

Nonlinear control of neurodegenerative diseases. A case study on optical illusion networks disrupted by diabetic retinopathy

A.G. Giannari ^{a,*}, A. Astolfi ^{a,b}

^a Department of Electrical and Electronic Engineering, Imperial College London, London, SW7 2AZ, UK

^b Dipartimento di Ingegneria Civile e Ingegneria Informatica, Università di Roma "Tor Vergata", Via del Politecnico, 1 00133 Roma, Italy

ARTICLE INFO

Communicated by X. Li

Keywords:

2D lateral inhibition
Optical illusions
Neurodegenerative diseases
Diabetic retinopathy
Drug optimisation
Iterative learning control

ABSTRACT

We present an efficient computational framework for the design of optimal drug delivery control strategies that can successfully treat a family of neurodegenerative diseases that originate from channelopathies and synaptopathies. To this end, we extend our previously introduced scalable and adaptable modelling framework that models heterogeneous Hodgkin–Huxley (HH) neuronal networks to account for the modular organisation of the neurons in the brain, e.g. interconnecting sub-networks of heterogeneous neurons. Based on this framework, we introduce a novel design of lateral inhibition networks to successfully reproduce 2D optical illusions that are known to occur in the human retina. We model the dynamic behaviour of Diabetic Retinopathy (DR), a neurodegenerative disease that progressively hinders the inherent ability of patients to distinguish optical illusions. We implement nonlinear control on accurate models of diabetic lateral inhibition neuronal networks to recover their functionality and investigate the effects of virtual drug administration. We utilise the healthy and diabetic optical illusions generated by these networks as a ‘computational’ phenotype to design therapies based on an adaptive terminal error iterative learning controller (TE-ILC). Therefore, we provide a comprehensive computational framework that is able to imitate the dynamics of healthy and diseased neuronal networks and we propose an adaptive nonlinear control strategy based on the error between output images that correspond to healthy and diseased conditions.

1. Introduction

Neurodegenerative diseases are defined as chronic medical conditions of the nervous system that are caused by the gradual deterioration and subsequent death of nerve cells within the brain [1]. They are known to impair the normal operation of the brain by disturbing its robustness to disturbances and sensitivity to external stimuli. A few of the most common neurodegenerative diseases are Alzheimer’s disease, Parkinson’s disease, and Huntington’s disease, with all displaying an early manifestation of synaptic malfunction [2]. This translates into severed communication between neurons and neuronal network structures that hinders the relay of information and has a detrimental effect in normal brain functionality that is expressed with the appearance of neurological symptoms. In addition to synaptic deterioration, ionic channel dysfunction within the neurons can also be responsible for a series of neurological abnormalities that result in neurodegeneration [3]. Both synaptopathies and channelopathies are disorders known to play an important role in the on-set and progression of neurodevelopmental (e.g. autism, bipolar, epilepsy) and neurodegenerative diseases, so they form ideal therapeutic targets [3,4]. Attenuating the level of

ionic channel malfunction via blockers or activators has demonstrated positive results in various neurological conditions such as neuropathic pain and epilepsy [5,6]. Impaired synaptic function has been linked to the appearance of symptoms for both Alzheimer’s and Huntington’s disease and can be considered a catalyst for the development of novel therapies that specifically target synapses [7–9]. The use of ketamine, a known synapse receptor antagonist, has demonstrated positive outcomes on the management of depression and anxiety [10]. Therefore, it is obvious that improving and potentially restoring the function of synaptic connections via targeted optimal drug delivery can lead to effective treatments for a wide range neurodegenerative diseases.

Modelling the electrophysiological dynamics of brain networks can provide an effective framework to study the complex mechanisms surrounding the on-set and progression of a variety of neurodegenerative disorders as well as explore the application of drugs on diseased neuronal networks for therapeutic purposes in a non-clinical set-up. The integration of mathematical modelling, medical information on diseases, and drug discovery can enhance the understanding on the processes underlying the transition from health to disease and assist

* Corresponding author.

E-mail addresses: ag3614@ic.ac.uk (A.G. Giannari), a.astolfi@imperial.ac.uk (A. Astolfi).

<https://doi.org/10.1016/j.neucom.2023.127099>

Received 26 May 2023; Received in revised form 28 September 2023; Accepted 6 December 2023

Available online 11 December 2023

0925-2312/© 2023 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

the development of novel treatment strategies [11]. Modelling neurological diseases requires an accurate and bio-physically meaningful model of neurons and neuronal network dynamics that incorporates the majority of the potential diseased states and parameters and gives the opportunity for the incorporation of external input, equivalent to a virtual drug. The Hodgkin–Huxley (HH) model fulfils the above requirements and is considered the most accurate, reliable, and efficient model of neuron dynamics [12]. The HH formalism has been utilised to model neurodegenerative diseases by modifying the original model accordingly and studying the resulting diseased neuronal behaviour. Perez et al. have used an augmented HH model to study the impaired neuronal activity observed in Alzheimer's disease in [13]. Ying et al. have combined the HH and neural mass model to study the effect of anti-epileptic drugs on neural dynamics in [14], while Knox et al. have used the HH formalism to study the mechanisms of pathogenesis and medication effects on childhood absence epilepsy in [15].

Mathematical modelling of diseased neuronal network dynamics in combination with control theory methods can have a radical impact on the design of optimal drug administration for the maintenance and treatment of a variety of neurodegenerative diseases. Controlling the behaviour of a neuronal dynamical system from a diseased to a healthy condition is highly non-trivial because of the complexity of the brain as a biological system that is characterised by strong nonlinearities and large dimensionality. There have been multiple applications of control on neuron dynamics to revert abnormal firing activity. In multiple instances bifurcation control has been applied to the HH model to investigate the change of bifurcation point as the means to avoid unwanted oscillations linked to Parkinson and epilepsy [16–19], while Frohlich et al. have applied a model-based feedback control scheme to control the generation of action potentials of single neurons in [20]. Ullah et al. have explored a Kalman filter based controller to annihilate seizures and restore normal neuronal activity in [21]. Finally, Schmetterling et al. have applied model-reference adaptive control to modulate conductance-based neuronal models in [22]. While the control of single neurons has been studied extensively, the control of large-scale brain neuronal networks remains ambiguous due to the complexities arising from heterogeneous nonlinear systems (the neurons) interacting with each other via heterogeneous potentially nonlinear routes (the synapses) under the effect of pharmacodynamics. The majority of attempts related to the control of neuronal networks concerns the synchronisation and desynchronisation of neuronal assemblies [23–25] and firing pattern tracking [26,27] via feedback and Kalman filtering control schemes.

The biological plausibility of the majority of the control attempts on neuronal networks is limited because of the idealistic use of the neurons voltage as a measurable output and the use of the external input current as the control variable which is not always feasible, especially when the treatment corresponding to the disease is in the form of a drug. Therefore, despite an increasing interest in the synergy between computational neuroscience and control theory there is a lack of an established bio-physically meaningful approach that combines accurate mathematical modelling of diseased neuronal networks in combination with nonlinear control strategies whereby a virtual drug drives a diseased network model to a healthy state by using plausible measurable outputs as feedback.

Previously, we have introduced a novel scalable and adaptable modelling framework to accurately model HH neuronal networks composed of neurons with different dynamic properties and distinct firing patterns based on a control-inspired feedback structure [12]. In addition, we have utilised the aforementioned framework to model bio-physically meaningful large-scale networks of lateral inhibition that successfully reproduce the 1D Mach Band optical illusion commonly occurring in the visual system [28]. We have argued that the structure of the proposed framework is ideal for applications of control methods both for modelling the effect of pharmacological substances as well as for modelling diseased neuron and network conditions.

In this paper, we present an efficient computational framework for the design of nonlinear control strategies that can successfully treat a family of neurodegenerative diseases originating from synaptopathies or channelopathies. For this purpose, we modify the structure of the proposed modelling framework to incorporate modular heterogeneous neuronal networks. Modularity, in this context, refers to the ability of the model to mimic the modular network organisation observed in the brain by allowing the interconnection of heterogeneous sub-networks. Modularity in the network ensures a good level of robustness and adaptability [29] and its modelling is therefore essential. This model adjustment gives the opportunity for the novel design of lateral inhibition networks that successfully reproduce 2D optical illusions that are known to take place in the human retina and can be an important indicator for normal retinal function. Our model successfully imitates the behaviour of the 2D Mach Band illusion and the Hermann–Hering grid illusion and therefore verifies the validity of our proposed extended modelling framework. We model the dynamic behaviour of Diabetic Retinopathy by treating it primarily as a synaptopathy and subsequently a neurodegenerative disease that progressively hinders the inherent ability of patients to distinguish optical illusions [30]. We implement nonlinear control on accurate models of diabetic lateral inhibition neuronal networks to recover their functionality and investigate the effects of virtual drug administration. We utilise the healthy and diabetic optical illusions generated by these networks as a ‘computational’ phenotype to design therapies based on an adaptive terminal error iterative learning controller (TE-ILC). Therefore, we provide a comprehensive computational framework that is able to imitate the dynamics of healthy and diseased neuronal networks and we propose an adaptive nonlinear control strategy based on the error between output images that correspond to healthy and diseased conditions. The accuracy of the healthy and diabetic lateral inhibition models, in this context, is determined by their ability to reproduce the known optical illusions as perceived by healthy individuals and patients with diabetic retinopathy. To guarantee the model accuracy, we have chosen Hodgkin–Huxley neuronal network dynamics with bio-meaningful parameters, we have incorporated the basic minimal structure of heterogeneous lateral inhibition networks in the retina as described in the literature [31] and we have manipulated the corresponding parameters according to observed neurodegeneration targets [32,33].

The novelty of the work presented in this paper is the combination of concepts in neuroscience, modelling, and control to tackle a complex problem in a non-standard way. This special application introduces a biologically-plausible modular, scalable, and adaptable computational framework based on augmented Hodgkin–Huxley equations to accurately model the function of 2D lateral inhibition networks. To the best of our knowledge, this is the first time the 2D Mach Band and Hermann–Hering grid illusions have been quantitatively modelled and accurately reproduced via simulations. In addition, this is the first time 2D optical illusions have been modelled in normal and diseased conditions and used to design a virtual therapy regimen for diabetic retinopathy. In this novel approach, a tangible and realistically measurable output has been used as feedback for the design of a controller that acts on a biologically plausible model of heterogeneous neuronal networks. Finally, the proposed controller, though inspired by common ILC techniques, has been specifically adapted for the needs of this model taking advantage of the established projection algorithm and model-specific constraints.

This paper is organised as follows. Section 2 analytically describes the modelling of modular networks using heterogeneous HH neuronal networks. Section 3 introduces the 2D lateral inhibition model based on the computational framework introduced in Section 2. Section 4 presents two 2D optical illusions: the 2D Mach Band and the Hermann–Hering grid illusions. Section 5 describes the process of modelling DR on lateral inhibition networks. Section 6 introduces the optimal drug administration design based on an adaptive TE-ILC controller, Section 7 provides simulation results and discusses future directions while Section 8 summarises our work. Appendix A clarifies the definition of some basic mathematical operations and Appendix B provides tables with important parameter values for reproducibility.

2. Modular network design

The modelling of modular heterogeneous brain neuronal networks can be achieved via a structural modification of the novel modelling framework introduced in [12,28]. In this paper we have incorporated the case of interconnections between different groups of heterogeneous networks. We define a modular network of N neurons consisting of K modules. Each module M_k ($k = 1, \dots, K$) contains N_k heterogeneous neurons with distinct firing patterns: N_k^{FS} Fast Spiking (FS) neurons, N_k^{RSA} Regular Spiking with Adaptation (RSA) neurons, and N_k^{IB} Intrinsic Bursting (IB) neurons. The coupling between neurons belonging to the same module or between neurons of different modules is achieved via electrical and chemical synapses. This, as explained in [12], can be modelled via the incorporation of feedback loops on the augmented HH network model as seen in Fig. 1.

Therefore, the vectorised network equations for an heterogeneous

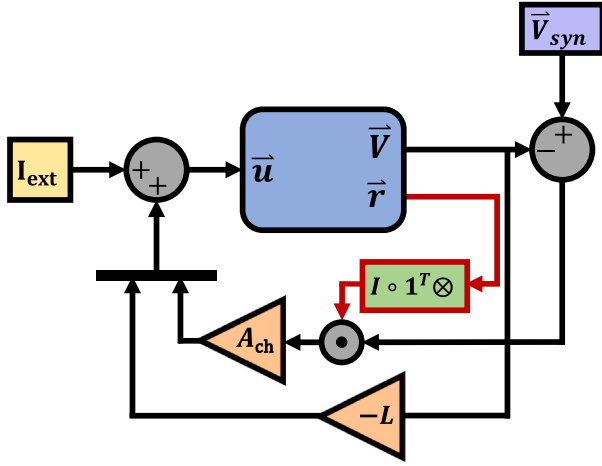


Fig. 1. Feedback structure of an heterogeneous neuronal network with electrical and chemical couplings.

modular network are

$$\begin{aligned}
 \dot{V}(t) &= 1 \oslash C_M \oslash (I_{ext} - \bar{g}_K \oslash n^4(t) \oslash (V(t) - V_K) - \\
 &\quad \bar{g}_M \oslash p(t) \oslash (V(t) - V_K) - \\
 &\quad \bar{g}_{Na} \oslash m^3(t) \oslash h(t) \oslash (V(t) - V_{Na}) - \\
 &\quad \bar{g}_{Ca} \oslash q^2(t) \oslash s(t) \oslash (V(t) - V_{Ca}) - \\
 &\quad \bar{g}_L \oslash (V(t) - V_L) - LV(t) + \\
 &\quad A_{ch} (I_N \oslash (1^T \otimes r(t)) \hat{V}(t)) \\
 \dot{n}(t) &= a_n(t) \oslash [1 - n(t)] - \beta_n \oslash n(t), \\
 \dot{m}(t) &= a_m(t) \oslash [1 - m(t)] - \beta_m \oslash m(t), \\
 \dot{h}(t) &= a_h(t) \oslash [1 - h(t)] - \beta_h \oslash h(t), \\
 \dot{p}(t) &= \frac{p_\infty(t) - p(t)}{\tau_p(t)}, \\
 \dot{q}(t) &= a_q(t) \oslash [1 - q(t)] - \beta_q \oslash q(t), \\
 \dot{s}(t) &= a_s(t) \oslash [1 - s(t)] - \beta_s \oslash s(t), \\
 \dot{r}(t) &= (1 \oslash \tau_r - 1 \oslash \tau_d) \oslash (1 - r(t)) \oslash \\
 &\quad (1 + e^{-V(t)+V_0}) - r(t) \oslash \tau_d
 \end{aligned} \tag{1}$$

where $\oslash$ denotes the Hadamard division, $\oslash$ the Hadamard product or power, and $\otimes$ the Kronecker product (see Appendix A). The definitions of the variables and parameters in Eq. (1) are given in Table 1 and Table 2 while the values of the parameters are given in Table 3 and Table 4 in Appendix B. $C_M \in \mathbb{R}^{N \times 1}$ is the membrane capacitor vector, $I_{ext} = S \oslash I_{inj} \in \mathbb{R}^{N \times 1}$ is the external current applied to all or some of the neurons based on the selection column vector $S \in \mathbb{R}^{N \times 1}$, $\bar{g}_X \in \mathbb{R}^{N \times 1}$, and $V_X \in \mathbb{R}^{N \times 1}$ are the maximum conductance and resting potential vectors of the potassium, slow potassium, sodium, calcium, and leak

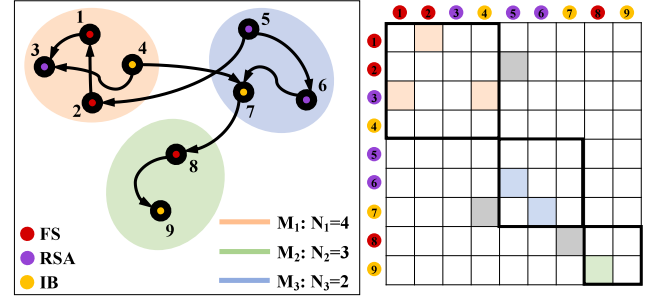


Fig. 2. An example of a modular heterogeneous network of 9 neurons and 3 modules consisting of 3 FS neurons, 3 RSA neurons and 3 IB neurons. The adjacency matrix corresponding to the network contains 3 diagonal blocks and 6 biadjacency blocks.

chloride channels, where $X = \{K, M, Na, Ca, L\}$ and $\bar{X} = X - \{M\}$. The synaptic input due to the electrical couplings is given by $u_{el} = -LV$ where L the Laplacian matrix and $V = [V_{M_1}, \dots, V_{M_K}]^T$, where

$$V_{M_k} = \begin{bmatrix} V_{\tilde{N}_k+1}, \dots, V_{\tilde{N}_k+N_k^{FS}}, \\ V_{\tilde{N}_k+N_k^{FS}+1}, \dots, V_{\tilde{N}_k+N_k^{FS}+N_k^{RSA}}, \\ V_{\tilde{N}_k+N_k^{FS}+N_k^{RSA}+1}, \dots, V_{\tilde{N}_k+N_k} \end{bmatrix} \tag{2}$$

with $\tilde{N}_k = \sum_{l=1}^k N_{l-1}$, and $\tilde{N}_1 = 0$. Similarly, the synaptic input due to chemical couplings is given by $u_{ch} = A_{ch}(I_N \oslash (1^T \otimes r)) \hat{V}$, where $\hat{V} = V - V_{syn}$, V_{syn} is the synaptic potential vector and A_{ch} is the adjacency matrix of the underlying graph. The rest of the variables and parameters of the model follow the same pattern as the vector V in Eq. (2) to compactly represent the interaction between heterogeneous neurons that belong to the same or different modules.

The last two terms of $\hat{V}$ in Eq. (1) are the result of the synaptic connections between the neurons and depend on their connectivity on an inter-modular and intra-modular level. As previously mentioned, two neurons can be connected via electrical or chemical synapses. The electrical and chemical couplings between the neurons of the network and their respective synaptic strengths or weights can be defined by block bipartite adjacency matrices of the following form

$$A = \begin{bmatrix} A_{11} & B_{12} & \dots & B_{1K} \\ B_{21} & A_{22} & \ddots & \vdots \\ \vdots & \ddots & \ddots & B_{K-1,K} \\ B_{K1} & \dots & B_{K,K-1} & A_{KK} \end{bmatrix} = \begin{bmatrix} \epsilon_{11} & \dots & \epsilon_{1N} \\ \vdots & \ddots & \vdots \\ \epsilon_{N1} & \dots & \epsilon_{NN} \end{bmatrix},$$

in which the diagonal blocks $A_{11}, \dots, A_{KK}$ are related to the interconnections within the modules while the bi-adjacency blocks B are related to the couplings between neurons belonging to different modules, e.g. block B_{12} describes the relay of information from neurons in module 2 to neurons in module 1. The synaptic weight ϵ_{ij} represents the strength of the connection from a presynaptic neuron j to a post-synaptic neuron i . Suppose a random modular heterogeneous network of $N=9$ neurons and $K=3$ modules with both intra-modular and inter-modular couplings as illustrated in Fig. 2. The sample network consists of 3 FS, 3 RSA, and 3 IB neurons unevenly distributed in distinct interconnected modules. Neuron 7 receives input from both neuron 4 in M_1 and neuron 6 in M_2 and therefore $\epsilon_{74} = 1 \in B_{21}$ and $\epsilon_{76} = 1 \in A_{22}$. The interconnections between the neurons can be described by an $N \times N$ binary adjacency matrix with $K=3$ diagonal blocks with sizes $N_k \times N_k$, where $k=1, \dots, K$.

Therefore, the synaptic input currents produced by the electrical and chemical couplings between neurons can be fully described by the directed weighted adjacency matrices A_{el} and A_{ch} with synaptic weights ϵ^{el} and ϵ^{ch} respectively. The Laplacian matrix L can be derived from A_{el} via the relationship $L = D - A_{el}$ where D is the diagonal Degree matrix

$$D = \text{diag} \left(\sum_{j=1}^N \epsilon_{1j}^{el}, \dots, \sum_{j=1}^N \epsilon_{Nj}^{el} \right),$$

where both ϵ_{ij}^{el} and ϵ_{ij}^{ch} have units of conductance.

The modelling of a modular heterogeneous neuronal network requires the specification of the network structure and connectivity strengths via the Adjacency and Laplacian matrices as well as the selection of the neurons receiving external input. All the neuron and network parameters can be manipulated freely to examine the functions of modular networks under various healthy and diseased conditions.

3. Minimal 2D lateral inhibition model

Given the 1D model of lateral inhibition network [28] and utilising the aforementioned expanded computational framework we have designed a compact, scalable and flexible model of lateral inhibition in 2D that is able to produce 2D optical illusions such as the 2D Mach band and the Hermann-Hering illusions further showcasing the ability of our model to produce complex functions related to contrast sensitivity. To model 2D lateral inhibition networks we have designed a network of $N = N_M K = (N^{in} + N^{md} + N^{out})K$ neurons where N^{in} is the number of excitatory RSA neurons that comprise the input layer and they receive the external input current, N^{md} is the number of inhibitory FS interneurons that comprise the intermediate layer, and N^{out} is the number of excitatory output RSA neurons that form the output layer of a single module M . The number of inhibitory neurons in each module is directly related to the number of input neurons via the following relationship: $N^{md} = 2(N^{in} - 2)$. The number of input RSA neurons in each module N^{in} determines the size of the horizontal dimension, while the total number of modules K determines the size of the vertical dimension. In the case in which $N_M = K$ the network processes a square input image. Each module corresponds to a 1D lateral inhibition network, while the

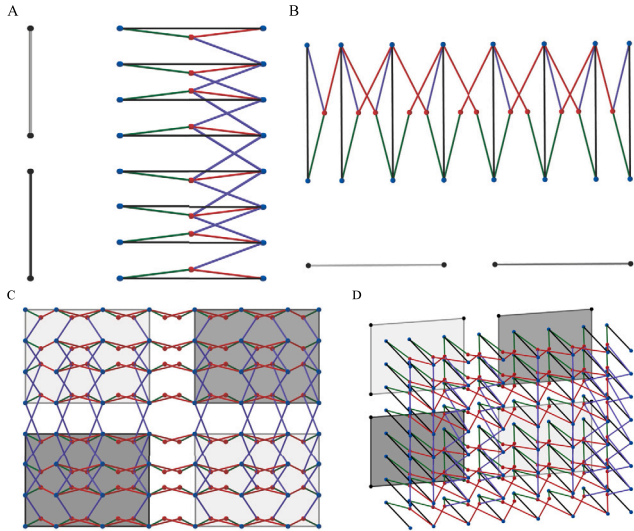


Fig. 3. Schematic representation of a 2D lateral inhibition network from various angles: Side view (A), top view (B), front view (C) and angled view (D). The grey squares represent the input image.

inter-modular couplings are executed by chemical synaptic connections originating from the inhibitory neurons. Fig. 3 illustrates the schematic representation of the smallest possible 2D lateral inhibition network with $N = 224$ neurons in total that consists of $K = 8$ identical modules (see Fig. 3A), each module having an equal number of $N_M = 28$ neurons for $M \in [1, K]$ (see Fig. 3B). The network consists of 64 input RSA neurons, 64 output RSA neurons and 96 FS neurons. Fig. 3C-D illustrates the front and side views of the model where the grey-scale squares represent a 2D input image of size $N^{in} \times K = 8 \times 8$ with two distinct levels of brightness that is received by the input layer. The input RSA neurons excite both the output RSA neurons (black lines)

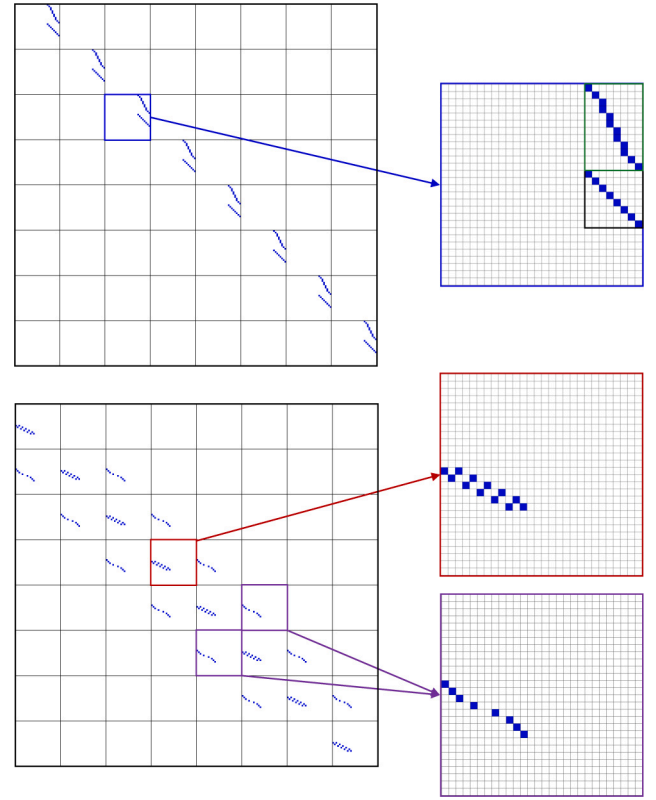


Fig. 4. Schematic representation of the connectivity matrices corresponding to electrical (top) and chemical couplings (bottom).

and the intermediate inhibitory FS neurons (green lines). In turn, the FS neurons inhibit the neighbour output RSA neurons of the same module (red lines) as well as the neighbouring output RSA neurons of the neighbouring modules (purple lines). As previously mentioned, the connectivity of the 2D lateral inhibition network can be described by a set of sparse adjacency matrices that correspond to electrical and chemical synaptic connections. The electrical adjacency matrix A^{el} contains 8 identical blocks on the main diagonal corresponding to the intra-modular couplings via electrical synapses (see Fig. 4 top). Each diagonal block contains two distinct sub-blocks corresponding to the relay of information from the input RSA neurons to the FS neurons (green) and the output RSA neurons (black). The chemical adjacency matrix A^{ch} contains 8 identical blocks on the main diagonal corresponding to the intra-modular connections via chemical synapses and 12 identical blocks below and above the main diagonal corresponding to the inter-modular connections via chemical synapses (see Fig. 4 bottom). Each block corresponds to the inhibition acting on neighbour output RSA neurons from the FS neurons within (red) and between modules (purple).

4. 2D optical illusions

The model of 2D lateral inhibition network has been utilised to produce common 2D optical illusions that are crucial indicators of normal operation of networks known to perform important functions such as contrast enhancement and edge detection. A grey-scale image of size $N^{in} \times K$ has been used as an input to the 2D model of lateral inhibition and the output spiking frequencies of the output RSA neurons are calculated and are subsequently transformed into another grey-scale image that corresponds to the post-processed output of the initial visual information. During the calculation of the output frequencies, the first and last output neurons in both directions are ignored for symmetry

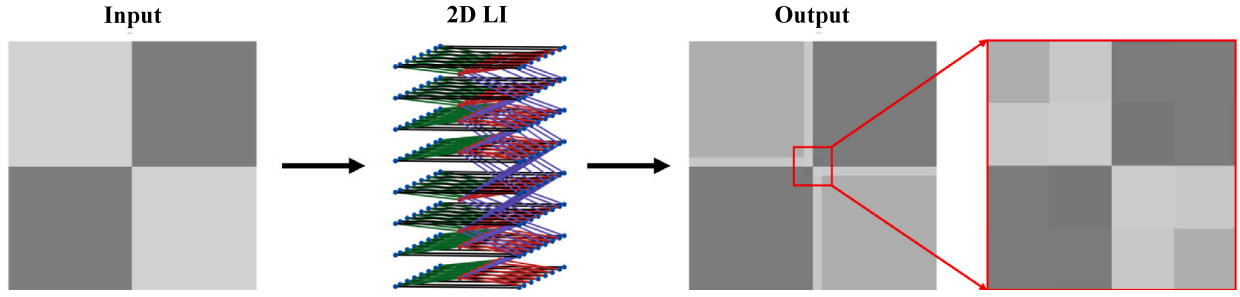


Fig. 5. 2D Mach band illusion. An input image is processed by a 2D network of lateral inhibition to produce the output image.

purposes to avoid distortion of the image due to unbalanced inhibition at these regions. All neurons are assumed to be evenly distributed in space [34] and the visual stimulus is considered to be a time-invariant input current I_{ext} with spacial alterations depending on the optical illusions to be modelled. The synaptic weights used for the production of the illusions are given in Table 5 in Appendix B.

4.1. 2D Mach Band illusion

Suppose a network of $N = 3480$ with $K = 30$ modules and $N^{in} = 30$ input neurons per module. The 30×30 grey-scale input image is modelled as a piecewise constant signal that varies in space and has values that correspond to two different levels of brightness. This gives the matrix representation

$$Im^{in} = \begin{bmatrix} a \cdot \mathbf{1}_{\frac{N_M}{2}, \frac{N^{in}}{2}} & b \cdot \mathbf{1}_{\frac{N_M}{2}, \frac{N^{in}}{2}} \\ b \cdot \mathbf{1}_{\frac{N_M}{2}, \frac{N^{in}}{2}} & a \cdot \mathbf{1}_{\frac{N_M}{2}, \frac{N^{in}}{2}} \end{bmatrix},$$

where $a = 1$, $b = 0.6$ and $\mathbf{1}$ is a selection matrix of ones that determines the distribution of the brightness in space. The image Im^{in} is used as a visual stimulus to the input RSA neurons of the 2D lateral inhibition network and the frequencies of the output RSA neurons are calculated as the inverse of the inter-spike intervals.

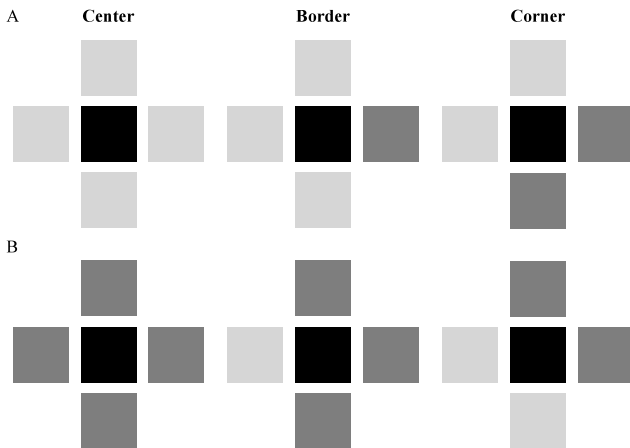


Fig. 6. A neuron of interest with neighbour-dependent firing frequency surrounded by 4 neurons.

Subsequently, the output frequencies are transformed into another grey-scale image, the output image (see Fig. 5). As previously mentioned, not all neurons are taken into consideration at the calculation of the frequencies and as a result the output image is 28×28 in size. The output image exhibits 6 levels of intensity compared to the original image due to the effect of the lateral inhibition on the frequency of the output neurons and the relative location of the output RSA and FS neurons. Focusing on the top left light section of the image one

identifies 3 different scenarios: center, border and corner position (see Fig. 6A). Centrally, all output RSA neurons receive identical excitation from the input RSA neurons and are inhibited by 4 surrounding FS neurons with identical firing rates. Therefore, the frequency forms a plateau of high brightness that is lower than that of the input image. At the border, the output neurons fire at a higher rate due to the inhibition received by high and low rate FS neurons at a ratio 3 to 1. This results in a band of higher frequency and therefore higher brightness. At the corner, the output neuron is inhibited by a combination of high and low rate FS neurons at a ratio 2:2 and therefore it displays the lowest frequency of the set of neurons belonging to the light region of the image. Similarly, at the top right dark section of the image the 3 position scenarios (see Fig. 6B) result in a band of lower brightness at the borders and a pixel of the lowest possible brightness. Fig. 7 illustrates the plateaus of high and low brightness as well as the edges that correspond to the bands and the spikes that correspond to the 4 pixels with the maximum and lowest brightness.

The resulting differences between the original and the output image constitute the Mach band phenomenon, a 2D optical illusion that performs contrast enhancement and edge detection in an image with two distinct levels of grey.

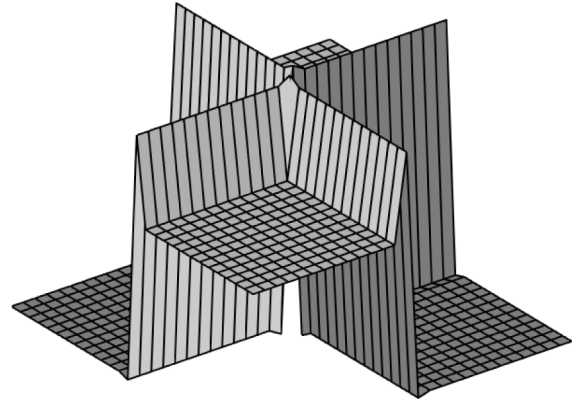


Fig. 7. Frequency of the output neurons in space.

4.2. Hermann-Hering Grid illusion

For the simulation of the Hermann-Hering grid illusion, the same 2D lateral inhibition network is subjected to an image that consists of a light grey grid on a dark grey background and the frequency of the output neurons is again transformed into the output image (see Fig. 8). The effect of lateral inhibition on the input image produces the Hermann-Hering grid illusion that is characterised by the appearance of medium-grey spots at the intersections. The principle behind the illusion is the same as the one of the Mach band illusion. At the intersections, the output RSA neurons are inhibited by 4 surrounding FS neurons that fire at a high frequency as they are excited by input

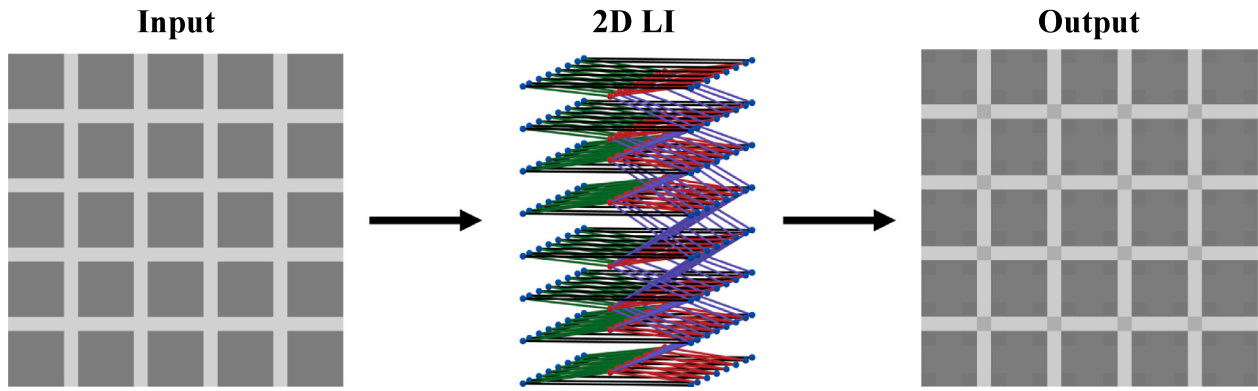


Fig. 8. Hermann-Hering Grid Illusion. An input image is processed by a 2D network of lateral inhibition to produce the output image.

neurons that receive high intensity current. As a result, the neurons at the intersections fire at a higher frequency than the ones located inside the dark areas, but at a lower frequency than the neurons in the rest of the light-grey grid resulting in dark spots that do not exist in the original image. Fig. 9 illustrates the plunge of the output frequency at the intersections.

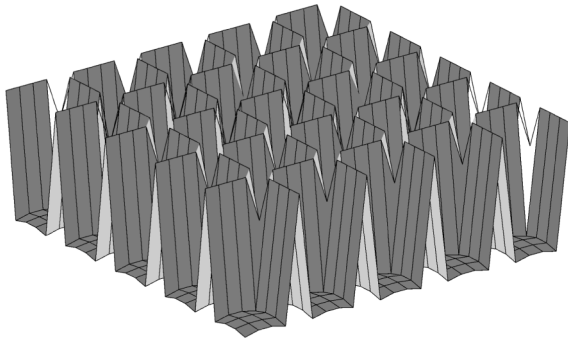


Fig. 9. Frequency of the output neurons in space.

5. Modelling neurodegenerative diseases - Case study: Diabetic retinopathy

Diabetic retinopathy (DR) is recognised as one of the most significant ocular complications of diabetes mellitus and is one of the leading causes of blindness worldwide [35–37]. For many years, DR has been considered primarily a microvascular disease and its diagnosis has relied on the detection of vascular lesions [38]. Recent evidence suggest that the DR is also a neurodegenerative disease that causes functional and structural abnormalities in the retina that manifest before the onset of the vascular symptoms [39]. The precedence of the neurological symptoms suggests that the Diabetic Retina Neurogeneration (DRN) may actually be the leading cause of vascular damage [39–41] and should be recognised for its serious role on the deterioration of the visual system [30]. This hypothesis opens up the possibility for non-invasive early detection of DR way before the appearance of vascular lesions as well as personalised targeted treatment strategies that focus on neurological phenotypes [42].

Diabetes is known to cause serious functional changes on the retina including abnormal contrast sensitivity [43,44]. The significant reduction of contrast sensitivity in diabetic patients implies damages on the network of lateral inhibition that is responsible for this function [45]. The abnormal perception of the Hermann-Hering grid illusion in patients with diabetes indicates the causal relationship between diabetes mellitus and lateral inhibition network malfunction [30]. The exact changes that occur in the network due to diabetes have been under investigation although the mechanisms still remain unclear.

Castilho et al. [32] have isolated the damage on the inhibitory chemical synapses between amacrine and ganglion cells with lower conductances being observed under the influence of diabetes. The reduced channel conductance of the inhibitory synapses in diabetic patients has been also concluded in [33]. The lower synaptic conductance in diabetic amacrine cells has been linked to lower and slower release of GABAergic neurotransmitters (inhibitory) or reduced number of receptors and has been proven to cause major disruption within the rod pathway of the retina [31]. The retinal rod pathway includes layers of excitatory Rod Bipolar Cells (RBC), three types of inhibitory amacrine cells distinguished by different neurotransmitter release: the glycinergic AII amacrine cells, the gabergic GABA AC and the dopaminergic DA cells and the excitatory Ganglion Cells (GC) [31].

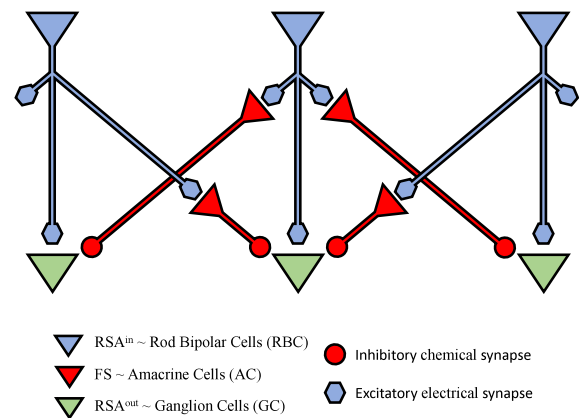


Fig. 10. Minimal rod pathway.

In the introduced minimal model of lateral inhibition the input RSA^{in} neurons play the role of RBC, the FS neurons mimic the behaviour of the GABA AC and the output RSA^{out} neurons represent the GC (see Fig. 10). The excitatory synaptic connections have been modelled via electrical synapses, while the inhibitory couplings have been modelled via chemical synapses. To model diabetic lateral inhibition networks we have focused on the manipulation of the parameter related to the synaptic conductance of the chemical couplings between the amacrine and ganglion cells, which corresponds to $g_{syn} = \epsilon^{ch} r$. We have decreased the value of g_{syn} by decreasing the value of the weight ϵ^{ch} in our model while leaving the dynamics of r unchanged. In other words, we have changed the values of the A_{ch} adjacency matrix to match the damage that is observed in the networks of lateral inhibition during the onset of diabetes. In what follows the parameters g_{syn} and ϵ^{ch} are used interchangeably.

6. Therapy design - nonlinear controller

To design the controller, two output images of the modelled Hermann-Hering grid illusion are produced for two different values of the inhibitory synaptic conductance between the FS and RSA^{out} neurons that correspond to healthy ($\hat{g}_{syn}^*$) and diabetic (g_{syn}^*) states, with $g_{syn}^* < \hat{g}_{syn}^*$ to match the observed lower conductance of inhibitory synapses between the amacrine and the ganglion cells. The output diabetic image Im is compared to the output healthy image $\hat{Im}$ and an error signal is created according to the mean squared error

$$e = \frac{1}{N^{im}} \sum_{i=1}^{N^{im}} [\hat{Im}(i) - Im(i)]^2,$$

where $i = 1, \dots, N^{im}$ and $N^{im} = 2(N^{out} - 1)$ is the number of pixels in the image that corresponds to the number of output neurons that are involved in the calculation of the output frequency. The error signal e is used as feedback to the controller to produce the virtual drug u that acts on the defective g_{syn}^* of the lateral inhibition network according to the function

$$g_{syn}(u) = f(u) = (1 + \beta u) g_{syn}^*, \quad (3)$$

where g_{syn} is the synaptic conductance and β is the absorbance rate of the administered drug. Fig. 11 illustrates the closed-loop process of determining optimal drug administration with an undetermined controller that acts on the defective synaptic conductance of the diseased lateral inhibition network such that the optical illusions produced by the two models are identical. Therefore, the control problem is defined as finding the optimal drug administration u such the error e between the diabetic and the healthy output images is minimised.

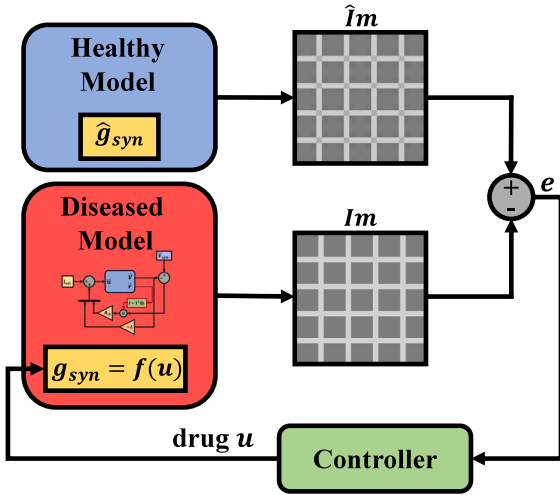


Fig. 11. Block diagram of the closed-loop error-model.

6.1. Input - Error map

Multiple diseased models with defective $g_{syn}^* = 80\% \hat{g}_{syn}^*$ have been simulated in open-loop for a variety of inputs $u \in [0, 30]$ and the relationship between e and u has been established to be of quadratic form with plateaus as shown in Fig. 12. The red region of the Input-Error plot corresponds to the set of values of u that produce zero error between the healthy and the diseased images. The existence of plateaus validates the robustness of neurons and neuronal networks to conductance alterations that are known to cause little or no change to neuronal firing activity [46,47]. For the design of an optimal drug delivery the Input-Error relationship has been approximated as a discrete quadratic map of the form

$$e_{k+1} = \mathcal{M}(u_k) = (u_k - \hat{u})^2$$

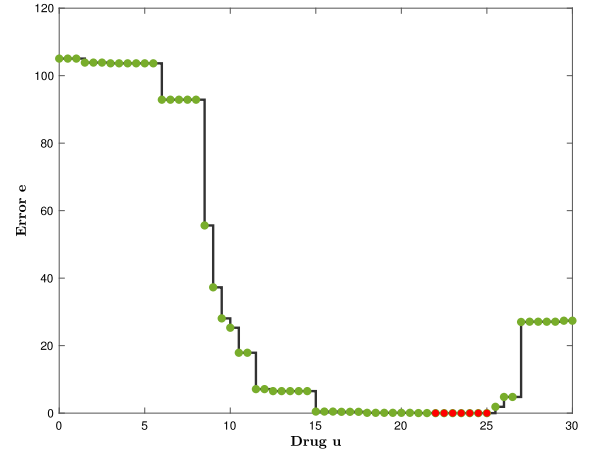


Fig. 12. Input - Error Map.

where k is the iteration index and $\hat{u}$ is the optimal drug dosage that corresponds to $g_{syn} = \hat{g}_{syn}^*$.

6.2. Terminal Error Iterative Learning Controller

To achieve an optimal drug administration strategy we have introduced a Terminal Error Iterative Learning Controller (TE-ILC) [48] that is designed based on the predefined Input-Error Map. We consider the 3rd order discrete-time nonlinear system

$$\begin{aligned} e_{k+1} &= (u_k - \hat{u})^2, \\ u_{k+1} &= u_k + \vartheta_1 e_k + \vartheta_2 w_k, \\ w_{k+1} &= e_k, \end{aligned} \quad (4)$$

where e_k is the error between the two images at iteration k , $w_k = e_{k-1}$, u_k is the drug dosage at iteration k , $\hat{u}$ is the optimal drug dosage, and ϑ_1 and ϑ_2 are the controller parameters to be tuned. The control law u_{k+1} is a Proportional-Derivative (PD) type update rule with constant gains that is updated at the end of the k th diabetic image formation as shown in Fig. 13. The objective of the TE-ILC is to achieve the condition $\lim_{k \rightarrow \infty} e_k = 0$.

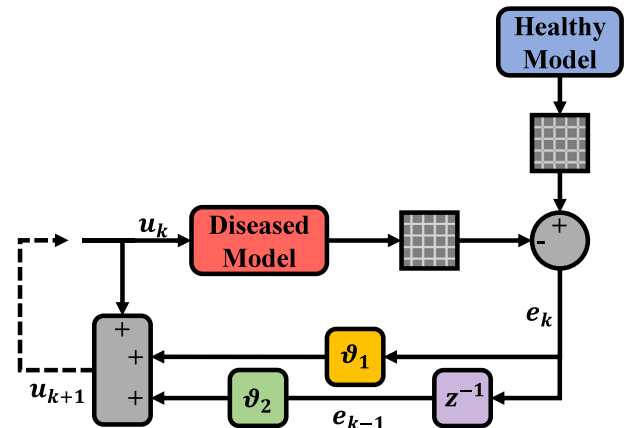


Fig. 13. Block diagram of the ILC.

6.3. Center Manifold theorem

The stability of the operating equilibrium of the approximated system can be proven using the Center Manifold theorem [49,50]. The equilibrium point of the system in Eq. (4) is $(e_{eq}, u_{eq}, w_{eq}) = (0, \hat{u}, 0)$. A coordinates transformation of the form $x_k = e_k, y_k = u_k - \hat{u}, z_k = w_k$

yields the equilibrium point $(x_{eq}, y_{eq}, z_{eq}) = (0, 0, 0)$. Separating the resulting system into linear and nonlinear part gives the equation

$$\begin{bmatrix} x_{k+1} \\ y_{k+1} \\ z_{k+1} \end{bmatrix} = \underbrace{\begin{bmatrix} 0 & 0 & 0 \\ \vartheta_1 & 1 & \vartheta_2 \\ 1 & 0 & 0 \end{bmatrix}}_F \begin{bmatrix} x_k \\ y_k \\ z_k \end{bmatrix} + \begin{bmatrix} y_k^2 \\ 0 \\ 0 \end{bmatrix}. \quad (5)$$

Computing the eigenvalues of the map linearised around the origin gives the repeated eigenvalue $\lambda_{1,2} = 0$ and the eigenvalue $\lambda_3 = 1$. Therefore, there is a two-dimensional stable (s) manifold and a one-dimensional center (c) manifold. To block diagonalise the matrix F we consider the transformation matrix T

$$T = \begin{bmatrix} 0 & 0 & c_1 \\ 1 & -\vartheta_2 & c_2 \\ 0 & 1 & c_3 \end{bmatrix},$$

where the entries c_1 , c_2 , and c_3 , with $c_1 \neq 0$ are to be determined such that matrix F is transformed to a block diagonal matrix

$$A = \begin{bmatrix} \underbrace{\lambda_3}_{c} & 0 & 0 \\ 0 & \underbrace{\lambda_1 \quad 1}_{s} \\ 0 & 0 & \underbrace{\lambda_2}_{s} \end{bmatrix} = T^{-1}FT$$

arranged such that the eigenvalue corresponding to the center manifold is at the top left corner. This is achieved by setting $c_1 = 1$, $c_2 = -\vartheta_1 - \vartheta_2$ and $c_3 = 0$. Decoupling the linear part of the system into center (A) and stable (B) subsystems yields

$$\begin{bmatrix} q_1^+ \\ q_2^+ \\ q_3^+ \end{bmatrix} = \underbrace{\begin{bmatrix} 1 & 0 & 0 \\ 0 & 0 & 1 \\ 0 & 0 & 0 \end{bmatrix}}_B \begin{bmatrix} q_1 \\ q_2 \\ q_3 \end{bmatrix} + \underbrace{\begin{bmatrix} (\vartheta_1 + \vartheta_2)(\vartheta_2 q_2 - q_1 + q_3(\vartheta_1 + \vartheta_2))^2 \\ 0 \\ (\vartheta_2 q_2 - q_1 + q_3(\vartheta_1 + \vartheta_2))^2 \end{bmatrix}}_f \quad (6)$$

where $q^T = [q_1, q_2, q_3]^T = T^{-1} [x_k, y_k, z_k]^T$ and $q^+ = q_{k+1}$. The center manifold can be locally represented as [51]

$$W^c(0) = \{ (q_1, q_2, q_3) \in \mathbb{R}^3 \mid q_2 = h_1(q_1), \\ q_3 = h_2(q_1); h_i(0) = Dh_i(0) = 0, i = 1, 2 \}$$

for q_1 sufficiently small. We consider an approximation of the center manifold of the form

$$h(q_1) = \begin{bmatrix} h_1(q_1) \\ h_2(q_1) \end{bmatrix} = \begin{bmatrix} \alpha_1 q_1^2 + \beta_1 q_1^3 + \mathcal{O}(q_1^4) \\ \alpha_2 q_1^2 + \beta_2 q_1^3 + \mathcal{O}(q_1^4) \end{bmatrix}.$$

This satisfies the equation [50]

$$\mathcal{N}(h(q_1)) = h(Aq_1 + f(q_1, h(q_1))) - Bh(q_1) - g(q_1, h(q_1)) = 0,$$

up to order 3. Substituting $h(q_1)$ into $\mathcal{N}(h(q_1))$ to find $\alpha_1, \alpha_2, \beta_1, \beta_2$ yielding the reduced map

$$q_1^+ = q_1 + (\vartheta_1 + \vartheta_2) q_1^2 + (-2\vartheta_1^2 - 6\vartheta_1\vartheta_2 - 4\vartheta_2^2) q_1^3$$

Setting $\vartheta_1 = -2\vartheta_2 \neq 0$ makes the zero equilibrium of the center manifold attractive for all initial conditions in the set $[0, 1/\vartheta_2]$.

Therefore, we conclude that the equilibrium $(0, 0, 0)$ of the system in Eq. (5) is locally attractive provided $q_1 \geq 0$ and small. We verify this fact with the Verhulst diagram as illustrated in Fig. 14A where the iteration converges to zero for the initial condition $q_1(0) = 0.5$. The center manifold (W^c) and the tangent plane to the stable (E^s) manifold are depicted in Fig. 14B.

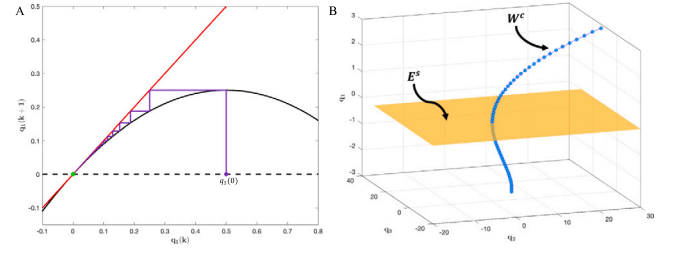


Fig. 14. Verhulst diagram (A) and plot of the reduced centre manifold (B).

6.4. Adaptive TE-ILC

The local attractivity properties of the approximated system do not guarantee convergence of the error signal to zero when the controller is applied to the model of diabetic lateral inhibition due to approximation of the error-signal map and the distance of the initial condition of the system from the neighbourhood of the equilibrium point. In addition, the existence of plateaus on the actual input-error map makes the use of constant controller parameters $\vartheta_{1,2}$ restrictive. To achieve convergence and ‘escape’ from the plateaus we utilise a projection algorithm [52] for optimal adaptation of the varying parameters $\hat{\vartheta}_1$ and $\hat{\vartheta}_2$. The approximated system thus becomes

$$\begin{aligned} e_{k+1} &= (u_k - \hat{u})^2, \\ u_{k+1} &= u_k + \hat{\vartheta}_1(k)e_k + \hat{\vartheta}_2(k)w_k, \\ w_{k+1} &= e_k. \end{aligned}$$

To design the update laws we minimise the cost

$$J = \frac{1}{2} \|\hat{\vartheta}^+ - \hat{\vartheta}\|^2,$$

where $\hat{\vartheta}^+ = \hat{\vartheta}(k+1)$ and $\hat{\vartheta} = \hat{\vartheta}(k)$ subject to the constraint

$$u_k = \varphi_k^T \hat{\vartheta}^+ = [e_k, w_k] \begin{bmatrix} \hat{\vartheta}_1^+ \\ \hat{\vartheta}_2^+ \end{bmatrix} \quad (6)$$

where φ is a regression vector and $\hat{\vartheta}$ is the unknown parameter vector. Introducing the Lagrange multiplier λ for the constraint in Eq. (6) yields the Lagrange function

$$\mathcal{L} = \frac{1}{2} \|\hat{\vartheta}^+ - \hat{\vartheta}\|^2 + \lambda (u_k - \varphi_k^T \hat{\vartheta}^+)$$

from which we obtain the necessary conditions of optimality

$$\left(\frac{\partial \mathcal{L}}{\partial \hat{\vartheta}^+}, \frac{\partial \mathcal{L}}{\partial \lambda} \right) = (0, 0). \quad (7)$$

The solution of Eq. (7) yields the following projection algorithm for the update of the controller parameters ϑ_1 and ϑ_2 described by

$$\begin{aligned} \hat{\vartheta}_1^+ &= \hat{\vartheta}_1 + \frac{a_1 e_k}{c_1 + (e_k^2 + w_k^2)} [u_k - (e_k \hat{\vartheta}_1 + w_k \hat{\vartheta}_2)], \\ \hat{\vartheta}_2^+ &= \hat{\vartheta}_2 + \frac{a_2 w_k}{c_2 + (e_k^2 + w_k^2)} [u_k - (e_k \hat{\vartheta}_1 + w_k \hat{\vartheta}_2)], \end{aligned}$$

in which the tuning parameters $a_{1,2}$ and $c_{1,2}$ have been added to the original solution for convergence speed regulation.

7. Results and discussion

We have utilised the methodology in Section 6 to design optimal drug administration for a diabetic lateral inhibition network of the human retina. The diseased network comprising of $N = 224$ neurons produces an output image that fails to showcase the features of the Mach band optical illusion that are extensively described in Section 4.1. The drug u produced by the Adaptive TE-ILC is applied on the defective synaptic conductance g_{syn}^* according to Eq. (3) and the output

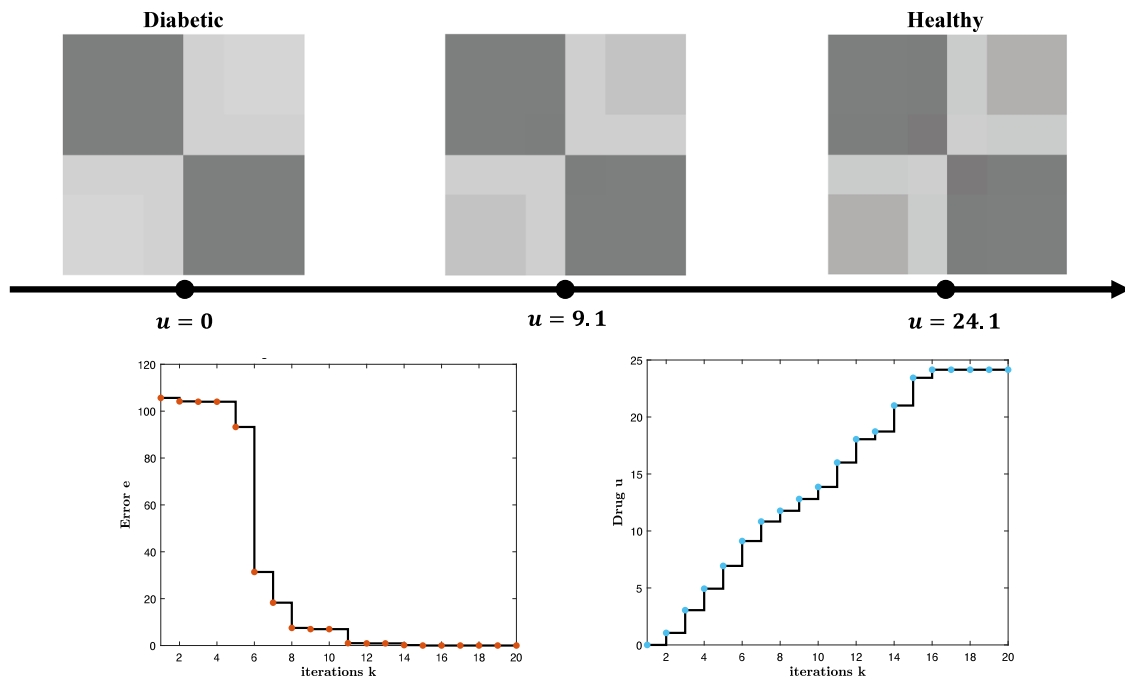


Fig. 15. Optimal drug dosage for a diabetic lateral inhibition model. Top: Output images for three values of drug amount u . Bottom: The error e and the corresponding drug amount u at each iteration k .

image progressively improves until the Mach Band illusion is clearly visible and the error e between the healthy and the diabetic output images $\hat{I}_m$ and I_m is minimised. The regulation of the error signal is achieved via the adaptive TE-ILC controller and is directly influenced by the tunable controller parameters. The difficulty originating from the plateaus appearing in the error function have been dealt with by adequately selecting the adaptive controller parameters. The constant tuning parameters $a_{1,2}$ and $c_{1,2}$ of the controller are chosen for a fast plateau 'escape' and subsequently fast convergence to zero. The controller achieves error minimisation after 16 iterations and the gradual amelioration of the output image is characterised by the appearance of both light and dark bands for drug amount $u = 9.1$ as well as the light and dark pixels at the center for drug amount $u = 24.1$ as shown in Fig. 15. The simulations were performed in Matlab 2021b and the time complexity for the provided example with 224 neurons, equivalent to 1792 nonlinear differential equations, and 20 iterations simulated on a computer with a 24-Core Processor and 1TB RAM is 1 hour.

The robustness of the lateral inhibition network to small variations in the synaptic conductance allows for a range of values of drug dosage u to be acceptable solutions for the error minimisation and therefore it is normal that the final synaptic conductance does not match the healthy value exactly. This collective characteristic of the neurons comprising the network allows for the possibility to examine the effect of applying different values of drug amount in each neuron as well as to take into consideration that neurons might not absorb the drug at the same rate. In this work, only the diseased synaptic conductances receive the virtual drug and therefore the effect of the possible drug absorbance by healthy neurons that leads to the appearance of side effects has not been considered. Variations in drug absorbance and the appearance of side effects due to the drug altering the activity of healthy neurons will be studied in a future work with the purpose of reducing the gap between our model and the actual system taking into account the complexity of the human retina, of the drug administration regimen and the underlying pharmacokinetics. In addition, we will study the efficacy of the proposed framework for model identification purposes to explore the aspect of personalised medicine by matching patients to respective models using information from the optical illusion images.

8. Conclusion

We have presented an efficient computational framework for the modelling of retinal neuronal networks affected by a family of neurodegenerative diseases that originate from synaptopathies and channelopathies. Based on this, we have studied the dynamic behaviour of diabetic retinopathy and we have produced images of common optical illusions that correspond to healthy and diseased conditions. Treating these images as computational phenotypes, we have designed an adaptive terminal error controller that successfully determines the optimal drug amount for the restoration of the model parameter responsible for the deterioration based solely on the error between the healthy and the diabetic images. To the extent of our knowledge, this is the first time a tangible and realistically measurable output has been used as feedback for the design of a controller that acts on a biologically plausible model of heterogeneous neuronal networks. This work can potentially improve the study of neurodegenerative diseases and the effect of pharmacological substances in a non-clinical set-up via a possible neurodegenerative disease virtual simulator.

CRedit authorship contribution statement

A.G. Giannari: Conceptualization, Methodology, Software, Validation, Formal analysis, Writing – original draft, Visualization. **A. Astolfi:** Conceptualization, Validation, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Table 1

HH model variables and definitions..

Variables	Units	Definitions
V	mV	the membrane potential
n, m, h, p, q, s		dimensionless variables between 0 and 1 associated with the activation and inactivation of the channels
r		fraction of receptors bound to the neurotransmitters

Table 2

HH model parameters and definitions..

Parameters	Definitions
I_{inj}	injected current per unit area
C_M	membrane capacitance
$\bar{g}_X$	channel maximum conductance
V_X	channel resting potential
τ_{max}	time constant associated with RSA neurons
I_{ext}	external input signal
τ_r	synapse rise time constant
τ_d	synapse decay time constant
V_{syn}	synapse potential
V_0	synapse reversal potential

Table 3

HH model parameters and values for each neuron type..

Model parameters	Units	FS	RSA	IB
C_M	$\frac{\mu F}{cm^2}$	0.5	1	1
V_K	mV	-90	-90	-90
V_{Ca}	mV	-	-	120
V_{Na}	mV	50	56	50
V_L	mV	-70	-70.3	-70
V_T	mV	-56.2	-56.2	-56.2
$\bar{g}_K$	$\frac{mS}{cm^2}$	10	6	5
$\bar{g}_M$	$\frac{mS}{cm^2}$	-	0.075	0.03
$\bar{g}_{Ca}$	$\frac{mS}{cm^2}$	-	-	0.2
$\bar{g}_{Na}$	$\frac{mS}{cm^2}$	56	56	50
$\bar{g}_L$	$\frac{mS}{cm^2}$	$1.5 \cdot 10^{-2}$	$2.05 \cdot 10^{-2}$	0.01
τ_{max}	ms	1	608	608

Acknowledgments

This work was partially supported by the European Union's Horizon 2020 Research and Innovation Program under Grant 739551 (KIOS Centre of Excellence); and by the EPSRC, UK grant "Model reduction from data" (EP/W005557/1).

Appendix A

Definition 1. The Hadamard product of two matrices with the same dimensions $A = [a_{ij}] \in \mathbb{R}^{m \times n}$ and $B = [b_{ij}] \in \mathbb{R}^{m \times n}$ is defined as $A \circ B = [a_{ij}b_{ij}] \in \mathbb{R}^{m \times n}$ [53].

Definition 2. The Hadamard division or element-wise division of two matrices with the same dimensions $A = [a_{ij}] \in \mathbb{R}^{m \times n}$ and $B = [b_{ij} \neq 0] \in \mathbb{R}^{m \times n}$ is defined by $A \oslash B = [a_{ij}/b_{ij}] \in \mathbb{R}^{m \times n}$ [54].

Definition 3. The Hadamard power of a matrix $A = [a_{ij}] \in \mathbb{R}^{m \times n}$ is defined by $A^{\circ k} = [a_{ij}^k] \in \mathbb{R}^{m \times n}$ with $k \in \mathbb{R}$ and $a_{ij} > 0$ [55].

Table 4

Synapse parameters and values for each neuron type..

Synapse parameters	Units	FS	RSA	IB
τ_r	ms	0.5	0.5	0.5
τ_d	ms	8	8	8
V_{syn}	mV	[-80, -50]	20	20
V_0	mV	-20	-20	-20

Table 5

Synaptic weights for 2D lateral inhibition networks..

Synaptic couplings	e^{el}	e^{eh}
$RSA^{in} - FS$	0.1	
$RSA^{in} - RSA^{out}$	0.16	
$FS - RSA^{out}$		0.075

Definition 4. The Kronecker product of two matrices $A = [a_{ij}] \in \mathbb{R}^{m \times n}$ and $B = [b_{ij}] \in \mathbb{R}^{p \times q}$ gives the block matrix $A \otimes B = \begin{bmatrix} a_{11}B & \dots & a_{1n}B \\ \vdots & \ddots & \vdots \\ a_{m1}B & \dots & a_{mn}B \end{bmatrix} \in \mathbb{R}^{pm \times qn}$ [56].

Appendix B

See Tables 1–5.

References

- [1] F. Roselli, P. Caroni, From intrinsic firing properties to selective neuronal vulnerability in neurodegenerative diseases, *Neuron* 85 (2015) 901–910.
- [2] T.H. Gillingswater, T.M. Wishart, Mechanisms underlying synaptic vulnerability and degeneration in neurodegenerative disease, *Neuropathol. Appl. Neurobiol.* 39 (2013) 320–334.
- [3] I. Rivolta, A. Binda, A. Masi, J.C. DiFrancesco, Cardiac and neuronal HCN channelopathies, *Pflügers Arch.-Eur. J. Physiol.* 472 (2020) 931–951.
- [4] K. Lepeta, M.V. Lourenco, B.C. Schweitzer, P.V. Martino Adami, P. Banerjee, S. Catuara-Solarz, M. de La Fuente Revenga, A.M. Guillem, M. Haidar, O. M. Ijomone, et al., Synaptopathies: synaptic dysfunction in neurological disorders—A review from students to students, *J. Neurochem.* 138 (2016) 785–805.
- [5] S.R.A. Alles, P.A. Smith, Peripheral voltage-gated cation channels in neuropathic pain and their potential as therapeutic targets, *Front. Pain Res.* 2 (2021) 106.
- [6] S.E. Heron, I.E. Scheffer, S.F. Berkovic, L.M. Dibbens, J.C. Mulley, Channelopathies in idiopathic epilepsy, *Neurotherapeutics* 4 (2007) 295–304.
- [7] R. Nisticò, M. Pignatelli, S. Piccinin, N.B. Mercuri, G. Collingridge, Targeting synaptic dysfunction in Alzheimer's disease therapy, *Mol. Neurobiol.* 46 (2012) 572–587.
- [8] E. Taoufik, G. Kouroupi, O. Zygogianni, R. Matsas, Synaptic dysfunction in neurodegenerative and neurodevelopmental diseases: an overview of induced pluripotent stem-cell-based disease models, *Open Biol.* 8 (2018) 180138.
- [9] J. Jackson, E. Jambrina, J. Li, H. Marston, F. Menzies, K. Phillips, G. Gilmour, Targeting the synapse in Alzheimer's disease, *Front. Neurosci.* 13 (2019) 735.
- [10] R.S. Duman, G.K. Aghajanian, Synaptic dysfunction in depression: potential therapeutic targets, *science* 338 (2012) 68–72.
- [11] A. Lloret-Villas, T.M. Varusai, N. Juty, C. Laibe, N. Le Novère, H. Hermjakob, V. Chelliah, The impact of mathematical modeling in understanding the mechanisms underlying neurodegeneration: evolving dimensions and future directions, *CPT: Pharmacometr. Syst. Pharmacol.* 6 (2017) 73–86.
- [12] A.G. Giannari, A. Astolfi, Model design for networks of heterogeneous Hodgkin-Huxley neurons, *Neurocomputing* 496 (2022) 147–157.
- [13] C. Perez, J. Ziburkus, G. Ullah, Analyzing and modeling the dysfunction of inhibitory neurons in Alzheimer's disease, *PLoS One* 11 (2016) e0168800.
- [14] T. Ying, A.N. Burkitt, T. Kamenewa, Combining the neural mass model and Hodgkin-Huxley formalism: Neuronal dynamics modelling, *Biomed. Signal Process. Control* 79 (2023) 104026.
- [15] A.T. Knox, T. Glauser, J. Tenney, W.W. Lytton, K. Holland, Modeling pathogenesis and treatment response in childhood absence epilepsy, *Epilepsia* 59 (2018) 135–145.
- [16] Y. Xie, L. Chen, Y.M. Kang, K. Aihara, Controlling the onset of Hopf bifurcation in the Hodgkin-Huxley model, *Phys. Rev. E* 77 (2008) 061921.
- [17] J. Wang, L. Chen, X. Fei, Analysis and control of the bifurcation of Hodgkin-Huxley model, *Chaos Solitons Fractals* 31 (2007) 247–256.
- [18] U. Feudel, A. Neiman, X. Pei, W. Wojtenek, H. Braun, M. Huber, F. Moss, Homoclinic bifurcation in a Hodgkin-Huxley model of thermally sensitive neurons, *Chaos* 10 (2000) 231–239.

- [19] O.R. Doruk, Control of hopf bifurcations in Hodgkin-Huxley neurons by automatic temperature manipulation, *NeuroQuantology* 16 (2018).
- [20] F. Fröhlich, S. Jezernik, Feedback control of Hodgkin-Huxley nerve cell dynamics, *Control Eng. Pract.* 13 (2005) 1195–1206.
- [21] G. Ullah, S.J. Schiff, Tracking and control of neuronal Hodgkin-Huxley dynamics, *Phys. Rev. E* 79 (2009) 040901.
- [22] R. Schmetterling, T.B. Burghi, R. Sepulchre, Adaptive conductance control, *Annu. Rev. Control* (2022).
- [23] C.A.S. Batista, R.L. Viana, F.A.S. Ferrari, S.R. Lopes, A.M. Batista, J.C.P. Coninck, Control of bursting synchronization in networks of Hodgkin-Huxley-type neurons with chemical synapses, *Phys. Rev. E* 87 (2013) 042713.
- [24] P. Danzl, J. Hespanha, J. Moehlis, Event-based minimum-time control of oscillatory neuron models: phase randomization, maximal spike rate increase, and desynchronization, *Biol. Cybern.* 101 (2009) 387–399.
- [25] A. Nabi, J. Moehlis, Single input optimal control for globally coupled neuron networks, *J. Neural Eng.* 8 (2011) 065008.
- [26] J. Liu, K.G. Oweiss, H.K. Khalil, Feedback control of the spatiotemporal firing patterns of neural microcircuits, in: 49th IEEE Conference on Decision and Control, CDC, 2010, pp. 4679–4684.
- [27] S.J. Schiff, Kalman meets neuron: the emerging intersection of control theory with neuroscience, in: 2009 Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 2009, pp. 3318–3321.
- [28] A.G. Giannari, A. Astolfi, Model of lateral inhibition using a network of heterogeneous Hodgkin-Huxley neurons, in: 2022 European Control Conference, ECC, 2022, pp. 1–6.
- [29] D. Meunier, R. Lambiotte, E.T. Bullmore, Modular and hierarchically modular organization of brain networks, *Front. Neurosci.* 4 (2010) 200.
- [30] N.P. Davies, A.B. Morland, The Hermann-Hering grid illusion demonstrates disruption of lateral inhibition processing in diabetes mellitus, *Br. J. Ophthalmol.* 86 (2002) 203–208.
- [31] E.D. Eggers, T.A. Carreon, The effects of early diabetes on inner retinal neurons, *Vis. Neurosci.* 37 (2020) E006.
- [32] Á. Castilho, A.F. Ambrósio, E. Hartveit, M.L. Veruki, Disruption of a neural microcircuit in the rod pathway of the mammalian retina by diabetes mellitus, *J. Neurosci.* 35 (2015) 5422–5433.
- [33] D.J. Ramsey, H. Rippes, H. Qian, Streptozotocin-induced diabetes modulates GABA receptor activity of rat retinal neurons, *Exp. Eye Res.* 85 (2007) 413–422.
- [34] A. Szél, P. Röhlich, A.R. Caffé, T. Van Veen, Distribution of cone photoreceptors in the mammalian retina, *Microsc. Res. Techniq.* 35 (1996) 445–462.
- [35] L.M. Aiello, Perspectives on diabetic retinopathy, *Am. J. Ophthalmol.* 136 (2003) 122–135.
- [36] A.W. Stitt, T.M. Curtis, M. Chen, R.J. Medina, G.J. McKay, A. Jenkins, T.A. Gardiner, T.J. Lyons, H-P Hammes, R. Simo, N. Lois, The progress in understanding and treatment of diabetic retinopathy, *Progr. Retinal Eye Res.* 51 (2016) 156–186.
- [37] D.A. Antonetti, R. Klein, T.W. Gardner, Mechanisms of disease diabetic retinopathy, *N. Engl. J. Med.* 366 (2012) 1227–1239.
- [38] W. Wang, A.C.Y. Lo, Diabetic retinopathy: pathophysiology and treatments, *Int. J. Mol. Sci.* 19 (2018) 1816.
- [39] S.K. Lynch, M.D. Abramoff, Diabetic retinopathy is a neurodegenerative disorder, *Vis. Res.* 139 (2017) 101–107.
- [40] R. Simó, A.W. Stitt, T.W. Gardner, Neurodegeneration in diabetic retinopathy: does it really matter? *Diabetologia* 61 (2018) 1902–1912.
- [41] M.G. Rossino, M. Dal Monte, G. Casini, Relationships between neurodegeneration and vascular damage in diabetic retinopathy, *Front. Neurosci.* 13 (2019) 1172.
- [42] M.H. Madeira, I.P. Marques, S. Ferreira, D. Tavares, T. Santos, A.R. Santos, J. Figueira, C. Lobo, J. Cunha-Vaz, Retinal neurodegeneration in different risk phenotypes of diabetic retinal disease, *Front. Neurosci.* (2021) 1663.
- [43] M.A.S. Di Leo, S. Caputo, B. Falsini, V. Porciatti, A. Minnella, A.V. Greco, G. Ghrilanda, Nonselective loss of contrast sensitivity in visual system testing in early type I diabetes, *Diabetes Care* 15 (1992) 620–625.
- [44] S. Safi, A. Rahimi, A. Raeesi, H. Safi, M.A. Amiri, M. Malek, M. Yaseri, M. Haeri, F.A. Middleton, Eduardo Solessio, H. Ahmadi, Contrast sensitivity to spatial gratings in moderate and dim light conditions in patients with diabetes in the absence of diabetic retinopathy, *BMJ Open Diabetes Res. Care* 5 (2017) e000408.
- [45] A.A. Dosso, E.R. Bonvin, Y. Morel, A. Golay, J.P. Assal, P.M. Leuenberger, Risk factors associated with contrast sensitivity loss in diabetic patients, *Graefes Arch. Clin. Exp. Ophthalmol.* 234 (1996) 300–305.
- [46] E. Marder, A.L. Taylor, Multiple models to capture the variability in biological neurons and networks, *Nature Neurosci.* 14 (2011) 133–138.
- [47] M.S. Goldman, J. Golowasch, E. Marder, L.F. Abbott, Global structure, robustness, and modulation of neuronal models, *J. Neurosci.* 21 (2001) 5229–5238.
- [48] R. Chi, N. Lin, H. Zhang, R. Zhang, Discrete-Time Adaptive Iterative Learning Control: From Model-Based to Data-Driven, Vol. 1, Springer Nature, 2022.
- [49] A. Isidori, Nonlinear Control Systems, Springer, London, 1995, pp. 503–508.
- [50] J. Carr, Applications of Centre Manifold Theory, Vol. 35, Springer Science & Business Media, 2012, pp. 33–35.
- [51] S. Wiggins, Introduction to Applied Nonlinear Dynamical Systems and Chaos, Vol. 2, Springer, 2003, p. 259.
- [52] G.C. Goodwin, K.S. Sin, Adaptive Filtering Prediction and Control, Courier Corporation, 2014, pp. 50–53.
- [53] R.A. Horn, C.R. Johnson, Topics in Matrix Analysis, Vol. 40, Cambridge University Press, 1991, p. 298.
- [54] B. Cyganek, Object Detection and Recognition in Digital Images: Theory and Practice, John Wiley & Sons, 2013, pp. 152–153.
- [55] R. Reams, Hadamard inverses, square roots and products of almost semidefinite matrices, *Linear Algebra Appl.* 288 (1999) 35–43.
- [56] C.F. Van Loan, The ubiquitous Kronecker product, *J. Comput. Appl. Math.* 123 (2000) 85–100.



Anastasia Giannari was born in Athens, Greece, in 1996. She received a Master of Engineering Degree in Biomedical Engineering from Imperial College London, London (UK) in 2018. In 2018, she joined the Control and Power Research Group at Imperial College London, London (UK) where she is currently working towards her Ph.D. degree in modelling and control of brain neuronal networks. Her research is mainly focused on therapy design for neurodegenerative diseases via nonlinear control.



Alessandro Astolfi was born in Rome, Italy, in 1967. He graduated in electrical engineering from the University of Rome in 1991. In 1992 he joined ETH-Zurich where he obtained a M.Sc. in information theory in 1995 and the Ph.D. degree with Medal of Honor in 1995 with a thesis on discontinuous stabilisation of nonholonomic systems. In 1996 he was awarded a Ph.D. from the University of Rome La Sapienza for his work on nonlinear robust control. Since 1996 he has been with the Electrical and Electronic Engineering Department of Imperial College London, London (UK), where he is currently Professor of Nonlinear Control Theory and Head of the Control and Power Group. From 1998 to 2003 he was also an Associate Professor at the Department of Electronics and Information of the Politecnico di Milano. Since 2005 he has also been a Professor at Dipartimento di Ingegneria Civile e Ingegneria Informatica, University of Rome Tor Vergata. He has been/is Visiting Lecturer in Nonlinear Control in several universities, including ETH Zurich (1995–1996); Terza University of Rome (1996); Rice University, Houston (1999); Kepler University, Linz (2000); SUPELEC, Paris (2001), Northeastern University (2013), University of Cyprus (2018–), Southeast University (2019–). His research interests are focused on mathematical control theory and control applications, with special emphasis for the problems of discontinuous stabilisation, robust and adaptive control, observer design and model reduction. He is the author of more than 165 journal papers, of 30 book chapters and of over 380 papers in refereed conference proceedings. He is the author (with D. Karagiannis and R. Ortega) of the monograph “Nonlinear and Adaptive Control with Applications” (Springer-Verlag). He is the recipient of the IEEE CSS A. Ruberti Young Researcher Prize (2007), the IEEE RAS Googol Best New Application Paper Award (2009), the IEEE CSS George S. Axelby Outstanding Paper Award (2012), the Automatica Best Paper Award (2017). He is a “Distinguished Member” of the IEEE CSS, IEEE Fellow, IFAC Fellow, IET Fellow, and member of the Academia Europaea. He served as Associate Editor for Automatica, Systems and Control Letters, the IEEE Transactions on Automatic Control, the International Journal of Control, the European Journal of Control and the Journal of the Franklin Institute; as Area Editor for the International J. of Adaptive Control and Signal Processing; as Senior Editor for the IEEE Transactions on Automatic Control; and as Editor-in-Chief for the European Journal of Control. He is currently Editor-in-Chief of the IEEE Transactions on Automatic Control. He served as Chair of the IEEE CSS Conference Editorial Board (2010–2017) and in the IPC of several international conferences. He was a Member of the IEEE Fellow Committee (2016/2019–2022).