Analysis of minimal embedding networks on an Immune System

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Summer 2015
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- Immunology is a group, or a network, of chemical reactions that describe certain interactions between cells.
Background

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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 APCs
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

- Used CoNtRol, a web-based program that analyzes networks of chemical reactions. It analysis the network for the possibility 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.
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Making the equations: Case 4

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

Resulting system of ODEs:

\[ \dot{A} = k + mBD - lA - qAC \]
\[ \dot{B} = lA - mBD \]
\[ \dot{C} = r - qAC \]
\[ \dot{D} = qAC - mBD \]
Solving for steady states: Case 4

\[ \dot{C} + \dot{D} \Rightarrow r = mB \cdot D \cdot r = B \cdot r = mC \cdot A \cdot l = 0 \Rightarrow A = k - lA - \dot{D} \Rightarrow k - lA \cdot \dot{C} = 0 \Rightarrow \dot{C} = l = qAC \Rightarrow r = q \cdot r = l \cdot C \Rightarrow \dot{A} = k - lA - \dot{D} \Rightarrow k - lA = 0 \Rightarrow A = k \cdot l = r \text{ must hold to have any real positive steady states.} \]
Solving for steady states: Case 4

\[ \dot{C} + \dot{D} \Rightarrow r = mB^*D^* \Rightarrow B^* = \frac{r}{mD^*} \]
Solving for steady states: Case 4

- $\dot{C} + \dot{D} \Rightarrow r = mB^*D^* \Rightarrow B^* = \frac{r}{mD^*}$

- $\dot{B} : IA^* - r = 0 \Rightarrow A^* = \frac{r}{l}$

$k = \frac{r}{l}$ must hold to have any real positive steady states.
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\[ \dot{C} + \dot{D} \Rightarrow r = mB^*D^* \Rightarrow B^* = \frac{r}{mD^*} \]

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- \( \dot{A} = k - lA - \dot{D} \Rightarrow k - lA^* = 0 \Rightarrow A^* = \frac{k}{l} \)
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Theoretical analysis: Case 4

- Usually if such a condition is necessary there must be a conservation relationship. This means that some combination of equations add up to become a constant.
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- We know:
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  \]

- \[
  \dot{A} - \dot{D} + \dot{B} = 0 \Rightarrow \dot{A^*} - D^* + B^* = 0
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- We know:

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  \[ \dot{B} = IA - r \]

- \[ \dot{A} - \dot{D} + \dot{B} = 0 \Rightarrow A^* - D^* + B^* = 0 \]

- \[ B^* - D^* = \text{constant} \]
Graphical representation of meaning

Figure: $B^*$ as a function of $D^*$ with $A^*, C^*$ fixed
Making the equations: Case 3

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

Resulting system of ODEs:

\[
\begin{align*}
\dot{A} &= k + mAB \\
\dot{B} &= p - nB - mAB \\
\dot{C} &= mAB - oCD \\
\dot{D} &= nB - oCD
\end{align*}
\]
Solving for steady states: Case 3

\[ \dot{A} \Rightarrow k = mA^*B^* \Rightarrow A^* = \frac{k}{mB^*} \]
Solving for steady states: Case 3

\[
\begin{align*}
\dot{A} & \Rightarrow k = mA^* B^* \Rightarrow A^* = \frac{k}{mB^*} \\
\dot{B} : p & = B^* (mA^* - n) \Rightarrow B^* = \frac{p}{mA^* - n} \Rightarrow \\
& \Rightarrow B^* = \frac{pB^*}{k - nB^*}
\end{align*}
\]
Solving for steady states: Case 3

- $\dot{A} \Rightarrow k = mA^*B^* \Rightarrow A^* = \frac{k}{mB^*}$

- $\dot{B} : p = B^*(mA^* - n) \Rightarrow B^* = \frac{p}{mA^* - n} \Rightarrow$
  
  $B^* = \frac{pB^*}{k - nB^*}$

- Replacing $B$ with $x$, we get that the following polynomial equation for the solution of the steady states of $B$:
  
  $nx^2 + (p - k)x = 0$
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- Replacing \( B \) with \( x \), we get that the following polynomial equation for the solution of the steady states of \( B \):
  \( nx^2 + (p - k)x = 0 \)

- choose \( n > 0 \), then \( p < k \) to have a single positive solution.

- choose \( n < 0 \), then \( k < p \) to have a single positive solution.
Solving for steady states: Case 3

\[ \dot{D} : nB^* = oC^*D^* \Rightarrow D^* = \frac{nB^*}{oC^*} \]
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- No conservation relationship, used Matlab fsolve function to solve the system of nonlinear equations to find a unique solution.

At \((A^*, B^*, C^*, D^*) = (1.59, 1.25, 0.5, 0.9).\)
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- No conservation relationship, used Matlab fsolve function to solve the system of nonlinear equations to find a unique solution.

- Only one steady state occurred at \( (A^*, B^*, C^*, D^*) = (1.59, 1.25, 0.5, 0.9) \).
Wait, did I mess up?

My Matlab results showed only one unique positive steady state, but that steady state occurs at a lower value meaning there is less of a certain species.

Control showed that adding in outflows resulted in the loss bistability of each subnetwork, case 3 and case 4.

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 bistability if I included outflows.
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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.

- 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 describe 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.
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