A Computational Immune Approach for Modeling Different Levels of Severity in COVID-19 Infections

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Overview

Introduction

What is COVID-19?

- COVID-19 is the disease caused by the SARS-CoV-2 virus, first identified in Wuhan, China in 2019.
- The virus spread rapidly across the world, leading the World Health Organization to declare a pandemic in March 2020.
- Over 777 million cases and 7 million deaths have been registered worldwide, as of February 2025.

Why This Study?

We wanted to understand why COVID-19 causes mild illness in some people and critical illness in others.

- In this study, we adapt a model to simulate disease severity[1]. The model is calibrated using differential evolution and validated against data from the literature, including:
  - $CD4^+$ and $CD8^+$ T cells,
  - Viral load,
  - Antibodies.
- We consider three severity scenarios: **(1)** mild, **(2)** severe, and **(3)** critical.

[1] Reis, Ruy Freitas, et al. "A validated mathematical model of the cytokine release syndrome in severe COVID-19." *Frontiers in Molecular Biosciences* 8 (2021): 639423.

Methods

How the Model Works

The mathematical model consists of 12 ordinary differential equations (ODEs). It represents key components of the immune response to SARS-CoV-2 infection, including:

- Antigen-presenting cells (APCs),
- T cells,
- B cells.

Mathematical Model: Virus and APCs

- Virus (V):

$$\frac{d}{dt}V = \pi_v V - \frac{c_{v1}V}{c_{v2}+V} - k_{v1}VA - k_{v2}VT_{ke}$$

- Immature antigen-presenting cells (A_p):

$$\frac{d}{dt}A_p = \alpha_{ap}(A_{p0} - A_p) - \beta_{ap}A_p\frac{c_{ap1}V}{c_{ap2}+V}$$

- Activated antigen-presenting cells (A_{pm}):

$$\frac{d}{dt}A_{pm} = \beta_{ap}A_p\frac{c_{ap1}V}{c_{ap2}+V} - \delta_{apm}A_{pm}$$

Mathematical Model: T helper cells

- Naïve CD4+ T cells (T_{hn}):

$$\frac{d}{dt}T_{hn} = \alpha_{th}(T_{hn0} - T_{hn}) - \beta_{th}A_{pm}T_{hn}$$

- Effector CD4+ T cells (T_{he}):

$$\frac{d}{dt}T_{he} = \beta_{th}A_{pm}T_{hn} + \pi_{th}A_{pm}T_{he} - \delta_{th}T_{he}$$

Mathematical Model: T killer cells

- Naïve CD8+ T cells (T_{kn}):

$$\frac{d}{dt}T_{kn} = \alpha_{tk}(T_{kn0} - T_{kn}) - \beta_{tk}A_{pm}T_{kn}$$

- Effector CD8+ T cells (T_{ke}):

$$\frac{d}{dt}T_{ke} = \beta_{tk}A_{pm}T_{kn} + \pi_{tk}A_{pm}T_{ke} - \delta_{tk}T_{ke}$$

Mathematical Model: B cells

- B cells (B):

$$\frac{d}{dt}B = \alpha_b(B_0 - B) + \pi_{b1} VB + \pi_{b2} T_{he} B - \beta_{ps} A_{pm} B - \beta_{pl} T_{he} B - \beta_{bm} T_{he} B$$

- Short-lived plasma cells (P_s):

$$\frac{d}{dt}P_s = \beta_{ps} A_{pm} B - \delta_{ps} P_s$$

- Long-lived plasma cells (P_l):

$$\frac{d}{dt}P_l = \beta_{pl} T_{he} B - \delta_{pl} P_l + \gamma_{bm} B_m$$

- Memory B cells (B_m):

$$\frac{d}{dt}B_m = \beta_{bm} T_{he} B + \pi_{bm1} B_m \left(1 - \frac{B_m}{\pi_{bm2}}\right) - \gamma_{bm} B_m$$

Mathematical Model: Antibodies

- Antibodies (A):

$$\frac{d}{dt}A = \pi_{ps}P_s + \pi_{pl}P_l - \delta_a A$$

Adjusting the Model to Fit the Data

To make our model realistic, we used a method called Differential Evolution (DE).

- The DE is applied to optimize a set of parameters p, aiming to find numerical results that best fit experimental data. The target variables include:
  - Populations of mature $CD4^+$ and $CD8^+$ T cells,
  - Viral load,
  - Antibody concentration.
- We evaluate the relative error between the experimental data and our computer simulation:

$$\min \; O(p) = \omega_{T_{he}} \frac{\| T_{he} - \overline{T_{he}} \|_2}{\| T_{he} \|_2} + \omega_{T_{ke}} \frac{\| T_{ke} - \overline{T_{ke}} \|_2}{\| T_{ke} \|_2} + \omega_V \frac{\| V - \overline{V} \|_2}{\| V \|_2} + \omega_A \frac{\| A - \overline{A} \|_2}{\| A \|_2}$$

Numerical Results

Implementation

- The mathematical model was implemented in C++ using the CVODE package to solve systems of ordinary differential equations;
  - Backward Differentiation Formula (BDF) was used to integrate the ODE system;
- Moreover, a library implementing the DE algorithm was utilized.[2]

[2] `https://github.com/ruyfreis/differential_evolution.git`

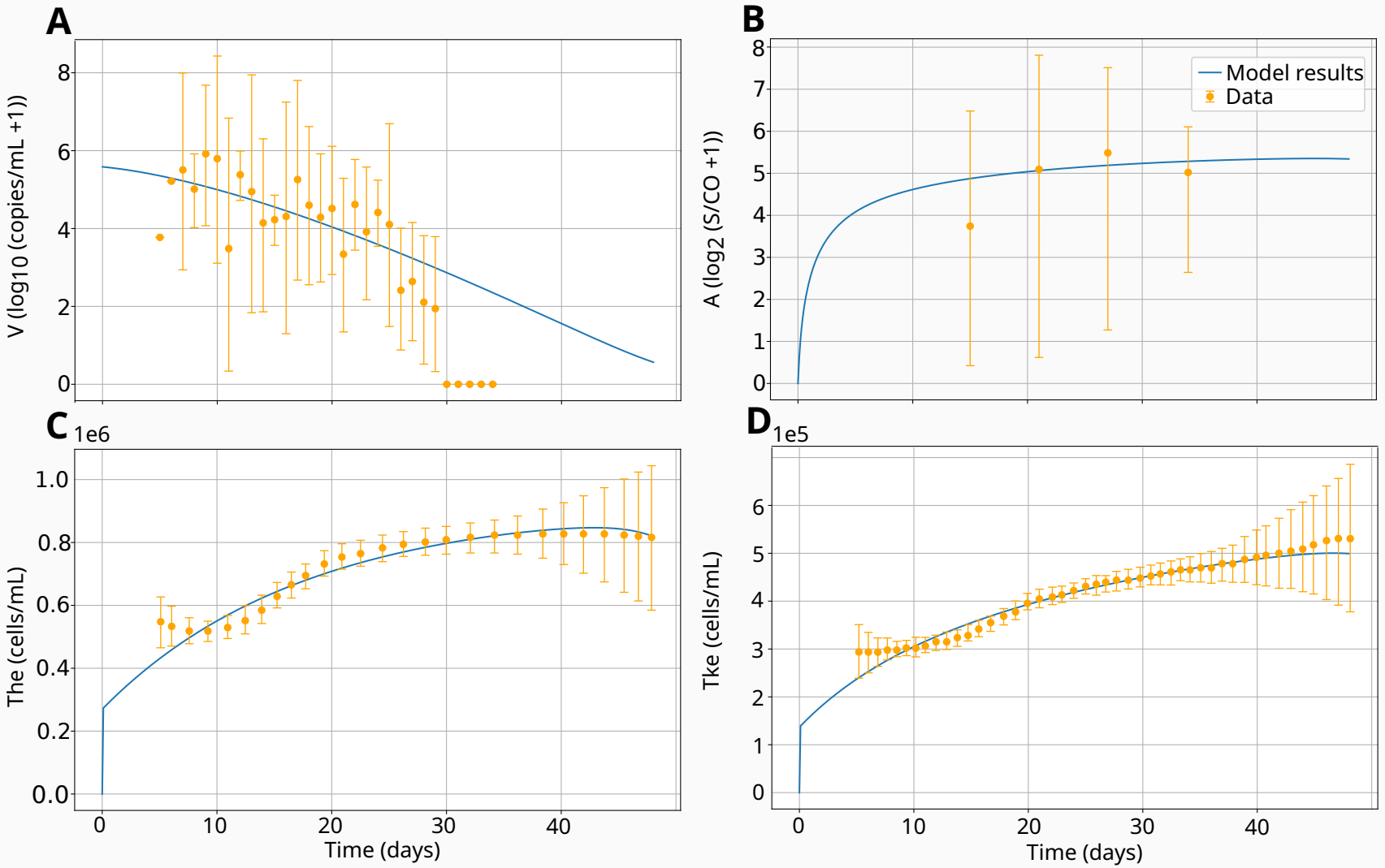
Simulating Mild, Severe, and Critical Cases

- Three scenarios—**mild, severe, and critical**—are considered for simulations, based on $CD4^+$ and $CD8^+$ T cell population data from the literature.
- Each scenario uses distinct lymphocyte data, while virus concentration and antibody levels are taken from a shared dataset.

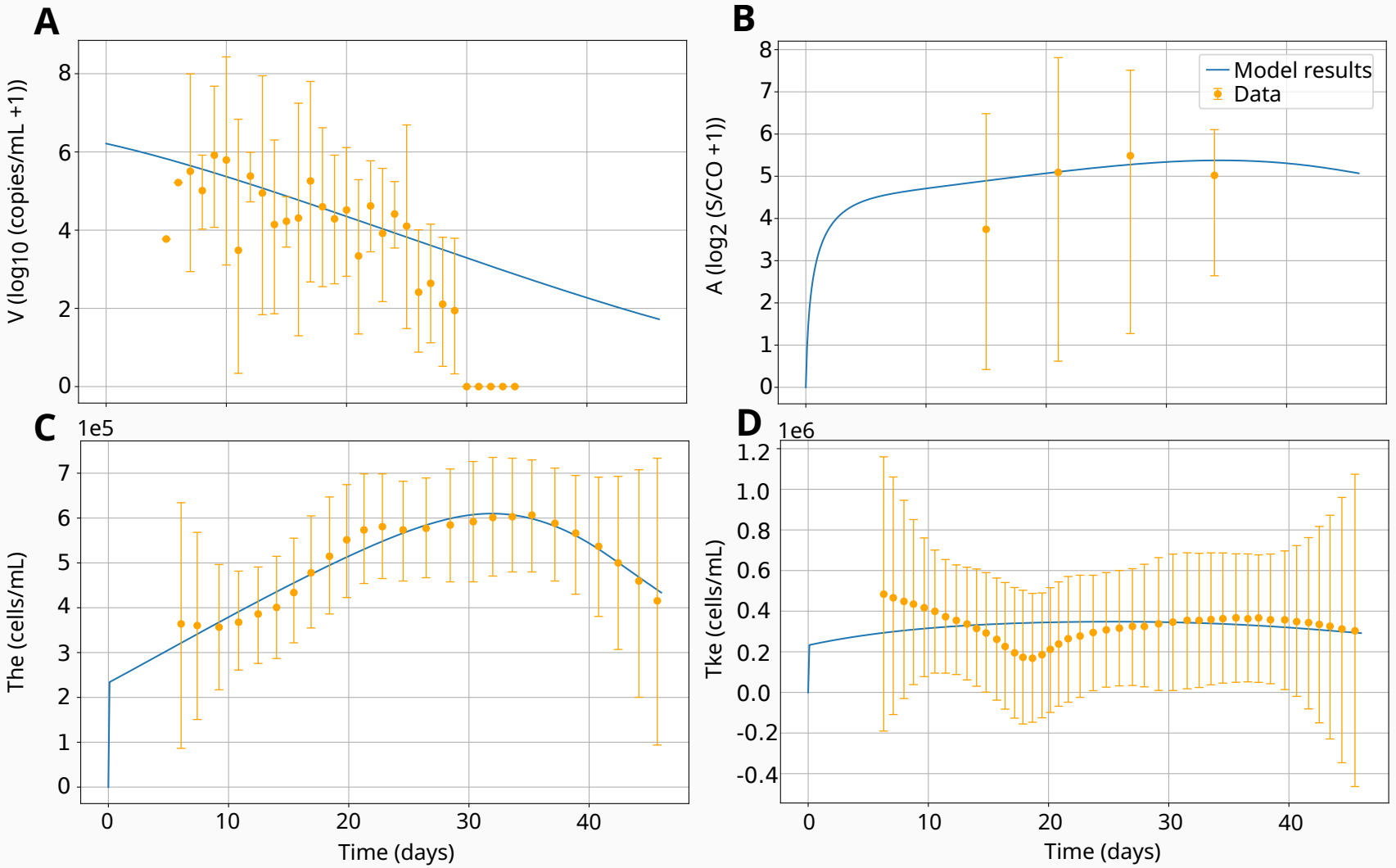
Parameters calibration

- Parameter adjustments are made for all scenarios:
  - **Mild and severe cases:** 15 parameters (14 model parameters and one initial condition) are optimized.
  - **Critical case:** 12 parameters (11 model parameters and one initial condition) are adjusted.

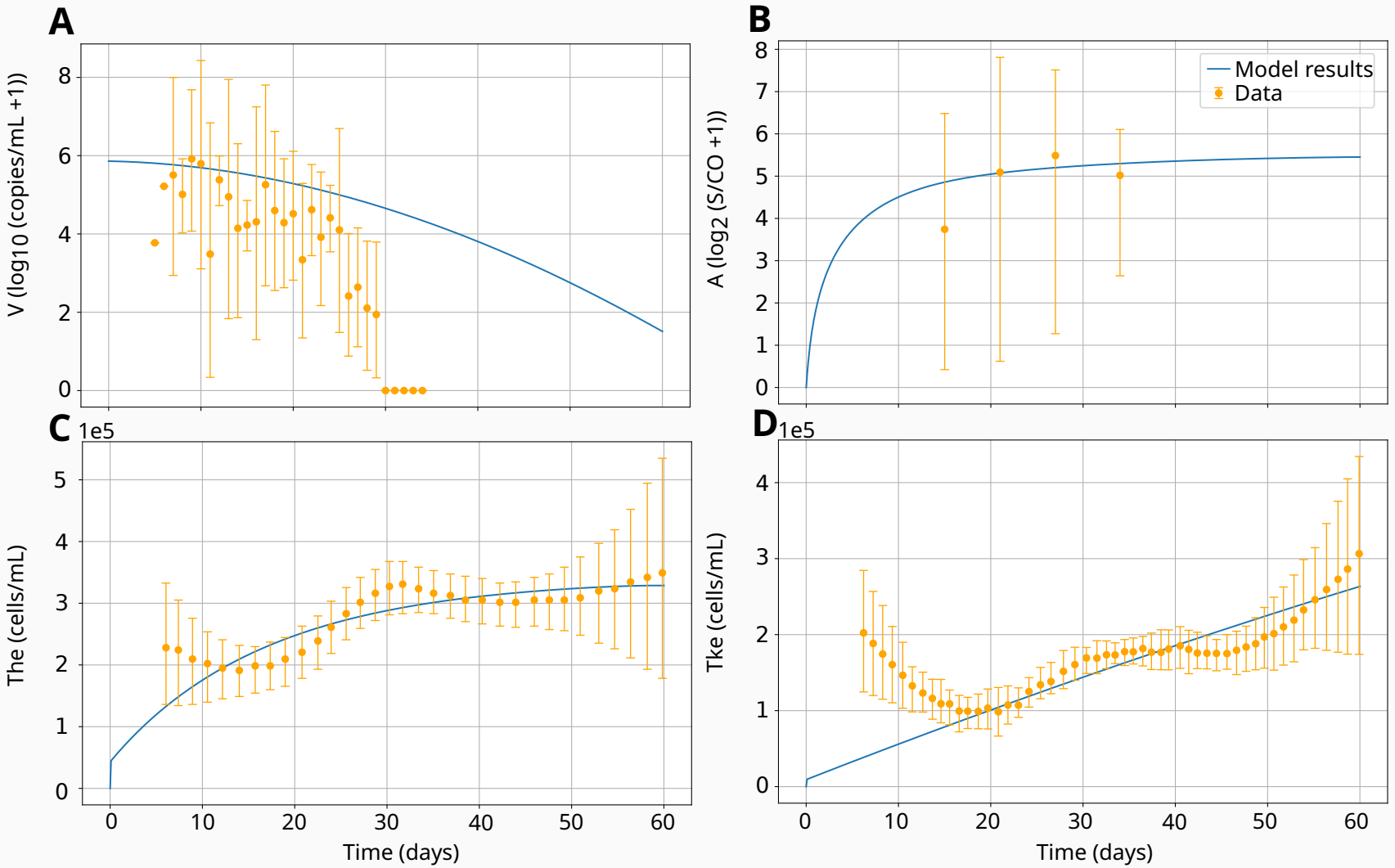
The Mild Case Scenario



The Severe Case Scenario



The Critical Case Scenario



Key Findings

- Our simulations match the data from real patients and show how the immune system behaves in different levels of COVID-19 severity.
- Overall, the results indicate a severity-linked immune dysfunction:
  - Milder cases exhibit higher T cell levels and faster viral clearance.
  - Critical cases display a reduced immune response and prolonged viral presence.

Conclusion and Future Works

Conclusion

- This study presented a computational model for simulating the immune response to SARS-CoV-2, validated using experimental data.
- The model successfully captured the dynamics of mature $CD4^+$ and $CD8^+$ T cells, viral load, and antibody levels.
- The simulated curves generally remained within the experimental confidence intervals, demonstrating the model's qualitative validity.

Future Works

- Some ideas for future work to improve the model's accuracy and computational efficiency include:
  - Uncertainty quantification;
  - Sensitivity analysis;
  - High-performance computing.

Acknowledgements

Obrigado!

Thanks!

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