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A stochastic microscopic model for the dynamics of antigenic variation

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HIGHLIGHTS

- We introduce a branching process to model the dynamics of antigenic variation.
- We completely characterize the different phases in the space of parameters in a rather general setting.
- Parameters as random variables allow to capture relevant features observed in nature.
- The model is simple and allows generalizations to more complicated situations.
- The interplay between immune evasion and immune response alone does not lead to persistent oscillatory behavior (parasitemia waves).

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ABSTRACT

We present a novel model that describes the within-host evolutionary dynamics of parasites undergoing antigenic variation. The approach uses a multi-type branching process with two types of entities defined according to their relationship with the immune system: clans of resistant parasitic cells (i.e. groups of cells sharing the same antigen not yet recognized by the immune system) that may become sensitive, and individual sensitive cells that can acquire a new resistance thus giving rise to the emergence of a new clan. The simplicity of the model allows analytical treatment to determine the subcritical and supercritical regimes in the space of parameters. By incorporating a density-dependent mechanism the model is able to capture additional relevant features observed in experimental data, such as the characteristic parasitemia waves. In summary our approach provides a new general framework to address the dynamics of antigenic variation which can be easily adapted to cope with broader and more complex situations.

1. Introduction

Parasites have evolved a diversity of sophisticated strategies to evade the host's immune response, among which antigenic variation is perhaps one of the most striking ones. This strategy consists of periodically changing a protective coat composed of an abundant and immunogenic protein. In this mechanism the parasites express only one variant antigenic protein copy from a large repertoire of silent genes. The mechanism allows transient immune evasion, since after changing the variable protein that is being expressed, an entirely new parasite population arises that is not recognized by the host's immune system, which has only developed an antibody response directed against the previous antigen. By repeating this cycle during the course of an infection, parasites are able to remain in the host for long periods of time.

Perhaps the most paradigmatic example is that of African trypanosomes (responsible for producing sleeping sickness in humans), but antigenic variation is also observed in *Giardia llambia* and the malaria agents belonging to the *Plasmodium* genus. Some viruses are also able to evade the immune response in a strategy similar to that just described. However in the latter systems, antigenic diversity is generated by the introduction of point mutations in the gene encoding the antigen, rather than by switching the expressed gene. This implies some substantial differences in the dynamics since the new antigen is most likely somewhat similar to the previous one (parental) and perhaps is recognized (yet with lower affinity) by the same antibodies.

Several models have been developed to study and predict the population dynamics of parasites and viruses during the course of an infection within a single host. Most of them are based on a system of coupled differential equations inspired on variations of predator-prey models (see Kosinski, 1980; Barry and Turner, 1991; Agur et al., 1989; Agur, 1992; Antia et al., 1996; Frank, 1999; Nowak and May, 2000.). In short, this approach consists of a set of differential equations describing the dynamical interaction between antigens and the host's

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immune system, in such a way that the outcome of one equation is a modulating parameter of the others, and including in some cases cross-reactive immune responses as well as other possible interactions (Antia et al., 1996). Stochasticity is incorporated ad hoc into the models by the emergence of new variants (which are not recognized by immune system) at random times, usually driven by a Poisson process (see Nowak and May, 2000 and references therein).

Very recently Gurarie et al. (2012) implemented a discrete time computer model for the case of malaria. This modeling approach, termed agent-based, consists of a set of coupled difference equations that describe the transition between successive iterations of the parasite population (i.e. parasite generations) and its interaction with the immune system. According to the authors the advantage of this approach is that, owing to its discrete nature, stochastic components are incorporated more easily by adding random factors to the variables that represent the efficiency of immune system.

In spite of the existence of these models of antigenic variation, in our opinion it is worth re-addressing the problem from a different perspective. Here we present a model that tackles this topic from a microscopic point of view that consists of following the pathway and behavior of its individual elements through a multi-type branching process. Iwasa et al. (2004) already used this methodology to study problems related to the ones presented here; however these authors focused on the evolutionary dynamics of viruses to escape antiviral therapy.

The model presented here has the following advantages: the role of each one of its parameters has a straightforward biological interpretation; its versatility easily permits the incorporation of increasing complexity and realism; the process can be studied backwards in time, as in population genetics' coalescent theory. Finally, its simplicity allowed us to obtain analytical expressions for the critical surface separating subcritical from supercritical regimes in the parameter space, both in the simplest version of the model as well as for its generalizations.

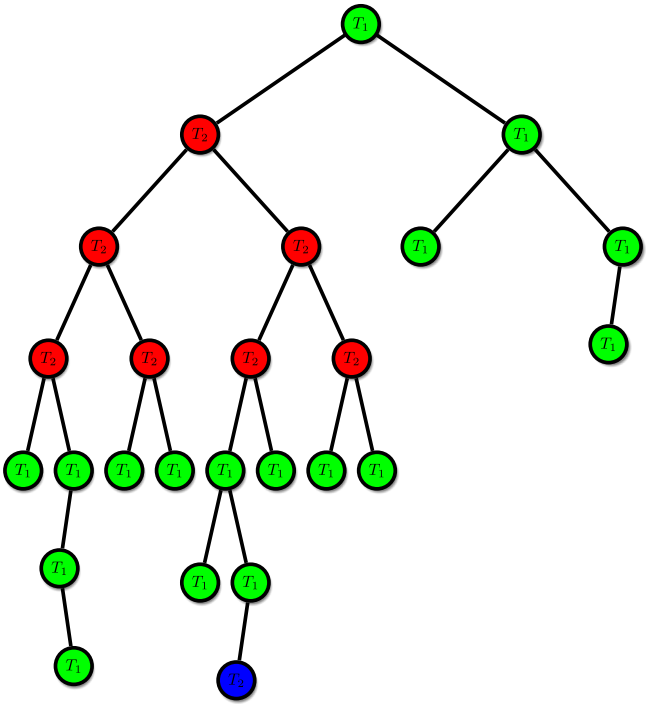

Fig. 1. Green cells are sensitive. Red and blue cells represent clans of antigen variants not recognized by the immune system. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

2. The model

Our model, a discrete-time non-independent multi-type branching process, assumes the existence of two types of *cells/infective particles* (viral particles, parasites, etc.) which are defined according to the host's immune system ability to recognize them; namely, sensitive (type-1) and resistant (type-2) cells.

The model in its simplest version involves three parameters, $\delta, \mu, p \in [0,1]$, that are defined as follows:

The population of cells proliferates by binary division and the offspring of sensitive cells die, independently, with probability δ (and consequently survive with probability $1-\delta$). Surviving cells may become resistant (i.e. start producing a new antigen variant) with probability μ.

A newly arisen resistant cell creates a clan (or lineage) of resistant cells in the following, recursive, way: at a given time the whole progeny of resistant cells divides into resistant cells, which remain as such with probability equal to p. In other words, $1-p$ is the probability that the immune system acquires the ability to recognize this particular clan, i.e. the clan bearing this specific variant antigen.

This means that for a given resistant cell appearing at generation n we take a geometric random variable, N, of parameter $1-p$, and consider the whole dividing resistant clan until generation $n+N$, where resistant cells become sensitive.

Summarizing: parameter δ measures the efficiency of immune response against sensitive cells; parameter μ represents the rate at which new resistant variants appear; and parameter p is related to the delay times spent by the immune systems to recognize a new variant.

Fig. 1 illustrates a realization of the process: a sensitive (green) cell originates a resistant descendant clan (red) which in turn becomes sensitive (green) after three generations. At the bottom of the figure, the emergence of a new resistant variant (blue) is represented. Different clans of resistant cells, and sensitive cells, evolve independently.

We remark that this is not a standard multi-type branching process as for example those considered in Kimmel and Axelrod (2002), in the sense that resistant cells in a given clan do not evolve independently: instead, their destiny is determined by immune system capacity, which does or does not recognize the whole population of cells carrying a specific variant antigen. The model could also be envisaged as a percolation process on the complete binary tree in presence of a random environment (the clans of resistant cells of random sizes).

3. Extinction probability

To compute the extinction/survival probabilities of the process – and thus obtain the critical surface as a function of the parameters – we introduce an additional multi-type branching process which has the same extinction/survival probabilities as the antigenic variation model introduced before. This independent multi-type branching process with two types of cells is obtained from the antigenic variation model by *collapsing* to one generation each clan of resistant cells.

3.1. Independent multi-type branching process

Let us consider two types of cells that evolve independently. The progeny of each cell is as follows: type-1 (sensitive) cells give birth to

- two type-1 cells with probability $(1-\mu)^2(1-\delta)^2$,
- two type-2 cells with probability $\mu^2(1-\delta)^2$,