DOI 10.18699/SBB-2022-508

Mathematical modelling of antiviral immune responses to SARS-CoV-2 infection

Bocharov G.[1, 2]*, Grebennikov D.[1, 2], Savinkov R.[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: SARS-CoV-2 infection, immune-physiological responses, mathematical model, sensitivity of dynamics, multi-modal therapies

Motivation and Aim: Infections of humans with SARS-CoV-2 known as COVID-19 disease represents a global biomedical problem. The course, severity and outcome of COVID-19 disease are characterized by enormous variability related to the specific kinetics of virus spreading, which depend on viral entry sites and tissue tropism, and the dynamics of immune reactions determined by the genetic make-up of the host and the spatial organization of immune system [1]. Consideration of the 'numbers game' and the 'immune geography' in quantitative terms is required for characterization of the host protection and its limits. A systems biology approach combining experimental/clinical data from murine- and human coronavirus infections in conjunction with mathematical modeling has been extensively advanced during the last few years. Systematic analysis of the advances and limitations of the so far developed mathematical models of SARS-CoV-2 infection is critical for implementation of the data-based mathematically-driven exploration of the pathogenicity mechanisms and for predicting the dynamics and severity of COVID-19.

Methods and Algorithms: We develop a multiscale multiphysics approach [2] to describe, analyze and predict the in-host COVID-19 dynamics. The model integrates the description of virus-host interaction at a single cell-, organ/tissue cell populations- and the whole organism levels. The respective mathematical modules describe the virus life-cycle, immune-physiological responses of the host, the immune cell motility and systemic transport processes. These are represented by a combination of deterministic and stochastic frameworks.

Results: The sensitivity of coronavirus disease severity to the dose of infection and the virus growth rate, and the limits of protection provided by the type I interferon (IFN) system that acts at the front line of the virus-host interaction are predicted [2]. Mathematical model of intracellular replication of SARS-CoV-2 has been developed and calibrated [3]. It was used to identify the stages of virus replication with a significant effect on the reduction of viral progeny produced by the infected cell. The stochastic version of the model predicted a strong inhibitory effects of IFN on viral progeny and a much lower sensitivity of the produced SARS-CoV-2 to the ACE2 binding affinity [4]. The dynamics, severity and outcome of COVID-19 in relation to the parameters of the immune-physiological reactions has been examined in quantitative terms using the calibrated mathematical model of SARS-CoV-2 infection.

Conclusion: The presented results identify novel targets for multi-modal therapies combining the antiviral drugs, reinvigoration of cellular immune responses and control of harmful of inflammatory responses. The models provide an interface between the

infection phenotypes and epidemiological studies by quantifying the dynamics of viral load which determines the infectivity of individuals at various stages of SARS-CoV-2 infection.

Acknowledgements: The study is supported by the Russian Foundation for Basic Research (grants 20-04-60157; 20-01-00352) and the Russian Science Foundation (grant 18-11-00171).

References

1. Bocharov G. et al. Mathematical immunology: from phenomenological to multiphysics modelling. *Russ J Numer Anal Math Modelling*. 2020;35(4):203-213.
2. Bocharov G et al. Numbers Game and Immune Geography as Determinants of Coronavirus Pathogenicity. *Front Cell Infect Microbiol*. 2020;10:559209.
3. Grebennikov D. et al. Intracellular Life Cycle Kinetics of SARS-CoV-2 Predicted Using Mathematical Modelling. *Viruses.* 2021;13(9):1735.
4. Sazonov I. et al. Sensitivity of SARS-CoV-2 Life Cycle to IFN Effects and ACE2 Binding Unveiled with a Stochastic Model. *Viruses.* 2022;14:403.