Bioinformatics-inspired non-parametric modelling of pharmacokinetics-pharmacodynamics systems using differential neural networks

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***Abstract*—Bionformatics and pharmacokinetics-pharmacodynamics (PKPD) systems are two conjugated tools to intensively explore the effect of new drugs on the human body running in-silico analysis. Usually, PKPD models do not consider all the biological reactions that explain the pharmaceutical effect. A complementary non-parametric modeling can be useful to recover the PKPD dynamics despite the uncertainties and external perturbations effect, which can reduce the degree of uncertainties on the drug evaluation. The aim of this study is to get a feasible non-parametric model of PKPD models using a bioinformatics inspired evaluation of antibacterial drug doses. A class of bioinformatics inspired differential neural networks (DNNs) responding to the dose modification provides the non-parametric approximation of the PKPD dynamics. The DNN modeling strategy was applied to approximate the dynamics of PKPD models under four different dosing regimes. The modeling strategy estimated the bacteria survival (measured as the logarithm of the colony forming units per milliliter) after the drug application. The same adjusted DNN-based model confirmed the ability of designing an off-line lab for evaluating diverse dosing strategies of antibacterial pharmaceutical.**

I. Introduction

The classical pharmacology science considers a unique route for testing the effectiveness of new drugs. Usually, the controlled administration of such drugs is proposed to connect the processes between medication dose and its physiological response. These studies are considered the fundamental basis of the drug kinetic and dynamic mechanisms [1]. The collected data from these studies can be used to derive abstract relations between drug dose and the specific physiological reactions. The results of such abstract formulations are known as pharmacokinetic-pharmacodynamic (PKPD) models. Such modeling structures have been used in modern pharmacology as powerful predicting tools and their applications have saved enormous amounts of money [2], [3]. Moreover, the adequate instrumentation of these models has contributed to reduce the animal testings of new drugs, for which the secondary effects are completely unknown, and maybe adverse.

Nowadays, PKPD modelling and simulation techniques are becoming popular as a result of their low cost and rapid implementation [4]. In the last few years, the number of publications regarding the applications of PKPD models as critical elements in drug effect pre-testing has been growing and growing. Just to mention a few, the study proposed by [5] reviews several well-settled PKPD models employed in the field of anesthesia. This study shows how anesthesiologists apply such models to evaluate the drug dosage according to the specific characteristics of each patient. Some measured variables during the anesthesia procedure (obtained by non-invasive continuous monitoring systems) are used as outputs of the model. The individualization of the suggested model provides a formal manner to evaluate the potential long-term effect of anesthesia over each patient.

Shah et al. in [6] applied a PKPD model to establish an in vivo-in vitro correlation of antibody drug conjugates. This study used two mathematical models to characterize the efficacy of chemotherapeutic drugs; signal distribution [7] and cell distribution models [8]. The models were adjusted with the aim of evaluating the antibody efficiency on the patients, once a pretesting has been realized on in-vitro cultured tissue.

The previous two examples show that individualizing the PKPD models for each patient plays a key role to make these models useful within the in-silico drug dosing evaluation. Such individualization requires adjusting the PKPD model for each set of data coming from each patient. This process can be highly time consuming and sometimes expensive. There is an alternative option to complete the individualization processes based on a combined modeling strategy. This mixed model uses a nominal form (the PKPD) and an adaptive model which compensates the individual characteristics of each patient. The compensating model can use different approximation options including polynomials, wavelets, Legrende functions and many others. One of the most advanced options to generate the approximate model are the artificial neural networks (ANNs).

ANNs are nonlinear forms connecting sigmoidal functions which try to emulate the highly parallel and powerful information processing ability of animals brain. There are several artificial realizations for ANN in literature. Depending on the structural form of the ANN, it can work as a static map connecting input-output static related data. On the other hand, if the ANN works using internal output feedback, then it

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is called dynamic. This ANN variant seems to be the more efficient way to complement the PKPD model and produce a reliable feasible and individualized representation of a certain drug effect on the proposed target physiological tissue, organ or system.

This study provides a formal application of dynamic ANN to realize an individualization of PKPD adaptable models for relating drug dose and the bacteria survival for patients suffering an infection. The PKPD model complemented with the ANN estimated the bacteria concentration for all the evaluated patients. A nominal PKPD model provides a preliminary approximation to the bacterial surviving which was complemented with the ANN dynamics. This mixed model offers a more practical modelling strategy to realize suitable predictions for the potential effect of the drug concentration on a certain patient.

The main contribution of this study is the design of a mixed model for individualizing the application of PKPD to reproduce the relationship between a pharmaceutical dose and the corresponding surviving bacteria concentrations. The mixed model uses a classical bi-compartmental PKPD model and the dynamic ANN.

This paper is organized as follows: Section II presents the general fundamentals of PKPD perturbed models. Section III details the design of the approximated model based on dynamic ANN considering a class of affine representation with respect to the weights and considering a single outut layer. Section IV shows the numerical results corresponding to the application of the proposed mixed PKPD model plus the approximated model. Section V closes the paper with some final remarks.

II. Pharmacokinetics-pharmacodynamics systems with uncertain models

Let consider a mathematical model for the perturbed PKPD system represented by:

$$\dot{x}(t) = f_{Ph}(x\,(t)\,, I\,(t)) + \xi\,(x\,(t)\,, t) \tag{1}$$

Here x represents the time dependent profile of $Pr(log(CFU/ml) < 0)$, that is the bacterial concentration forced by the selected drug dose I on the renal function group which operates as an index of the drug antibacterial efficiency. The nonlinear vector field f_{Ph} refers to the pharmaceutical effect of the input drug I at the time t. The input $I\,(t)$ is the patient data related to age, body weight and gender but also creatinine clearance (ClCr) and dosage regimes during time t. In this study, let us assume that this function can be represented as the composition of a nominal PKPD model f_{PKPD} plus the approximate ANN based approximate model, namely f_{ANN}. The class of proposed ANN model corresponds to a class of differential neural network. DNN is a type of NN described by a set of ordinary differential equations (ODEs) [9]. These ODEs may be used to obtain an approximated model of the relationship between the patient age, body weight, gender, creatinine clearance (ClCr) and dosage regimes. These characteristics can serve as input to the DNN and the time dependent profile of $Pr(log(CFU/ml) < 0)$.

Assumption 1: The time dependent profiles $Pr(log(CFU/ml) < 0)$ associated to the renal function can be represented as an absolutely continuous function ∞, namely $x(t)$. This assumption makes possible to represent the profiles $Pr(log(CFU/ml) < 0)$ as the solution of an uncertain ordinary differential equation

$$\begin{gathered}\dot{x}(t) = f_{PKPD}(x\,(t)\,, I\,(t)) + f_{ANN}(x\,(t)\,, I\,(t)) + \\ \tilde{f}_{ANN}(x\,(t)\,, I\,(t)) + \xi\,(x\,(t)\,, t)\end{gathered} \tag{2}$$

Here, the function $\tilde{f}(\cdot,\cdot)$ represents the modeling error produced by the ANN and it is associated to all the biological reactions that explain the pharmaceutical effect on the body as a function of the drug dose. This representation is used to approximate the response obtained by the renal functional group.

The code represented by $f_{ANN}(\cdot,\cdot)$ is actually unknown and particular for each patient. Nevertheless, one can assume that such function is the same for all subjects plus a degree of uncertainties represented by $\xi\,(t) \in \mathbb{R}$. This function $\xi\,(t)$ symbolizes the perturbations and uncertainties associated to the relationship between the patient data or treatment, and the renal function group. A natural consequence of the assumption described above is: **1**. The function $f_{Ph}(\cdot,\cdot)$ satisfies the Lipschitz condition, that is $\|f(x_1,u_1) - f(x_2,u_1)\|^2 \leq L_x \|x_1 - x_2\|^2$.

2. The uncertainties belong to the patient characteristics and treatment represented by

$$\|\xi\,(x,t)\|^2 \leq \xi_0 + \xi_1 \|x\|^2 \quad \forall t \geq 0 \tag{3}$$

Considering these both restrictions, one can propose the use of DNN to obtain a suitable numerical approximation of the underlying model relating the patient data /treatment and the index of antibacterial efficiency.

III. Non-parametric modeling using DNNs of PKPD systems

The modelling problem addressed in this work can be rephrased in the following manner; To design a parallel adaptive identifier combining the DNN approximation with an adaptive structure using several correction terms to adjust the identifier trajectories, the so called DNN weights. The mixed structure working together with the adaptive DNN identification can be presented as

$$f_{ANN}(\hat{x}_t) = \tilde{h}_0(\hat{x}_t, \Theta_t), \quad \hat{z}_0 \; is \; fixed$$

$$\dot{\Theta}_t := R_t(t, \Theta_t, \delta_t) \tag{4}$$

Here $\hat{h}_0(\hat{x}_t, \Theta_t)$ represents the adapted version of the function $h_0(x_t, \Theta^0)$ produced by the DNN. Therefore, the problem tackled in this paper can be reformulated as follows: to achieve an adequate selection of matrices and in the identifier **(4)** (which is adjusted with the learning algorithm defined by $R_t(t, \Theta_t, \delta_t)$ in such a way that identification error defined

as $\beta := \overline{\lim_{t\to\infty}} \parallel x_t - \hat{x}_t \parallel_Q$ can be stabilized within a small ball around zero. The volume of this ball will be dependent on the power of noises and uncertainties. This averaged error is quiet similar to the mean squared error that is commonly used in NN theory.

The identifier used in this paper is described by the following structure

$$\frac{d}{dt}\hat{x}_t = A\hat{x}_t + W_{1,t}^{\top}\Psi_1(\hat{x}) + W_{2,t}^{\top}\Psi_2(\hat{x})u_t \tag{5}$$

where $A \in \Re, W_{1,t}^i \in \Re^{n_1}, W_{2,t} \in \Re^{n_2}$ The scalar $\hat{x}_t \in \Re$ defines the identifier state. $W_{1,t}^i$ and $W_{2,t}^i$ are adaptive parameters that should be adjusted to reproduce (as well as possible) the ANN dynamics, that is the index of antibacterial efficiency. Usually in NN, the weights $(W_{j,t}, j = 1,2)$ provide the function approximation capacity. The functions $\Psi_1(\hat{x}) \in \Re^{n_1}$ and $\Psi_2(\hat{x}) \in \Re^{n_2 * s}$ were selected as Chebyshev polynomials.

The non-linear weight *updating* (learning) law is described by following matrix differential equations

$$W_{j,t} = -k_j P \Delta_t \Pi_j^T + 2^{-1} k_j \tilde{W}_{j,t} \tag{6}$$

Matrices $\tilde{W}_{1,t}$ and $\tilde{W}_{2,t}$ represent the distance between the current values of $W_{1,t}$ and $W_{2,t}$ to their corresponding best fitted values $W_{1,t}^0$ and $W_{2,t}^0$, that is $\tilde{W}_{j,t} = W_{j,t} - W_{j,0}$. The time varying Δ_t function is the identification error. Matrices $W_{j,0}$ are weights that adjust perfectly the trajectories of the uncertain system. These weights always exist (based on the Stone-Weisstrass theorem) but they are unknown. Evidently, the accuracy of these values depends on the number of weights adopted to represent the identifier dynamics. The variables k_j $j = 1,2$ are the learning rates. Matrix P is the positive definite solutions for the Riccati equations

$$\begin{gathered} Ric(P) := PA + A^{\intercal}P + PRP + Q \\ R = W_1^0(\Lambda_2)^{-1}[W_1^0]^T + W_2^0(\Lambda_4)^{-1}[W_2^0]^T + \Lambda_1 + \Lambda_3 \\ Q = \lambda_{\max}(2\Lambda_2)l_1)I_{nxn} + Q_0 \end{gathered} \tag{7}$$

Here $\Lambda_k \in \Re, k = \overline{1,4}$ and are positive definite too. In fact, they must be selected (over a large set of possible values) just to ensure the existence of the solution for the previous equations. These results give the theoretical support to ensure that DNN algorithm may be used to reproduce the time course profiles $Pr(log(CFU/ml) < 0)$ by renal function group.

Remark 1: The identifier structure introduced in (5) has been deeply studied by several authors. Some interesting descriptions of such description may be founded in [10].

The following theorem describes the convergence of the identifier response to time course profiles $Pr(log(CFU/ml) < 0)$ by renal function group.

Theorem 1: Assuming that upper bounds given in (3) are valid, lets consider the DNN identifier (5) to be adjusted with the adaptive laws (6), and if there exist matrices $\Lambda_r = (\Lambda_r)^{\intercal} > 0, \Lambda_r \in \Re^{n\times n}, r = \overline{1,4}, Q \in \Re^{n\times n}$ such that the set of Riccati inequalities presented before has positive solution, then

a) The identification error $\Delta_t := \hat{x}(t) - x(t)$ is ε-practically stable, that is: $\overline{\lim_{t\to\infty}} \Delta^{\intercal}(t) P \Delta(t) \leq \frac{\beta}{\alpha_Q}$

where $\alpha_Q := \lambda \min((P)^{-1/2} Q (P)^{-1/2}) > 0$ and $\beta := \lambda \min((P)^{-1/2} \Lambda_2 (P)^{-1/2}) \xi_0$. Here $\lambda_{\min}(\Omega)$ is the minimum eigenvalue of the matrix Ω.

b) The weights trajectories $\tilde{W}_1(t)$ and $\tilde{W}_2(t)$ are also bounded in the large as follows: $\overline{\lim_{t\to\infty}} \left\| \tilde{W}_j(t) \right\|^2 \leq 2k_j \frac{\beta}{\alpha_Q}$, $j = 1,2$

Notice that the proposed identifier uses the information collected from diverse patients to get individual approximation based on their own information. These approximate models can serve in an eventual use of the approximate model for individualizing relation between drug doses and the bacterial surviving.

IV. Numerical Evaluation

A. The PKPD system

The system presented in this study was taken from [11]. This study aims to model and simulate effective dosage regimens of doripenem by a PKPD theory, to explain in vitro bactericidal kinetics of doripenem for several *Pseudomonas aeruginosa* strains (Figure 1). The study perform simulations with dosage regimens of 250mg a day (b.i.d.), 250mg three times a day (t.i.d.), 500mg a day (b.i.d.) and 500mg three times a day (t.i.d.), for the infusion a period of 0.5h was set for all the patient simulations. A Monte Carlo simulations generated the individual values for the 5000 patients, please refer to [11] for the parameter employed for the simulation.

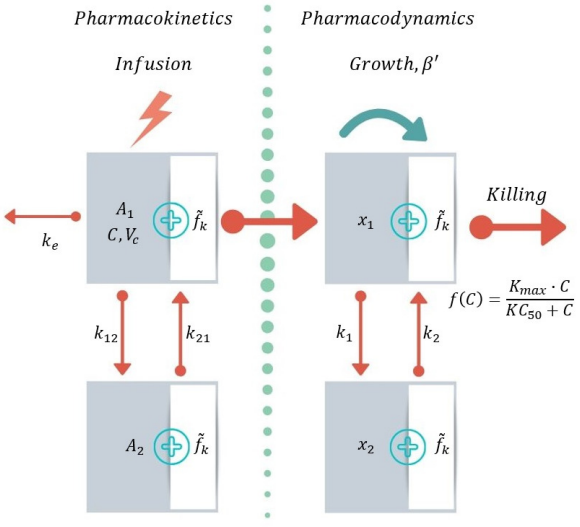

Fig. 1: Scheme of the DNN model for bactericidal kinetics.

The trajectories of the PKPD model were generated from the Matlab toolbox named *SimBiology*, where all the data can be downloaded. Also, their proposed models of time dependent profiles achieving the criterion $(log(CFU/mL) < 0)$ can be test.

B. Simulated implementation

The parameters for the DNN simulation where; $k_1 = 1.3$, $k_2 = 1.6$, $P = 1$ and $A =$, the mean value for the weights for time-course profiles of $Prlog(CFU/mL) < 0$ by renal function group with different dosage regimens can be seen in figures 2 and 3.

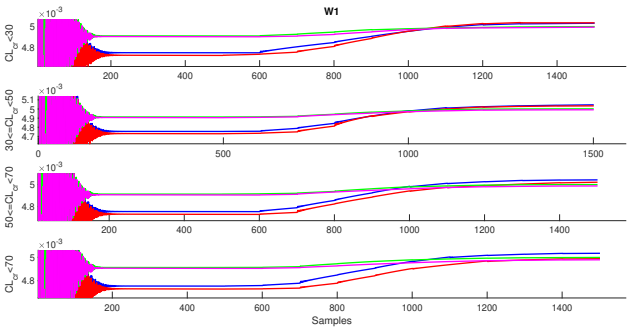

Fig. 2: Weights W1 for the renal function group at different dosage regimens; in blue 250mg b.i.d., in red the 250mg t.i.d., in green the 500mg b.i.d. and in purple the 500mg t.i.d.

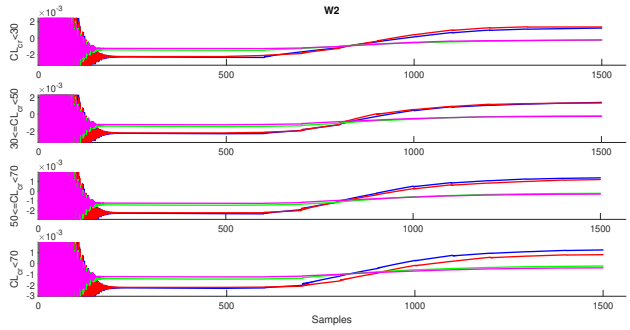

Fig. 3: Weights W2 for the renal function group at different dosage regimens; in blue 250mg b.i.d., in red the 250mg t.i.d., in green the 500mg b.i.d. and in purple the 500mg t.i.d.

As mentioned before, the time-course profiles of probability achieving the criterion $(log(CFU/mL) < 0)$ for the different dosages was employed as reference trajectory for the DNN. The renal function for the different patients are; normal renal function $CL_{cr} <= 70mL/min$ and severe renal dysfunction $(CLcr < 30mL/min)$.

Figure 4 shows the DNN approximation for cases of patients with severe renal dysfunction. Figure 5 dects the cases of patients with renal function values between $30 <= CL_{cr} < 50mL/min$. The patients with renal function values between $50 <= CL_{cr} < 70mL/min$ and the DNN approximation to their response with respect to different dosing regimens can be seen in figure 6. Finally, the patients with normal renal function response to the selected doses was approximated by the DNN are represented in figure 7.

V. Conclusion

In this work a novel approach for the non-parametric modelling of PKPD to explore the effect of dosage regimens of doripenem in 5000 virtual patients by DNN is presented. The model can be useful to recover the PKPD dynamics despite the uncertainties and external perturbations effect, this perturbations are often misrepresented by the traditional modelling strategies that do not consider the full dynamics of the drug with the human body.

The proposed DNN takes into account the full characteristics of each patient and for its training the response of the previous developed modelling. As a result the DNN is able to approximate the response of each patient to the dosages regimes according to the virtual patient renal function. The renal function strategy is also useful because is a way to estimated the bacteria survival after the drug application.

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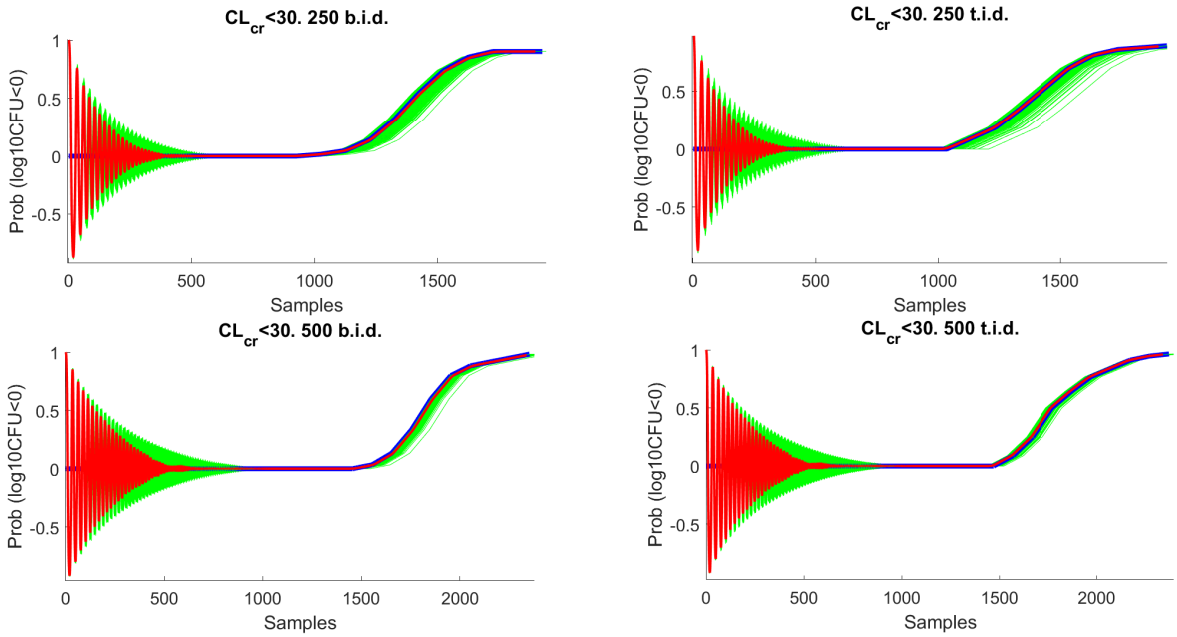

Fig. 4: Time-course profiles of probability achieving the criterion $(log(CFU/mL) < 0)$ for the evaluation of antibacterial efficacy by renal function obtained by [11] is represented by the purple line, the DNN approximation for the 5000 patients is shown in the green lines, finally the DNN mean value is depicted by the red line.

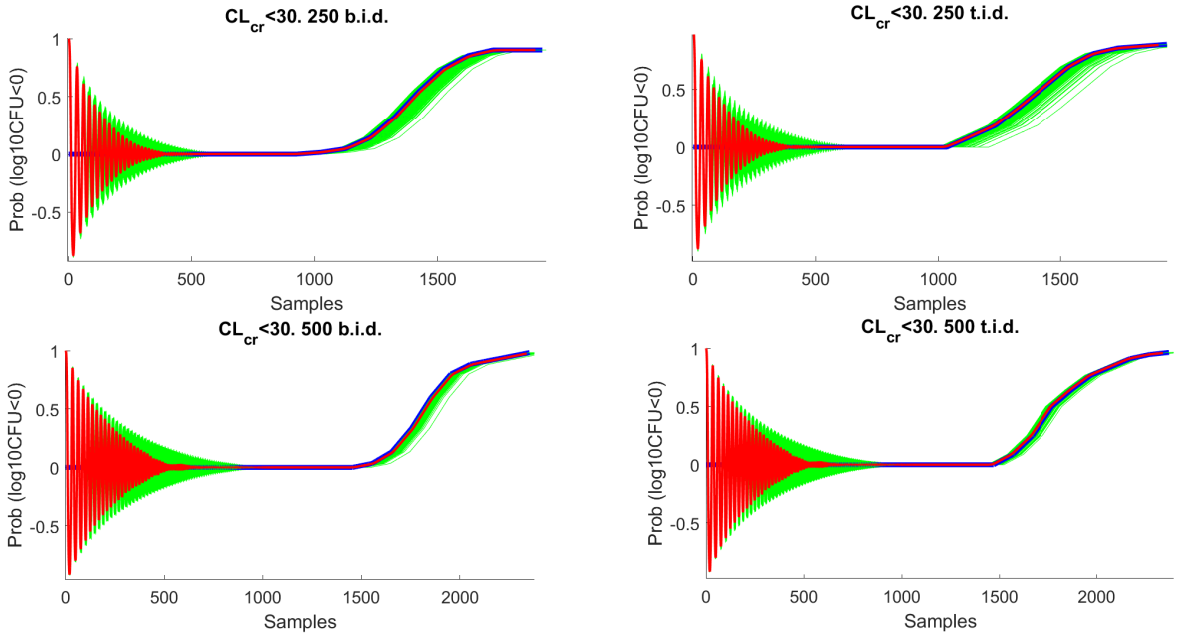

Fig. 5: Time-course profiles of probability achieving the criterion (log(CFU/mL)¡0) for the evaluation of antibacterial efficacy by renal function obtained by [11] is represented by the purple line, the DNN approximation for the 5000 patients is shown in the green lines, finally the DNN mean value is depicted by the red line.

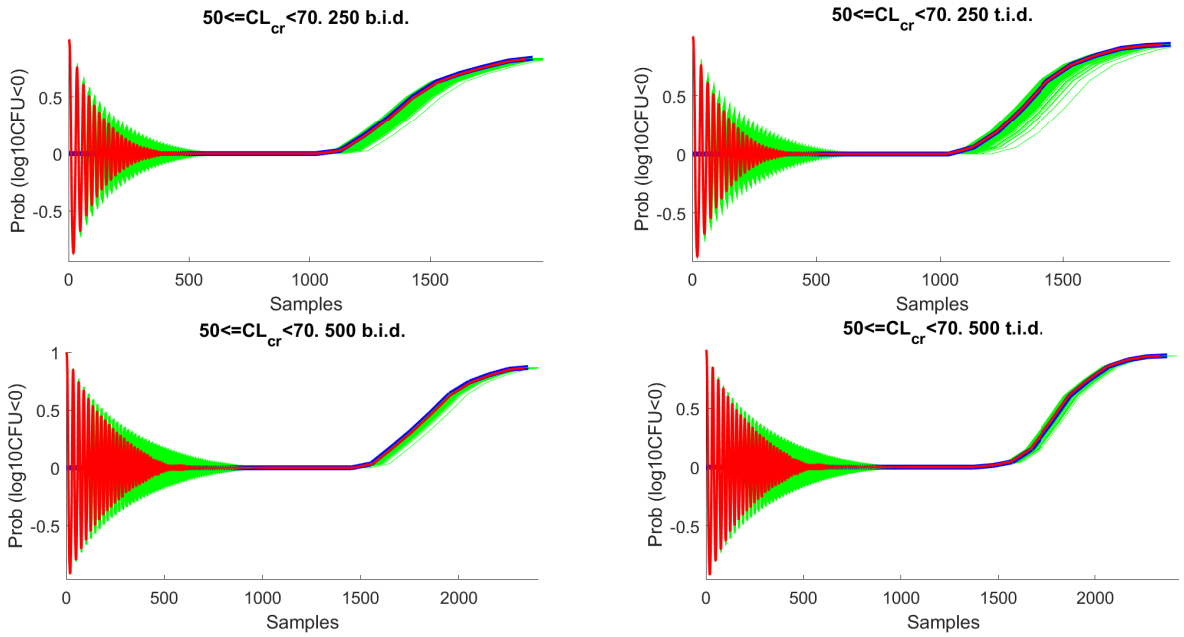

Fig. 6: Time-course profiles of probability achieving the criterion (log(CFU/mL)¡0) for the evaluation of antibacterial efficacy by renal function obtained by [11] is represented by the purple line, the DNN approximation for the 5000 patients is shown in the green lines, finally the DNN mean value is depicted by the red line.

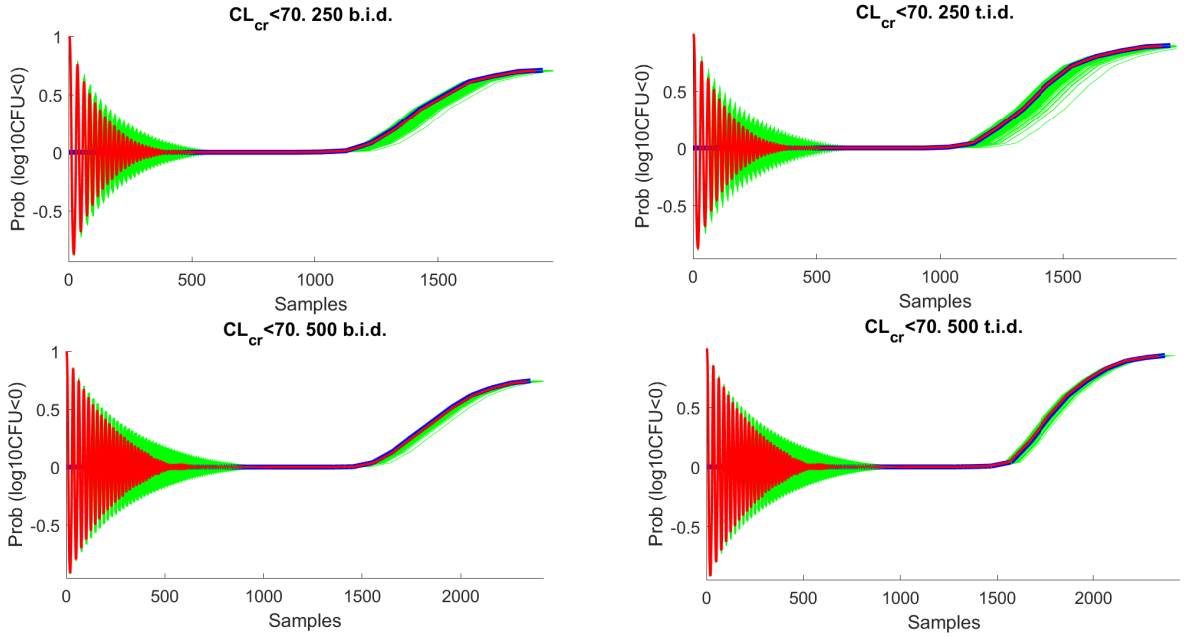

Fig. 7: Time-course profiles of probability achieving the criterion (log(CFU/mL)¡0) for the evaluation of antibacterial efficacy by renal function obtained by [11] is represented by the purple line, the DNN approximation for the 5000 patients is shown in the green lines, finally the DNN mean value is depicted by the red line.