PERGAMON Mathematical and Computer Modelling 33 (2001) 1275–1287

MATHEMATICAL AND COMPUTER MODELLING

www.elsevier.nl/locate/mcm

Modeling Tumor Regrowth and Immunotherapy

V. A. KUZNETSOV
Civilized Software, Inc.
Silver Spring, MD 20906, U.S.A.
and
Institute of BioChemical Physics
Kosygin Street 4/8, Moscow, 117977, Russia
www.civilized.com

G. D. KNOTT
Civilized Software, Inc.
Silver Spring, MD 20906, U.S.A.
www.civilized.com

Abstract—Deterministic models describing mechanisms underlying tumor growth, suppression, and regrowth are proposed and fit to kinetic data on B cell lymphoma in mice. It is demonstrated that either a modest change in the effectiveness of killer cell suppression, or the existence of a variant nonimmunogenic clone of the tumor cells, can explain the regrowth of a tumor after initial suppression. Adjuvant immunotherapy after establishing the cancer dormancy is modeled as a stimulated increase of the flow of killer cells into the tumor or a local increase of the rate of proliferation of these cells in a tumor. We modeled the immunotherapy consisting of impulse injections of immune lymphocytes in the vicinity of the tumor. Our numerical experiments show that this immunotherapy does not completely destroy the tumor, although thereafter the tumor may persist in a dormant cancer state or have its regrowth markedly delayed.

Keywords—Mathematical models, Tumor regrowth, Immune response, Immunotherapy.

1. INTRODUCTION

Tumors that originate in the body via a variety of mechanisms usually grow slowly. Many months or years may be needed for the existence of such a tumor to manifest itself. This near-steady-state existence of a tumor is described by the term *cancer dormancy* [1,2]. Cancer dormancy is a well-recognized clinical phenomenon in which malignant cells persist for a prolonged period of time with little or no increase in the tumor cell population. This state may occur naturally or following apparently-effective therapy.

There are at least two plausible independent pathways to the clinically "quiescent state" of a tumor. The first pathway corresponds to intrinsic properties of the tumor cells (related to the expression of suppressor genes, production of growth, and/or antigrowth factors and corresponding receptors, etc.). The second pathway corresponds to approaching an equilibrium of interaction between the growing tumor cell population and various cellular and molecular components of the

0895-7177/01/$ - see front matter Typeset by AMS-TEX
PII: S0895-7177(00)00314-9

immune system. In either or both situations, the tumor appears to be dormant. Nevertheless, tumor dormancy is not necessarily a stable state. Many factors—concomitant infection, stress, immunodepression events, changes in endocrine status, etc.—may disturb the balance between the host and the dormant tumor.

We will present a mathematical model for tumor growth and suppression below and show that this model can describe the regrowth of a dormant tumor by either of two distinct mechanisms. The first mechanism is a modest decrease in the efficiency of immune-suppression of the tumor which, prior to this decrease, has been able to maintain an equilibrium state wherein the tumor does not exhibit growth. Variants of this mechanism have been studied in [3,4]. The second mechanism we explore is the existence of a mutant clone of tumor cells which is not effectively suppressed by an immune response, and hence, grows unchecked, except for natural constraints imposed by nutrient resources.

In our model, tumor growth is reversed and then held in check by the continual attack of killer cells; however, when the equilibrium relationship between the killer cell and the tumor cell populations is suitably perturbed, the tumor "escapes" control and grows.

2. SINGLE CLONE MODEL FOR TUMOR REGROWTH

Let $c(t)$ denote the number of cancer cells present at time t, measured in units of one million cells. Let $e(t)$ denote the number of cytotoxic killer cells present at time t, measured in units of one million cells. Then the growth-rate of the cancer cell population is defined by the differential equation

$$c'(t) = kc(t)\,(1 - bc(t)) - ape(t)c(t).$$

The term $kc(1 - bc)$ is the intrinsic rate of tumor cell growth. The parameter k is the maximal rate of tumor-cell growth (when $b = 0$, the tumor grows at the rate k,) and the parameter b is the reciprocal of the maximal tumor cell population size; i.e., $1/b =$ (the maximum number of tumor cells permitted to arise)$/10^6$.

The term $apec$ specifies the rate of destruction of tumor cells. We assume that killer cells bind with tumor cells, and that when this occurs then either

(1) the tumor cell is destroyed, or
(2) the killer cell is destroyed or inactivated.

(The event that both cells are destroyed is deemed negligible.)

The parameter p is the proportion of tumor cells bound with killer cells that will be destroyed, and $1 - p$ is the proportion of tumor-cell-killer-cell bound pairs where the killer cell is destroyed. The parameter a is defined so that $a(1 - p)$ is the rate of killer cell destruction (after binding with a tumor cell), and ap is the rate of tumor cell destruction (after binding with a killer-cell). Note that $1 - a$ is the rate of neither cell killing the other after binding, and unbinding to try again. Thus, ap is the "kinetic" constant that multiplies e and c to form the overall tumor-cell destruction rate term $apec$.

The growth-rate of the killer-cell population (which changes size as new killer cells are attracted and arrive via the lymph system) is defined by the differential equation

$$e'(t) = r + \left(\frac{f(t)c(t)}{(g + c(t))}\right) e(t) - de(t) - (a(1 - p)c(t))\,e(t).$$

The parameter r is the base rate of arrival of killer cells at the tumor via the lymph system: we take r to be a derived parameter defined as $e_0 d$, where $e_0 = 0.3$ (0.3 million is our estimate of the number of killer cells present in the absence of tumor cells taken from [3,4]). The term $(f(t)c/(g + c))e$ is the additional rate of both local proliferation and arrival of killer cells due to the chemokine and cytokine stimulation signals induced by the tumor-cell population of size c.

The expression $f(t)c/(g + c)$ is a logistic growth rate expression in which $f(t) =$ if $t = 0$ then v else if $t < u$ then 0 else v. (The notation "if D, then E_1 else E_2" defines a function with a

discontinuity, so that "if D then E_1 else E_2" is the value of the expression E_1 when the condition D holds, and is the value of the expression E_2, otherwise.) The parameter v is the maximal rate of logistic growth of killer-cell population due to tumor growth, and the parameter u is the delay time of the immune response before "new" killer cells can be applied to attack the tumor; i.e., u is the time for precursor cells to mature into killer cells. The function f "cancels" the additional growth term until $t > u$. The parameter g is the midpoint (IC-50) logistic parameter in the additional arrival rate term. The parameter d is the natural rate of death of killer cells. Finally, the term $a(1-p)ce$ is the rate of killer-cell death or inactivation due to the presence of H_2O_2, gangliosides, cytolytic peptides produced by the tumor, etc.

We have used the experimental data due to [5], where BCL_1 lymphoma tumor cells were injected into the spleens of chimeric mice, and the resulting tumor growth was followed. In particular, we are given the mean number of tumor cells at various times seen in four groups of mice (numbered 0, 1, 2, 3). These seeded tumors were initially of approximate size 0.5 million cells per mouse in Group 0, 0.5 million cells per mouse in Group 1, five million cells per mouse in Group 2, and 50 million cells per mouse in Group 3. In Groups 1, 2, and 3, the resulting tumors respond to the action of the immune system. Group 0 mice have no immune response; tumor-size data from this group will be used to help estimate the parameters that define tumor growth by fitting the pure growth model $c'(t) = kc(t)(1 - bc(t))$ with $c(0) = 0.5$.

It is appropriate to both fit and view the data and our fitted models in logarithmic form; doing this is equivalent to weighting the data to assume the error in the tumor-size observations is more nearly log-normal than normal. The main purpose, however, is to introduce convenient units for both fitting and viewing. In order to fit the data, we replicated our model for each of the Group 1, 2, and 3 data-sets, and introduced the pure-growth differential equation model mentioned just above for the Group 0 data. We have assumed that the initial number of killer cells contained in the spleen of the chimeric mice of Groups 1, 2, and 3 is 0.3 million, so we used the initial conditions $e(0) = e_0$ for each replicated differential equation, where $e_0 = 0.3$. This indicates that $e_0 10^6$ is the number of killer cells that were initially present when the tumor cells were injected.

We used the `MLAB` mathematical and statistical modeling system from Civilized Software Inc., Bethesda, MD, (see `www.civilized.com` [6]) to fit our models and draw the corresponding graphs, since `MLAB` is especially designed to deal with differential equation models, including large systems of stiff equations. For the four data-sets used, fitting our model consists of fitting four functions defined by seven differential equations to estimate the eight parameters d, u, v, p, a, k, b, and g. This fitting required various exploratory computations and careful search of the parameter space for suitable initial guesses that lead to physiologically-plausible values. Our result is $d = 0.5910007682$, $u = 28.05445851$, $v = 0.524999404$, $p = 0.9982002827$, $a = 0.138698686$, $k = 0.1877015458$, $b = 0.001880059483$, and $g = 0.1607110637$. Note particularly that 28 days is an appropriate estimate of the maturation time for $CD8^+$ cytotoxic T lymphocytes. Figure 1 shows this fit. Note that for Groups 1, 2, and 3, the tumor growth is suppressed and enters a equilibrium state of apparent dormancy. The limiting stable steady state of our model in this situation may be interpreted as the tumor dormant state.

Now, if we modify our model to have the parameter p change from 0.9982002827 to 90 percent of that value after 150 days, then tumor regrowth is exhibited as shown in Figure 2. This is done by replacing p in our seven differential equations by the expression $h(t)$, and defining $h(t) =$ if $t < 150$ then p else $0.9p$. This result indicates that a modest decrease in immune response effectiveness, corresponding to a small increase in the proportion $1-p$ of killer lymphocytes being inactivated by tumor cells, dramatically changes the outcome of the disease.

It is worthwhile to note that suitably changing the parameters v, d, or k can produce a similar regrowth event. However, increasing the parameter g from 0.16 to 5 did not change approaching the tumor dormancy steady state. Thus, our modeling suggests that regrowth of a dormant tumor may be associated with diminishing immune system activity, caused by a variety of mechanisms.

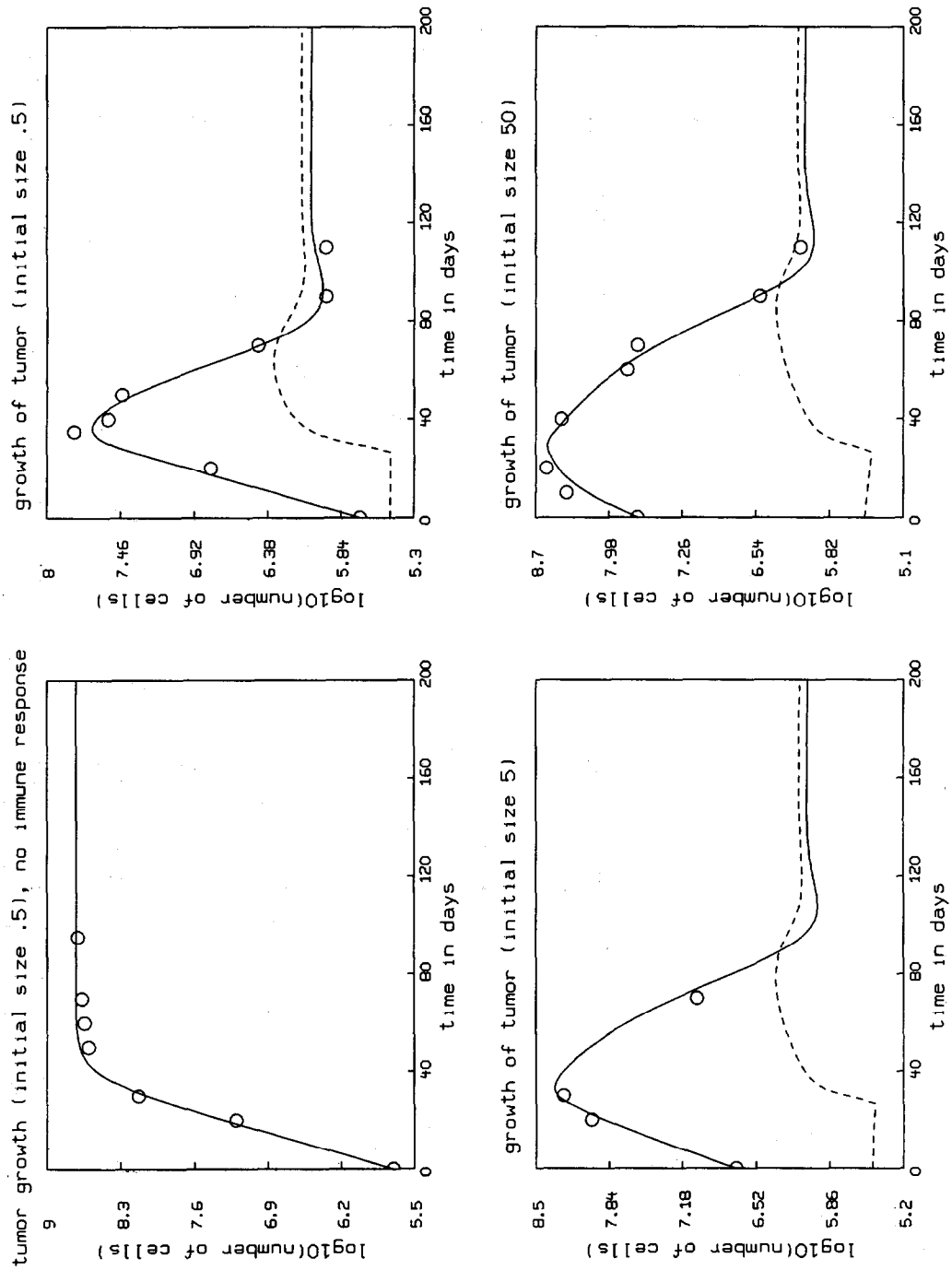

Figure 1. Fit of immune-response model to Group 0-3 data. Dashed line = killer cells, solid line = tumor cells, circles = data of Sui *et al.* [5].

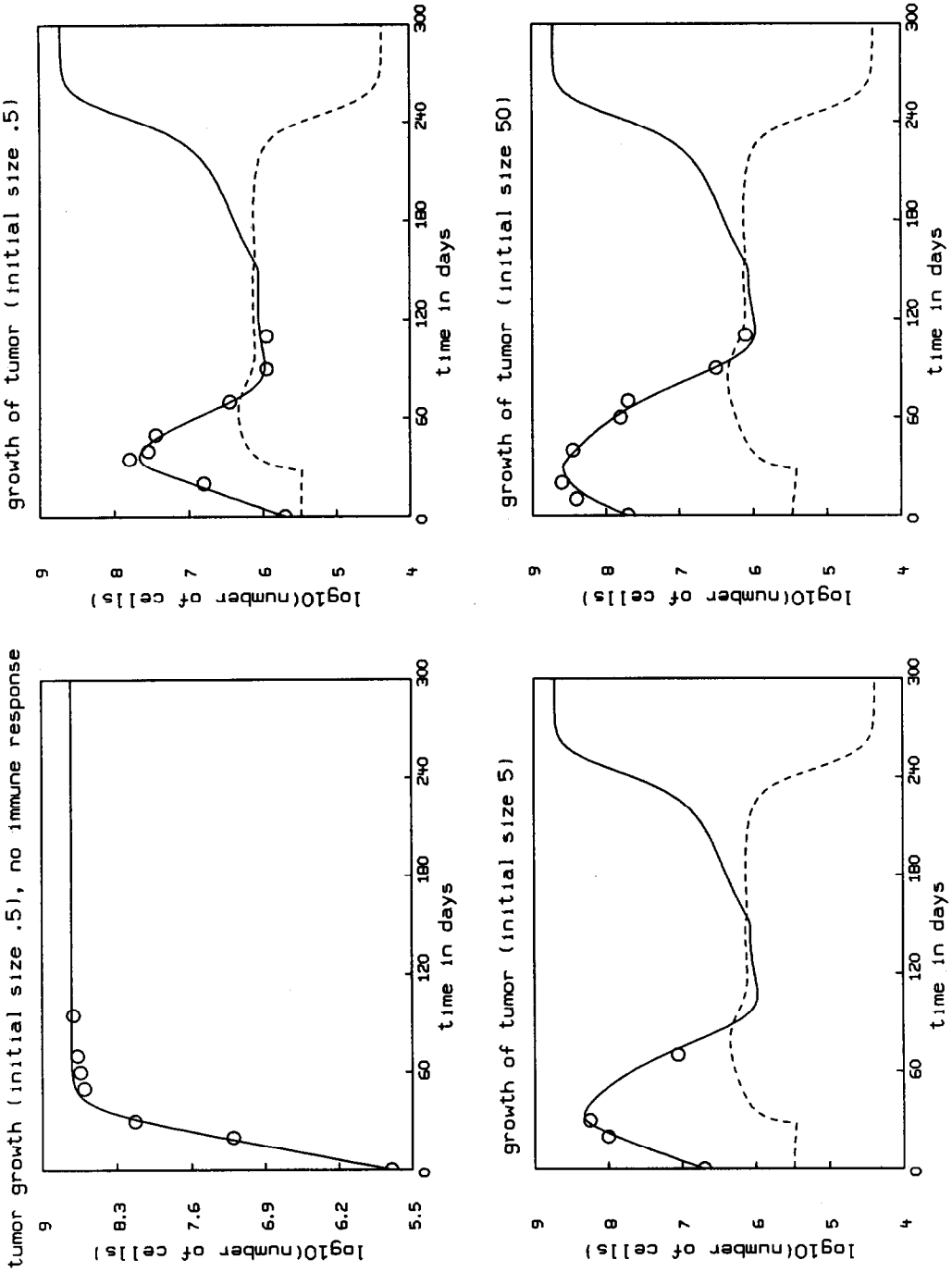

Figure 2. Fit of immune-response model to Group 0–3 data with 10% lower killing probability after 150 days. Regrowth is apparent. Dashed line = killer cells, solid line = tumor cells.

Many immune functions are reduced with age [7] or chronic stress [8]. We explored the effect of diminishing the various immunological parameters in our model; we observed that slowly reducing the parameters p, v, d, or k with age induced regrowth of the dormant tumor. Figure 3 shows that introducing a linear reduction of parameter v causes the tumor to leave the dormant state and regrow to a very large mass by 250 to 300 days after the initial challenge. The rate of tumor regrowth is about three times slower than the rate of primary tumor growth. This result agrees with the experimental data of Sui *et al.* [5] and Vitetta *et al.* [2]. The simulation of regrowth with diminishing immune activity shown in Figure 3 was done by linearly decreasing the parameter v by replacing v with the expression $v(1-\rho(t-\eta))$, where $\eta = 150$ days and $\rho = 0.002$ (1/day).

3. TWO CLONE MODEL FOR TUMOR REGROWTH

Another explanation of tumor regrowth is that there is a small population of immune-resistant cancer cells that are either initially-present or that develop and which grow unchecked by the action of killer cells. We can explore the behavior of such an aberrant clone population by introducing a pure growth model for such a population via the differential equation $m'(t) = 0.33km(t)(1-b(m(t)+c(t)))$ with $m(0) = sc(0)$ and modifying the growth term $kc(t)(1-bc(t))$ to be $kc(t)(1-b(m(t)+c(t)))$ in the differential equation that defines the function c. The parameter s is the proportion of the initial population of cells that matches the size of the initial population of aberrant immune-resistant cells.

Thus, the two clones model for cancer regrowth is written

$$\begin{aligned} c'(t) &= kc(t)\left(1-b\left(c(t)+m(t)\right)\right) - ape(t)c(t), \\ m'(t) &= 0.33km(t)\left(1-b\left(m(t)+c(t)\right)\right), \\ e'(t) &= r + \left(\frac{f(t)c(t)}{(g+c(t))}\right)e(t) - de(t) - \left(a(1-p)c(t)\right)e(t), \end{aligned}$$

with $c(0) = c_0$, $m(0) = sc_0$, $e(0) = e_0$, and $f(t) =$ if $t < u$ then 0 else v, where $e_0 = 0.3$ and c_0 is variously equal to 0.5, 5, and 50.

We can estimate the value of s that causes the total tumor size $c(t)+m(t)$ to rise to the value 500 after 290 days by simultaneously curve-fitting replicates of the function $c(t)+m(t)$ to the point $(290, 500)$ for Groups 1, 2, and 3, along with the data for each group of chimeric mice. We also fit these model functions to the additional data point $(110, 1)$, corresponding to 10^6 being the number of dormant tumor cells present initially at days 100 to 110 as estimated in [1]. MLAB permits such simultaneous fitting of many functions indirectly defined by differential equations. We obtained $s = 4.081604 \cdot 10^{-5} \pm 1.86 \cdot 10^{-5}$. The result is shown in Figure 4.

4. SIMULATION OF IMMUNOTHERAPY FOR AN ESTABLISHED DORMANT CANCER

Inducing an increased presence of various cytokines, chemokines, and/or other immunomodulators in tumor tissue may augment the function of the immune system, and this can accomplished via vaccine agents without serious toxicity, provided a rational approach is used [9]. Such therapeutic vaccine agents can indirectly enhance the influx of killer cells into tumor tissue.

In Figure 5, we show the results of numerically simulating the effects of changing the dynamics of the immune system via various vaccine regimes, thus modifying its action on an established dormant tumor. Such a change will result in reducing the tumor mass. However, this response is temporary, and tumor regrowth may occur after stopping the immunotherapy and thereby reducing the influx of killer cells.

Figure 5a shows the result of increasing the flow of killer cells into a dormant tumor in three steps due to three imagined vaccine immunization treatments administered on day 180, day 194, and day 215. The modeled tumor is characterized by the parameters of a "normal" mouse

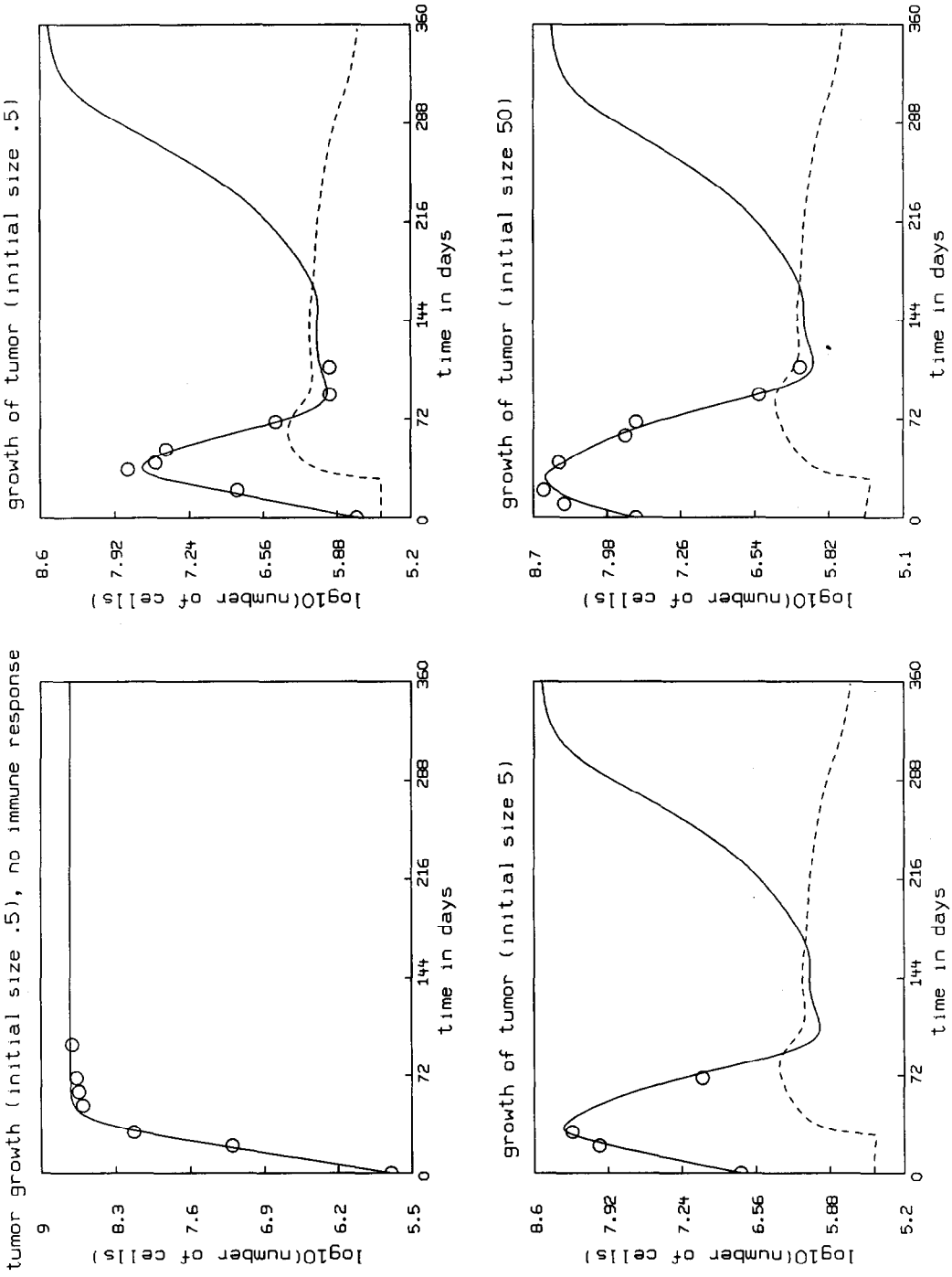

Figure 3. Regrowth of dormant tumor due to slow reduction of immune reactivity in aging mice. Dashed line = killer cells, solid line = tumor cells.

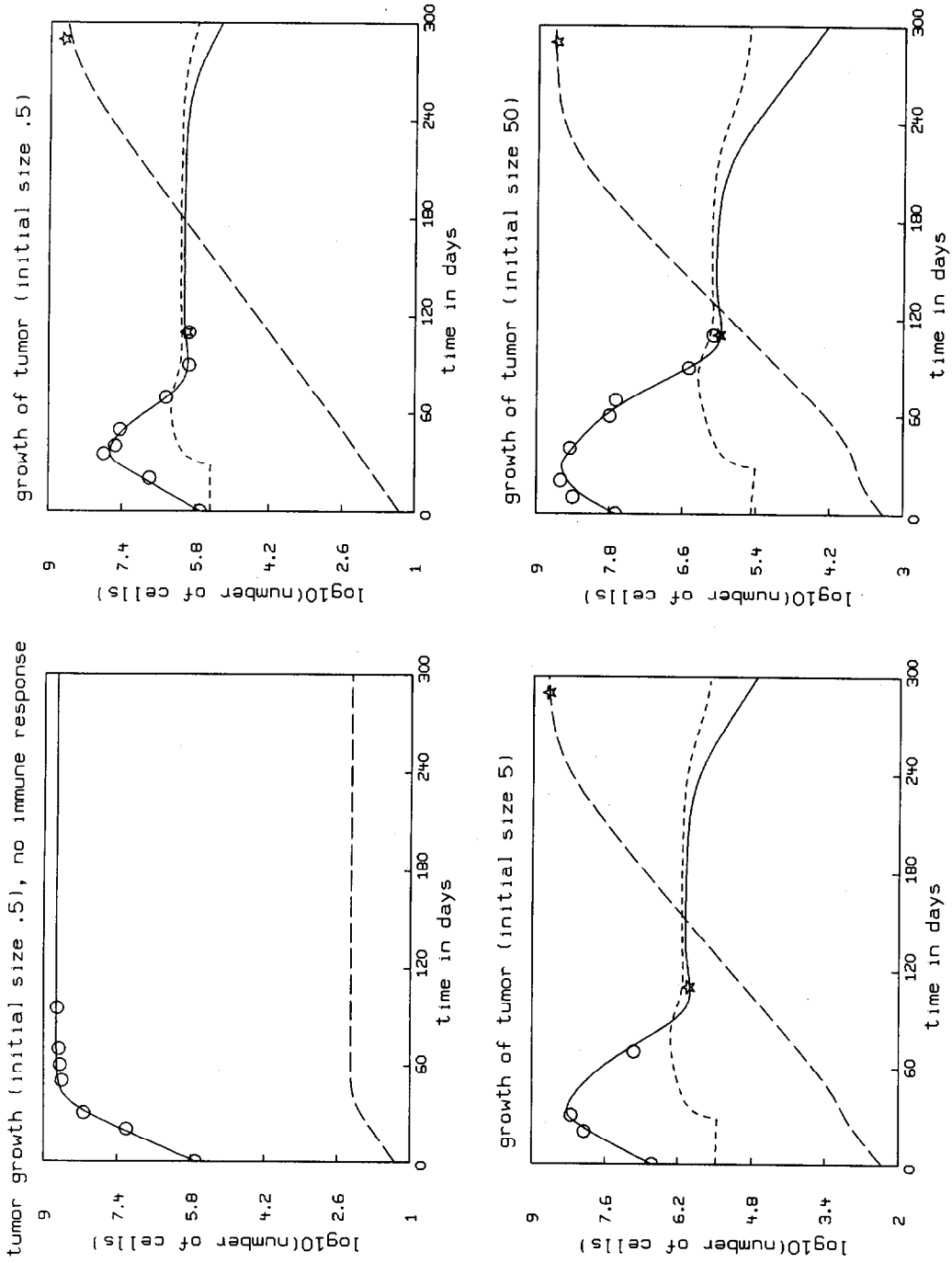

Figure 4. Antitumor immune response model with resistant aberrant clone fit to Group 0–3 data with 10^6 killer cells at day 110. Dashed line = killer cells, solid line = tumor cells, long dashed line = aberrant clone tumor cells.

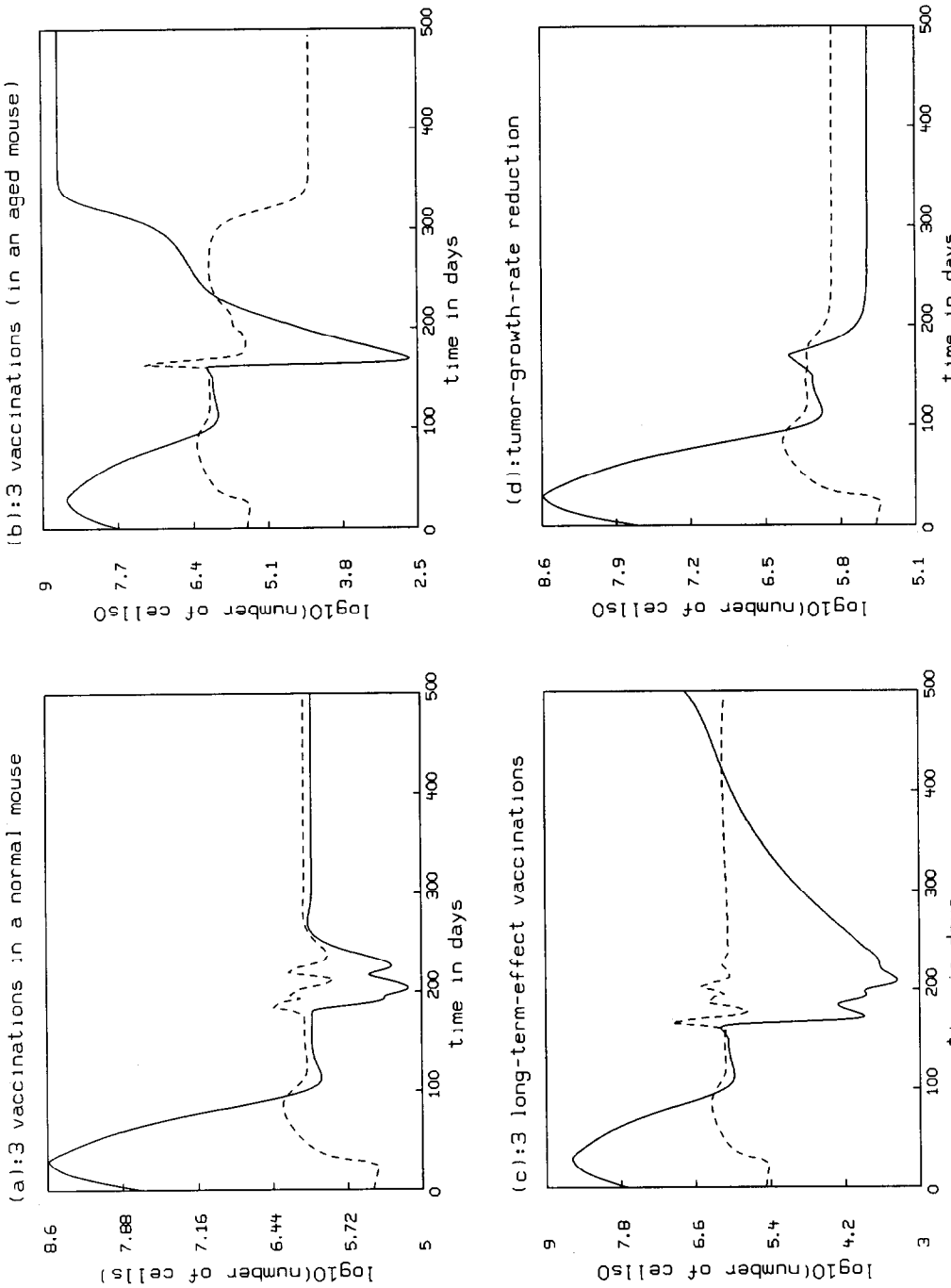

Figure 5. Simulation of adjuvant immunization. (a) during dormancy; (b) after start of tumor regrowth; (c) immunization with long-life memory cells; (d) induction of diminished tumor growth rate. Dashed line = killer cells, solid line = tumor cells.

obtained by fitting and exhibited in Figure 1. In this case, we assume the vaccination provokes a temporary rise in the size of the population of killer cells available to attack the tumor; this increase is independent of the (dormant) tumor-size. This is done by modifying the "base arrival rate" $0.3d$ by multiplying by factors that are temporarily greater than one, corresponding to each vaccine injection.

The therapeutic effect of vaccination shown in Figure 5a was modeled by the following equations:

$$\begin{aligned} e'(t) &= q(t)(0.3d) + \left(\frac{f(t)c(t)}{(g+c(t))}\right) e(t) - de(t) - a(1-p)e(t)c(t), \text{ and} \\ c'(t) &= kc(t)\,(1 - bc(t)) - ape(t)c(t), \text{ with} \\ f(t) &= \text{if } t < u \text{ then } 0 \text{ else } v. \end{aligned}$$

The effects of the vaccinations are described by the "multiplier" function q, where

$$\begin{aligned} q(t) &= f_1(t)f_2(t)f_3(t), \text{ and} \\ f_1(t) &= 1 + w\,(t, u_1)\,, \\ f_2(t) &= 1 + w\,(t, u_2)\,, \\ f_3(t) &= 1 + w\,(t, u_3)\,, \text{ and} \\ w(t,z) &= \text{if } t < z \text{ then } 0 \text{ else } 60\,(\exp(-0.35(t-z)) - \exp\,(-0.4(t-z))\,. \end{aligned}$$

The function $w(t, z)$ is 0 until time z; at time z it rises to a maximum of nearly three at about time $z+7$ (indicating a four-fold increase of the arrival-rate of killer cells); and thereafter, exponentially decays to nearly zero by day $z + 18$.

We used the initial conditions $e(0) = 0.3$, $c(0) = 50$, and the parameter values used for Figure 1, together with $u_1 = 180$, $u_2 = 194$, and $u_3 = 215$.

Figure 5b shows the result of modeling such imagined immunizations beginning ten days after tumor regrowth has started in a mouse with a diminished immune response as modeled in Figure 2; thus, the vaccinations occur at days 160, 174, and 195. Also, in this case, we assume our vaccine works by increasing the proliferation of killer cells in response to the logistic tumor size function, rather by increasing the arrival rate independently of the tumor size. This is done by multiplying the tumor-size dependent growth term for the killer cell population by factors which are temporarily greater than one, rather than modifying the base arrival rate as done above. Also, we assume that, although the number of killer cells increases in response to vaccination, their effectiveness, as measured by the parameter p, remains diminished at a level 10% lower than the "normal" mice modeled in Figure 1.

Our model is given by the following differential equations:

$$\begin{aligned} e'(t) &= 0.3d + q(t)\left(\frac{f(t)c(t)}{(g+c(t))}\right) e(t) - de(t) - a(1-p)e(t)c(t), \text{ and} \\ c'(t) &= h(t)kc(t)\,(1 - bc(t)) - ape(t)c(t), \text{ with} \\ f(t) &= \text{if } t < u \text{ then } 0 \text{ else } v, \text{ and} \\ h(t) &= \text{if } t < 150 \text{ then } p \text{ else } 0.9p. \end{aligned}$$

The effects of the vaccinations are here described by the "multiplier" function, q, defined in terms of the functions f_1, f_2, f_3, and w given above; f_1, f_2, f_3, and w are defined as they were above, except that $u_1 = 160$, $u_2 = 174$, and $u_3 = 195$.

We used the initial conditions $e(0) = 0.3$, $c(0) = 50$, and the parameter values used for Figure 2, together with $u_1 = 160$, $u_2 = 174$, and $u_3 = 195$.

Figure 5c shows the result of our simulation of the effect of immunotherapy by injecting immune memory cells in a mouse with a regrowing tumor due to a diminished immune response as modeled

in Figure 2 (and Figure 5b). We assumed that, soon after injection, the memory cells will increase the immune response to the tumor due to enhanced stimulation of the production of killer cells for a period of about 150 days. This mechanism of adaptive immunotherapy is modeled with the differential equations

$$e'(t) = 0.3d + q(t)\left(\frac{f(t)c(t)}{(g + c(t))}\right)e(t) - de(t) - a(1-p)e(t)c(t), \text{ and}$$
$$c'(t) = h(t)kc(t)\,(1 - bc(t)) - ape(t)c(t), \text{ with}$$
$$f(t) = \text{if } t < u \text{ then } 0 \text{ else } v, \text{ and}$$
$$h(t) = \text{if } t < 150 \text{ then } p \text{ else } 0.9p.$$

The effects of the vaccinations are here again described by the "multiplier" function, q, defined in terms of the functions f_1, f_2, f_3, and w; f_1, f_2, and f_3 are defined as they were above, except that $u_1 = 160$, $u_2 = 174$, and $u_3 = 195$. The function w has the same form as before, except that it has been "lengthened" (by changing 0.35 to 0.35/10 and 0.4 to 0.4/10) to correspond to an enhanced rate of proliferation of killer cells proportional to the logistic tumor size for a time period of about 150 days. We used the initial conditions $e(0) = 0.3$, $c(0) = 50$, and the parameter values used for Figure 2, together with $u_1 = 160$, $u_2 = 174$, and $u_3 = 195$.

Figure 5d depicts the simulated situation where we modeled administering a "cytostatic" drug that has the effect of reducing the logistic growth-rate parameter k that governs the rate of tumor regrowth; this might be an agent that reduces the tumors' nutrient supply, for example. In particular, we again used a reduced immune response mouse as described in Figure 2 which exhibits tumor regrowth starting at day 150. We imagine administering a drug that cuts the value of k in half on day 170. This is done mathematically by replacing k with the function $\lambda(t) = \text{if } t < 170 \text{ then } k \text{ else } k/2$.

5. DISCUSSION

Animal models of tumor dormancy are essential for understanding fundamental aspects of cancer biology and for exploring therapeutic strategies that may reduce the risk of tumor relapse [1]. Nevertheless, tumor dormancy has received surprisingly little scientific attention and experimental studies have been minimal. In this article, we have focused on the mathematical analysis of well-established data of BCL_1 lymphoma induced in chimeric mice [5] and explored its prognosis under various assumptions.

The assumption that, after the introduction of tumor cells (at time 0), no enhanced immune response occurred during the first 28 days after the mice were challenged with such injections was key to obtaining the excellent fits exhibited in Figure 1. The probability of inactivation of an immune killer cell after binding to a tumor cell is also a crucial parameter of the model. The value of p, as well as the numerical values of the other kinetic parameters of our model, are typical of the kinetic characteristics of $CD8^+$ cytotoxic T lymphocytes involved in the allogenic immune response in mice.

Recently, two distinct experimental groups [9,10] have reported that cytotoxic T lymphocytes are a major component in the regulation of tumor dormancy of BCL_1 lymphoma. This is further confirmation that our killer cell population is primarily composed of CD8 T lymphocytes as assumed in [3,4]. It has been shown that immune T lymphocytes can recognize idiotype determinants of immunoglobulin molecules on the surface of B-cell lymphoma cells and can induce the local production of interferon-γ (see [1]).

We have studied two related mechanisms of tumor regrowth. The first model predicted that a small permanent reduction in the level of antitumor immune response may provoke the regrowth of a monoclonal tumor from a dormant state. Reducing the probability of killing or inactivation of a tumor cell by an immune killer lymphocyte, or reducing the rate of arrival of the immune

lymphocytes into the tumor region, were the most critical factors in inducing the model to exhibit tumor regrowth. Various factors, i.e., aging, stress, infection, etc., may explain why such a tumor-growth-inducing change might occur. Recently, Flood *et al.* [7] have observed a decline in a number of antigen-specific $CD8^+$ cytotoxic T lymphocytes in mice with age and noted that this decline is associated with the susceptibility to an immunogenic tumor in such older animals, as our modeling corroborates.

Our second two-clone tumor model also agreed with the experimental observations. Under the assumption that a small fraction (0.004%) of the tumor cell population injected initially into the mice is nonimmunogenic and that the growth of this clone is three times slower than the growth rate of the major immunogenic tumor cell population, this model unsurprisingly predicted eventual tumor regrowth. Unlike our first model, this second model also predicts that size of the tumor after dormancy is determined by the initial number of injected tumor cells. Variability of initial doses of injected cells explains the high dispersion of the time of clinical detection of regrown tumor after dormancy [2], under the assumptions of our second model. Moreover, immunological abnormality of a minor fraction of BCL_1 lymphoma cells was reported in the same study [2].

Note that the curves describing tumor regrowth presented above have distinct shapes. It would be interesting to see if tumor regrowth known to be due to immune system decline matches the regrowth profile in our first model while tumor regrowth due to the presence of a abnormal clone matches the regrowth profile of our second model.

Conducting a comparative immunological and genetic analysis of abnormal cell patterns in the original tumor and in tumor cells after dormancy would provide key information to validate or correct our models. The abnormalities sought for could be defined by mutation or by epigenetic adaptation mechanisms.

Clinical and experimental observation confirms that intensive limited-term immunotherapy does not provide complete tumor elimination, as predicted via modeling. Immunotherapy may reduce tumor mass to a handful of cells; however, if the functional activity of the immune system is slightly impaired, tumor regrowth after immunization is likely. Model-fitting predicts that the life time of killer cells is short (about two days). Long term maintenance of anticancer immunity after stopping immunotherapy could be improved if long-life immune memory cells could be activated during immunization. Our modeling thus suggests that immune memory killer cells could be a critical target for immunization and vaccination strategies against BCL_1 lymphoma. Moreover, memory cells could act to establish stable tumor dormancy and, perhaps in some cases, also eliminate dormant primary tumors and small metastatic tumors.

Finally, it would be useful to analyze the data of [5] with other models of cancer dormancy and its regrowth, such as models which follow a Gompetzian growth law [12,13]. The development of physical-chemical models which take into account the spatiotemporal distribution and dynamics of tumor cells, immune cells, and cytokines as explored in [13–16], could be helpful in better understanding cancer regrowth mechanisms and in optimizing therapeutic strategies to reduce the risk of tumor relapse.

REFERENCES

1. J.W. Uhr, R.H. Scheuermann, N.E. Street and E.S. Vitetta, Cancer dormancy: Opportunities for new therapeutic approaches, *Nature Med.* **3**, 505–509, (1997).
2. E.S. Vitetta, T.F. Tucker, E. Racila, Y.W. Huang, R. Marches, N. Lane, R.H. Scheuermann, N.E. Street, T. Watanabe and J.W. Uhr, Tumor dormancy and cell signalling. V. Regrowth of the BCL_1 tumor after dormancy is established, *Blood* **89**, 4425–4436, (1997).
3. V.A. Kuznetsov, A mathematical model for the interaction between cytotoxic T lymphocytes and tumour cells. Analysis of the growth, stabilization, and regression of a B-cell lymphoma in mice chimeric with respect to the major histocompatibility complex, *Biomedical Science* **2**, 465–476, (1991).
4. V.A. Kuznetsov, I.A. Makalkin, M.A. Taylor and A.S. Perelson, Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis, *Bull. Math. Biol.* **56**, 95–119, (1994).

5. H. Sui, E.S. Vitetta, R.D. May and J.W. Uhr, Tumor dormancy I: Regression of BCL_1 tumor and induction of a dormant tumor state in mice chimeric at the major histocompatibility complex, *J. Immunol.* **137**, 1376–1382, (1986).
6. `www.civilized.com`.
7. P.M. Flood, X. Liu, R. Alexander, H. Schreiber and S. Haque, Loss of resistance to a highly immunogenic tumor with age corresponds to the decline of CD8 T cell activity, *J. Immunother.* **21**, 307–316, (1998).
8. B.L. Andersen, W.B. Farrar, D. Golden-Kreutz, L.A. Kutz, R. MacCallum, M.E. Courtney and R. Glaser, Stress and immune responses after surgical treatment for regional breast cancer, *J. Natl. Cancer Inst.* **90**, 30–36, (1998).
9. K.A. Smith, Rational interleukin-2 therapy, *Cancer J. Sci. Am.* **Suppl 1**, s137–s140, (1997).
10. S. Morecki, T. Pugatssch, S. Levi, Y. Moshel and S. Slavin, Tumor-cell vaccination induces tumor dormancy in a murine model of B cell leukemia/lymphoma (BCL_1), *Int. J. Cancer* **65**, 204–208, (1996).
11. J.D. Farrar, K.H. Katz, J. Windsor, G. Thrush, R.H. Scheuermann, J.W. Uhr and N.E. Street, Cancer dormancy. VII: A Regulatory role for CD8+ T cells and IFN-gamma in establishing and maintaining the tumor-dormant state, *J. Immunol.* **162**, 2842–2849, (1999).
12. M. Marusic, Z. Bajzer, S. Vuk-Pavlovic and J.P. Freyer, Tumor growth *in vivo* as multicellular spheroids compared by mathematical models, *Bull. Math. Biol.* **56**, 617–631, (1994).
13. J.A. Adam and N. Bellomo, Editors, *A Survey of Models for Tumor-Immune System Dynamics*, Birkhäuser, Boston, (1996).
14. V.A. Kuznetsov, *Dynamics of Immune Process During Tumor Growth*, (in Russian), Nauka, Moscow, (1992).
15. M.R. Oven and J.A. Sherratt, Pattern formation and spatio-temporal irregularity in the model for macrophage-tumor interaction, *J. Theor. Biol.* **189**, 63–80, (1997).
16. M.A.J. Chaplain, V.A. Kuznetsov, Z.H. James and L.A. Stepanova, Spatio-temporal dynamics of the immune system response to cancer, In *Mathematical Models in Medical and Health Sciences*, (Edited by M.A. Horn *et al.*), pp. 1–28, Vanderbilt Univ. Press, Nashville, TN, (1998).