# Parameter sensitivity analysis in a stochastic birth–death model for B-cells dynamics

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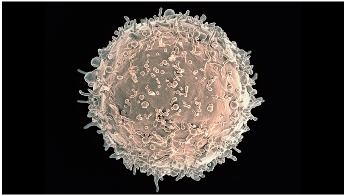
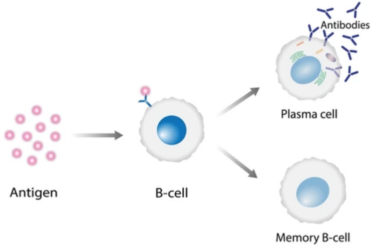
# The immune system and B cells

A network of biological systems protecting an organism from infections and external substances.

B cells (or B lymphocytes) are a type of white blood cells that play a crucial role in the adaptive immune system.

- antibody production
- antigen-presenting cells (APCs): recognition of external elements such as bacteria and viruses through surface receptors → B cell receptors (BCRs)

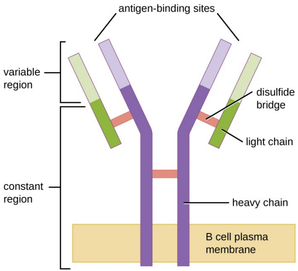




# B cell receptors

BCRs are transmembrane proteins that acquire antigens from immunological synapses and regulate B-cell activation.

- They bind antigens through the variable regions at their ends
- the binding does not always occur successfully
- the BCR–antigen complex is internalized by the B cell after the antigen has been processed by the cell
- the B cell produces new BCRs once the antigen-related process is completed




Our goal: to develop a stochastic model to analyze the behavior of BCRs over time.

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# The stochastic model

Let $M$ be the total number of BCRs that a B cell can produce. At each time $t$, we consider:

- $X(t)$: number of free receptors (active on the membrane but not bound to antigens)
- $Y(t)$: number of occupied receptors
- $M - X(t) - Y(t)$: number of "potential" receptors (currently being produced by the B cell, which will replace BCRs that complete antigen processing)

We consider a two-dimensional birth–death process

$$\chi = \{(X(t), Y(t)),\ t \geq 0\}$$

with state space

$$\mathcal{S} = \{(x, y) : x, y \in \mathbb{N}_0,\ x + y \leq M\}.$$

# Transitions of the process $\mathcal{X}$

Let $t \geq 0$ and $(x, y) \in S$. We consider the transition probability

$$p_t(x, y|\tilde{x}, \tilde{y}) := \mathrm{P}[X(t+\tau) = x, Y(t+\tau) = y \mid X(t) = \tilde{x}, Y(t) = \tilde{y}].$$

For any $t \geq 0$, the following transition rates hold:

(i) $q_t(x-1, y+1 \mid x, y) = \lambda\, u(t)\, x$
rate at which each free receptor binds an antigen

(ii) $q_t(x, y-1 \mid x, y) = \mu\, y$
rate at which an occupied receptor completes the immune response to the antigen

(iii) $q_t(x+1, y \mid x, y) = \nu \cdot (M - x - y)$
rate at which potential receptors are produced by the B cell

(iv) $q_t(\tilde{x}, \tilde{y} \mid x, y) = 0$ for all $(\tilde{x}, \tilde{y}) \in \mathcal{S} \setminus \{(x, y)\}$.

$(X, Y) \xrightarrow{\lambda u(t) X} (X-1, Y+1)$ Free BCR binds an antigen

$(X, Y) \xrightarrow{\mu Y} (X, Y-1)$ BCR completes the immune response to the antigen

$(X, Y) \xrightarrow{\nu\ (M-x-y)} (X+1, Y)$ Potential BCR is activated

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# Probability generating function for $\mathcal{X}$

**Lemma**

Let

$$G(s,z;t) = \mathrm{E}[s^x z^y] = \sum_{(x,y)\in S} s^X z^Y p(x,y;t)$$

Then, $G(s,z;t)$ satisfies the partial differential equation (PDE)

$$\begin{aligned}\frac{\partial}{\partial t}G(s,z;t) = &-\nu M(1-s)G(s,z;t) + [\lambda u(t)(z-s) + \nu s(1-s)]\frac{\partial}{\partial s}G(s,z;t) \\ &+ [\nu z(1-s) + \mu(1-z)]\frac{\partial}{\partial z}G(s,z;t),\end{aligned} \tag{1}$$

with initial condition

$$G(s,z;0) = s^{x_0} z^{y_0}, \qquad x_0, y_0 > 0.$$

# First-order moments

Assume that $u(t) = u > 0.$, and define

$$\Lambda := \lambda u, \qquad \Delta := (\nu + \mu + \Lambda)^2 - 4\mu\nu \in \mathbb{R}, \qquad \alpha := \Lambda(\nu + \mu) + \mu\nu > 0.$$

## Theorem

Let $\mathcal{X} = \{(X(t), Y(t)),\ t \geq 0\}$. Then:

- If $\Delta > 0$, that is $\Lambda < (\sqrt{\nu} - \sqrt{\mu})^2 \cup \Lambda > (\sqrt{\nu} + \sqrt{\mu})^2$,

$$\begin{aligned} \mathrm{E}[X(t)] &= \frac{\mu\nu M}{\alpha} - \frac{1}{2\Lambda}[c_1 e^{-\frac{t}{2}(\nu+\mu+\Lambda+\sqrt{\Delta})}(\nu - \mu + \Lambda + \sqrt{\Delta}) \\ &\quad + c_2 e^{-\frac{t}{2}(\nu+\mu+\Lambda-\sqrt{\Delta})}(\nu - \mu + \Lambda - \sqrt{\Delta})] \\ \mathrm{E}[Y(t)] &= \frac{\Lambda\nu M}{\alpha} + c_1 e^{-\frac{t}{2}(\nu+\mu+\Lambda+\sqrt{\Delta})} + c_2 e^{-\frac{t}{2}(\nu+\mu+\Lambda-\sqrt{\Delta})}, \end{aligned}$$

$$\text{where} \quad \begin{cases} c_1 = \dfrac{y_0}{2} - \dfrac{2\Lambda x_0 + (\Lambda + \nu - \mu)y_0}{2\sqrt{\Delta}} - \dfrac{\Lambda\nu M}{2\alpha}\left(1 - \dfrac{\Lambda + \nu + \mu}{\sqrt{\Delta}}\right), \\[2ex] c_2 = \dfrac{y_0}{2} + \dfrac{2\Lambda x_0 + (\Lambda + \nu - \mu)y_0}{2\sqrt{\Delta}} - \dfrac{\Lambda\nu M}{2\alpha}\left(1 + \dfrac{\Lambda + \nu + \mu}{\sqrt{\Delta}}\right). \end{cases}$$

- If $\Delta = 0$, that is $\Lambda = (\sqrt{\nu} \pm \sqrt{\mu})^2$:

$$\mathrm{E}[X(t)] = \frac{\mu\nu M}{(\nu+\mu \pm \sqrt{\nu\mu})^2} + \frac{e^{-t(\nu+\mu\pm\sqrt{\nu\mu})}}{\nu+\mu\pm 2\sqrt{\mu\nu}}[d_2 \mp (d_1 + d_2 t)(\sqrt{\mu\nu} \pm \nu)]$$

$$\mathrm{E}[Y(t)] = \frac{(\nu+\mu\pm 2\sqrt{\mu\nu})\nu M}{(\nu+\mu\pm\sqrt{\nu\mu})^2} + e^{-t(\nu+\mu\pm\sqrt{\nu\mu})}(d_1 + d_2 t),$$

$$\text{where} \quad \begin{cases} d_1 = y_0 - \dfrac{(\nu+\mu\pm 2\sqrt{\mu\nu})\nu M}{(\nu+\mu\pm\sqrt{\nu\mu})^2} \\ d_2 = (\nu+\mu\pm 2\sqrt{\mu\nu})x_0 + (\nu\pm\sqrt{\mu\nu})y_0 - \frac{(\nu+\mu\pm 2\sqrt{\mu\nu})\nu M}{(\nu+\mu\pm\sqrt{\nu\mu})^2}, \end{cases}$$

- if $\Delta < 0$, that is $(\sqrt{\nu} - \sqrt{\mu})^2 < \Lambda < (\sqrt{\nu} + \sqrt{\mu})^2$:

$$\mathrm{E}[X(t)] = \frac{\mu\nu M}{\alpha} + \frac{e^{-\frac{t}{2}(\nu+\mu+\Lambda)}}{2\Lambda u}\Big\{[f_2\sqrt{|\Delta|} - (\nu+\mu+\Lambda)f_1]\cos\left(\frac{\sqrt{|\Delta|}t}{2}\right)$$

$$- [f_1\sqrt{|\Delta|} + (\nu-\mu+\Lambda)f_2]\sin\left(\frac{\sqrt{|\Delta|}t}{2}\right)\Big\}$$

$$\mathrm{E}[Y(t)] = \frac{\Lambda\nu M}{\alpha} + e^{-\frac{t}{2}(\nu+\mu+\Lambda)}\left[f_1\cos\left(\frac{\sqrt{|\Delta|}t}{2}\right) + f_2\sin\left(\frac{\sqrt{|\Delta|}t}{2}\right)\right],$$

$$\text{where} \quad \begin{cases} f_1 = y_0 - \dfrac{\Lambda\nu M}{\alpha} \\ f_2 = \dfrac{1}{\sqrt{|\Delta|}}\left[2\Lambda x_0 + (\nu-\mu+\Lambda)y_0 - \dfrac{\Lambda\nu M(\nu+\mu+\Lambda)}{\alpha}\right]. \end{cases}$$

## Outline of the proof

Recalling the relations

$$\mathrm{E}[X(t)] = \sum_{(x,y)\in S} x\, p(x,y;t) = \frac{\partial}{\partial s} G(s,z;t)\Big|_{s=z=1}, \quad \mathrm{E}[Y(t)] = \sum_{(x,y)\in S} y\, p(x,y;t) = \frac{\partial}{\partial z} G(s,z;t)\Big|_{s=z=1},$$

by differentiating the PDE (1) with respect to $s$ and $z$ one obtains the system of ODEs

$$\begin{cases} \dfrac{d}{dt}\mathrm{E}[X(t)] = -(\nu+\Lambda)\mathrm{E}[X(t)] - \nu\mathrm{E}[Y(t)] + \nu M \\[2mm] \dfrac{d}{dt}\mathrm{E}[Y(t)] = \Lambda\mathrm{E}[X(t)] - \mu\mathrm{E}[Y(t)]. \end{cases}$$

Through simple calculations one obtains the non-homogeneous second-order ODE

$$\frac{d^2}{dt^2}\mathrm{E}[Y(t)] = -(\nu+\mu+\Lambda)\frac{d}{dt}\mathrm{E}[Y(t)] - \alpha\mathrm{E}[Y(t)] + \Lambda\nu M,$$

$$\text{with initial conditions} \quad \begin{cases} \mathrm{E}[X(0)] = x_0 \\ \mathrm{E}[Y(0)] = y_0, \end{cases} \qquad x_0, y_0 > 0.$$

The solution of the homogeneous ODE depends on the sign of the discriminant of the characteristic polynomial ($\Delta$). By summing the solutions and recalling that

$$\mathrm{E}[X(t)] = \frac{1}{\Lambda}\left[\frac{d}{dt}\mathrm{E}[Y(t)] + \mu\mathrm{E}[Y(t)]\right],$$

the final expressions are obtained.

# Some properties of the moments

| | $\Delta > 0$ | $\Delta = 0$ | $\Delta < 0$ |
|---|---|---|---|
| $\lim_{t\to\infty} E[X(t)]$ | $\dfrac{\mu\nu M}{\alpha}$ | $\dfrac{\mu\nu M}{(\nu+\mu\pm\sqrt{\mu\nu})^2}$ | $\dfrac{\mu\nu M}{\alpha}$ |
| $\lim_{t\to\infty} E[Y(t)]$ | $\dfrac{\Lambda\nu M}{\alpha}$ | $\dfrac{(\sqrt{\nu}-\sqrt{\mu})^2\nu M}{(\nu+\mu\pm\sqrt{\mu\nu})^2}$ | $\dfrac{\Lambda\nu M}{\alpha}$ |

Values of $\lim_{t\to\infty} E[X(t)]$ and $\lim_{t\to\infty} E[Y(t)]$ for different choices of $\Delta$.

**Remark:**

$$\lim_{\Lambda\to 0} \mathrm{E}[X(t)] = (1-e^{-\nu t})M + x_0 e^{-\nu t} - \frac{y_0\nu}{\nu-\mu}(e^{-\mu t}-e^{-\nu t}),$$

$$\lim_{\Lambda\to 0} \mathrm{E}[Y(t)] = y_0 e^{-\mu t}.$$

# Second-order moments

## Theorem

Given the process $\mathcal{X}$, with $\Delta > 0$, its second-order moments are:

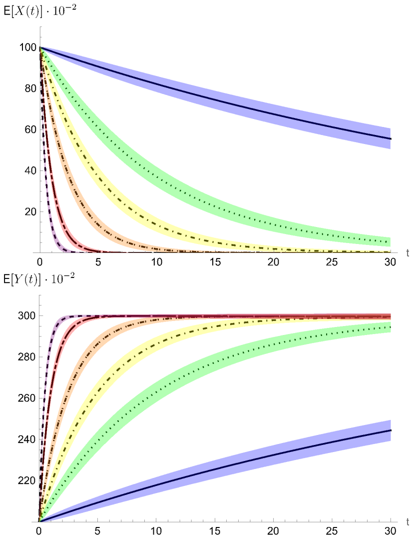
$$\begin{aligned}
\mathrm{E}[X^2(t)] &= \frac{\Lambda(\mu+\nu)+(2M-1)\mu\nu}{\alpha}\,\mathrm{E}[X(t)] - M(M-1)\left(\frac{\mu\nu}{\alpha}\right)^2 \\
&\quad + g_1 e^{-t(\nu+\mu+\Lambda+\sqrt{\Delta})} + g_2 e^{-t(\nu+\mu+\Lambda)} + g_3 e^{-t(\nu+\mu+\Lambda-\sqrt{\Delta})} \\
\mathrm{E}[Y^2(t)] &= \frac{\Lambda(\mu+M\nu)+\mu\nu}{\alpha}\,\mathrm{E}[Y(t)] - M(M-1)\left(\frac{\Lambda\nu}{\alpha}\right)^2 \\
&\quad + \frac{1}{2\nu^2}\Big\{2\Lambda\nu g_2 e^{-t(\nu+\mu+\Lambda)} \\
&\quad + [(\nu-\mu+\Lambda)(\nu-\mu+\Lambda-\sqrt{\Delta})-2\Lambda\nu]g_1 e^{-t(\nu+\mu+\Lambda+\sqrt{\Delta})} \\
&\quad + [(\nu-\mu+\Lambda)(\nu-\mu+\Lambda+\sqrt{\Delta})-2\Lambda\nu]g_3 e^{-t(\nu+\mu+\Lambda-\sqrt{\Delta})}\Big\} \\
\mathrm{E}[X(t)Y(t)] &= \frac{\nu(M-1)}{\alpha}\{\Lambda\mathrm{E}[X(t)]+\mu\mathrm{E}[Y(t)]\} - M(M-1)\Lambda\mu\left(\frac{\nu}{\alpha}\right)^2 \\
&\quad - \frac{1}{2\nu}\Big\{(\nu-\mu+\Lambda-\sqrt{\Delta})g_1 e^{-t(\nu+\mu+\Lambda+\sqrt{\Delta})} + (\nu-\mu+\Lambda)g_2 e^{-t(\nu+\mu+\Lambda)} \\
&\quad + (\nu-\mu+\Lambda+\sqrt{\Delta})g_3 e^{-t(\nu+\mu+\Lambda-\sqrt{\Delta})}\Big\},
\end{aligned}$$

where the constants $g_1, g_2$ and $g_3$ are the solutions of a system obtained from the initial conditions.

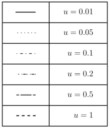
# Use of the model in a immunological context

Aim: observe the behavior of the moments of $\mathcal{X}$ by choosing the parameters in a way that is consistent with the functioning of B cells.

- The number of BCRs on the membrane of a B cell can reach up to 120000 $\rightarrow$ we fix $x_0 = 10000$, $y_0 = 20000$ and $M = x_0 + (1+\phi)y_0 = x_0 + \theta y_0$, with $\theta = 1.8$.
- We estimate the average time needed by a B cell to process an antigen to be 2 hours (7200 seconds) $\rightarrow \mu = 1.38 \cdot 10^{-4}\, s^{-1}$. Similarly, we estimate that the average time required by the cell to produce a new BCR is 1.5 hours (5400 seconds) $\rightarrow$ $\nu = 1.85 \cdot 10^{-4}\, s^{-1}$.
- The time required to complete the binding between an antigen and a receptor is a few seconds $\rightarrow \lambda = 2\, s^{-1}$.
- We perform different choices of $u$ according to the strength of the viral load.




| $u$ | $\lim_{t\to\infty} \mathrm{E}[X(t)]$ | $\lim_{t\to\infty} \mathrm{E}[Y(t)]$ |
|---|---|---|
| 0.01 | 181.08 | 26243.04 |
| 0.05 | 36.33 | 26325.94 |
| 0.1 | 18.17 | 26336.34 |
| 0.2 | 9.09 | 26341.54 |
| 0.5 | 3.64 | 26344.67 |
| 1 | 1.82 | 26345.71 |



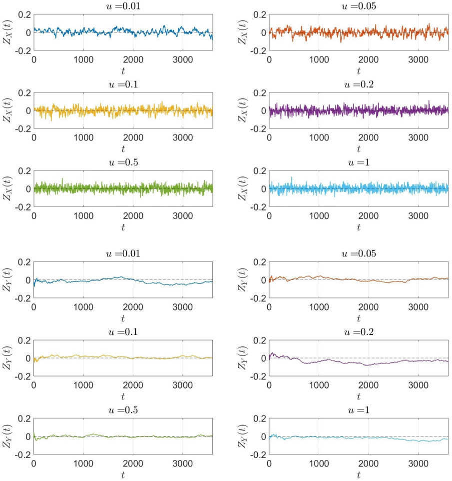

Plots of $\mathrm{E}[X(t)] \pm \mathrm{sd}(X(t))$ and $\mathrm{E}[Y(t)] \pm \mathrm{sd}(Y(t))$, on a $10^{-2}$ scale, for $t \in [0, 30]$.

# Analytic model vs. stochastic simulations

- We verify the accuracy of $\mathsf{E}[X(t)]$ and $\mathsf{E}[Y(t)]$ by comparing them with simulated sample-paths of $\mathcal{X}(t)$ and $Y(t)$ $\rightarrow$ Stochastic Simulation Algorithm (SSA)
- the standardized residuals for $X(t)$ and $Y(t)$, i.e.

$$Z_\Sigma(t) := \frac{\mathsf{E}[\Sigma(t)] - \widehat{\mu}_\Sigma(t)}{\widehat{\sigma}_\Sigma(t)},$$

for $\Sigma \in \{X, Y\}$, allow us to better visualize the (small) differences between the realizations.



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# Sensitivity analysis

- We want to analyze how the expected values found for $X(t)$ and $Y(t)$ respond to variations in the parameters
- the study is divided into two parts:
  - analyzing the variation of the parameters over a specific domain $\rightarrow$ Variance-based sensitivity analysis
  - evaluating the impact of small perturbations of one of the parameters around a fixed point $\rightarrow$ Elasticity analysis

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## Variance-based sensitivity analysis (VBSA)

**VBSA**: global sensitivity analysis technique that quantifies the effect on the variance that can be attributed to each input parameter, as well as to their interactions with the other parameters $\rightarrow$ the Sobol' indices are evaluated for each varying parameter $(\Lambda, \mu, \nu)$ of $\mathrm{E}[X(t)]$ and $\mathrm{E}[Y(t)]$.

# Sobol' indices and variance decomposition

Given any model $\boldsymbol{Y}$, it can be seen as a function of its inputs, namely

$$\boldsymbol{Y} = f(\boldsymbol{\eta}) = f(\eta_1, \eta_2, \dots, \eta_n).$$

Then it can be decomposed as

$$\boldsymbol{Y} = f_0 + \sum_{i=1}^{n} f_i(\eta_i) + \sum_{i<j}^{n} f_{ij}(\eta_i, \eta_j) + \cdots + f_{1,2,\dots,n}(\eta_1, \eta_2, \dots, \eta_n),$$

with

$$f_0 = \mathrm{E}(\boldsymbol{Y}), \qquad f_i(\eta_i) = \mathrm{E}(\boldsymbol{Y} \mid \eta_i) - f_0,$$
$$f_{ij}(\eta_i, \eta_j) = \mathrm{E}(\boldsymbol{Y} \mid \eta_i, \eta_j) - f_0 - f_i(\eta_i) - f_j(\eta_j) \qquad \text{etc.}$$

Then the variance can be written as

$$\mathrm{Var}(\boldsymbol{Y}) = \sum_{i=1}^{n} V_i + \sum_{i<j}^{n} V_{ij} + \cdots + V_{12\dots n},$$

where

$$V_i = \mathrm{Var}_{\eta_i}\left(\mathrm{E}_{\boldsymbol{\eta}_{\sim i}}(\boldsymbol{Y} \mid \eta_i)\right), \qquad V_{ij} = \mathrm{Var}_{\eta_{ij}}\left(\mathrm{E}_{\boldsymbol{\eta}_{\sim ij}}(\boldsymbol{Y} \mid \eta_i, \eta_j)\right) - V_i - V_j \quad \text{etc.}$$

**Note**: $\boldsymbol{\eta}_{\sim i}$ denotes the vector of parameters obtained from $\boldsymbol{\eta}$ by excluding $\eta_i$.

## Definition

Let $f(\boldsymbol{\eta})$ be a function depending on a given set of independent and possibly varying parameters $\boldsymbol{\eta} = (\eta_1, \dots \eta_n)$. Then, the first-order Sobol' indices $S_i$ (first-order) and total-effect indices $S_{T_i}$ (total-effect) with respect to any parameter $\eta_i$, for $i = 1, \dots, n$, are given by

$$S_i = \frac{\mathrm{Var}_{\eta_i}(\mathsf{E}[f \mid \eta_i])}{\mathrm{Var} f},$$

$$S_{T_i} = \frac{\mathsf{E}_{\boldsymbol{\eta}_{\sim i}}(\mathsf{Var}_{\eta_i}(f \mid \boldsymbol{\eta}_{\sim i}))}{\mathsf{Var}\, f} = 1 - \frac{\mathrm{Var}_{\eta_{\sim i}}(\mathsf{E}[f \mid \eta_{\sim i}])}{\mathsf{Var} f},$$

where $\mathsf{Var}\, f$ is the variance of the function that takes into account the uncertainty of the entire parameter vector $\boldsymbol{\eta}$.

**Note**: given $\mathcal{T} = \{\tau_1, \dots, \tau_m\}$,, for each $t \in \mathcal{T}$ we will evaluate $S_i = S_i(t)$ and $S_{T_i} = S_{T_i}(t)$, $i = 1, \dots, n$. We also recall that

$$0 \leq S_i^{\Sigma}(t) \leq S_{T_i}^{\Sigma}(t) \leq 1, \qquad t \in \mathcal{T}, \quad i = 1, \dots, n, \quad \Sigma \in \{X, Y\}.$$

# Estimation of Sobol' indices

- our model has $n = 6$ parameters, namely $\boldsymbol{\eta} = (\mu, \nu, \Lambda, x_0, y_0, M)$
- To simulate the samples, Saltelli sampling is used instead of Monte Carlo simulations.

## Saltelli sampling

⋆ A $N \times 2n$ matrix of random numbers is generated in the chosen intervals (see table), with $N$ sufficiently large

⋆ It is divided into two $N \times n$ matrices $\rightarrow A, B$

⋆ For $i = 1, \dots, n$, a matrix $C_i$ is obtained by taking all columns of $B$ except the $i$-th one, taken from $A$

⋆ The $N \times 1$ vectors are obtained

$$y_A = \Sigma(A), \qquad y_B = \Sigma(B), \qquad y_{C_i} = \Sigma(C_i),$$

with $\Sigma \in \{X, Y\}$.

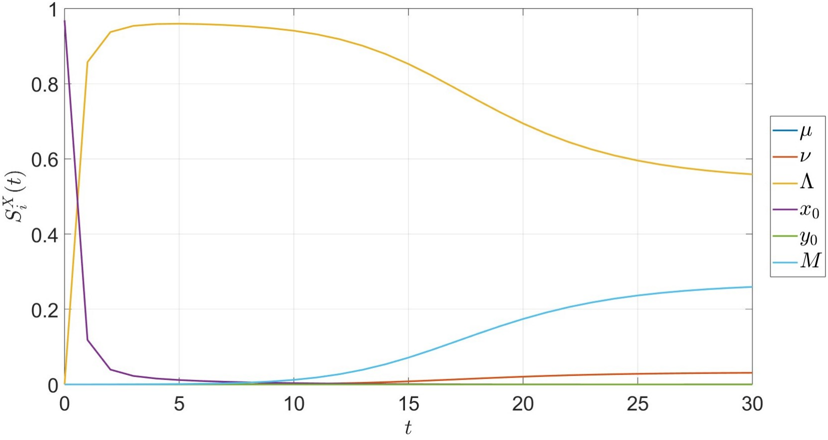
| | | |
|---|---|---|
| $\mu$ | $\eta_1$ | $[10^{-3};\ 2\cdot 10^{-3}]$ |
| $\nu$ | $\eta_2$ | $[10^{-3};\ 2\cdot 10^{-3}]$ |
| $\Lambda$ | $\eta_3$ | $[0.02;\ 2]$ |
| $x_0$ | $\eta_4$ | $[5000;\ 10000]$ |
| $y_0$ | $\eta_5$ | $[15000;\ 20000]$ |
| $M$ | $\eta_6$ | $[41000;\ 46000]$ |

Ranges of variation of the parameters involved in the model

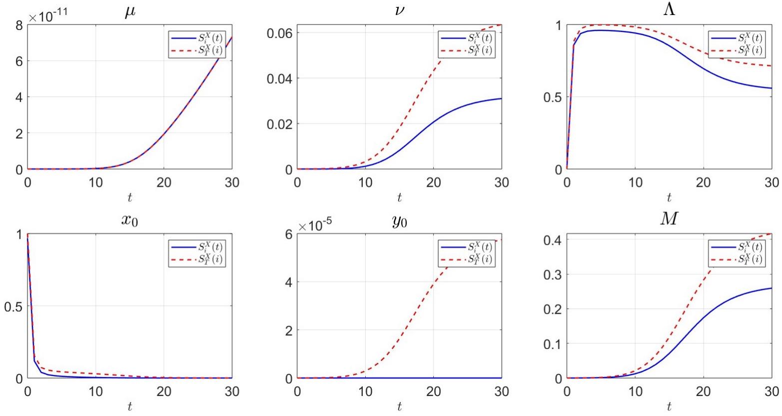
The estimators of the first-order and total-effect indices are

$$\widehat{S}_i := \frac{(1/N)\sum_{j=1}^{N} y_A^{(j)} y_{C_i}^{(j)} - \Sigma_0^2}{(1/N)\sum_{j=1}^{N} (y_A^{(j)})^2 - \Sigma_0^2}, \qquad \widehat{S}_{T_i} := \frac{(1/N)\sum_{j=1}^{N} y_B^{(j)} y_{C_i}^{(j)} - \Sigma_0^2}{(1/N)\sum_{j=1}^{N} (y_A^{(j)})^2 - \Sigma_0^2},$$

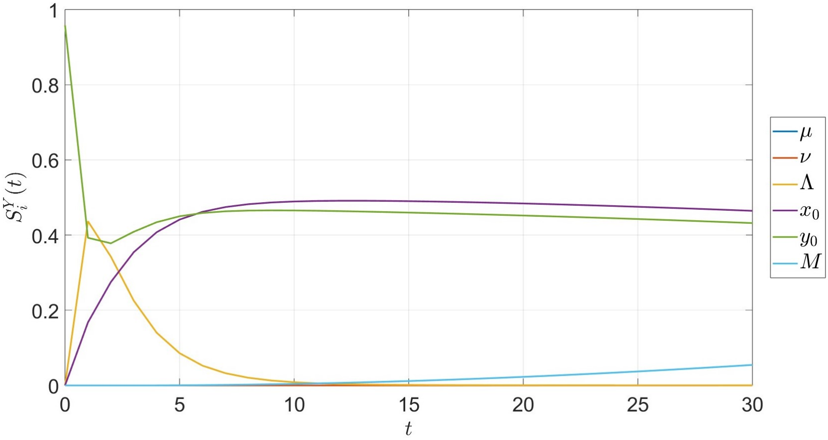
where $\Sigma_0^2 := \left(\frac{1}{N}\sum_{j=1}^{N} y_A^{(j)}\right)^2.$



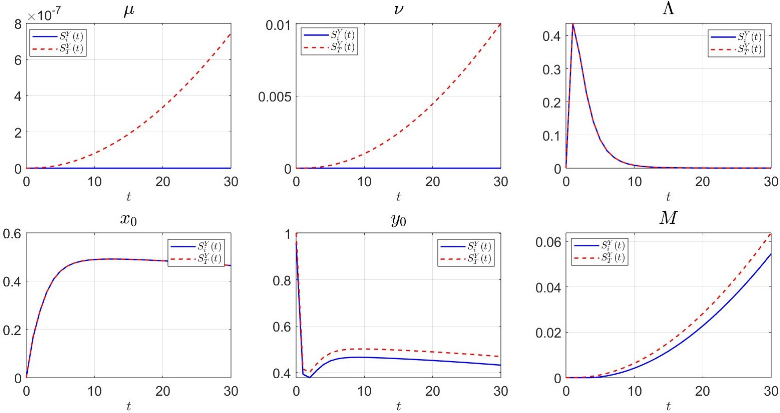

Plots of the first-order sensitivity indices $S_i^X(t)$, for $t \in [0, 30]$, $i \in \{1, \ldots, 6\}$, evaluated with respect to the parameters $\mu, \nu, \lambda, x_0, y_0$ and $M$.




Plots of the first-order sensitivity indices $S_i^X(t)$ and total-effect indices $S_{T_i}^X(t)$, for $t \in [0, 30]$, $i \in \{1, \ldots, 6\}$, for each parameter $\mu, \nu, \lambda, x_0, y_0$ and $M$.




Plots of the first-order sensitivity indices $S_i^Y(t)$, for $t \in [0, 30]$, $i \in \{1, \dots, 6\}$, evaluated with respect to the parameters $\mu, \nu, \lambda, x_0, y_0$ and $M$.




Plots of the first-order sensitivity indices $S_i^X(t)$ and total-effect indices $S_{T_i}^X(t)$, for $t \in [0, 30]$, $i \in \{1, \dots, 6\}$, for each parameter $\mu, \nu, \lambda, x_0, y_0$ and $M$.

# Analysis of elasticity functions

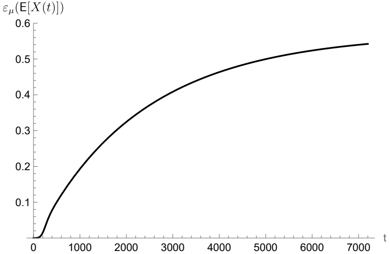
## Elasticity analysis

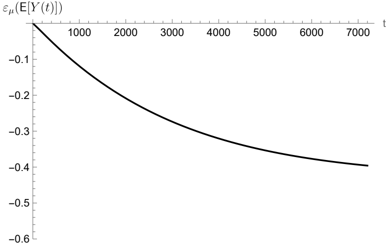
local sensitivity analysis technique, focused on local relative variations of the first-order moments, in response to small perturbations of each parameter $\rightarrow$ the derivatives of $\mathrm{E}[X(t)]$ and $\mathrm{E}[Y(t)]$ with respect to the parameters are used to obtain the pointwise elasticity functions

## Definition

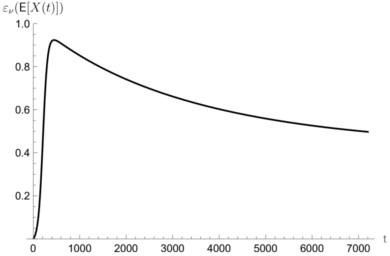
Let $f(\eta) = f(\eta_1, \ldots, \eta_n)$ be a function differentiable with respect to $\eta_j$, with $j = 1, \ldots, n$, and such that $f(\boldsymbol{\eta}) \neq 0$. The elasticity function of $f$ with respect to $\eta_j$ is defined as

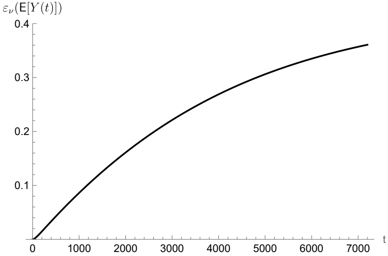
$$\varepsilon_{\eta_j} f := \frac{\text{Percentage variation of } f}{\text{Percentage variation of } \eta_j} = \frac{\partial f(\mathbf{x})}{\partial \eta_j} \cdot \frac{\eta_j}{f(\mathbf{x})}.$$



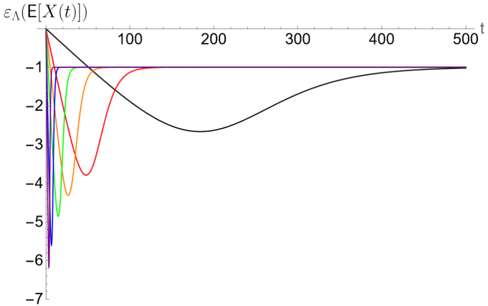



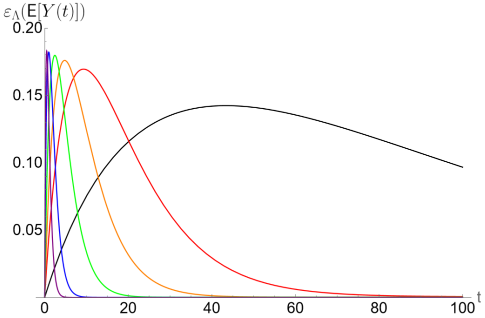

$$\lim_{t\to\infty} \varepsilon_\mu \mathsf{E}[X(t)] = \frac{\Lambda\nu}{\Lambda(\mu+\nu)+\mu\nu}, \qquad \lim_{t\to\infty} \varepsilon_\mu \mathsf{E}[Y(t)] = \frac{-\mu(\Lambda+\nu)}{\Lambda(\mu+\nu)+\mu\nu}$$




$$\lim_{t\to\infty} \varepsilon_\nu \mathsf{E}[X(t)] = \frac{\Lambda\mu}{\Lambda(\mu+\nu)+\mu\nu}, \qquad \lim_{t\to\infty} \varepsilon_\nu \mathsf{E}[Y(t)] = \frac{\Lambda\mu}{\Lambda(\mu+\nu)+\mu\nu}$$




$$\lim_{t \to \infty} \varepsilon_\Lambda \mathsf{E}[X(t)] = -\frac{\Lambda(\mu+\nu)}{\Lambda(\mu+\nu)+\mu\nu}$$

| | $u$ |
|---|---|
| ——— (black) | 0.01 |
| ——— (red) | 0.05 |
| ——— (orange) | 0.1 |
| ——— (green) | 0.2 |
| ——— (blue) | 0.5 |
| ——— (purple) | 1 |

$$\lim_{t \to \infty} \varepsilon_\Lambda \mathsf{E}[Y(t)] = \frac{\mu\nu}{\Lambda(\mu+\nu)+\mu\nu}$$

1 Introduction

2 The stochastic model

3 Theoretical results

4 Sensitivity analysis

5 Conclusions

What we have done:

- We obtained a closed-form expression for the model describing the dynamics of BCRs
- We used the model in an immunological context $\rightarrow$ coherent reproduction of the real behavior of B cells when interacting with external antigens
- The sensitivity analysis showed that the model is mainly influenced by the time required for BCRs to correctly bind to antigens

What we can do:

- Extend the model to include more detailed cases during antigen processing (e.g., interruption of the antigen–BCR binding)

- Investigate the effects of defining $u(t)$ as a known function

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Thank you for your attention!