# Cancer phenotype as the outcome of an evolutionary game between normal and malignant cells

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## Abstract

**Background:** There is variability in the cancer phenotype across individuals: two patients with the same tumor may experience different disease life histories, resulting from genetic variation within the tumor and from the interaction between the tumor and the host. Up to now, phenotypic variability has precluded a clear-cut identification of the fundamental characteristics of a given tumor type.

**Methods:** Using multiple myeloma as an example, we apply the principles of evolutionary game theory to determine the fundamental characteristics that define the phenotypic variability of a tumor.

**Results:** Tumor dynamics is determined by the frequency dependent fitness of different cell populations, resulting from the benefits and costs accrued by each cell type in the presence of others. Our study shows how the phenotypic variability in multiple myeloma bone disease can be understood through a game theoretical approach that allows the identification of key genotypic features in a tumor *and* provides a natural explanation for phenotypic variability. This analysis also illustrates how complex biochemical signals can be translated into cell fitness that determines disease dynamics.

**Conclusion:** The present paradigm is general and extends well beyond multiple myeloma, and even to non neoplastic disorders. Furthermore, it provides a new perspective in dealing with cancer eradication: Instead of trying to kill all cancer cells, therapies should aim at reducing the fitness of malignant cells compared to normal cells, allowing natural selection to eradicate the tumor.

## Introduction

The origin of cancer requires the appearance of a new and *aberrant* cell type due to at least one mutation in a normal cell (Hanahan & Weinberg, 2000; Vogelstein & Kinzler, 2004). Cancer development is associated with the expansion of the mutant clone, and is normally described in terms of *frequency independent* evolutionary dynamics: Cancer cells have a different relative fitness compared to normal cells, leading to clonal expansion, *independent* of the relative abundance of different cell lineages. However, whenever one lineage expands, it often influences and is influenced by the current abundance of other cell populations (including normal cells). Such dynamic behavior is best described in terms of *frequency dependent* selection (and mutation), akin to Evolutionary Game Theory (EGT ) (Hofbauer & Sigmund, 1998; Maynard-Smith, 1982). Up to now the applications of EGT to cancer have been mostly explorative in nature, without succeeding in providing insights into specific diseases (Axelrod *et al*, 2006; Tomlinson, 1997; Tomlinson & Bodmer, 1997). Here we demonstrate how detailed biochemical knowledge accumulated over the last two decades helps us in defining such games.

Let us consider the case of MM bone disease, an important cause of morbidity due to pain, the risk of pathological fractures and neurological deficits. Bone loss may be focal (lytic lesions) (Berenson, 2001; Kyle & Rajkumar, 2004)or diffuse leading to osteoporosis(Harper & Weber, 1998). The appearance of MM cells alters (and is altered by) bone remodeling. *Normal* bone remodeling is a consequence of the dynamic balance between osteoclast (OC) mediated bone resorption and bone formation from osteoblast (OB) activity (Figure 1-a), partly dependent on the receptor activator of nuclear factor-κB (RANK), RANK ligand (RANKL) and osteoprotegerin (OPG) axis (Roodman, 2004; Terpos *et al*, 2007). The appearance and expansion of MM cells disrupts this dynamic equilibrium between OB and OC, with a disease progression time scale of the order of a few years (Kyle & Rajkumar, 2004). The presence of MM cells alters the OB-OC balance in favor of OC (Berenson, 2001; Roodman, 2004; Terpos *et al*, 2007). This process can be subdivided into two components:

i) MM and stromal cells produce a variety of cytokines including interleukin 1β, (IL-1β) (Dinarello, 2009a), RANKL (Croucher *et al*, 2001) and MIP-1α (Choi *et al*, 2000) (summarized as 'osteoclast activating factors', OAF (Roodman, 2004; Roux & Mariette, 2004)) that recruit OC precursors and stimulate growth of the OC population; and

ii) Secretion of Dickkopf-1 (DKK1) by myeloma cells directly inhibits Wnt3a regulated differentiation of osteoblasts, reduces OPG expression and alters the OPG-RANKL axis against OB activity (Qiang *et al*, 2008a; Qiang *et al*, 2008b; Qiang *et al*, 2008c; Roux & Mariette, 2004; Terpos *et al*, 2007)**.**

The biochemical interactions between MM, OC and OB cells highlight the dependence of MM cells on the bone marrow microenvironment, at least early in the course of the disease (Epstein & Yaccoby, 2003; Kuehl & Bergsagel, 2002).

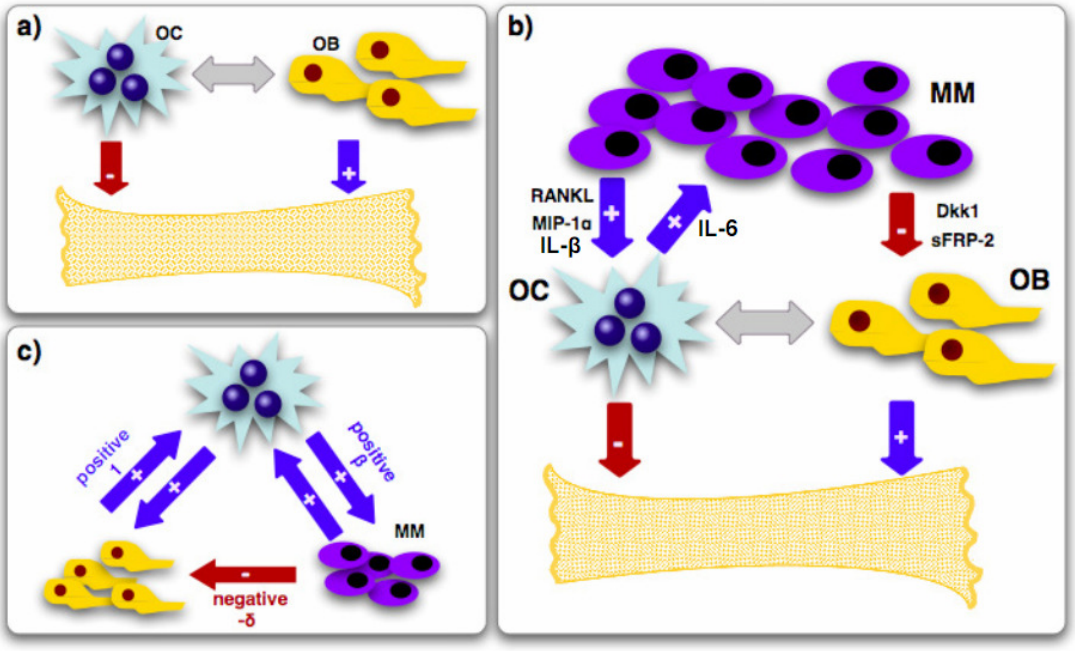


**Figure 1. Bone turnover under normal and pathologic conditions. a)** Normal bone remodeling reflects the balance between osteoclasts (OC) that resorb bone and osteoblasts (OB) that regenerate bone. **b)** The presence of multiple myeloma cells (MM) alters bone homeostasis by cytokine production (e.g., IL-1β, RANKL, MIP-1α) that recruit and activate OC, increasing resorption. OC may also produce growth factors (IL-6) for MM cells, which may also secrete cytokines that suppress OB activity. The synergy between MM and OC confers them an advantage with respect to OB. **c)** Cytokine exchanges between cells lead to net effects associated with payoff matrix entries.

As shown in Figure 1, IL-6 (Jelinek, 1999) and osteopontin (Abe *et al*, 2004), produced by OC cells stimulate growth of the MM cell population, hence conferring a *net* benefit to MM cells. On the other hand, production of OAF by MM cells (i) confers a *net* benefit to OC cells. Mechanism ii) also leads to a potential disadvantage for OB cells in the presence of MM cells, while MM cells are unaffected by the presence of OB cells. Figure 1-c provides a useful scheme to translate the complex exchange of chemical signals between different cell types into net benefits and costs of each cell type. We can therefore recast the frequency

dependent balance between these cell populations in terms of an evolutionary game encompassing three "strategies" – OC, OB and MM, and the following payoff matrix:

$$\begin{array}{c} \\ OC \\ OB \\ MM \end{array} \begin{array}{c} \begin{array}{ccc} OC & OB & MM \end{array} \\ \begin{bmatrix} 0 & a & b \\ e & 0 & -d \\ c & 0 & 0 \end{bmatrix} \end{array} . \qquad (1)$$

The present formulation is the mathematical equivalent of an ecosystem where the interactions between species (MM, OC and OB) are determined by matrix (1). Without loss of generality (see Methods) we assume that interactions between cells of the same type are neutral. In the absence of MM cells ($a$, $b$, $c$, $d$ and $e$ are non-negative), there is a stable balance between OC and OB cells with a OC-frequency given by $a/(e+a)$ such that increasing $e$ moves the equilibrium towards OB (Nowak, 2006). Hence, in the absence of MM cells, OB and OC engage in a co-existence game, the internal equilibrium of which reflects normal physiology. Any disturbance from this state induces an evolutionary dynamics that acts to restore the equilibrium (enabling normal tissue to adapt to changing demands and repair after injury). When we embed the OB-OC dynamics in a more general framework, including MM cells, the nature of the OB-OC equilibrium possibly changes from stable to a saddle point (for a certain set of parameters) or remains stable (otherwise). In the first case, even a small number of MM cells will be able to invade and disease will progress; in the second, the natural dynamics will prevent the system from the invasion of MM cells and OB-OC equilibrium will be restored.

## Methods

Our analysis is based on the replicator equation describing the frequency dependent evolutionary dynamics of three well-mixed cell populations(Hofbauer & Sigmund, 1998). Consequently, we assume that i) no new mutations occur during tumor dynamics except those which initiated the tumor and ii) deterministic cell population dynamics. While the first issue is often justified (Dingli *et al*, 2008; Traulsen *et al*, 2007), cell dynamics often reflects a stochastic behavior which may lead to additional disease variability not captured at this level of description. The generation of the first MM cell is a multistep process requiring a series of mutations that transform a normal plasma cell into an MM cell (Bergsagel & Kuehl, 2005; Kuehl & Bergsagel, 2002). We start our dynamics assuming that this first MM is present and follow its clonal expansion.

Tumor dynamics is conveniently represented in the simplex (an equilateral triangle for three strategies) at every point of which we have the relative frequencies of OB, OC and MM populations that sum up to 1. Let us denote by $x_i(t)$ the relative frequencies of the cell-types: $x_1(t)$ (OC cells), $x_2(t)$ (OB cells) and $x_3(t)$ (MM cells). The replicator equations read

$$\dot{x}_i(t) = x_i(t)\left[F_i(x_1, x_2, x_3) - < F >\right] \quad (i = 1,2,3)$$

where the fitness of each cell type is given in terms of a game payoff matrix $A_{ij}$ by

$$F_i(x_1, x_2, x_3) = \sum_{k=1}^{3} A_{ik} x_k$$

whereas the average fitness of the population reads

$$< F >= \sum_{i=1}^{3}\sum_{k=1}^{3} x_i A_{ik} x_k$$

The replicator equations reflect a simple and intuitive dynamics for each cell type - depending on whether the fitness of a given cell type is higher (lower) than the average fitness of the entire population, that cell type will increase (decrease) in the total population as a rate specified by the replicator equations.

The benefits and costs resulting from the interacting cell populations are captured in the initial payoff matrix (1), here associated with matrix $A_{ij}$. We reduce this matrix to the minimal payoff matrix

$$B_{ij} = \begin{array}{c} \\ OC \\ OB \\ MM \end{array} \begin{array}{c} \begin{array}{ccc} OC & OB & MM \end{array} \\ \begin{bmatrix} 0 & 1 & \beta \\ 1 & 0 & -\delta \\ \beta & 0 & 0 \end{bmatrix} \end{array} \qquad (2)$$

by taking into account that the nature of the fixed points of the evolutionary dynamics (though *not* their location) remains unaffected under a projective transformation of the relative cells frequencies (Hofbauer & Sigmund, 1998). In the present case, the matrices are related by $B_{ij} = \frac{A_{ij}}{\phi_j}$, where $\phi_i$ are positive constants given by $(\phi_1, \phi_2, \phi_3) = (e, a, be/c)$, such that $\beta = \frac{c}{e}$ and $\delta = \frac{dc}{be}$. The matrix transformation may be shown to correspond to the following projective transformation of the relative frequencies $x_i \to y_i$ (Hofbauer & Sigmund, 1998) : $y_i = \frac{\phi_i x_i}{\sum_{k=1}^{3} \phi_k x_k}$ which, by rescaling the relative frequencies, changes the location of the fixed

points on the simplex, without changing their stability nature. Note further, that the replicator equations and associated dynamics remain unaffected if we add an arbitrary constant to each column of the payoff matrix. In other words, it is always possible to zero all the diagonal elements of the game payoff matrix.

The fixed points $(x_1^*, x_2^*, x_3^*)$ of the evolutionary dynamics under matrix $B_{ij}$ are readily found. Two vertices of the simplex, (0,1,0) and (1,0,0) are unstable fixed points whereas the third is a saddle point. The fixed point (½,½,0) associated with normal physiology is unstable whenever β>1, being stable otherwise; the fixed point (½,0, ½) is a stable fixed point whenever β>1 or whenever β<1 but β+δ>1; in this last situation, a saddle point arises in the interior of the simplex, located at

$$q^* = \left(\frac{\delta}{1+\delta+\beta(\delta+\beta-2)}, \frac{\beta(\delta+\beta-1)}{1+\delta+\beta(\delta+\beta-2)}, \frac{1-\beta}{1+\delta+\beta(\delta+\beta-2)}\right).$$

Indeed, we easily prove the following

**Theorem**: $q^*$ is in the interior of the simplex if β<1 and β+δ>1.

**Proof**: $q^*$ is in the interior of the simplex if $\frac{\delta}{1+\delta+\beta(\delta+\beta-2)} > 0$, $\frac{\beta(\delta+\beta-1)}{1+\delta+\beta(\delta+\beta-2)} > 0$ and $\frac{1-\beta}{1+\delta+\beta(\delta+\beta-2)} > 0$. The first two conditions readily imply that β+δ>1while the third one is equivalent to demand that β<1. ■

Furthermore, we also prove that

**Theorem**: If $q^*$ is in the interior of the simplex, then it is a saddle.

**Proof**: The eigenvalue associated with $q^*$ reads

$$\lambda^* = \frac{\beta\delta \pm \sqrt{-\beta\delta(4-8\beta-4\delta+3\beta\delta+4\beta^2)}}{2(2\beta-1-\delta-\beta\delta-\beta^2)}.$$

Since $3\beta^2\delta^2 < -\beta\delta(4-8\beta-4\delta+3\beta\delta+4\beta^2)$, this means that the first eigenvalue is positive and the second is negative. ■

In our framework, additional mutations within the expanding MM population can act to effectively change the values of the interacting parameters β and/or δ; in general, however, we expect that such modifications will contribute to change the time scale of the dynamics but not their nature or the final outcome. Similarly, if we consider cytotoxic chemotherapy that significantly reduces the MM population, this will act to reset the clock and, in some cases, significantly increase life expectancy, but will not alter the final outcome (i.e. the

equilibrium). This is supported by ample clinical data whereby high dose chemotherapy and stem cell transplantation lead to significant reductions in tumor burden with improvement in survival but the disease invariably relapses (Attal *et al*, 2003; Attal *et al*, 1996).

## Results

Figure 2 provides an overview of the possible scenarios that emerge from the evolutionary dynamics associated with payoff matrix (2). The three strategy game leads to unstable equilibria whenever the population is monotypic: the presence of a single cell of any of the other types leads to the coexistence of the two strategies, as the pair-wise games OB-OC and OC-MM are co-existence games (Maynard-Smith, 1982). The number and nature of the fixed points in the simplex will depend on the relative balance between $\beta$ and δ in the payoff matrix, as shown in Figure 2 (and Methods).

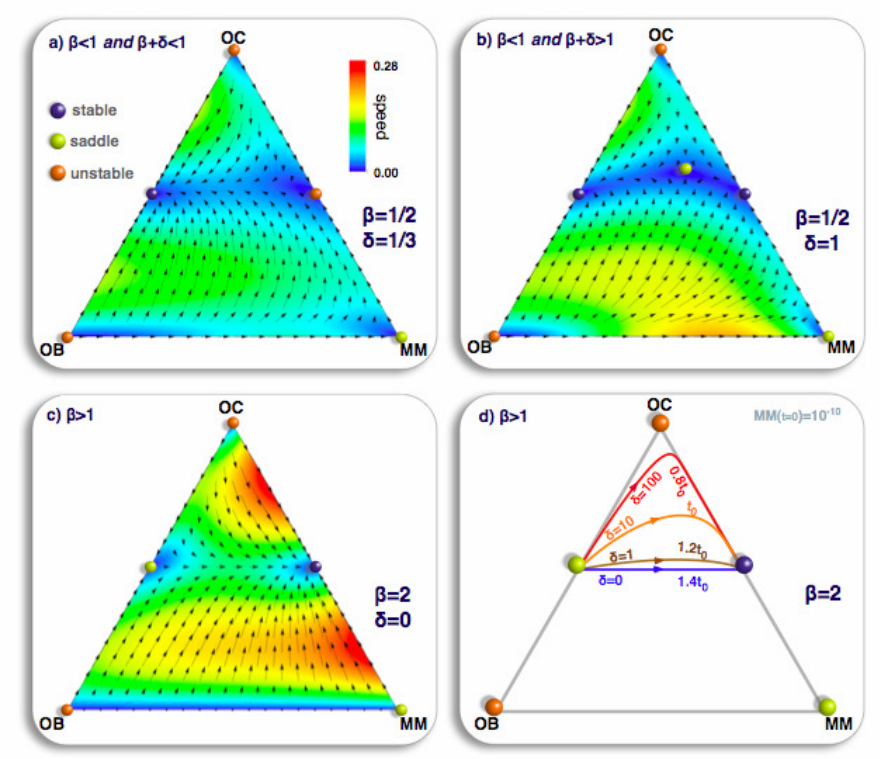


**Figure 2. Evolutionary dynamics of OC, OB and MM cell types.** Vertices mean that cell population is monotypic. Bone homeostasis occurs in the absence of MM (OC-OB line), remaining stable in the presence of MM if $\beta < 1$ (upper panels). The fixed point along OC-MM is unstable whenever $\beta + \delta < 1$, being stable otherwise. For $\beta > 1$ only the OC-MM coexistence equilibrium is stable (lower panels). Color gradients represent the rate of disease progression. **d)**. δ affects both the path *and* progression time between OB-OC and OC-MM equilibrium. OB-OC equilibrium was disturbed by introducing 1 MM cell (in a population of $10^{10}$ cells), for different values of δ.

If the net benefit that OC cells obtain from MM cells is smaller than what they get from OB cells ( $\beta < 1$ ), the population of MM cells can go extinct and OB and OC may again re-establish the stable dynamic equilibrium (Figure 2-a). However, various studies suggest that $\beta < 1$ is the exception rather than the norm (Epstein & Yaccoby, 2003; Roodman, 2002). Whenever $\beta > 1$, the only stable equilibrium is the co-existence of MM and OC cells (Figures 2-c, 2-d and 3). In this extreme situation a part of bone is completely devoid of OB and as the bone approaches this state is at increasing risk of fracture, a common feature of MM (Bataille & Harousseau, 1997; Kyle & Rajkumar, 2004). One need not postulate a negative effect of MM on OB: even if $\delta = 0$ (MM and OB are neutral with respect to each other) the only stable equilibrium is the co-existence of MM and OC (Figure 2-c).

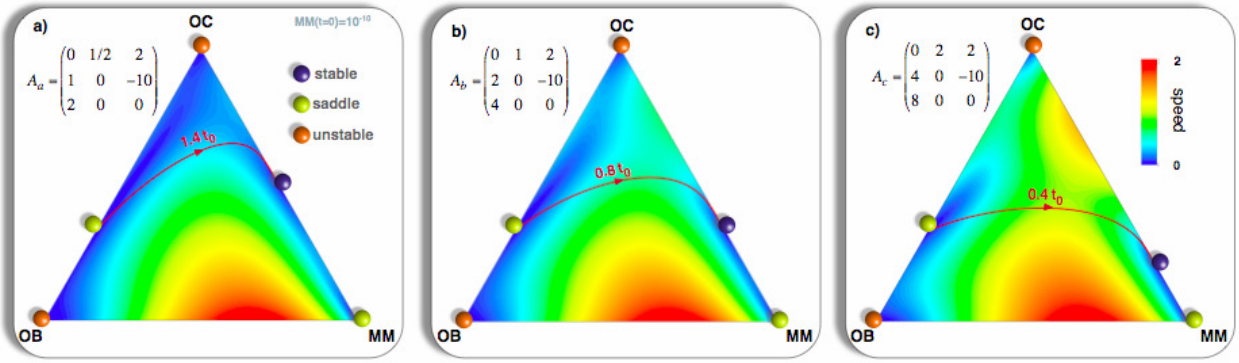


**Figure 3. Host specific tumor progression.** The values *b* and *c* in matrix (1) alter the position of the equilibrium on the OC-MM line, whereas *a* and *e* change the equilibrium between OC and OB cells**,** producing deviations both in the disease path and on the characteristic evolutionary time-scale. Each panel shows a different path with the associated matrix, all leading to the same payoff matrix (2) with δ=10 and β=2. We start with a small perturbation of the OC-OB equilibrium and $t_0$ stands for the progression time of the configuration δ=10 and β=2 in payoff matrix (2) (Figure 2-d).

However, changes in $\delta$ may have a significant impact on the life history of the disease and associated progression time, as shown in Figure 2-d: Increasing $\delta$ for fixed $\beta$ - that is, increasing the disadvantage of OB cells in the presence of MM cells - leads to disease dynamics in which considerable bone loss occurs without a significant increase in the MM population. This may explain instances of myeloma induced osteoporosis without a massive MM cell burden. Similarly, increasing β leads to more bone destruction, higher tumor burden and faster tumor progression. This behavior is observed clinically: patients with higher MIP-1α levels (increasing β) tend to have more bone resorption and lytic bone lesions (Hashimoto *et al*, 2004; Terpos *et al*, 2003) and shorter survival due to a higher tumor burden (Terpos *et al*, 2003). Consequently, therapies which suppress or reduce β (inhibiting, e.g., MIP-1α

secretion or IL-1β (Dinarello, 2009b; Lust *et al*, 2009)) should decrease the number of lytic lesions and the speed of disease progression, prolonging survival (Choi *et al*, 2001). Similarly, any therapy that decreases δ (e.g. Dkk-1), should reduce the myeloma burden, slow the progression of the disease, and improve bone mass (Yaccoby *et al*, 2007).

We also used the model to understand the impact of high-dose therapy and stem cell transplantation that is often offered to patients with myeloma. This therapy normally leads to ~3 log reduction in tumor burden (Dingli *et al*, 2007a; Dingli *et al*, 2007b). Patients going to transplant have variable tumor burden, so we evaluated the impact of initial tumor burden and depth of response on bone and tumor cell population dynamics (Figure 4). Across a wide range of parameters, we find that bone healing does not occur: i.e. the ratio of OB/OC does not return to normal as long as MM cell persist (Figure 4b, d, e). As the depth of response increases, the time to relapse increases (Figure 4b versus d). Moreover, the speed of relapse depends on both the MM population at the time of transplant as well as the degree of tumor cytoreduction achieved with transplantation.

The payoff matrix (2) provides a minimal description of the disease and identifies the kernel features which determine tumor behavior and dynamics. It is important to stress that the non-trivial identification of the key parameters β and δ could not be anticipated from the rationale underlying the model setup, as illustrated in Figure 1 and out of which matrix (1) was derived. Instead, it results from a rigorous mathematical property of evolutionary game dynamics, which dictates that the evolutionary outcome of the disease can be equivalently analyzed in terms of matrix (2). Under the present assumptions, $\beta$ and $\delta$ are sufficient to characterize myeloma bone disease. However, it is well known that the natural history of the disease is variable, presumably due to genetic and epigenetic differences in myeloma cells from different patients. Normal physiology also varies from individual to individual. Payoff matrix (1) takes this variability into account by incorporating those effects which do not relate directly to MM disease (e.g. pre-existing disease that could alter the tumor-host interactions) but can affect the overall disease dynamics. Figure 3 shows how different entries in payoff matrix (1) sensitively affect disease progression *paths* and *times*. We assumed that the OB-OC equilibrium does not change qualitatively from patient to patient, as opposed to what one may expect concerning the OC-MM final equilibrium. The actual values of payoff matrix (1) affect both the location of the fixed points and the time associated with disease progression. These are expected to be patient specific, reflecting tumor-host

interactions and variability of disease due to differences in the host rather than the malignant cell genotype.

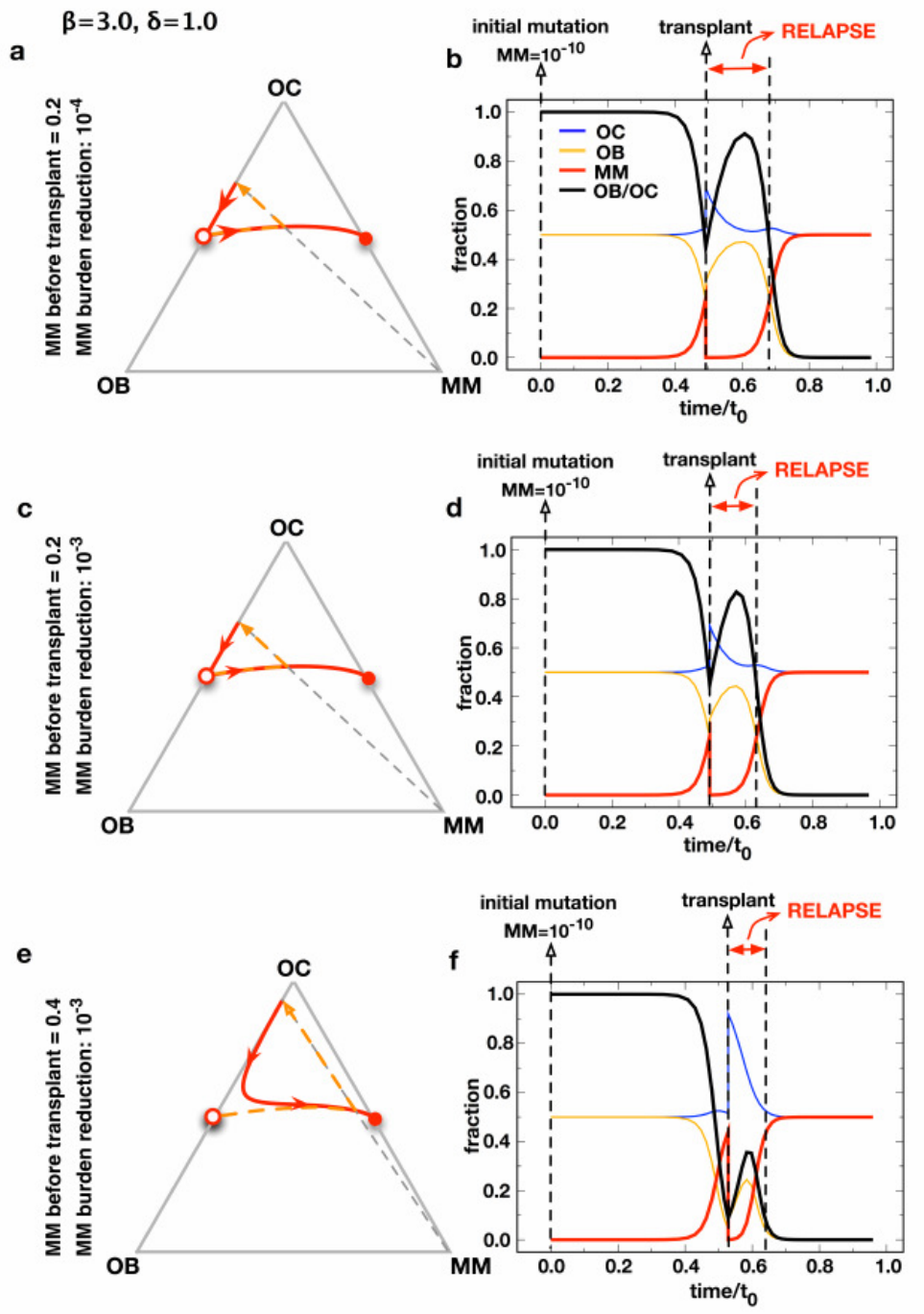


**Figure 4. Population dynamics in response to therapy.** Starting with different fractions of MM cells (a, c, e), we determined the population trajectories as a function of reduction in MM burden (b, d, f). The general behavior did not change across a wide range of parameter values. However, the speed of relapse is related to the starting size of the MM population. Note that the OB/OC ratio does not return to normal as long as MM cells persist.

## Discussion

Besides giving a broad view of the overall features of the disease (captured by $\beta > 1$ and $\delta \geq 0$), our approach provides important insights on therapeutic priorities to ameliorate the patient's condition. Therapies that kill MM cells can slow the speed of disease evolution and prolong patient survival while simultaneously improving bone structure. Unfortunately, this will not alter the final outcome. Indeed high dose chemotherapy and stem cell transplantation, the current 'standard of care' for eligible patients, lead to significant reductions in tumor burden with improvement in survival but the disease invariably relapses and many patients ultimately die of relapsed or refractory disease (Attal *et al*, 2003; Attal *et al*, 1996). In contrast, agents such as bisphosphonates can change disease dynamics by altering the "game" (reducing β) and consequently reduce the number of lytic bone lesions or myeloma induced osteoporosis. Whenever therapies succeed in reversing the sign of (β-1), they may inhibit disease progression. For example, antisense therapy against MIP-1α blocked bone destruction in a mouse model of myeloma (Choi *et al*, 2001). Similarly, therapies that reduce the effective value of δ may significantly attenuate morbidity by slowing the speed of bone loss. In this respect, an antibody directed against *Dkk-1* reduced both bone loss and the myeloma tumor burden in a preclinical model (Yaccoby *et al*, 2007). This general behavior is also supported by data from a human clinical trial. A recent study by Lust *et al* showed that neutralization of IL-1β (an osteoclast activating factor that also stimulates IL-6 production) with an interleukin 1 receptor antagonist (IL-1Ra, known as anakinra), slows the progression of smoldering to active multiple myeloma. This finding can be easily understood in light of the present model: anakinra effectively reduces β, which has precisely the same implications regarding disease progression as shown in Figure 2. Patients treated with this agent had a reduction in the rate of proliferation of plasma cells and accumulation of lytic bone lesions (Dinarello, 2009b; Lust *et al*, 2009).

It is worth stressing the fact that whenever $\beta<1$ and $\beta+\delta>1$ (Figure 2-b), the appearance of an interior fixed point may be of particular relevance in what concerns the development of new therapies. Indeed, our model predicts that by altering the relative fitness of one cell type with respect to the others, one may effectively change the overall disease evolution, in this case to the appearance of such an internal saddle point. Thus, our model suggests that therapies directed against *Dkk-1* may be useful is reducing bone loss and slow the accumulation of tumor burden in patients with smoldering myeloma. It is therefore important to determine at which stage of disease evolution such a therapeutic procedure is

implemented. Therapies that bring the disease into this regime may be effective in patients, that at the time of diagnosis are in a disease state that is metaphorically located "to the left" of the saddle point, in which case evolutionary dynamics will naturally lead to the decline of the MM cell population. The location of this saddle point is determined in part by the detailed interactions of the cell populations with each other. In our model we do not consider the possible existence of various subpopulations of MM cells that are dependent on the marrow microenvironment to variable extents and for which this model may or may not apply. If experimental data describing the interaction of such MM subpopulations (e.g. myeloma stem cells) becomes available, this can be incorporated into the model at the expense of increased mathematical complexity.

Finally, there is variability in the precise location of the fixed points and the different possible *paths* that join them. One should not overlook the message from Figures 2d and 3 – the variability in tumor genotype/phenotype determines a corresponding variability of the time scales and life-histories associated with disease progression. Our model illustrates how interactions between the genotype of normal and neoplastic cell populations, combined with the individual host specificities, determine both the phenotype and the dynamics of the disease, including disease progression times. As shown in Figure 2-d, the nature of the interaction between MM and OB cells, controlled by $\delta$, plays a very crucial role in both disease progression and expression. Patients with a disease characterized by a large $\delta$ will experience insidious disease with a small population of MM cells leading to significant and rapid bone loss, a feature that could lead to a misdiagnosis of osteoporosis rather than myeloma. In this era of individualized medicine, every patient is a special case and it is crucial to understand the tumor and host characteristics in order to better understand the patient's unique disease dynamics.

The model can be used to evaluate the potential for bone healing as the MM burden is reduced. Currently, there are no therapeutic options than can cure the disease, so elimination of the whole MM population is not possible. As the MM cell burden is reduced, one expects healing of bone and increased life expectancy of the patient. However, the model predicts that bone healing would be a slow process and, given the low likelihood of eliminating all the MM cells relapse will take place, except perhaps by development of therapies that effectively change $\beta$ and $\delta$.

In the current model we consider tumor burden as the only parameter that has an impact on survival. While patients with multiple myeloma can also die due to infection, renal

failure or unrelated causes, there is a clearly defined relationship between tumor burden and mortality. Indeed, both the Durie-Salmon staging system and the more recent International Staging System depend directly or indirectly on an estimation of the tumor burden to predict survival (Durie & Salmon, 1975; Greipp *et al*, 2005).

The approach developed here is general and readily applicable to other diseases. Furthermore, it provides a new paradigm for dealing with cancer eradication: Instead of trying to kill all cancer cells, therapies should aim at changing the rules of engagement between different cell types: in our case parameters $\beta$ and $\delta$. In the mathematical language of EGT, this means that therapies should aim at literally *changing the dynamics*, enabling normal cells to out-compete the malignant clone, consequently leading to its evolutionary extinction.

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