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Cancer initiation with epistatic interactions between driver and passenger mutations

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HIGHLIGHTS

- Most models of cancer initiation have considered independent mutations so far.
- Epistatic interactions can lead to a dynamics distinct from the smooth accumulation of mutations.
- In Burkitt Lymphoma, there is strong evidence for epistatic interaction between key mutations.
- We present a multi-type branching model which allows an analytical consideration of the dynamics.

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ABSTRACT

Q3 We investigate the dynamics of cancer initiation in a mathematical model with one driver mutation and several passenger mutations. Our analysis is based on a multi-type branching process: we model individual cells which can either divide or undergo apoptosis. In the case of a cell division, the two daughter cells can mutate, which potentially confers a change in fitness to the cell. In contrast to previous models, the change in fitness induced by the driver mutation depends on the genetic context of the cell, in our case on the number of passenger mutations. The passenger mutations themselves have no or only a very small impact on the cell's fitness. While our model is not designed as a specific model for a particular cancer, the underlying idea is motivated by clinical and experimental observations in Burkitt Lymphoma. In this tumor, the hallmark mutation leads to deregulation of the *MYC* oncogene which increases the rate of apoptosis, but also the proliferation rate of cells. This increase in the rate of apoptosis hence needs to be overcome by mutations affecting apoptotic pathways, naturally leading to an epistatic fitness landscape. This model shows a very interesting dynamical behavior which is distinct from the dynamics of cancer initiation in the absence of epistasis. Since the driver mutation is deleterious to a cell with only a few passenger mutations, there is a period of stasis in the number of cells until a clone of cells with enough passenger mutations emerges. Only when the driver mutation occurs in one of those cells, the cell population starts to grow rapidly.

1. Introduction

Tumors develop by accumulating different mutations within a cell, which affect the cell's reproductive fitness (Armitage and Doll, 1954; Lengauer et al., 1998; Hanahan and Weinberg, 2000; Michor et al., 2004; Wodarz and Komarova, 2005; Sjoblom et al., 2006; Greenman et al., 2007; Wood et al., 2007; Jones et al., 2008; Attolini and Michor, 2009; Parmigiani et al., 2009; Gerstung and Beerenwinkel, 2010). As Bozic et al. (2010), we refer to the fitness of a mutated cell as the ratio between the cell's rate to proliferate and the cell's rate of apoptosis compared to wild type cells. The higher the fitness, the more likely it is for the cell to proliferate. For high fitness values, the population of cells grows very fast and stochastic effects play a minor role. In our model, this can be thought of as the formation of a tumor.

However, many mutations have no impact on the cell's fitness, e.g. mutations not affecting coding or regulatory sequences. Other mutations may lead to a fitness disadvantage, which implies that the cell's risk of apoptosis is higher than its chance of proliferation. However, the same mutations in combination with other mutations within the same cell might lead to a large fitness advantage.

We were motivated by genetic studies in Burkitt Lymphoma, a highly aggressive tumor, where a single genetic alteration has an impact on a wide range of other genes, some of them affect cell growth while others induce apoptosis. More specifically, a chromosomal translocation between the *MYC* protooncogene on

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chromosome 8 and one of three immunoglobulin (*IG*) genes is found in almost every case of Burkitt Lymphoma (Richter et al., 2012; Allday, 2009; Hummel et al., 2006; Sander et al., 2012). This leads to deregulated expression of the *MYC* RNA and in consequence, to deregulated MYC protein expression. The MYC protein acts as a transcription factor and has recently been shown to be a general amplifier of gene expression (Nie et al., 2012; Lin et al., 2012), targeting a wide range of different genes. Most importantly, *MYC* expression induces cell proliferation. In Burkitt Lymphoma, the *IG-MYC* fusion is evidently the key mutation for tumorigenesis (Salaverria and Siebert, 2011; Zech et al., 1976; Schmitz et al., 2014; Campo, 2012). However, *MYC* plays also a key role in inducing apoptosis (Pelengaris et al., 2002; Wang et al., 2011; Hoffman and Liebermann, 2008). Thus, the *IG-MYC* translocation alone would lead to cell death. Therefore, the *IG-MYC* translocation has to be accompanied by additional mutations, which deregulate the apoptosis pathways, such as mutations affecting e.g. *TP53* or *ARF* (Richter et al., 2012; Allday, 2009; Sander et al., 2012). These additional mutations have probably only little direct impact on the cell's fitness, since apoptosis is rare. Hence, these mutations cannot be considered as primary driver mutations in the context of Burkitt Lymphoma. However, in combination with the *MYC* mutation these additional mutations decrease the apoptosis rate. Consequently, the cells proliferate fast and the population grows accordingly, leading to tumorigenesis. Because all cells carry the *MYC* mutation in Burkitt Lymphoma, but fast growth does not start immediately with that mutation, it seems to confer its large fitness advantage only in a certain genetical context. Thus, interactions between different mutations may crucially affect the dynamics of cancer progression. Due to the fact that those additional mutations do not confer a direct fitness advantage, they cannot be considered as driver mutations. Nevertheless, at least some of them are necessary in order for the *MYC* mutation to become advantageous for the cell. Therefore, they cannot be regarded as true passenger mutations, either. Throughout this paper, we therefore call these additional mutations "secondary driver mutations".

Besides Burkitt Lymphoma, epistatic effects in cancer initiation seem also to be relevant for other cancers. For example, we can think of the inactivation of a tumor suppressor gene discussed by Knudson in the context of retinoblastoma (Knudson, 1971). This inactivation is neutral for the first hit but highly advantageous for the second hit, and can hence be viewed as an interaction of genes (Nowak et al., 2002, 2004; Vogelstein and Kinzler, 2004; Iwasa et al., 2005). Another case is found in lung carcinomas, where activation of each of two oncogenes (*SOX2* and *PRKCI*) alone is insufficient, but in concert they initiate cancer (Justilien et al., 2014). In other cases, there is clear evidence for sign epistasis: the *ras* family of proto-oncogenes is also discussed to underlie epistatic effects. Amplification of *ras* leads to senescence in the cell. Nevertheless, *ras* is a well known oncogenic driver gene. Hence, the *ras* mutation needs to be accompanied by other mutations (Elgendy et al., 2011; Serrano et al., 1997). Moreover, the difficulty to distinguish between drivers and passengers (Futreal, 2007; Frohling et al., 2007) suggests that for a full understanding of cancer initiation it is insufficient to think of these two types of mutations only.

So far, most models have focused on the idea that passenger mutations have no effect or only a little effect, whereas each driver mutation increases the fitness of the cell (Michor et al., 2004; Beerenwinkel et al., 2007; Bozic et al., 2010; Gerstung and Beerenwinkel, 2010; Antal and Krapivsky, 2011; Reiter et al., 2013; Durrett et al., 2010; Datta et al., 2013). Other models focus on the neutral accumulation of mutations (Durrett et al., 2009; Luebeck and Moolgavkar, 2002). Moreover, different mutations are typically treated as independent, which is a strong assumption that will often not be fulfilled. In our model, mutations are interacting in an epistatic way (Wolf et al., 2000): the change in fitness induced by the driver mutation depends strongly on the genetic environment, i.e. in our case on the number of secondary driver mutations that are present in that cell. In addition we assume that the secondary driver mutations alone have almost no fitness advantage. Such a dependence between mutations can strongly affect the dynamics of cancer initiation. In evolutionary biology, epistatic systems are often analyzed regarding the structure or ruggedness of the landscape and the accessibility of different pathways (Weinreich et al., 2005; Franke et al., 2011; Szendro et al., 2013). The experimental literature also studies which factors can lead to epistasis (de Visser et al., 2011; Szappanos et al., 2011). Here, we are interested in the dynamics of such an epistatic model, which we illustrate by stochastic, individual based simulations. In addition, we derive analytical results for the average number of cells with different combinations of mutations and find a good agreement with the average dynamics in individual based computer simulations. Furthermore, we discuss the computation of the waiting time until cancer initiation. Our results show that the dynamics in such systems of epistatic interactions are distinct from previous models of cancer initiation (Michor et al., 2004; Beerenwinkel et al., 2007; Bozic et al., 2010; Gerstung and Beerenwinkel, 2010; Antal and Krapivsky, 2011; Reiter et al., 2013), which may have important consequences for the treatment of such cancers. While in previous models there is a steady increase in growth with every new mutation, in our model there is a period of stasis followed by a rapid tumor growth.

Of course, the biology of Burkitt Lymphoma is much more complex than modeled herein. To make the model more realistic one would have to distinguish between the different secondary driver mutations, since different genes contribute differently to the cells fitness, especially in a cell where the *IG-MYC* fusion is present. Our model is not aimed to realistically describe such a situation in detail. Instead, we focus on the extreme case of the so-called *all-or-nothing* epistasis (Barrick and Lenski, 2013; Meyer et al., 2012) to illustrate its effect on the dynamics of cancer initiation. As there is no theoretical analysis of epistatic effects in cancer initiation so far, a well understood minimalistic model seems to be necessary in order to illustrate the potential impact of epistasis on cancer progression. Our minimalistic model clearly shows that epistasis can lead to a qualitatively different dynamics of cancer initiation.

2. Mathematical model

We analyze cancer initiation in a homogenous population of initially N cells with discrete generations. In every generation, each of the N cells can either die or divide. If a cell divides, its two daughter cells can mutate with mutation probabilities μ_D for the driver mutation and μ_P for secondary driver mutations (where the P indicates that these would be called passenger mutations in closely related models). In principle, we could drop the assumption that these two mutation probabilities are independent on the cell of origin, but this would lead to inconvenient notation. We neglect back mutations and multiple mutations within one time step, because their probabilities are typically very small. Fig. 1 summarizes the possible mutational pathways of the model.

A cell's probability for apoptosis and proliferation depends on the presence of the primary driver mutation and on the number of secondary driver mutations it has accumulated. For cells with no mutations, the division and apoptosis probabilities are both equal to $\frac{1}{2}$. This implies that the number of cells is constant on average as long as no further mutations occur. We assume that the initial number of cells is high and thus we can neglect that the population would go extinct (Haccou et al., 2005). For our

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