

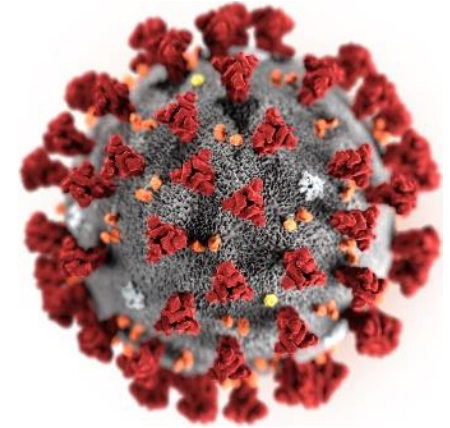
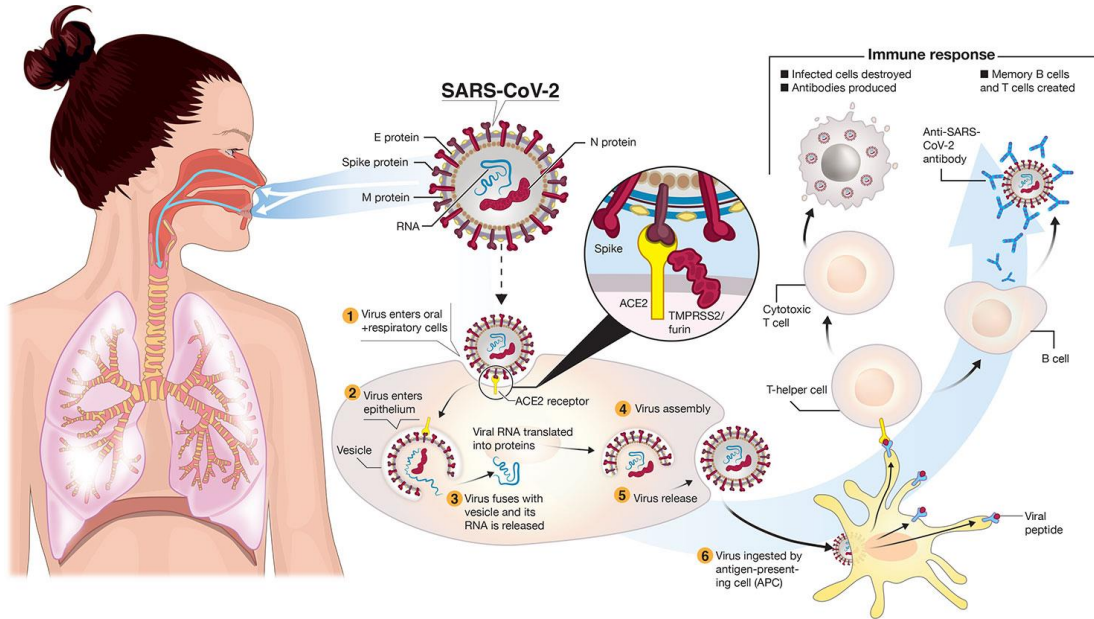


О моделировании иммунного ответа и вакцинации


Кристина Леон

01.11.2022г.

Introduction



3D model of SARS-CoV-2



What do we want to understand?



The causes of high interpatient variations in symptoms and the severity of the disease.



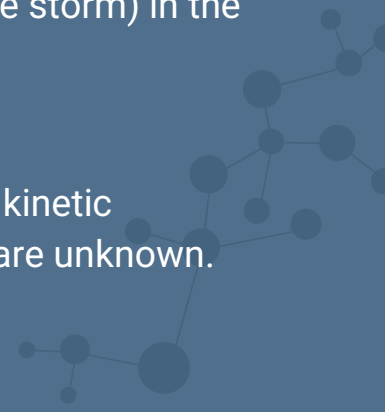
Cause of long incubation time followed by the severe (or mild) manifestation of the disease.



Abnormal inflammation response (hypercytokinemia, cytokine storm) in the part of patients.



Establish the values of the kinetic constants, many of which are unknown.



Methodology

1

MODEL DESIGN

Take the general
immune response
models

2

MODEL CALIBRATION

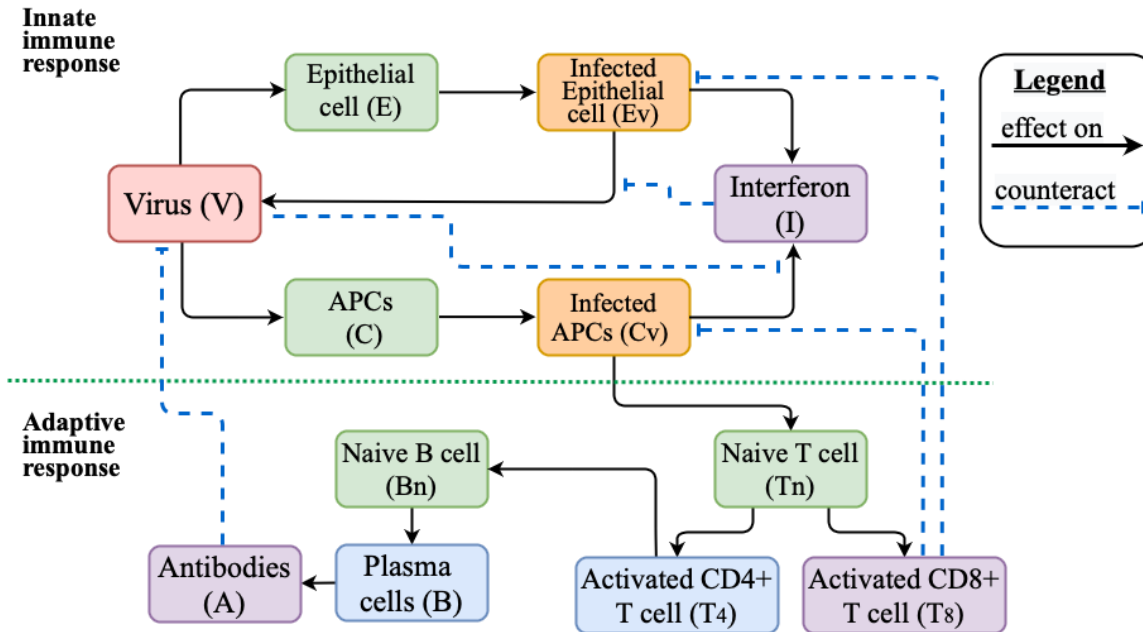
Adjust them to
SARS-CoV-2
peculiarities

3

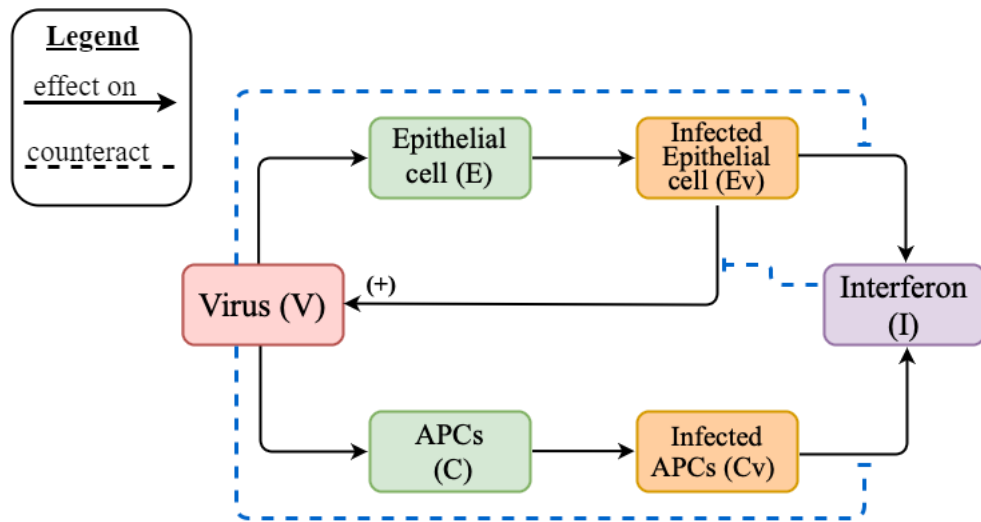
RESULTS

Study properties of the
obtained model

Immune response modelling (to SARS infection)



Innate immune response model (6 eq.)

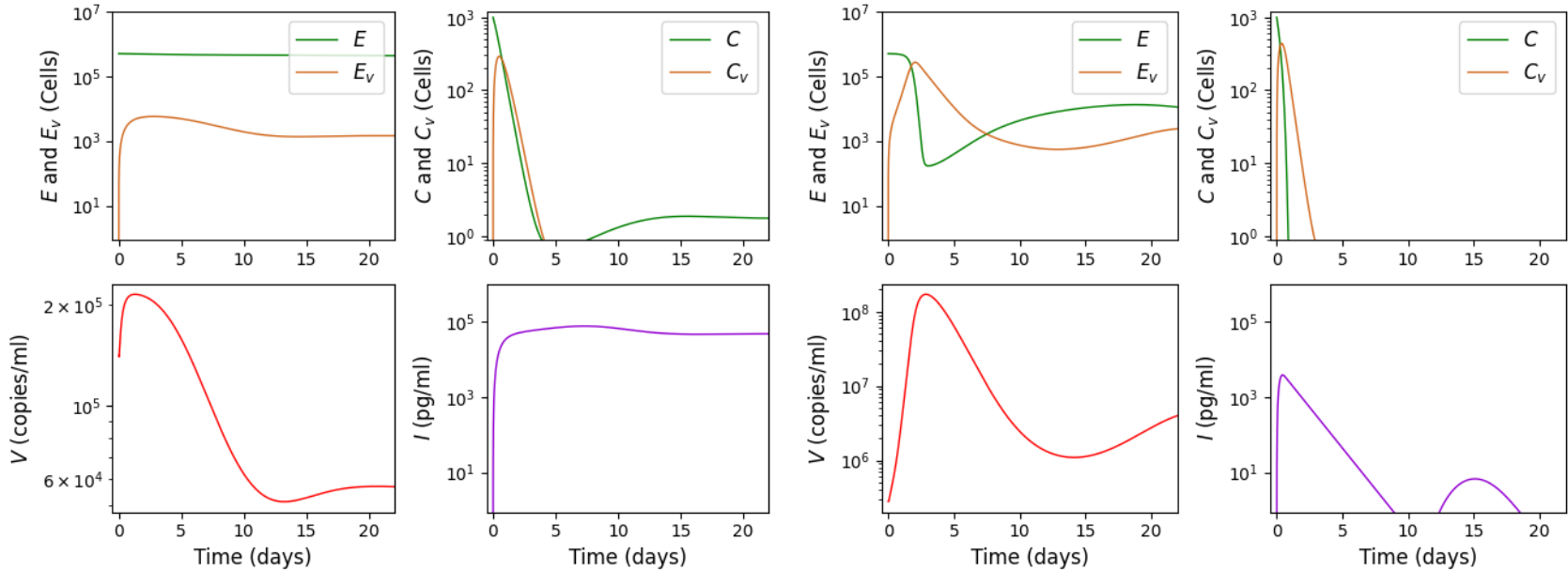
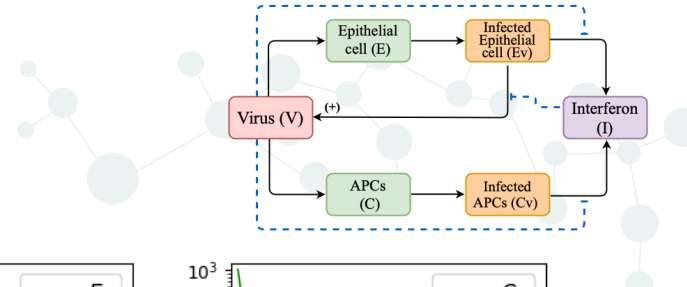


- Interferon blocks cell reproduction processes

$$\begin{cases}
 \frac{dE}{dt} = k_1(E_0 - E) - k_2EV, \\
 \frac{dE_v}{dt} = k_2EV - \sigma_1E_v, \\
 \frac{dC}{dt} = k_3(C_0 - C) - k_4CV, \\
 \frac{dC_v}{dt} = k_4CV - \sigma_2C_v, \\
 \frac{dV}{dt} = f(I)E_v - \sigma_3V, \\
 \frac{dI}{dt} = g(V)(C_v + \kappa E_v) - \sigma_4I,
 \end{cases}$$

$$f(I) = \frac{f_0}{1 + f_1I}, \quad g(V) = g_0e^{-g_1V}.$$

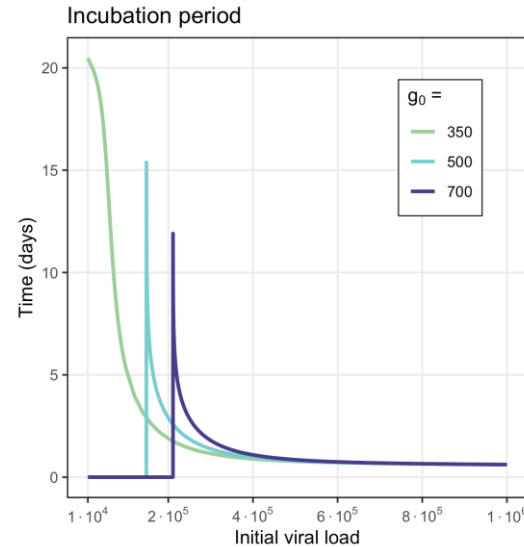
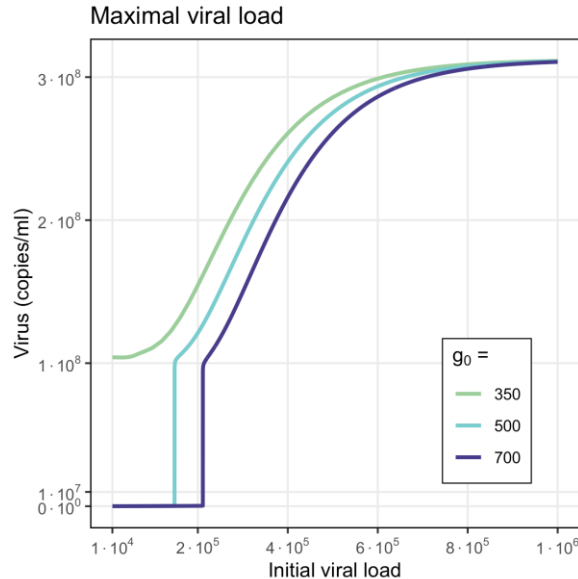
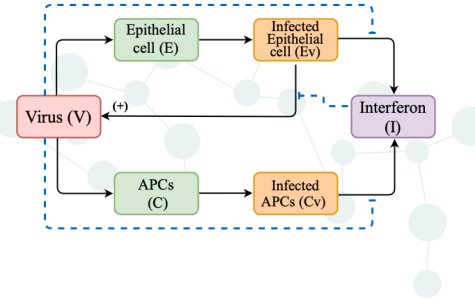
Interferon vs virus



It all depends on the initial viral load.

Incubation period of the virus

g_0 – interferon secretion rate

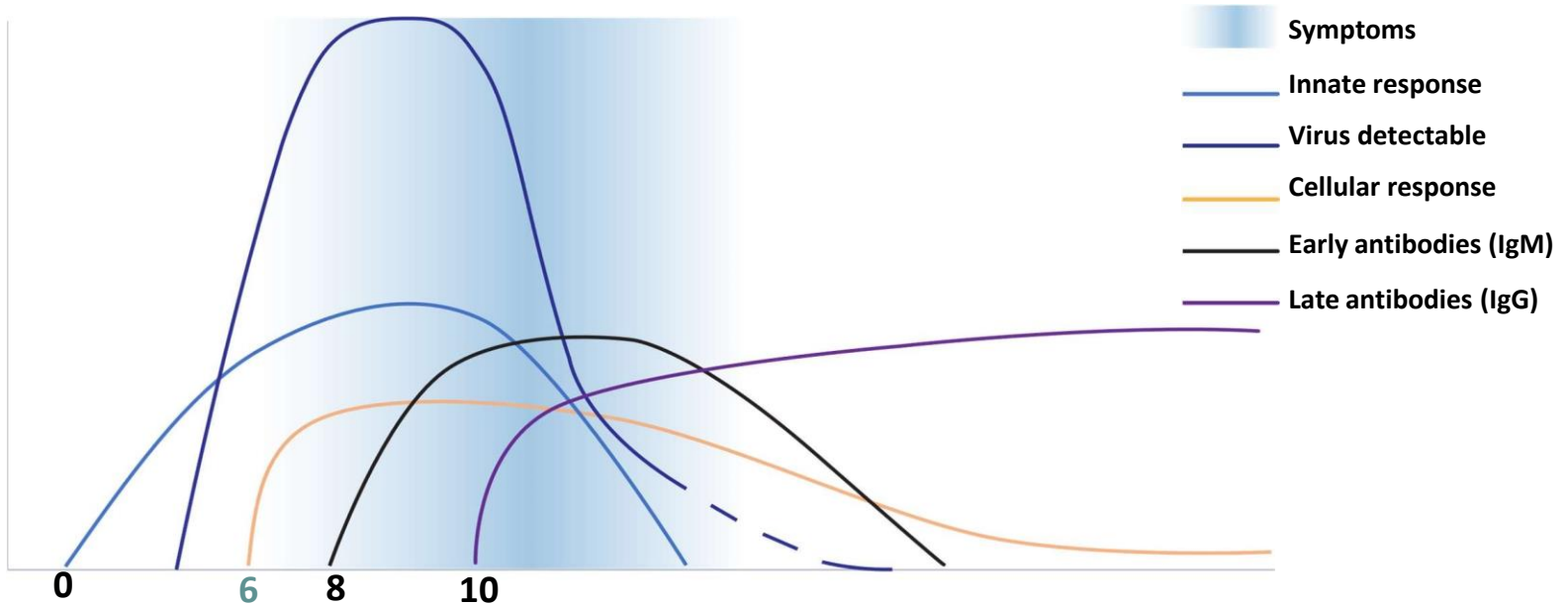


$$\frac{dI}{dt} = g(V)(C_v + \kappa E_v) - \sigma_4 I,$$

$$g(V) = \underline{g_0} e^{-g_1 V}.$$

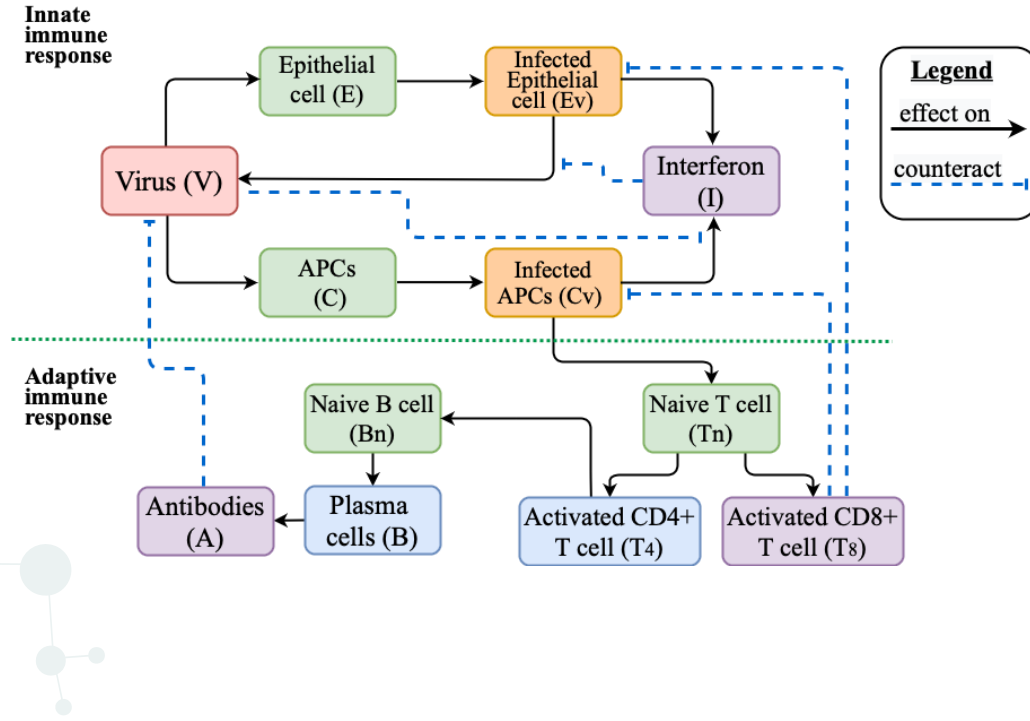
1. High initial viral load shortens the incubation time and increases maximal viral load.
2. Disease severity should depend on the initial viral load

Immune response sequence



[2] The latest on covid-19 immunity and the current global situation // WHO, coronavirus update 34, August 2020. URL(Accessed 07-04-2021): https://www.who.int/docs/default-source/coronaviruse/risk-comms-updates/update-34-immunity-2nd.pdf?sfvrsn=8a488cb6_2

Innate + adaptive immune response (12 eq.)



From day 0

From day 6

Day 8

$$\begin{aligned} \frac{dE}{dt} &= k_1(E_0 - E) - k_2EV, \\ \frac{dE_v}{dt} &= k_2EV - \sigma_1E_v - \gamma_1T_8E_v, \\ \frac{dC}{dt} &= k_3(C_0 - C) - k_4CV, \\ \frac{dC_v}{dt} &= k_4CV - \sigma_2C_v - \gamma_2T_8C_v, \\ \frac{dV}{dt} &= f(I)E_v - \sigma_3V - \gamma_3AV, \\ \frac{dI}{dt} &= g(V)(C_v + \kappa E_v) - \sigma_4I, \\ \frac{dT_n}{dt} &= h_0 - h_1(C_v)T_n - h_2(C_v)T_n, \\ \frac{dT_4}{dt} &= h_1(C_v)T_n - \sigma_5T_4, \\ \frac{dT_8}{dt} &= h_2(C_v)T_n - \sigma_6T_8, \\ \frac{dB_n}{dt} &= q_0 - q_1(T_4)B_n, \\ \frac{dB}{dt} &= q_1(T_4)B_n - \sigma_7B, \\ \frac{dA}{dt} &= k_5B - \sigma_8A - \gamma_3AV, \end{aligned}$$

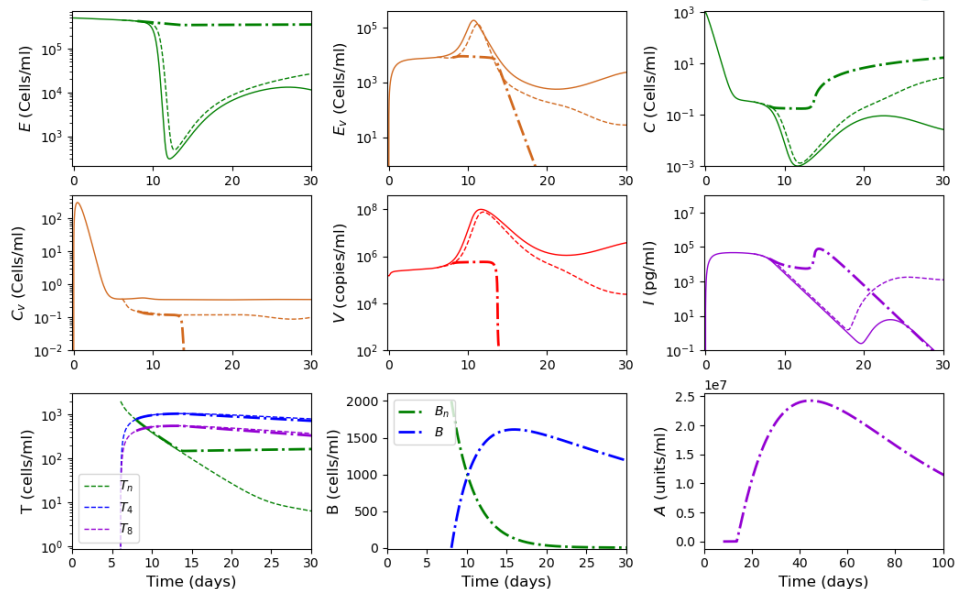
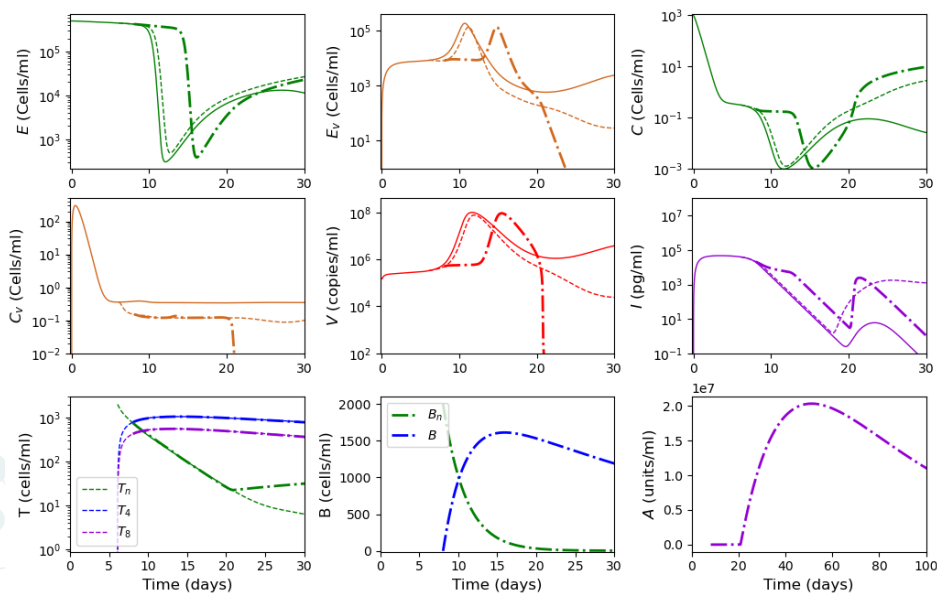
Simulations

$$\frac{dA}{dt} = \underline{k_5}B - \sigma_8A - \gamma_3AV,$$

k_5 – antibodies secretion rate

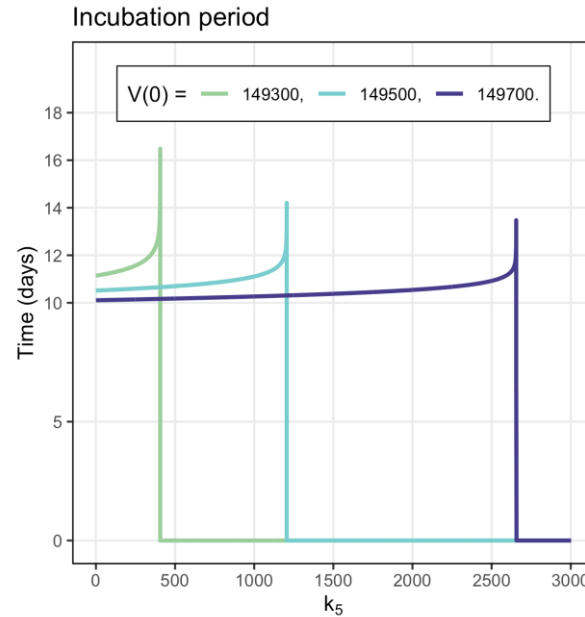
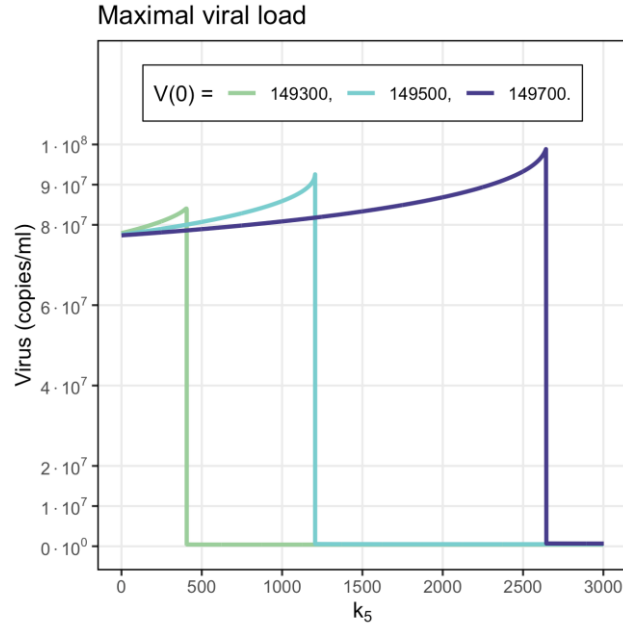
$k_5 = 1205.62 \text{ (клеток} \cdot \text{день)}^{-1} \text{ (ед./мл)}$

$k_5 = 1205.63 \text{ (клеток} \cdot \text{день)}^{-1} \text{ (ед./мл)}$



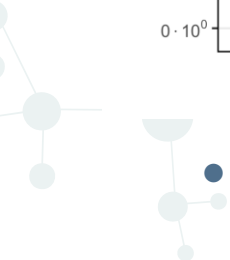
It all depends on the initial viral load.

Antibodies production vs virus



$$\frac{dA}{dt} = \underline{k_5}B - \sigma_8A - \gamma_3AV,$$

- Full virus elimination depends on sufficient antibody production characterized by the parameter k_5



AIR

$$\frac{dE}{dt} = k_1(E_0 - E) - k_2EV,$$

$$\frac{dE_v}{dt} = k_2EV - \sigma_1E_v - \gamma_1T_8E_v,$$

$$\frac{dC}{dt} = k_3(C_0 - C) - k_4CV,$$

$$\frac{dC_v}{dt} = k_4CV - \sigma_2C_v - \gamma_2T_8C_v,$$

$$\frac{dV}{dt} = f(I)E_v - \sigma_3V - \gamma_3AV,$$

$$\frac{dI}{dt} = g(V)(C_v + \kappa E_v) - \sigma_4I,$$

$$\frac{dT_n}{dt} = h_0 - h_1(C_v)T_n - h_2(C_v)T_n,$$

$$\frac{dT_4}{dt} = h_1(C_v)T_n - \sigma_5T_4,$$

$$\frac{dT_8}{dt} = h_2(C_v)T_n - \sigma_6T_8,$$

$$\frac{dB_n}{dt} = q_0 - q_1(T_4)B_n,$$

$$\frac{dB}{dt} = q_1(T_4)B_n - \sigma_7B,$$

$$\frac{dA}{dt} = k_5B - \sigma_8A - \gamma_3AV,$$

where

$$g(V) = g_0e^{-g_1V}, \quad h_1(C_v) = \frac{h_1^0C_v}{1 + h_1^1C_v}, \quad h_2(C_v) = \frac{h_2^0C_v}{1 + h_2^1C_v}, \quad q_1(T_4) = \frac{q_1^0T_4}{1 + q_1^1T_4}.$$

From day 0

From day 6

Day 8

Vaccination model

$$\frac{dC}{dt} = k_3(C_0 - C) - k_4CV_{ac},$$

$$\frac{dC_v}{dt} = k_4CV_{ac} - \sigma_2C_v - \gamma_2T_8C_v,$$

$$\frac{dV_{ac}}{dt} = -\sigma_3V_{ac} - \gamma_3AV_{ac},$$

$$\frac{dT_n}{dt} = h_0 - h_1(C_v)T_n - h_2(C_v)T_n,$$

$$\frac{dT_4}{dt} = h_1(C_v)T_n - \sigma_5T_4,$$

$$\frac{dT_8}{dt} = h_2(C_v)T_n - \sigma_6T_8,$$

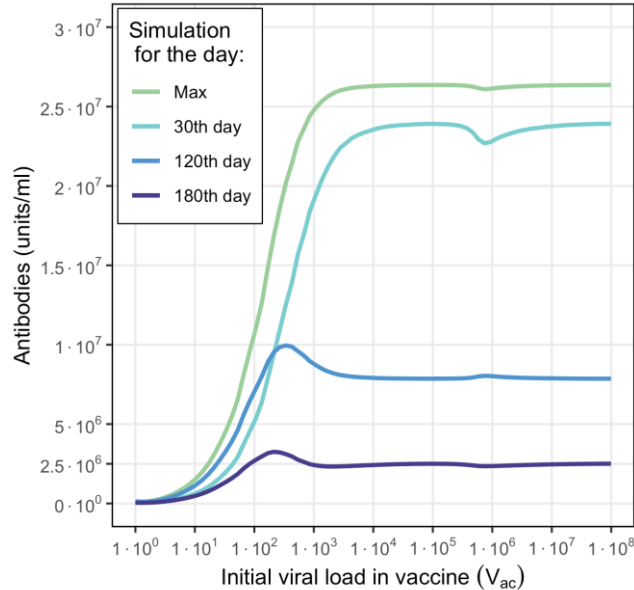
$$\frac{dB_n}{dt} = q_0 - q_1(T_4)B_n,$$

$$\frac{dB}{dt} = q_1(T_4)B_n - \sigma_7B,$$

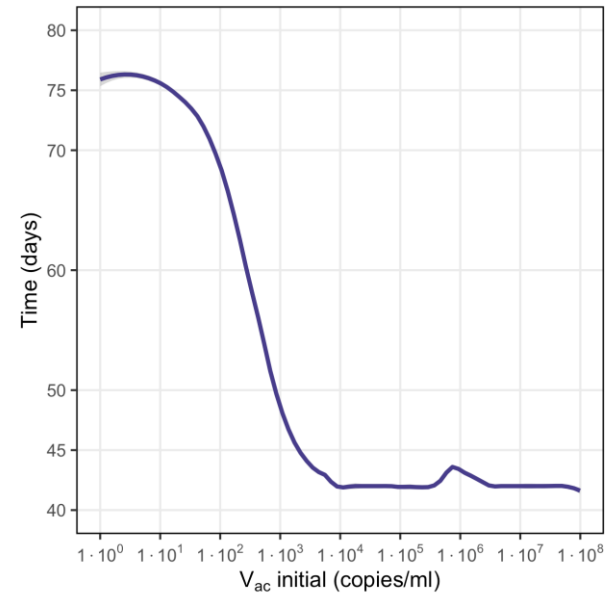
$$\frac{dA}{dt} = k_5B - \sigma_8A - \gamma_3AV_{ac},$$

Optimal dose?

Vaccine dose-response



Day of maximum antibody concentration



The highest production of antibodies is obtained for the initial viral load in vaccine equivalent to $1e5$. This phenomenon is observed mainly due to parameter $k3$.



Innate immunity shows bi-stability and threshold-like response to the initial viral load.



Above the threshold, high initial viral load shortens the incubation time and increases maximal viral load.



Antibodies play the major role in the fight against the virus (compared to CTLs).



High viral loads lead to a disproportionate increase in pro-inflammatory cytokines.

Conclusions



Wear masks!

*...and better yet,
get vaccinated!*





Our Team



V. Volpert^{1,2}
Leader of the project



A. Tokarev^{1,3}



C. Leon^{1,5,6}

- 1. Peoples' Friendship University of Russia (RUDN University)
- 2. Institut Camille Jordan, UMR 5208 CNRS, University Claude Bernard Lyon 1
- 3. N.N. Semenov Federal research center for Chemical Physics RAS
- 5. M&S decisions
- 6. РЭУ им. Плеханов



Thanks!

DO YOU HAVE ANY QUESTIONS?

