Analysis of minimal embedding networks on an Immune System

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Introduction

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- $A + B \xrightarrow{k_i} C$,
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- Immunology is a group, or a network, of chemical reactions that describe certain interactions between cells.

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- Pathogens can come in contact with our cells in two ways: extracellularly and intracellularly.
- We have two different immune cells that response to these two pathogen types: B cells and T cells

Motivation for study

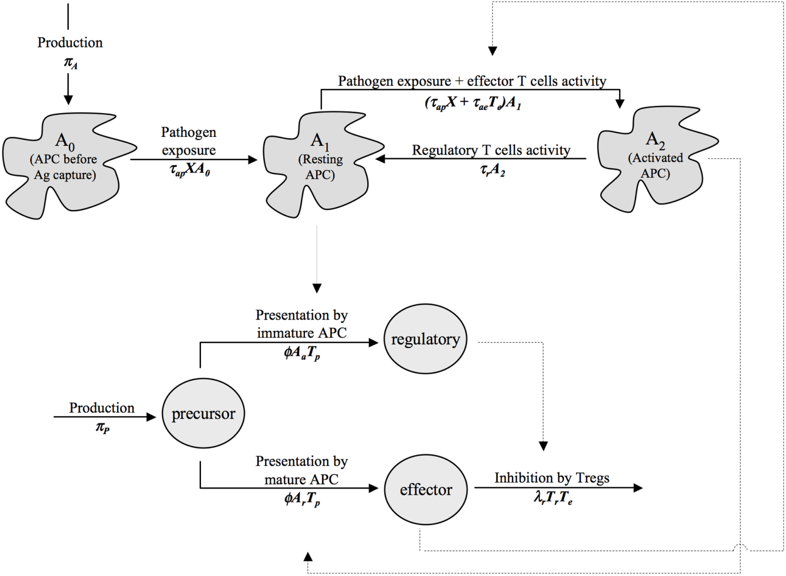

Figure: Immune System Network made by Fouchet and Regeos

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- My approach is analyzing subnetworks of the system previously shown.
- Joshi and Shiu, 2013: *A network with inflows/outflows admits multiple steady states if and only if some* **embedded subnetwork** *admits multiple steady states.*

1st approach: Case studies

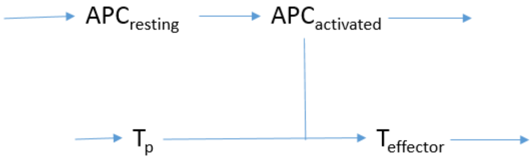

Figure: Case 1: Subnetwork of all APCs and effector T cell interaction

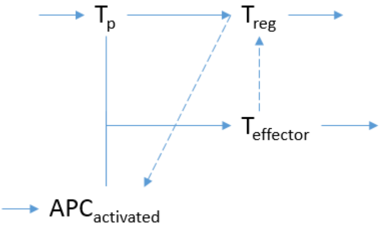

Figure: Case 2: Subnetwork of all T cell interaction with only activated APC

1st approach: Case studies

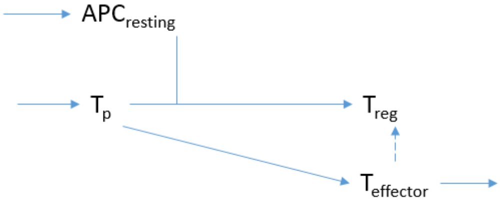

Figure: Case 3: Subnetwork of all T cells interactions with resting APC

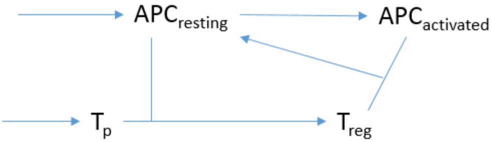

Figure: Case 4: Subnetwork all APCs and only regulatory T cell

Results of case study

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- Used CoNtRol, a web-based program that analyzes networks of chemical reactions. It analysis the network for the possibiliy of multiple steady states.
- Only Case 3 and Case 4 had the possibility of bistability. They were the only cases with regulatory T cell and resting APC interaction.
- *Conj: Any immunological subnetwork will be bistable if there exists a subnetwork with regulatory T cell interactions.*

Making the equations: Case 4

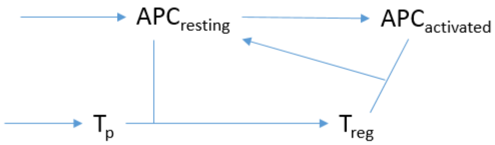

Figure: Case 4: Subnetwork of Treg on both types of APCs

Resulting system of ODEs:

$$\dot{A} = k + mBD - lA - qAC$$
$$\dot{B} = lA - mBD$$
$$\dot{C} = r - qAC$$
$$\dot{D} = qAC - mBD$$

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- $\dot{A} = k - lA - \dot{D} \Rightarrow k - lA^* = 0 \Rightarrow A^* = \dfrac{k}{l}$
- $k = r$ must hold to have any real postive steady states.

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- $B^* - D^* = \text{constant}$

Graphical representation of meaning

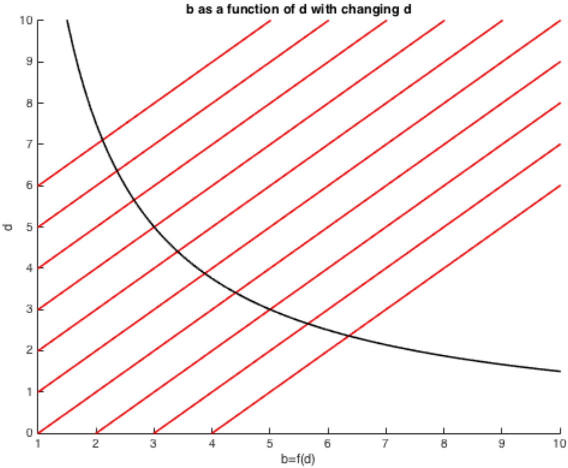

Figure: B^* as a function of D^* with A^*, C^* fixed

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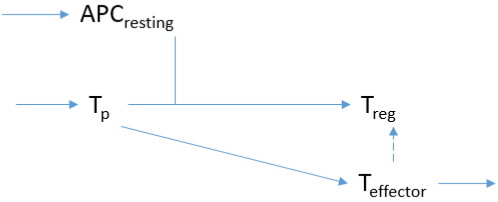

Figure: Case 3: Subnetwork of all T cells interactions with resting APC

Resulting system of ODEs:

$$\dot{A} = k + mAB$$
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  $nx^2 + (p - k)x = 0$
- choose $n > 0$, then $p < k$ to have a single positive solution.
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Solving for steady states: Case 3

- $\dot{D}: nB^* = oC^*D^* \Rightarrow D^* = \dfrac{nB^*}{oC^*}$
- No conservation relationship, used Matlab fsolve function to solve the system of nonlinear equations to find a unique solution.
- Only one steady state occured at $(A^*, B^*, C^*, D^*) = (1.59, 1.25, 0.5, 0.9)$.

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- This is in accordance to recent findings in which the addition of inflows and outflows, however arbitrarily small, resulted in the loss of bistability in a chemical network. (Grinfield and Webb, 2009)
- That is why I ignored the outflows, because I would never be able to find the cause of the bistablity if I included outflows.

Discussion

- This result was counterintuitive in the sense that these types of analysis usually end up with a theoretical proof that proves your prediction. In this case, it was the complete opposite.

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- I proved any subnetwork that retains biological meaning is not bistable. There could be other subnetworks that I did not analyze that cause the bistability, but they wouldn't be biological relevant.
- Ultimately, my work validates Fouchet and Regeos' model as the most concise and precise way to descibe self vs. nonself tolerance. This means that all of the interactions outlined in their model are necessary to include in a model if further research is done on the subject.