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Multiphysics modelling of immune processes using distributed parameter systems

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Abstract — The immune system is a complex distributed system consisting of cells, which circulate through the body, communicate and turnover in response to antigenic perturbations. We discuss new approaches to modelling the functioning of the immune system of humans and experimental animals with a focus on its 'complexity'. Emerging mathematical and computer models are reviewed to describe the immune system diversity, the cell/cytokine network communication structures, hierarchical regulation, and evolutionary dynamics of immune repertoires.

Keywords: Immune system, complexity, diversity, homeostasis, antigenic forcing, repertoire dynamics, distributed parameter systems

MSC 2010: 92-10

1. Diversity as a key feature of the immune system

The immune system of humans and animals is a hierarchically organized, spatially structured, and pleiotropically regulated ensemble of recirculating cells and humoral factors that function to control the antigenic homeostasis of a host organism [36]. To unravel the mechanisms of clinically relevant immune-mediated processes, a broad spectrum of analytical tools are in use based on the latest advances in physics, chemistry, biology, and computer science. These include multi-color flow cytometry, high-dimensional immune-profiling, immunohistochemistry, multiplex assays, in vivo imaging, metabolome, proteomic and transcriptomic analysis, single-cell RNA sequencing, etc. However, until today, all these data types summarized in Fig. 1 have not been integrated into a holistic multi-physics description of the immune system functioning. Rather, only qualitative general immunology rules and schemes were established to characterize the behaviour of the immune system [27, 63, 67]. To go beyond, it would be necessary to apply information and mathematical technologies and combine that with fundamental and translational research [62].

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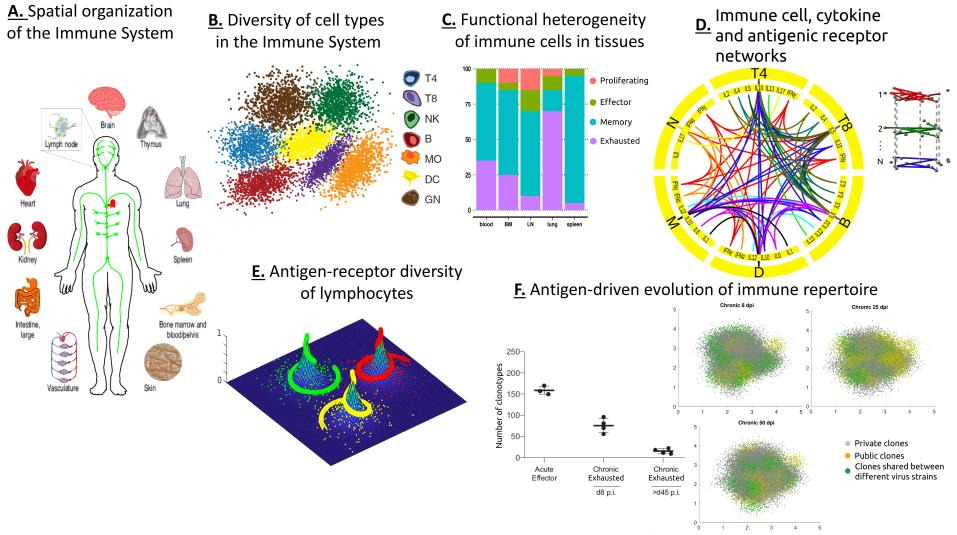

Figure 1. Diversity features of the immune system. A: Spatial distribution of the lymphatic system and the patrolled organs/tissues. B: Major immune cells populations (CD4 T cells, CD8 T cells, Natural killer cells, B cells, Monocytes, Dendritic cells, Granulocytes). C: Organ/tissue specific functional diversity of immune cells. D: Immune cell/cytokine interaction network (left), and T-cell receptor (TCR) or B-cell receptor (BCR) networks for different similarity index values (right). E: Fitness landscape (viral protein sequences) determining the evolution trajectories of immune clones. F: Dynamics of clonotypes (left) and public/private clones (right) during acure/chronic LCMV infection. Abstracted from [8, 37, 43, 51, 55, 58].

Lack of a complete mechanistic understanding of the pathogenesis and cause-effect relationships of many immune-related diseases, like COVID-19, hepatitis B, and AIDS, as well as the inability to predict the outcome of novel therapies (e.g. checkpoint inhibitors, chimeric antigen receptor (CAR) T cells, genome editing, bioengineering of lymphoid tissues), calls for the development of quantitative systems immunology approaches that combine various 'omics-' technologies with multi-physics type of mathematical modelling. The mainstream research in mathematical immunology is associated with the construction and study of mathematical models of low dimensions within a single level of detail of processes for the study of infectious diseases (influenza, viral hepatitis, HIV). Typical examples are provided by the recent work on the modelling of various aspects of infections with hepatitis B viruses [22], HIV [7], and SARS-CoV-2 [21, 33]. The respective mathematical models are characterized by a mono-scale approach both in the nature of the regulation principles (e.g., systems of the 'predator–prey' type), the clonal repertoire of adaptive immune receptors, and in the type of mathematical descriptions used to represent the system dynamics [29]. The models do not consider the system level of regulation of the immune processes and further developments based on hybrid multi-scale approaches [44] combining data-driven and mechanistic modelling [62] are necessary for proper holistic consideration [56] of numerous regulatory processes and motifs in the cells of the immune system and in cellular networks, which

determine the homeostasis of the immune repertoire and its change in response to various antigenic perturbations [49].

In the present study, we aim to review a novel class of mathematical models for a multiphysics description and analysis of functioning of the immune system under normal conditions and in the course of infectious diseases. To build mathematical models that meet the requirements of the current depth of research in immunology, the distributed parameters systems in physical, genotypic and phenotypic spaces (e.g., affinity/avidity of B-cell receptor (BCR) or T-cell receptor (TCR)), the network representation of interacting cellular ensembles, and structural modules of intracellular regulation are increasingly utilized. Fundamentally new elements of modelling and analysis seem to be (1) the use of methods of evolutionary dynamics on adaptive landscapes to describe the connectivity of immune cell populations and the immune system clonal repertoire under the influence of fluctuating antigenic forcing, (2) the consideration of fitness landscapes to assess the information-entropy characteristics of the immune system and predict the changes in its complexity and efficiency, and (3) the description of a hierarchical organization of regulatory processes.

2. Models of immune system as a set of clones with adaptive receptor repertoire

The immune system is composed of about 10^{13} cells differing in their spatial location $\mathbf{x}$ in the system and functional properties. The immune system controls the antigenic homeostasis of the host. This occurs via specific molecular-based recognition of antigens expressed by pathogens achieved through B-cell receptors and T-cell receptors. The adaptive immune repertoire is a characteristic of the individual's immune system. It is supposed that there are at about 10^8 different lymphocyte receptor specificities in an individual human at any time [48]. The lymphocytes are continually undergoing a process similar to natural selection. The immune repertoire is evolving within the immune receptor sequence space $\mathbf{r}$. The repertoire dynamics reflects the evolution of immune homeostasis, which is defined by multi-scale and multi-physics set of processes taking place over the time scale from days (acute responses) to years (chronic infections, autoimmune diseases) and engaging molecular (biochemical) and cellular (biological) levels of regulation [43].

The advent of high-throughput adaptive immune receptor repertoire (AIRR) sequencing about a decade ago provided the opportunity to analyze and model the high-dimensional immune receptor sequence landscape. The so far developed computational approaches provide the means for quantifying the specificity, complexity, and evolution of AIRR [43].

Various options exist for mapping the biochemical structure of antigens and lymphocyte receptors. One of them is the concept of a 'shape space' [60]. It is defined via a 'generalized shape' of an antigen $\mathbf{a}$ or lymphocyte receptor which is represented as a set of coordinates in a real-valued d-dimensional Euclidian space. The second option is representation of the antigenic- or antigen binding receptor

structures as a sequence of amino acids of certain length using specific symbols, thus following a Hamming shape space framework. For example, BCRs and antigens were represented by strings of 20 symbols in the computational model developed for studying the dynamics of B-cell receptor repertoire [59]. Various approaches are used to reduce the dimensionality of the space representing the antigen and receptors. One of them is known as antigenic cartography [61]. It is based on linking the antigenic distance to the immunoglobulin-type receptor in the shape space to the logarithm of the hemagglutination inhibition (HI) assay. The HI binding assay quantifies the ability of viruses (influenza in the cited work) to agglutinate red blood cells and the ability of antibodies to block this.

2.1. Models of immune system as a set of distinct clones

One of the first models of immune repertoire dynamics was proposed in [1]. The repertoire of lymphocytes is described by a final set of n clones with abundances $c_i,\ i = 1,\dots,n$. The total population of lymphocytes is $C(t) = \sum_{i=1}^{n} c_i$. The population dynamics of the clones and the total immune cell population are described by the following equations

$$\frac{\mathrm{d}c_i}{\mathrm{d}t}(t) = c_i^*(t) + ma_i^*(t) + c_i(t)\left[S(C) + f - d\right], \quad i = 1,\dots,n \tag{2.1}$$

and

$$\frac{\mathrm{d}C}{\mathrm{d}t}(t) = c^* n + amn + C(t)\left[S(C) + f - d\right] \tag{2.2}$$

respectively. The equations consider the following processes:

- Random input of lymphocytes with receptors produced by V(D)J recombination followed by further positive/negative selection at rate $c_i^*(t)$ with exponentially distributed waiting times between inputs;
- Antigen-driven stimulation modelled by a so called fluctuating antigenic landscape [15] (e.g., the stimulation of clone i occurs by a randomly introduced specific antigen $a_i^*(t)$ with exponentially distributed waiting times between stimulations) or deterministically with a constant antigen abundance $a = E[a_i(t)]$;
- Cross-reactive stimulation as averaged constant forcing f;
- Homeostatic proliferation $S(C)$;
- Natural death of cell d.

The model was used to study the parameters affecting the longevity of immune memory and the repertoire dynamics.

2.2. Stochastic and continuum-type models for immune repertoire dynamics

Further development of the above class of quasi-deterministic models was based on considering (i) stochastic processes to represent the fluctuating antigenic landscape and (ii) a continuum-type description of the abundance of lymphocyte clones. A representative example is the Stochastic Differential Equations (SDE)-type model describing the clone dynamics in a fluctuation antigenic landscape [15]. The system of equations described the dynamics of cell clones $C_i(t)$ comprising the immune system

$$\frac{\mathrm{d}C_i}{\mathrm{d}t}(t) = \left(\nu + \sum_j K_{ij} a_j(t) - \mu\right) C_i(t) + B\xi_i(t), \quad i,j = 1,\ldots,n. \tag{2.3}$$

Here the antigenic forcing is a time-dependent exponentially decaying function $a_j(t) = a_{j,0}\mathrm{e}^{-\lambda(t-t_j)}$, which describes its introduction at random times t_k. The matrix K_{ij} specifies the cross-reactivity function, $\xi_i(t)$ is a unit Gaussian white noise. The model was used to understand the emergence of a power-law in lymphocyte clone size distribution. To this end, model (2.3) was reformulated as a system of SDEs for the dynamics of individual clones $C_i(t)$ and the SDEs (Ornstein–Uhlenbeck processes) for the fluctuations of the net growth rate of the ith clone $f_i(t)$ due to stochastic dynamics of the clone-specific antigens as follows:

$$\frac{\mathrm{d}C_i}{\mathrm{d}t}(t) = (f_0 + f_i(t))\, C_i(t) + B\xi_i(t), \quad i = 1,\ldots,n \tag{2.4}$$

and

$$\frac{\mathrm{d}f_i}{\mathrm{d}t}(t) = -\lambda f_i(t) + \sqrt{2}\gamma\nu_i(t), \quad i = 1,\ldots,n \tag{2.5}$$

where γ represents the amplitude of variability in the antigenic forcing. The collective population dynamics of the clones can be characterized in terms of the distribution function for the clone sizes $\rho(x,f,t)$, where $x = \log(C)$. The respective Fokker–Planck equation for the distribution ρ of a clone abundance x and the average antigen-induced growth rate (referred to as fitness) f is

$$\frac{\partial\rho}{\partial t}(x,f,t) = -(f_0+f)\frac{\partial\rho}{\partial x}(x,f,t) + \lambda\frac{\partial\rho}{\partial f}(x,f,t) + \gamma^2\frac{\partial^2\rho}{\partial f^2}(x,f,t) + s(x,f). \tag{2.6}$$

Here, the last term describes the export of new clone from the primary lymphoid organs with fitness f normally distributed. Under certain simplifying assumptions, the steady-state solution gives a power law clone size distribution $\rho(C) \sim C^{-\alpha}$.

The above considered models and their modifications do not take into account the antigen-regulated processes of functional exhaustion and activation-induced cell death by apoptosis, which are considered to play a key role for the long-term persistence of lymphocytes clones [42, 52], and hence, the dynamics of immune repertoire. The parameterization of antigen-induced exhaustion of lymphocytes can be represented by a bell-shaped function increasing for small antigen loads and decreasing for high loads (see an example in [4]).

3. Generic model for immune system dynamics under antigenic forcing

3.1. Processes algebra

The construction of mathematical models of the human immune system, adequate in terms of the description detail to the level of understanding of its structure and functional components achieved at the present time, due to the intensive development and application of methods of multiplex analysis, visualization, 'omics' and bioinformation technologies of research, as well as the evolution of adaptive immune receptor repertoire, remains to be a great challenge [14, 31, 46]. At the same time, it is necessary to develop a computational technology for constructing meaningful mathematical models that allow one to quantitatively describe as a single hierarchical system a set of multiscale, multilevel multiphysics processes taking into account a large number of regulatory relationships that determine the functioning of the immune system [12, 53].

One of the computational approaches to formulate complex models of the immune systems can be developed following the *process algebra* framework. The algebra of processes was originally viewed as an approach of how to compose complex processes of simpler components [3], i.e., to bridge different scales. Nowadays, many process algebra techniques have been developed to establish a theory of all parallel and distributed systems in computer science [2].

The state of individual lymphocytes is regulated by a spectrum of signals coming through the binding of respective receptors. Understanding of how the signals add together is considered to be crucial for predicting the immune cell behaviour response to antigen and cytokine perturbations. To this end, a framework for signal integration within a cell called *cellular calculus* was proposed [19]. The framework provided a computational modeling method to identify qualitative rules of lymphocyte fate decision ranging from cell expansion to loss [30, 32, 40]. The availability of the rules of how individual immune cells behave and interact provide an opportunity to derive the cell populations level model directly from the individual level description [41]. The authors used the processes algebra Weighted Synchronous Calculus of Communicating Systems (WSCCS) to develop a predator-prey model of immune response allowing to derive the functional form immune cell activation for clonal expansion by pathogen. The same tool was used in a recent study on modelling immune cell–tumour cell interactions [64]. However, the available works on using process algebra tools for modelling in immunology since the pioneer study of [45] still remain at the level of *proof of concept* and further research is needed.

The generic mathematical model linking the population dynamics of antigens and immune cells to the level of system description needs to consider the following set of processes:

- Homeostasis of lymphocyte clones resulting from generation in primary lymphoid organs (LO), migration to peripheral LOs and natural death;
- Antigen-induced clonal expansion taking into account cross-reactivity;
- Antigen-induced induction of anergy (functional exhaustion) and apoptosis;

Table 1. Definition of model parameters.

Parameter meaning	Notation
Spatial coordinate	$\mathbf{x} \in \Omega_X$
Antigenic space coordinate	$\mathbf{a} \in \Omega_A$
Lymphocyte receptor space coordinate	$\mathbf{r} \in \Omega_R$
Pathogen density in time, physical- and antigenic space	$V(t,\mathbf{x},\mathbf{a})$
Lymphocyte density in time, physical- and immune receptor sequence space	$C(t,\mathbf{x},\mathbf{r})$
Influx of antigen-specific lymphocytes following V(D)J-genes rearrangement	$S(t,\mathbf{x},\mathbf{r})$
Diffusion coefficient of virions in physical space	D_{xV}
Diffusion coefficient of virions in antigenic space (mutations)	D_{aV}
Diffusion coefficient of immune cells in physical space	D_{xC}
Diffusion coefficient of immune cells in antigenic receptor sequence space	D_{rC}
Chemotactic coefficient for immune cell migration	χ_C
Exponential growth rate constant of virions	$b_V(\mathbf{a})$
Carrying capacity of the tissue for virisons	K_V
Natural degradation of virions	d_V
Immune-mediated elimination of virions	d_{IC}
Kernel representing the binding strength (affinity or avidity)	$I(\mathbf{a}-\mathbf{r})$
between antigen $\mathbf{a}$ and receptor $\mathbf{r}$, e.g.,	$e^{(-\rho(\mathbf{a}-\mathbf{r})/\rho_0)^q}$ [9]
Noise intensity in viral dynamics	σ_V
Gaussian space-time white noise (a standard Wiener process)	$\xi_V(W_{V(t),t\geqslant 0})$
Immune cell division rate	$b_C(\mathbf{r})$
Carrying capacity of lymphoid tissues	K_C
Natural death rate of immune cells	d_C
Bell-shaped activation/exhaustion function of immune cells	$\varphi(V(t,\mathbf{x},\mathbf{a}),C(t,\mathbf{x}.\mathbf{r}))$
Activation-induced immune cell death process	$\psi(V(t,\mathbf{x},\mathbf{a}))$
Apoptosis death rate constant	d_{AC}
Kernel representing avidity-dependent induction of apoptosis	$A(\mathbf{a}-\mathbf{r})$
Noise intensity in immune cell dynamics	σ_C
Gaussian space-time white noise (a standard Wiener process)	$\xi_C\ (W_{C(t),t\geqslant 0})$
Kernel characterizing chemokine gradient	$h(\mathbf{a})$

- Spatial migration (diffusion, transport, and active motility via chemo- or haptotaxis);
- Diffusion in antigen receptor space (e.g., B-cell receptor variation via somatic hypermutation);
- Evolution in antigenic- and lymphocyte receptor spaces;
- Random fluctuations in antigenic load (e.g., *white noise* in time-space);
- Infection spreading and immune-mediated elimination.

The mathematical structure of such an immune system level model is presented below. Note that it can be expanded, reduced, or tuned in various ways depending on the specific immune-dependent phenomenon or feature under consideration.

3.2. Governing equations

The specific notation of the variables and parameters is listed in Table 1. The governing equations are the following:

$$\begin{aligned}
\frac{\partial}{\partial t}V(t,\mathbf{x},\mathbf{a}) = &\underbrace{\nabla\cdot(D_{xV}\nabla V(t,\mathbf{x},\mathbf{a}))}_{\text{spatial diffusion}} + \underbrace{\nabla\cdot(D_{aV}\nabla V(t,\mathbf{x},\mathbf{a}))}_{\text{diffuion in antigenic space}} \\
&+\underbrace{b_V(\mathbf{a})V(t,\mathbf{x},\mathbf{a})\,(K_V - J(V))}_{\text{infection growth}} - \underbrace{d_V V(t,\mathbf{x},\mathbf{a})}_{\text{natural death}} \\
&\underbrace{-d_{IC}V(t,\mathbf{x},\mathbf{a})\int_{\Omega_R} I(\mathbf{a}-\mathbf{r})C(t,\mathbf{x},\mathbf{r})\,\mathrm{d}\mathbf{r}}_{\text{immune-mediated elimination}} + \underbrace{\sigma_V\xi_V(t,\mathbf{x},\mathbf{a})}_{\text{random forcing}} \qquad (3.1)\\
&\text{in } \Omega_X\times\Omega_A\times\Omega_R \quad \text{for } t>0; \quad J(V)\equiv\int_{\Omega_X\times\Omega_A} V(t,\mathbf{x},\mathbf{a})\,\mathrm{d}\mathbf{x}\,\mathrm{d}\mathbf{a} \\
V(t,\mathbf{x},\mathbf{a}) &= V_{\partial\Omega}(t,\mathbf{x},\mathbf{a}) \quad \text{on } \partial\Omega_X\times\partial\Omega_A, \quad \text{for } t>0; \\
V(0,\mathbf{x},\mathbf{a}) &= V_0(\mathbf{x},\mathbf{a}) \quad \text{in } \Omega_X\times\Omega_A
\end{aligned}$$

$$\begin{aligned}
\frac{\partial}{\partial t}C(t,\mathbf{x},\mathbf{r}) = &\underbrace{S(t,\mathbf{x},\mathbf{r})}_{\text{primary LO source}} + \underbrace{\nabla\cdot(D_{xC}\nabla C(t,\mathbf{x},\mathbf{r}))}_{\text{spatial diffusion}} + \underbrace{\nabla\cdot(D_{rC}\nabla C(t,\mathbf{x},\mathbf{r}))}_{\text{diffusion in receptor space}} \\
&+\underbrace{b_C(\mathbf{r})\varphi(V(t,\mathbf{x},\mathbf{a}))C(t,\mathbf{x},\mathbf{r})\,(K_C - J(C))}_{\text{bell-shaped clonal growth}} - \underbrace{d_C C(t,\mathbf{x},\mathbf{r})}_{\text{natural death}} \\
&\underbrace{-d_{AC}C(t,\mathbf{x},\mathbf{r})\int_{\Omega_A}\psi(V(t,\mathbf{x},\mathbf{a}))A(\mathbf{a}-\mathbf{r})\,\mathrm{d}\mathbf{a}}_{\text{activation-induced apoptosis}} + \underbrace{\sigma_C\xi_C(t,\mathbf{x},\mathbf{r})}_{\text{random forcing}} \qquad (3.2)\\
&\underbrace{-\nabla\cdot\left(\chi_C C(t,\mathbf{x},\mathbf{r})\nabla\int_{\Omega_A} h(\mathbf{a})\mathbf{V}(\mathbf{t},\mathbf{x},\mathbf{a})\,\mathrm{d}\mathbf{a}\right)}_{\text{chemotaxis}} \\
&\text{in } \Omega_X\times\Omega_A\times\Omega_R \quad \text{for } t>0; \quad J(C)\equiv\int_{\Omega_X\times\Omega_R} C(t,\mathbf{x},\mathbf{r})\,\mathrm{d}\mathbf{x}\,\mathrm{d}\mathbf{r} \\
C(t,\mathbf{x},\mathbf{r}) &= C_{\partial\Omega}(t,\mathbf{x},\mathbf{r}) \quad \text{on } \partial\Omega_X\times\partial\Omega_R, \quad \text{for } t>0; \\
C(0,\mathbf{x},\mathbf{r}) &= C_0(\mathbf{x},\mathbf{r}) \quad \text{in } \Omega_X\times\Omega_R.
\end{aligned}$$

Another type of boundary conditions can be prescribed (e.g., Robin or Neumann type). The above stochastic PDEs are formulated to represent the physical (immunobiological) sense of the driving processes. The mathematical setting for the respective function spaces and probabilistic interpretations of the equations, as well as the specific functional forms, which can be used to parameterize the processes, are outside the focus of this study. The following two partial examples of the generic model shed some light on its direct relation to real-life models.

3.3. Example 1: acute LCMV infection with spatial diffusion

As a first example of the implementation of the above general model, we formulate a spatially extended model of LCMV infection based on the calibrated description developed for a 0D case in [5]. The model describes the population dynamics of viruses and immune cells (CD8+ T lymphocytes) determined by the interaction between virus replication, immune activation, anergy, and apoptosis in a spatial 1D setting, $x \in [0, L]$. The system of reaction–diffusion type model reads:

$$\begin{aligned}
\frac{\partial V}{\partial t}(t,x) &= b_V V(t,x)\left(1 - \frac{V(t,x)}{V_{mvc}}\right) - \gamma C(t,x)V(t,x) + D_{xV}\frac{\partial^2}{\partial x^2}V(t,x) \\
\frac{\partial C}{\partial t}(t,x) &= S_C^* + b_C \frac{V(t,\mathbf{x})C(t,\mathbf{x})}{(1+\int_0^t \sigma V(s,x)\mathrm{e}^{-\mu_m(t-s)}\,\mathrm{d}s)^2} \\
&\quad - d_C C(t,x) - d_{AC}V(t-\tau_A,x)V(t,x)C(t,x) + D_{xC}\frac{\partial^2}{\partial x^2}C(t,x) \\
\frac{\partial V}{\partial x}(t,0) &= \frac{\partial V}{\partial x}(t,L) = 0, \quad \frac{\partial C}{\partial x}(t,0) = \frac{\partial C}{\partial x}(t,L) = 0 \\
V(0,x) &= V_0(x), \quad C(0,x) = C_0.
\end{aligned} \tag{3.3}$$

The spatio-temporal dynamics of viral load and CTL abundance is shown in Fig. 2. The infection starts at the center of the spatial domain and spreads as two waves in opposite directions until the clonal expansion of CTLs reaches a threshold required for an overall elimination of the virus population. The solution corresponds to an acute infection. Note that a reduction in diffusion constants of viruses and lymphocytes results in a chronic infection (data not shown).

3.4. Example 2: chronic HBV infection under random fluctuations in CTL immunity

To study the phenomenon of spontaneous recovery from the chronic hepatitis B virus (HBV) infections, we have previously developed a SDE type model to examine the random forcing effect on HBV kinetics [38]. Here we consider an extended version of the model in which the random fluctuations both in the immune response and viral load are considered. The model represents a simplified case of the above general model for a single CTL clone with no spatial considerations and a bounded rate activation function for lymphocytes.

$$\mathrm{d}V(t) = b_V V(t)\,(K_V - V(t))\,\mathrm{d}t - d_{IC}V(t)C(t)\,\mathrm{d}t + \sigma_V\,\mathrm{d}W_V(t), \quad t \geqslant 0 \tag{3.4}$$

$$\mathrm{d}C(t) = S_C^*\,\mathrm{d}t + b_C\frac{V(t)}{\theta + V(t)}C(t)\,\mathrm{d}t - d_C C(t)\,\mathrm{d}t + \sigma_C\,\mathrm{d}W_C(t), \quad t \geqslant 0. \tag{3.5}$$

An ensemble of ten single runs of the model is presented in Fig. 3. The set of parameters corresponds to acute HBV infection. One can see that after clearance of infection, the HBV-specific clones continue to fluctuate around the homeostatic

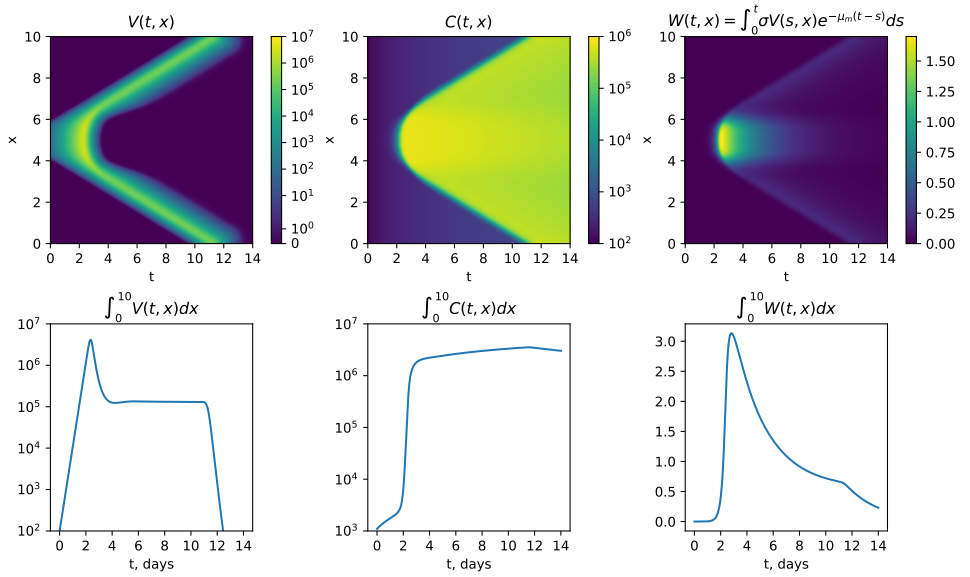

Figure 2. Numerical solution of the reaction–diffusion model of LCMV infection in 1D, $x \in [0, L]$, $L = 10$. The viral load V, CTL density C and cumulative viral load factor W are shown. The initial conditions are $V_0(x) = V^* \exp(-(1-(x-5)^2)^{-1})$ for $x \in (4,6)$ and $V_0(x) = 0$ otherwise, $\int_0^L V_0(x)\,\mathrm{d}x = 100$; $C_0 = 110$. The parameters are $D_{xV} = 0.01$; $D_{xC} = 0.024$; $b_C = 2 \times 10^{-5}$ and $\sigma = 1.7 \times 10^{-6}$ and the other parameters are adapted from [5]. The model was numerically solved in a weak sense using variational formulation with the second-order finite element spatial discretization on a uniform grid and the Crank–Nicolson scheme in time using the DUNE-FEM Python package.

level due to random forcing generated by a combination of multi-physics impacts including bystander stimulation, low-level antigen persistence, etc. The level of HBV-specific CTL cells at the eclipse phase of infection results in a variability of duration of acute infection.

For a set of parameters corresponding to chronic HBV infection, the random forcing acting on viral and CTL populations can result in a spectrum of behaviours including a spontaneous recovery as shown in Fig. 4. The HBV-specific CTL clone can either completely disappear or persist at a low level similar to the post acute HBV infection described above. The model can be extended by expanding the virus population from a wild type to a quasi-species consideration as well as by detailing the composition of the immune response and multi-clonal dynamics should the empirical data for calibration be available.

4. Functional performance vs fitness

The functional performance of an immune system is related to its ability to effectively control the antigenic homeostasis of the host organism. Various characteristics are used to quantify it, including the completeness of antigen-specific lymphocyte receptor repertoire [10, 13, 35], the responsiveness of immune cells [26, 66], the diversity of immune cell types [18, 36], etc.

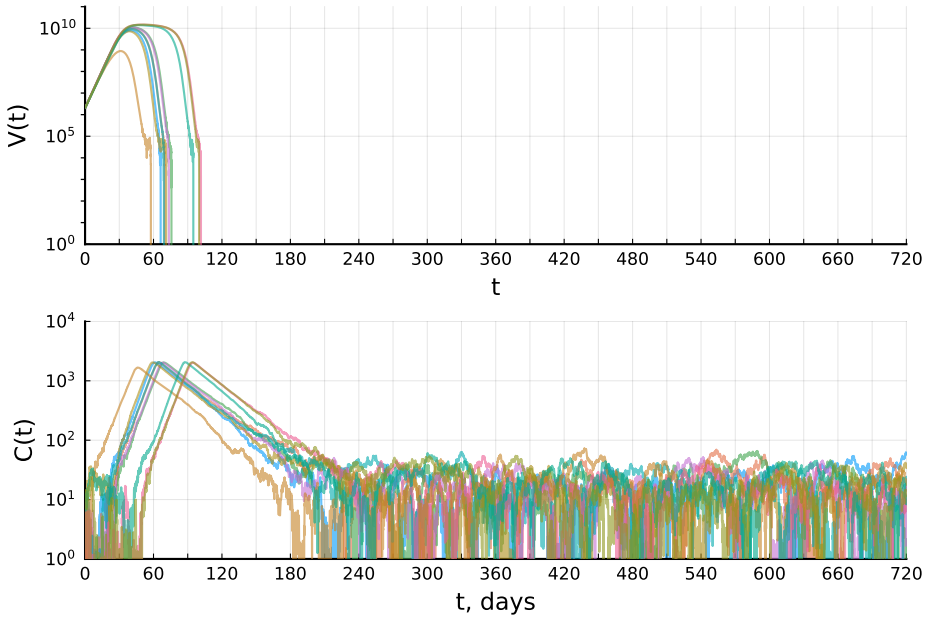

Figure 3. Numerical solutions of the SDE model of acute hepatitis B virus infection dynamics with parameters $\sigma_V = 3 \times 10^4$, $\sigma_C = 5$, and the other parameters adapted from [38]. The initial conditions are $V(0) = 2 \times 10^6$, $C(0) = 7$. The model was numerically solved using the stability-optimized adaptive strong order 1.5 stochastic Runge–Kutta method implemented in DifferentialEquations.jl Julia package.

The immune TCR/BCR repertoires of an individual are considered to consist of two parts, the public ones (core groups of highly related receptor sequences present in many individuals) and private repertoire (unique receptors observed in a few individuals) [11]. The receptor repertoires are dynamically determined by a combination of the following processes: V(D)J gene rearrangement (a random process, which can generate from 10^{15} to 10^{61} clonotypes, i.e., unique V(D)J nucleotide sequences), selection in primary lymphoid organs, homeostatic proliferation, and antigen-driven expansion [11, 43]. For dynamically changing AIRR, a quantitative descriptive framework is considered to be the evolution of AIRR on fluctuating antigenic landscape. The evolution is inherently linked to the notions of *fitness*, *clonotype*, and *selection*. At the molecular level, the fitness of a receptor can be determined by TCR/BCR affinity. However, already at the single cell level, the fitness for survival and clonal expansion is determined by multiple factors such as avidity, co-receptors expression and co-stimulatory receptor signalling [11]. At the immune system level, the link between its fitness (functional capacity) and TCR/BCR diversity is considered to be obscure as autoimmune disorders and infection-triggered T-cell-mediated tissue damage can be caused by the presence of public and private antigenic repertoires. Another quantitative way to represent the global performance of the immune system, e.g., the immune repertoire structure, could be the *Shannon entropy* or other diversity indices. It allows one to characterize the diversity of

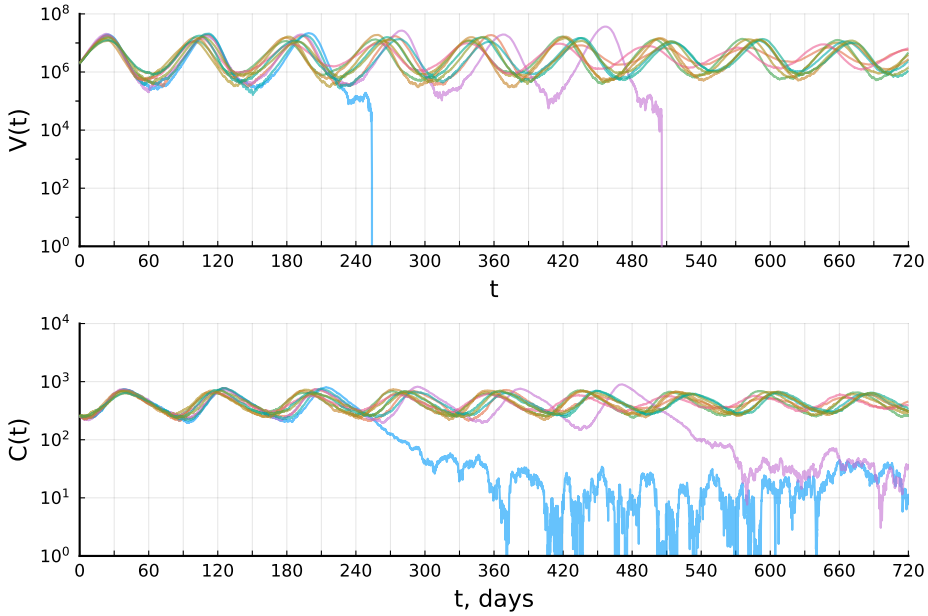

Figure 4. Numerical solutions of the SDE model of chronic hepatitis B virus infection dynamics with parameters $\sigma_V = 3 \times 10^4$, $\sigma_C = 5$, and the other parameters adapted from [38]. The initial conditions are $V(0) = 2 \times 10^6$, $C(0) = 256$. The model was numerically solved using the stability-optimized adaptive strong order 1.5 stochastic Runge–Kutta method implemented in DifferentialEquations.jl Julia package.

TCR/BCR receptors in sequence space and was implemented in [37, 47] under the maximum entropy inference approach [20].

Mathematical models developed for the analysis of the dynamics of adaptive immune repertoires [15, 16] define the clone fitness as an effective growth rate (quantified as a difference between lymphocyte division and death rate constants). The fluctuating antigenic environment is taken into account in the dynamics of clones as described by equations (2.4)–(2.5). The effect of inter-clonal competition is described via a parameter entering the cumulative antigenic stimuli function, which in turn defines the antigen-specific intensity of clone stimulation. In addition, the intra-clonal competition was considered in the form of carrying capacity. The models were used to understand the factors responsible for the heavy-tailed clone size distributions, e.g., to show that antigenic fluctuations affecting the lymphocytes fitness are responsible for the heavy tail clone size distributions [15]. Later on, the need to take into account the impact of self-antigens was highlighted [16]. To this end, a conceptual view of the role of subthreshold interactions in the immune system developed by Grossman and Paul [24, 25, 26] can be applied.

Further development of the models for evolutionary dynamics of immune cell repertoires was related to explicit modelling of the viral dynamics [9, 39]. The viral strain is described in a d-dimensional antigenic space via a discrete random walk model $a_{t+1} = a_t + \sigma_V \nu_{t+1}$, where ν_t is a normally distributed d-dimensional vari-

able [9]. The change in the number of lymphocytes of clonotype $n_{x,t}$ follows a binomial distribution with an exponential-type cross-reactivity kernel (see Table 1) and their receptors drawn randomly according to normally distributed process $\xi(\bullet)$: $x_j = a_t + \sigma\xi_j$. By introducing a function that takes into account the cumulative cost of protection against infection, the parameters for an optimal balance between long-term immune coverage and metabolic requirements for affinity maturation were examined.

An implicit description of the viral evolution in population of infected hosts was modelled in [39] using SDE-type of equation:

$$\frac{\partial n}{\partial t}(t,\mathbf{x}) = f(t,\mathbf{x})n(t,\mathbf{x}) + D\frac{\partial^2}{\partial \mathbf{x}^2}n(t,\mathbf{x}) + \sqrt{n(t,\mathbf{x})}\xi(t,\mathbf{x}). \tag{4.1}$$

Here, the virus strain effective growth rate is put identical to its fitness $f(t,\mathbf{x})$, which is in turn parameterized via the basic reproduction number and the coverage of strain $\mathbf{x}$ by immune memories of the population (see [39] for further details). The model was used to examine the shape and speed of the viral evolution wave in a finite-dimensional antigenic space in relation to mounted immune response memories.

The stochastic evolutionary modelling for studying the lymphocyte clonal dynamics has been recently used to analyze the longitudinal repertoire sequencing data from healthy individuals in the absence of strong antigenic perturbations [34]. The calibration of the inherent experimental noise was key to the overall inference procedure. The research question was the estimation of parameters of T cell clonotype persistence, characterizing a typical lifetime of individual clones and amplitude of fluctuations of clonal sizes. Following a maximum likelihood approach, the authors estimated the typical clonal decay rates (lifetimes ranging from a few years up to 50 years) and fluctuation amplitude (up to several orders of magnitude) from adult healthy donors' data and showed that geometric Brownian motion consistently describes the clonal dynamics and predicts a steady state, which agrees with the observed power-law distribution of the clone sizes.

5. Network-type organization

The complex, high-dimensional nature of the immune system with many organs, cell populations and humoral factors requires a fine-tuned communication and coordination of their activity. A system-wide view of the immune processes requires the application of network analyses to describe and assess its performance. Indeed, the network-type mathematical methods provide powerful analytical tools for characterizing interactions among cells, molecules, and genes. However, the respective studies are still rare. One of the first application of system-wide network-type analysis of the communication structures and connections between immune cells was presented in [51]. The authors identified network structures, which integrate the cellular- and molecular (receptor and ligand gene) levels of communications using the sender-receiver view for cell-type and context-dependent communication structures.

Network analysis of the immune state of mice was developed in [17]. The authors used previously published data set of the immune state of hundreds of wild and laboratory mice characterizing serum proteins, cytokines, and cellular populations and sub-populations, totalling 120 immune measures. By constructing correlation networks from the data, the community structure of the immune networks was analyzed, resulting in a number of revealed immunological functional units.

A mechanistic wiring diagram for the human immune system was constructed in [57]. Using a high-throughput surface receptor screening tools, the authors systematically mapped the direct immune cell surface protein interactions and produced a network-type description of receptor wiring that connects the cells in the human immune system [57]. A comprehensive set of cell-surface proteins (more than 600 different protein or protein complexes) was analyzed. The study provides fundamental details on how the linking of cells through physical and biochemical interactions organizes the immune system into dynamically interconnected cellular communities. Using the Law of Mass Action, the authors developed a proof-of concept mathematical model of the contacts made between human immune cells that combines the cell proteins interaction network with a data set of absolute proteomics quantification of the cell-surface proteins expressed on different immune cell types, thus exhaustively modeling all the binding events between cell populations. Importantly, an interactive atlas of immune cell connections across the human body was developed [57].

The network analysis is considered to be a powerful approach to examine the similarity of architecture of T-cell and B-cell repertoires. Whereas immune repertoire diversity characterizes the frequency distribution of immune clones, the sequence similarity provides an insight into frequency-independent clonal immune receptors' similarity that directly influences the antigen recognition breadth [43]. The network-type analysis was used to identify the architecture of the antibody sequence space [23]. For construction of networks, a sparse triangle matrix of pairwise Levenshtein distances (LD) between complementarity determining region 3 (CD3) nodes was used. The networks represent antibody repertoires of similar CDR3 nodes connected by edges when amino acid CDR3 sequences differ by a predetermined LD. The subset of repertoire clones connected at a given LD was considered as a similarity layer (see Fig. 1D, right). Various topological characteristics of networks were quantified including the degree distribution, diameter, density, clustering, assortativity. It was discovered that the architecture of antibody repertoire networks is robust with respect to removal of 50–90% of private clones but fragile to removal of public clones.

6. Conclusions

The immune system is a complex distributed parameter system consisting of cells, which circulate through the body, communicate and turnover in response to antigenic perturbations [57]. It has been stated in [17] that despite the complexity of the immune system, it is often analyzed following a low-dimensional approach

with a restricted set of immunological parameters. In this study, we tried to identify new approaches to modelling the functioning of the immune system of humans and experimental animals and methods for analyzing its 'complexity'. New classes of mathematical and computer models are presented, which are used to describe the network- and repertoire structures, hierarchical regulation, and evolutionary dynamics of immune responses under normal conditions and in infectious diseases.

These approaches capture various aspects of the immune system complexity. However, a methodology for their computational integration into a holistic framework is missing. Distinctive features of the emerging mathematical description of the immune system can be delineated as follows: (a) integrative multi-physics consideration of immune reactions (including physical, molecular-biological and cellular-population processes), (b) consideration of a wide range of reactions of innate and adaptive immunity to changes in antigenic homeostasis, taking into account the heterogeneity of cellular ensembles and variability of the immune repertoire reflecting past and current antigenic forcing using methods of evolutionary dynamics and the notions of fitness and adaptive fitness landscape, (c) identification of the topological structure of cellular and molecular regulation networks in healthy individuals and infectious diseases, (d) use of distributed parameters systems in the space of genotypic, phenotypic and physical traits, (e) development of parametric computational models of immune and lymphatic systems, and (e) identification of the regulation laws of immune processes as elements of a hierarchical distributed decentralized system of automatic control. To be properly implemented, a special attention needs to be given to topics ranging from conceptual issues of modelling the evolution of mutating populations characterized by fitness diversity [6, 54] to computational methods for hybrid stochastic-deterministic models [50], and the novel tools for dimensionality reduction, e.g., tensor train-based decomposition [65], of the immune systems state space (antigenic-, lymphocyte receptor space). Overall, mathematical models are expected to provide analytical tools for assimilation and analyses of big-data on structure and function of the immune system characterized by various diversities. They should take an instructive role in driving the field towards a predictive understanding of an individual's immune system response to various perturbations ranging from environmental factors to vaccination and combination immune therapies [28, 49].

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