Numerical modeling of T-cell dynamics by reaction-diffusion problems

Raffaele D'Ambrosio[1], Beatrice Paternoster[1], Carmela Scalone[2]

Abstract—The paper proposes a numerical model for T-cell dynamics, based on a reaction-diffusion problem originated by adding a diffusion term in the model introduced in [1] and based on ordinary differential equations. The model here introduced is specifically intended to provide a mathematical description of the homeostasis of T-cells, mainly due to a *quorum-sensing* mechanism. The introduced reaction-diffusion problem is then discretized by means of a finite difference numerical scheme. Numerical experiments supporting the approach are provided.

Keywords—T-cell dynamics, partial differential equations, reaction-diffusion problems, method of lines, finite differences.

I. Framework: modeling homeostasis of T-cells by ordinary differential equations

Homeostasis can be defined as the natural property of living organisms to preserve their internal stability, in response to changes in external conditions. A specific example of homeostasis regards the immune system, where the number of cells playing a key role in the immune response (the so-called T-cells) is normally retained along the adult life of an individual [6]. Homeostasis of T-cells is believed to be due to a *quorum-sensing* mechanism, normally typical of bacteria, according to which CD4+ cells (i.e. those T-cells which are responsible of activating the immune response, by sending signals to another family of T-cells, the so-called CD8 killer cells) could control their own expansion, thanks to their ability to perceive the density of their own populations, in order to prevent uncontrolled lymphocyte proliferation during immune responses.

In this homeostatic mechanism Interleukin-2 (IL-2), which is a protein regulating the activities of lymphocytes responsible for immunity, plays a significant role, very well described for instance in [1] and references therein. In particular, the authors have developed in [1] a mathematical model based on ordinary differential equations (ODEs), describing CD4+ T-cell homeostasis in terms of the time evolution of the following cellular populations:

- $n_1(t)$, naïve T-cells;
- $n_2(t)$, IL-2 producing cells;
- $n_3(t)$, activated/memory non-IL-2 producing cells;
- $n_4(t)$, regulatory CD4+ T-cells.

The corresponding system of ODEs assumes the following form [1]

$$
\begin{aligned}
n_1{}'(t) &= \nu_1 - \mu_1 n_1(t) + \lambda_{1TCR} n_1(t)\left(1 - \frac{n_1(t)}{k}\right) \\
&\quad - \alpha_{12} n_1(t) - \alpha_{13} n_1(t), \\
n_2{}'(t) &= -\mu_2 n_2(t) + \lambda_{2TCR} n_2(t)\left(1 - \frac{n_2(t)}{k}\right) \\
&\quad + \lambda_{2IL-2} n_2(t) n_2(t) + \alpha_{12} n_1(t) - \alpha_{23} n_2(t) \\
&\quad + \alpha_{32} n_3(t) - \beta n_2(t) n_4(t), \\
n_3{}'(t) &= -\mu_3 n_3(t) + \lambda_{3TCR} n_3(t)\left(1 - \frac{n_3(t)}{k}\right) \\
&\quad + \lambda_{3IL-2} n_2(t) n_3(t) + \alpha_{13} n_1(t) + \alpha_{23} n_2(t) \\
&\quad - \alpha_{32} n_3(t) + \beta n_2(t) n_4(t), \\
n_4{}'(t) &= \nu_4 - \mu_4\left(\frac{k_2}{k_2 + n_2(t)}\right) n_4(t) \\
&\quad + \lambda_{4IL-2} n_2(t) n_4(t),
\end{aligned}
\tag{1}
$$

equipped by the initial conditions at time $t = 0$

$$
n_1(0) = 100, \quad n_2(0) = n_3(0) = 0, \quad n_4(0) = 1.
$$

The constants in (1) have the following meanings and values:

- Natural death rates:
  $\mu_1 = 10^{-3}, \quad \mu_2 = \mu_3 = \mu_4 = 10^{-2}, \quad k_2 = 10;$
- proliferation rates in response to T-cell receptor (TCR) mediated signals:
  $\lambda_{1TCR} = \lambda_{2TCR} = 2 \cdot 10^{-2}, \quad \lambda_{3TCR} = 5 \cdot 10^{-2}, \quad k = 10^3;$
- IL-2 induced proliferation:
  $\lambda_{2IL-2} = 5 \cdot 10^{-5}, \quad \lambda_{3IL-2} = 2 \cdot 10^{-5}, \quad \lambda_{4IL-2} = 10^{-4};$
- Differentiation rates of naïve T-cells into IL-2 producing cells or memory cells:
  $\alpha_{12} = 10^{-1}, \quad \alpha_{13} = 10^{-2};$
- Differentiation rates of IL-2 producing cells into memory cells:
  $\alpha_{32} = 10^{-3};$
- Reactivation of memory cells to produce IL-2:
  $\alpha_{23} = 10^{-2};$
- Regulatory T-cells suppression:
  $\beta = 2 \cdot 10^{-4};$

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- The thymus output terms are neglected: $\nu_1 = 0, \quad \nu_4 = 0.$

As claimed by the authors in [1], the quorum-sensing mechanism described by (1) provides that regulatory T-cells count and regulate the number of activated T-cells through the detection of the IL-2 and the number of interactions between these two populations, of which a specified proportion (encoded within the parameters of the model) leads to cellular events such as division, survival or suppression. The novelty with respect to previous models (see [1], [2], [8], [31], [43] and references therein), is given by the fact that the suppression mechanism is mathematically provided by a nonlinear density dependent term in the equation for the IL-2 producing cells.

II. A reaction-diffusion model for CD4+ T-cells homeostasis

We now present a new model describing CD4+ T-cells homeostasis, that gives an extension of (1) obtained by the introduction of a second independent variable x in the four populations functions $n_i(x,t)$, $i = 1,2,3,4$, that still retain the same meaning described in Section 1. This additional dependency clearly produces a change in the mathematical nature of the model, that becomes a system of partial differential equations (PDEs). The purpose aimed to be achieved is to investigate the behavior of the four cells populations, when the homeostasis, based on the quorum sensing hypothesis, is thought as a diffusive phenomenon respect to the new variable x. Hence, the novel structure of the system is held by the introduction of a diffusion term in every equation in (1). The novel PDEs based model is then given by the following reaction-diffusion problem in the rectangular domain $[0,X]\times[0,T]$

$$
\begin{aligned}
\frac{\partial n_1(x,t)}{\partial t} &= \frac{\partial^2 n_1(x,t)}{\partial x^2} + \nu_1 - \mu_1 n_1(x,t) \\
&+ \lambda_{1TCR}\, n_1(x,t)(1 - n_1(x,t)/k) \\
&- \alpha_{12} n_1(x,t) - \alpha_{13} n_1(x,t), \\
\frac{\partial n_2(x,t)}{\partial t} &= \frac{\partial^2 n_2(x,t)}{\partial x^2} - \mu_2 n_2(x,t) \\
&+ \lambda_{2TCR} n_2(x,t)(1 - n_2(x,t)/k) \\
&+ \lambda_{2IL-2}\, n_2(x,t) n_2(x,t) \\
&+ \alpha_{12} n_1(x,t) - \alpha_{23} n_2(x,t) + \alpha_{32} n_3(x,t) \\
&- \beta n_2(x,t) n_4(x,t), \\
\frac{\partial n_3(x,t)}{\partial t} &= \frac{\partial^2 n_3(x,t)}{\partial x^2} - \mu_3 n_3(x,t) \\
&+ \lambda_{3TCR} n_3(x,t)(1 - n_3(x,t)/k) \\
&+ \lambda_{3IL-2}\, n_2(x,t) n_3(x,t) \\
&+ \alpha_{13} n_1(x,t) + \alpha_{23} n_2(x,t) - \alpha_{32} n_3(x,t) \\
&+ \beta n_2(x,t) n_4(x,t), \\
\frac{\partial n_4(x,t)}{\partial t} &= \frac{\partial^2 n_4(x,t)}{\partial x^2} + \nu_4 \\
&- \mu_4 (k_2/(k_2 + n_2(x,t))) n_4(x,t) \\
&+ \lambda_{4IL-2}\, n_2(x,t) n_4(x,t).
\end{aligned}
\tag{2}
$$

The problem is equipped by initial conditions analogous to those of the ODE model, i.e.

$$n_1(x,0) = 100, \quad n_2(x,0) = n_3(x,0) = 0, \quad n_4(x,0) = 1,$$

and in correspondence of mixed Neumann-Dirichlet boundary conditions

- $\dfrac{\partial n_i(0,t)}{\partial x} = 0, \ \ \forall t \in [0,T], \ \ i = 1,2,3,4,$
- $n_i(0,t) = 10^3, \ \ \forall t \in [0,T], \ \ i = 1,2,3,4.$

In order to provide numerical simulations of the dynamics described by (2), we consider the discretized version of (2) originated by a finite difference numerical scheme [28], [33], [46], [47]. For this purpose, we introduce the spatially discretized domain

$$
\begin{aligned}
D_h = \{(x_i,t) : x_i = ih, \quad & i = 0,\ldots,N-1, \\
& h = X/(N-1), \quad t \in [0,T]\},
\end{aligned}
$$

and, in correspondence of this domain, the system of PDEs (2) can be recasted as a system of ordinary differential equations

$$
\begin{aligned}
n'_{i,0}(t) &= n'_{i,2}(t), \quad i = 1,2,3,4, \\
n'_{1,j}(t) &= \Delta_m[n_1(t),h] + \nu_1 - \mu_1 n_{1,j}(t) \\
&+ \lambda_{1TCR}\, n_{1,j}(t)(1 - n_{1,j}(t)/k) \\
&- \alpha_{12} n_{1,j}(t) - \alpha_{13} n_{1,j}(t), \\
n'_{2,j}(t) &= \Delta_m[n_2(t),h] - \mu_2 n_{2,j}(t) \\
&+ \lambda_{2TCR} n_{2,j}(t)(1 - n_{2,j}(t)/k) \\
&+ \lambda_{2IL-2}\, n_{2,j}(t) n_{2,j}(t) \\
&+ \alpha_{12} n_{1,j}(t) - \alpha_{23} n_{2,j}(t) + \alpha_{32} n_{3,j}(t) \\
&- \beta n_{2,j}(t) n_{4,j}(t), \\
n'_{3,j}(t) &= \Delta_m[n_3(t),h] - \mu_3 n_{3,j}(t) \\
&+ \lambda_{3TCR} n_{3,j}(t)(1 - n_{3,j}(t)/k) \\
&+ \lambda_{3IL-2}\, n_{2,j}(t) n_{3,}(t) \\
&+ \alpha_{13} n_{1,j}(t) + \alpha_{23} n_{2,j}(t) \\
&- \alpha_{32} n_{3,j}(t) + \beta n_2(t) n_{4,j}(t), \\
n'_{4,j}(t) &= \Delta_m[n_4(t),h] + \nu_4 \\
&- \mu_4 (k_2/(k_2 + n_{2,j}(t))) n_{4,j}(t) \\
&+ \lambda_{4IL-2}\, n_{2,j}(t) n_{4,j}(t), \\
n'_{i,N-1}(t) &= 0, \quad i = 1,2,3,4,
\end{aligned}
\tag{3}
$$

with $1 \le j \le N-2$, being $n_{i,j}(t) = n_i(x_j,t)$ and $\Delta_m[n_i(t),h]$ a finite difference on m equispaced grid points.

III. Numerical results

We now present the numerical evidence originated by solving the discretized system (3) in the domain $[0,1]\times[0,1]$. We choose $N = 11$ and solve the system of ODEs by the Matlab built-in command `ode15s`.

Figures 1 and 2 represent the solutions of (2) with Neumann-Dirichlet boundary conditions. The choice of mixed conditions is quite typical for diffusion problems (compare [14], [19], [44]), while employing pure Dirichlet or Neumann

conditions lead to plane solutions. We observe that the solutions obtained in Figures 1 and 2 well model the homeostatic behaviour, but the solver stops quickly along the time. Such a situation is not advisable if periodic free-flow boundary conditions are used

- $n_i(0,t) = n_i(0+h,t), \quad i = 1,2,3,4,$
- $n_i(1,t) = n_i(1-h,t), \quad i = 1,2,3,4,$

begin h is the spatial discretization step, as visible in Figures 3 and 4, where the employed domain is $[0,1]\times[0,50]$. Moreover, the most important feature achieved by the computed numerical solution is their boundedness: indeed, By considering the homeostasis as phenomenon developing according to a Quorum Sensing mechanism and, afterwards, joining to it a spatial diffusion, it preserves a character of controlled expansion, thus the model and the numerical results look reasonably coherent with the biological dynamics.

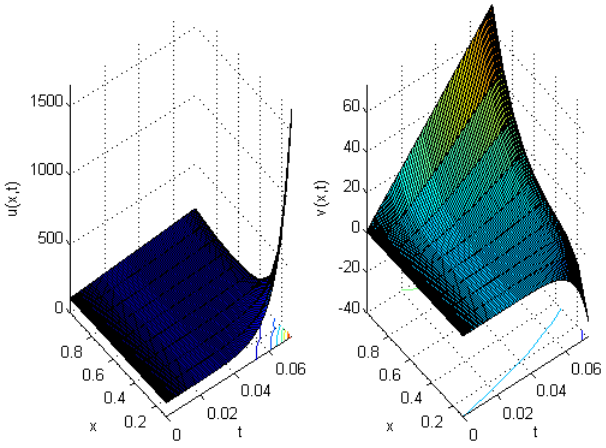

Fig. 1. Profiles of the solutions $n_1(t)$ and $n_2(t)$ in (2) with mixed boundary conditions

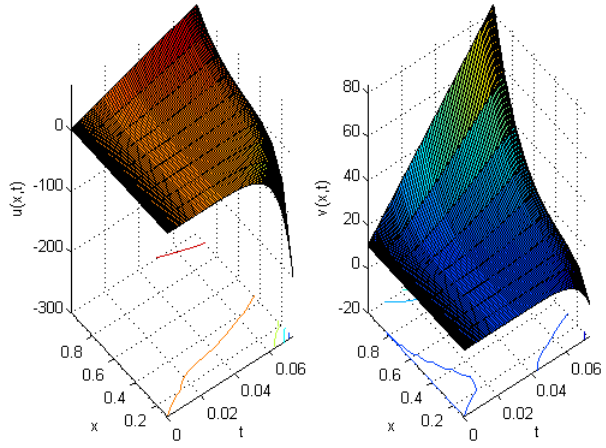

Fig. 2. Profiles of the solutions $n_3(t)$ and $n_4(t)$ in (2) with mixed boundary conditions

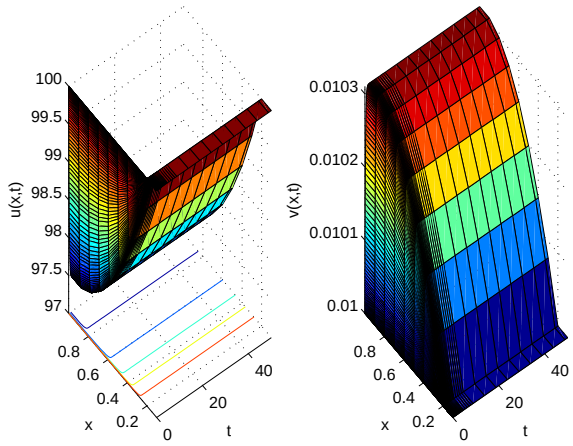

Fig. 3. Profiles of the solutions $n_1(t)$ and $n_2(t)$ in (2) with free-flow boundary conditions

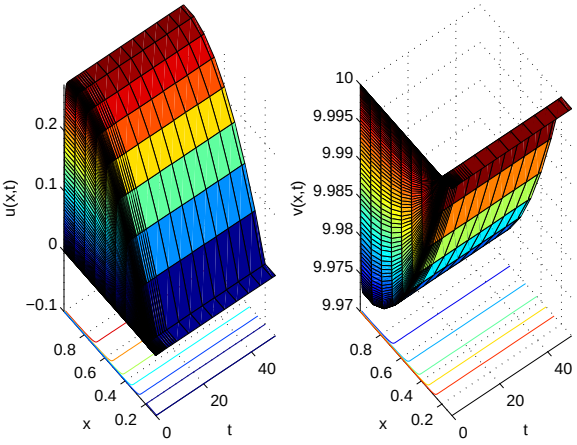

Fig. 4. Profiles of the solutions $n_3(t)$ and $n_4(t)$ in (2) with free-flow boundary conditions

IV. Conclusions

We have proposed a reaction-diffusion problem modeling T-cell dynamics. The specific feature of the developed model (2) is given by CD4+ T-cells homeostasis, extending the ideas in (1) by introducing evolution with respect to a further variable denoted by x in (2). Such a system of partial differential equations preserve the homeostasic behaviour, based on the quorum sensing hypothesis, thought as a diffusive phenomenon respect to the new variable x. The model has been solved by the method of lines, hence spatially discretized and then integrated in time by a built-in Matlab time integrator. Numerical evidence highlights the homeostatic behaviour of the analyzed populations of cells both in space and in time. Future approaches regard the possibility to provide alternative space-time discretization, such as those in [7], [9], [11], [12], [19], [20], [41], [42].

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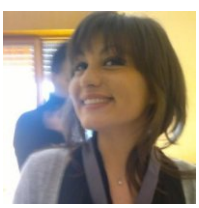

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APPENDIX

Mathematical modeling for T-cells have been carried out in many various ways and we now aim to provide a very brief state-of-the-art to present the main features of the involved operators. A survey of the existing literature concerning the mathematical modeling of the dynamics of T-cells exhibits the prevalent employ of ordinary differential equations, partial differential equations, delay differential equations, fractional differential equations and stochastic differential equations. More specifically, [31] briefly summarizes some advantages and disadvantages in the use of different mathematical models:

- ordinary differential equations are very common models in Immunology (we suggest the review paper [31] for specific references and many areas of application) and are able to model a high level of biological complexity in an elegant and efficient way, without heightening the computational cost. They are particularly suitable in the case of regulatory networks that do not take delayed feedbacks, spatial distribution of the cells or probabilistic events into account;
- models based on delay differential equations generally take into account incubation times [10], [23], [32], [35], [36], [51], [52];
- models based on fractional differential equations [3], [22], [50] are able to preserve some typical properties of the phenomenon: for instance, the positivity of the solution (which is, indeed, a density of populations);
- partial differential equations [2], [37] are particularly suitable to model a spatio-temporal dynamic, for cellular systems gradually changing their behavior in time, also in relation to their age, or remain localized over long times. From a computational point of view, these models are much more expensive than systems of ODEs and DDEs;
- stochastic differential equations [21] are the least explored model so far in the immunologic modeling. However, they can be considered effective in the description of populations regarded as collective groups rather than individual agents.

It is also important to highlight that many systems of interest in life sciences have been successfully modelled by oscillatory reaction-diffusion equations, especially for those problems typically exhibiting the generation of periodic waves along their dynamics. For instance, cell cycles are frequently clock-like [24], [34], behaving if they are driven by an autonomous biochemical oscillator.

These situations are also typically encountered in intracellular calcium signalling [45]: indeed, calcium shows many differrent types of oscillations in time and space, in response to various extracellular signals [5]. Among many existing mathematical models, that described in [45] is based on the release of calcium from intracellular stores through channels that are sensitive to the regulatory molecule IP_3: the main idea, first presented in [4], is that external stimuli produce increased concentrations of IP_3, causing the release of calcium from these internal stores. Under the mathematical point of view, in the model provided in [4], [45], the dynamics of this process

is governed by two partial differential equations

$$\begin{aligned} \frac{\partial c}{\partial t} &= D_c \frac{\partial^2 c}{\partial x^2} + k_{flux}\mu n \left(b + \frac{1-b}{k_1 + c} \right) - \frac{\gamma c}{k_\gamma + c}, \\ \tau_n \frac{\partial n}{\partial t} &= \frac{k_2^2}{k_2^2 + c^2} - n. \end{aligned} \tag{4}$$

in the unknowns $c(x,t)$ and $n(x,t)$, respectively denoting the local calcium concentration and the fraction of receptors that have not been inactivated by calcium. As it arises from [4], D_c denotes the cytosolic diffusion coefficient of calcium, k_{flux} is the maximum total calcium flux, b represents a basal current through sensitive channels, γ gives the rate of calcium pumping out of the cytosol, k_γ is the calcium concentration at which the rate of calcium pumping from the cytosol is at half-maximum, τ_n is the time constant for the dynamics of $n(x,t)$, k_2 is the rate of production of new receptors. Coherently with the biological evidence, the solutions derived in [45] under suitable initial and boundary conditions, exhibit an oscillatory dynamics both in space and in time.

As regards numerical modeling, it is important to ensure that the numerical scheme chosen to discretize the operator involved in the model takes into account the qualitative properties of the problem. For instance, in the case of oscillatory dynamics (as said, typical of biological oscillations), the periodic character of the problem suggests to propose a numerical solution which takes into account this qualitative behavior, i.e. by means of a *special purpose* numerical solver more tuned to follow the periodic behavior, in the spirit of the so-called *exponential fitting* technique (compare the recent review paper on the topic [41] and references therein and the classical monograph [30]; in the case of differential equations, we specifically refer to [11], [12], [14]–[18], [25]–[27], [29], [38], [42], [48], [49] and references therein).

The existing literature on EF-based methods has provided a certain number of adaptations of classical numerical methods to better numerically follow known qualitative behaviors (e.g. periodicity, oscillations, exponential decay of the solution). This problem-oriented approach differs from the classical one, given by the employ of *general purpose* methods, which would require a very small stepsize to accurately follow the prescribed dynamics, if compared to problem-based methods, with a subsequent deterioration of the numerical performances, especially in terms of efficiency. For this reason, many classical numerical methods have been adapted in order to more efficiently approach oscillatory problems.

A special purpose numerical method for the solution of functional equations is developed in order to exactly integrate (within round-off error) problems whose solution lies in a finite dimensional linear space (the so-called *fitting space*) spanned by a set of functions other than polynomials, properly chosen according to the behaviour of the solution. The main difference between general and special purpose numerical methods is that the former are characterized by constant coefficients, while the latter depend on variable coefficients, which are functions of the parameters characterizing the solution (e.g. the frequency of the oscillations in case of oscillatory problems or the rate of decay in case of problems with exponentially decaying solutions).

In this direction, two main problems arise

- (i) choosing a fitting space which is as much as possible suitable to represent the solution of the problem;
- (ii) accurately computing/estimating the parameters on which the numerical method depends.

In many cases of practical interest, both problems (i) and (ii) can be accurately approached by taking into account the existing theoretical studies on the problem. More issues on these aspects can are discussed in [41] and references therein, as well as in [12]–[14], [19].