doi 10.18699/bgrs2024-12.2-07

Frontier modelling challenges in mathematical immunology

Bocharov G.[1, 2]

[1] *Marchuk Institute of Numerical Mathematics, RAS, Moscow, Russia*

[2] *Institute of Computer Science and Mathematical Modelling, Sechenov University, Moscow, Russia*

g.bocharov@inm.ras.ru

Key words: mathematical modelling; immune system; cellular ensembles; regulatory networks; intracellular regulation; evolutionary dynamics; information complexity; infectious

Motivation and Aim: In description, analysis and prediction of infectious diseases that depend on the reactions of the immune system a range of challenges exist. These include the curse of dimensionality of the immune system state (clonal repertoire) space, the multiplicity of dynamics trajectories of pathological processes, the nonlinearity of regulation loops, and the heterogeneity and variability of innate- and adaptive immunity [1]. To overcome these challenges, the deployment of novel mathematical models and computational approaches is needed. These analytical tools should enable a multi-physics description of the immune system dynamics in the high-dimensional space of physical and phenotypic traits, allow a cause-and-effect type of analysis of infectious disease pathogenesis and a robust quantitative predictions of the host immune system reaction to combination therapies.

Methods and Algorithms: To build mathematical models that meet the requirements of the current level of research in immunology, the distributed parameters systems in the space of phenotypic traits (e.g., affinity/avidity of receptors) and physical characteristics, the network models of interaction of cellular ensembles, structural modules of intracellular regulation are developed [1]. New elements of the presented multi-physics modelling approach and the developed analysis tools are as follows: (1) the use of methods of evolutionary dynamics on adaptive landscapes to describe the connectivity of populations of immune cells and the clonal repertoire under the influence of random antigenic forcing, (2) the formation of fitness landscapes to assess the information-entropy characteristics of the system and predict changes in its complexity and system efficiency, (3) the description of a hierarchical organization of regulatory processes, and (4) the application of meta-analysis algorithms for calibration of the processes described in models. The numerical implementation of the models requires elaboration of problem-oriented methods and algorithms. In particular, a geometric model of the murine lymphatic system has been developed and characterized in terms of its structural organization (graph topological properties) and the lymph transfer function [2].

Results: A mathematical model of lymphocytic choriomeningitis virus (LCMV) replication in infected cells has been developed and calibrated [3]. The murine LCMV infection is a fundamental model system in experimental immunology. By studying the sensitivity of the mathematical model, potential targets for the development of antiviral drugs have been identified. Processes that determine the development of experimental LCMV infection into the acute or chronic phenotypes were examined. Mathematical model describing the turnover kinetics of exhausted CD8 T cell population in chronic LCMV infection has been constructed and used to make predictions of the effect of anti-PDL-1 therapies. Based on the systems biology concept of multi-stability and the

prediction of multiplicative cooperativity between virus-specific cytotoxic T cells and neutralising antibodies, we argue for the requirements to engage multiple immune system components for functional cure strategies. The arguments are derived from LCMV model system studies and are translated to HIV-1 infection [4].

Conclusion: The fundamental result of our study is the elaboration of 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 being developed enabling a mechanistic description of the network and repertoire structures, hierarchical regulation, and evolutionary dynamics of immune processes under normal conditions and in infectious diseases.

Funding: The study is funded by the Russian Science Foundation (grant No. 23-11-00116, https://rscf.ru/project/23-11-00116/).

References

1. Bocharov G. et al. Multiphysics modelling of immune processes using distributed parameter systems. *Russ J Numer Anal Math Modelling*. 2023;38(5):279-292
2. Grebennikov D. et al. Network Modeling of Murine Lymphatic System. *Algorithms*. 2023;16(3):168
3. Sergeeva J. et al. Mathematical Model Predicting the Kinetics of Intracellular LCMV Replication. *Mathematics*. 2023;11(21):4454
4. Bocharov G. et al. Functional cure of a chronic virus infection by shifting the virus – host equilibrium state. *Front Immunol*. 2022;13:904342