

Population Dynamics of Regulatory T-Lymphocytes

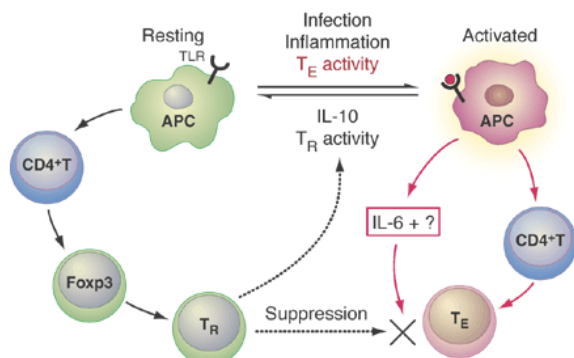
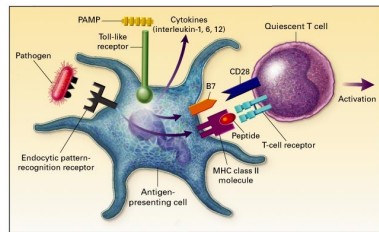
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Introduction

- 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.



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

Question: Does this system exhibit switch behavior?

Model Equations

$$A_A + A_R = 1$$

$$\frac{dA_A}{dt} = IA_R + k_1 T_E A_R - k_2 T_R A_A$$

$$\frac{dT}{dt} = -k_E A_A T - k_R A_R T + \sigma - \delta T$$

$$\frac{dT_E}{dt} = k_E A_A T + \frac{pT_E^2}{K + T_E} - \mu T_E^2 - \delta T_E$$

$$\frac{dT_R}{dt} = k_R A_R T - \delta T_R$$

A_A, A_R - APC, active/resting state
 T - Naive CD4+ T cells
 T_E, T_R - Effector/regulatory T cells
 I - inflammation
 k_1, k_2, k_E, k_R - transition rates
 σ - source (from thymus)
 δ - natural death of T cells
 p, K - proliferation parameters
 μ - non-linear death parameter for T_E

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 of T_E due to activation induced cell death (by Fas/Fas-ligand interactions), but μ is small.
- Inflammation/infection (I) is a given time-dependent function, and treated like a parameter.

Steady State Analysis

- With $I = 0$, $A_A = 0, T_E = 0, A_R = 1, T = \frac{\sigma}{\delta + k_2}, T_R = \frac{k_R \sigma}{\delta(\delta + k_R)}$ is a stable steady state provided that $k_2 k_R > k_1 k_E$

Stability of the trivial state \implies parameter constraint.

- Other steady states satisfy

$$\rightarrow T_E = \frac{k_2 k_R \sigma A_A}{k_1 \delta (k_E A_A + k_R (1 - A_A) + \delta)} - \frac{I}{k_1} \quad \text{"}A_A \text{ nullcline"}$$

$$T = \frac{\sigma}{k_E A_A + k_R (1 - A_A) + \delta}$$

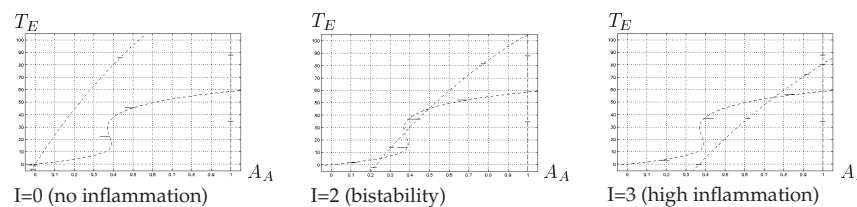
$$\rightarrow \frac{\sigma A_A}{k_E A_A + k_R (1 - A_A) + \delta} = \frac{1}{k_E} \left(-\frac{pT_E^2}{K + T_E} + \mu T_E^2 + \delta T_E \right) \quad \text{"}T_E \text{ nullcline"}$$

$$T_R = \frac{k_R \sigma (1 - A_A)}{\delta (k_E A_A + k_R (1 - A_A) + \delta)}$$

\implies We can find steady states in the A_A, T_E plane.

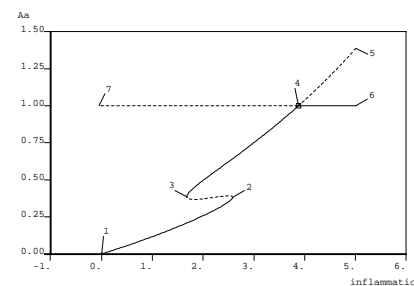
The A_A, T_E plane

For a range of parameters two stable steady states are possible. One corresponding to low T_E and A_A , which is considered a *regulated* response, and one corresponding to high T_E and A_A which is a proper, active immune response.



Bifurcation Diagram

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



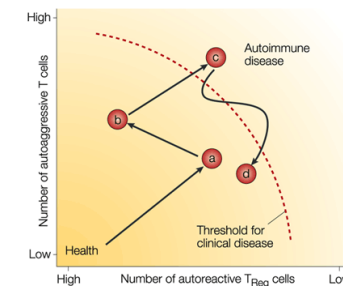
Indeed Powrie and Maloy's description can exhibit "switch" behavior.

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 p and K imply there may necessarily be additional suppression mechanisms at work to make the switch robust.

Relation to Autoimmunity

The development of autoimmune disease may result from a disturbed equilibrium between T_E and T_R cells [2].



- a) a local autoimmune process initiates
- b) regulation by T_R cells
- c) regulation fails and clinical disease results
- d) possible clinical immune intervention

Model Extensions

- Suppression mechanisms

T_R cells are thought to suppress T_E through a reducing the proliferation rate. This reduction is blocked by sufficient IL-6. To model this replace the proliferation term with

$$p \frac{(K_s + \alpha A_A)^2}{(K_s + \alpha A_A)^2 + T_R^2} \frac{T_E}{K + T_E}$$

where α and K_s are parameters.

- How can viruses trigger autoimmunity? [3]

- Inflammation is a function of viral load, A_A/T_E cytokines, and bystander signals.
- Previously we assumed antigen presentation sites on APCs were proportional to the cell population fractions A_A and A_R . We can, however, include dynamics on the amount and quality of antigen presented:
- Let S_A and S_R represent antigen presentation sites on A_A and A_R , respectively.
- Let V represent the viral population.

$$\frac{dV}{dt} = rV - d_T T_E V - d_A A_A V$$

$$\frac{dS_A}{dt} = \psi(V + b) A_A - \delta S_A$$

$$\frac{dS_R}{dt} = \epsilon(V + b) A_R - \delta S_R$$

The basic model provides a framework for further study of the above mentioned extensions.

Future Research

- Improve parameter estimates for quantitative results to compare with experimental allergic encephalomyelitis (EAE) and animal models of viruses which mimic demyelinating disease.
- Add spatial compartments for cell interactions which occur in the lymph nodes, circulation, and target tissue.
- Consider a range of cross-reacting T cells of different specificities.

References

- [1] K.J. Maloy, R. Powrie. 2003. Regulating the Regulators *Science*. **299**: 1030-1031.
- [2] M.G. von Herrath, L.C. Harrison. 2003. Antigen-induced Regulatory T Cells in Autoimmunity. *Nature Reviews: Immunology*. **3**: 223-232.
- [3] R.S. Fujinami. 2001. Viruses and autoimmune disease - two sides of the same coin? *TRENDS in Microbiology*. **9(8)**: 377-381.

Acknowledgements

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