# Kinetic modelling of autoimmune diseases

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**Recent advances in kinetic equations and applications**

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# Structure of the talk

1. **Introduction**
   Motivation & biological considerations
   Autoimmune diseases
2. **The model for autoimmunity**
   Cellular interactions
   Kinetic equations
   Macroscopic equations
3. **Qualitative analysis**
   Existence and uniqueness result
   Positivity and asymptotic behaviour of the solution
4. **Numerical tests**
   Results & biological interpretation

# Motivation

**Normally**, the immune system

- **identifies** the difference between foreign cells and our own cells;
- **protects against** germs, like bacteria and viruses;
- **recognizes foreign invaders** and sends out cells to attack them.

An **autoimmune disease** is a condition in which our immune system wrongly attacks our own cells.

In many cases, it is **chronic**, and patients alternate
periods of **relapse** having **suffering** symptoms, with
periods of **remittance** in which symptoms are **absent**.

# Our objective

To construct a mathematical model of **kinetic type** in order to describe the **immune system interactions** in the context of **autoimmune disease**.

# State of the art

**It is well known** that the immune system can be regarded, at the cellular level, as a system constituted by a large number of cells, belonging to **several interacting populations**.

**Cellular interactions** can modify the behaviour or **activity** of cells and can also modify the **size** of populations.

**The behaviour** can be modelled within a **kinetic theory** approach in terms of the statistical distribution of all states possessed by each cell population.

# State of the art

After the pioneering work

Jager & Segel (1992), for population of social organisms,

**Kinetic modelling approaches** have been used to describe **tumor-immune system interactions** and **immune competition**

Bellomo & Forni (1994)
Arlotti & Bellomo (1995)
Arlotti & Lachowicz & Latrach (1996)
Arlotti & Bellomo & Latrach (1999)
Delitala (2002)
Kolev (2003, 2005)
Kolev & Nikolova (2007)
Angelis & Lods (2008)
Bellouquid & Angelis (2011)
Conte & Groppi & Spiga (2018)

# Cell populations

We consider three interacting populations in the autoimmune competition

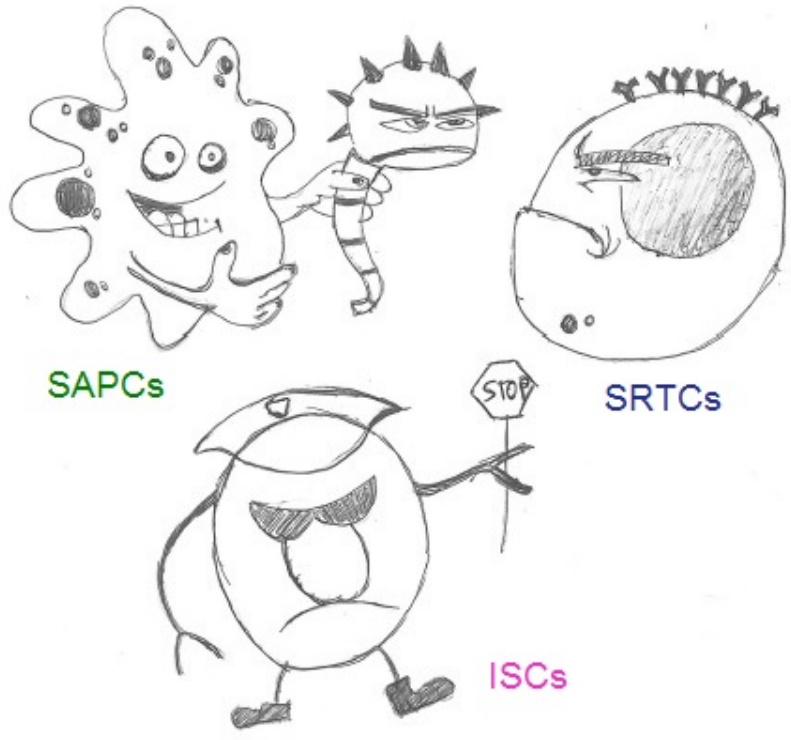
**(SAPCs) Self Antigen Presenting Cells (A)**

**(SRTCs) Self Reactive T cells (R)**

**(ISCs) Immunosupressive Cells (S)**

**SRTCs** are activated when they encounter a SAPC that has digested a self-antigen.

**(ISCs)** regulate the activity of **SRTCs** and SAPCs.



# Assumptions

- Only **binary interactions** between cells are significant.
- Interactions are **instantaneous** and homogeneous in space.
- The functional state of each population is described by the **biological activity** variable, $u \in [0, 1]$;
- Interactions can be **conservative**, **proliferative** and **destructive**.

# Cellular activity

The behaviour of cells is described by distribution functions

$$f_i : [0, \infty] \times [0, 1] \to \mathbb{R}^+, \; i = 1, 2, 3$$

and the expected number of cells of the $i$-population at time $t$ is given by

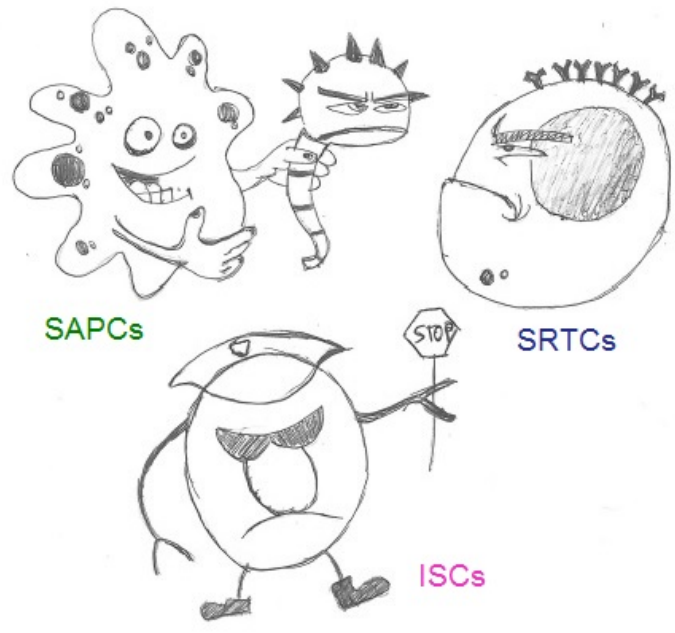
$$n_i(t) = \int_0^1 f_i(t, u) \, \mathrm{d}u, \qquad i = 1, 2, 3. \tag{1}$$

# Cellular activity (meaning)

**(SAPCs) Self Antigen Presenting Cells**

their activity $u$ is the ability to stimulate and activate SRTCs

$u = 0$ means that
the simulation by SAPCs does not activate SRTCs
does not induce an autoimmune response



# Cell activity

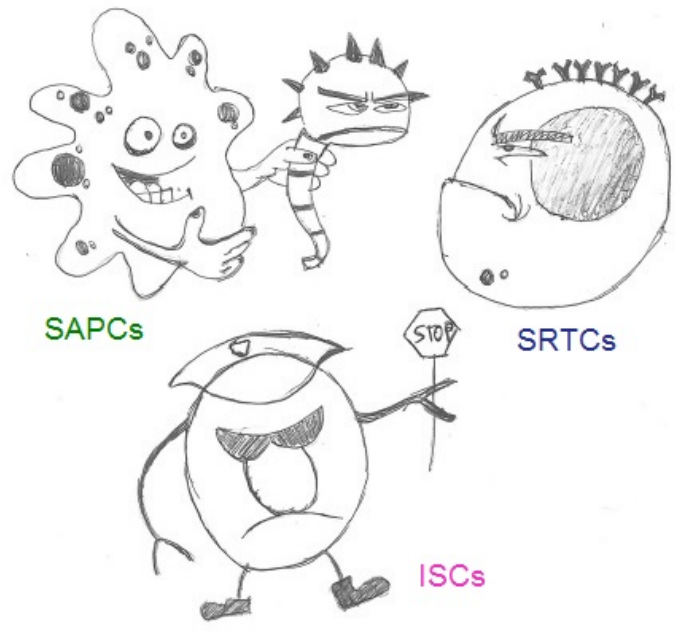
**(SRTCs) Self Reactive T cells**

their activity $u$ is the secretion of cytokines

$u = 0$ means that the SRTCs do not produce cytokines

SRTCs are tolerant to SAPCs

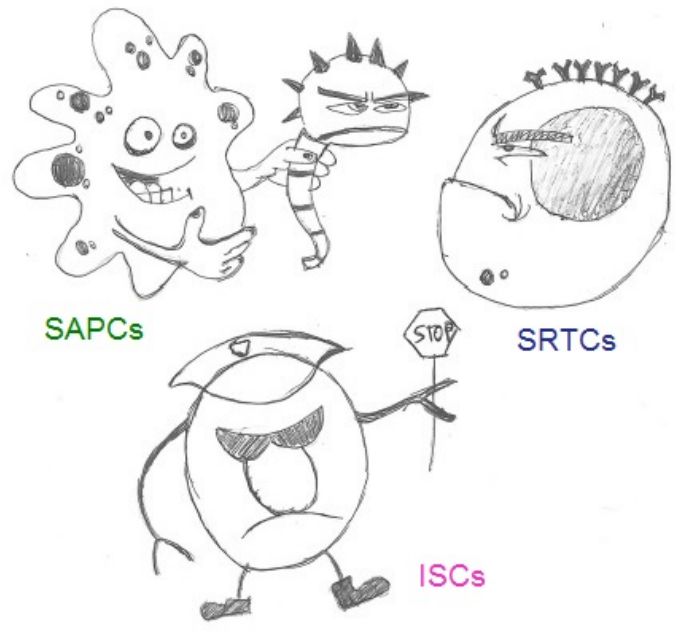
no inflammatory process is triggered



# Cell activity

**(ISCs) Immunosupressive Cells**

their activity $u$ is the ability to inhibit the autoimmune response
suppressing the activity of SAPCs and SRTCs
or eliminating SAPCs and SRTCs



# Kinetic equations

$$\frac{\partial f_i}{\partial t}(t,u) = G_i[f](t,u) - L_i[f](t,u) + S_i[f](t,u)\,, \quad i = 1,2,3,$$

where

$$f = (f_1, f_2, f_3)$$

and

- $G_i[f](t,u) - L_i[f](t,u)$ corresponds to conservative interactions
- $S_i[f](t,u)$ corresponds to proliferative or destructive interactions

The cellular interaction terms have the **structure**

$$
\begin{aligned}
G_i[f](t,u) &= \sum_{j=1}^{3} \int_0^1 \int_0^1 \eta_{ij}(v,w)\psi_{ij}(v,w;u) f_i(t,v) f_j(t,w) dv dw \\
L_i[f](t,u) &= f_i(t,u) \sum_{j=1}^{3} \int_0^1 \eta_{ij}(u,v) f_j(t,v) dv \\
S_i[f](t,u) &= f_i(t,u) \sum_{j=1}^{3} \int_0^1 s_{ij}(u,v) f_j(t,v) dv
\end{aligned}
$$

where

$\eta_{ij}(v,w) \geq 0$ is the **encounter rate** of a conservative interaction

$s_{ij}(u,v)$ is the **proliferation** or **destruction rate**

$\psi_{ij}(v,w;u) \geq 0$ is the **transition probability density**

and satisfies

$$
\int_0^1 \psi_{ij}(v,w;u) du = 1\,, \quad i,j = 1,2,3\,, \quad v,w \in [0,1]
$$

# Cellular interactions (from biological considerations)

## Conservative interactions

Interactions SAPCs–ISCs decrease the activity of SAPCs

Interactions SRTCs–ISCs decrease the activity of SRTCs

Interactions SAPCs–SRTCs increase the activity of SAPCs and also that of SRTCs

## Proliferative interactions

Interactions SRTCs–SAPCs increase the number of SRTCs and also the number of SAPCs (autoimmune cascade)

Interactions SAPCs–ISCs increase the number of ISCs

## Destructive interactions

Interactions ISCs–SAPCs result in the elimination of SAPCs

Interactions ISCs–SRTCs decrease the number of SRTCs

# Cellular interactions (from biological considerations)

**In proliferative interactions**, we consider that

- the newborn cells inherit the same aggressive state as the mother cells
- the proliferation rates are constant

**In destructive interactions**, we consider that

- the destructive rates are constant

**For the population of ISCs**, we consider that

- the distribution function is independent of its functional state

# The kinetic equations are given by

**Population $p_1$ of SAPCs**

- $$\frac{\partial f_1}{\partial t}(t,u) = 2c_{12}\int_0^u (u-v)f_1(t,v)\mathrm{d}v \int_0^1 f_2(t,w)\mathrm{d}w$$
$$-c_{12}(u-1)^2 f_1(t,u)\int_0^1 f_2(t,w)\mathrm{d}w$$
$$+2c_{13}f_3(t)\int_u^1 (v-u)f_1(t,v)\mathrm{d}v - c_{13}u^2 f_1(t,u)f_3(t)$$
$$+p_{12}f_1(t,u)\int_0^1 f_2(t,w)\mathrm{d}w$$
$$-d_{13}f_1(t,u)f_3(t)$$

**Populations $p_2$ of SRTCs and populations $p_3$ of ISCs**

- $$\frac{\partial f_2}{\partial t}(t,u) = 2c_{21}\int_0^u (u-v)f_2(t,v)dv \int_{w^\star}^1 f_1(t,w)dw$$
$$-c_{21}(u-1)^2 f_2(t,u)\int_0^1 f_1(t,w)dw$$
$$+2c_{23}f_3(t)\int_u^1 (v-u)f_2(t,v)dv - c_{23}u^2 f_2(t,u)f_3(t)$$
$$p_{21}f_2(t,u)\int_0^1 f_1(t,w)dw - d_{23}f_2(t,u)f_3(t)$$

- $$\frac{df_3}{dt}(t) = p_{31}f_3(t)\int_0^1 f_1(t,w)dw$$

$w^\star$ is a parameter related to **tolerance** of SRTCs to SAPCs

For this system, we consider the following initial data

$$f_1(0,u)=f_1^0(u),\ f_2(0)=f_2^0(u),\ f_3(0)=f_3^0,\ \text{ with }\ f_i^0>0,\ \text{ for }\ i=1,2,3.$$

# The macroscopic equations

From the **kinetic equations** we formally derive balance equations for the **cellular density of each population**.

Integrating over the biological activity variable, $u \in [0,1]$, we obtain

$$\dot{n}_1(t) = p_{12} n_1(t) n_2(t) - d_{13} n_1(t) n_3(t)$$
$$\dot{n}_2(t) = p_{21} n_2(t) n_1(t) - d_{23} n_2(t) n_3(t)$$
$$\dot{n}_3(t) = p_{31} n_3(t) n_1(t)$$

As usual, **we loose the effects of conservative interactions**.

For this system, we consider the following initial data

$$n_1(0) = n_1^0, \; n_2(0) = n_2^0, \; n_3(0) = n_3^0, \quad \text{with} \quad n_i^0 > 0, \; \text{for} \; i = 1,2,3.$$

# Wellposedeness of the IVP (kinetic)

A result of paper [1], for $\eta_{ij}$ and $\psi_{ij}$ real valued, measurable and uniformly bounded, implies

## Theorem 1 (local existence)

Assume initial data $f_i(0)$ in $L^1[0,1]$.
Then, there exists $T_0 > 0$ such that a unique positive solution to the Cauchy problem for our **kinetic system** exists in $L^1[0,1]$, for $t \in [0, T_0]$.

[1] L. Arlotti, N. Bellomo, K. Latrach. *Mathl. Comput. Modelling*, **30**, 15–40 (1999).

# Kinetic *versus* macro

Thanks to a result of paper [2],

• the **boundedness** of the solution to the **macroscopic** system implies the **boundedness** of the solution to the **kinetic** system

• if the solution to the **macroscopic** system **blows up** then so does the solution to the **kinetic** system

The basic assumptions are

- **constant** destruction and proliferation rates
- cloned cells (proliferative encounters) **inherit the** same aggressive state as their mother cells

**Therefore**, the basic information about our kinetic system can be "extracted" from the corresponding macroscopic equations.

[2] L. Arlotti, M. Lachowicz, *Mathl. Comput. Modelling*, **23**, 11–29 (1996).

# Positivity of the existing solution

## Theorem 2

If $(n_1(t), n_2(t), n_3(t))$ is a solution to the Cauchy problem for the **macroscopic equations** defined on the time interval $[0, T]$, with $0 < T < \infty$, then this solution is **positive**, that is

$$n_1(t) > 0\,, \quad n_2(t) > 0\,, \quad n_3(t) > 0\,, \quad t \in [0, T]\,.$$

# Existence, uniqueness and asymptotic behaviour

## Theorem 3

If the proliferative rates $p_{21}$, $p_{31}$ are such that $p_{21} < p_{31}$, then the **Cauchy problem** for the **macroscopic equations** has a unique global solution $(n_1(t), n_2(t), n_3(t))$ defined on all $\mathbb{R}^+$.
This solution is **bounded** and

$$\lim_{t\to\infty} n_1(t) = 0,$$

$$\lim_{t\to\infty} n_2(t) = 0,$$

$$\lim_{t\to\infty} n_3(t) = \alpha < +\infty,$$

whatever are the corresponding initial data.

# Numerical tests

## Simulations

We **solve** numerically the kinetic system, by **discretizing** the equations in the **activation** variable and using a **quadrature** rule (trapezoidal).

## Objective

**Investigate the influence** of certain parameters on the behaviour of the solution.

## Idea

Which **trends** or **reactions** typical in autoimmune diseases can be reproduced by our kinetic model?

# Numerical scheme

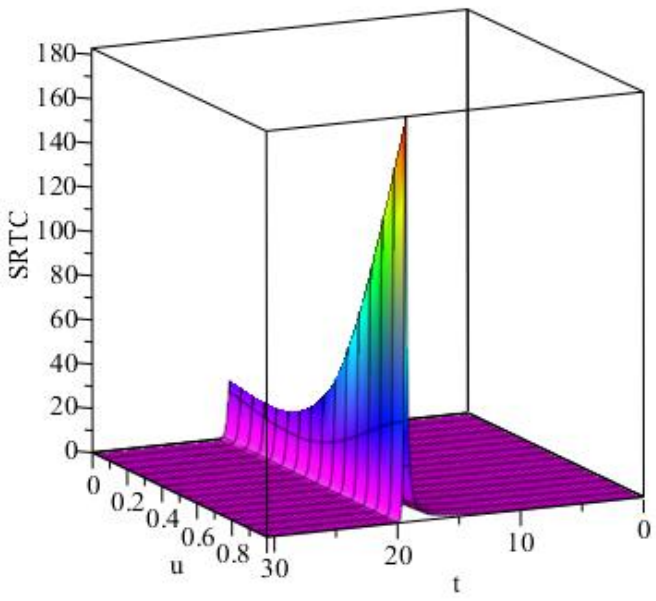
The discretization of the activation state variable $u$, combined with quadrature approximations, leads to a system of $2(m+1)+1$ ODEs,

$$\begin{aligned}
\frac{df_1^k}{dt}(t) &= 2c_{13}f_3(t)\Big(\mathcal{Q}_k^m[vf_1(t,v)] - u_k\mathcal{Q}_k^m[f_1(t,v)]\Big) - c_{13}u_k^2 f_1^k(t)f_3(t) \\
&\quad + c_{12}\left[2\left(u_k\mathcal{Q}_0^k[f_1(t,v)] - \mathcal{Q}_0^k[vf_1(t,v)]\right) - (u_k-1)^2 f_1^k(t)\right]\mathcal{Q}_0^m[f_2(t,v)] \\
&\quad + p_{12}f_1^k(t)\mathcal{Q}_0^m[f_2(t,v)] - d_{13}f_1^k(t)f_3(t), \qquad k = 0,\dots,m, \\
\frac{df_2^k}{dt}(t) &= 2c_{23}f_3(t)\Big(\mathcal{Q}_k^m[vf_2(t,v)] - u_k\mathcal{Q}_k^m[f_2(t,v)]\Big) - c_{23}u_k^2 f_2^k(t)f_3(t) \\
&\quad + c_{21}\left[2\left(u_k\mathcal{Q}_0^k[f_2(t,v)] - \mathcal{Q}_0^k[vf_2(t,v)]\right)\mathcal{Q}_\ell^m[f_1(t,v)] - (u_k-1)^2 f_2^k(t)\mathcal{Q}_0^m[f_1(t,v)]\right] \\
&\quad + p_{21}f_2^k(t)\mathcal{Q}_0^m[f_1(t,v)] - d_{23}f_2^k(t)f_3(t), \qquad k = 0,\dots,m, \\
\frac{df_3}{dt}(t) &= p_{31}f_3(t)\mathcal{Q}_0^m[f_1(t,v)].
\end{aligned}$$

# Numerical tests

## Trending to illness

**ISCs are unable to regulate** the autoimmune reaction.
The result is a full autoimmune cascade and trending to illness.



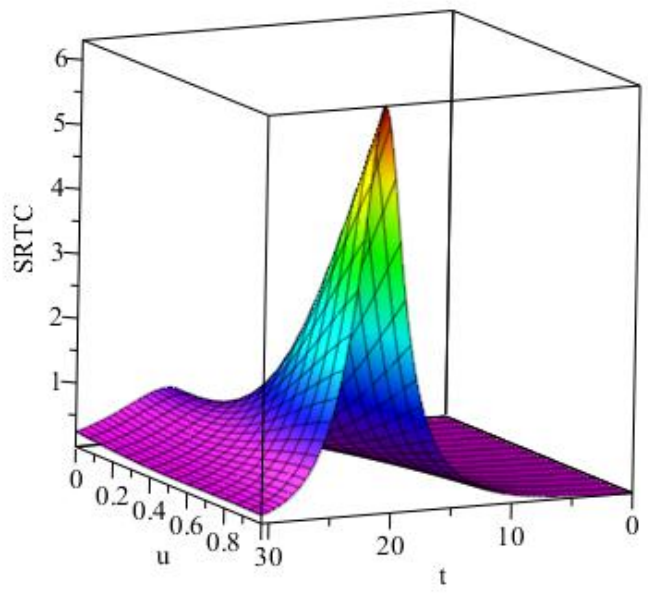

Mass proliferation of very active SRTCs due to insufficient regulation by ISCs or insufficient destruction of SRTCs and SAPCs by ISCs or low tolerance of SRTCs to self-antigens.

$p_{12} = 20$, $p_{21} = 19$, $p_{31} = 20$,
$d_{13} = 0.35$, $d_{23} = 0.025$, $w^\star = 1/30$.

# Numerical tests

## Immunosupression

**ISCs are efficient in aborting** the autoimmune reaction.
The result is the suppression of the autoimmune reaction.




Very low proliferation of active **SRTCs** due to an efficient regulation by **ISCs**

**SAPCs** are less efficient in increasing the activity of **SRTCs**

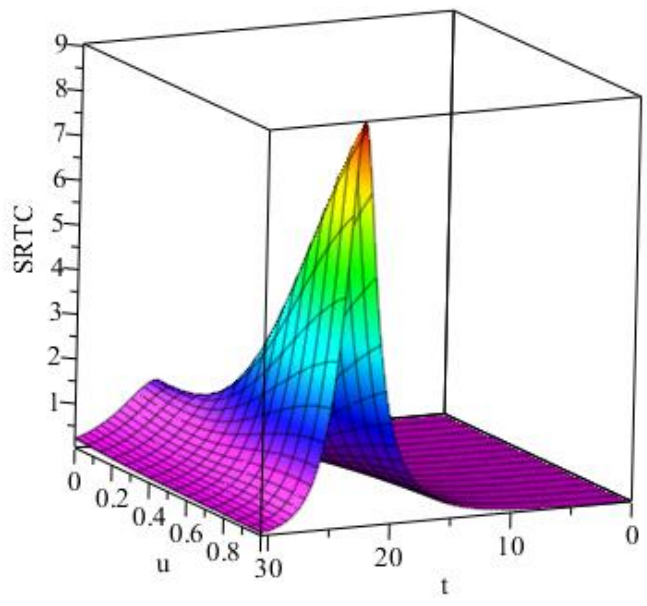
$p_{12} = 20$, $p_{21} = 19$, $p_{31} = 22$,
$d_{13} = 0.35$, $d_{23} = 0.025$, $w^\star = 1/30$.

# Numerical tests

## Immunotolerance

**SRTCs** become more tolerant to **SAPCs**

The result is a lowering effect on the number of **SRTCs** with high activity




Very low proliferation of active **SRTCs**

**SRTCs** become more tolerant to **SAPCs**

$p_{12} = 20,\ p_{21} = 19,\ p_{31} = 20,$

$d_{13} = 0.35,\ d_{23} = 0.025,\ w^{\star} = 5/6.$

# Perspectives

## Work in progress

- An **immunotherapy treatment** was introduced in the description
- A **fourth population** of Interleukin-2 (IL-2) is considered to induce the proliferation of **ISCs**
- An artificial inlet representing an **external drug therapy** is introduced

## Future work

- Other biological relevant populations can be introduced in the model
- A time delay can be included in the model to describe the **chronicity** of the autoimmune disease.

**Thank you for your attention!**