Mathematical models in immunology: weekly neutralizing antibodies, antibody dependent enhancement and reinfection

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Outline

Motivation: host-virus-immune system model

- GOAL: : mathematical, numerical and clinical study of the host-virus-immune system interaction

- BASED ON: joint paper with A. Danchin, O. Pagani, & G. Yahiaoui [7] ; further information, slides: available at https://turinici.com

- Important ingredients (cf. COVID-19 and not only):
  1. re-infection,
  2. variable antibody neutralization capacity
  3. antibody disease enhancement (ADE: pediatric cases and not only)

Outline

Full model construction

- compartmental model (cf. [13, 8, 12, 17, 6, 9, 5])
- the viral-host interaction (w/o immune response) = basic model of virus dynamics (see [18, eq (3.1) page 18], [22, eqns. (2.3)-(2.4) page 26], [16, 4, 10])

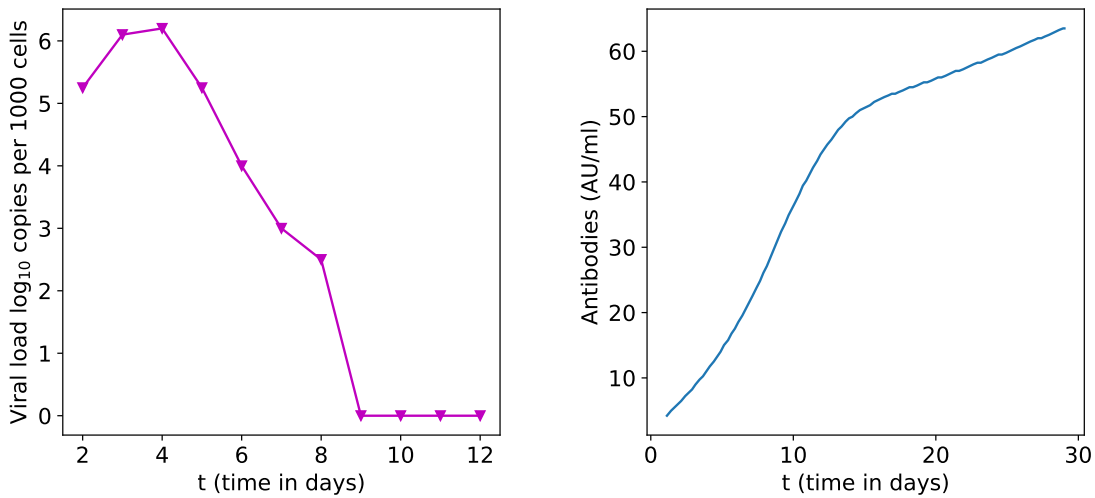

Figure: **Left:** Clinically observed typical variation of SARS-CoV-2 viral load in nasopharyngeal swab normalised using cell quantification. Data taken from [14, figure 3 page 703, patient 4]. **Right:** : Typical time variations for IgG. Data taken from [19, figure 2 page 1085]. Note that the antibody data is a mean over several days and corresponds to a different patient cohort.

Full model construction

- T : target cells, I : infected cells, V : the free virus, A : the antibodies, cf. fig 2.
- $\delta > \mu$, cf. [22, 18];
- the immune reaction starts at the threshold $V^t = \sigma/a$; alternative proposals for dA/dt possible (e.g. André and Gandon [1], Pawlek et al. [20])

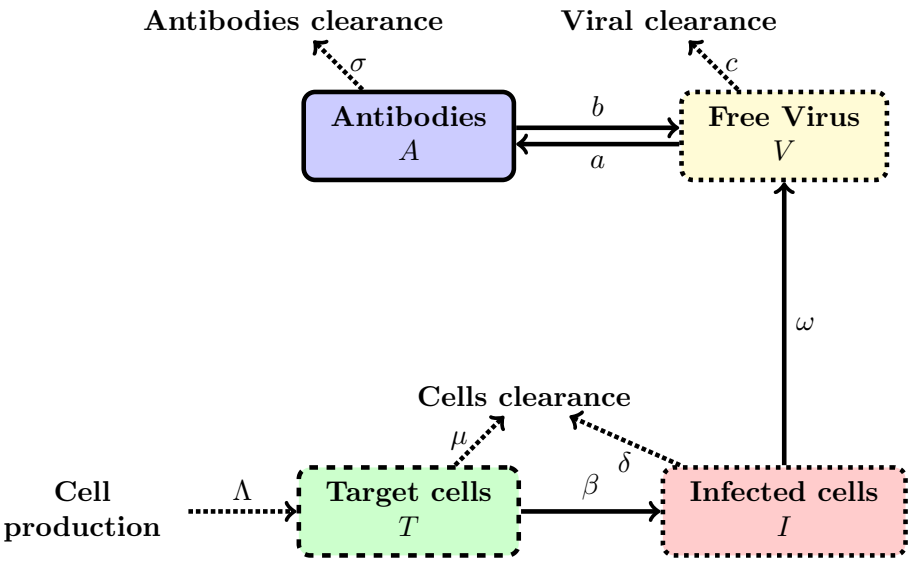

Figure: Flow in the model (1)-(5).

$$dT/dt = \Lambda - \mu T - \beta(A)VT \quad (1)$$

$$dI/dt = \beta(A)VT - \delta I \quad (2)$$

$$dV/dt = \omega I - cV - bAV \quad (3)$$

$$dA/dt = aVA - \sigma A \quad (4)$$

$$\beta(A) = \beta_0 + \beta_1 A. \quad (5)$$

Building blocks

• No infection, target cells only (see [22, 18]): $dT/dt = \Lambda - \mu T$, cv. to stable equilibrium $T^\star = \Lambda/\mu$.
• Model with virus but no immune response: basic model of virus dynamics, see [18, eq (3.1) page 18],[22, eqns. (2.3)-(2.4) page 26]

$$dT/dt = \Lambda - \mu T - \beta_0 VT, \tag{6}$$
$$dI/dt = \beta_0 VT - \delta I, \tag{7}$$
$$dV/dt = \omega I - cV. \tag{8}$$

$$\text{Initial conditions : } T(0) = T^* = \Lambda/\mu,\ I(0) = 0,\ V(0) > 0, \tag{9}$$

$$\text{Assumption 1:} \quad \delta > \mu. \tag{10}$$

$$\text{Infection only if : } R_0 = \frac{\beta_0 \omega \Lambda}{c\delta\mu} > 1. \tag{11}$$

Building blocks: equilibria

$$dT/dt = \Lambda - \mu T - \beta_0 VT, \tag{12}$$
$$dI/dt = \beta_0 VT - \delta I, \tag{13}$$
$$dV/dt = \omega I - cV. \tag{14}$$

Equilibrium no. 1: trivial equilibrium: $T = T^* = \Lambda/\mu$, $V = I = 0$.

Jacobian $\begin{pmatrix} -\mu & 0 & -\beta_0 T^* \\ 0 & -\delta & \beta_0 T^* \\ 0 & \omega & -c \end{pmatrix}$. The eigenvalues are all real but not all negative: one of them is $\lambda_1 = -\mu$ but the product of the other two is $\delta c - \omega\beta_0 T^* \leq 0$ thus at least one is positive. Therefore, under assumption (11), ($R_0 > 1$) this critical point is not a stable equilibrium.

Building blocks: equilibria

Equilibrium no. 2 : the "immunosuppression" equilibrium (15)

$$T = T^{is} = \frac{\delta c}{\beta_0 \mu},\ V = V^{is} := (R_0 - 1)\frac{\mu}{\beta_0},\ I = I^{is} := (R_0 - 1)\frac{c\mu}{\omega\beta_0}. \quad (15)$$

the characteristic polynomial of the Jacobian $P(X) = (X+\delta)(X+c)(X+\mu+\beta_0 V^{is}) - \delta c(X+\mu)$ has all roots with negative real part. Therefore the equilibrium is stable.

V^{is} = viral load in a completely immunodeficient individual. We expect V^{is} to be very high, in particular higher than the threshold $V^t = \sigma/a$ for the initiation of the immune response. This motivates

$$\text{Assumption 2:} \qquad (R_0 - 1)\frac{\mu}{\beta_0} > \frac{\sigma}{a}. \quad (16)$$

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Outline

Model: virus and immune response but no enhancement $\beta_1 = 0$

Proposition (GT et al 2022)

Under assumptions 1 et 2, the model w/o ADE ($\beta(A) = \beta_0$)

$$dT/dt = \Lambda - \mu T - \beta(A)VT \tag{17}$$
$$dI/dt = \beta(A)VT - \delta I \tag{18}$$
$$dV/dt = \omega I - cV - bAV \tag{19}$$
$$dA/dt = aVA - \sigma A \tag{20}$$

has a single stable equilibrium given by:

$$T = T^{is} := \frac{\Lambda}{\mu + \beta_0 V^t},\ I = \frac{\beta_0 \Lambda V^t}{\delta(\mu + \beta_0 V^t)},\ V = V^t,\ A = \frac{c(V^{is} - V^t)}{\beta_0 b(\mu + \beta_0 V^t)}. \tag{21}$$

Proof of the stability w/o ADE ($\beta_1 = 0$)

- In general this is very difficult (sometimes impossible) to check (highly nonlinear); very few general approaches exist to study theoretically stability w/r to parameters for a 4-dim system ... existing works by M. Li and J. Muldowney [15] based on geometric approaches like Poincare-Bendixon (non-$\exists$ of chaotic solutions), also Ballyk et al. [2], Bruono Buonomo & Deborah Lacitignola [3], etc.
- there are 3 equilibria, two of them with $A = 0$ (like in the model w/o immune system) which are unstable, as before
- only remaining equilibrium, the one in the proposition.
- Stability = eigenvalues of the Jacobian have negative real parts = $P_0(X) = det(X \cdot I - J)$ is stable
- Denote $P_0(X) = \gamma_4 X^4 + \gamma_3 X^3 + \gamma_2 X^2 + \gamma_1 X^1 + \gamma_0$
- Routh-Hurwitz criterion [21], [11, p. 1076], stability when

$$\gamma_k > 0, k = 0, 1, 2, 3, 4 \tag{22}$$

$$\gamma_1 \gamma_2 \gamma_3 > \gamma_4 \gamma_1^2 + \gamma_3^2 \gamma_0. \tag{23}$$

Proof of the stability w/o ADE ($\beta_1 = 0$)

- Idea: change of variables: $\zeta = \delta - \mu > 0$, $w = R_0 - 1 - \frac{\sigma\beta_0}{\mu a} > 0$.

Then $\gamma_0 = c\delta\mu\sigma w$, $\gamma_1 = \frac{c\sigma\left(a^2\delta\mu w + a^2\mu^2 w + a\beta_0\delta\mu w + a\beta_0\delta\mu + a\beta_0\mu\sigma w + \beta_0^2\delta\sigma\right)}{a(a\mu+\beta_0\sigma)}$,

$\gamma_2 = \frac{a^2c\mu^2 w + a^2c\mu^2 + a^2c\mu\sigma w + a^2\delta\mu^2 + a\beta_0 c\mu\sigma w + 2a\beta_0 c\mu\sigma + 2a\beta_0\delta\mu\sigma + \beta_0^2 c\sigma^2 + \beta_0^2\delta\sigma^2}{a(a\mu+\beta_0\sigma)}$,

$\gamma_3 = \frac{a^2\delta\mu + a^2\mu^2 + a\beta_0\delta\sigma + 2a\beta_0\mu\sigma + ac(a\mu(w+1)+\beta_0\sigma) + \beta_0^2\sigma^2}{a(a\mu+\beta_0\sigma)}$, $\gamma_4 = 1$.

condition (22) ($\gamma_i > 0$, $i = 0, .., 4$) = OK

condition (23) : $\gamma_1\gamma_2\gamma_3 > \gamma_4\gamma_1^2 + \gamma_3^2\gamma_0$

$$\gamma_1\gamma_2\gamma_3 - (\gamma_4\gamma_1^2 + \gamma_3^2\gamma_0) = \frac{ac}{a^3\left(a\mu + \beta_0\sigma\right)^3} Q_0(w, a, c, \beta_0, \mu, \sigma, \zeta), \quad (24)$$

$Q_0(w, a, c, \beta_0, \mu, \sigma, \zeta) = w^3a^6c^2\mu^5 + 2w^3a^6c^2\mu^4\sigma + w^3a^6c^2\mu^3\sigma\zeta + w^3a^5c^2\beta_0\mu^5 + 3w^3a^5c^2\beta_0\mu^4\sigma + w^3a^5c^2\beta_0\mu^4\zeta + ...$ (cca 170 terms !)

Negative coefficients monomials are combined with other e.g.

$w^3a^6c^2\mu^3\sigma\zeta/2 - w^2a^5c\beta_0\mu^3\sigma\zeta^2 + wa^4\beta_0^2\mu^3\sigma\zeta^3/2 = \frac{wa\mu^3\sigma\zeta}{2}(wac - \beta_0\zeta)^2 \geq 0$, etc. ..., which concludes the proof.

Full model

Proposition (GT et al. 2021)

The full model (1)-(4) *has three equilibria:*

1. *the trivial equilibrium* $T = T^* = \Lambda/\mu$, $V = I = A = 0$ *which is unstable;*
2. *the immmunosuppression equilibrium, also unstable :* $T = T^{is} = \frac{\delta c}{\beta_0 \mu}$, $V = V^{is} := (R_0 - 1)\frac{\mu}{\beta_0}$, $I = I^{is} := (R_0 - 1)\frac{c\mu}{\omega\beta_0}$.
3. *and a third equilibrium:* A^f = *unique positive solution of* $\omega\beta(A)\Lambda = \delta(c + bA)(\mu + \beta(A)V^t)$, $T^f = \frac{\delta(c+bA^f)}{\omega\beta(A^f)}$, $I^f = \frac{V(c+bA^f)}{\omega}$, $V = V^t = \frac{\sigma}{a}$. *Then :*
   1. *when* β_1 *is small enough this equilibrium is stable;*
   2. *when* β_1 *is large enough this equilibrium is stable;*
   3. *however there exist choices of parameters (in particular values of* β_1*) for which this equilibrium is unstable.*

Proof idea:

1. for β_1 small enough we are near the situation $\beta_1 = 0$ treated previously
2. we can find numerically some counter-examples for intermediate values of β_1: for $a = \sigma = c = b = \omega = 1$, $\mu = 1.e-3$, $\delta = 2$, $\Lambda = 4$, $\beta_0 = 0.0011$ and $\beta_1 = 0.01188$ all hypotheses are satisfied, equilibrium values are $T = 333.33, I = 1.83, V = 1, A = 0.83$, eigenvalues are -3.45, 0.50, 0.01 and -0.90: unstable (at least one is positive).
3. for $\beta_1 \to \infty$ (others kept fixed) we can use similar techniques as in the previous proof (cf. [7] for details).

Outline

Dynamical aspects

• The equilibrium does not yet tell the full story of the evolution of the system (1)-(4).

• possible behavior: initially A will increase in reaction to $V > V^t$; this drives both I and V to small values : stochastic effects lead to complete remission (virus clearance) $T \to \Lambda/\mu$, $A \to 0$;

• If however during the slow decay of A a challenge is presented in the form of a virus load $V > V^t$ a new infection will start and V and I will rise again.

• a distinct possibility: before reaching the stable equilibrium T goes to very low values (severe respiratory difficulties, other organ destruction) or A to high values (autoimmune presentations, organ destruction): infection wins

• numerical simulations are needed in particular situations to explore the limits of the model; the precise dynamics depends crucially on the parameters b (antibody neutralization capacity) and β_1 (ADE)

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Outline

Empirical results: initial infection

Numerical procedure to fit the model parameters to reproduce at best the viral load data in fig. 1: resulting numerical simulation in fig. 3.

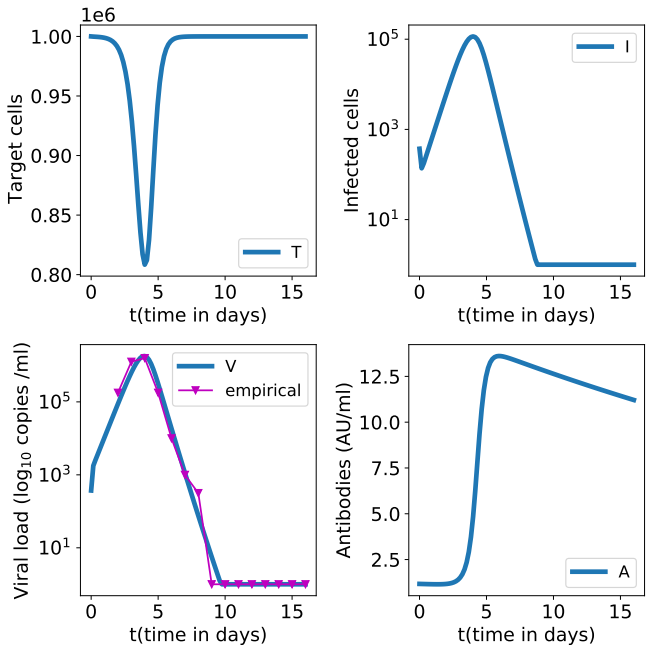


Figure: Numerical simulation of the first infection (no ADE) (1)-(4) for $\mu = 9.66$, $\Lambda = 9.66 \times 10^6$, $\omega = 59.74$, $\beta_0 = 1.28 \times 10^{-6}$, $\beta_1 = 0$, $\delta = 16.22$, $c = 1.45$, $b = 0.52$, $a = 9.15 \times 10^{-7}$, $\sigma = 0.02$, $I(O) = 372.11$, $V(0) = 994.84$, $A(0) = 1.17$.

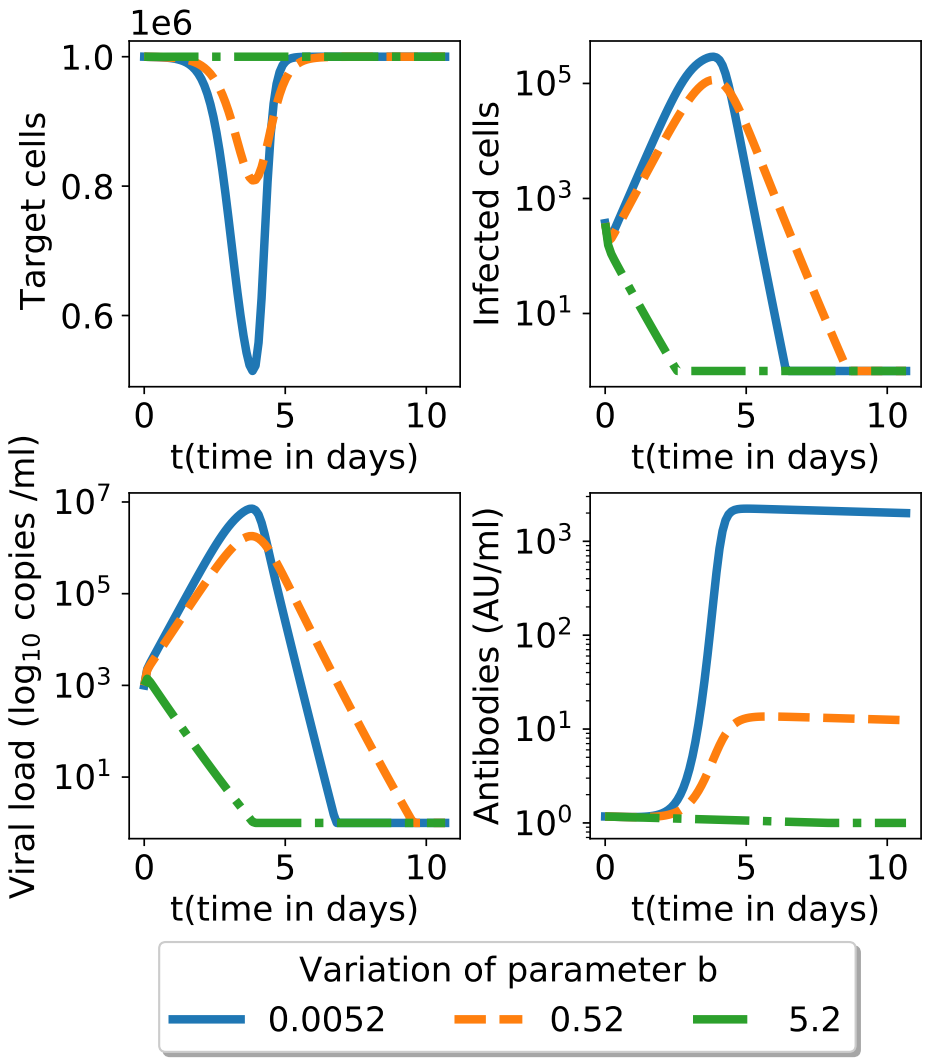
- good fit $V(t)$, not so for $A(t)$ (joint $V(t)/A(t)$ data not available).
- 20% fall of target cells; $V(t)$ peaks around 4-5 days;
- equilibrium state (21) when $\beta_1 = 0$ (no ADE present) is reached after 2 years BUT $V(t)$ and $I(t)$ reach a minimum within several weeks then increase and oscillate toward the equilibrium state (21) (simulations not shown here): in practice the equilibrium state (21) is stable but not reached, the patient is cured before.

Empirical results: secondary infection, variants, vaccination

Scenario : the immuno-kinetic parameters (b, β_1) change (e.g., a primary infection with a different variant, vaccination, or some immune evolution, aging, ...).

- **Variation of the neutralizing capacity b changed around the nominal value $b = 0.52$ (no ADE):**

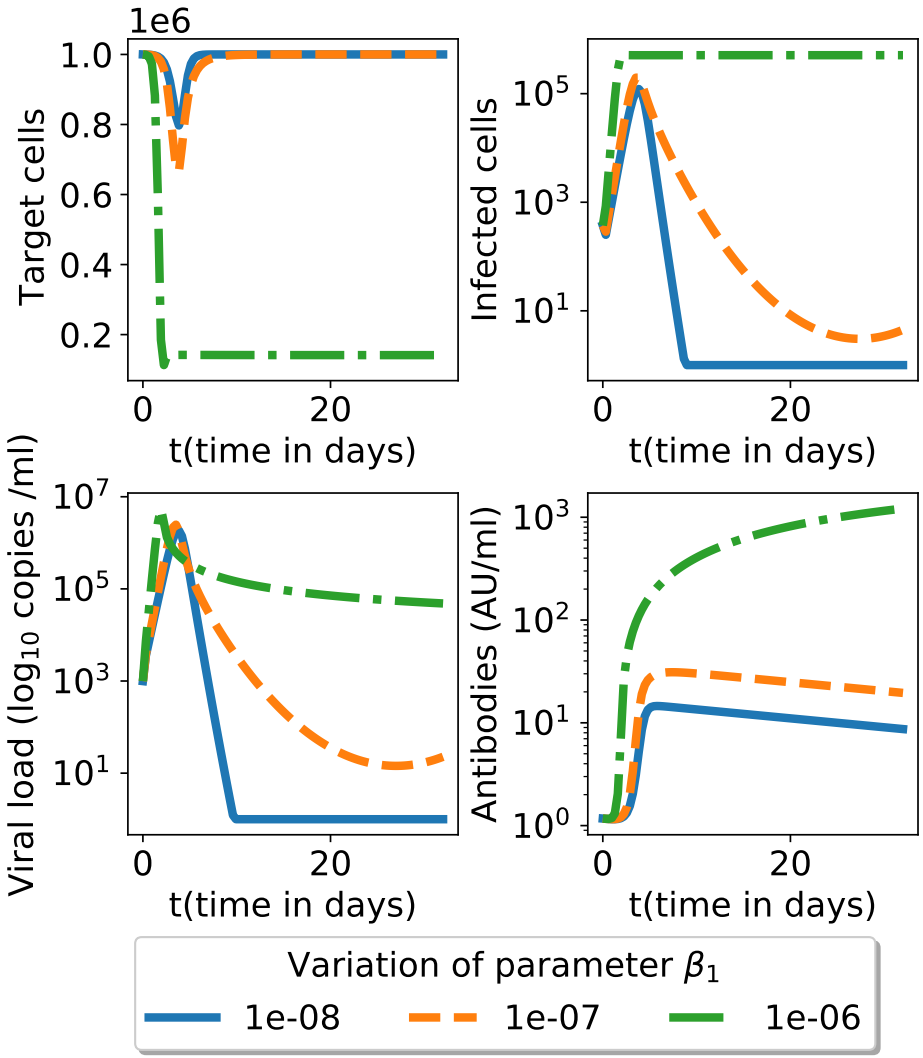
$b \downarrow$: $V \uparrow, A \uparrow$, massive T destruction, largely pejorative.



Empirical results: secondary infection, variants, vaccination

Scenario : the immuno-kinetic parameters (b, β_1) change (e.g., a primary infection with a different variant, vaccination, or some immune evolution, aging, ...).

- **Presence of ADE ($\beta_1 > 0$) : then $\beta_1 \uparrow$ lead to $T \downarrow$ (significant, possibly total !), $I \uparrow$, $V \uparrow$, $A \uparrow$ (but limited); higher β_1 cannot be compensated by more antibodies, may lead to respiratory function disruption.**



Longer time span dynamics

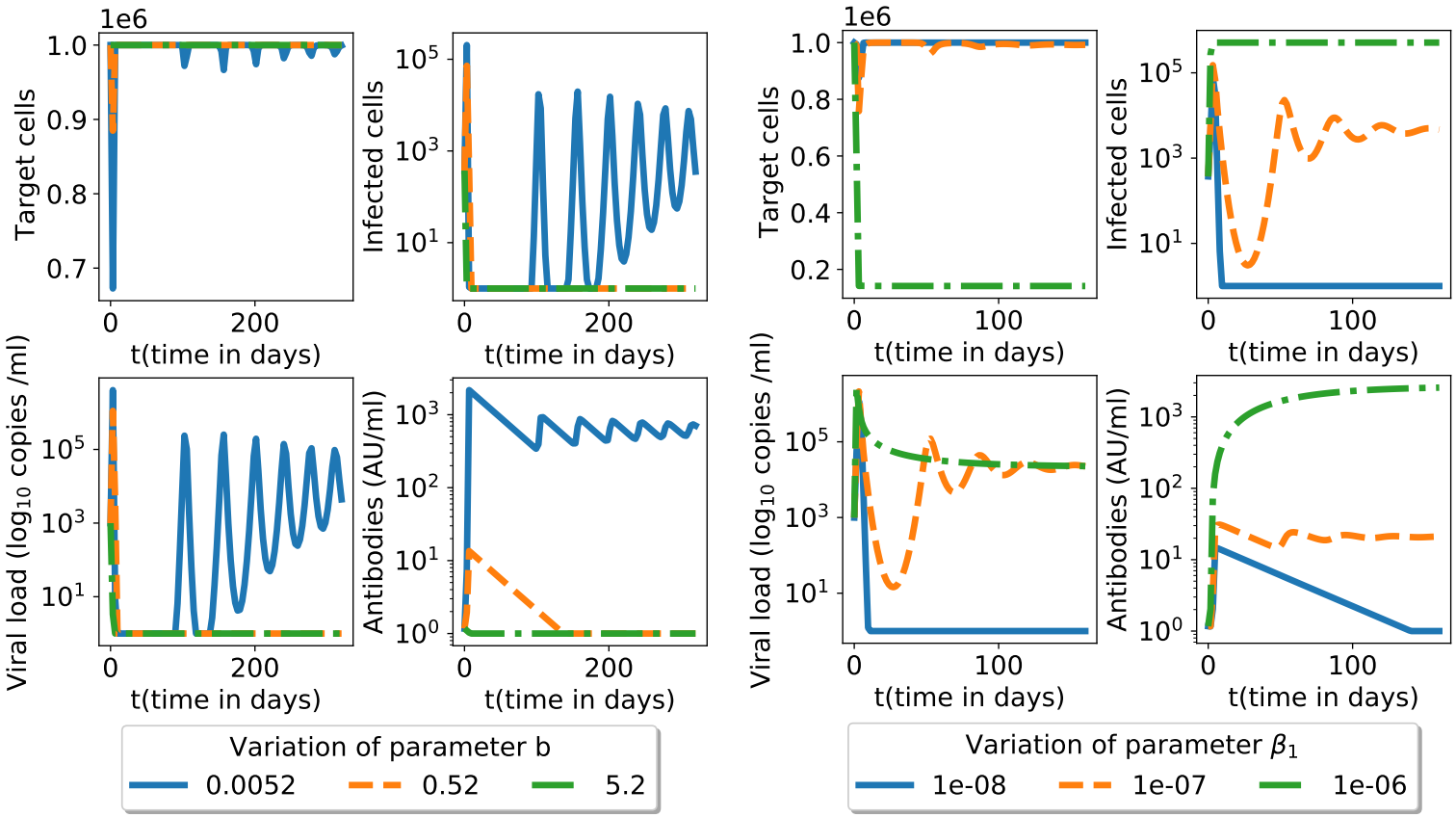


Figure: **Left:** Simulation in fig. 4 (b variation) for a longer time span. For the smallest value of b (blue line) the theoretic equilibrium is not reached in practice. **Right** Simulation in fig. 5 (β_1 variation) for a longer time span.

Outline

Conclusions and future work

Further questions:

• a technique that allows to analyze stability for a nonlinear system of 4 dimensions

• dynamical aspects are important (limits of the model)

• further work : finer description of the $A(t)$ part, add distinction between short term / long term immunity (e.g., IgM vs. IgG)

• test more real data

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