Population Dynamics of Regulatory T-Lymphocytes

BRYNJA KOHLER AND JAMES P. KEENER
University of Utah, Salt Lake City, Utah

Introduction

- Our modeling goals are to better understand mechanisms behind the onset and progression of autoimmune disorders such as multiple sclerosis.
- A healthy immune response to a pathogen (typically an infectious microbe) includes an explosion in effector T cells (T_E).
- Regulatory T cells (T_R) play an important role in preventing autoimmune responses. Clinical intervention to boost regulatory cell response may be an effective therapy for autoimmune disease.
- We present a mathematical model for the T_R population and its influence on effector T cell (T_E) dynamics through interactions with antigen presenting cells (APCs).

Biological Background

- Naive CD4+ T cells must receive appropriate signalling from APCs to differentiate into the effector type.
- The activation state of the antigen presenting cell is critical in properly priming a T_E response.
- Feedback through cytokines or direct activity changes the balance of the APC activation state.

Steady State Analysis

- With I = 0, A_E = 0, T_E = 0, A_R = 1, T = T_E, T_R = T_E is a stable steady state provided that
- Stability of the trivial state → parameter constraint.
- Other steady states satisfy

\[ T_E = \frac{h_R \cdot A_R}{h_E \cdot A_R + h_I \cdot A_I + h_T \cdot A_T} \]

\[ T = \frac{h_R \cdot A_R + h_I \cdot A_I + h_T \cdot A_T}{h_E} + \theta \]

\[ k_I A_I + A_E \frac{dT}{dt} + \frac{1}{2} (T^2 + \theta T) + \delta T_E \]

\[ k_R A_R + h_R \cdot A_R + h_T \cdot A_T \]

- We can find steady states in the A_E, T_R plane.

The A_E, T_R plane

For a range of parameters two stable steady states are possible. One corresponding to low T_R and A_E, which is considered a regulatory state, and one corresponding to high T_R and A_E, which is a pro-active immune state.

Schematic diagram illustrating how APCs control T_R development and activation based on recent experimental findings [1].

Bifurcation Diagram

The saddle-node bifurcations indicated in the above phase planes are illustrated here.

Model Equations

\[ A_I + A_E = 1 \]

\[ \frac{dT}{dt} = h_E \cdot A_R \cdot A_T - h_R \cdot A_I \cdot T - h_T \cdot A_T \cdot T \]

\[ \frac{dI}{dt} = -a \cdot I + h_I \cdot A_I + h_T \cdot A_T \cdot T \]

\[ \frac{dA_E}{dt} = -a \cdot A_E + h_E \cdot A_E \cdot T + \alpha \cdot I \]

\[ \frac{dA_R}{dt} = h_R \cdot A_R \cdot T - \beta \cdot A_R + \gamma \cdot A_E \]

\[ \frac{dA_T}{dt} = -h_R \cdot A_R \cdot T - \delta \cdot A_T \]

Model Assumptions

- Cells “well-mixed” as in a lymph node.
- Total antigen presentation remains constant during the time modeled.
- Non-linear proliferation rate of T_E due to cytokine production (IL-2).
- Non-linear death rate of T_E due to activation induced cell death (by Fas/Fas-ligand interactions), but \( \mu \) is small.
- Inflammation/infection (I) is a given time-dependent function, and treated like a parameter.

Implications

- Consistent with experiment: a critical dose of Freud’s adjuvant required for activating and immune responses.
- System can exhibit hysteresis. The implications here require a more precise notion of inflammation.
- Parameter constraints derived in the stability condition.
- Parameter sensitivity, particularly to \( \gamma \) and \( K \), imply there may necessarily be additional suppression mechanisms at work to make the switch robust.

References


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