

A BIODYNAMICAL REGULATORY MODEL OF THE HUMAN T-CELL SYSTEM

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Abstract-We describe a biodynamical regulatory model of the human T-cell system based on a set of coupled ordinary differential equations. The model incorporates subsystems representing bone marrow, thymus and peripheral (mature T cell) compartments and allows simulations of viral challenges to the system which lead to various disorders such as leukemia-like syndromes, AIDS, and herpes infections. We provide two examples, one of normative data across the lifespan and the other acute human herpes virus (HHV-6) infection.

Keywords - T-cells, system modeling, immunology

I. INTRODUCTION

T cells are an essential weapon in the human body's response to external viral and biologic agents. They defend against a host of immune-related diseases such as AIDS, transplant rejection and various cancers. Normal development and function of such cells relies on a robust yet finely tuned network of immune system compartments and their regulators. Disturbances in the dynamical regulation of this network can lead to immune system imbalance and progression to disease including immune deficiency, autoimmune disorders and cancer. We describe here the ongoing development of a biocomputational model of the T cell system based on a hypothesis of immunologic (dys)regulation (see [1] for review). We are using the model to study effects of various viral infections on the body, *e.g.*, human herpes virus type 6 (HHV-6) [2,3], human T cell leukemia virus type 1 (HTLV-1) [4], and human immunodeficiency virus type 1 (HIV-1) [5,6]. Each targets the CD4 T helper cell population differently, leading to divergent clinical outcomes.

II. METHODOLOGY

The model is a predator-prey type, implemented as a coupled set of continuous ordinary differential equations (ODE) with both linear and simple nonlinear interaction terms [7]. The ODE's are solved using fourth-order Runge-Kutta integration with variable stepsize (coded in Matlab). It consists of four serially-linked compartments (or subsystems) in the T cell development chain and a virus that "stimulates" the system. Fig. 1 is a conceptual block diagram of the model. w represents the number of CD34 cells produced at time t in the bone marrow, x the number of CD38 cells in the early (pre)thymus, y the number of CD4+8 cells in the thymic medulla, z the number of mature T cells (sum of CD4 and CD8 cells) in the peripheral blood, and v the number of virus particles challenging the immune system.

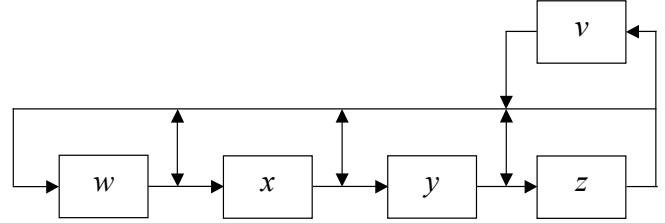


Fig. 1. Block diagram of the T-cell model. w - z are state variables representing compartment cell counts, v is number of virus particles.

There is feedforward from the bone marrow compartment to the peripheral blood; feedback from peripheral blood to bone marrow, early thymic cortex and thymic medulla; feedback from thymic medulla to early thymic cortex and bone marrow; and feedback from early thymic cortex to bone marrow. In addition, each compartment has negative self-feedback. The virus (*e.g.*, HHV-6, HTLV-1, or HIV-1) interacts directly with only the peripheral blood compartment and indirectly through the others. The model equations are

$$\begin{aligned}
 \dot{w} &= \mu_w + w(P_w - D_w - I_w + ax + by + cz), \\
 \dot{x} &= \mu_x + x(P_x - D_x - I_x + dy + ez) + fw, \\
 \dot{y} &= \mu_y + y(P_y - D_y - I_y + gz) + hx, \\
 \dot{z} &= \mu_z + z(P_z - D_z - I_z + i\psi_1 v) + jy + k\psi_2 v, \\
 \dot{v} &= v(l\rho_1 + m\rho_2 z),
 \end{aligned} \tag{1}$$

where the dot notation represents the derivative wrt time for the system variables w - z , each μ term represents the slope of the linear response region of the respective compartment, the P 's represent one or more proliferation factors, the D 's differentiation factors, and the I 's inhibitory factors (*e.g.*, apoptosis) for each compartment, a - m are (currently implemented as) scalar gain parameters, and

$$\begin{aligned}
 \psi_{1,2} &= \frac{1}{1 + \exp\{\lambda'_{1,2}(t - \tau_{1,2})\}}, \\
 \rho_{1,2} &= \frac{1}{1 + \exp\{\lambda'_{1,2}(t - \tau'_{1,2})\}},
 \end{aligned} \tag{2}$$

are sigmoids and introduce time delays. Choosing the proper signs for model parameters is a critical key for producing clinically meaningful simulations.

III. RESULTS

A. Stable Operating Regions and Normative Data

Simulations of the model (without viral stimulation) were first performed in order to determine stable operating parameter ranges for the system. We accomplished this by adopting parameters and initial conditions based on physiologically plausible “textbook” data for normative immunologic function [8]. We used a combination of empirical search based on these data and some heuristics along with an objective function minimization procedure matched to clinical data to arrive at parameter estimates (details provided in [7]). We found that approximately 10% variation in parameter values does not appreciably change the normative behavior of the system. Fig. 2 shows a typical simulation run of normative developmental data across the lifespan from birth to 80 years. The main feature we observe is the slowly exponentially decreasing peripheral blood T cell counts (z) across the lifespan that compares well with actual lymphocyte numbers in humans [9].

B. Acute HHV-6 Infection

HHV-6 infection causes a reactive hyperplasia of T cell populations producing a clinical picture similar to infectious mononucleosis. All compartment cell values return to normal levels after a relatively short time. Our simulations were based on data from 10 adult patients with active HHV-6 variant A infections and clinical infectious mononucleosis-like disease (IM) studied for 32 weeks following disease onset [2]. We used the normative parameters (see section A above), set $v(t_0) = 100$ DNA copies, and found optimized parameter values for $k-m$ (1) and the 4 λ 's and τ 's in (2). Fig. 3 shows a typical simulation run (v and z) with these values.

IV. DISCUSSION

We have developed a biodynamical regulatory model of the human T cell development system and presented data on two examples here. In this framework, external stimuli (such as viruses) can cause dysregulation of the immunological network which produces T cells and leads to different clinical manifestations as seen in various immune-related disorders. Simulation studies using the model are serving to better target the types of clinical investigations necessary to be carried out and reduce their numbers. Such research is assisting us in understanding the mechanisms of uncontrolled cell proliferation, tumor development, immune deficiency, and aplasia. It will also provide additional bases for new diagnostic procedures and for therapeutic planning of lymphoproliferative and aplastic disorders.

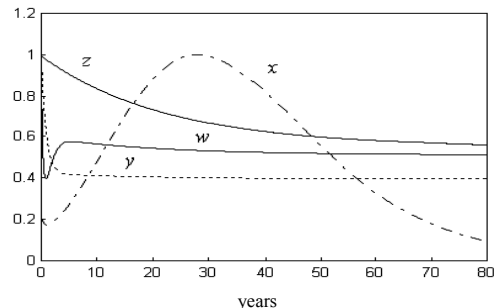


Fig. 2. Simulation of normative T cell data across the lifespan from birth to 80 years of age (data normalized to fit graph).

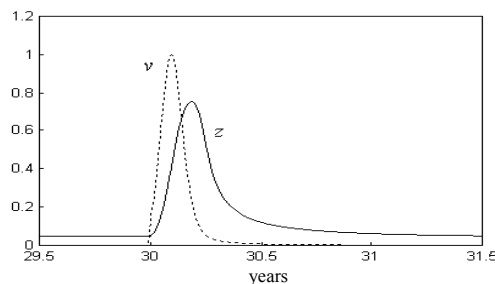


Fig. 3. Simulation of an HHV-6 infection in an adult at 30 years of age (v and z , data normalized to fit graph).

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