoring of creatinine and urea in peritoneal dialysis," *Sensors and Actuators B: Chemical*, vol. 120, pp. 732-735, 2007.
- [8] B. Gilbert, "Translinear circuits: a proposed classification," *Electronics Letters*, vol. 11, pp. 14-16, 1975.

- [9] P. Bergveld, "Thirty years of ISFETOLOGY: What happened in the past 30 years and what may happen in the next 30 years," *Sensors and Actuators B: Chemical*, vol. 88, pp. 1-20, 2003.
- [10] S. Caras and J. Janata, "Field effect transistor sensitive to penicillin," *Analytical Chemistry*, vol. 52, pp. 1935-1937, 1980.
- [11] J. Anzai, *et al.*, "Urea sensor based an ion-sensitive field effect transistor. IV. Determination of urea in human blood," *Chemical and Pharmaceutical Bulletin*, vol. 35, pp. 693-698, 1987.
- [12] O. A. Boubriak, *et al.*, "Study of immobilisation and properties of urease to create biosensor based on semiconductor structures," *Ukr. Biochem*, pp. 66-71, 1992.
- [13] Y. Miyahara, *et al.*, "Integrated enzyme fets for simultaneous detections of urea and glucose," *Sensors and Actuators*, vol. 7, pp. 1-10, 1985.
- [14] B. H. van der Schoot and P. Bergveld, "ISFET based enzyme sensors," *Biosensors*, vol. 3, pp. 161-186, 1987.
- [15] F. Gardies, *et al.*, "Micro-enzyme field effect transistor sensor using direct covalent bonding of urease," *Analytica Chimica Acta*, vol. 231, pp. 305-308, 1990.
- [16] N. W. Tietz, *Textbook of Clinical Chemistry*, 1st ed. Philadelphia, 1986.
- [17] D. G. Pijanowska and W. Torbicz, "pH-ISFET based urea biosensor," *Sensors and Actuators B: Chemical*, vol. 44, pp. 370-376, 1997.
- [18] S. Nakamoto, *et al.*, "A lift-off method for patterning enzyme-immobilized membranes in multi-biosensors," *Sensors and Actuators*, vol. 13, pp. 165-172, 1988.
- [19] J. Kimura, *et al.*, "An immobilized enzyme membrane fabrication method using an ink jet nozzle," *Biosensors*, vol. 4, pp. 41-52, 1989.
- [20] I. Karbue, *et al.*, "A microsensor for urea based on an ion-selective field effect transistor," *Analytica Chimica Acta*, vol. 185, pp. 195-200, 1986.
- [21] Y. Hanazato, *et al.*, "Multi-enzyme electrode using hydrogen-ion-sensitive field-effect transistors," *Electron Devices, IEEE Transactions on*, vol. 33, pp. 47-51, 1986.
- [22] B. H. van der Schoot, *et al.*, "The pH-static enzyme sensor: Design of the pH control system," *Sensors and Actuators B: Chemical*, vol. 1, pp. 546-549, 1990.
- [23] P. Temple-Boyer, *et al.*, "Modelling of EnFETs for the creatinine detection," *Sensors and Actuators B: Chemical*, vol. 118, pp. 47-52, 2006.

- [24] A. P. Soldatkin, *et al.*, "Creatinine sensitive biosensor based on ISFETs and creatinine deiminase immobilised in BSA membrane," *Talanta*, vol. 58, pp. 351-357, 2002.
- [25] Y. I. Korpan, *et al.*, "Development of highly selective and stable potentiometric sensors for formaldehyde determination," *Biosensors and Bioelectronics*, vol. 15, pp. 77-83, 2000.
- [26] P. Bergveld, "ISFET, Theory and Practice," presented at the IEEE Sensor Conference Toronto, Toronto, 2003.
- [27] O. A. Boubriak, *et al.*, "Determination of urea in blood serum by a urease biosensor based on an ion-sensitive field-effect transistor," *Sensors and Actuators B: Chemical*, vol. 27, pp. 429-431, 1995.
- [28] S. Alegret, *et al.*, "ISFET-based urea biosensor," *Sensors and Actuators B: Chemical*, vol. 16, pp. 453-457, 1993.
- [29] J.-L. Chiang, *et al.*, "Study on the temperature effect, hysteresis and drift of pH-ISFET devices based on amorphous tungsten oxide," *Sensors and Actuators B: Chemical*, vol. 76, pp. 624-628, 2001.
- [30] J. C. Chou and C. N. Hsiao, "The hysteresis and drift effect of hydrogenated amorphous silicon for ISFET," *Sensors and Actuators B: Chemical*, vol. 66, pp. 181-183, 2000.
- [31] Y. Ito, "Long-term drift mechanism of Ta<sub>2</sub>O<sub>5</sub> gate pH-ISFETs," *Sensors and Actuators B: Chemical*, vol. 64, pp. 152-155, 2000.
- [32] J. Mahattanakul, *et al.*, "Understanding Wilson current mirror via the negative feedback approach," in *Circuits and Systems, 2001. ISCAS 2001. The 2001 IEEE International Symposium on*, 2001, pp. 532-535 vol. 1.

## Chapter 7

# Conclusion and Future Work

### 7.1 Conclusion

The starting point of the research reported in this thesis is the original idea of combining an ISFET and a current-conveyor type II (CCII+) to create a new integrated circuit biochemical sensor, which the author has named the chemical current conveyor or CCCII+. In Chapter 2, the first of the two key elements of the CCCII+, the ISFET, was reviewed in details and non-ideal properties discussed. In Chapter 3, the second key element, the CCII+, was reviewed and its full capability as an extremely versatile analog signal processing building-block was examined for subsequent exploitation in the design and application of the CCCII+. The concept, original design, development, and production and evaluation of the first monolithic CCCII+ were presented in Chapter 4, and applied to the measurement of pH and buffer index ( $\beta$ ) in Chapter 5. In Chapter 6, a different application area for the CCCII+ was presented, namely the design and development of a renal parameter diagnostic measurement system (urea, creatinine and urea:creatinine) again using the core CCCII+ as an ‘off-the-shelf’ component, further

demonstrating the versatility and utility of this new device for biochemical measurement system design. In this closing chapter of the thesis, the author reflects on the work reported and also presents his thoughts on future ideas and directions for the monolithic CCCII+.

There is no doubt that the ISFET has proved to be a very powerful and universal biochemical sensing element and in the last 40 years since its inception by Bergveld has become central to many biochemical sensing applications. ISFET development was incremental for over many years but more recently the unmodified CMOS ISFET has made integrated circuit ISFET based sensors a practical reality, with the advantages of low cost, small size and compatibility with integrated circuit technology. There are still non-ideal features of the ISFET that require further advances, such as reduction of drift, thermal effects, noise, trapped charges and variation in threshold voltage. Also there is still work to be done on improving the design and miniaturisation of the reference electrode to take full advantage of the potential of the ISFET. One advantage of the fact that the ISFET is such a universal sensing device so that there will be a significant weight of research work effort to improve ISFET performance in the coming years.

Combining the ISFET and the CCCII+ forms the CCCII+, and this was demonstrated initially with a system level simulation, followed by a full CMOS technology implementation. Clearly, there is work that could be undertaken on advancing the CCCII+ circuit design and its implementation. However, the original design performance was considered more than adequate (low power in the  $\mu\text{W}$  range, bandwidth of several megahertz, close to Nernstian sensitivity) so further circuit level optimisation was deemed unnecessary at this point and the research focus was moved to applications of the CCCII+ to see what can be achieved.

The next application area after pH measurement to be explored was using the CCCII+ for buffer capacity measurement. Measurement of both pH and  $\beta$  is desirable to achieve a clinically viable instrument with more meaningful output values that match the  $\beta$  dependence to the actual concentration values. A viable system was developed and demonstrated practically, the computational ability of the embedded CCII+ being used to advantage in the design of the system. The design and evaluation of the system as a monolithic device will require further work, including addressing drift and solving drift limitations but the system concept was proven.

A feasibility study of using an ISFET to sense fast chemical stimulus in the order of 1 millisecond was developed. Changes in signal monitored by the ISFET show its capability to sense up to 1ms injected period of  $H^+$  generation. Since local pH change is achievable, it can be concluded that the ISFET is a potential chemical sensor for fast chemical sensing application such as for rapid DNA-sequencing or chemical synapse applications in an integrated circuit form. Moreover, a further experiment to determine ISFET response time is of interest. However, this is limited by the instrumentation which requires a high precision control unit in order to obtain the precise distance between the ISFET surface and the tip of micropipette less than micrometer.

The last application area to be studied was using the CCCII+ for a renal diagnostic measurements system with the target of producing three output values, namely (i) urea concentration, (ii) creatinine concentration and (iii) urea to creatinine ratio. The system developed was successful and the three outputs were indeed obtained. There is room for EnFET and system optimization/rationalisation with the introduction of a Urea-CCCI- device to replace the Urea-CCCI+ device, and thereby removing the need for the additional op-amp based signal inversion circuitry. Although the system described in this thesis is capable of being integrated into a single monolithic circuit, this has not yet been

undertaken. To take this concept into a fully developed instrument would require further development including rationalisation and optimisation of the system circuitry, followed by realisation of the system as a single-chip design.

## 7.2 Future work: Determination and monitoring of cells culture using array CCCII+ platform

The idea presented below has emerged from the research reported in this thesis, but as yet is only an idea. It has been included here for future exploration as a novel CCCII+ application in biochemical engineering. Interest is growing in monitoring bio-electrochemical activity of living cells in real-time. This will be made a reality with the production of miniature ISFET based sensor arrays. The requirement is to be able to obtain information of the physiological state of a cell population non-invasively [1].

Monitoring the increase in pH of cells gives a useful indicator of their metabolic activity and therefore the health of the cell [2]. An equation relating pH change to metabolic activity is [1, 3]

$$\frac{dpH}{dt} \cong \frac{C_{den}[H^+]}{D\beta}$$

**Equation 7-1**

where  $C_{den}$  is the number of cells per unit area,  $[H^+]$  is the proton generated,  $D$  is the cell population-sensor distance and  $\beta$  is the buffer capacity of the medium.

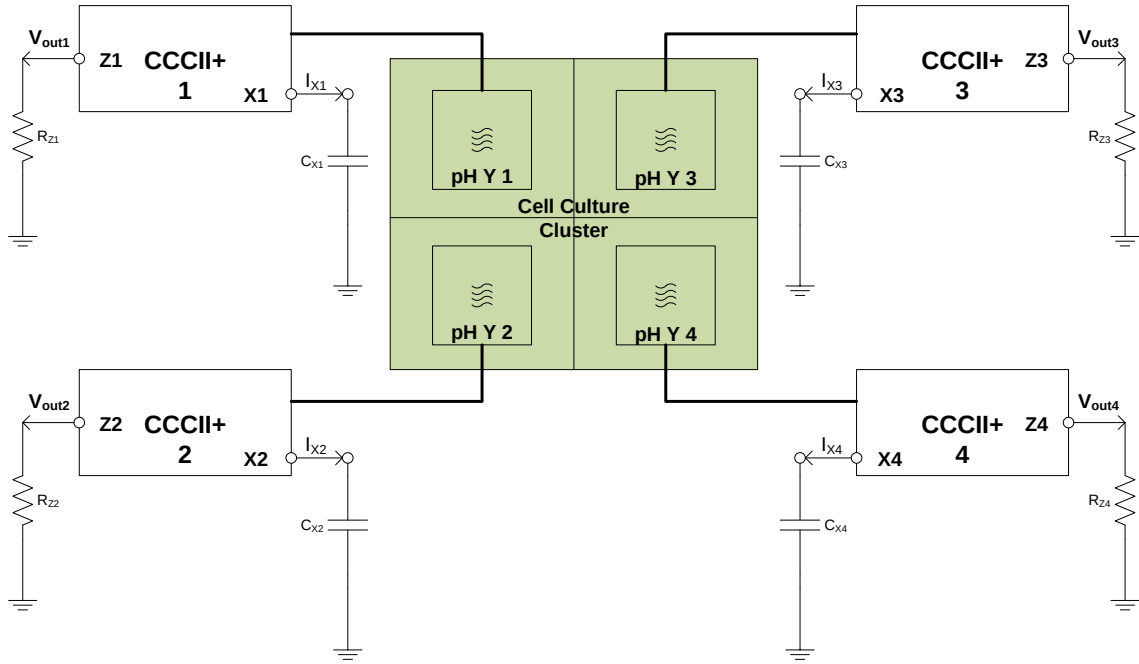


**Figure 7-1.** Monitoring cell culture using CCCII+ array-based micro-system

The CCCII+ array-based micro-system is used to monitor cell culture as shown in Figure 7-1. Only 4 CCCII+ devices are shown for clarity. Each pH monitor is the ISFET with its corresponding CCCII+, as shown. The output from each CCCII+ is taken as a voltage from the high output impedance Z-node of the CCCII+, which is described in Chapter 4 and rewritten here again as

$$V_{out} = C_x R_z \frac{dpH}{dt}$$

**Equation 7-2**

where  $C_x R_z$  is the time constant of the system. By substituting Equation 7-1 into Equation 7-2 the final output of each CCCII+ device can be obtained as

$$V_{out} \cong C_X R_Z \frac{C_{den}[H^+]}{D\beta}$$

**Equation 7-3**

This proposed system will provide a set of voltages indicating the ‘health’ of each area of the culture. Clearly, there is a requirement here for miniaturisation of the ISFET array which could be some distance from the bulk of the CCCII+ devices. Representation of the health of the culture could then be obtained using a 3-dimensional image of the area. The output could also be used to provide a closed-loop feedback system for automated growing system.

Finally, it can be concluded that the CCCII+ is in extremely useful building-block for use to construct biochemical sensing systems. It has been designed successfully using conventional CMOS technology and applied to a range of biochemical measurement applications, and one new areas of further development have been presented in this chapter.

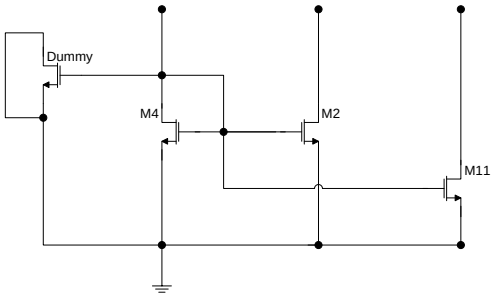
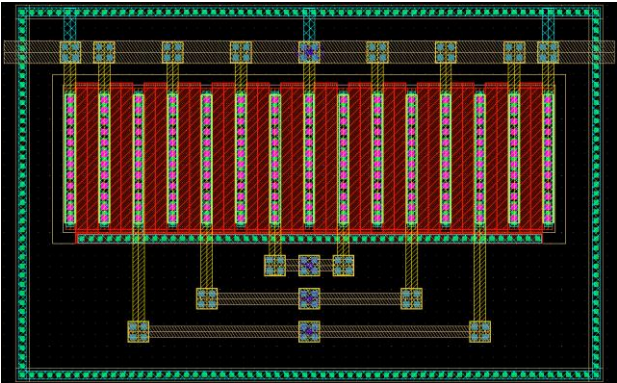
## 7.3 References

- [1] S. Martinoia, *et al.*, "Development of ISFET array-based microsystems for bioelectrochemical measurements of cell populations," *Biosensors and Bioelectronics*, vol. 16, pp. 1043-1050, 2001.
- [2] J. C. Owicki and J. Wallace Parce, "Biosensors based on the energy metabolism of living cells: The physical chemistry and cell biology of extracellular acidification," *Biosensors and Bioelectronics*, vol. 7, pp. 255-272, 1992.
- [3] P. Georgiou and C. Toumazou, "An adaptive ISFET chemical imager chip," in *Circuits and Systems, 2008. ISCAS 2008. IEEE International Symposium on*, 2008, pp. 2078-2081.

Appendix A

Matching of Transistors, Common-Centroid Layout and Dummy Transistors for CCCII+

Table 7-1. Schematic and layout of N-CCCI+

| Schematic                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Layout                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  <p>The schematic diagram shows an N-CCCI+ circuit. It consists of a PMOS transistor labeled 'Dummy' at the top left, connected to a common source node. Below it is an NMOS transistor labeled 'M4'. To the right of 'M4' is another NMOS transistor labeled 'M2'. At the bottom right is an NMOS transistor labeled 'M11'. The gates of 'M4' and 'M2' are connected together. The gates of 'M2' and 'M11' are connected together. The sources of 'M4' and 'M2' are connected to a common source node, which is connected to the source of 'M11'. The drains of 'M4' and 'M2' are connected to a common drain node. The drain of 'M11' is connected to ground. The output is taken from the common drain node.</p> |  <p>The layout diagram shows the common-centroid layout of the N-CCCI+ circuit. It features a central area with red hatched regions representing the transistors. The layout is symmetrical and includes dummy transistors (green hatched regions) at the edges to ensure matching. The layout is enclosed in a black border with green hatched regions.</p> |



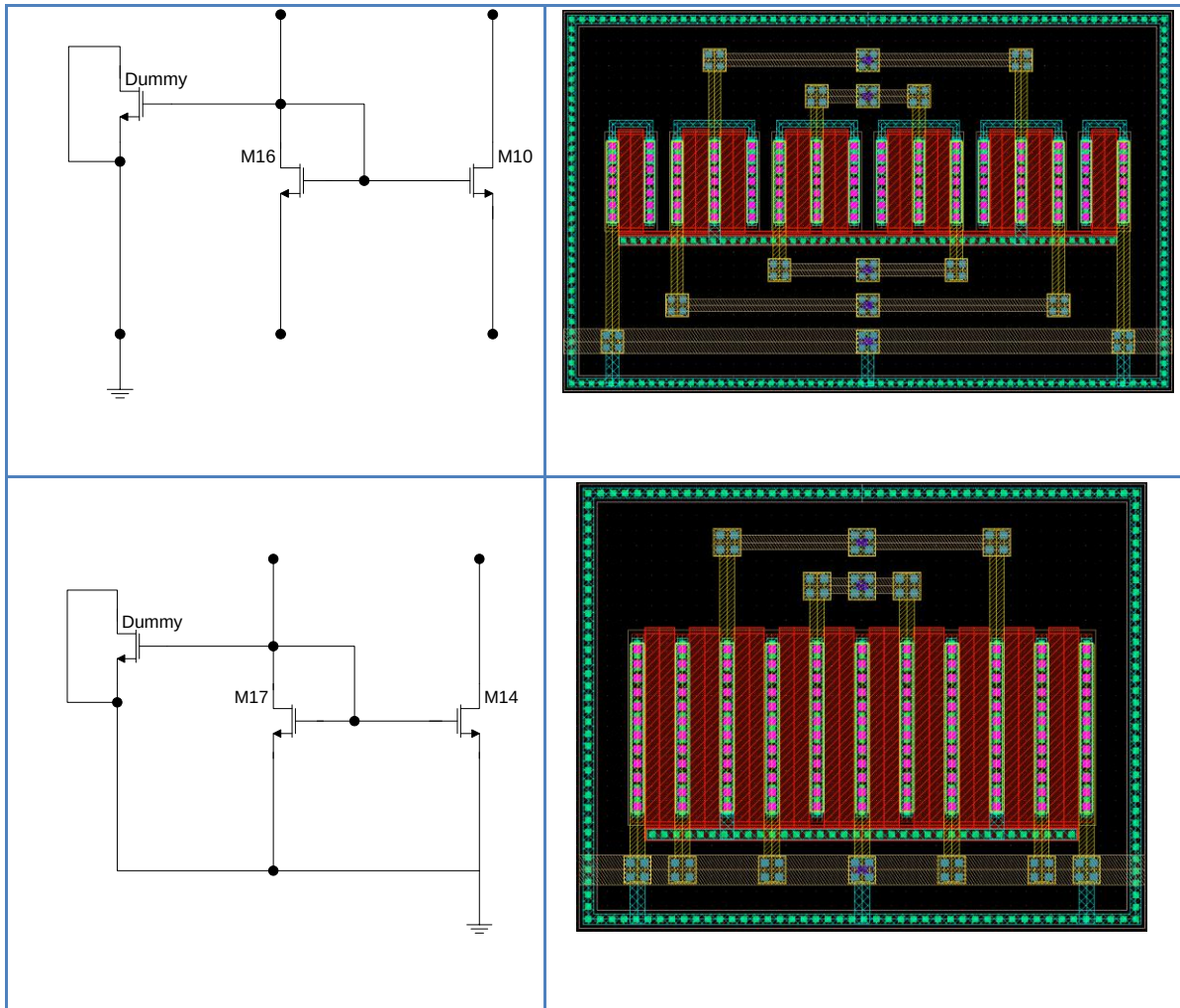
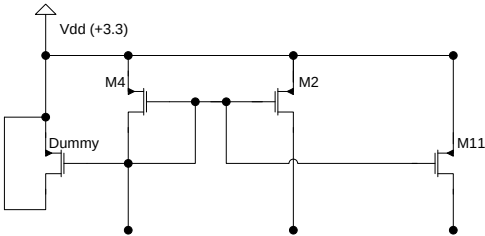
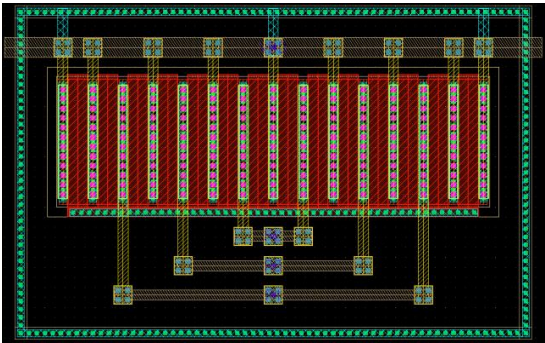
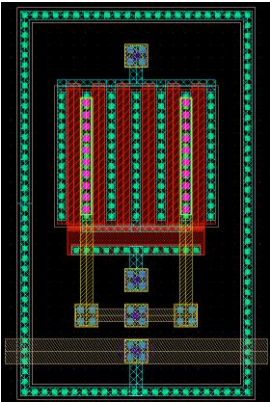
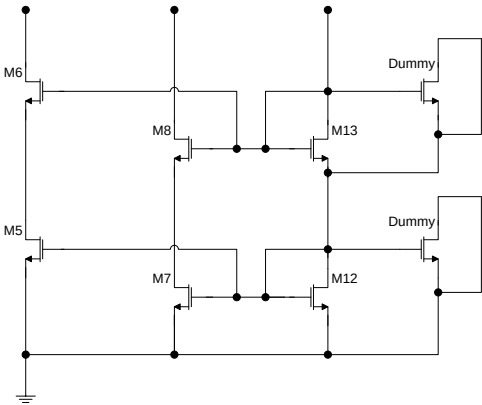
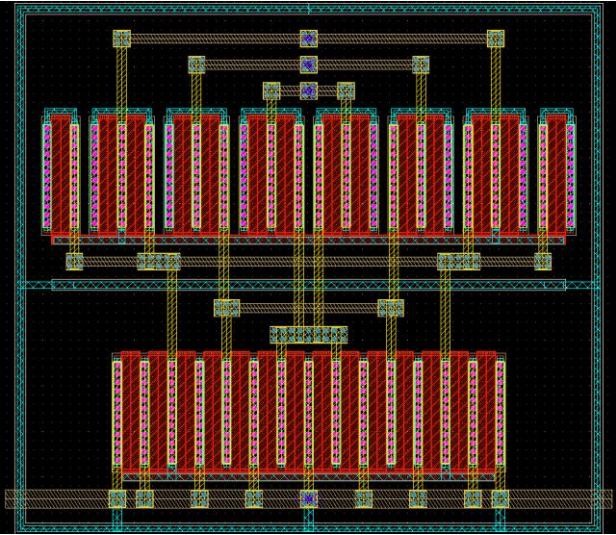
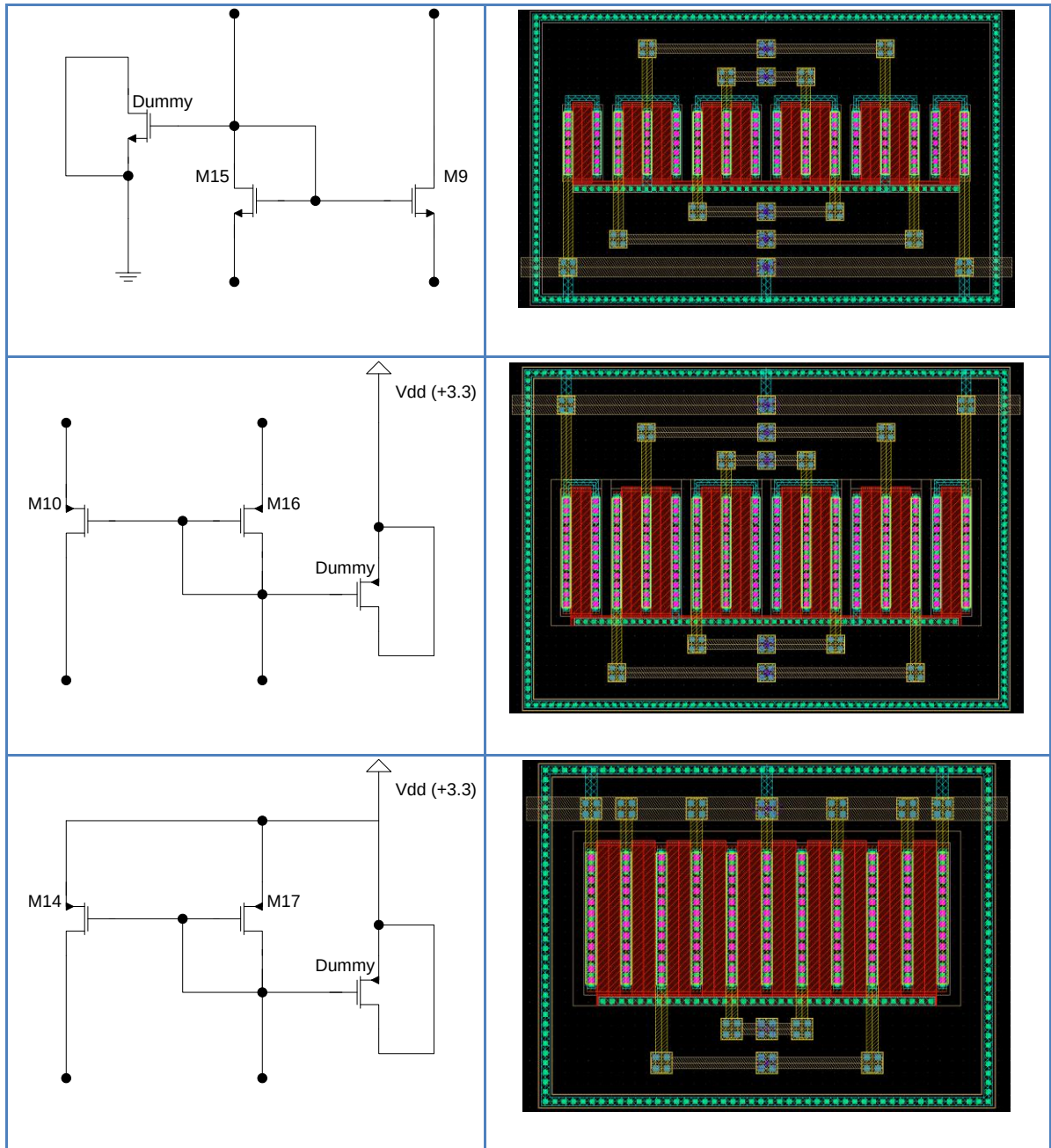


Table 7-2. Schematic and layout of N-CCCII+

| Schematic                                                                           | Layout                                                                               |
|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
|    |    |
|    |   |
|  |  |



## Appendix B

### The Full Circuit Schematic of the CCCII+ Test and Application Board

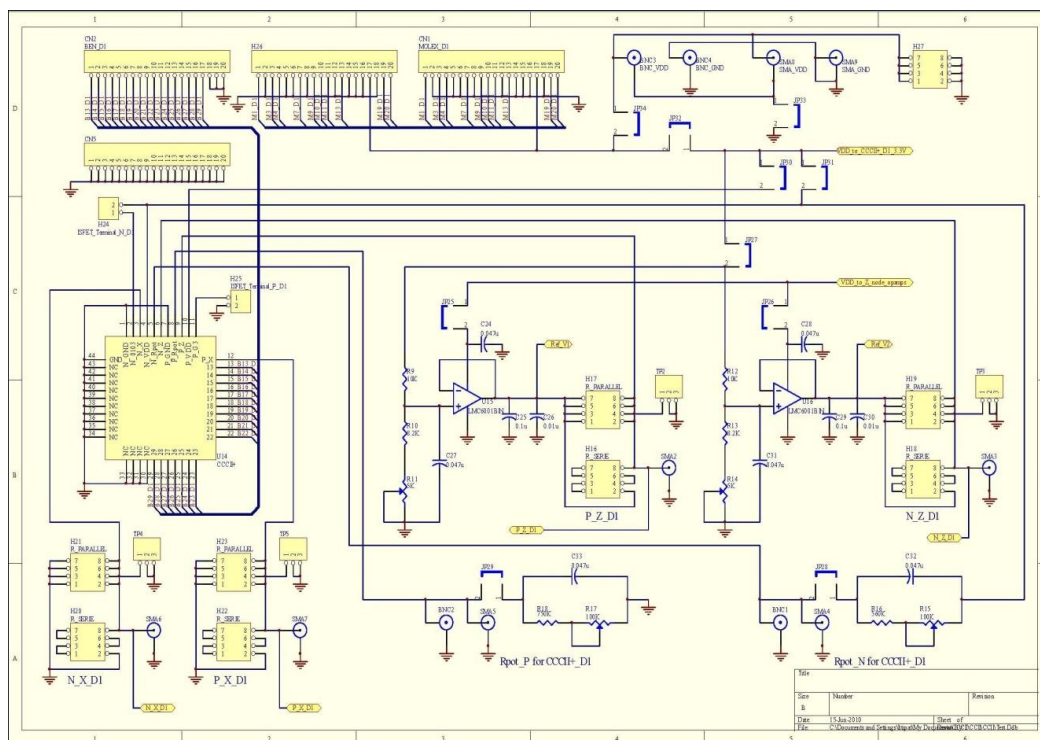


**Figure 7-2.** Readout circuit schematic for CCCII+ Chip\_D1

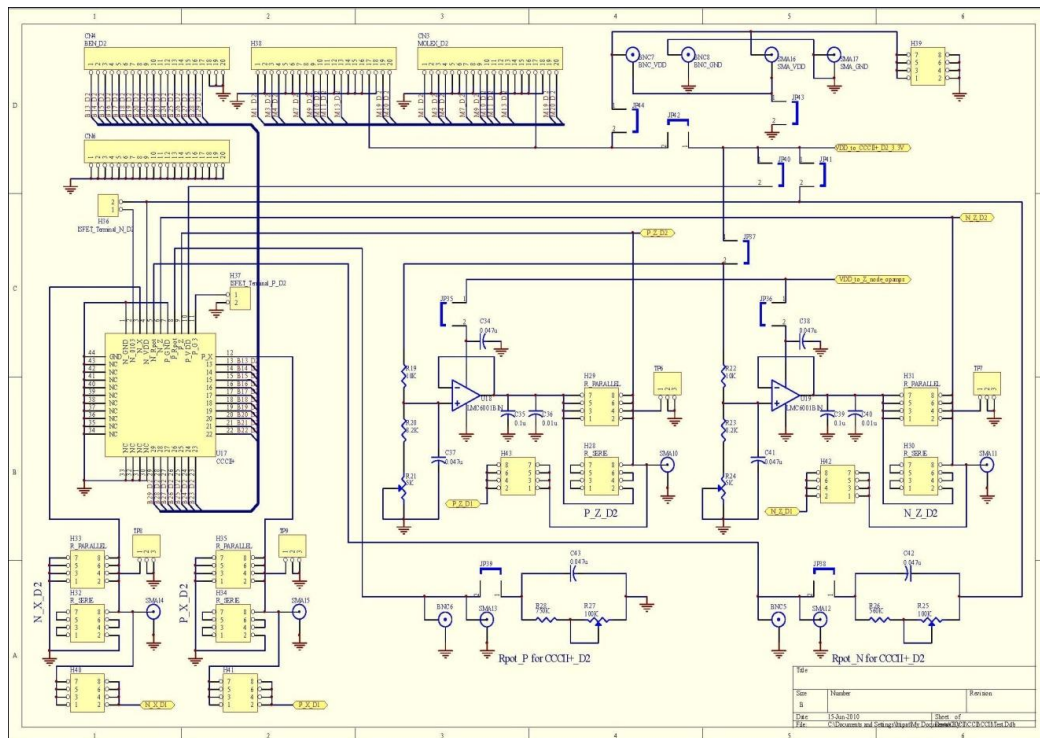


**Figure 7-3.** Readout circuit schematic for CCCII+ Chip\_D2

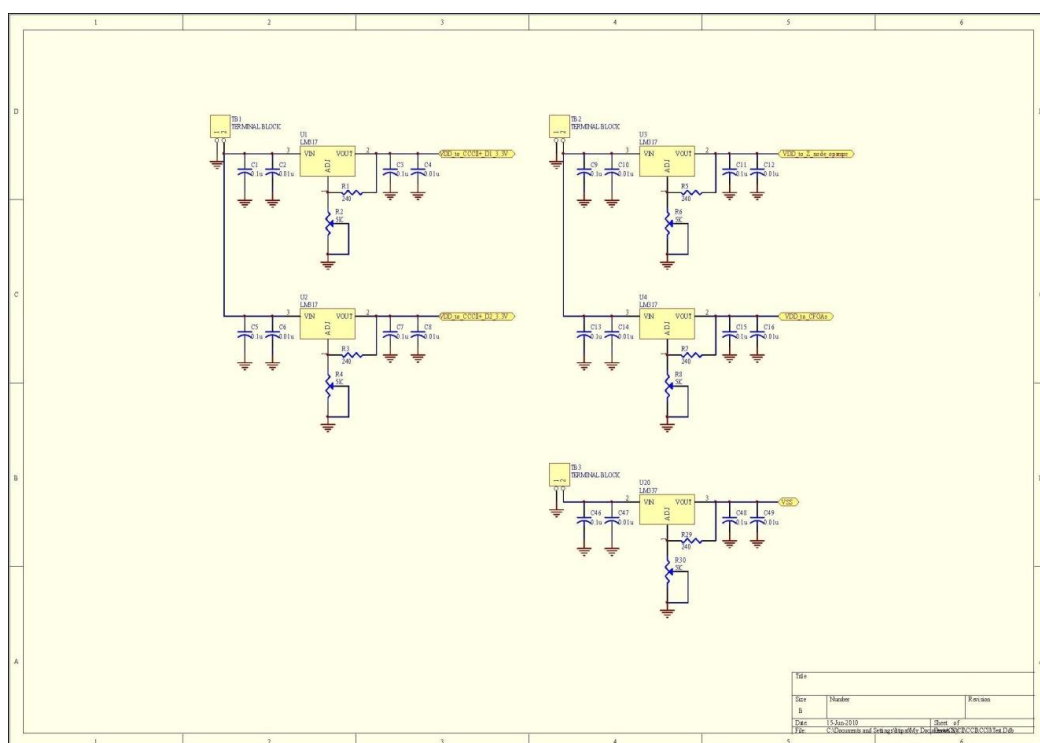


**Figure 7-4.** Power supplies schematic for all the test and application circuits in the board

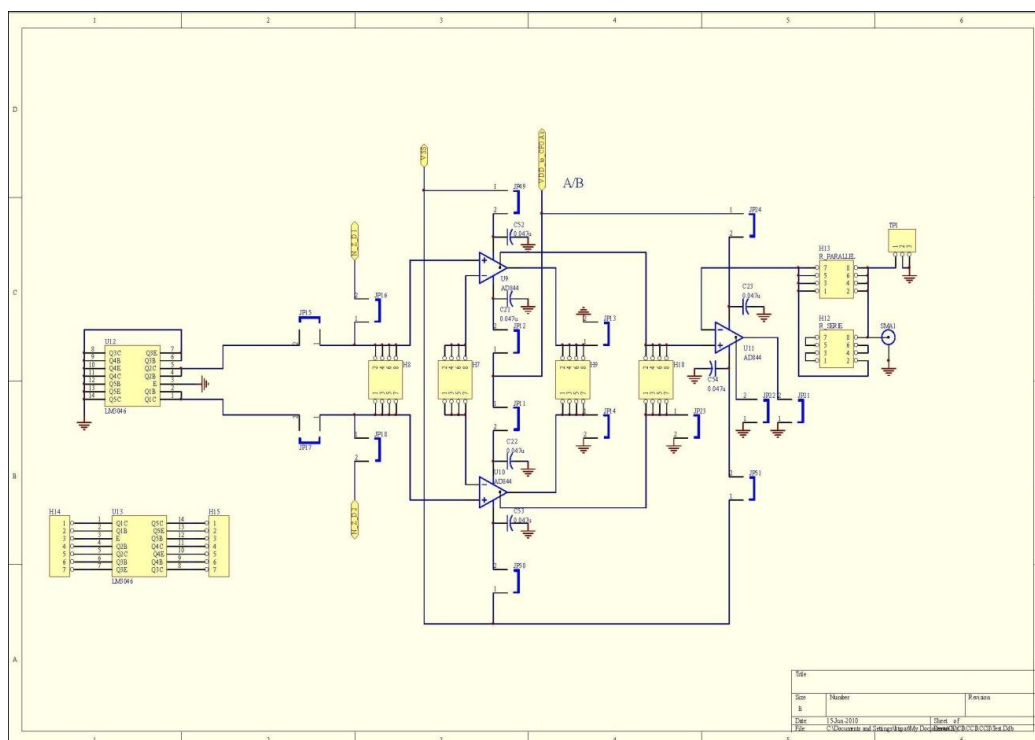


**Figure 7-5.** Division circuit schematic for urea-to-creatinine ratio using CCCII+

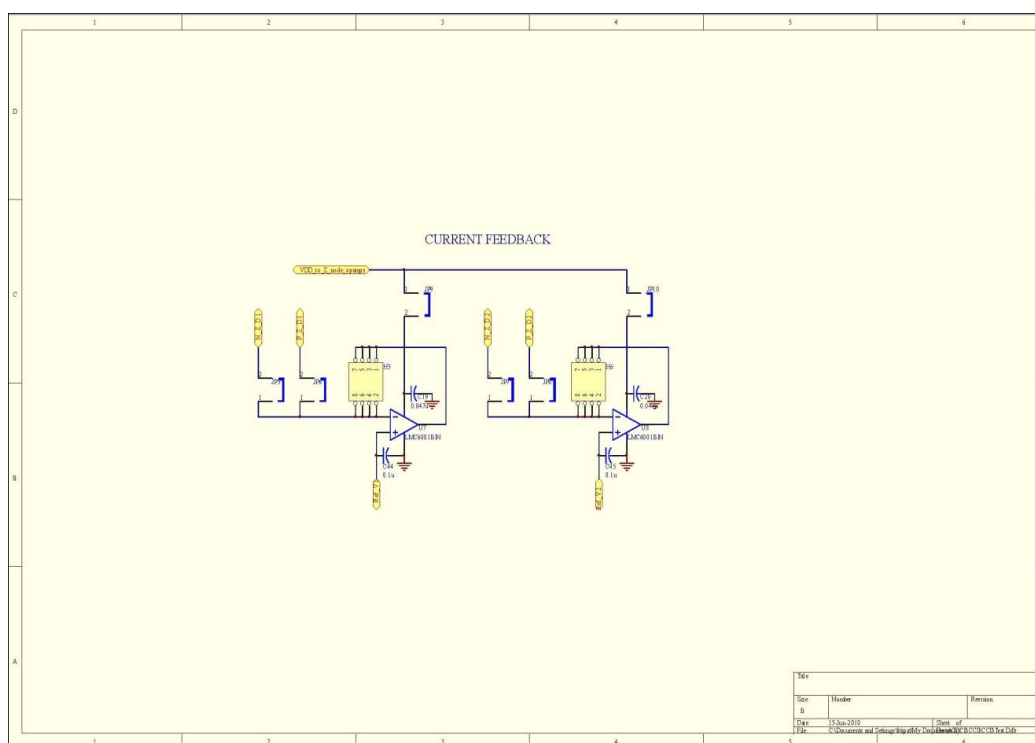


**Figure 7-6.** Voltage to current converter circuit schematic used in buffer capacity measurement

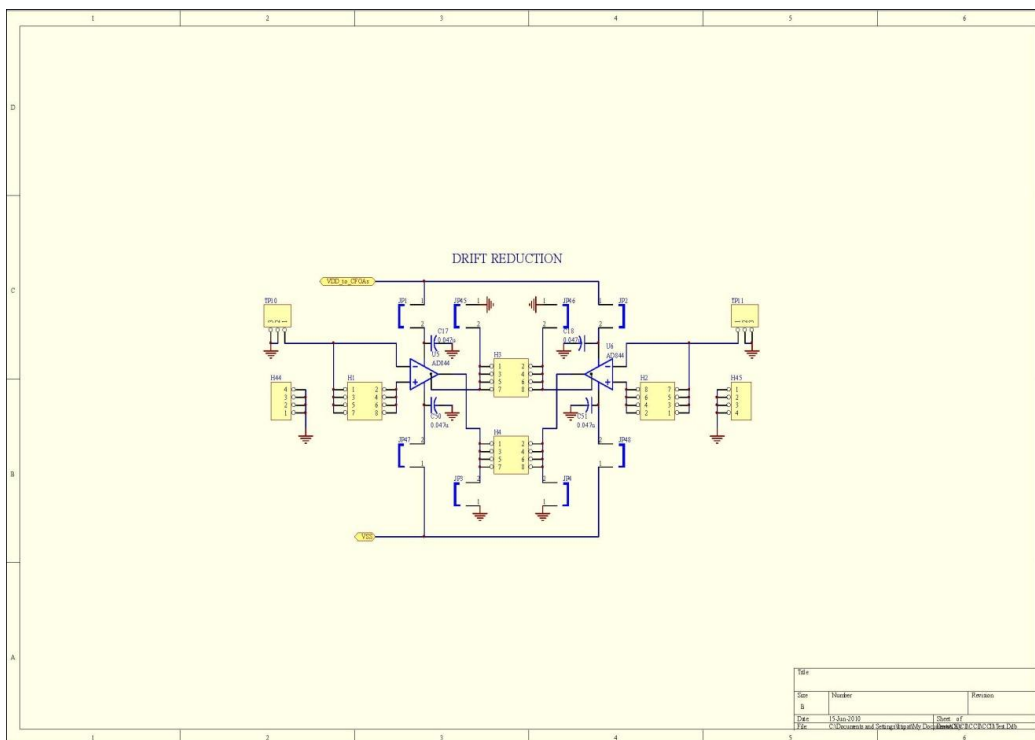


**Figure 7-7.** Instrumentation amplifier circuit schematic using CCCII+

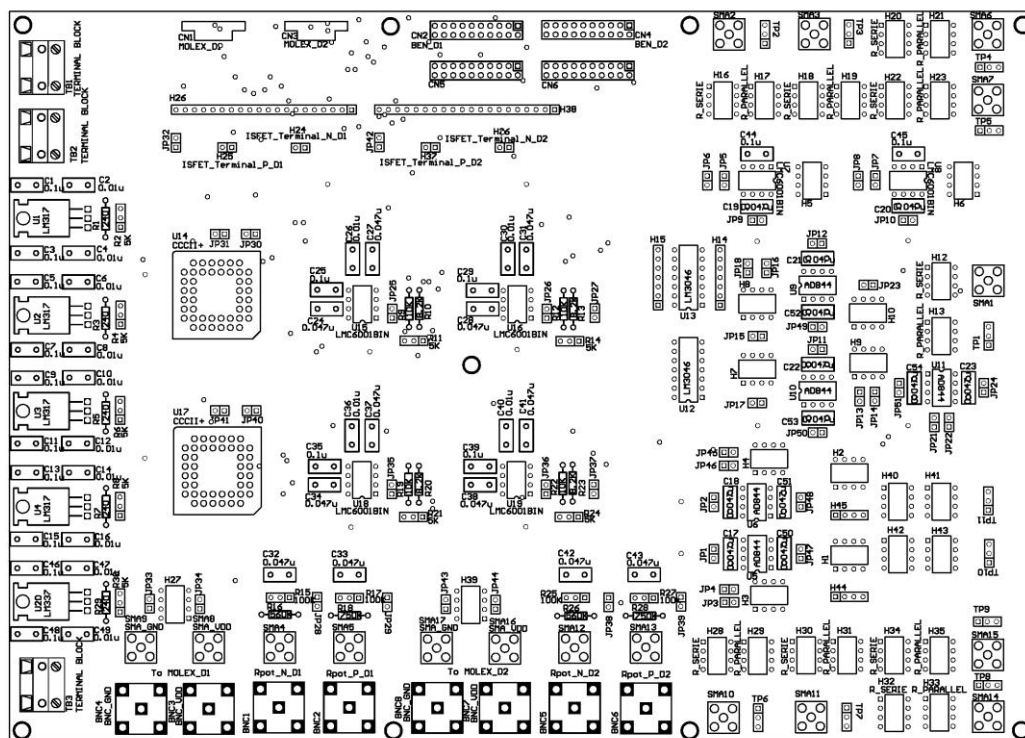


**Figure 7-8.** Top overlay layout

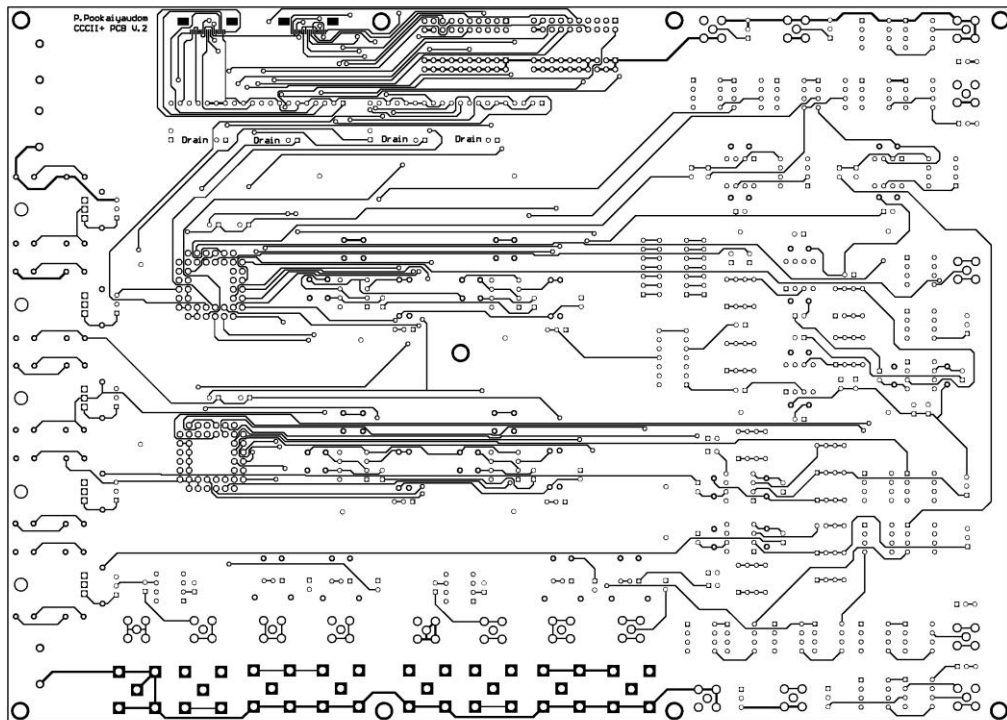


Figure 7-9. Top layer layout

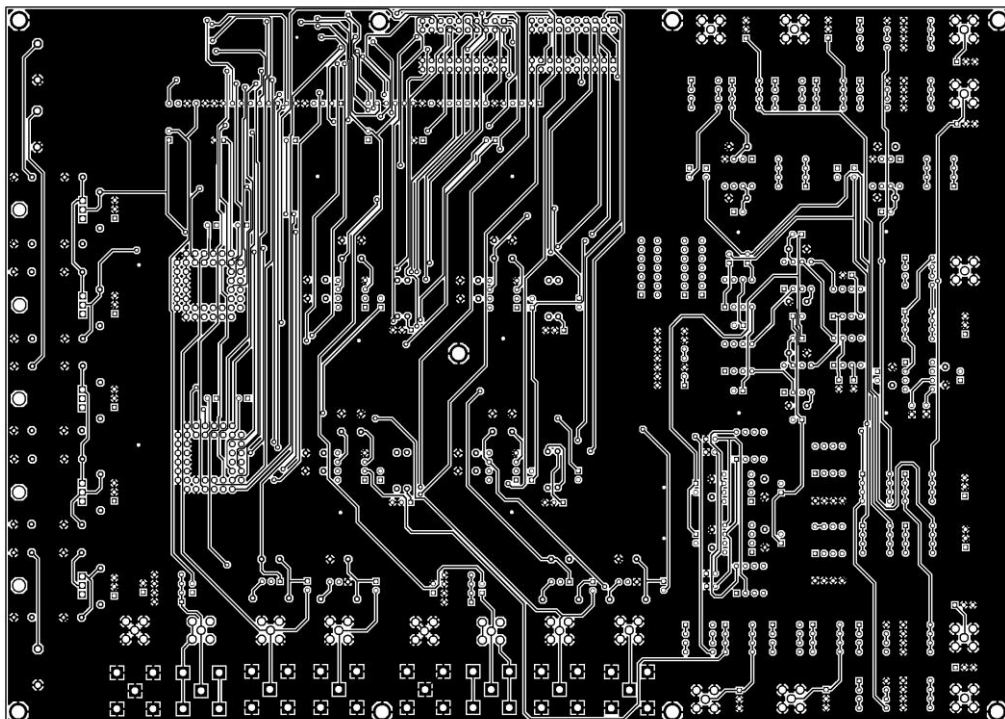


Figure 7-10. Bottom layer layout

## Appendix C

### CCCI<sup>+</sup>: Voltage Input/Output Transfer and Titration test

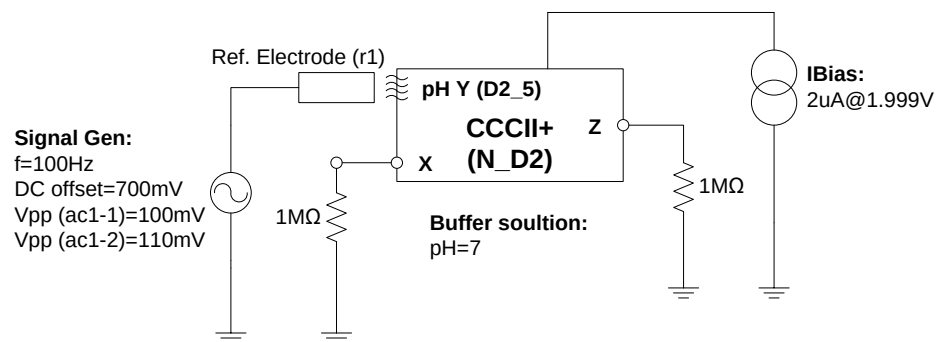


**Figure 7-11.** Parameters for voltage transfer test of CCCII<sup>+</sup> (N\_D2) and Sentron ISFET N-Channel (D2\_5)

**Table 7-3.** Measured results of Sentron ISFET N-Chanel (D2\_5), Test (ac1-1), using CCCII+ and source-follower benchmark readout circuit

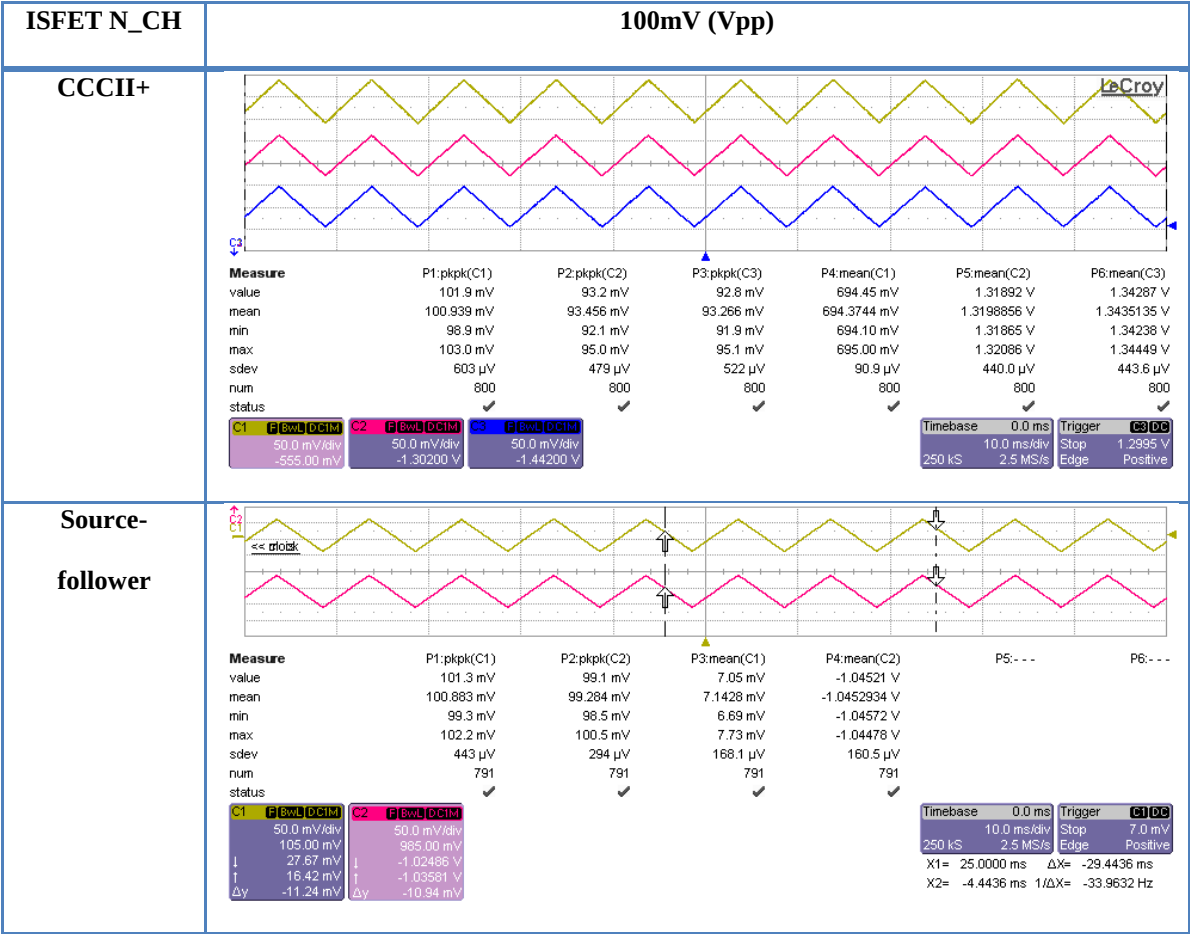
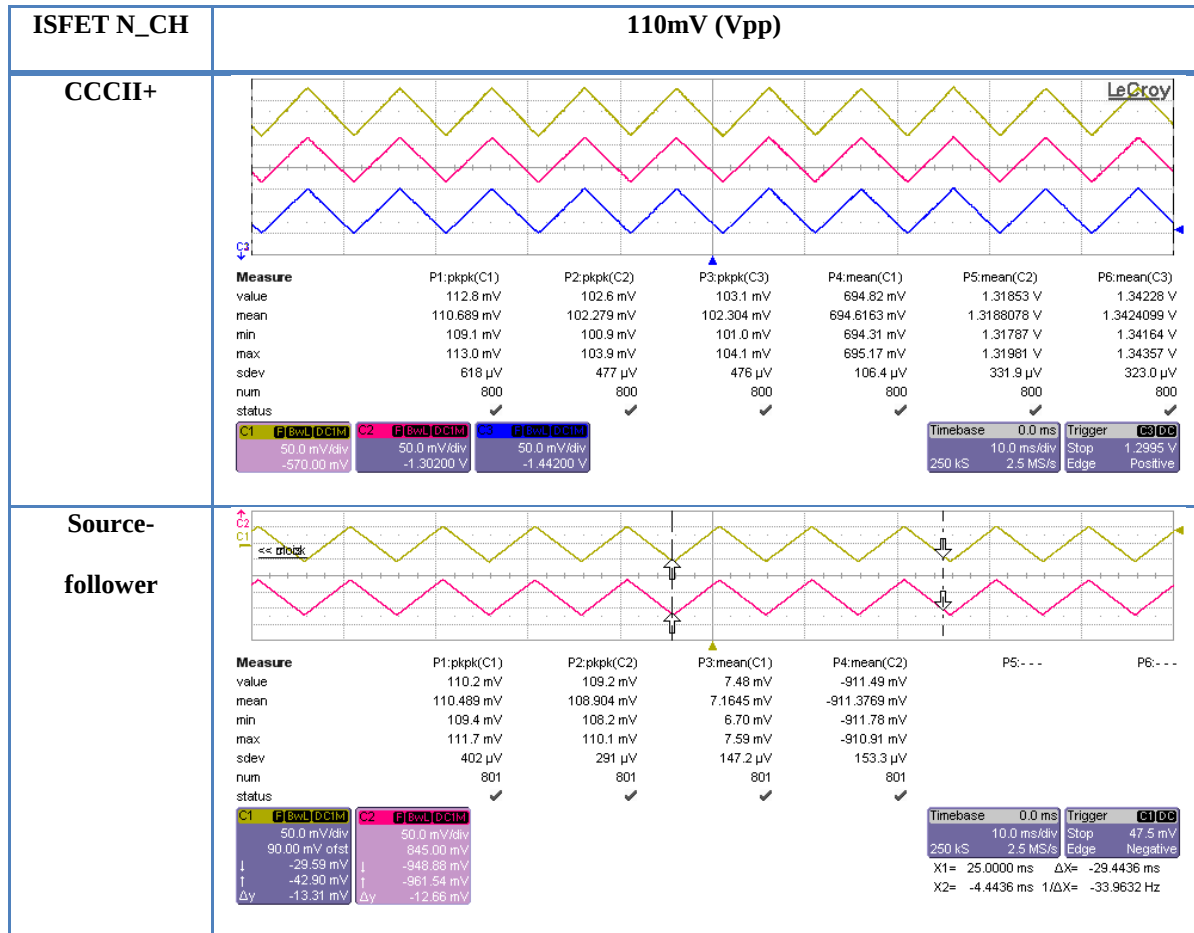


**Table 7-4.** Measured results of Sentron ISFET N-Chanel (D2\_5), Test (ac1-2), using CCCII+ and source-follower benchmark readout circuit



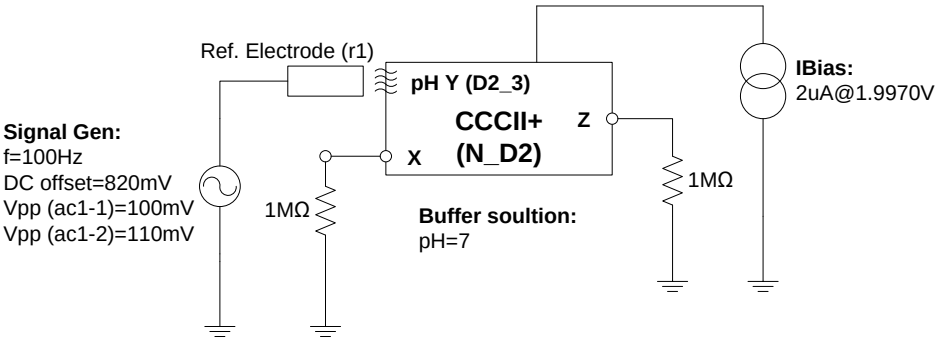


Figure 7-12. Parameters for voltage transfer test of CCCII+ (N\_D2) and Sentron ISFET N-Chanel (D2\_3)

Table 7-5. Measured results of Sentron ISFET N-Chanel (D2\_3), Test (ac1-1), using CCCII+ and source-follower benchmark readout circuit

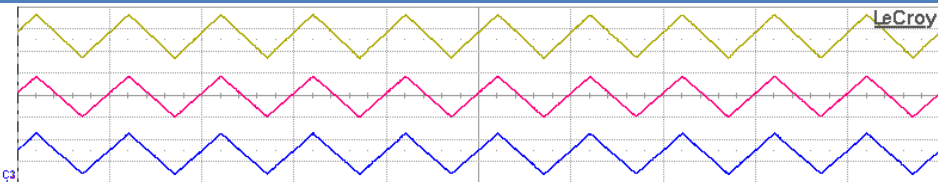
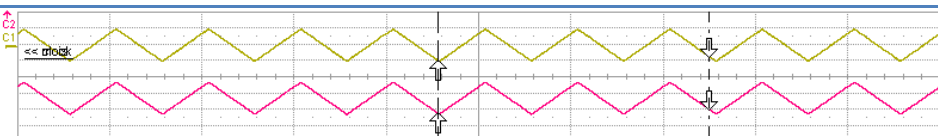
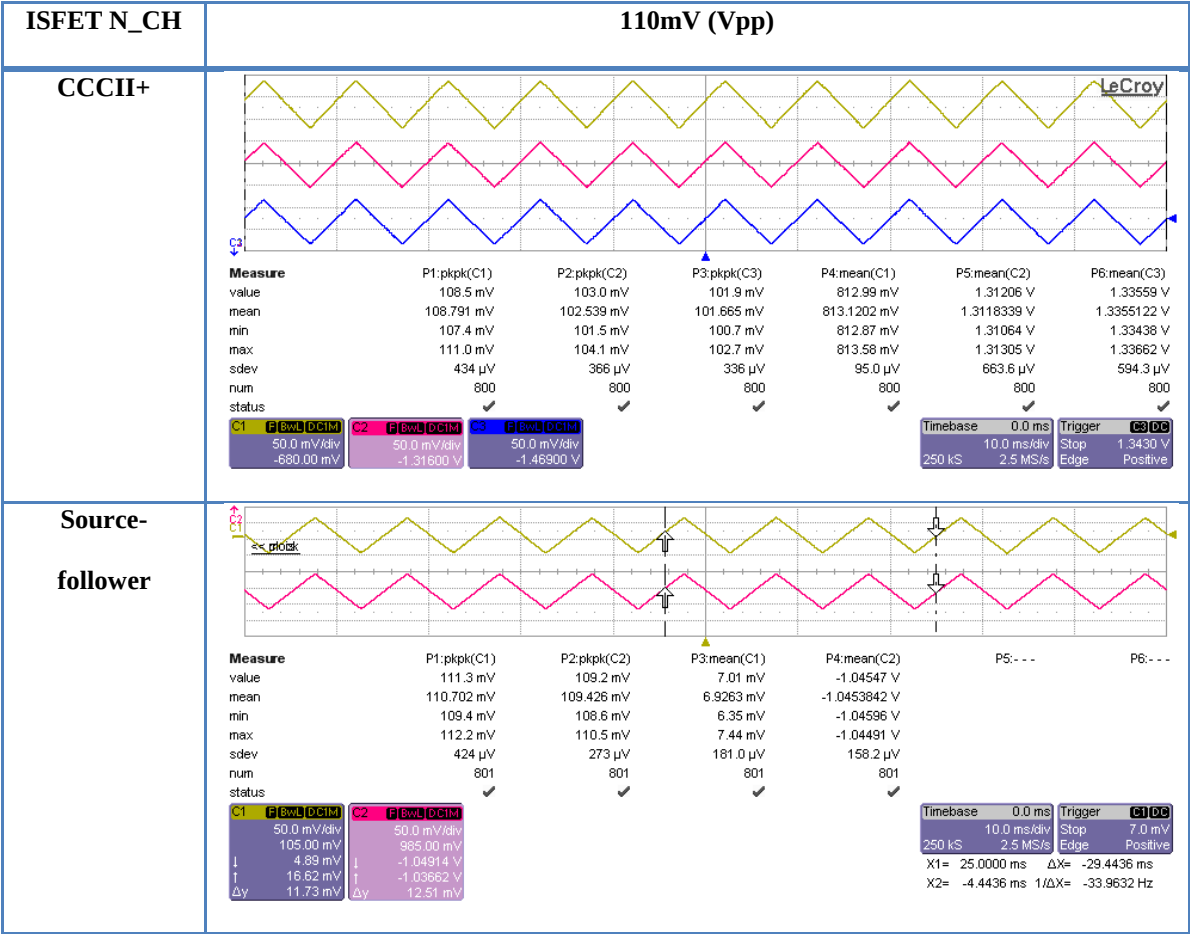
| ISFET N_CH      | 100mV (Vpp)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |             |             |              |             |             |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |          |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|-------------|--------------|-------------|-------------|-------------|-------------|-------|----------|---------|---------|------------|-----------|-----------|------|------------|-----------|-----------|--------------|-------------|-------------|-----|---------|---------|---------|------------|-----------|-----------|-----|----------|----------|---------|------------|-----------|-----------|------|--------|--------|----------|----------|----------|----------|-----|-----|-----|-----|-----|-----|-----|--------|---|---|---|---|---|---|
| CCCII+          | <div></div> <table><tr><th>Measure</th><th>P1:pkpk(C1)</th><th>P2:pkpk(C2)</th><th>P3:pkpk(C3)</th><th>P4:mean(C1)</th><th>P5:mean(C2)</th><th>P6:mean(C3)</th></tr><tr><td>value</td><td>99.1 mV</td><td>93.3 mV</td><td>93.9 mV</td><td>813.19 mV</td><td>1.31253 V</td><td>1.33598 V</td></tr><tr><td>mean</td><td>99.412 mV</td><td>93.424 mV</td><td>93.680 mV</td><td>813.1412 mV</td><td>1.3135809 V</td><td>1.3370128 V</td></tr><tr><td>min</td><td>98.1 mV</td><td>92.4 mV</td><td>92.6 mV</td><td>812.86 mV</td><td>1.31186 V</td><td>1.33507 V</td></tr><tr><td>max</td><td>101.3 mV</td><td>95.9 mV</td><td>95.9 mV</td><td>813.75 mV</td><td>1.31537 V</td><td>1.33900 V</td></tr><tr><td>sdev</td><td>485 μV</td><td>408 μV</td><td>370 μV</td><td>113.1 μV</td><td>874.9 μV</td><td>894.7 μV</td></tr><tr><td>num</td><td>801</td><td>801</td><td>801</td><td>801</td><td>801</td><td>801</td></tr><tr><td>status</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td></tr></table> <div><div>C1: 50.0 mV/div<br/>50.0 mV/div<br/>-680.00 mV</div><div>C2: 50.0 mV/div<br/>50.0 mV/div<br/>-1.31600 V</div><div>C3: 50.0 mV/div<br/>50.0 mV/div<br/>-1.46900 V</div></div> <div>Timebase: 0.0 ms<br/>10.0 ms/div<br/>250 kS</div> <div>Trigger: Stop<br/>1.3430 V<br/>Edge<br/>Positive</div> | Measure     | P1:pkpk(C1) | P2:pkpk(C2)  | P3:pkpk(C3) | P4:mean(C1) | P5:mean(C2) | P6:mean(C3) | value | 99.1 mV  | 93.3 mV | 93.9 mV | 813.19 mV  | 1.31253 V | 1.33598 V | mean | 99.412 mV  | 93.424 mV | 93.680 mV | 813.1412 mV  | 1.3135809 V | 1.3370128 V | min | 98.1 mV | 92.4 mV | 92.6 mV | 812.86 mV  | 1.31186 V | 1.33507 V | max | 101.3 mV | 95.9 mV  | 95.9 mV | 813.75 mV  | 1.31537 V | 1.33900 V | sdev | 485 μV | 408 μV | 370 μV   | 113.1 μV | 874.9 μV | 894.7 μV | num | 801 | 801 | 801 | 801 | 801 | 801 | status | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Measure         | P1:pkpk(C1)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | P2:pkpk(C2) | P3:pkpk(C3) | P4:mean(C1)  | P5:mean(C2) | P6:mean(C3) |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |          |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| value           | 99.1 mV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 93.3 mV     | 93.9 mV     | 813.19 mV    | 1.31253 V   | 1.33598 V   |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |          |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| mean            | 99.412 mV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 93.424 mV   | 93.680 mV   | 813.1412 mV  | 1.3135809 V | 1.3370128 V |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |          |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| min             | 98.1 mV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 92.4 mV     | 92.6 mV     | 812.86 mV    | 1.31186 V   | 1.33507 V   |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |          |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| max             | 101.3 mV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 95.9 mV     | 95.9 mV     | 813.75 mV    | 1.31537 V   | 1.33900 V   |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |          |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| sdev            | 485 μV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 408 μV      | 370 μV      | 113.1 μV     | 874.9 μV    | 894.7 μV    |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |          |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| num             | 801                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 801         | 801         | 801          | 801         | 801         |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |          |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| status          | ✓                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | ✓           | ✓           | ✓            | ✓           | ✓           |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |          |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| Source-follower | <div></div> <table><tr><th>Measure</th><th>P1:pkpk(C1)</th><th>P2:pkpk(C2)</th><th>P3:mean(C1)</th><th>P4:mean(C2)</th><th>P5:--</th><th>P6:--</th></tr><tr><td>value</td><td>100.0 mV</td><td>99.2 mV</td><td>6.87 mV</td><td>-911.10 mV</td><td></td><td></td></tr><tr><td>mean</td><td>100.645 mV</td><td>99.143 mV</td><td>7.1656 mV</td><td>-911.0331 mV</td><td></td><td></td></tr><tr><td>min</td><td>99.7 mV</td><td>98.3 mV</td><td>6.64 mV</td><td>-911.49 mV</td><td></td><td></td></tr><tr><td>max</td><td>102.2 mV</td><td>100.2 mV</td><td>7.71 mV</td><td>-910.58 mV</td><td></td><td></td></tr><tr><td>sdev</td><td>409 μV</td><td>287 μV</td><td>180.6 μV</td><td>149.2 μV</td><td></td><td></td></tr><tr><td>num</td><td>802</td><td>802</td><td>802</td><td>802</td><td></td><td></td></tr><tr><td>status</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td></tr></table> <div><div>C1: 50.0 mV/div<br/>90.00 mV orst<br/>-28.31 mV<br/>-40.59 mV<br/>-12.28 mV<br/>Δy</div><div>C2: 50.0 mV/div<br/>845.00 mV<br/>-945.79 mV<br/>-956.99 mV<br/>-11.20 mV<br/>Δy</div></div> <div>Timebase: 0.0 ms<br/>10.0 ms/div<br/>250 kS</div> <div>Trigger: Stop<br/>47.5 mV<br/>Edge<br/>Negative</div> <div>X1= 25.0000 ms<br/>X2= -4.4436 ms<br/>ΔX= -29.4436 ms<br/>1/ΔX= -33.9632 Hz</div>     | Measure     | P1:pkpk(C1) | P2:pkpk(C2)  | P3:mean(C1) | P4:mean(C2) | P5:--       | P6:--       | value | 100.0 mV | 99.2 mV | 6.87 mV | -911.10 mV |           |           | mean | 100.645 mV | 99.143 mV | 7.1656 mV | -911.0331 mV |             |             | min | 99.7 mV | 98.3 mV | 6.64 mV | -911.49 mV |           |           | max | 102.2 mV | 100.2 mV | 7.71 mV | -910.58 mV |           |           | sdev | 409 μV | 287 μV | 180.6 μV | 149.2 μV |          |          | num | 802 | 802 | 802 | 802 |     |     | status | ✓ | ✓ | ✓ | ✓ |   |   |
| Measure         | P1:pkpk(C1)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | P2:pkpk(C2) | P3:mean(C1) | P4:mean(C2)  | P5:--       | P6:--       |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |          |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| value           | 100.0 mV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 99.2 mV     | 6.87 mV     | -911.10 mV   |             |             |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |          |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| mean            | 100.645 mV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 99.143 mV   | 7.1656 mV   | -911.0331 mV |             |             |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |          |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| min             | 99.7 mV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 98.3 mV     | 6.64 mV     | -911.49 mV   |             |             |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |          |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| max             | 102.2 mV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 100.2 mV    | 7.71 mV     | -910.58 mV   |             |             |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |          |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| sdev            | 409 μV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 287 μV      | 180.6 μV    | 149.2 μV     |             |             |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |          |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| num             | 802                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 802         | 802         | 802          |             |             |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |          |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| status          | ✓                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | ✓           | ✓           | ✓            |             |             |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |          |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |

**Table 7-6.** Measured results of Sentron ISFET N-Chanel (D2\_3), Test (ac1-2), using CCCII+ and source-follower benchmark readout circuit



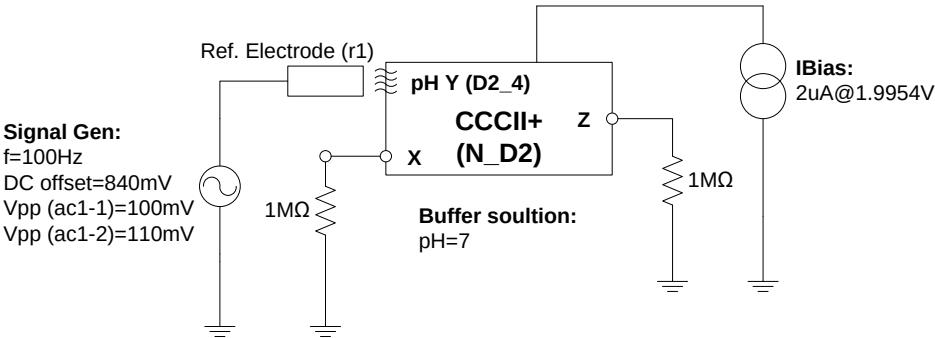
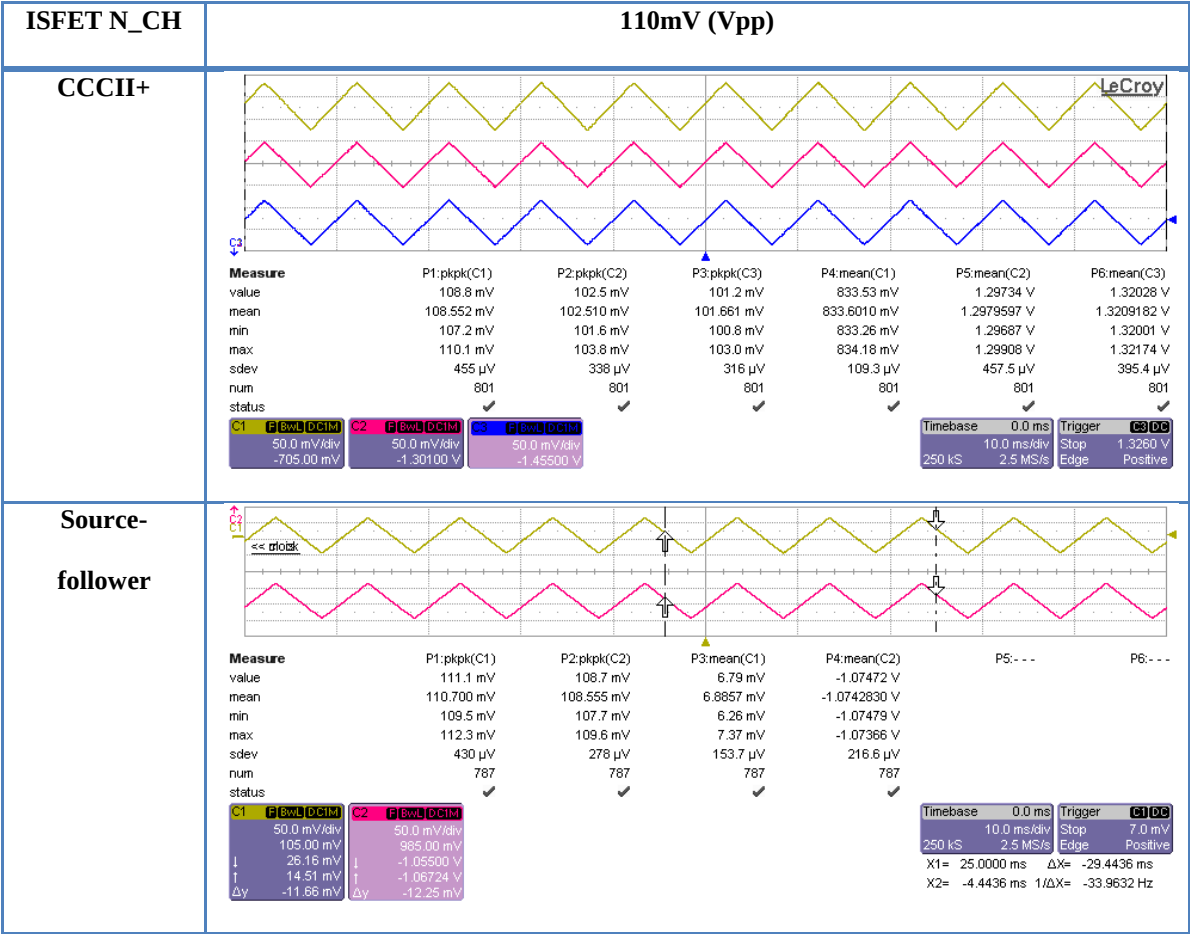


Figure 7-13. Parameters for voltage transfer test of CCCII+ (N\_D2) and Sentron ISFET N-Chanel (D2\_4)

Table 7-7. Measured results of Sentron ISFET N-Chanel (D2\_4), Test (ac1-1), using CCCII+ and source-follower benchmark readout circuit

| ISFET N_CH      | 100mV (Vpp)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |             |             |              |             |             |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |         |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|-------------|--------------|-------------|-------------|-------------|-------------|-------|----------|---------|---------|------------|-----------|-----------|------|------------|-----------|-----------|--------------|-------------|-------------|-----|---------|---------|---------|------------|-----------|-----------|-----|----------|---------|---------|------------|-----------|-----------|------|--------|--------|----------|----------|----------|----------|-----|-----|-----|-----|-----|-----|-----|--------|---|---|---|---|---|---|
| CCCII+          | <div><table><tr><th>Measure</th><th>P1:pkpk(C1)</th><th>P2:pkpk(C2)</th><th>P3:pkpk(C3)</th><th>P4:mean(C1)</th><th>P5:mean(C2)</th><th>P6:mean(C3)</th></tr><tr><td>value</td><td>99.8 mV</td><td>93.0 mV</td><td>93.6 mV</td><td>833.24 mV</td><td>1.29994 V</td><td>1.32268 V</td></tr><tr><td>mean</td><td>99.304 mV</td><td>93.086 mV</td><td>93.376 mV</td><td>833.3506 mV</td><td>1.3004172 V</td><td>1.3234222 V</td></tr><tr><td>min</td><td>98.3 mV</td><td>92.0 mV</td><td>92.3 mV</td><td>833.04 mV</td><td>1.29936 V</td><td>1.32254 V</td></tr><tr><td>max</td><td>100.6 mV</td><td>94.2 mV</td><td>94.6 mV</td><td>833.78 mV</td><td>1.30180 V</td><td>1.32463 V</td></tr><tr><td>sdev</td><td>398 μV</td><td>321 μV</td><td>344 μV</td><td>101.2 μV</td><td>454.0 μV</td><td>435.9 μV</td></tr><tr><td>num</td><td>837</td><td>837</td><td>837</td><td>837</td><td>837</td><td>837</td></tr><tr><td>status</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td></tr></table><div><div>C1: 50.0 mV/div, -705.00 mV</div><div>C2: 50.0 mV/div, -1.30100 V</div><div>C3: 50.0 mV/div, -1.45500 V</div></div><div>Timebase: 0.0 ms, 10.0 ms/div, 250 kS</div><div>Trigger: Stop, 1.3260 V, Edge, Positive</div></div> | Measure     | P1:pkpk(C1) | P2:pkpk(C2)  | P3:pkpk(C3) | P4:mean(C1) | P5:mean(C2) | P6:mean(C3) | value | 99.8 mV  | 93.0 mV | 93.6 mV | 833.24 mV  | 1.29994 V | 1.32268 V | mean | 99.304 mV  | 93.086 mV | 93.376 mV | 833.3506 mV  | 1.3004172 V | 1.3234222 V | min | 98.3 mV | 92.0 mV | 92.3 mV | 833.04 mV  | 1.29936 V | 1.32254 V | max | 100.6 mV | 94.2 mV | 94.6 mV | 833.78 mV  | 1.30180 V | 1.32463 V | sdev | 398 μV | 321 μV | 344 μV   | 101.2 μV | 454.0 μV | 435.9 μV | num | 837 | 837 | 837 | 837 | 837 | 837 | status | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Measure         | P1:pkpk(C1)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | P2:pkpk(C2) | P3:pkpk(C3) | P4:mean(C1)  | P5:mean(C2) | P6:mean(C3) |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |         |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| value           | 99.8 mV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 93.0 mV     | 93.6 mV     | 833.24 mV    | 1.29994 V   | 1.32268 V   |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |         |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| mean            | 99.304 mV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 93.086 mV   | 93.376 mV   | 833.3506 mV  | 1.3004172 V | 1.3234222 V |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |         |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| min             | 98.3 mV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 92.0 mV     | 92.3 mV     | 833.04 mV    | 1.29936 V   | 1.32254 V   |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |         |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| max             | 100.6 mV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 94.2 mV     | 94.6 mV     | 833.78 mV    | 1.30180 V   | 1.32463 V   |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |         |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| sdev            | 398 μV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 321 μV      | 344 μV      | 101.2 μV     | 454.0 μV    | 435.9 μV    |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |         |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| num             | 837                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 837         | 837         | 837          | 837         | 837         |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |         |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| status          | ✓                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | ✓           | ✓           | ✓            | ✓           | ✓           |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |         |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| Source-follower | <div><table><tr><th>Measure</th><th>P1:pkpk(C1)</th><th>P2:pkpk(C2)</th><th>P3:mean(C1)</th><th>P4:mean(C2)</th><th>P5:---</th><th>P6:---</th></tr><tr><td>value</td><td>100.4 mV</td><td>99.0 mV</td><td>6.84 mV</td><td>-1.07360 V</td><td></td><td></td></tr><tr><td>mean</td><td>100.822 mV</td><td>98.862 mV</td><td>6.8647 mV</td><td>-1.0726227 V</td><td></td><td></td></tr><tr><td>min</td><td>99.6 mV</td><td>98.1 mV</td><td>6.39 mV</td><td>-1.07398 V</td><td></td><td></td></tr><tr><td>max</td><td>102.2 mV</td><td>99.8 mV</td><td>7.50 mV</td><td>-1.06945 V</td><td></td><td></td></tr><tr><td>sdev</td><td>435 μV</td><td>280 μV</td><td>163.4 μV</td><td>944.3 μV</td><td></td><td></td></tr><tr><td>num</td><td>798</td><td>798</td><td>798</td><td>798</td><td></td><td></td></tr><tr><td>status</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td></tr></table><div><div>C1: 50.0 mV/div, 105.00 mV</div><div>C2: 50.0 mV/div, 985.00 mV</div></div><div>Timebase: 0.0 ms, 10.0 ms/div, 250 kS</div><div>Trigger: Stop, 7.0 mV, Edge, Positive</div><div>X1= 25.0000 ms, X2= -4.4436 ms, ΔX= -29.4436 ms, 1/ΔX= -33.9632 Hz</div></div>                                                                    | Measure     | P1:pkpk(C1) | P2:pkpk(C2)  | P3:mean(C1) | P4:mean(C2) | P5:---      | P6:---      | value | 100.4 mV | 99.0 mV | 6.84 mV | -1.07360 V |           |           | mean | 100.822 mV | 98.862 mV | 6.8647 mV | -1.0726227 V |             |             | min | 99.6 mV | 98.1 mV | 6.39 mV | -1.07398 V |           |           | max | 102.2 mV | 99.8 mV | 7.50 mV | -1.06945 V |           |           | sdev | 435 μV | 280 μV | 163.4 μV | 944.3 μV |          |          | num | 798 | 798 | 798 | 798 |     |     | status | ✓ | ✓ | ✓ | ✓ |   |   |
| Measure         | P1:pkpk(C1)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | P2:pkpk(C2) | P3:mean(C1) | P4:mean(C2)  | P5:---      | P6:---      |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |         |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| value           | 100.4 mV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 99.0 mV     | 6.84 mV     | -1.07360 V   |             |             |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |         |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| mean            | 100.822 mV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 98.862 mV   | 6.8647 mV   | -1.0726227 V |             |             |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |         |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| min             | 99.6 mV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 98.1 mV     | 6.39 mV     | -1.07398 V   |             |             |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |         |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| max             | 102.2 mV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 99.8 mV     | 7.50 mV     | -1.06945 V   |             |             |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |         |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| sdev            | 435 μV                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 280 μV      | 163.4 μV    | 944.3 μV     |             |             |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |         |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| num             | 798                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 798         | 798         | 798          |             |             |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |         |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |
| status          | ✓                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | ✓           | ✓           | ✓            |             |             |             |             |       |          |         |         |            |           |           |      |            |           |           |              |             |             |     |         |         |         |            |           |           |     |          |         |         |            |           |           |      |        |        |          |          |          |          |     |     |     |     |     |     |     |        |   |   |   |   |   |   |

**Table 7-8.** Measured results of Sentron ISFET N-Chanel (D2\_4), Test (ac1-2), using CCCII+ and source-follower benchmark readout circuit



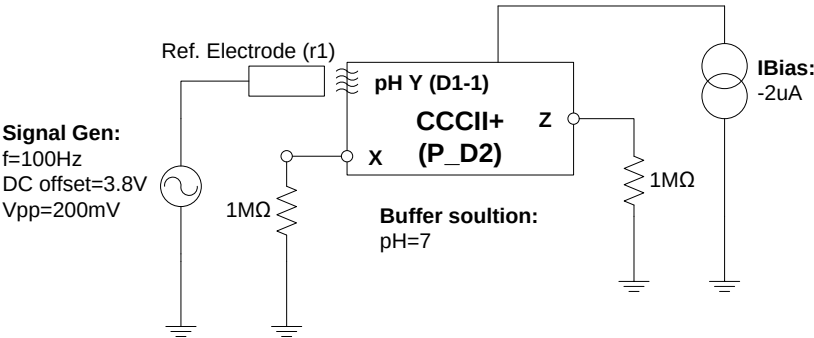
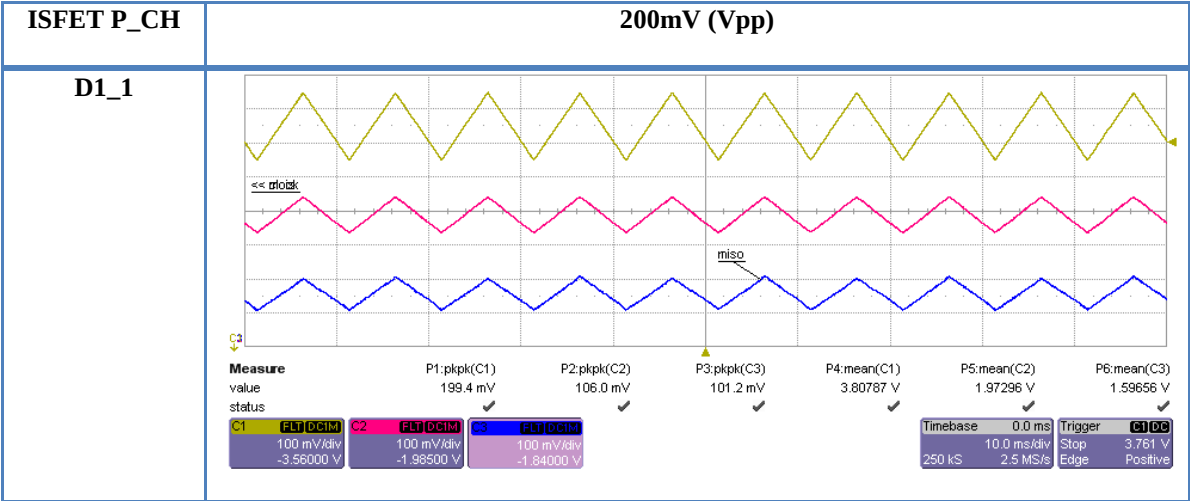


Figure 7-14. Parameters for voltage transfer test of CCCII+ (P\_D2) and DNA-E ISFET P-Chanel (D1\_1)

Table 7-9. Measured results of DNA-E ISFET P-Chanel (D1\_1)



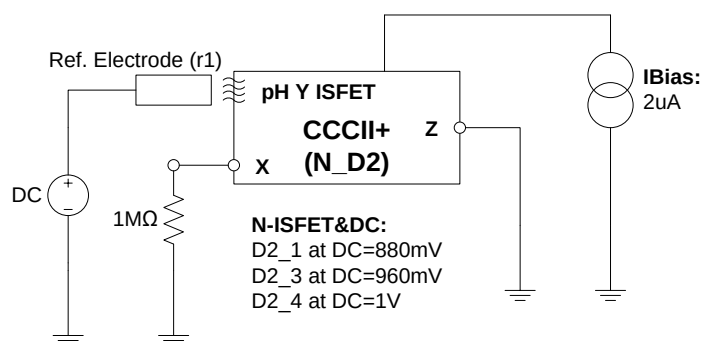


**Figure 7-15.** Parameters for titration test of CCCII+ (N\_D2) and Sentron ISFET N-Channels (D2\_1, D2\_3, D2\_4)

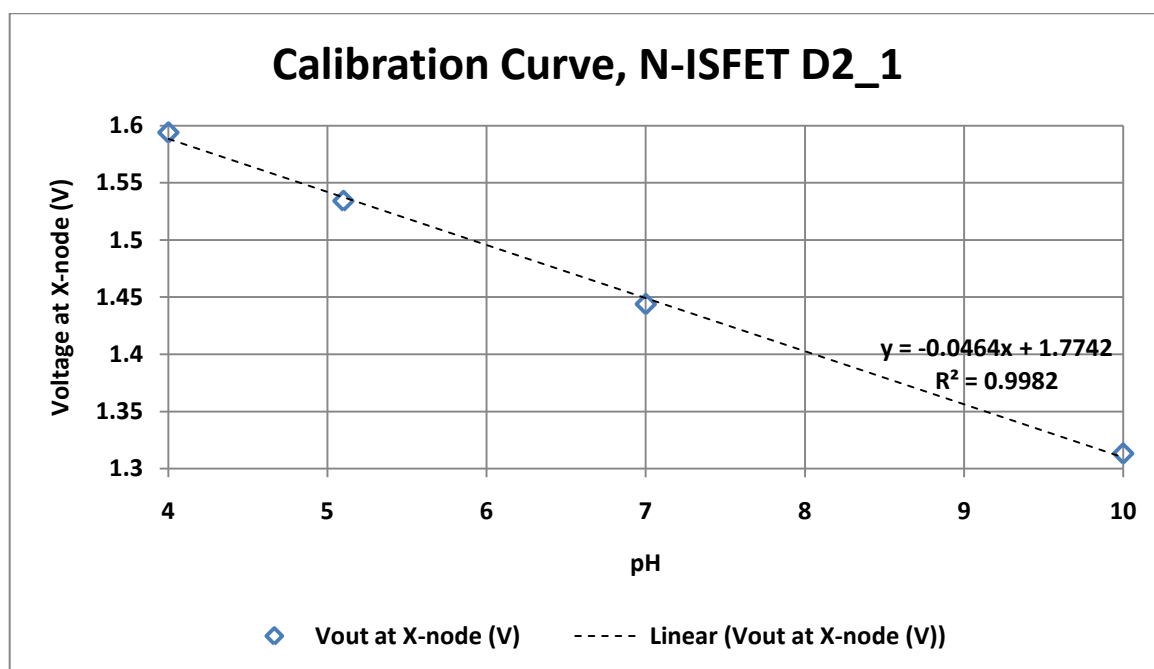


**Figure 7-16.** Measured titration curve of N-channel CCCII+ (N\_D2) with Sentron ISFET N-Chanel (D2\_1)

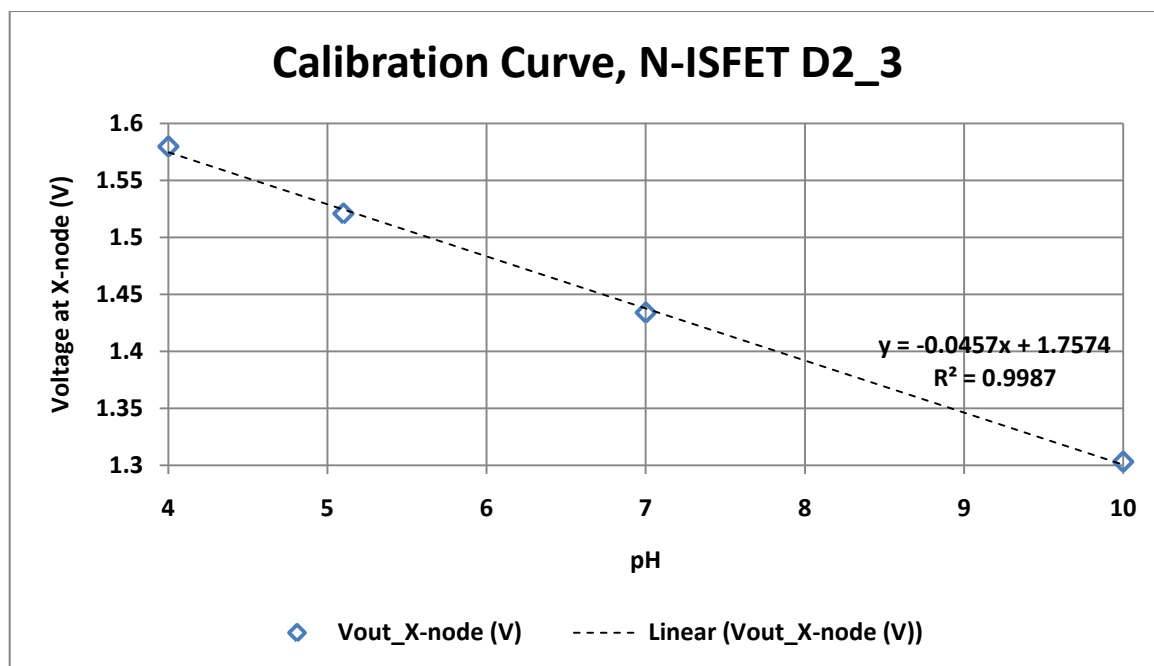


**Figure 7-17.** Measured titration curve of N-channel CCCII+ (N\_D2) with Sentron ISFET N-Chanel (D2\_3)

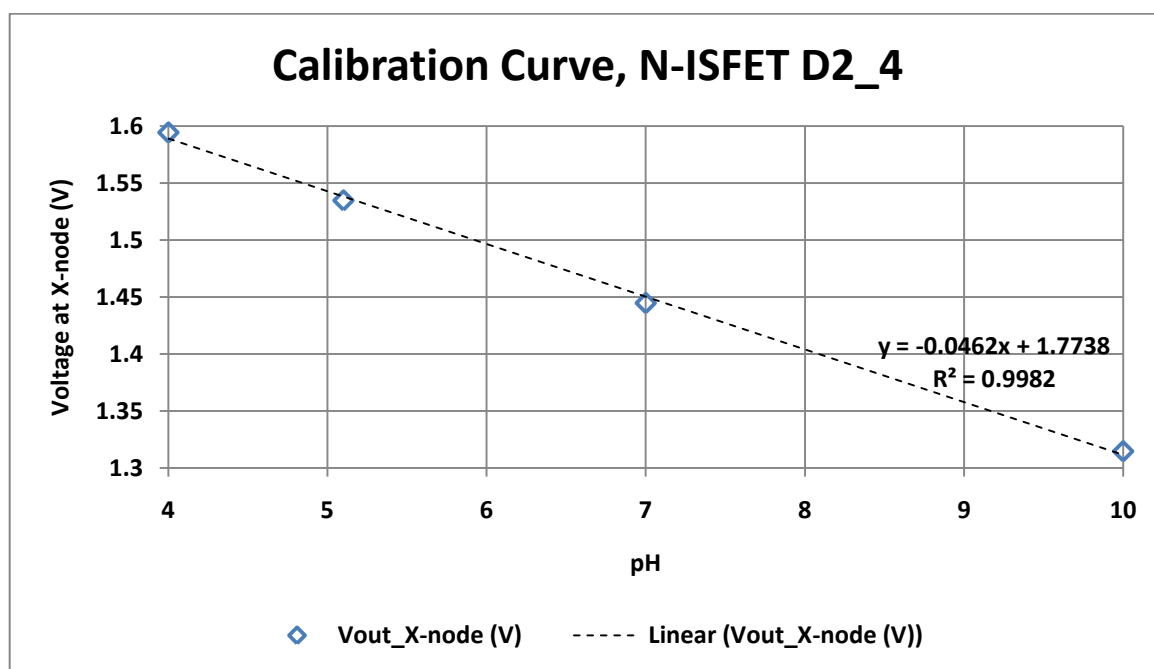


**Figure 7-18.** Measured titration curve of N-channel CCCII+ (N\_D2) with Sentron ISFET N-Chanel (D2\_4)

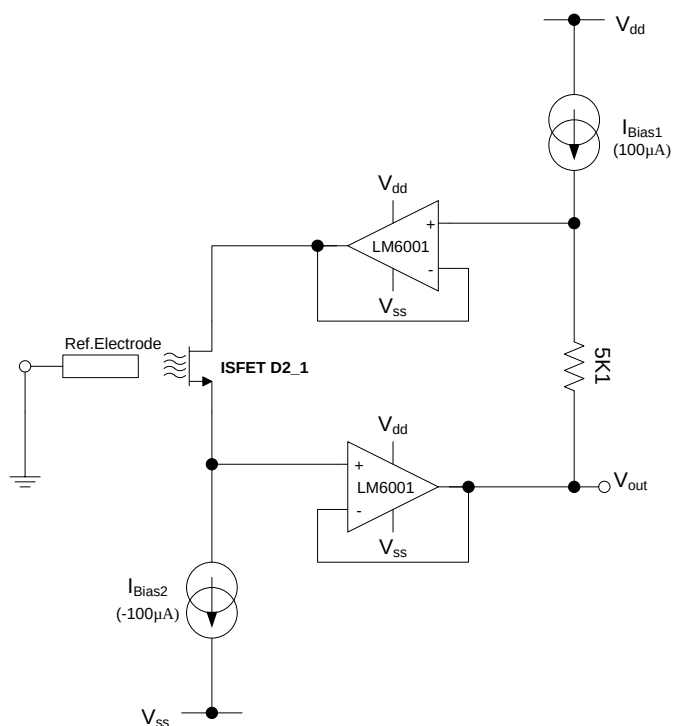


**Figure 7-19.** Parameters of source-follower bench mark circuit and Sentron ISFET N-Channels (D2\_1)

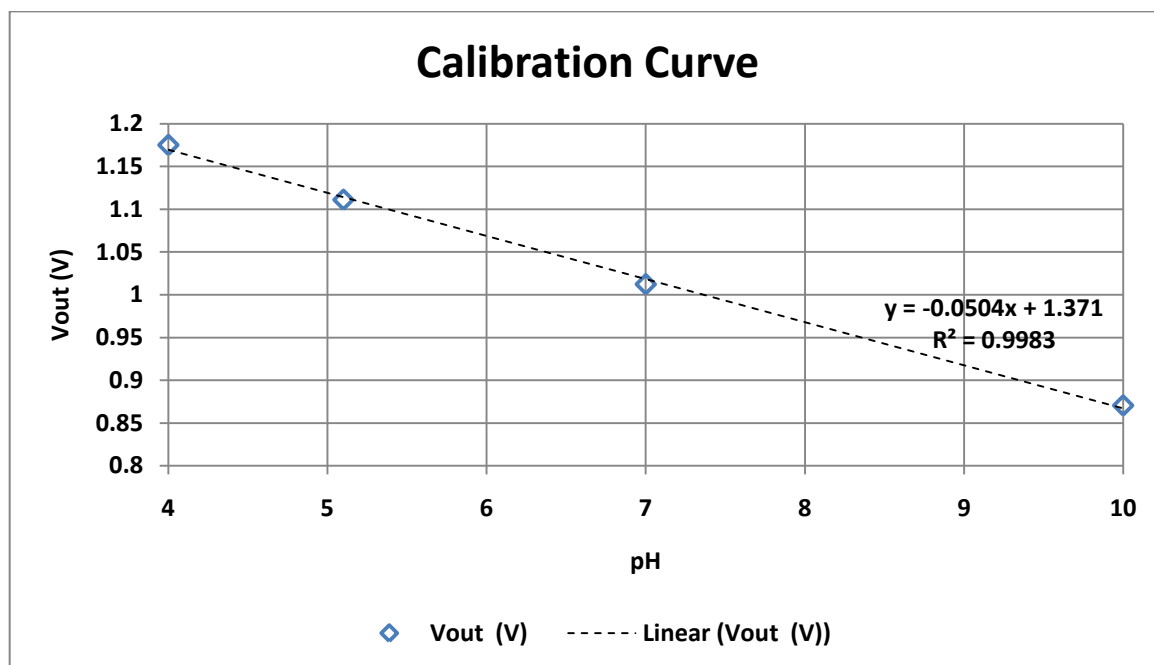


**Figure 7-20.** Measured titration curve of source-follower bench mark circuit with Sentron ISFET N-Chanel (D2\_1)

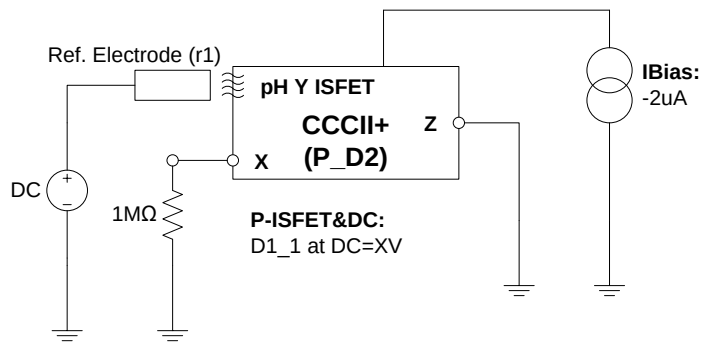


Figure 7-21. Parameters for titration test of CCCII+ (P\_D2) and DNA-E ISFET P-Channels (D1\_1)

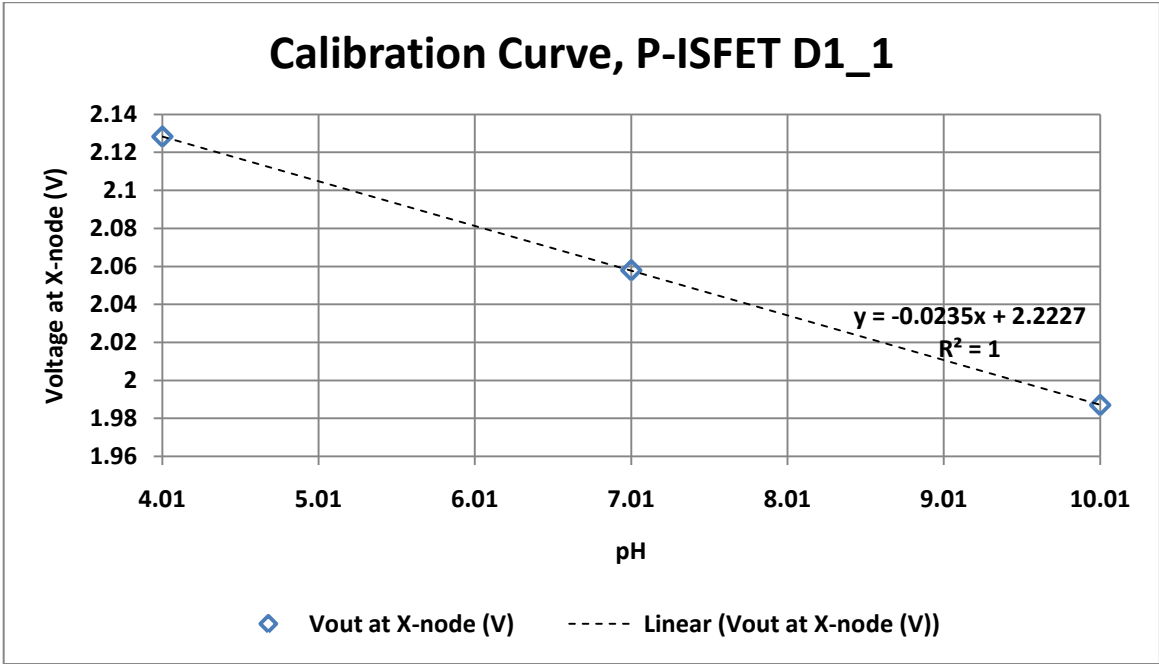


Figure 7-22. Measured titration curve of P-channel CCCII+ (P\_D2) with DNA-E ISFET P-Chanel (D1\_1)