doi 10.18699/bgrs2024-12.2-11

A modular model of immune response as a computational platform to investigate a pathogenesis of infection disease

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Key words: coronavirus; SARS-CoV-2; COVID-19; mathematical model; BioUML, immune response

Motivation and Aim: Since the initial applications of mathematical methods for modeling an immune response are dated in the 1970's [1], a multitude of models have emerged, covering all areas of immunology from autoimmune disorders to infectious diseases. Despite promising prospects, the field's evolution has been hampered by limited access to experimental data, insufficient methodology development, and the absence of suitable software to construct multicompartmental models with complex structure and functional interrelationships between biological entities. While some challenges have been effectively addressed, others, such as data availability, persist. The landscape dramatically shifted with the onset of the COVID-19 pandemic. The unprecedented scale and severity of the disease prompted international collaboration among numerous scientific groups, accelerating joint efforts to address this common challenge. The collective attempt yielded a lot of experimental data, significantly facilitating the validation process and contributing to the emergence of novel mathematical models for studying COVID-19 [2]. Taking into account some shortcomings of these models (a limited set of compartments, a small amount of used experimental data, and the absence of key components of the immune response), we aimed to develop a modular mathematical model of the SARS-CoV-2 infection process and the subsequent innate and adaptive immune responses. Our goal is not only to investigate the corresponding disease at a systemic level but also to provide a framework for further development and research in the field of host-pathogens (existing and future) interactions.

Methods and Algorithms: As a modeling tool, we employed our own open-source computational platform for systems biology, BioUML [3]. To build the modular model, we utilized the system of ordinary differential equations (ODEs) supplemented by the integration of delay differential equations (DDEs), which effectively capture the time-dependent dynamics of cell development and migration. Model simulations were conducted using the Java Variable-Coefficient ODE (JVODE) solver, which is integrated within the BioUML environment. Model validation was performed using experimental data of time-series measurements obtained from adult individuals with moderate COVID-19 symptoms, including viral load in the Upper Airways (UA) and Lungs, CD4+ and CD8+ T cells, and levels of key cytokines including IL-6, IL-12, and IFNγ. Following manual calibration, three optimization algorithms implemented in the BioUML platform [4–6], were applied to refine the model parameters. Then we selected the best scored one from a set of obtained parameter solutions. In addition, to evaluate the impact of different parameters and their variations on the progression of COVID-19, we performed a local sensitivity analysis also implemented in the BioUML platform.

Results: We have developed a multicompartmental model consisting of the Upper Airways, Lungs, and draining Lymph Nodes (Fig. 1). The Upper Airways represent a simplified version of the model, including only the coronavirus, epithelial cells in different states, and immature dendritic cells. The draining lymph nodes encompass CD8+ T and B cells, with the former differentiating into cytotoxic T cells responsible for eliminating infected epithelial cells. The latter differentiate into plasma cells that produce antibodies. In the lungs, which serve as the primary model, both macrophages and dendritic cells are included, reflecting the innate immunity component. In addition to CD8+ T cells, the lungs' draining lymph nodes also harbor CD4+ T cells, which differentiate into T helper type 1 and T follicular helper cells. Furthermore, the lymph nodes contain various types of cytokines, including IL-2, IL-6, IL-12, and IFNγ.

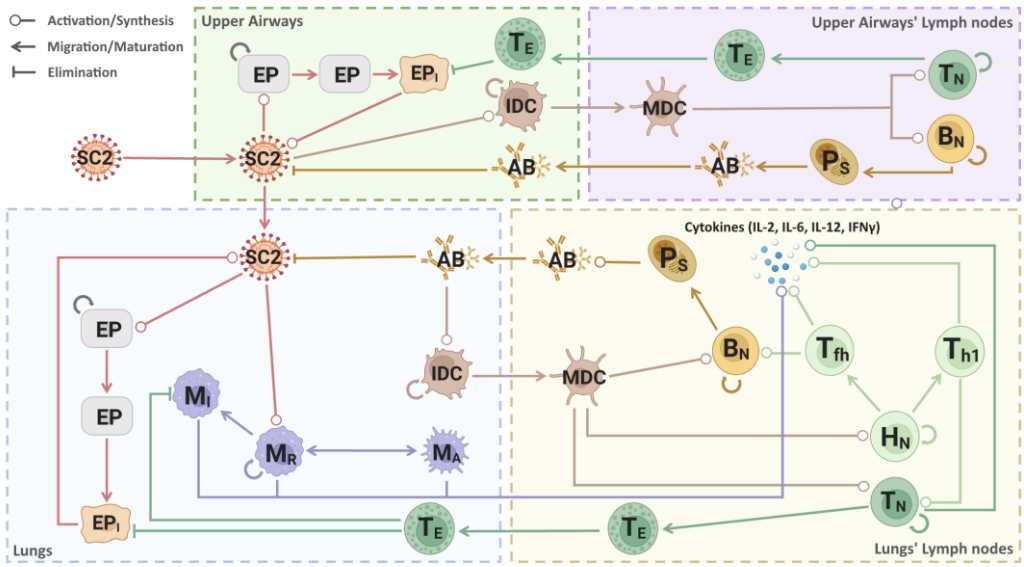

Fig. 1. A conceptual diagram of the model. SC2 – SARS-CoV-2, EP – Epithelial Cells, EP_I – Infected Epithelial Cells, M_R – Resting Macrophages, M_I – Infected Macrophages, M_A – Activated Macrophages, IDC – Immature Dendritic Cells, MDC – Mature Dendritic Cells, B_N – Naïve B Cells, T_N – Naïve CD8+ T Cells, H_N – Naïve CD4+ T Cells, Th1 – T Helper Type 1 Cells, Tfh – T Follicular Helper Cells, T_E – Cytotoxic T Cells, P_S – Plasma Cells, AB – Antibodies

After fitting the model to experimental quantitative data, we reproduced the main disease severity scenarios: moderate, severe, and critical (Fig. 2). We used the level of IL-6 as an indicator of the severity extent, as it most strongly correlates with worse outcomes. In addition to this, we considered the degree of epithelial cell damage and viral load. To model severe disease, we adjusted parameters associated with aging-related alterations in the immune system, given that age is a major risk factor for deteriorating the COVID-19 outcome [7]. Additionally, we investigated the potential differences among SARS-CoV-2 variants in terms of infectivity, transmissibility, and their ability to evade the immune response. Furthermore, we modeled the immune response to the infection in patients with HIV and demonstrated how interferon treatment affects the course of the disease.

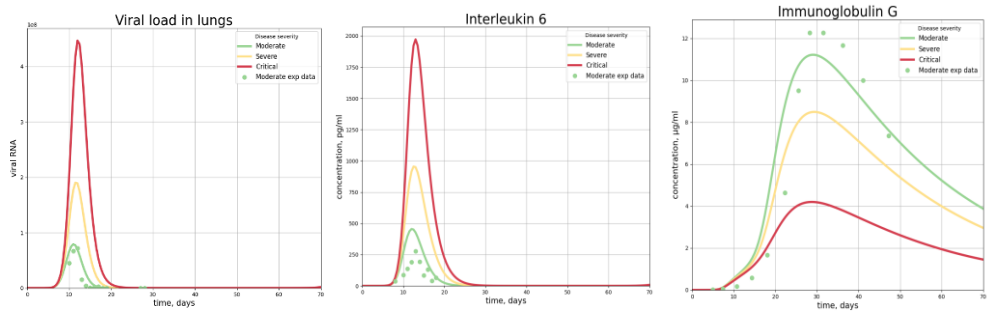

Fig. 2. The modular model simulations of viral load, IL-6 and IgG for different COVID-19 severity scenarios. Green line represents moderate progression, yellow line designates severe progression and red line indicates critical progression according to the model simulations, while dots represent experimental measurements for corresponding variables

Conclusion: Consequently, the developed modular model encompasses 31 ODEs and 114 parameters. It not only simulates diverse disease scenarios, including moderate or severe progression, but also is able to reproduce the co-infection with HIV, which implies different extent of immunosuppression. Furthermore, it simulates primary changes in SARS-CoV-2 variants, such as differences between Omicron and other strains as well as various treatment strategies. It is worth to note that constructed modules of the model can be employed as "building blocks" for simulating other infectious diseases taking into account follow-up immune response. The modular model and all experimental data are available at gitlab: https://gitlab.sirius-web.org/diploms/modular-immune-system.

Funding: The study is supported by the Ministry of Science and Higher Education of the Russian Federation, (Agreement 075-10-2021-093, Project CMB-RND-2123: "Virtual patient").

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