Closed-loop Control for Precision Antimicrobial Delivery: an *In Silico* Proof-of-Concept

Pau Herrero, Timothy M Rawson, Akash Philip, Luke SP Moore, Alison H Holmes and Pantelis Georgiou, *Senior Member, IEEE*

***Abstract*—Objective: Inappropriate dosing of patients with antibiotics is a driver of antimicrobial resistance, toxicity, and poor outcomes of therapy. In this paper, we investigate, *in silico*, the hypothesis that the use of a closed-loop control system could improve the attainment of pharmacokinetic-pharmacodynamic targets for antimicrobial therapy, where wide variations in target attainment have been reported. This includes patients in critical care, patients with renal disease and patients with obesity.**
Methods: The presented *in silico* study focuses on vancomycin delivery, a first line therapy for *Methicillin-resistant Staphylococcus aureus* (MRSA) that has serious side effects, including nephrotoxicity. For this purpose, an *in silico* platform for the simulation of pharmacokinetics of vancomycin agents was developed including 24 virtual non-critically ill adult subjects obtained from routinely collected data from two prospective audits of vancomycin therapy. Intra-day variability on renal clearance, sensor error and infusion constraints were taken into account. Proportional Integral Derivative (PID) controller was chosen because of its simplicity of implementation and satisfactory performance.
Results: Even though significant intra-day variability and sensor error were considered in the simulations, by assuming a minimum inhibitory concentration of 1 mg/l for MRSA, the proposed controller was able to reach the well-established therapeutic target of 24-hour area under curve to minimum inhibitory concentration ratio equal to 400 $mg \cdot h/l$ for all the studied subjects, while staying significantly below toxic levels.
Conclusion: A PID controller has the potential to precisely deliver a vancomycin therapy in a non-critically ill adult population.
Significance: Closed-loop control for precision Vancomycin delivery can potentially reduce toxicity and poor therapeutic outcomes, as well as reduce antimicrobial resistance.

***Index Terms*—Antimicrobial resistance, closed-loop control, PID control, precision medicine**

I. Introduction

Antimicrobial agents (i.e., drugs that kill or stop the growth of microorganisms including bacteria, thereby treating infections) commonly used to treat infections are becoming less effective over time as bacteria develop resistance to them. Antimicrobial usage leads to the development and spread of antimicrobial resistance [1]. This is a major threat to patient safety with over 700,000 people dying because of drug resistant infections each year. By 2050, it is estimated that this figure could be as high as 10 million deaths per year. To conserve the effectiveness of antimicrobials we need to develop ways to use them more effectively [2]. One way to do this is ensure that we are providing the best dose (i.e., amount of drug) of an antimicrobial to kill the organism causing infection, whilst ensuring that we do not cause toxic side effects or promote the growth of antimicrobial resistance through giving too much or too little of a treatment.

A growing body of evidence is emerging to suggest that we are failing to dose patients appropriately with many commonly used antimicrobial agents [3], [4]. This has led to calls for the development of individualised antimicrobial regimens that consider intra- and inter-individual variation which drives observed drug pharmacokinetic (PK) variation. Despite evidence that optimisation of antimicrobial PK can improve patient outcomes in secondary care [3], very little progress has been made outside of controlled trial environments. The implementation of individualised dosing has been challenging for several reasons. This includes, difficulties in access and availability of appropriate antimicrobial assays, poor integration of dosing software into electronic health records and decision support systems, the reliance on transport of blood products for laboratory analysis, and the technical nature of population PK with very few healthcare professionals with knowledge of this field. There is clinical evidence that the administration of vancomycin for the treatment of Gram-positive infections by continuous infusion is associated with a significantly lower risk of nephrotoxicity and better clinical outcomes of infection when compared with intermittent infusion of the drug [5] [6]. Therefore, we strongly believe that the development of a closed-loop antimicrobial delivery system will help to address these challenges, allowing the wide-scale practice of precision prescribing and delivery of antimicrobial agents.

The concept of automated drug delivery (i.e., closed-loop control) is well described and has been successfully applied in different fields such as controlling blood glucose levels in diabetes [7] and in delivering anaesthetic drugs for automated sedation [8]. However, to our knowledge, no work has been done for automated antimicrobial delivery. Figure 1 shows a graphical representation of a generic system for automated closed-loop drug delivery in a hospital setting.

In this work, we evaluate the feasibility of a closed-loop controller for precision antimicrobial dosing. The system is composed of: a continuous sensor for measuring antimicrobial concentration in blood, or interstitial fluid; a control algorithm that computes the antimicrobial dose based on the antimicrobial concentration; and a delivery system (e.g. intravenous pump) used to administer the antimicrobial drug.

P. Herrero*, Akash Philip and P. Georgiou are with the Centre for Bio-Inspired Technology, Department of Electrical and Electronic Engineering, Imperial College London, London SW7 2AZ, UK. Timothy M Rawson, Luke SP Moore and Alison H Holmes are with the Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance, Imperial College London, United Kingdom.(correspondence e-mail: pherrero@imperial.ac.uk)

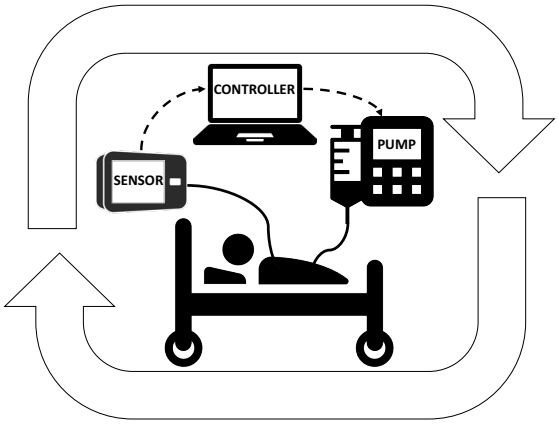

Fig. 1: Graphical representation of a generic system for automated closed-loop drug delivery in a hospital setting.

This work clearly falls in this field of personalized medicine, also termed precision medicine, since it tailors the treatment to the individual patient rather than to the population [9].

This work assumes the availability of a continuous sensor for measuring antimicrobial concentration in blood, which at the moment it is not commercially available. However, significant research is currently ongoing towards developing a minimally invasive (e.g. subcutaneous) sensor [10] [11] [12], [13]. Finally, the selected route for delivering the antimicrobial agent (i.e., vancomycin) was intravenously.

II. Methods

A. Closed-loop controller

Closed-loop control systems work on the principle of feedback in which a signal (e.g. drug concentration) to be controlled is compared to a reference signal (e.g. therapeutic drug concentration). The error between the two signals is then used to tabulate a corrective action (e.g. increase or decrease drug dosage). Figure 2 shows a block diagram of the proposed closed-loop control system for precision antimicrobial delivery.

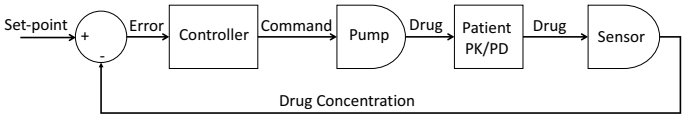

Fig. 2: Block diagram corresponding to a closed-loop control system for precision antimicrobial delivery.

In this work, a Proportional Integral Derivative (PID) closed-loop controller has been chosen. This was considered adequate given the dynamics of the system to be controlled, which do not include significant time delays, and due to its simplicity of implementation. However, other control strategies (e.g. model predictive control) could also have been employed. A PID controller is described by Equation 1.

$$u(t) = K_p e(t) + K_i \int_0^t e(\tau)d\tau + K_d \frac{de(t)}{dt}, \qquad (1)$$

where u represents the rate of infusion into the central compartment (e.g. blood); e is the error between the process variable to control (PV) (i.e. drug concentration) and the set point (SP) (i.e. $e(t) = PV(t) - SP(t)$); K_p, K_i and K_d denote the coefficients for the proportional, integral, and derivative terms, respectively. Finally, the coefficients of the PID controller are related as $Kd = K_p/T_d$ and $Ki = K_p T_i$, where T_d and T_i are tunable time constants.

B. Simulation model

To test the selected PID controller for precision antimicrobial delivery, an *in silico* platform for the simulation of the pharmacokinetics (PK) of the chosen antimicrobial agent was developed in Matlab (Matworks, Natick, MA, US). Pharmacokinetics (PK) describes the relationship between drug-dosing and the drug concentration-time profile in the body. Drug concentration refers to the amount of drug in a given volume of blood plasma, described in milligrams per litre (mg/L). In general, PK models show the movement and fate of a drug in a biological system after it has been administered. In this work, the antimicrobial agent vancomycin was selected since there is a detailed understanding of its clinical utility given that therapeutic drug monitoring is routinely performed for this drug in routine practice. Vancomycin is a glycopeptide antimicrobial chemotherapeutic agent typically used in the treatment of *Staphylococcus aureus* infections which show a resistance to beta-lactams. It is the first line therapy for *Methicillin-resistant Staphylococcus aureus* (MRSA), but has some serious side effects including nephrotoxicity. This is a particular problem in patients with impaired renal function, if used drug concentrations are not closely monitored and controlled. Hence the importance of dosing it appropriately. A two-compartment model was chosen to model the PK of vancomycin [14]. A two-compartment model, as the name implies, has two compartments, a central one, representing blood and well perfused organs, and a peripheral compartment, representing poorly perfused tissues like muscle or fat tissue. The schematic of the two-compartment model is shown in Figure 3.

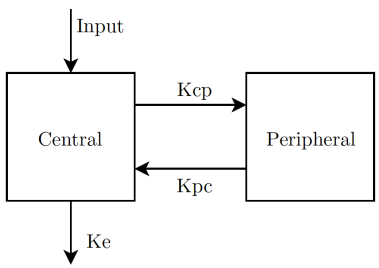

Fig. 3: Two-compartment Model

When the drug is introduced into the body, it first reaches the central compartment and subsequently moves into the

peripheral compartment shown by the transfer rate constant k_{cp}. The movement of drug between the two compartments can be represented either with inter-compartmental clearance, or in terms of transfer rate constants, k_{cp} and k_{pc}. The volume of the peripheral compartment is given by

$$V_p = \frac{k_{cp}}{k_{pc}} V_c, \tag{2}$$

where k_{cp} is the first order transfer rate constant from central to peripheral compartment; k_{pc} is the first order transfer rate constant from peripheral to central compartment; V_p is the volume of peripheral compartment; and V_c is the volume of central compartment. The rate of change of the drug concentrations in any compartment is equal to the net sum of the rates of drug transfer into the compartment minus the sum of rates of drug transfer out of the compartment. Hence the differential equations for the simplest case of a intravenous (IV) bolus administration can be represented as follows.

The rate of change in the central compartment is described by

$$\frac{dC_c(t)}{dt} = u(t) + k_{pc}C_p(t) - k_{cp}C_c(t) - k_e C_c(t), \tag{3}$$

and in the peripheral compartment by

$$\frac{dC_p(t)}{dt} = k_{cp}C_c(t) - k_{pc}C_p(t), \tag{4}$$

where C_c is the amount of drug in central compartment and C_p is the amount of drug in peripheral compartment. k_e is the elimination rate constant computed as $k_e = Cl/V_c$, with Cl the patient's renal clearance. u is the intravenous drug infusion rate. Finally, a forward Euler's method with 1-minute step size was used to simulate the model.

C. Parameter identification

The parameters of the chosen two-compartment model were identified using data obtained from non-critically ill patients managed in three hospitals in North West London (UK). Routinely collected data from two prospective audits of vancomycin therapy were interrogated. Identified subjects not on renal replacement therapy had their demographic and therapeutic drug monitoring (TDM) data extracted for analysis. Age, gender, ethnicity, body weight, height, and glomerular filtration rate (GFR), were all collected for investigation as model covariates. A total of 24 patients were included. Median (range) age (years) of the included subjects was $56.5\ (21-87)$ with the majority being male (18/30, 60%). Mean (STD) height (cm) was $168\ (11)$, and the total mean (STD) body weight (kg) was $74\ (15)$. Median (IQR) GFR was $75.85\ (38.8{-}107.8)\ ml/min/1.73m^2$. Since a complete set of data is only available for each patient at the onset of treatment, parameters were assumed to stay constant throughout the treatment period for analysis of the dataset [4]. Population and individual pharmacokinetic parameters we estimated with Pmetrics, an R programming language package developed by the USC Laboratory of Applied Pharmacokinetics (LAPK) (Los Angeles, CA, US) for non-parametric and parametric PK-PD modelling and simulation [15]. Figure 4 shows the observed vs. predicted graphs for two-compartment model without covariates (R^2=0.857). The distribution (i.e., mean (STD)) of the identified parameters was: $Cl = 2.7\ (1.5)$ l/h, $V_c = 27.6\ (6.7)$ L, $k_{cp} = 1.2\ (1.0)\ h^{-1}$ and $k_{pc} = 3.7(2.7)\ h^{-1}$. Individual posterior estimated PK parameters can be found in Table I.

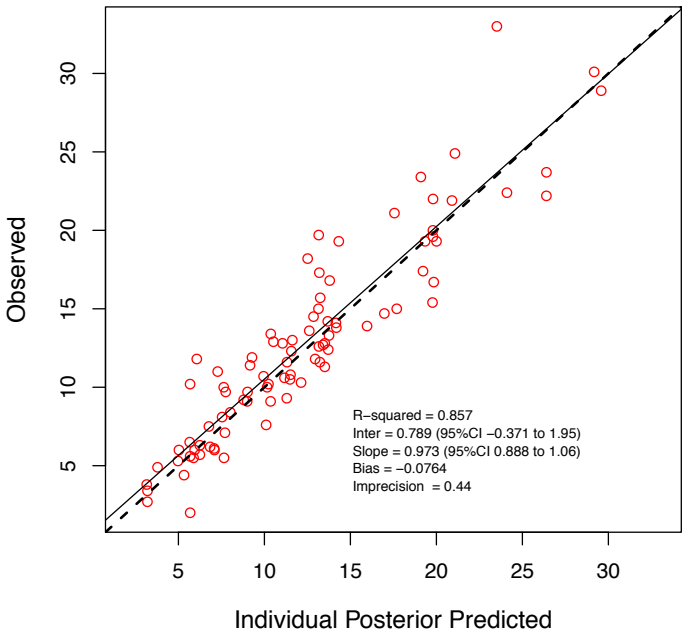

Fig. 4: Observed vs. Predicted plot for the two-compartment model

D. Pharmacokinetic target

Pharmacokinetic-pharmacodynamic (PK-PD) indices are used to determine the likelihood of therapeutic success for the individual patient. Vancomycin displays concentration-dependent antibacterial activity. The 24-hour Area Under Curve (AUC_{24h}) to Minimum Inhibitory Concentration (MIC) ratio (AUC_{24h}/MIC) is the pharmacodynamic index that best links drug exposure with the antibacterial effect [14]. Studies have suggested that the clinical and bacteriological response to vancomycin therapy was superior in patients with a AUC_{24h}/MIC value of greater than 400 $mg \cdot h/l$ [1]. However, in the UK, most therapeutic drug monitoring (TDM) guidelines continue to monitor vancomycin based on peak or trough concentration levels. Such monitoring has been shown to under achieve acceptable levels in clinical practice [16]. Generally, a trough level higher than 10 mg/l is expected. This has been shown to correspond to an AUC_{24h}/MIC of approximately 250 $mg \cdot h/l$ [17]. Therefore, if an organisms MIC is greater than 0.5 mg/l, the treatment is unlikely to be therapeutic.

Furthermore, trough levels of greater than 20 mg/L have been associated with increased risk of nephrotoxicity in patients receiving therapy. This equates to an AUC_{24h}/MIC of approximately 700 $mg \cdot h/l$ [17]. Since the most commonly identified MIC value for *Staphylococcus aureus* is 1 mg/l, the

TABLE I: Individual posterior Bayesian estimated pharmacokinetic from the two-compartment model for the 24 virtual subjects.

$Subj/Param$	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Cl (l/h)	3.6	2.8	3.7	0.2	1.3	1.5	2.7	2.0	2.0	4.8	1.1	1.0	1.3	3.7	1.5	3.3	3.1	7.1	3.8	3.7	3.7	3.8	1.8	1.4
V_c (l)	26.2	24.5	27.6	27.1	38.4	41.6	26.0	20.1	22.8	21.7	32.1	20.0	21.0	29.2	41.5	26.5	20.5	39.8	24.9	26.9	29.0	23.6	31.4	20.7
k_{cp} (h^{-1})	1.9	1.2	2.2	2.6	0.6	0.07	3.3	0.02	0.02	0.14	1.7	0.04	0.3	2.2	0.08	2.0	1.0	0.1	2.2	2.2	2.2	2.2	0.08	0.4
k_{pc} (h^{-1})	3.5	5.8	2.9	0.2	4.1	0.1	0.5	9.5	8.4	2.1	5.2	9.3	3.8	2.2	0.1	3.0	5.9	0.05	3.9	3.2	2.3	4.4	4.5	3.8

AUC_{24h}/MIC most often will simply becomes dependent on AUC_{24h}.

E. Intra-patient variability

During the course of antimicrobial treatment, the patient's condition can significantly change (e.g. dehydration). For example, patients renal clearance (Cl) can vary during treatment due to impaired renal function. Variation in Cl will have an impact on the amount of drug in the system due to the lack of ability to clear it. If doses are not adjusted accordingly, this may cause an accumulation of drug resulting in increased risk of developing toxicity. Vancomycin is almost completely renally cleared and thus total body clearance of the drug is dependent on the kidney, and is correlated with glomerular filtration rate and creatinine clearance [18], [19]. Therefore, the controller should be able to account for variations in Cl and rectify the doses accordingly to achieve the necessary target AUC. For this purpose, intra-day variability affecting renal clearance have been introduced by means of the time varying function

$$Cl(t) = ACl_0 \sin\left(\frac{2\pi}{1440}t + 2\pi\phi\right), \tag{5}$$

where Cl_0 is the identified clearance parameter, A is the amplitude of the variation and ϕ is a randomly generated number per individual between 0 and 1. In particular, A was set to 0.2 to model a 20% variability in clearance. Figure 5 shows a a particular example of renal clearance variability over 24 h.

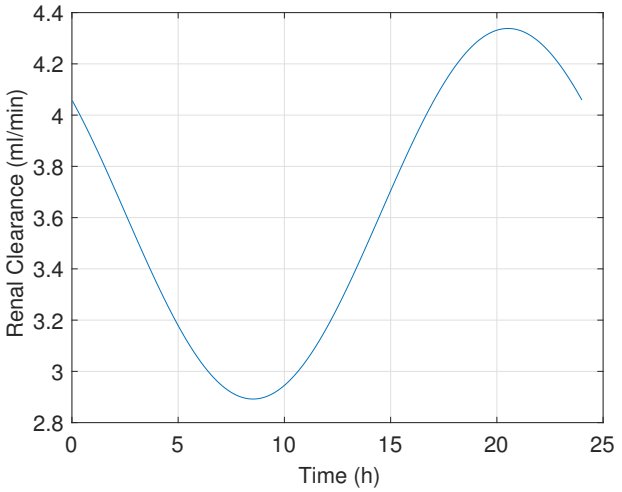

Fig. 5: Variation of renal clearance (Cl) over time for a particular virtual patient.

F. Variable set-point

Since the objective is to achieve the PK target AUC_{24h}/MIC of 400 $mg \cdot h/l$, the closed-loop controller target (SP), i.e. plasma drug concentration, should be set to $400/24$ mg/l along the 24 hours. It is important to remark that the closed-loop controller is delivering a continuous infusion in this scenario. However, this target is not realistic due to the transient response, intra-subject variability, and perturbation in the system. Therefore, the set-point needs to be recalculated overtime in order to achieve the desired AUC_{24h}/MIC target. For this purpose, a six-hour window was chosen to recalculate the set-point to let enough time to pass the transient response. The set-point at time t (hours) is recalculated as expressed by Equation 6.

$$SP(t) = \frac{1}{MIC}\frac{AUC_{24h} - \int_0^t C_c(\tau)d\tau}{24 - t}. \tag{6}$$

Finally, we aimed for 95% of patients to achieve the target of a 95 % of the patients were aimed to achieve the target $380 < AUC_{24h}/MIC < 420$ $mg \cdot h/l$ during simulated therapy. Note that a AUC_{24h}/MIC slightly above or below 400 $mg \cdot h/l$ is equally effective from a therapeutic point of view.

G. Sensor error and pump constraints

As previously mentioned, a continuous sensor for measuring antimicrobial concentration in blood, or interstitial fluid, is not commercially available. Therefore, it is currently not possible to precisely know the sensor dynamics and accuracy of such a sensor. In this work, we consider the existence of a subcutaneous continuous sensor the dynamics of which are assumed to be similar to that of a glucose sensor reported by Breton et al [20]. In particular, the characteristics of the employed sensor error were: mean±SD of -2.1±5.7%; interquartile range of 6.9%; and minimum and maximum of -21.7% and 38.4%, respectively. Figure 6 show an example of the sensor error dynamics over a 24-hour scenario. Finally, a $\pm 2\%$ infusion error and a maximum infusion rate of 999 ml/h were chosen for the virtual infusion pump, which corresponds to an Alaris Syringe (Becton Dickinson, St Albans, UK).

H. Tuning and initialisation

Regarding the two-compartment simulation model, the initial concentrations in the central and peripheral compartments were assumed to be 0 mg/l. The parameters of the PID controller were manually tuned and fixed to $K_p = 0.1$, $T_i = 0.5$, $T_d = 1$ and $T_i = 0$ for all subjects. The integral error of the PID controller was calculated over a sliding time

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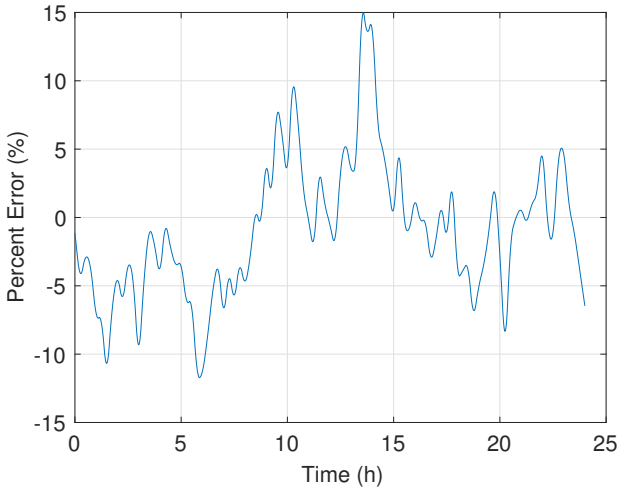

Fig. 6: Sensor error dynamics over a 24-hour scenario.

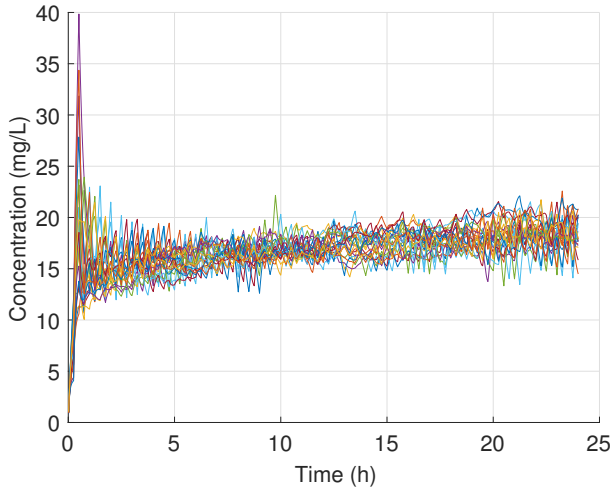

Fig. 7: Vancomycin plasma concentration over 24 hours corresponding to the 24 studied virtual patients.

window of six hours. The duration of the simulation was 24 hours and the sensor sampling time was assumed to be every 15 minutes. Renal clearance variability and sensor noise were randomly generated for each patient. Finally, the initial vancomycin infusion rate was assumed to be 1 mg/min.

III. Results

Figure 7 shows the plasma vancomycin concentration profiles for the 24 studied virtual patients over 24 hours. Figure 8 shows the corresponding drug infusion rate. The observed oscillations on drug concentration levels and on infusion rate are partly due to the variations in renal clearance, sensor error and variable set-point. Maximum vancomycin dose delivered over 24 hours was 4260 mg, which is higher than the maximum recommended dose (i.e., 3000 mg). However, the attained AUC_{24h}/MIC levels were significantly below the toxic threshold (i.e. 700 $mg{\cdot}h/l$) [17]. Finally, Figure 9 shows the corresponding cumulative AUC/MIC over 24 hours. At the end of the simulation, the defined target was achieved for all 24 virtual subjects. It is worth remarking that when the variable set-point was not taken into account, none of the patients achieved the target.

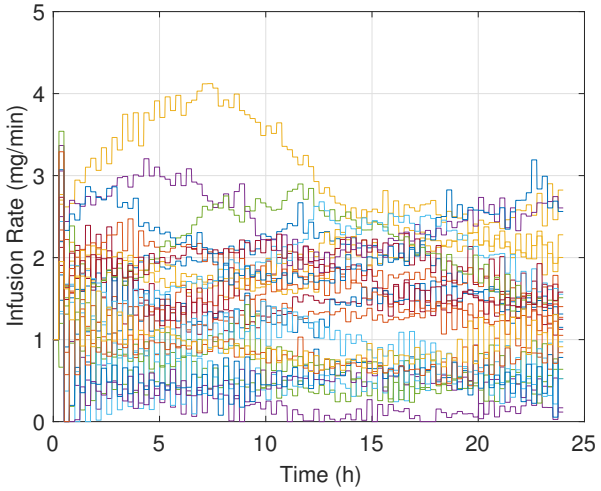

Fig. 8: Vancomycin delivery rate over 24 hours corresponding to Figure 7

IV. Discussion

The presented study provides an *in silico* proof-of-concept for the use of a closed-loop system to optimise vancomycin delivery in a non-critically ill patient cohort. However, there are some limitations in this analysis that need to be mentioned. First of all, the data set used to identify the PK model to carry out the *in silico* study is relatively small (n=24). Therefore, the obtained virtual cohort might not be represent the whole spectrum of non-critically ill patients.

Although intra-day variability in renal clearance and sensor error have been taken into account in the simulations, other sources of variability and uncertainty would probably be present in a real scenario, which might further challenge the performance of the controller, such as sensor artefacts or pump occlusions. Furthermore, further tests should be carried out with a model of an actual subcutaneous vancomycin sensor.

Adjusting the varying set-point has been proven to be an effective strategy to attain the AUC_{24h}/MIC target. However, this strategy might induce abrupt changes in the set-point which can cause an overaggressive control action. Although this has not been an issue within this study, it could be easily resolved in future scenarios by saturating the derivative term of the PID controller. A unique tuning of the PID has been proven to be sufficient for attaining the desired target. However, individualised tuning could lead to even better performance of the controller (e.g. less overshoot). In addition, this tuning could be based on patient demographics and therapeutic drug monitoring data.

It is well stablished that *in silico* studies are not a replacement to clinical trials. However, they can be very useful tool to speed up, and reduce cost, in the development of

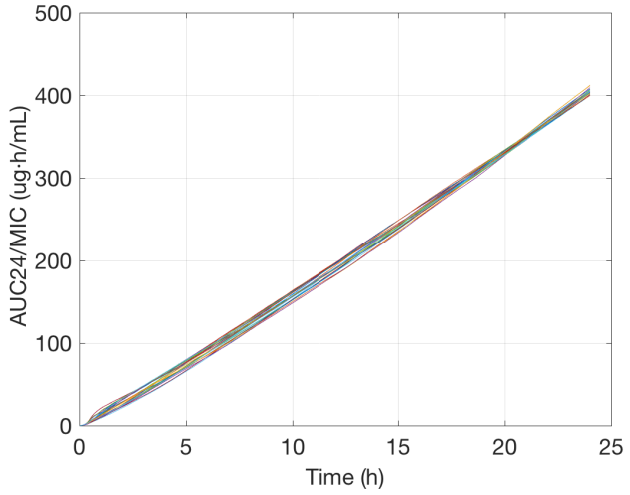

Fig. 9: Cumulative AUC/MIC over 24 hours corresponding to Figure 7.

automated drug delivery systems [21]. Finally, the proposed approach could be easily extrapolated to the delivery of other antimicrobial drugs.

V. Conclusions and Future Work

A closed-loop system for precision vancomycin delivery composed by a PID controller, a subcutaneous sensor and an intravenous pump has the potential to improve infection outcomes in a non-critically ill population. In particular, an *in silico* study including 24 virtual subjects, showed that the proposed controller was able to reach the well-established therapeutic target of AUC_{24h}/MIC equal to 400 $mg \cdot h/l$ for all the studied subjects. Future work includes the comparison of the proposed PID controller against other closed-loop controllers such as Model Predictive Control (MPC). Finally, the proposed closed-loop system is planned to be clinically validated using a micro-array-based real-time sensor for the continuous measurement of antimicrobial concentration in the dermal interstitial fluid, which is currently being developed by our group.

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References

[1] A. H. Holmes, L. S. P. Moore, A. Sundsfjord, M. Steinbakk, S. Regmi, A. Karkey, P. J. Guerin, and L. J. V. Piddock, "Understanding the mechanisms and drivers of antimicrobial resistance," *The Lancet*, vol. 387, no. 10014, pp. 176 – 187, 2016. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0140673615004730

[2] O. Jim, "Review on antimicrobial resistance: Tackling drug resistant infections globally." *UK Prime Minister*, 2016. [Online]. Available: https://amr-review.org/

[3] J. A. Roberts, M. H. Abdul-Aziz, J. Lipman, J. W. Mouton, A. A. Vinks, T. W. Felton, W. W. Hope, A. Farkas, M. N. Neely, J. J. Schentag *et al.*, "Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions," *The Lancet Infectious Diseases*, vol. 14, no. 6, pp. 498–509, 2014.

[4] T. M. Rawson, E. Charani, L. Moore, P. Herrero, J. S. Baik, A. Philip, M. Gilchrist, E. T. Brannigan, P. Georgiou, W. Hope *et al.*, "Vancomycin therapy in secondary care; investigating factors that impact therapeutic target attainment." *The Journal of infection*, vol. 74, no. 3, p. 320, 2017.

[5] M. A. Cataldo, E. Tacconelli, E. Grilli, F. Pea, and N. Petrosillo, "Continuous versus intermittent infusion of vancomycin for the treatment of gram-positive infections: systematic review and meta-analysis," *Journal of antimicrobial chemotherapy*, vol. 67, no. 1, pp. 17–24, 2012.

[6] J. A. Roberts, F. S. Taccone, A. A. Udy, J.-L. Vincent, F. Jacobs, and J. Lipman, "Vancomycin dosing in critically ill patients: robust methods for improved continuous-infusion regimens," *Antimicrobial agents and chemotherapy*, vol. 55, no. 6, pp. 2704–2709, 2011.

[7] S. J. Russell, F. H. El-Khatib, M. Sinha, K. L. Magyar, K. McKeon, L. G. Goergen, C. Balliro, M. A. Hillard, D. M. Nathan, and E. R. Damiano, "Outpatient glycemic control with a bionic pancreas in type 1 diabetes," *New England Journal of Medicine*, vol. 371, no. 4, pp. 313–325, 2014.

[8] A. R. Absalom, N. Sutcliffe, and G. N. Kenny, "Closed-loop control of anesthesia using bispectral indexperformance assessment in patients undergoing major orthopedic surgery under combined general and regional anesthesia," *The Journal of the American Society of Anesthesiologists*, vol. 96, no. 1, pp. 67–73, 2002.

[9] R. Mirnezami, J. Nicholson, and A. Darzi, "Preparing for precision medicine," *New England Journal of Medicine*, vol. 366, no. 6, pp. 489–491, 2012.

[10] J. W. Ndieyira, N. Kappeler, S. Logan, M. A. Cooper, C. Abell, R. A. McKendry, and G. Aeppli, "Surface-stress sensors for rapid and ultrasensitive detection of active free drugs in human serum," *Nature nanotechnology*, vol. 9, no. 3, pp. 225–232, 2014.

[11] S. A. Ranamukhaarachchi, C. Padeste, M. Dübner, U. O. Häfeli, B. Stoeber, and V. J. Cadarso, "Integrated hollow microneedle-optofluidic biosensor for therapeutic drug monitoring in sub-nanoliter volumes," *Scientific reports*, vol. 6, 2016.

[12] B. S. Ferguson, D. A. Hoggarth, D. Maliniak, K. Ploense, R. J. White, N. Woodward, K. Hsieh, A. J. Bonham, M. Eisenstein, T. E. Kippin *et al.*, "Real-time, aptamer-based tracking of circulating therapeutic agents in living animals," *Science translational medicine*, vol. 5, no. 213, pp. 213ra165–213ra165, 2013.

[13] T. Rawson, S. Sharma, P. Georgiou, A. Holmes, A. Cass, and D. O'Hare, "Towards a minimally invasive device for beta-lactam monitoring in humans," *ELECTROCHEMISTRY COMMUNICATIONS*, vol. 82, pp. 1–5, 2017. [Online]. Available: http://dx.doi.org/10.1016/j.elecom.2017.07.011

[14] M. J. Rybak, "The pharmacokinetic and pharmacodynamic properties of vancomycin," *Clinical Infectious Diseases*, vol. 42, no. Supplement 1, pp. S35–S39, 2006. [Online]. Available: http://cid.oxfordjournals.org/content/42/Supplement_1/S35.abstract

[15] R. Jelliffe, A. Schumitzky, D. Bayard, R. Leary, M. Van Guilder, S. Goutelle, A. Bustad, A. Botnen, A. Zuluaga, J. Bartroff *et al.*, "The mm-uscpack pmetrics research software for nonparametric population pk/pd modeling, and the rightdose clinical software for individualizing maximally precise dosage regimens," in *21st Annual Meeting of the Population Approach Group in Europe (PAGE)., Venice, Italy*, 2012, pp. 5–8.

[16] R. F. Chhim, S. R. Arnold, and K. R. Lee, "Vancomycin dosing practices, trough concentrations, and predicted area under the curve in children with suspected invasive staphylococcal infections," *Journal of the Pediatric Infectious Diseases Society*, vol. 2, no. 3, pp. 259–262, 2013. [Online]. Available: http://jpids.oxfordjournals.org/content/2/3/259.abstract

[17] M. N. Neely, G. Youn, B. Jones, R. W. Jelliffe, G. L. Drusano, K. A. Rodvold, and T. P. Lodise, "Are vancomycin trough concentrations adequate for optimal dosing?" *Antimicrobial Agents and Chemotherapy*, vol. 58, no. 1, pp. 309–316, 2014. [Online]. Available: http://aac.asm.org/content/58/1/309.abstract

[18] S. J. Vandecasteele and A. S. D. Vriese, "Recent changes in vancomycin use in renal failure," *Kidney International*, vol. 77, no. 9, pp. 760 – 764, 2010. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0085253815543676

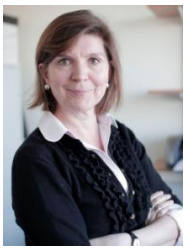
[19] M. J. Rybak, "The pharmacokinetic and pharmacodynamic properties of vancomycin," *Clinical Infectious Diseases*, vol. 42, no. 1, pp. 35–39, 2006.
[20] M. Breton and B. Kovatchev, "Analysis, modeling, and simulation of the accuracy of continuous glucose sensors," *Journal of diabetes science and technology*, vol. 2, no. 5, pp. 853–862, 2008.
[21] B. P. Kovatchev, M. Breton, C. Dalla Man, and C. Cobelli, "In silico preclinical trials: a proof of concept in closed-loop control of type 1 diabetes," pp. 44–55, 2009.

Pau Herrero received the MSc degree in Information Technologies from University of Girona (Spain) in 2002 and the Ph.D. degree in Automation from University of Angers (France) in 2007. He is currently a Research Fellow within the department of Electrical and Electronic Engineering at Imperial College London (UK). He holds two patents. His main research interest lies in the field of diabetes technology and antimicrobial resistance. In particular, he is involved in the development of an artificial pancreas system and intelligent decision support systems for diabetes management and antimicrobial prescription.

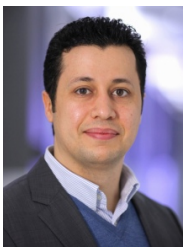
Timothy M Rawson is a medical doctor currently working as an NIHR invention for innovation (i4i) clinical research fellow at the NIHR HPRU for HCAI and AMR, Imperial College London, undertaking a PhD investigating novel precision prescribing interventions to improve antimicrobial prescribing across secondary care. Tim has previously been involved in several phase 1 studies, including a CTIMP and non-CTIMP trials investigating novel mechanisms for appetite suppression and weight loss at Imperial College London.

Akash Philip received the MEng degree from the department of Electrical and Electronic Engineering at Imperial College London (UK). His work has been focused on PKPD-modeling and precision antimicrobial delivery. He currently works at the Defence Science and Technology Agency in Singapore.

Luke SP Moore is consultant infectious diseases and clinical microbiology at Chelsea and Westminster Hospital NHS Foundation Trust (UK) with special interests in critical care infections, antimicrobial resistance, and decision support systems. He holds a PhD in this field, two Masters degrees in Public Health and in Clinical Microbiology, both with distinction, and he is a Fellow of the Royal College of Pathologists and a Member of the Royal College of Physicians. He works clinically for secondary and tertiary care patients with infections in London, whilst his current research focuses on the epidemiology of antimicrobial resistance and outbreak detection, and on intelligent systems to aid antimicrobial stewardship.



Alison H Holmes is Professor of Infectious Diseases at Imperial College London (UK), head of the Health Protection Research Unit for Healthcare Associated Infections and Antimicrobial Resistance, and Director of Infection Prevention and Control at Imperial College Healthcare NHS Trust. Professor Holmes research focuses on prescribing behaviour, healthcare associated infection surveillance, and technological interventions to improve these areas including smartphone applications, mobile health interventions and educational games.



Pantelis Georgiou (AM05M08SM13) received the M.Eng. degree in electrical and electronic engineering and the Ph.D. degree from Imperial College London, London (UK), in 2004 and 2008, respectively. He is currently a Reader with the Department of Electrical and Electronic Engineering, ICL, where he is also the Head of the Bio- Inspired Metabolic Technology Laboratory, Centre for Bio-Inspired Technology. His research includes bio-inspired circuits and systems, CMOS based Lab-on-Chip technologies, and application of microelectronic technology to create novel medical devices. He has made significant contributions to integrated chemical sensing systems in CMOS, conducting pioneering work on the development of ISFET sensors, which has enabled applications, such as point-of-care diagnostics and semiconductor genetic sequencing and has also developed the first bio-inspired artificial pancreas for treatment of Type I diabetes using the silicon-beta cell. He received the IET Mike Sergeant Medal of Outstanding Contribution to Engineering in 2013. He is a member of the IET and serves on the BioCAS and Sensory Systems technical committees of the IEEE CAS Society. He is also the CAS representative on the IEEE Sensors council and the IEEE Distinguished Lecturer in Circuits and Systems.