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REVIEW ARTICLE

Interactions Between the Immune System and Cancer: A Brief Review of Non-spatial Mathematical Models

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Abstract We briefly review spatially homogeneous mechanistic mathematical models describing the interactions between a malignant tumor and the immune system. We begin with the simplest (single equation) models for tumor growth and proceed to consider greater immunological detail (and correspondingly more equations) in steps. This approach allows us to clarify the necessity for expanding the complexity of models in order to capture the biological mechanisms we wish to understand. We conclude by discussing some unsolved problems in the mathematical modeling of cancer-immune system interactions.

Keywords Cancer · Immunology · Tumor-immune system interaction · Ordinary differential equations (ODEs)

1 Introduction

In recent years, evidence has accumulated indicating that the immune system can recognize and eliminate malignant tumors (Parish 2003; Smyth et al. 2001). Much research has focussed on how to enhance the anti-tumor activity, by stimulating the immune system with vaccines or by direct injection of T cells or cytokines (Rosenberg 1991; Rosenberg et al. 2004). Of course, the development of powerful cancer

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immunotherapies requires first an understanding of the mechanisms governing the dynamics of tumor growth.

Early work on tumor growth focussed on trying to understand how "normal" cells can mutate into cancer cells (Greenblatt et al. 1994; Knudson 1971; Nowak et al. 2002). In the last 20 years, it has become evident that the oversimplified concept of a single type of normal cell is inadequate; interactions among multiple cell types and chemicals play fundamental roles in the initiation and progression of tumors (Kammertoens et al. 2005; Mueller and Fusenig 2004). The *tumor microenvironment* includes immune cells, fibroblasts, and other connective tissue cells, endothelial cells (which line the interior walls of blood vessels), the extracellular matrix, signaling molecules (chemokines and cytokines), and growth factors (including cytokines and hormones). The interactions between tumor cells and other components of the tumor micro-environment are complex and continuously changing (e.g., because interaction strengths are density-dependent or concentration-dependent). Consequently, understanding these interactions sufficiently to derive cancer immunotherapies (e.g., vaccines), has proven a very challenging task (Gajewski 2007; Rosenberg et al. 2004).

As a tool to make sense of the interactions among the many components of the tumor microenvironment, researchers have used mathematical models (see, for example de Boer et al. 1985; de Pillis et al. 2005; Goldstein et al. 2004; Kronik et al. 2008). Models can investigate interactions on different biological scales (e.g., molecular, cellular, and tissue scales), and can also investigate the emergent properties of the system, even when the properties of the individual components are not fully known. These mathematical models are used to distill the essential components of the interactions, thus identifying the most plausible mechanisms that can lead to the observed outcomes.

There are many existing reviews of mathematical models of tumor growth and tumor-immune system interactions (Araujo and McElwain 2004; Bellomo and Preziosi 2000; Bellomo et al. 2008; Byrne et al. 2006; Martins et al. 2007; Nagy 2005; Roose et al. 2007; Chaplain 2008). Some of these reviews follow a historical approach (Araujo and McElwain 2004), while others focus on multi-scale modeling (Bellomo et al. 2008; Martins et al. 2007; Bellomo and Preziosi 2000), or on particular aspects of tumor evolution, such as tumor necrosis (Nagy 2005). The majority of these reviews focus on spatial models, which are described either by partial differential equations (PDEs) or cellular automata (e.g., Araujo and McElwain 2004; Roose et al. 2007; Chaplain 2008). One class of models that has been reviewed very recently is based on the mathematical kinetic theory of active particles and describes the early stages of cancer development; these models use integro-differential equations to investigate tumor-immune system interactions (Bellomo and Delitala 2008).

Few reviews focus on non-spatial models, which are described by ordinary differential equations (ODEs) (but see, for example, Adam and Bellomo 1997; Dullens et al. 1986; Bajzer et al. 1996; Sachs et al. 2001; Nagy 2005). While ODE models do not address spatial spread, they provide a simpler framework within which to explore the interactions among tumor cells and the different types of immune and healthy tissue cells. Existing reviews of ODE models focus mostly on models described by one equation, and very briefly treat two-equation or three-equation models (as in Bajzer et al. 1996; Sachs et al. 2001). They also tend to focus on particular

aspects of tumor development, such as competition between different types of tumor cells (as in Nagy 2005).

In this article, we review ODE models starting from the very simplest (involving a single equation) and build up to much more complex models that include successively more features of the tumor micro-environment and the immune system. This approach allows us to clearly articulate the limitations of particular models and to identify the dynamical effects of including greater biological detail. We do not attempt a comprehensive review of all relevant ODE models. Rather, our goal here is to present some of the mathematical approaches taken to investigate different aspects of tumor-immune system interactions, to elucidate the complexity of the problem, and to summarize both the strengths and weaknesses of ODE models.

Cancer immunotherapy research has focused primarily on the anti-tumor activity of white blood cells, especially T cells (usually $CD8^+$ T cells), natural killer (NK) cells, and macrophages. It has been shown experimentally that the these immune cells can lyse (kill by breaking the cell membrane of) tumor cells very effectively (Quesnel 2008). For this reason, most tumor-immune system ODE models focus on the interactions between white blood cells and tumor cells. Some models also include interactions with normal tissue cells, or with cytokines (e.g., IL-2, IFN-γ) and chemokines (chemotactic cytokines). Many of the models incorporate different therapeutic strategies such as administration of cytokines or adoptive transfer of activated T cells (Kirschner and Panetta 1998). We will discuss all these aspects of tumor-immune system modeling.

We begin in Sect. 2 with the simplest models derived to investigate the dynamics of populations of cancer cells (ignoring normal cells). In Sect. 3, we consider elementary models that incorporate a caricature of the mechanism of *immune surveillance*, whereby the immune system identifies and kills foreign cells; these models consider two cell types, cancer cells and generic immune cells. In Sect. 4, we review models (involving three equations) that examine interactions between cancer cells, immune cells, and other type of cells or signaling proteins (i.e., cytokines and chemokines); these models consider interactions among cancer, normal tissue, and immune cells; cancer and two types of immune cells; or cancer, immune cells, and cytokines. In Sect. 5, we review models of four interacting components of the tumor microenvironment (hence involving four equations) and in Sect. 6 we briefly mention some very complex ODE models that incorporate more detailed interactions between the immune system and tumor cells. Finally, in Sect. 7, we summarize and discuss some recent advances in tumor immunology that suggest new avenues for useful mathematical modeling research.

2 One-Equation Models: Tumor Growth

The first step in understanding tumor growth is simply to describe the growth patterns. Extensive patient data has accumulated over many decades as a result of diagnostic imaging, especially through chest X-rays and mammograms (Spratt et al. 1996). These data, such as mammograms taken both before and after the detection of a tumor, indicate that 15–77% of diagnosed breast cancers arise between annual

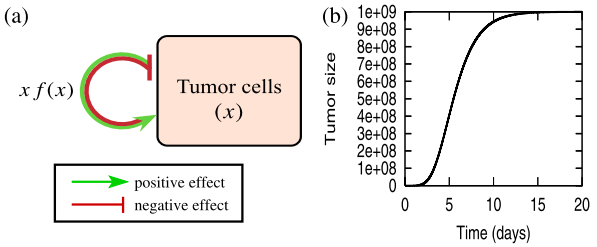

Fig. 1 (**a**) Schematic representation of the dynamics of cancer cells as a result of autoregulatory cell–cell interactions. Autoregulation can have either a positive or negative effect depending on the sign of the regulating factor $f(x)$ (2). (**b**) Sigmoidal curve describing the growth of untreated tumors. Shown is a Gompertzian growth typical for aggressive mice tumors

mammograms. This suggests that the initial growth of a tumor (before it is detectable with diagnostic imaging) is much faster than the growth of detectable tumors (Lala and Patt 1966; Spratt et al. 1996). Gompertz (1825) first explained this type growth by mathematically modeling cell replication and death (and nothing else). His simple model yields a sigmoidal population growth curve (Fig. 1(b)), which shows accelerating growth for small populations and decelerating growth for large populations. In the case of a tumor cell population, the decelerating dynamics displayed by the sigmoidal curve can be explained by the finite nutrient level available to the tumor cells.

Since Gompertz's paper, many mathematical models have been derived to fit and explain tumor growth data, to predict patient survival, and to suggest therapeutic options (Norton 1988). Some of these models assume that the tumors grow exponentially (Skipper and Schabel 1982), but the majority consider decelerating growth (Laird 1964; Hart et al. 1998; von Bertalanffy 1957). The most general equation describing the dynamics of tumor growth can be written

$$x' = xf(x), \tag{1}$$

where x is the cell population size at time t, $x(0) > 0$, and the factor $f(x)$ specifies the density dependence in the proliferation and death of tumor cells. The density dependence factor can be written more explicitly as

$$f(x) = p(x) - d(x), \tag{2}$$

where $p(x)$ describes cell proliferation and $d(x)$ describes cell death. The simplest examples can be expressed as power laws,

$$p(x) = ax^{\alpha}, \tag{3a}$$

$$d(x) = bx^{\beta}, \tag{3b}$$

with $\alpha = 0$ and $\beta = 1$ for the logistic model (Hart et al. 1998), and $\alpha = -1/3$ and $\beta = 0$ for the von Bertalanffy model (von Bertalanffy 1957). If $p(x) = a$ and $d(x) = b\ln(x)$, then (1) reduces to the Gompertz model (Laird 1964). Such models have been reviewed from the perspective of description of growth (Bajzer et al. 1996) and

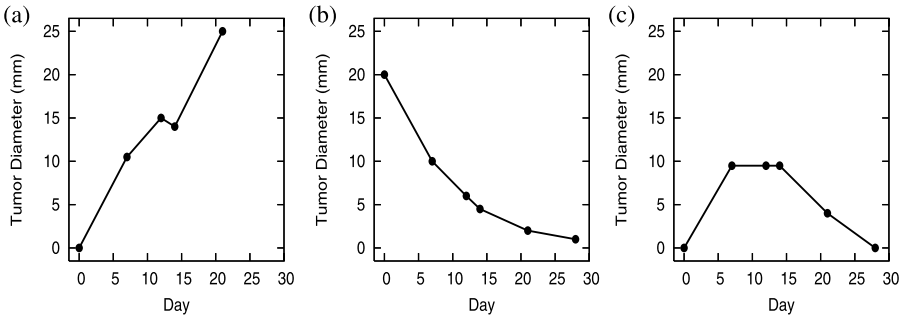

Fig. 2 Examples of possible dynamics of malignant cells. (**a**) Tumor growth. (**b**) Tumor elimination. (**c**) Tumor growth followed by elimination. Panels (**a**) and (**c**) are based on experimental data and are redrawn from Hamilton and Bretscher (2008). Panel (**b**) shows exponential decay, which can occur in mathematical models described by (1)

from a clinical perspective, i.e., ability to predict relapse or response to chemotherapy (Panetta 1998).

While one-equation models sometimes fit data very well (Norton 1988), the applicability of some of these models is restricted. For example, the Gompertz model displays unbounded growth as the density tends to zero,

$$\lim_{x\to 0^+} f(x) = +\infty. \tag{4}$$

Since the proliferation rate of cell populations is eventually bounded by the cell division time, the Gompertz model is not appropriate to describe the dynamics of very small tumors (which is often a serious limitation) (d'Onofrio 2008; Weldon 1988).

For the logistic, Gompertz and many other simple forms of density dependence, there are well-known analytical solutions of (1), making it very easy to use these models to predict the tumor dynamics given a measurement of tumor size at a specific time (and estimates of the model's parameters). Overall, these models have been successful at explaining tumor growth patterns in spite of being based on a single equation describing cell-cell interactions (see Fig. 1(a)). In addition, these models can be used in practice to classify tumors according to aggressivity of growth (Chignola and Foroni 2005) and to quantify the relationship between tumor growth rates and patient age (Weedon-Fekjaer et al. 2008).

Equation (1) can successfully model tumor growth ($p(x) > d(x)$; Fig. 2(a)), decay ($p(x) < d(x)$; Fig. 2(b)) or dormancy ($p(x) = d(x)$). A single equation cannot, however, model the situation shown in Fig. 2(c) in which initial tumor growth is followed by regression (this is mathematically impossible with a single autonomous equation: for a given density x, the right-hand side of (1) always has the same sign, so there is no density at which the population can be increasing at one time and decreasing at another time). However, the behavior described in Fig. 2(c) can be obtained with a one-equation model that incorporates a time-dependent treatment term (Sachs et al. 2001),

$$x' = x\big[p(x) - d(x)\big] - a\phi(t)x, \tag{5}$$

where $a > 0$ represents the strength of the chemotherapeutic agent and $\phi(t)$ represents the concentration of the agent during the treatment schedule. This term can also be interpreted as a time-dependent immune response.

Even if the time-dependent term $\phi(t)$ can explain the macroscopic behavior of tumors that grow and then regress, it cannot offer insight into the mechanisms leading to this behavior. In order to investigate the biological mechanisms most likely to lead to tumor growth and elimination, we must expand the model. In the next section, we do this by including interactions between tumor cells and other cells that can inhibit their growth.

3 Two-Equation Models: Interactions Between Tumor Cells and Generic Effector Cells

The immuno-surveillance hypothesis formulated in the 1950s suggested that the immune system is capable of inhibiting the growth of very small tumors and eliminating them before they become clinically evident (Burnet 1957, 1967). This motivates the derivation of mathematical models of the interactions between tumor cells and immune cells (see Fig. 3). The simplest way to do this is by adding one equation to the family of models described by (1).

The precise nature of the immune cell population that we include need not be specified at this point, but the idea is to mimic the behavior of *cytotoxic immune cells*, such as $CD8^+$ T cells (Boon and van der Bruggen 1996) or NK cells (Khar 1997). These cells, also called *effector cells*, can control tumor growth by recognizing tumor antigens (substances within tumor cells that trigger an immune response) or tumor cell surface ligands (molecules on the surface of tumor cells, which bind to receptors on the surface of immune cells that trigger their activation). For the class of simple models depicted in Fig. 3, we consider a generic

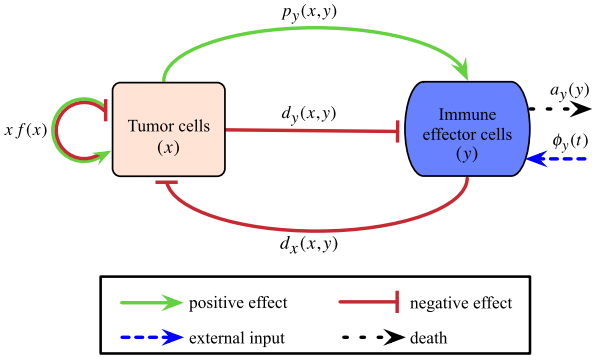

Fig. 3 A schematic representation of the interactions involved in the two-equation models in Sect. 3. This contrasts the simple auto-regulation mechanism in the one-equation models described in Sect. 2 and Fig. 1. Note that positive effects are associated with positive terms in the associated equations, while negative effects are associated with negative terms in the equations. Positive effects promote the growth of the component they are affecting; however, the magnitude of a positive effect does not necessarily increase with the cell populations that contribute to it (e.g., $x/(1+y)$ is always positive, but gets smaller in value as y is increased)

Table 1 Notation used in this article

State variables	Meaning
x	Cancer cells
y	Immune cells
z, w	Other cells or cytokines
Rate functions	**Description**
$f(x)$	Growth of cancer cells
d_j, $j = x, y, z, w$	Inhibition of cells/cytokines (type j) by other cells/cytokines
p_j, $j = y, z, w$	Proliferation of cells/cytokines (type j)
$a_j(j)$, $j = y, z, w$	Death (apoptosis) of cell (type j)
$\phi_j(t)$, $j = y, z, w$	Time-dependent or time-independent treatment, or influx of cells/cytokines of type j

effector cell population interacting with tumor cells. These interactions are described by two equations, which are usually of predator-prey type (Forys et al. 2006; Michelson et al. 1987; Michelson and Leith 1993; Stepanova 1980; de Vladar and González 2004). The immune cells play the role of the predator, while the tumor cells are the prey. All such models can be expressed as (d'Onofrio 2005, 2008)

$$x' = xf(x) - d_x(x, y), \tag{6a}$$

$$y' = p_y(x, y) - d_y(x, y) - a_y(y) + \phi(t), \tag{6b}$$

where x represents the size or density of the tumor cell population and y represents the size or density of the effector cell population. Note that the structure of (6a) for the tumor is quite similar to (1), the only difference being that cancer cell death now results from both predation by effector cells ($d_x(x, y)$) and autoregulation ($xd(x)$; see (2)). Equation (6b) for the immune cells includes a growth term ($p_y(x, y)$) and a death term ($d_y(x, y)$), both of which depend on interaction between the cancer cells and effector cells. There is also an apoptosis term ($a_y(y)$) and a time-dependent *treatment term* ($\phi(t)$). When $\phi(t) = c_1$ (constant), the term describes continuous production of immune cells, even in the absence of cancer cells (Kuznetsov et al. 1994). These terms are summarized in Table 1.

For particular functions $f(x)$, $d_x(x, y)$, $p_y(x, y)$, $d_y(x, y)$, $a_y(y)$, and $\phi(t)$, the generic model (6) reduces to specific models derived in the literature (Forys et al. 2006; Galach 2003; Kuznetsov et al. 1994; Stepanova 1980; Sotolongo-Costa et al. 2003; de Vladar and González 2004). For instance, the model derived in Kuznetsov et al. (1994) is obtained by setting

$$f(x) = a(1 - \beta x), \tag{7a}$$

$$d_x(x, y) = nxy, \tag{7b}$$

$$p_y(x, y) = \frac{\rho x y}{g + x}, \tag{7c}$$

$$d_y(x, y) = m x y, \tag{7d}$$

$$a_y(y) = d y, \tag{7e}$$

$$\phi(t) = s. \tag{7f}$$

While not as simple as the single equation models in Sect. 2, the two-equation models (6) are still sufficiently simple that their qualitative dynamics can be completely determined using standard mathematical techniques (such as local and global stability analysis and bifurcation theory). For example, using the Dulac–Bendixson criterion (Perko 2001) it has been shown that a two-equation model without external treatment ($\phi(t) = 0$), and with $g(x)$ non-constant such that $\frac{d}{dx}(f(x)/g(x)) \leq 0$, cannot display closed orbits (periodic orbits, homoclinic orbits, or chains of heteroclinic orbits) (d'Onofrio 2005; Kuznetsov et al. 1994).

Linear analysis and bifurcation techniques can help to further illuminate how the behaviors of the immune and cancer cells depend on the various parameters. In particular, phase portraits for the models reveal the existence of saddle points, nodes, and foci. Local and global stability analysis of these points reveal conditions on the parameters—such as those that define the functions describing the tumor-immune interactions—that can lead to local or global eradication of the tumor, or to the coexistence of immune and cancer cells (d'Onofrio 2008). Moreover, these equilibrium points suggest four types of behavior: exponential growth or decay, and oscillatory growth or decay (Kuznetsov et al. 1994; Sotolongo-Costa et al. 2003). The introduction of a periodic treatment $\phi(t)$ (Sotolongo-Costa et al. 2003), or a time delay in the immune response $p_y(x(t-\tau), y(t-\tau))$ (Galach 2003), can lead to a fifth behavior, namely persistent oscillations. A detailed analysis of the possible behaviors exhibited by (6) can be found in d'Onofrio (2008).

Since many papers in the literature present mathematical analyses and phase portraits without showing sample time series (d'Onofrio 2005; Lin 2004; Takayanagi and Ohuchi 2001; de Vladar and González 2004), in Fig. 4, we show examples of each of the possible types of temporal dynamics that can be obtained with the two-equation models (6). Note that for the purpose of drawing these graphs we used the models introduced in Kuznetsov et al. (1994) and Sotolongo-Costa et al. (2003), but the other models mentioned in this section display similar dynamics. In Fig. 4, panels (a) and (b) show exponential decrease and increase in tumor size, respectively, while panels (c) and (d) show oscillatory decay and oscillatory growth of tumors. Panels (e) and (f) show two types of persistent oscillatory behavior: (e) coexistence of cancer cells and immune cells; (f) periodic elimination of the tumor.

Numerical simulations also show the existence of an "immunological barrier", meaning that the immune system can eliminate small tumors, but is overwhelmed by large tumors (Kuznetsov et al. 1994). In other parameter regimes, simulations show the existence of a "sneaking through barrier", whereby tumors that have been reduced in size are never quite eliminated, and ultimately escape the immune response and grow larger (Kuznetsov et al. 1994). Two-equation models (6) can also describe dormant or persistent small tumors; for example, de Vladar and González (2004)

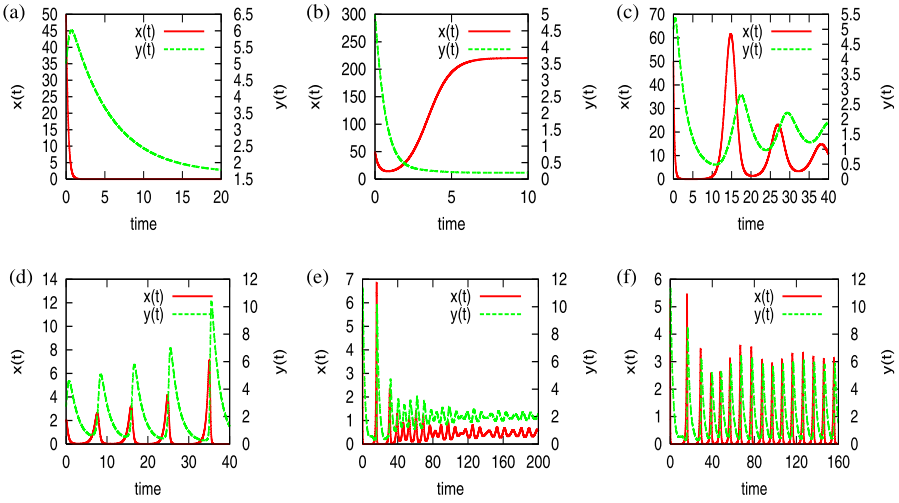

Fig. 4 Tumor-immune system dynamics displayed by the two-equation models described in Sect. 3. The *continuous curve* shows the time-evolution of the cancer cell population, while the dashed curve shows the time-evolution of the immune cell population. In panels (**a**)–(**d**), there is no treatment ($\phi(t) = 0$). (**a**) Tumor size decreases exponentially after interactions with the immune cells; (**b**) Initially, the tumor size decreases through the interactions with immune cells. When the immune cell population decays under a certain level, the tumor grows again. (**c**) Tumor size decays in an oscillatory manner. (**d**) Tumor size grows in an oscillatory manner. This also leads to growth in the immune cell population. The addition of periodic treatment ($\phi(t) \neq 0$) or time delay can lead to persistent oscillations: (**e**) oscillations with the coexistence of tumor and immune cells, and (**f**) oscillations with the temporary elimination of the tumor cells. Panels (**a**)–(**c**) were obtained with the model of Kuznetsov et al. (1994); the initial conditions for the simulations were $x(0) = 50$, $y(0) = 5$. Using the notation of Kuznetsov et al. (1994), the parameter values were: (**a**) $s = 0.318$, $d = 0.1908$, $b = 2 \times 10^{-3}$; (**b**) $s = 0.318$, $d = 2.0$, $b = 4 \times 10^{-3}$; (**c**) $s = 0.1181$, $d = 0.3743$, $b = 2 \times 10^{-3}$. For all three panels, the remaining parameters were: $\rho = 1.131$, $g = 20.19$, $m = 0.00311$, $a = 1.636$, $n = 1$. Panels (**d**)–(**f**) were obtained using the model of Sotolongo-Costa et al. (2003) with initial conditions $x(0) = 2.1$, $y(0) = 2.7$ for panel (**d**), and $x(0) = 5.3$, $y(0) = 6.7$ for panels (**e**) and (**f**). Using the notation in Sotolongo-Costa et al. (2003), the parameter values were: (**d**) $V = 0$, $\beta = 0.34$; (**e**) $V = 0.25$, $\beta = 0.34$; (**f**) $V = 0.25$, $\beta = 0.32$; remaining parameters: $\alpha = 2.0$, $k = 0.2$, $\sigma = 0.05$

showed that if the quotient of the tumor growth rate and the rate at which the tumor cells are eliminated is small, then the tumor will stay small (either microscopic or benign). Such behavior can be explained either by strong, direct anti-tumor activity or by strong background immunity (Forys et al. 2006).

In Sect. 2, we noted that because Gompertzian growth is unbounded as tumor density becomes small, Gompertzian models cannot describe the dynamics of small populations of tumor cells. Analysis of two-equation models reveals further that Gompertzian growth is not compatible with the immuno-surveillance hypothesis: the immune response cannot completely eradicate cancer cells that grow according to the Gompertzian law (d'Onofrio 2005), despite the fact that it can fit the data from some *in vivo* tumors (Castro et al. 2003).

Another type of two-equation model (which we have not discussed here) considers state variables associated with the cancer cell population and with the tumor carrying capacity (which is determined by endothelial support, i.e., blood ves-

sels in and around the tumor). The equation for the (time-dependent) carrying capacity incorporates an indirect effect of the immune system (Sachs et al. 2001; Ledzewicz et al. 2009).

3.1 Summary of Two Equation Models

Models that are expressible by (6) can be fitted to most observed tumor-immune system dynamics. They are, therefore, very helpful for elucidating basic (generic) mechanisms that can induce observed behaviors, such as tumor regression and tumor dormancy. The models display a greater variety of dynamics than is observed experimentally; in particular, we are not aware of any examples of oscillatory dynamics in solid tumors (though this might occur in systemic diseases such as leukemia, Menta and Agarwal 1980).

Because they are so generic, two-equation models are not adequate to develop therapies based on specific components of the immune system that might be possible to target experimentally. For example, it is intuitive that either strong innate immunity (Forys et al. 2006) or strong anti-tumor activity (Lejeune et al. 2008; de Vladar and González 2004) can eradicate a tumor. But anti-tumor activity can be produced by a variety of immune cells, such as $CD8^+$ T cells, NK cells, or macrophages, and each cell type can interact with cancer cells in a multitude of ways. Moreover, when thinking about the effects of specific immunotherapies, non-linear density-dependent interactions among different immune cell populations may be very important. In subsequent sections, we review models of increasing complexity that consider more details of the interactions among different types of cells and signaling molecules.

4 Three Equation Models: Interactions Among Cancer Cells and Two Other Components of the Tumor Micro-Environment

The most natural way to incorporate more biological detail is to start with one of the previous two-equation models and add one more component. This component could be either a different type of cell (e.g., immune cells, or healthy tissue cells), or cytokines present in the tumor microenvironment (see Fig. 5).

In the past 10–20 years, experimental results have shown that $CD8^+$ T cells (Naito et al. 1998), NK cells (Quesnel 2008; Waldhauer and Steinle 2008), and macrophages (Fidler 1985) are associated with good cancer prognosis, being involved in the lysis of cancer cells. Each of these immune cells uses a different mechanism and plays a different role in cell lysis. In an attempt to shed light on these mechanisms, various mathematical models have been developed to investigate the interactions between cancer cells and multiple immune cells (de Pillis and Radunskaya 2003b), or between cancer cells, immune cells, and healthy tissue cells (Owen and Sherratt 1998).

Another important component of the anti-tumor immune response is represented by the cytokines. These molecules, which are used in cellular communication, play a very important role in the activation and development of immune responses, as shown by many experimental results (Dranoff 2004). For this reason, cytokines

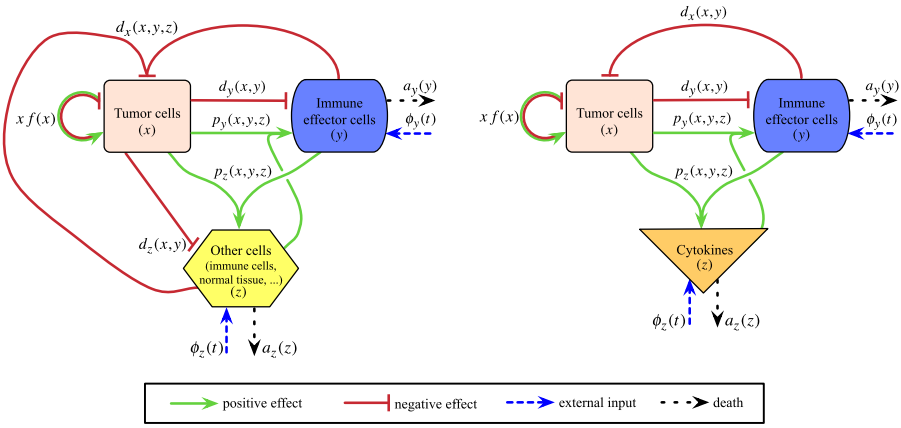

Fig. 5 Schematic representation of the three-component models of cancer-immune system interactions described in Sect. 4. (**a**) Models involving three types of cell. (**b**) Models involving two types of cell and one type of signaling molecule. Note that "death" of cytokines refers to natural decay of these molecules (and the consequent reduction in their concentration)

are the focus of many cancer immunotherapies, though the mechanisms through which they interact with cancer cells are not completely understood (Dranoff 2004; Kim-Schulze et al. 2007; Parmiani et al. 2000). To help with the investigation of these mechanisms, some simple mathematical models have been derived based on the interactions among immune cells, cancer cells, and certain cytokines (Kirschner and Panetta 1998).

In this section, we will review some of the most cited mathematical models that have followed these two approaches. We focus on three types of interactions:

(1) Interactions between cancer cells and two types of effector cells, which are usually $CD8^+$ T cells and NK cells (see, for example, de Pillis and Radunskaya 2003b; de Pillis et al. 2005).
(2) Interactions between cancer cells, effector cells, and normal tissue cells (see, for example, Owen and Sherratt 1998).
(3) Interactions between cancer cells, effector cells, and cytokines (such as IL-2, TGF-β, IFN-γ) (see, for example, Arciero et al. 2004; Kirschner and Panetta 1998).

There are other three-equation models that focus on different types of interactions. For example, some models investigate the interactions among cancer cells, effector cells, and naïve effector cells (Moore and Li 2004). Other models investigate the interactions among antibodies and two types of cancer cells, either proliferating or quiescent (Page and Uhr 2005), or the interactions among cancer cells, normal effector cells and resting effector cells (Banerjee and Sarkar 2008; Merola et al. 2008; Sarkar and Banerjee 2005). Many of these models are classical ODE models (Moore and Li 2004), but some incorporate stochastic effects (Sarkar and Banerjee 2005) or time delays (Banerjee and Sarkar 2008).

Many of the models mentioned below in this section include treatment protocols, such as continuous injection of cytokines (Kirschner and Panetta 1998; Owen and

Sherratt 1998), continuous transfer of effector cells (Kirschner and Panetta 1998), pulse-like or continuous administration of certain drugs (de Pillis and Radunskaya 2003a) or immunization with dendritic cells (Castiglione and Piccoli 2007). Some authors have applied control theory (Kirk 2004) to their models in an attempt to identify optimal therapy protocols (de Pillis and Radunskaya 2001; Swan 1985). In this review, we focus only on the possible dynamical behaviors of the models and not on the analysis of optimal treatment regimes.

Figure 6 summarizes the types of behaviors exhibited by many of these three-equation models. The continuous curve shows the time evolution of the cancer cell population. The other two (dashed and dotted) curves show the time evolution of various immune cells or cytokines. These three-equation models can exhibit exponential decay (cases (a)–(b)) or growth of tumor cells (cases (c), (e)), oscillatory decay (case (d)), or persistent oscillations (case (f)). To create Fig. 6, we used the models introduced in Kirschner and Panetta (1998) and Moore and Li (2004).

While these three-equation models do not appear to produce any distinct behaviors beyond those displayed by the two-equation models discussed in Sect. 3, they do shed light on the interactions among different types of cells, between cells and cytokines, and the influence of these factors on tumor size. In the following subsections, we consider how the three-equation models help to uncover the possible mechanisms underlying such interactions.

4.1 Tumor Growth Modulated by Two Effector Cell Types

The general equations describing interactions among cancer cells and two different cell populations (as in Fig. 5(a)) are

$$x' = xf(x) - d_x(x, y, z), \tag{8a}$$

$$y' = \phi_y(t) + p_y(x, y, z) - a_y(y) - d_y(x, y), \tag{8b}$$

$$z' = \phi_z(t) + p_z(x, y, z) - a_z(z) - d_z(x, z). \tag{8c}$$

In (8a), $f(x)$ describes the modulation of cancer cell growth through auto-regulation, while $d_x(x, y, z)$ is the rate at which cancer cells are killed in interactions with the other two cell types, y and z. The terms $p_y(x, y, z)$ and $p_z(x, y, z)$ (in (8b) and (8c)) give the rates at which the y and z cell types grow in the presence of cancer cells. The terms $a_y(y)$ and $a_z(z)$ describe apoptosis (cell death), while the terms $d_y(x, y)$ and $d_z(x, z)$ describe inactivation of immune cells by cancer cells, or competition between normal and cancer cells (as will be shown in Sect. 4.2). As in Sect. 3, the terms $\phi_y(t)$ and $\phi_z(t)$ can model time-dependent or time-independent ($\phi_{y,z} = \text{constant}$) treatments, or can model the influx of immune cells into the tumor microenvironment. In this latter case, the influx terms are usually constant (see, for example, de Pillis et al. 2005). All our notation is summarized in Table 1.

Equations (8) describe generic interactions among cancer cells and two types of effector cells, which could be any of the many types of immune cells present at a tumor site. de Pillis and Radunskaya (2003b) derived a specific example of (8) to investigate the effect of $CD8^+$ T cells (z) and NK cells (y) on tumor regression.

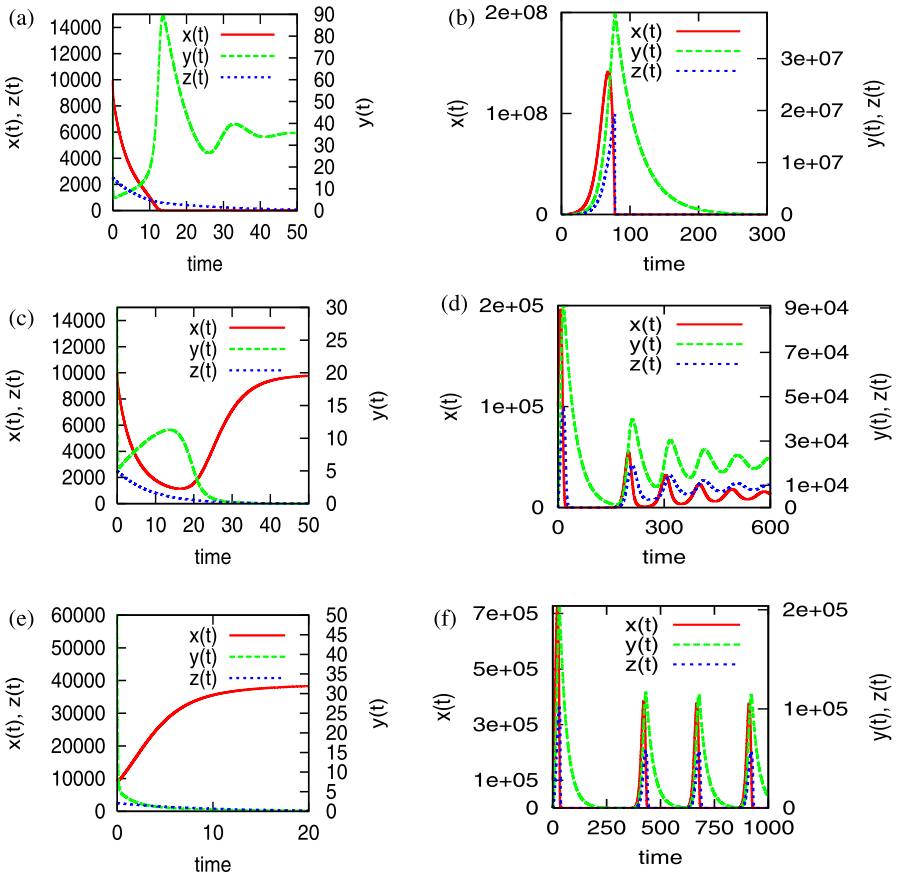

Fig. 6 Tumor-immune system dynamics displayed by the three-equation models described in Sect. 4. The time-evolution of the cancer cell population is shown by the *continuous curve* in each panel. The *dashed* and *dotted curves* show the time-evolution of two different immune cell populations (panels (**a**), (**c**), and (**e**)), or immune cells and cytokines (panels (**b**), (**d**), and (**f**)). The graphs in panels (**a**), (**c**) and (**e**) were made using the model of Moore and Li (2004). The initial conditions and the parameters (using the notation in Moore and Li 2004) are: (**a**) $r_c = 0.23$, and the initial condition $x(0) = 10^4$, $y(0) = 50$, $z(0) = 2500$; (**c**) $r_c = 0.23$ and the initial condition $x(0) = 10^4$, $y(0) = 30$, $z(0) = 2500$; (**e**) $r_c = 0.43$, and the initial condition $x(0) = 10^4$, $y(0) = 50$, $z(0) = 2500$. The remaining parameters values were: $s_n = 0.071$, $d_n = 0.05$, $d_e = 0.12$, $d_c = 0.68$, $k_n = 0.063$, $\eta = 43$, $\alpha_n = 0.56$, $\alpha_e = 0.93$, $c_{\max} = 19 \times 10^4$, $\gamma_e = 1.9 \times 10^{-3}$, $\gamma_c = 0.048$. Panels (**b**), (**d**), and (**f**) were made using the model of Kirschner and Panetta (1998) with initial conditions $y(0) = 10$, $x(0) = 10^5$, $z(0) = 0$. The parameter values (using the notation in Kirschner and Panetta 1998) are: (**b**) $c = 0.002$, (**d**) $c = 0.05$, (**f**) $c = 0.02$; and remaining parameters $p_1 = 0.1245$, $g_1 = 2 \times 10^7$, $\mu_2 = 0.03$, $r_2 = 0.18$, $b = 10^{-9}$, $a = 1$, $g_2 = 10^5$, $\mu_3 = 10$, $p_2 = 5$, $g_3 = 10^3$

In their model, the authors consider logistic tumor growth ($f(x) = r(1 - bx)$), linear death of immune cells ($a_y(y) = i_1 y$, $a_z(z) = i_2 z$) and bilinear inactivation terms ($d_y(x, y) = pxy$, $d_z(x, z) = qxz$). Both the CD8$^+$ T cells and the NK cells can eliminate the cancer cells on their own (and there is not joint effect), so the elimination term can be written $d_x(x, y, z) = d_x^y(x, y) + d_x^z(x, z)$. Here $d_x^y(x, y)$ describes the elimination of cancer cells by the NK cells, while $d_x^z(x, z)$ describes the elimination

by the CD8$^+$ T cells. Fitting the model to data from Diefenbach et al. (2001), the authors discovered that lysis of tumor cells by effector cells can be better explained if one associates different mechanisms (i.e., different types of interaction terms) with cancer elimination by NK cells and by CD8$^+$ T cells. In particular, lysis of tumor cells by NK cells can be explained by an interaction of the form $d_x^y(x, y) = cxy^{1.44}$, whereas CD8$^+$ T cell-induced lysis is better described by a rational term that depends on the ratio of CD8$^+$ T cells to tumor cells (z/x): $d_x^z(x, z) = \frac{d_0(z/x)^\lambda}{1+(z/x)^\lambda}$. In addition, the recruitment of the NK cells and CD8$^+$ T cells by the immune system is better described by Michaelis–Menten dynamics:

$$p_y(x, y, z) = \frac{g_0 x^2 y}{d_x^z(x, z) + x^2}, \tag{9a}$$

$$p_z(x, y, z) = \frac{j_0[d_x^z(x, z)]^2 z}{k + [d_x^z(x, z)]^2}. \tag{9b}$$

The saturated form of these terms accounts for a limited immune response in the presence of the cancer. Even if these lysis and recruitment terms provide a good fit with experimental data, there is still the question of why the two types of immune cells (i.e., the CD8$^+$ T cells and NK cells) behave so differently when lysing the tumor cells and when proliferating. To answer this question, further laboratory experiments are required.

Later, the same authors (de Pillis et al. 2005) showed numerically that if the CD8$^+$ T cells or the NK cells are depleted, the immune system can eliminate up to 10^4 tumor cells but fails to inhibit larger innoculations (e.g., 10^6 injected tumor cells). In this case, the behavior is similar to that depicted in Fig. 6(a). Moreover, the depletion of the CD8$^+$ T cells has a different impact on the tumor compared to the depletion of the NK cells. In particular, the system without NK cells can control initial tumor burdens up to 10^5 cells, while the system without CD8$^+$ T cells can control tumor burdens only up to 10^4 cells. Only the combined effect of the CD8$^+$ T cells and NK cells can eliminate large tumors (i.e., 10^6 tumor cells). Also, the results suggest that the size of the tumor is most sensitive to the tumor growth rate (r) and to the parameter connecting the lysis rate with the effector/target ratio (λ). Note that the numerical behavior displayed by these models is similar to the ones in Figs. 6(b) and (d).

4.2 Tumor Growth Modulated by Effector Cells and Normal Cells Through Competition for Resources

Rather than focusing on other types of immune cells, some three-equation models describe a single immune cell population together with normal-tissue cells and their competition with cancer cells (Owen and Sherratt 1998; de Pillis and Radunskaya 2001, 2003a). Such models are used to investigate possible mechanisms involved in the reduction of tumor size, without the loss of too many normal cells. The interactions among the three cell types are usually described by two different competition terms:

i Competition for resources between normal cells and cancer cells (and sometimes also immune cells, as in Owen and Sherratt 1998);
ii Predator-prey competition between cancer cells and immune cells.

These types of interactions are described by equations similar to (8), where z represents the number (or density) of normal-tissue cells.

In the particular model considered by de Pillis and Radunskaya, de Pillis and Radunskaya (2001, 2003a), the terms describing the interactions between the different cells are

$$f(x) = r_1(1 - b_1 x), \tag{10a}$$

$$d_x(x, y, z) = c_2 xy + c_3 xz, \tag{10b}$$

$$p_y(x, y, z) = \frac{\rho xy}{\alpha + x}, \tag{10c}$$

$$p_z(x, y, z) = r_2 z(1 - b_2 z), \tag{10d}$$

$$a_y(y) = d_1 y, \tag{10e}$$

$$a_z(z) = 0, \tag{10f}$$

$$d_y(x, y) = c_1 xy, \tag{10g}$$

$$d_z(x, z) = c_4 xz, \tag{10h}$$

$$\phi_y(t) = s, \tag{10i}$$

$$\phi_z(t) = 0. \tag{10j}$$

Here, the growth of the normal cells ($p_z(x, y, z)$) is described by a logistic term, while the growth/recruitment of the immune cells ($p_y(x, y, z)$) is described by a Michaelis-Menten term to account for the limited immune response in the presence of cancer cells.

The model of Owen and Sherratt (1998) focuses on a particular type of immune cell population, the macrophages, and it is slightly different from the models described by (8). In particular, the authors take account of the fact that the growth of the macrophage population is limited by crowding from *all* cell types. This effect is described by non-standard Michaelis–Menten terms,

$$\frac{w_i(N + N_e)}{N + w_1 + w_2 + w_3}, \tag{11}$$

where w_i, $i = 1, 2, 3$ represent the different cell types, N_e is the total equilibrium density of all cell types in normal tissue, and N is a measure of the initial growth rate and the subsequent crowding response. After non-dimensionalization N_e disappears, and the terms describing the interactions among the cancer cells (x), macrophages (y), and normal cells (z) are

$$f(x, y, z) = \frac{\psi(N + 1)}{N + x + y + z} - x, \tag{12a}$$

$$d_x(x, y) = K_m yx^2, \tag{12b}$$

$$p_y(x, y, z) = \frac{Axy(N + 1)}{N + x + y + z} + s_0(1 + Sy), \tag{12c}$$

$$p_z(x, y, z) = \frac{z(N+1)}{N+x+y+z}, \tag{12d}$$

$$d_y(x, y) = K_l y x^2, \tag{12e}$$

$$d_z(x, z) = 0, \tag{12f}$$

$$a_y(y) = \delta_l y, \tag{12g}$$

$$a_z(z) = z, \tag{12h}$$

$$\phi_y(t) = s_0, \qquad \phi_z(t) = 0. \tag{12i}$$

Note that the presence of macrophages in the tumor is caused by a generic chemoattractant produced by cancer cells, which influences the parameters A and S in the proliferation function $p_y(x, y, z)$. The model makes the assumption that in the absence of tumor chemoattractants, there is a baseline influx of macrophages in the tissue from the circulating blood (s_0). Such an influx might be caused by other chemoattractants produced by other immune cells (see, for example, von Stebut et al. 2003).

Unlike the cases discussed in Sect. 4.1, the authors of both of the models that we have discussed in this section use analytical methods to better understand the dynamics of the three cell populations. The principal dynamical difference between the two models is that one supports a tumor-free equilibrium. de Pillis and Radunskaya (2003a) show that their model has a stable tumor-free steady state solution when the tumor growth rate is less than the "efficiency" of the immune system with respect to tumor elimination. This "efficiency" is measured by a combination of parameters including the rate at which the immune cells kill cancer cells, the constant influx rate of the immune cells at the tumor site, and the apoptosis (natural death) rate of the immune cells. In contrast, the model of Owen and Sherratt (1998) does not support a stable tumor-free steady state, so arbitrarily small tumors will grow. This instability is caused by a quadratic term in x describing the killing of cancer cells by macrophages ($d_x(x, y) = K_m y x^2$). The quadratic term arises from a pseudo-steady state approximation for the concentration of a generic chemical involved in the activation and proliferation of macrophages. The tumor-free steady state can be stabilized by introducing a continuous, constant influx of chemicals (which might correspond to drug treatment). If the approximations of Owen and Sherratt (1998) are valid, then their results suggest that macrophages alone cannot eradicate a tumor. (It has since been discovered experimentally that some macrophages (M2) actually promote tumor growth, Mantovani et al. 2002.)

In addition to stability analysis, the authors of both models use bifurcation techniques to locate points in parameter space where transitions occur between stable and unstable steady states. de Pillis and Radunskaya (2001) focus on how the model's behavior depends on the proliferation rate of the immune cells (ρ), while Owen and Sherratt (1998) focus on the effects of the rate at which a generic chemoattractant is produced (S) and on the reaction of macrophages to this chemoattractant. In both models, for intermediate parameter ranges it is possible to have multiple coexistence steady states, i.e., distinct (stable) steady states where a small tumor can coexist with normal cells and immune cells. In the immunological literature such coexistence steady states are called "the equilibrium phase" (Teng et al. 2008). They represent the

second phase of tumor-immune interactions, the other two phases being elimination and escape (Teng et al. 2008).

In conclusion, these two models are complex enough to be used to deduce conditions for different biologically relevant parameters which would ensure the elimination of a tumor, without a major loss of healthy tissue cells. On the other hand, the models are still simple enough to be investigated analytically. Analysis of these models shows that when the tumor-immune dynamics are described by first-order terms in x, the tumor can be eliminated permanently. On the other hand, when the dynamics are described by second-order terms in x, the tumor will relapse (in this case, a small perturbation of the tumor micro-environment will cause the tumor to grow again).

4.3 Tumor Growth Modulated by Effector Cells and Cytokines

One of the first models to investigate the role of cytokines on tumor regression was developed by Kirschner and Panetta (1998), who investigated the effect of IL-2 and cytotoxic T cells on the tumor-immune system dynamics (see Fig. 5(b)). The equations describing the dynamics between the cancer cells (x), immune cells (y), and cytokines (z) can be written in their most general form as

$$x' = xf(x) - d_x(x, y), \tag{13a}$$

$$y' = \phi_y + p_y(x, y, z) - a_y(y), \tag{13b}$$

$$z' = \phi_z + p_z(x, y, z) - a_z(z). \tag{13c}$$

The specific functional forms adopted by Kirschner and Panetta (1998) were

$$f(x) = r_2(1 - bx), \tag{14a}$$

$$d_x(x, y) = \frac{axy}{g_2 + x}, \tag{14b}$$

$$p_y(x, y, z) = cx + \frac{p_1 yz}{g_1 + z}, \tag{14c}$$

$$p_z(x, y, z) = \frac{p_2 xy}{g_3 + x}, \tag{14d}$$

$$d_y(x, y) = 0, \tag{14e}$$

$$a_y(y) = \mu_2 y, \tag{14f}$$

$$a_z(z) = \mu_3 z, \tag{14g}$$

$$\phi_y(t) = s_1, \tag{14h}$$

$$\phi_z(t) = s_2. \tag{14i}$$

The model investigates the results of giving two types of continuous treatment: (a) the injection of cytokines (when $s_1 > 0$), and (b) the adoptive transfer of immune cells (from one individual to another, or by *in vitro* amplification of harvested immune cells from one individual and re-injecting them) (when $s_2 > 0$).

Analytical and numerical results show that in the absence of any treatment ($s_1 = s_2 = 0$) model (13) can exhibit three behaviors: persistence of large tumors (for low antigenic tumors), oscillation between macroscopic and microscopic tumors (for moderately antigenic tumors) and persistence of dormant tumors, that is persistence of residual tumor cells (for highly antigenic tumors). The model allows for complete tumor clearance only if treatment is introduced. In particular, adoptive cellular immunotherapy ($s_1 > 0$, $s_2 = 0$) leads to a locally stable tumor-free state, provided that the treatment rate is above a certain critical level ($s_1 > s_{\text{crit}}^1 = r_2 g_2 \mu_2 / a$). Similarly, the administration of IL-2 alone ($s_1 = 0$, $s_2 > 0$) can lead to tumor clearance provided that the rate at which treatment is administered (cytokine concentration input per unit time) is above a critical level $s_{\text{crit}}^2 = \mu_2 \mu_3 g_1 / (p_1 - \mu_2)$. Unfortunately, this also leads to an unbounded immune response (i.e., $y = \infty$) which causes damage to the host. This mathematical result can be connected to the side effects (i.e., capillary leak syndrome) observed in some patients after the administration of large doses of IL-2 (Orucevic and Lala 1998). Giving both treatments simultaneously ($s_1, s_2 > 0$) improves the results only when the rate at which IL-2 is administered is below the critical level s_{crit}^2. In this case, it is possible to have a tumor-free state even for very weakly antigenic tumors.

4.4 Summary of Three Equation Models

Analysis of three-equation models has led to substantial biological insights. Interactions between cancer cells, effector cells, and cytokines (especially IL-2) can explain long-term tumor relapse. Examples of the possible behaviors exhibited by model (13) are shown in Figs. 6(b), (d), and (f). Analysis of the models indicates that for large doses of IL-2, the cytokine treatment alone cannot eliminate a tumor without causing immune problems (i.e., an unbounded immune response). A better treatment option is to use adoptive transfer of immune cells (either alone or in combination with IL-2).

5 Four Equation Models: Interactions Among Cancer Cells and Three Other Components of the Tumor Microenvironment

Explicitly modeling a third component of the tumor microenvironment led to new tumor-immune system dynamics and to the formulation of plausible explanations for these dynamics. This raises the question: Do we learn anything new by explicitly modeling a fourth component? This question seems particularly relevant if we consider the effect of IL-2 discussed in Sect. 4.3. This is only one of the many cytokines involved in the immune response. Moreover, IL-2 itself contributes to the production of other cytokines, such as IFN-γ, through the activation of other immune cells (e.g., $CD4^+$ and $CD8^+$ T cells) (Berner et al. 2007). Perhaps most significantly, IL-2 production is inhibited by cytokines such as IL-10 and TGF-β, which can be produced by tumors. This inhibition is completely absent from the three-equation models, so a natural question is: How are the tumor-immune system dynamics affected when we incorporate the effects of inhibitory cytokines?

In this section, we review models obtained from those in Sect. 4 by adding a fourth equation (see Fig. 7). This extra equation can describe, for example, the dynamics of

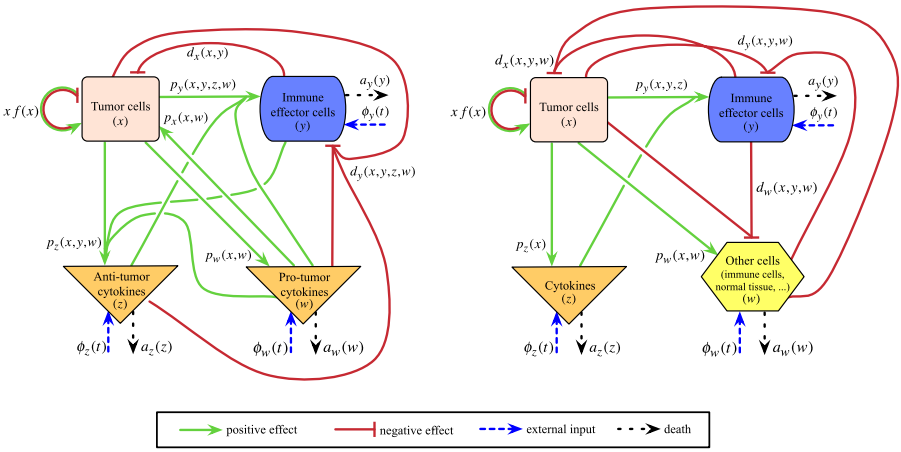

Fig. 7 Schematic representation of the four-component models of cancer-immune system interactions described in Sect. 5. (**a**) Models involving two types of cell and two types of signaling molecule (one that inhibits and one that promotes tumor growth). (**b**) Models involving three types of cell and one type of signaling molecule. In panel (**a**), note that the pro-tumor cytokines act directly on the tumor cells, but they also promote tumor growth indirectly: they inhibit the production of anti-tumor cytokines and reduce the growth of effector cells (which then have a weaker promoting effect on the anti-tumor cytokines)

a cytokine concentration (such as TGF-β in Arciero et al. 2004, or IL-2 in Nani and Freedman 2000), or the dynamics of a chemokine concentration (as in Byrne et al. 2004).

There are many dynamical models of tumor-immune interactions described by four equations (see, for example, Bunimovich-Mendrazitsky et al. 2007; Nani and Freedman 2000; Szymanska 2003; Villasana and Radunskaya 2003). Some of these models investigate only interactions among four different cell types (Bunimovich-Mendrazitsky et al. 2007; Szymanska 2003), while others focus on interactions among immune cells, cancer cells in different stages, and treatment drugs (Villasana and Radunskaya 2003). Some of the models include time delays (Villasana and Radunskaya 2003). All of them provide helpful insights concerning the dynamics of the systems. For example, secondary bifurcations observed mathematically in some of the models show how complicated the outcome of therapy can be (Nani and Freedman 2000).

In this section, we illustrate the value of four-equation models by reviewing two examples that extend models investigated in Sect. 4. These examples show how an additional equation that does not change the main dynamics of the tumor can still help us by clarifying the detailed interactions between four different components of the tumor microenvironment. These interactions are made clear mainly through extensive analytical investigations, based on linear and weakly non-linear approximations and bifurcation theory. Since these models do not display new tumor dynamics, we will not summarize numerical results, as we did in Sects. 3 and 4. Summaries of numerical simulations of four-equation models can be found in Arciero et al. (2004) and Szymanska (2003).

5.1 Two Types of Cells and Two Types of Cytokines

The general equations describing the interactions shown in Fig. 7(a), i.e., interactions among cancer cells, immune cells, and two types of cytokines, are

$$x' = xf(x) - d_x(x, y) + p_x(x, w), \tag{15a}$$
$$y' = \phi_y(t) + p_y(x, y, z, w) - d_y(x, y, z, w) - a_y(y), \tag{15b}$$
$$z' = \phi_z(t) + p_z(x, y, w) - a_z(z), \tag{15c}$$
$$w' = \phi_w(t) + p_w(x, w) - a_w(w). \tag{15d}$$

Here, x refers to the cancer cell population, y to the immune cell population, z to the concentration of the anti-tumor cytokines, and w to the concentration of the pro-tumor cytokines. Most of the terms in (15) are the same as those discussed in the context of the three-equation models in Sect. 4 (and are summarized in Table 1). The new terms are: $p_x(x, w)$, which models the positive effect of the cytokine w on tumor growth; $d_y(x, y, z, w)$, which models the negative effect that the pro-tumor cytokines and the tumor cells have on the proliferation of immune cells; $p_w(x, w)$ and $a_w(w)$, which respectively model the production—by tumor cells—and natural decay of the pro-tumor cytokine w.

In their attempt to include the inhibitory effects of TGF-β on IL-2, Arciero et al. (2004) specify the tumor-immune system interactions in (15) using

$$f(x) = r(1 - k_1 x), \tag{16a}$$
$$p_x(x, w) = \frac{p_2 wx}{g_3 + w}, \tag{16b}$$
$$d_x(x, y) = \frac{a_1 xy}{g_2 + x}, \tag{16c}$$
$$p_y(x, y, z, w) = \frac{cx}{1 + \gamma w} + \frac{p_1 yz}{g_1 + z}, \tag{16d}$$
$$d_y(x, y, z, w) = \frac{yz}{g_1 + z} \cdot \frac{q_1 w}{q_2 + w}, \tag{16e}$$
$$a_y(y) = 0, \tag{16f}$$
$$p_z(x, y, w) = \frac{p_3 xy}{(g_4 + x)(1 + \alpha w)}, \tag{16g}$$
$$a_z(z) = \mu_2 z, \tag{16h}$$
$$p_w(x, w) = \frac{p_4 x^2}{\tau_c^2 + x^2}, \tag{16i}$$
$$a_w(w) = \mu_3 w, \tag{16j}$$
$$\phi_y(t) = s, \qquad \phi_z(t) = \phi_w(t) = 0. \tag{16k}$$

Linear stability analysis, bifurcation analysis, and numerical simulations of this model show that the tumor exhibits the same three behaviors observed in the absence of TGF-β (Kirschner and Panetta 1998). In particular, the tumors can (a) grow very

large, (b) oscillate between very large and very small sizes or (c) undergo damped oscillations that converge to a small, dormant mass. Thus, like the simpler model without TGF-β, this model can exhibit tumor relapse, but there is an important difference: at high concentrations of TGF-β, it is possible to obtain a large, persistent tumor (regardless of the antigenicity of the tumor, unlike the simpler model). This suggests that more aggressive tumors, which produce higher concentrations of TGF-β, are more difficult to control.

5.2 Three Cell Types and One Cytokine or Chemokine

Another way to expand the three-equation framework of Sect. 4 is shown in Fig. 7(b). We can start with the models discussed in Sect. 4.2 and add another equation for the concentration of some cytokine or chemokine, or we can supplement the models of Sect. 4.3 with an equation for the number or density of normal tissue cells (or some other type of cell). In either case, the equations describing the interactions among all these cells and cytokines are

$$x' = xf(x) - d_x(x, y, w), \tag{17a}$$

$$y' = \phi_y(t) + p_y(x, y, z) - d_y(x, y, w) - a_y(y), \tag{17b}$$

$$z' = \phi_z(t) + p_z(x) - a_z(z), \tag{17c}$$

$$w' = \phi_w(t) + p_w(x, w) - d_w(x, y, w) - a_w(w). \tag{17d}$$

Here, x denotes the size of the cancer cell population, y is the size of the immune effector cell population, z is the concentration of the cytokine or chemokine, while w is the size of the normal tissue cell population.

A model that falls into this category was introduced by Byrne et al. (2004) and complements the model of Owen and Sherratt (1998) by focusing not on normal macrophages, but on macrophages engineered to kill cancer cells. Byrne et al. (2004) assumed that the infiltration of the macrophages into the tumor is induced by a chemoattractant produced by the tumor. The terms describing the interactions among the different cells and the chemokines are:

$$f(x) = \psi(1 - \phi x), \tag{18a}$$

$$d_x(x, y, w) = xy(\psi\phi + k_1) + \psi x w, \tag{18b}$$

$$p_y(x, y, z) = (y^* - y)\frac{\delta z}{1 + \alpha z}, \tag{18c}$$

$$d_y(x, y, w) = \sigma y(x + y + w), \tag{18d}$$

$$p_z(x) = x, \tag{18e}$$

$$a_z(z) = \lambda_0 z, \tag{18f}$$

$$p_w(x, w) = w(1 - w), \tag{18g}$$

$$d_w(x, y, w) = xw + yw, \tag{18h}$$

$$\phi_z(t) = \phi_y(t) = \phi_w(t) = 0. \tag{18i}$$

Even with four equations, the model is still simple enough to be investigated analytically. In particular, using linear and weakly non-linear stability analysis (i.e., non-linear analysis in the neighborhood of a bifurcation point, Stuart 1960; Matkowski 1970), as well as bifurcation theory (Kuznetsov 1994), Byrne et al. (2004) investigated the effects of two parameters (y^* and k_1) on the ability of the macrophages to eliminate the cancer cells. As for the model of Owen and Sherratt (1998), the results of Byrne et al. (2004) indicate that the cancer-free steady states are linearly unstable, and small perturbations in the tumor microenvironment lead to tumor relapse. The system usually evolves to a steady state in which several cell types coexist. When two parameters (y^* and k_1) are varied, the coexistence steady state with $w = 0$ (and $x, y, z \neq 0$) can undergo monotonic bifurcations (when the imaginary part of the growth rate is zero at the bifurcation point) or oscillatory bifurcations (when the imaginary part of the growth rate is non-zero at the bifurcation point) toward a coexistence steady state with $w \neq 0$ (and $x, y, z \neq 0$). Weakly non-linear analysis was further used to investigate these simultaneous bifurcations of the steady states. The analytical results showed the existence of two types of oscillatory solutions in which the tumor cells and the immune cells coexist, in one case with and in the other case without normal tissue cells. These oscillatory solutions were then confirmed with numerical simulations.

5.3 Summary of Four Equation Models

The models presented in Sects. 5.1 and 5.2 indicate that including the effects of one additional component of the tumor microenvironment does not lead to any new behavior (such as complete tumor regression). The patterns are similar to those obtained with three-equation models: exponential growth of tumor cells, oscillatory growth, or oscillatory decay. This suggests that the most essential mechanisms have already been captured with three equations. Nevertheless, more elaborate and biologically realistic models are useful because they can help us frame testable hypotheses. An elegant example was offered by Arciero et al. (2004) whose model suggested that regardless of the level of antigenicity, aggressive tumors will always grow toward their carrying capacities if the production of TGF-β is sufficiently large.

In spite of the complexity of these four-equation models, they are still simple enough to be amenable to extensive analytical investigation. Such investigations can reveal, for example, the amplitude of the immune response and its relation to the sizes of the tumor cell and normal tissue cell populations.

6 Models Involving Five or More Equations

More realistic models can be obtained by including more components of the tumor micro-environment and correspondingly more equations. The key costs of this greater realism are that the models are inevitably less well parameterized (more parameters must be estimated with the same amount of data) and they are much harder to analyze (typically, only numerical analysis is feasible). Nevertheless, models involving more than four equations have led to significant insights into the biological mechanisms governing tumor-immune system interactions.

Different authors have focussed on different biological details, ranging from interactions among distinct cytokines (e.g., TGF-β and IFN-γ) and major histocompatibility complex (MHC) class I and class II molecules (Kronik et al. 2008), to the interactions among multiple immune cell populations, dendritic cells and cytokines (e.g., Cappuccio et al. 2006; Castiglione and Piccoli 2007; de Boer et al. 1985).

One of the earliest and most complex ODE models for tumor-immune system interactions was developed by de Boer et al. (1985), who considered interactions among cancer cells, cytotoxic T lymphocytes, normal and cytotoxic macrophages, helper ($CD4^+$) T cells, and the production of signaling molecules such as IL-2 cytokines. de Boer et al. (1985) used eleven ordinary differential equations coupled with a further five algebraic equations. In spite of the complexity of their model, the authors were able to use it to develop biological hypotheses that could explain observed tumor-immune system dynamics. In particular, they showed that the magnitude of the effector cell (cytotoxic T lymphocyte) response depends on the time at which the helper T cells become activated. Early activation leads to a steep increase in the magnitude of the immune response. de Boer et al. (1985) also found that tumor antigenicity plays an important role in determining the type of the immune cells that are recruited for anti-tumor response. For example, the model indicates that weakly antigenic tumors are attacked mainly by macrophages, while strongly antigenic tumors can be eradicated only by the cytotoxic T lymphocytes. A brief review of this model and a comparison with other models of this type can be found in Dullens et al. (1986).

Many other multiple-equation models have been derived to study particular aspects of tumor-immune dynamics. For example, Cappuccio et al. (2006) used a six-equation model to investigate the role of IL-21 on the transition from innate immunity (represented by NK cells) to adaptive immunity (represented by $CD8^+$ T cells), and the possible implications for cancer immunotherapy. Their numerical simulations suggest that IL-21 should be used to control non-immunogenic tumors, but not highly immunogenic tumors.

One final example that we mention here is a model that investigated the effects of immunotherapy on malignant gliomas (a type of brain tumor). In this model, Kronik et al. (2008) considered interactions among cancer cells, cytotoxic T lymphocytes, two cytokines (TGF-β and IFN-γ), and MHC class I and II molecules. Numerical simulations of the model predicted the dose of cytotoxic T-lymphocytes required for therapeutic efficiency in the treatment of malignant gliomas (Kronik et al. 2008). The authors then validated the predictions by comparing them with two sets of empirical results (Burger et al. 1985; Kruse et al. 1997).

7 Discussion

7.1 Increasing Model Complexity in Steps

We began this review by considering the simplest possible models of tumor growth, involving a single ordinary differential equation (ODE). These models describe only one cell population (cancer cells), which are subject to self-regulation by density-dependent processes. While such models can be fitted successfully to many examples

of tumor growth data—and are useful for predicting tumor growth in the absence of treatment—they cannot display temporary growth followed by regression, and they do not allow us to investigate the effects of interactions with other types of cells and chemicals.

We then reviewed what has been learned from models of cancer cells interacting with one type of immune cell, before considering a third and fourth component of the tumor microenvironment, adding one equation at a time. Finally, we briefly described some more elaborate ODE models involving many equations for many types of cells and signaling molecules. We emphasized the overall structure of models, using generic functions in interaction terms, and referred to particular models by specifying the functional forms of these terms.

The authors whose work we have reviewed did not build up their models in steps the way that we have. Doing so has allowed us to develop a clearer view of the motivations, benefits and costs of increasing model complexity. In terms of the behavior of currently observable variables, simpler models often exhibit the same dynamics as more complex models, but models incorporating more biological detail allow us to conduct theoretical studies that clarify the underlying immuno-oncological mechanisms and suggest hypotheses—especially concerning treatment—that can be tested experimentally.

7.2 Related Research that We Have Not Reviewed

We have restricted attention entirely to ODE models, which approximate a cell population as a continuum and implicitly assume that all the different cell populations are homogeneously mixed. These approximations seem appropriate for studies of cancer-immune system interactions in the context of systemic disease that is not isolated in a single tumor, regardless of whether we know all the locations of the cancer cells in the body. It is less clear that ODEs are truly suitable for modeling immune cell interactions with a single isolated tumor. Ideally, the inferences drawn from ODE models should be checked using models that consider the discreteness of individual cells and/or spatial structure. There are several methods for doing this.

Discreteness and Stochasticity Any of the ODE models we have described can be recast as an event-driven Monte Carlo model, which deals with integer numbers of cells. Exact realizations of the associated stochastic processes can be generated using the standard Gillespie algorithm (Gillespie 1976). In the limit of very large cell and chemical populations, the behavior of the stochastic models converges to those of their ODE counterparts (Kurtz 1971), but for small populations the behavior is different. Because the tumor and immune cell populations are very large (e.g., in mice, they are of order 10^6–10^9 cells), this stochastic approach is rarely investigated at the cellular level for tumor-immune models (although there are published stochastic models that investigate various immune processes at the molecular level, Chatterjee et al. 2005; Samad et al. 2005).

Another source of stochasticity arises, for example, from genetic mutations that occur during the evolution of cancer cells, or from variations in the environment (e.g., nutrient supply). These stochastic effects have been incorporated into mathematical

models by (a) starting with a deterministic model and adding noise terms (see, for example Bose and Trimper 2009), or (b) using agent-based models, in which the time-evolution of individual cells of various types is described by computer algorithms (Lollini et al. 2006b; Pappalardo et al. 2006). Models of type (a) usually describe a small number of biological interactions that lead to tumor growth or regression. As an example, the model of Bose and Trimper (2009) is a one-equation model for tumor growth. Models of type (b) can include a very large number of biological interactions that describe complicated stochastic immune processes, such as the random generation of various immune cells or cell interactions following probabilistic laws. The model of Lollini et al. (2006b), for example, describes the evolution of 17 different variables.

Individual Agents Real immune systems are extremely complex, involving hundreds of distinct cell types and signaling molecules. Models that attempt to include a large proportion of this complexity can be analyzed only through simulation. The most realistic models are: (i) agent-based models, which are defined at the individual (biological cell) level, and (ii) cellular automata models, which are defined at the spatial location (physical cell) level. Agent-based models specify rules that apply to each individual biological cell, whereas cellular automata models specify rules that apply to each physical cell, each of which may or may not contain one or more biological cells.

Only a few agent-based and cellular automata models of tumor-immune interactions have been published (e.g., Malet and de Pillis 2006; Gerlee and Anderson 2009; Mansury and Diesboeck 2003; Lollini et al. 2006b; Alarcon et al. 2003). Some of these models are deterministic (Mansury et al. 2006), while others are stochastic (Lollini et al. 2006b). The majority of these models focus on the dynamics of cancer cells in response to the surrounding environment, which is comprised of other types of cells (immune and normal tissue cells) and nutrients (e.g., glucose and oxygen). The evolution of the nutrients is generally modeled by partial differential equations (Malet and de Pillis 2006; Gerlee and Anderson 2009; Mansury and Diesboeck 2003; Lollini et al. 2006b; Mansury et al. 2006).

While models of this type have the ability to provide the most accurate representation of tumor micro-environments (see, for example, Lollini et al. 2006b), they are extremely challenging to analyze because their complexity is bewildering, they must be simulated many times for each parameter set of interest, and they involve many parameters with values that cannot be reliably estimated from existing data (so must be guessed). Nevertheless, agent-based/cellular automata models have the potential to be exceptionally useful for testing very specific hypotheses that cannot even be represented in simpler models, and for checking that results obtained with simpler models are robust to the inclusion of much greater biological detail. For a more comprehensive review of these models, see Thorne et al. (2007).

Spatial Structure Partial differential equations (PDEs) have been used extensively to model spatial aspects of solid tumor growth and cancer-immune system interactions, and have been discussed in many research papers (e.g., Matzavinos et al. 2004; Owen et al. 2004; Webb et al. 2007; Wang et al. 2009 and the references therein)

and review articles (e.g., Byrne et al. 2006; Martins et al. 2007; Roose et al. 2007; Chaplain 2008; Nagy 2005). Unlike the cellular automata models discussed above—and in spite of the increased mathematical complexity arising from the spatial dimensions—many PDE models can be examined productively using well-known analytical techniques (e.g., techniques for proving the existence of various types of solutions, or traveling wave methods for estimating the growth of tumor spheroids).

7.3 Directions for Future Research

As indicated throughout this review, most mathematical models in the literature focus on the effector immune cells (e.g., $CD8^+$ T cells, NK cells and macrophages). However, recent experimental immunological results suggest new, potentially fruitful avenues for mathematical modeling research. We briefly mention two such directions below.

An Effector Role for $CD4^+$ T Cells Until recently, $CD4^+$ T cells have been assumed to have only a helper role, activating $CD8^+$ T cells to kill cancer cells (Bennett et al. 1997). New experimental results have suggested a more direct role for the $CD4^+$ T cells (Mattes et al. 2003; Perez-Diez et al. 2007; Zhang et al. 2009). In particular, these cells appear to have an effector role through the cytokines and chemokines that they produce (Mattes et al. 2003; Zhang et al. 2009). This means that $CD4^+$ T cells can kill cancer cells even in the absence of $CD8^+$ T cells and NK cells. Moreover, it seems that they are more efficient at rejecting tumors than $CD8^+$ T cells (Perez-Diez et al. 2007). To understand this theoretically, new mathematical models are needed that focus on the $CD4^+$ T cells and the particular biological mechanisms these cells use to attack cancer. Such models should facilitate the development of new hypotheses regarding the interactions between these cells and other types of immune cells, antigen-presenting cells, cytokines, and chemokines.

Potential models for cancer-$CD4^+$ T cell interactions should be described by at least three equations modeling the change in the number of tumor cells, $CD4^+$ T cells and the concentration of tumor-suppressive cytokines (such as IL-2 or IL-4). However, compared to (13) where the immune cells kill the cancer cells, in the new models, the cytokines would kill the cancer cells (and thus $d_x(x, z) \neq 0$). The only role of the immune cells would be to produce these cytokines following activation as a result of interactions with tumor-associated antigens.

Both Pro-Tumor and Anti-Tumor Effects of Macrophages A new direction in cancer immunotherapy has been stimulated by the potential to genetically engineer macrophages that kill cancer cells. In Sect. 5, we discussed the mathematical model of Byrne et al. (2004), which was designed to study such oncolytic macrophages. This model—as well as other ODE (Owen and Sherratt 1998) and PDE (Owen et al. 2004; Webb et al. 2007) models—focusses on the anti-tumor activity of the macrophages. However, natural (non-engineered) macrophages can induce both pro-tumor and anti-tumor effects depending on the cytokine environment (Leek and Harris 2002). In particular, they have an anti-tumor effect when activated in the presence of TNF-α or IFN-γ (classical activation) and a pro-tumor effect when exposed to IL-4 or IL-13 (Mantovani et al. 2002). In fact, recent studies have shown that in breast cancer,

tumor-associated macrophages have a primarily pro-tumor effect (Leek and Harris 2002). Hence, before deploying genetically engineered "designer macrophages" *in vivo* it would be useful to investigate their theoretical potential for cancer promotion as well as inhibition. This is a research direction where mathematical models can contribute significantly.

7.4 Conclusion

Mathematical models provide a valuable theoretical framework through which immuno-oncological mechanisms can be discovered or clarified. However, to our knowledge, the majority of the mechanisms discussed in this review have never been tested experimentally. Only a few of the mathematical models mentioned here (e.g., de Boer et al. 1985; Cappuccio et al. 2006; Lollini et al. 2006b) have received immunologists' attention (e.g., Horny and Horst 1986; di Carlo et al. 2007; Lollini et al. 2006a; Pappalardo et al. 2005). In most of these cases, the immunological papers merely acknowledge the results obtained with mathematical models (e.g., di Carlo et al. 2007). There are very few instances of experimental or clinical results being compared with the predictions of mathematical models (two examples are Horny and Horst 1986 and Pappalardo et al. 2005). We believe that closer interactions between cancer immunologists and mathematicians would benefit the field.

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