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Mathematically Investigating the Impacts of Antibody Dynamics on the Human Immune Response to SARS-CoV-2

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Introduction

SARS-CoV-2 is an RNA virus that causes COVID-19, a disease that has killed over six million people worldwide since 2019 [1]. It is important to understand the features of a SARS-CoV-2-specific immune response, which is comprised a general innate response and a disease-specific adaptive response (see Figure 1) [2,3]. Some aspects include:

- Neutrophils and macrophages ingest harmful foreign particles. Monocytes differentiate into macrophages.
- T cells kill infected host cells.
- Antibody secreting B cells produce antibodies, which are proteins that bind to the surface of antigens and facilitate removal. IgG is often an important indicator of long-term protection against a virus [5,6].

Mathematical models have been developed since the start of the COVID-19 pandemic to study the effects of SARS-CoV-2 in the human body. Jenner et al. 2021 developed a compartmental model of the immune response to this virus that is focused on innate and T cell dynamics during primary infection and does not yet consider humoral immune dynamics [4]. This study aims to introduce antibodies, namely immunoglobulin G (IgG), and antibody secreting B cells (ASC) into the model to study their effects on the human immune response to SARS-CoV-2.

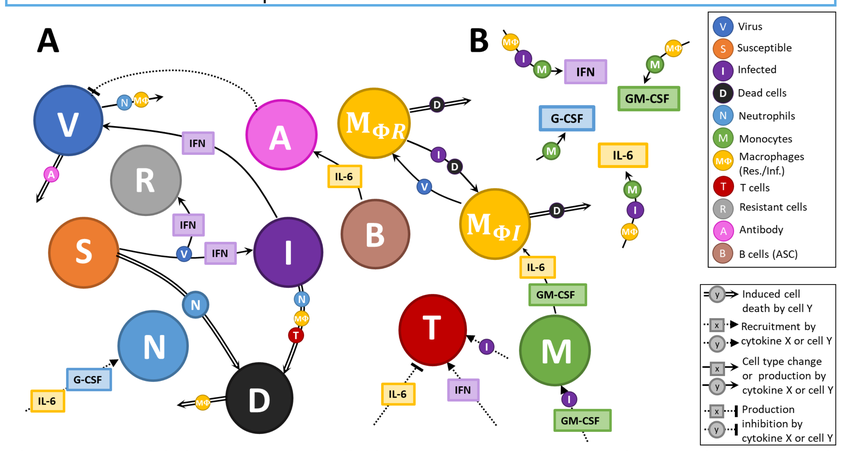

Figure 1. Modeled **A)** immune cell dynamics, **B)** cytokine production dynamics, and interactions, adapted from Jenner et al. 2021 [4].

Biological Questions

- What are the impacts of antibody dynamics on the human immune response to SARS-CoV-2?
- How does the presence of antibodies affect different disease and immune measures, such as viral load, infected cell count, immune activation, and viral clearance?

Mathematical Approach

We first develop and parameterize a submodel of antibody dynamics based on IgG and ASC behavior. Then, we incorporate the submodel into the systemic immune model by Jenner et al. 2021. Outputs of the new model with IgG and ASC are compared to the original model, and sensitivity of outputs to parameter values is assessed.

Parameter	Defined	Value	Units	Citation
d_V	viral decay rate	7.73	1/day	Fit to [7]
$\delta_{V,A}$	virus removal rate by IgG	116	1/day	Fit to [8]
n	amount of IgG bound to virus	1	dimensionless	Fit to [8]
$\epsilon_{V,A}$	half-effect of virus removal by IgG	4.51	titer	Fit to [8]
p_B	ASC production	2.54 x 10^{-5}	1/day	Fit to [9]
τ_B	ASC delay time	4.5	day	Estimated from [4]
d_B	ASC decay rate	0.23	1/day	Calculated from [10]
p_A	IgG production rate	2.75 x 10^6	titer/(cells/ml) /day	Fit to [8]
$\epsilon_{A,L}$	half-effect of IgG stimulation by IL-6	1	pg/ml	Fit to [8]
d_A	IgG decay rate	0.311	1/day	Fit to [8]
$n_{V,A}$	amount of IgG bound to virus	1	titer	n with units

Submodel & Parameterization

Submodel

$$\frac{dV}{dt} = pI - d_V V - \frac{\delta_{V,A} V A^n}{\epsilon_{V,A}^n + A^n} \qquad \frac{dS}{dt} = \lambda_S \left(1 - \frac{S+I+D}{S_{max}}\right) S - \beta S V$$

$$\frac{dI}{dt} = \beta S(t-\tau_I) V(t-\tau_I) - d_I I \qquad \frac{dD}{dt} = d_I I - d_D D$$

$$\frac{dB}{dt} = p_B I(t-\tau_B) - d_B B$$

$$\frac{dA}{dt} = p_A B \left(1 + \frac{L_B}{L_B + \epsilon_{A,L}}\right) - d_A A - \frac{n_{V,A} \delta_{V,A} V A^n}{\epsilon_{V,A}^n + A^n}$$

Parameterization

Datasets used in order of fitting:

B cells: ASC data taken from Rowntree et al [9].

IgG: Antibody data from Rode et al. Data are IgG titer, and all cases (mild, moderate, severe) were used [8].

Viral load: Virus data from Goyal et al. expressed in log(cop/ml) of RNA [7].

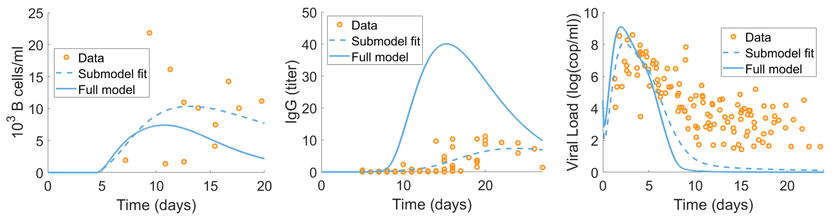

Figure 2. Full model outputs of ASC, IgG, and viral load plotted against the data used in parameterization as well as the best-fit parameterization of the submodel [7,8,9]. Differences can be attributed to additional equations present in the full model vs. smaller submodels used for fitting. Future calibration against other datasets could refine parameter values to more precisely capture data trends.

Results

When antibody dynamics are incorporated into the model, the length of infection is shortened. The delay in ASC production means that antibodies decrease viral load after virus peaks.

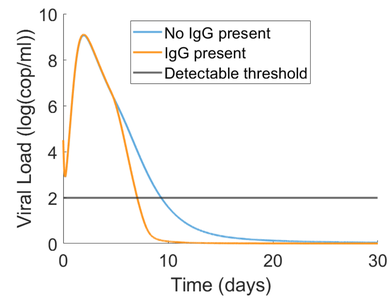

Figure 3. Viral load decreases rapidly between days 4 and 5 due to B cell activation at day 4.5. Virus passes under the detectable infection threshold around day 7 versus around day 9 when IgG is present in the model.

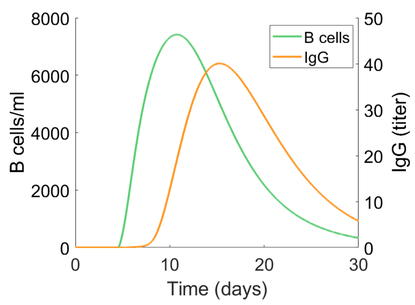

Figure 4. In a primary infection, antibody production is delayed until ASC are stimulated around day 4.5.

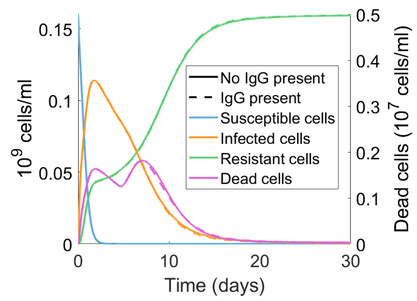

Figure 5. Epithelial cell dynamics from the antibody model are nearly identical to those of the model without antibody.

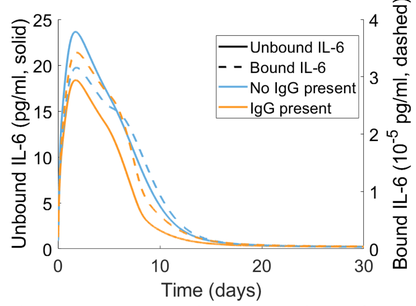

Figure 6. IL-6 stimulates IgG release from ASC, which decrease unbound IL-6 when IgG is present. Bound IL-6 increases due to additional receptors being present on ASC.

Acknowledgements

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Sensitivity Analysis

In the following figures, the original IgG model (baseline) parameter value is represented by the blue dotted line.

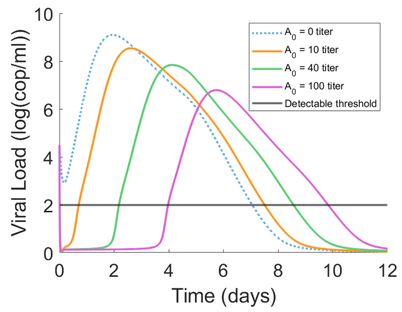

Figure 7. Varying the initial amount of antibody (A_0) is representative of monoclonal antibody treatment. Larger amounts of initial antibody delay infection and decrease total viral load.

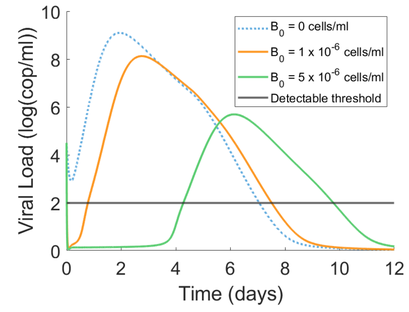

Figure 8. Increasing amounts of initial B cells (B_0), which mimics unmodeled immune memory, has the potential to delay infection and decrease disease severity in terms of viral load.

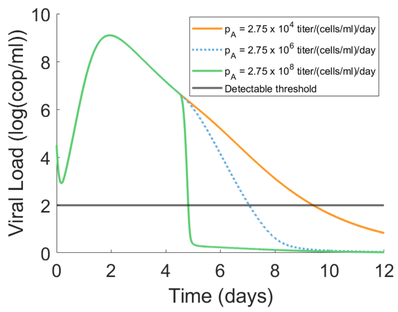

Figure 9. Varying the antibody production rate (p_A) can drastically change the length of detectable infection. A change of 10^2 titer/(cells/ml)/day shifts the infection period by about 2 days. With a larger p_A value, viral load drops immediately after IgG production initiates.

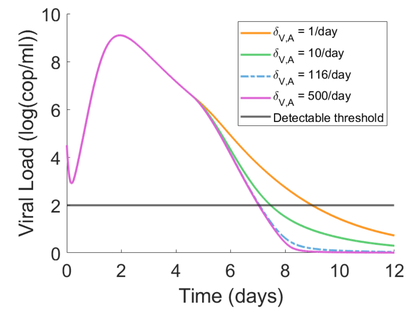

Figure 10. Varying the viral removal rate by antibody ($\delta_{V,A}$) can change the length of detectable infection. Viral load is more sensitive to smaller values of $\delta_{V,A}$.

Conclusions

- Modeling suggests IgG antibodies do not prevent or substantially decrease severity of primary SARS-CoV-2 infection, but they can shorten the duration of infection.
- Efficiency of antibody production and/or rate of virus removal by IgG determine how quickly viral load is lowered.
- An initial pulse of antibody, such as from monoclonal antibody treatment, may delay infection, but at modeled dosages, infection is not prevented. However, the curve of infection is flattened, and total virus (area under the curve) is lessened.
- Flatter curves associated with higher amounts of initial B cells suggest that unmodeled memory B cells could play a role in decreasing the severity of secondary infections of SARS-CoV-2.

Future Work

- Refine preliminary parameterization (see Figure 3).
- Validate model results against independent datasets.
- Use virtual cohorts to investigate individual patient antibody responses, as in Jenner et al. 2021 [4].
- Introduce memory B cells to model secondary infections.

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