Deterministic Mathematical Model of Cell Mediated Immune Responses

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Abstract: *Aspects of an organism's defense to infections are the main problems of practical immunology. Understanding the regularities in immune response provide the researchers and clinicians new powerful tools for the simulation of immune system in order to increase its efficiency in the struggle against antigen invasion. Such general regularities are revealed, as a rule, on the basis of analysis of the main components of an organism's vital activities along with the system of immune defense. In this connection the construction of models of immune response to an antigen irritant seems to be a right tactic in the cognition of above regularities, that is why this monograph is dedicated to the analysis of the facts accumulated in immunology as a united system on the basis of logical concepts and mathematical models.*
Immune response to an infection by a pathogen is supported by different populations
of cells (macrophages, B cells, CD4 T cells, CD8 T cells. . .).
Among the many pathogen type, we will concentrate on pathogens that live inside cells (intracellular pathogens). The majority of those are viruses.The life cycle of a virus can have both intracellular and extracellular stages. A virus is basically genetic material wrapped up in a protein coat. It does not have the metabolic machinery to reproduce. The analytical solutions of the model are obtained to reveal quantitatively the circumstances under which either of the two branches of immunity (Cell Mediated or Humoral immunity) dominate or when both branches are relatively strong.

I. Introduction

        Human beings are consistently threatened by invasion of Microorganisms and have evolved a system of immune defense to eliminate infective pathogens in the body. With more than 15% of genes in human genome being linked to immune function, the immune system comprises a range of cells, tissues and chemicals that interact to overcome infection, repair tissue damage and maintain the integrity of the body. Saxena, R., Voight, B. F., Lyssenko, V., Burtt, N. P., de Bakker, P. I., Chen, H., ... & Hughes, T. E. (2007). One of the most important features of the immune system is its ability to discriminate between antigenic determinants expressed by foreign substances, such as pathogenic microbes, and potential antigenic determinants expressed by the tissues of the host. The process is quite a sophisticated one, as the immune system needs to evolve and change in time, recognizing some non-self-substances as non-offending elements (eg. cellular feeding substances, growing embryos in the mother) and learning to identify new pathogen agents not previously encountered. The task is performed by several populations of specialized cells as well as by biochemical substances (proteins, enzymes etc.). The immune system reacts to pathogen agents by means of two different kinds of responses: innate response and specific/adaptive response. The innate response is quickly activated and occurs every time the infectious agent is encountered and detected through the recognition of its specific molecular pattern. The innate response uses two main components to fight the infection: specialized cells of the family of leukocytes and the complement system.The complement system is a large family of low–molecular weight proteins and cytokines: it responds to the detected infection with a re-action chain that starts increasing blood flow in the area, then attracts phagocytic cells by releasing molecules that active chemotaxis, and finally attempts to perforate the membrane of the target cell. The leukocytes involved in the innate response are phagocytic cells, like neutrophils and macrophages; cells that release inflammatory mediators, like basophils and eosinophils; and "natural killer" (cytotoxic) cells. They act by engulfing the pathogen agent or lysing it.

        Innate immune mechanisms provide a first line of defense against an invading pathogen. They include physical barriers like the skin, changes in environment of the body, such as fever, and immune cells that can

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fight pathogens in a nonspecific way. Instead they sense that an invader is present and react. While such responses slow down the initial growth of a pathogen, they are usually insufficient to clear an infection.The adaptive immune system has two main branches that directly fight infections, the Cell Mediated Immunity and the antibodies. The adaptive immune system, however, contains another branch: the CD4 T helper cells.Cell mediated immunity includes those specific immune responses in which antibody plays only a minor or subsidiary role, it involves the activation of phagocytes, antigen-specific cytotoxicT-lymphocytes (CTL), and the release of various cytokines in response to an antigen.Naïve CTL cells which have not encountered antigen are referred to as T precursor or type 0 cells. Upon engagement of their antigen receptors, these cells secrete the cytokine IL-2. Other local cells may also be stimulated to release cytokines and these will influence the further development of the T cells. The presence of IL-18 and IL-12 will lead to the development of type 1 effector or memory cells. The effector cells will secrete cytokines (most importantly interferon gamma INF gamma and tumor necrosis factor – TNF) that stimulate a range of cells leading to cell-mediated immunity(CMI). Conversely, the presence of IL-10 will lead to the development of type 2effector and memory cells. The effector cells secrete IL-4, IL-5, IL-6 and IL-13 which influence the humoral immune response and affect the class of antibody produced in response to the antigen. Both T helper and T cytotoxic cells develop these different cytokine secretion profiles. Eales, L. J. (2003). During a typical infection, the immune response unfolds in multiple waves. The cascade begins with almost immediate responses by innate immune cells, such as neutrophils, which create an inflammatory microenvironment that subsequently attracts dendritic cells and lymphocytes to initiate the adaptive immune response. Perhaps the reason the immune system operates in a series of successive waves rather than in one concentrated surge is that each burst of immune cells has to be tightly regulated, since some primed cells could potentially give rise an uncontrolled autoimmune response, and again most immune cells exist in different states (resting/active, immature/mature, naïve/effectors/memory) which provide further regulatory mechanisms. Kim, P. S., Levy, D., & Lee, P. P. (2009) This monograph elucidates how principles from mathematical modeling can shed light into understanding how the immune system functions as a self-regulating network.

Some key questions to arise in Bio-Mathematical modeling;

i. How can we understand systems as complicated as those arising in the biological science?
ii. How do we test whether our supposed understanding of the key processes is sufficient to describe how a system behaves?

In response to the concerns we will give more emphasis to the close connection many models have with experiment, clinical data and estimating real parameter values, the unifying aim of theoretical modeling and experimental.

However, it must be understood that mathematical descriptions of biological phenomenon are not biological explanations. Mathematics, rather than theoretical modeling must be used if we ever hope to genuinely and realistically convert an understanding into a predictive science. The aim of mathematical modeling is not to derive a mathematical model that takes into account every single process, because even if it were possible, the resulting model yield little or no single insight on the crucial interactions within the system. Rather the goal is to develop models which capture the essence of various interactions allowing their outcome to be fully understood. Murray, J. D. (2002).

II. Basic Immunology

Immune responses can be subdivided broadly into two categories: (i) Innate or nonspecific responses, and (ii) specific, adaptive responses. Innate immune mechanisms provide a first line of defense against an invading pathogen. They include physical barriers like the skin, changes in environment of the body,such as fever, and immune cells that can fight pathogens in a nonspecific way. Nonspecific is the key word here and means that these responses cannot specifically recognize the physical structure of the pathogen. Instead they sense that an invader is present and react. While such responses slow down theinitial growth of a pathogen, they are usually insufficient to clear an infection. For clearance, a specific and adaptive immune response tends to be required. Specific means that cells bear receptors that can recognize the physical structure of a pathogen. More precisely, they recognize proteins from which the pathogen is built. Upon recognition, these immune cells start to divide and expand. They dramatically increase in number, and this enables them to effectively fight the pathogen, resulting in the resolution of the infection. There is some terminology that is worth to point out here: A substance that is capableof inducing the generation of a specific immune response is called an *antigen*. The site of the antigen that is actually recognized by the receptor of the immune cell is called an *epitope*. The same pathogen can have a variety of epitopes, each of which is recognized by a separate specific immune cell. Therefore, multiple immune cell clones can respond against the same pathogen.

III. Model development

The aim of this mathematical model is not to include every molecular detail that is involved in the interactions between pathogen and immune system. In fact, this amount of complexity in a mathematical model would make it very difficult to achieve any meaningful insights by analysis.Instead, the aim of the model is to capture certain biological assumptions that are thought to be key factors driving the dynamics between pathogen and immune system, and to follow them to their precise logical conclusions. This can allow us to obtain an understanding that would otherwise not be possible, to interpret experimental data, to generate new hypotheses, and to design new experiments.

General aspects on the modelling of biological equations are dealt with in various books, such as Alt, Deutsch, Murray(2004) and Dunn (1997); and Jones and Sleeman (2003). An, G. (2009). the authors present spatially configured stochastic reaction chambers(SCSRC), that is, an agent-based modeling framework that incorporates an abstracted molecular "event" rule system with a spatially explicit representation of the relationship between signaling and synthetic compounds. The model was able to accurately reproduce the dynamics of TLR-4 signaling in response to LPS stimulation. In particular, it was capable of showing that there was a dose dependent proinflammatory response effect and also the establishment of tolerance.Brown, B. N., Price, I. M., Toapanta, F. R., DeAlmeida, D. R., Wiley, C. A., Ross, T. M., ... & Vodovotz, Y. (2011). developed a model to study the response of inflammatory cells (macrophages) and cells involved in remodeling (fibroblasts) to particulates exposure. The model was able to forecast the existence of biologically relevant aspects, that is, healing and return to baseline, localized tissue damage and fibrosis, and extensive damage and fibrosis.Bosch, F. X., Broker, T. R., Forman, D., Moscicki, A. B., Gillison, M. L., Doorbar, J., ... & Cuzick, J. (2013). The authors did a study on Human papillomavirus (HPV) a virus from the papillomavirus family that is capable of infecting humans. The main targets of HPV are the keratinocytes of the skin or mucous membranes. Some types of infections can trigger benignpapillomas, while others can lead to cancers of the cervix, vulva, vagina, penis, oropharynx, and anus. They combined cellular automata and agent-based modeling techniques to simulate the growth and the HPV life cycle, allowing the observations at different stages.Severins, M., Klinkenberg, D., & Heesterbeek, H. (2007) used NetLogo to implement a model to analyze the host dynamics of a protozoan parasite infecting chickens, including acquired immunity and repeated infection through a spatially structured environment. The choice to use an individual-based model allowed the authors to investigate stochastically emerging heterogeneity. Main emerging results were the possibility to examine the variation in the immune response, transmission, and movement of individuals.Lewis, C. J. (2011) discussed, formulated and analyzed deterministic and stochastic models of hantavirus infections in rodents and in humans. The goals of these model formulations and analyses was to demonstrate how the antibodies and cytotoxic T-lymphocytes (CTLs) compete with one another to eradicate the Hantavirus. This virus is responsible of Hantavirus pulmonary syndrome (HPS) and hemorrhagic fever with renal syndrome (HFRS). It was demonstrated through formulation and analysis of systems of ordinary and stochastic differential equations. The work presented here examines the immune system and its possible behaviors when a pathogen is introduced.

IV. Model assumptions

The specific biological assumptions we took into account when developing our model equations are based on accepted knowledge of immune system function. The assumptions include;

i. Precursors of the immunocompetent cells (Lymphocytes and Leukocytes) as well as precursors of blood cells are produced in the bone marrow.
ii. The virus does not infect the CD^+4 T cells.
iii. Cytotoxic T Lymphocyte (CTL) can kill infected cells or shut down virus replication in the cell and Anti bodies will fight (neutralize) free virus released by infected cells
iv. As part of specific immunity, pathogen-specific CTL and antibody responses are initiated once the virus is present.
v. Immune responses will eventually become inactivated after some number of encounters with virus or upon virus eradication.
vi. The CTL response and antibody response are independent

V. Model flow chart
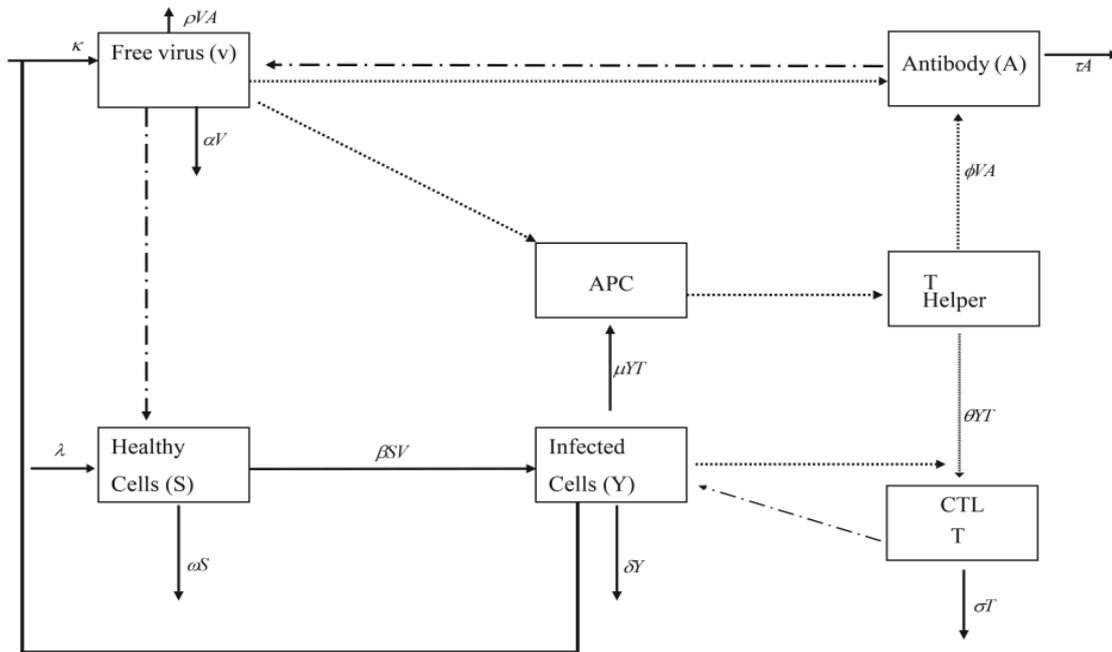
KEY

→ Transition from one state to another

·····► Stimulation

— · ► Interaction

Using the list of assumptions above, we describe the system as five coupled differential equations, where each equation gives the rate of change of the particular cell population in terms of growth and death, cell-cell kill, cell recruitment, and cell inactivation.

In the equations we denote five populations by

- $S(t)$ susceptible host cells at any time t

- $Y(t)$ infected cells at any time

- $V(t)$ free virus at any time t

- $A(t)$ antibodies at any time t

- $T(t)$ CTL at any time t.   Substituting specific mathematical forms for each of the growth, death, recruitment, and inactivation terms yields the following system of equations.

$$\dot{S}(t) = \lambda - \omega S - \beta SV \qquad\qquad 1$$

$$\dot{Y}(t) = \beta SV - \delta Y - \mu YT \qquad\qquad 2$$

$$\dot{V}(t) = \kappa Y - \alpha V - \rho VA \qquad\qquad 3$$

$$\dot{A}(t) = \varepsilon A + \phi VA - \tau A \qquad\qquad 4$$

$$\dot{T}(t) = \upsilon T + \theta YT - \sigma T \qquad\qquad 5$$

VI. Model Description

Susceptible host cells are produced at a rate λ, die at a rate ωS and become infected by virus at a rate βSV. Infected cells die at a rate δY and are killed by the CTL response at a rate μYT. Free virus is produced by infected cells at a rate κY, decays at a rate αV, and is neutralized by antibodies at a rate ρVA. The rate at which pathogen specific antibodies of immunological memory are lost at rate ε, the antibodies develop in response to free virus at a rate ϕVA and decay at a rate τA. The rate at which pathogen specific CTL of immunological memory are lost at rate υ. CTL expand in response to viral antigen derived from infected cells at a rate θYT, and decay in the absence of antigenic stimulation at a rate σT, εV and υT indicate that even in the absence of pathogen there will always be a (typically small) standing stock of both antibodies and CTL ready to fight an attack. Without this standing stock immune response system would take longer to respond to pathogen. For primary infections we will take $\varepsilon = \upsilon \cong 0$,

$E = \dfrac{1}{\varepsilon}$ and $G = \dfrac{1}{\upsilon}$ is the average duration of antibodies and CTL memory cells respectively.

VII. Analytical Results

A true analytical result presumes an analytical procedure without systematic errors. They can be detected by comparing the analytical results with the simulated results or with an accepted reference.

Equilibrium points and stability analysis
Infection free state
Failure to establish an infection is described by the equilibrium points

$$S_{e0} = \frac{\lambda}{\omega},\ Y_{e0} = 0,\ V_{e0} = 0,\ A_{e0} = 0,\ T_{e0} = 0$$

This equilibrium is always stable.
In the model described by equations 1 through 5 the virus exists in two compartments only. That is equations 2 and 3,
either in the infected cell or as free virus.
We compute the basic reproductive number, R_0 using the next-generation matrix approach as outlined by by Dickmann *et al.*, 1990, Van den Driesche and Watmough, 2002.

Using this approach two viral replication classes of the model are considered Y and V.
We define *f* as the matrix whose elements represents the rate of change of new viral materials, or the rate of appearance of new viruses but does not include terms which describe the transfer of infected cells from one compartment to another. Also let the matrix *h* denote the rate of change of cell populations through other means, i.e. the elements of *h* denotes the rate of transfer of individuals by other means in epidemiology. Then the difference $f - h$ gives the total rate of change of cell populations in the two compartments.
The next generation matrix FH^{-1} is formed from evaluating the partial derivatives of *f*
and *h* at the fixed points (DFE), that is,

$$F = \frac{\partial f_i(x_0)}{\partial x_j}$$

$$H = \frac{\partial h_i(x_0)}{\partial x_j}$$

The entries of FH^{-1} give the rate at which infected cells produce new infective viruses' times the average length of time a cell spends in a single visit to the compartment. R_0 is given by the spectral radius (dominant eigenvalue) of the matrix FH^{-1}.

Using this approach, we compute the basic reproductive ratio defined as $R_0 = \rho(FH^{-1})$

$$f = \begin{bmatrix} \beta S V \\ 0 \end{bmatrix} \qquad F = \begin{bmatrix} 0 & \beta S \\ 0 & 0 \end{bmatrix}$$

$$h = \begin{bmatrix} \delta Y \\ \kappa Y + \alpha V \end{bmatrix} \quad H = \begin{bmatrix} \delta & 0 \\ -\kappa & \alpha \end{bmatrix}$$

$$H^{-1} = \begin{bmatrix} \dfrac{1}{\delta} & 0 \\ \dfrac{\kappa}{\alpha\delta} & \dfrac{1}{\alpha} \end{bmatrix} \qquad \text{the next generation matrix is ;}$$

$$FH^{-1} = \begin{bmatrix} \dfrac{\beta S \kappa}{\alpha\delta} & \dfrac{\beta S}{\alpha} \\ 0 & 0 \end{bmatrix}$$

The Eigen values are $\begin{bmatrix} 0 \\ \dfrac{\beta S \kappa}{\alpha\delta} \end{bmatrix}$

The basic reproductive ration is $\dfrac{\beta S \kappa}{\alpha\delta}$ at $S_{e0} = \dfrac{\lambda}{\omega}$. Therefore $R_0 = \dfrac{\beta\lambda\kappa}{\alpha\delta\omega}$. It is required that this quantity be greater than one for establishment of any infection.

Immunity free state

Without any immune responses, both CTL and Antibody responses are not mounted. This may correspond the full blown AIDS stage when the immune system is highly compromised or any other infection that substantially impairs or kills the CD4 T helper cells, leading to failure in mounting an immune. The model equations will then involve equations 1 through 3. The system settles down to the following equilibrium points;

$$S_{e1} = \frac{\alpha\delta}{\beta\kappa}, Y_{e1} = \frac{\beta\lambda\kappa - \alpha\delta\omega}{\beta\delta\kappa}, V_{e1} = \frac{\beta\lambda\kappa - \alpha\delta\omega}{\alpha\beta\delta}, A_{e1} = 0, T_{e1} = 0$$

The Jacobian of the resulting matrix is

$$J = \begin{pmatrix} -\omega - \beta V_{e1} & 0 & -\beta S_{e1} \\ \beta V_{e1} & -\delta & \beta S_{e1} \\ 0 & \kappa & -\alpha \end{pmatrix}$$

To obtain a polynomial of Eigen values we subtract Λ from the diagonal elements of J and work out the determinant of the Jacobian i.e. $\det|J - \Lambda I| = 0$,where I is a 3X3 identity matrix. The characteristic equation is

$$\alpha\delta\eta - \alpha\eta^2 - \delta\eta^2 - \eta^3 + \frac{\alpha\alpha\delta\omega\beta\kappa}{\beta\delta\kappa} - \frac{\alpha\beta\beta\lambda\kappa\kappa}{\beta\delta\kappa} + \frac{\alpha\delta\omega\beta\eta\kappa}{\beta\delta\kappa} - \frac{\beta\beta\lambda\kappa\eta\kappa}{\beta\delta\kappa} + \frac{\alpha\alpha\delta\omega\beta\eta\kappa}{\beta\delta\kappa\delta} - \frac{\alpha\beta\beta\lambda\kappa\eta\kappa}{\beta\delta\kappa\delta} + \frac{\alpha\delta\omega\beta\eta^2\kappa}{\beta\delta\kappa\delta}$$
$$- \frac{\beta\beta\lambda\kappa\eta^2\kappa}{\beta\delta\kappa\delta} - \frac{\alpha\delta\alpha\delta\omega\beta^2\kappa^2}{\beta\delta\kappa\beta\kappa\delta} + \frac{\alpha\delta\beta^2\beta\lambda\kappa\kappa^2}{\beta\delta\kappa\beta\kappa\delta} - \alpha\delta\omega - \alpha\eta\omega - \delta\eta\omega - \eta^2\omega = 0$$

The analytic solution to the characteristic equation is infeasible. However, using the Routh–Hurwitz stability criterion the equilibrium is unstable

Assuming that the immune response can develop it requires the conditions $\varepsilon + \phi V(0) > \tau$ and $\upsilon + \theta T > \sigma$. With this, three possible cases arise as discussed below, in which we shall consider the primary infection.

Case 1: CTL Only Immune Response
        The CTL response develops and the antibody response cannot become established. This is because the CTL response is strong and reduces virus load to levels that are too low to stimulate the antibody response. In this case we only consider equations 1,2 and 3 (without the neutralizing term by antibodies) and 4.5. We obtain the following equilibrium points.

$$S_{e2} = \frac{\alpha\lambda\theta}{\alpha\theta\omega + \beta\kappa(\sigma-\upsilon)}, Y_{e2} = \frac{\sigma-\upsilon}{\theta}, V_{e2} = k\left(\frac{(\sigma-\upsilon)}{\theta}\right), A_{e2} = 0, , T_{e2} = \frac{\beta\lambda\kappa(\sigma-\upsilon))}{\alpha\omega\theta + \beta\kappa(\sigma-\upsilon)}$$ The

equations in V_{e2} and Y_{e2} can be expressed as $V_{e2} = kY_{e2}$ and $T_{e2} = \frac{\beta S_{e2}V_{e2} - \delta Y_{e2}}{\mu Y_{e2}}$ respectively. This tells

us that virus population is a function of the infected cells and CTL immune response is a function of infected cells and free virus.

Therefore, the behavior of the system at equilibrium can be determined by the Jacobian matrix of the system

$$J = \begin{pmatrix} -\omega - \beta V_{e2} & 0 & -\beta S_{e2} & 0 \\ \beta V_{e2} & -\delta - \mu T_{e2} & 0 & -\mu Y_{e2} \\ 0 & \kappa & -\alpha & 0 \\ 0 & \theta T_{e2} & 0 & \theta Y_{e2} - \sigma \end{pmatrix}$$

The determinant $\det|J - \Lambda I| = 0$ is given by

$-(\Lambda^2 (\alpha + \Lambda)(\alpha\lambda\theta\beta\kappa + \alpha\theta\omega\Lambda + \beta\kappa\sigma\Lambda))/(\alpha\theta\omega + \beta\kappa\sigma) + (\alpha\lambda\theta\beta^\wedge2\kappa^\wedge2 \Lambda\sigma)/(\alpha\theta\omega + \beta\kappa\sigma)\theta - (-\alpha\lambda\theta\beta\kappa + \alpha\theta\omega\delta + \beta\kappa\sigma\delta)\Lambda(\alpha + \Lambda)\sigma/(\alpha\theta\omega + \beta\kappa\sigma) + \beta\kappa\Lambda(\alpha + \Lambda)(\alpha\lambda\theta\beta\kappa + \alpha\theta\omega\Lambda + \beta\kappa\sigma\Lambda)\sigma/(\alpha\theta\omega + \beta\kappa\sigma)\theta - (\beta(-\alpha\lambda\theta\beta\kappa + \alpha\theta\omega\delta + \beta\kappa\sigma\delta)\kappa(\alpha + \Lambda)\sigma^\wedge2)/(\alpha\theta\omega + \beta\kappa\sigma)\theta + (\alpha + \Lambda)(\alpha\lambda\theta\beta\kappa\Lambda + \alpha\theta\omega\Lambda^\wedge2 + \beta\kappa\sigma\Lambda^\wedge2 + \alpha\lambda\theta\beta\kappa\sigma - \alpha\theta\omega\delta\sigma - \beta\kappa\sigma\delta\sigma)\omega/(\alpha\theta\omega + \beta\kappa\sigma)=0$

Although the solving for Eigen values, Λ, is daunting task the stability is found using Routh–Hurwitz stability criterion and is found to be stable if
$$\alpha\alpha\lambda\theta\beta\beta\kappa\kappa\sigma^2 + \alpha\alpha\lambda\theta\beta\kappa\theta\sigma\omega > \alpha\alpha\theta\omega\beta\delta\kappa\sigma^2 + \alpha\beta\beta\kappa\sigma\delta\kappa\sigma^2 + \alpha\alpha\theta\omega\delta\theta\sigma\omega + \alpha\beta\kappa\sigma\delta\theta\sigma\omega$$

Case 2: Antibody Only Immune Response
The antibody response develops and a sustained CTL response fails. This is because the antibody response is strong relative to the CTL response and reduces virus load to levels that are too low to stimulate the CTL. This is described by the following equilibrium.

$$S_{e3} = \frac{\lambda\phi}{\phi\omega + \beta(\tau-\varepsilon)}, Y_{e3} = \frac{\beta\lambda(\tau-\varepsilon)}{\delta(\phi\omega + \beta(\tau-\varepsilon))}, V_{e3} = \frac{\tau-\varepsilon}{\phi}, A_{e3} = \frac{\beta\phi\kappa\lambda}{\delta\rho(\phi\omega + \beta(\tau-\varepsilon))} - \frac{\delta}{\rho}, T_{e3} = 0$$

Equation in $A_{e3} = \frac{\kappa Y_{e3} - \alpha V_{e3}}{\rho V_{e3}}$ from which we can get an alternative expression for $V_{e3} = \frac{\kappa Y_{e3}}{\rho A_{e3} - \alpha}$.

The Jacobian matrix is

$$J = \begin{pmatrix} -\omega - \beta V_{e3} & 0 & -\beta S_{e3} & 0 \\ \beta V_{e3} & -\delta & \beta S_{e3} & 0 \\ 0 & \kappa & -\alpha - \rho A_{e3} & -\rho V_{e3} \\ 0 & 0 & \phi A_{e3} & \phi V_{e3} - \tau \end{pmatrix}$$

The determinant $\det|J - \Lambda I| = 0$ is given by

$$\frac{1}{\delta\rho^2\rho\phi(\beta\tau + \phi\omega)^2}\Big(-\delta\rho(\delta + \Lambda)\rho\tau(\beta\tau + \phi\omega)(\beta\tau\delta\delta\rho - \beta\phi\kappa\lambda\rho + \delta\delta\rho\phi\omega)(\beta\tau + \phi(\Lambda + \omega))$$
$$+ (\beta\phi\kappa\lambda\rho\phi - \beta\tau\delta\rho(\Lambda\rho + \rho\tau + \delta\phi) - \delta\rho(\Lambda\rho + \rho\tau + \delta\phi)\phi\omega)\big(\beta\delta\rho\kappa\lambda\phi\phi(\Lambda + \omega)$$
$$- (\delta + \Lambda)(\beta\tau\delta\rho(-\delta + \Lambda) + \beta\phi\kappa\lambda\rho - \delta\delta\rho\phi\omega + \delta\rho\Lambda\phi\omega + \alpha\delta\rho(\beta\tau + \phi\omega))(\beta\tau$$
$$+ \phi(\Lambda + \omega))\big)\Big) = 0$$

This represents a stable equilibrium

Case 3: CTL and Antibody Mediated Immune Responses

Both CTL and antibody responses develop. This equilibrium is described by the following;

$$S_{e4} = \frac{\lambda\phi}{\omega\phi + \beta(\tau - \varepsilon)}, Y_{e4} = \frac{\sigma - \upsilon}{\theta}, V_{e4} = \frac{\tau - \varepsilon}{\phi}, A_{e4} = \frac{\kappa\phi(\sigma - \upsilon)}{\theta\rho(\tau - \varepsilon)} - \frac{\alpha}{\rho},$$

$$T_{e4} = \frac{\beta\lambda\theta(\tau - \varepsilon)}{\mu(\sigma - v)(\omega\phi + \beta(\tau - \varepsilon))} - \frac{\delta}{\mu}$$

The Jacobian is
$$J = \begin{pmatrix} -\omega - \beta V_{e4} & 0 & -\beta S_{e4} & 0 & 0 \\ \beta V_{e4} & -\delta - \mu T_{e4} & \beta S_{e4} & 0 & -\mu Y_{e4} \\ 0 & \kappa & -\alpha - \rho A_{e4} & -\rho V_{e4} & 0 \\ 0 & 0 & \phi A_{e4} & \phi V_{e4} - \tau & 0 \\ 0 & \theta T_{e4} & 0 & 0 & \theta Y_{e4} - \sigma \end{pmatrix}$$

And $\det(J - \Lambda I) = 0$ is

$$-\frac{1}{\mu\mu\delta\mu\sigma\phi(\beta\tau + \omega\phi)^2}(\sigma(\beta\tau + \phi(\Lambda + \omega))(\beta\lambda\theta\tau\mu - \delta\mu\delta(\beta\tau + \omega\phi))(\rho\tau(\beta\lambda\theta\tau\mu - \delta\mu\sigma(\beta\tau + \omega\phi))$$
$$+ \Lambda(\beta\lambda\theta\tau\mu\rho + \beta\tau\mu\sigma(\Lambda\mu - \delta\rho) + \Lambda\mu\mu\sigma\omega\phi - \delta\mu\sigma\rho\omega\phi + \alpha\mu\mu\sigma(\beta\tau + \omega\phi))) + \Lambda(-\rho\tau(\beta\tau$$
$$+ \phi(\Lambda + \omega))(\beta\lambda\theta\tau\mu + \Lambda\mu\delta(\beta\tau + \omega\phi))(-\beta\lambda\theta\tau\mu + \delta\mu\sigma(\beta\tau + \omega\phi)) - \Lambda(\beta\kappa\lambda\phi\mu\mu\delta\mu\sigma\phi(\Lambda$$
$$+ \omega)(\beta\tau + \omega\phi) - (\beta\tau + \phi(\Lambda + \omega))(\beta\lambda\theta\tau\mu + \Lambda\mu\delta(\beta\tau + \omega\phi))(\beta\lambda\theta\tau\mu\rho + \beta\tau\mu\sigma(\Lambda\mu - \delta\rho)$$
$$+ \Lambda\mu\mu\sigma\omega\phi - \delta\mu\sigma\rho\omega\phi + \alpha\mu\mu\sigma(\beta\tau + \omega\phi)))))$$

This represents unstable equilibrium

VIII.   Conclusion

The simplest and most basic questions in model analysis concerns the correlates of immune response to control or clearance of the pathogen. Further analysis is required in order to determine the factors that determinepathogen load and the degree of control.

We also need to understand the conditions which lead to infectionsclearance, and when persistent infections established.

Mathematical models provide an essential tool that complements experimental observation in the study of immune responses dynamics. The complex and nonlinear nature of the interactions that occur during the generation of immune responses renders a rigorous understanding of the outcome of infection difficultto achieve by verbal arguments alone. Mathematical models go beyond verbal or graphical reasoning and provide a solid framework that captures a defined set of assumptions and follows them to their precise logical conclusions. This framework can be used to generate new insights, to create hypotheses, andto design new experiments. Such mathematical models of immune responses are the subject discussions in many scholarly fora a due to the challenge of diseases facing mankind.

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