APPLICATION OF SIMULATED ANNEALING FOR THE MATHEMATICAL MODELLING OF IMMUNE SYSTEMS

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ABSTRACT

Cellular kinetics formulate the basis of tumor immune system dynamics which may be synthesized mathematically as cascades of bilinear systems which are connected by nonlinear dynamical terms. In this manner, a foundation for the control of syngeneic tumors is presented. We have analyzed the mechanisms of controlling the infiltration of lymphocytes into tumor tissues.

Simulated annealing, a general-purpose method of multivariate optimization, is applied to combinatorial optimization, which is to find the minimum of a given function depending on many parameters.

We compare the results of the different methods including the global optimization algorithm, known as simulated annealing.

INTRODUCTION

It has been generally accepted that T cells have a crucial role in regulating tumor growth. Considerable interest has been centered on characterizing the function of lymphocyte infiltrating into tumors.

It is well known that the generation of cytotoxic T cells (CTL) is regulated by soluble factors that are produced by T cells or macrophages (Mϕ) in response to antigen. The existence and involvement of new lymphokines required for the generation of CTL against allogeneic tumor cells are described by many papers. However, in case of syngeneic tumor it had not been shown if the soluble factors are actually involved in the generation of CTL.

Dr. Uede and his colleagues demonstrate that tumor infiltrating T cells play an important role in the regulation of inoculated syngeneic tumor cell growth [1-5]. They show that cytotoxic cell generating factor (CGF) is produced by spleen cells of sensitized rats upon inoculation of syngeneic tumor cells. CGF promotes the generation of CTL against T-9 cells.

The main objectives of the present study are: 1) to establish a mathematical model of the mechanisms of mononuclear cells infiltrating into tumors; 2) to estimate parameters of the model; and 3) to draw possible conclusions.

MATHEMATICAL MODEL

A. Tumor Dynamics

Fisher rats were sensitized with T-9 cells as described in materials and methods in [1-2]. The results of the tumor growth in normal or sensitized rats are shown in [1-5]. We also reviewed briefly in [6].

A widely used deterministic tumor cell proliferation is given by a Gompertz equation of the following form [7-9]:

$$\frac{dN}{dt} = b\,N\,\ln\left(\frac{k}{N}\right) \tag{1}$$

where N(t): the measure of tumor size, i.e., the number of tumor cells,
k : the maximum tumor size, and
1/b : the length of time required for the specific growth rate to decrease by a factor of 1/e, i.e. the e-folding time.

The solution of the Gompertz equation (1) with initial value N(0) is

$$N(t) = N(0)\,\exp\left[\ln\left(\frac{k}{N(0)}\right)(1 - e^{-bt})\right]. \tag{2}$$

Dr. Uede mentioned that a million syngeneic gliosarcoma (T-9) cells injected subcutaneously are sufficient to kill Fisher rats within 2 months [1]. However, they didn't give the data of the largest tumor size enough to kill Fisher rats. Therefore, equation (2) are replaced using initial growth data as follows:

$$N(t) = N(0)\,\exp\left[\frac{A}{b}(1 - e^{-bt})\right] \tag{3}$$

where A: the initial specific growth rate.

The data are fitted using the least squares method and the estimated parameters are as follows:

$\hat{b} = 0.2755933$

$\hat{A} = 2.919033$

The curve fitted to data for unperturbed T-9 tumor cells is illustrated in Fig. 1.

B. Mechanisms of Mononuclear Cells Infiltrating into Tumors.

The functional description of our model is shown in Fig. 2.

Dr. Uede and his colleagues showed that the syngeneic tumor cells are killed by mainly cytotoxic T cells and the CTL in tumor region migrates in response to LMF-4d and

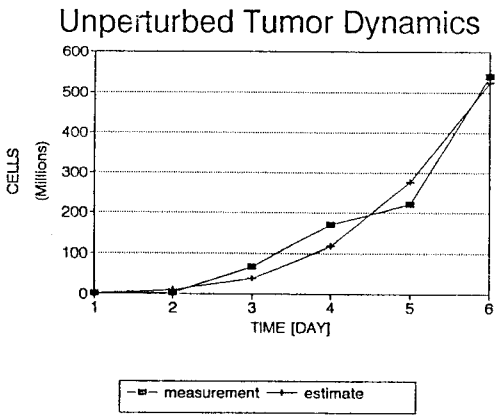

Fig. 1 Unperturbed T-9 tumor dynamics.

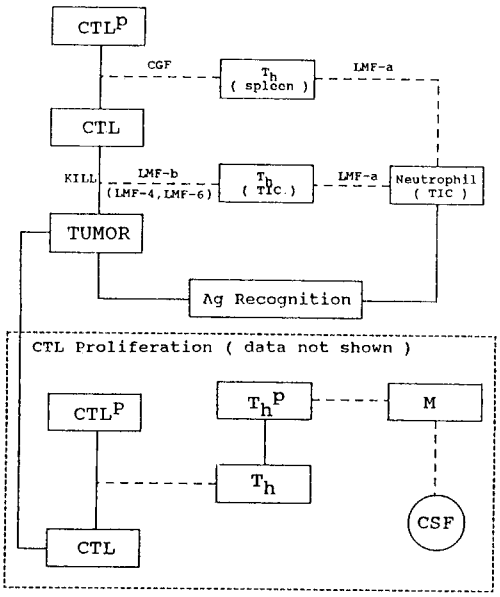

Fig. 2 Mechanisms of mononuclear cells infiltrating into tumors.

LMF-6d. However, they didn't exclude the CTL proliferation by virtue of interleukin-2 (IL-2).

Based on the phenomenological model, we can make a mathematical model of the mechanisms of mononuclear cells infiltrating into tumors due to cell kinetics. These cellular kinetics are quite well defined from conservation equations and chemical mass-action principles [10].

$$\frac{dx_1}{dt} = -\frac{x_1}{\tau_1} + u_1$$

$$\frac{dx_2}{dt} = -\frac{x_2}{\tau_2} + u_1$$

$$\frac{dx_3}{dt} = -\frac{x_3}{\tau_3} - \delta_1 x_3 + u_2 \qquad (4)$$

$$\frac{dx_4}{dt} = -\frac{x_4}{\tau_4} + \delta_2 x_3$$

$$\frac{dx_5}{dt} = b\, x_5 \ln\left(\frac{k}{x_5}\right) - kill\, x_5$$

$$u_1 = \begin{cases} 43 & \text{at } 0.25 < t < 0.5 \\ 3 & t > 1 \end{cases} \qquad : \text{LMF-a}$$

$$u_2 = \frac{\alpha_2 \cdot x_1}{k_2 + x_1} \qquad : \text{CGF}$$

$$\delta_2 = \delta_{20} + \alpha \tanh[\beta(x_2 - x_{20})] \qquad : \text{LMF-b}$$

$$kill = \frac{\alpha_4 \cdot x_4}{k_4 + x_4}$$

where x_i: state of each cell at a certain time instant. The subscripts are as follows: 1, T_h at spleen: 2, T_h at TIC: 3, CTL at spleen: 4, CTL at tumor: and 5, Tumor

δ_1 : CTL migration coefficient from spleen to other compartments

δ_2 : CTL migration coefficient from spleen to tumor
- δ_{20} : $(\delta_h + \delta_l)/2$
- δ_h : max. LMF
- δ_l : min. LMF
- α : $(\delta_h - \delta_l)/2$
- β : (slope at x_{20})/α

α_2 : CGF coefficient

k_2 : CGF saturation

α_4 : tumor killing rate

k_4 : tumor killing saturation

τ_i : death time constant
assumed $\tau_1=\tau_2$, $\tau_3=\tau_4$.

The model can be expressed mathematically as five nonlinear differential equations and three algebraic equations as above. The nine parameters form the vector, θ, given by: $\theta = [\tau_1, \tau_3, \delta_1, \delta_2, k_2, \beta, x_{20}, \alpha_4, k_4]$. The experimental data and initial conditions for the model simulation are shown in [6].

C. Nonlinear parameter Estimation

Parameter estimation arises in fitting model containing several unknown parameters to experimental data. The model consists of nonlinear differential and algebraic equations. The model is stiff and this infers an excessively small step size requiring enormous computing time to solve the system equations. Thus one must choose a reliable model solver before parameter estimation can begin. As a means of solving general stiff systems, the most commonly used methods are semi-implicit Runge-Kutta and Gear method [11]. In the present paper the IMSL routine DGEAR is used to integrate the ODE's. After a model is proposed and solution techniques are chosen, an objective function that determines the goodness of fit must be selected.

1) Maximum Likelihood Method

To apply the likelihood function assume a relationship of the form:

$$z_{uj} = y_{uj}(\theta) + \varepsilon_{uj} \qquad (5)$$

where z_{uj} = measured value for component j

$y_{uj}(\theta)$ = computed value of component j from in u^{th} experiment

θ = vector of adjustable model parameters

ε_j = residual error, assuming the model is correct.

Assume i) the errors in each experiment are Gaussian: ii) unknown covariance V, then :

$$\log L(\theta) = \frac{mn}{2}\left[\log\left(\frac{n}{2\pi}\right) - 1\right] - \frac{n}{2} \log \det M(\theta) \qquad (6)$$

Maximizing this is equivalent to minimizing

$$\phi(\theta) = (\frac{n}{2}) \log \det M(\theta). \quad (7)$$

If off-diagonal element of $M(\theta)$ is zero (i.e., uncorrelated), then the likelihood function reduces to a simple residual sum of squares which can be minimized to the fit the observed data, i.e:

$$\phi(\theta) = \frac{n}{2} \sum_{a=1}^{m} \log M_{aa}(\theta) \quad (8)$$

where $M_{aa}(\theta) = \sum_{u=1}^{n} e_u(\theta)\, e_u^T(\theta)$

$$= \sum_{u=1}^{n} (z_{uj} - y_{uj})\,(z_{uj} - y_{uj})^T$$

log L is maximized relative to θ by minimizing $M_{aa}(\theta)$. Maximum likelihood here is equivalent to unweighted least squares. This derivations apply only to experimental runs with no missing data [12].

2) Initial parameter Guess

In the above kinetic model, it is necessary to fit nonlinear equation to experimental data by applying least squares. Every parameter optimization methods require that one supply an initial guess θ_i for the values of the parameters. Unfortunately, the outcome of such an analysis often depends on the values of the unknown parameters supplied at the beginning of the program. The choice of a good initial guess can spell the difference between success and failure in locating the optimum, or between rapid and slow convergence to the solution. Since there is no single best way to begin this search, we must rely heavily on intuition and prior knowledge in selecting the initial guess. The techniques below are the most likely to succeed [13]: 1) use of prior information: 2) cyclic parameter estimation: 3) linearization: and 4) grid search.

RESULTS AND DISCUSSION

The problem under consideration here is that of using the least square method of curve fitting the model which may be nonlinear in its parameters. Also, all the measured variables are subject to error. This nonlinear minimization problem requires an iterative procedure starting from some initial approximations. As mentioned above, the ability to converge, the converged parameter values, and the sum of squares of residuals at convergence are heavily dependent upon the initial parameter estimates.

The IMSL routine DGEAR was used to find approximations to the solution of a system of first order ordinary differential equations with initial conditions. The finite difference, Levenberg-Marquardt routine ZXSSQ from the IMSL library was used to solve nonlinear least squares problems [14]. A partial summation was used in the objective function to account for the missing data. The problem considered is to estimate nine parameters from seventeen measurements which have incomplete data. The surface formed from sum of squares of residuals in the parameter space is too flat. This means that there exists lots of local minima. This is very difficult to find optimal solution.

The solution found by the investigator is shown in Fig. 3. The problem has common feature, that is, incomplete observation which is usually encountered in biomedical data. This can be overcomed using the EM algorithm which consists of an expectation step followed by a maximization step.

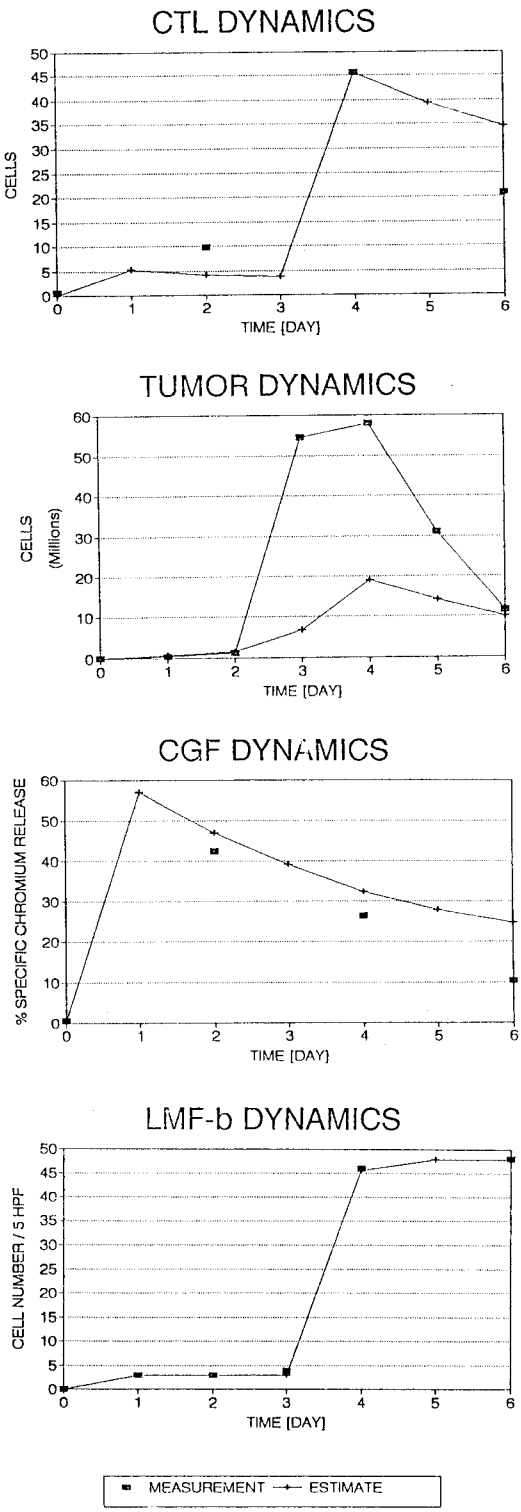

Fig. 3 Model with optimal parameter estimates.

The parameter estimation algorithm we have used converges rapidly for almost any initial estimates of the parameters. The rapid convergence is easy to fall into unfavorable local minima. The method of simulated annealing has recently attracted significant attention as suitable for optimization problems [15]. The method has the idea from the fact that the crystal is the state of minimum energy for the system and nature is able to find the minimum energy state as slowly cooling. In fact, if a liquid metal is cooled quickly or "quenched," it does not reach this state but rather ends up in a polycrystalline or amorphous state having somewhat higher energy.

SIMULATED ANNEALING TECHNIQUES

Simulated annealing is a well-known powerful global optimization algorithm, introduced in combinatorial optimizations [16]. It is based on random moves, and has the ability to overcome local minima, found on the way toward a better minimum, with uphill moves. For a more complete discussion, see [17].

The result has dependence on neither the initial condition of the metal, nor any of the details of the statistical annealing process. However, The drawback of using simulated annealing is that the computation time is quite long.

CONCLUSIONS

A simulated annealing algorithm for the mathematical modelling of immune systems with multiple parameters has been presented. We compare the results of the different methods including the global optimization algorithm, known as simulated annealing, when used to solve optimization problem.

Although simulated annealing is computationally very expensive, it may be an important method for the model building where numerous constraints are present.

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