XI CONGRESO LATINOAMERICANO
DE BIOLOGÍA MATEMÁTICA
SoLaBIMa 2019
Universidad Católica del Maule
22-25 de Octubre de 2019, Talca, Chile

A simple stochastic model for a pathogen population in the presence of the immune response

Fabio Lima Lopes*
Santiago, Chile

Resumen

In this work we present simple stochastic dynamics modeling a pathogen population in the presence of immune system of its host. In our dynamics, pathogens reproduce within their host, creating either clones of themselves or new pathogen types due to mutations that occur at random. While, from time to time, the host's immune system sends an immune response which is able to get rid of all pathogens of a certain type. More specifically, we assume that such immune response only can eliminate a certain pathogen type after it has already managed to eliminate its ancestors types with lower fitnesses. Our results include conditions determining whether or not a pathogen population can evade continuously the immune system of its host with positive probability, first when only beneficial mutations are considered and later when deleterious mutations are also considered.

This is a joint work with:
C. Grejo[1], Universidad Federal de São Carlos, São Paulo, Brasil.
F. Machado[2], Universidad de São Paulo, São Paulo, Brasil.
A. Roldan-Correa[3], Universidad de Antioquia, Medellin, Colombia.

1. Introduction

Certain pathogens can evade their host's immune system by altering their antigen expression e.g. point mutations on genes encoding their antigens or via other mechanisms such as antigen switching/gene conversion [3]. At the same time, the immune system of their host fights back against

*e-mail: f.marcellus@utem.cl
[1]e-mail: carolina@usp.br
[2]e-mail: fmachado@usp.br
[3]e-mail: alejandro.roldan@udea.edu.co

such evading attempts by preparing a more specific immune response created by its adaptative immune part. The constant interaction between pathogen antigens and the host immune surveillance system forces both host and pathogens to co-evolve.

Several mathematical models have been proposed to study the within-host dynamics of pathogen, an excellent survey on such models can be find in the book of Nowak and May [5]. Since the HIV epidemics started during 80's such models have been attracting considerable attention, because they help to understand and to test certain theoretical biological hypothesis concerning pathogen populations and their within-host dynamics. For instance, such models can help to understand the role of mutations and other evolution mechanisms on the ability of certain pathogens to evade the host's immune system, in changes in the level of virulence of certain pathogens, the emergence of drug resistance, success or failure of treatments which are based on lethal mutagenesis, etc.

One of the first questions addressed by such models is whether or not a pathogen population within a host can evade continuously the immune response of the host by relaying on point mutations which rare and occur at random. For instance, Nowak and May [5] considered different compartmental models for the within-host dynamics of viral infections such as HIV and Hepatitis B, which are based on ordinary differential equations. The analysis of their models shows that a pathogen population can evade the host's immune system when the mutation rate is sufficient large and cannot when it is small. Sasaki [6] proposed a model where most mutations are deleterious (lethal), and only a small fraction can lead to a different antigen. Furthermore, he considered two cases for the antigen landscape: (i) potential antigen types are indexed in a one-dimensional lattice (the stepping-stone model) and (ii) every mutation generates a new type of pathogen (infinite allele model). The analysis of his model shows that the pathogens may survive only if the mutation rate is intermediate. That is, if the mutation rate is too low or too high, the pathogens die out in his model. In the previous examples, the modeling is based on predator-prey dynamics, for instance, where the defense cells of the host's immune system act as predators and virions/or infected cells as their preys.

Aiming at answering the same question but with less mechanistic models, and where randomness plays a more explicit role, Schinazi and Schweinsberg [7] proposed simple stochastic dynamics for modeling the within-host dynamics of a pathogen population. They also considered these dynamics with and without spatial restrictions. Our work can be considered as an extensions of their analysis.

In their non-spatial model, the infection starts with a single pathogen at time zero. Each pathogen gives birth to a new pathogen at rate $\lambda > 0$. When a new pathogen is born, it has the same type as its parent with probability $1 - r$. With probability $r \in (0, 1]$, a mutation occurs, and the new pathogen has a different type from all previously observed pathogens. They assume that the response of the immune system can eliminate pathogens of a given type. As follows: when a new type appears in the population, it survives for an exponential amount of time with mean 1, independently of all the other types. All pathogens of the type are killed simultaneously. They show that for this model pathogens survive with positive probability if and only if $\lambda > 1$. That is, whether or not the pathogens can evade the host's immune system continuously depends only on the reproductive rate λ and not on the mutation rate r.

In the same article, they show that this is not the case for their dynamics on $\mathbb{Z}^d$. Next, we describe briefly their dynamics on $\mathbb{Z}^d$. Every site of $\mathbb{Z}^d$ is either occupied by a pathogen or empty. Each model is started with a single pathogen at the origin of $\mathbb{Z}^d$ and with all other sites empty.

The rules for births and mutations as for the non-spatial model. Let x be a site occupied by a pathogen and y be one of its $2d$ nearest neighbors. After a random exponential time with rate λ, the pathogen on x gives birth on y, provided y is empty (if y is occupied nothing happens). With

probability $1-r$ the new pathogen on y is of the same type as the parent pathogen on x. With probability r the new pathogen is of a different type.

They showed that for the spatial model, reproduction rate and mutation rate may play a role as well as the geometry on determining whether or not the pathogens can evade continuously the immune system. Later, they also studied their dynamics on infinite homogeneous trees [4].

Here, we propose an extension of one of the models studied by Schinazi and Schweinsberg [7]. While in the model of Schinazi and Schweinsberg all pathogen types have the same chance to be eliminated by the immune response (due to the lack of memory of exponential random variables), we propose a model in which the pathogen types have an ordering which must be followed by the immune response. This ordering can be interpreted as if descendant types have always higher fitness than their ancestor types, that is, the mutation generating the new type is beneficial. In terms of modeling our extension corresponds to the introduction of a new killing rule for the immune system in the model of Schinazi and Schweinsbergwhich. The new killing rule is similar to the one of Schinazi and Schweinsberg but we add the rule that a pathogen type only can be eliminated by the immune system after all its ancestor types have been eliminated. This killing rule is based on a model proposed by Aldous and Krebs [1] for the processing of databases. One can think of the immune system as a computer which has to process the different pathogen types, however, while a certain pathogen type is being processed, all its newly born descendants types have to queue and wait to be processed until all their ancestors types have been processed.

In section 2, we introduce the non-spatial and spatial version of model when all mutations are beneficial and some of our results. In section 3, we present a non-spatial version of our model when we also allow a fraction of the mutations to be deleterious (lethal).

2. Model with only beneficial mutations

2.1. Non-Spatial Model

Next, we introduce the non-spatial version of our which only considers beneficial mutations. It has two parameters, the reproduction rate of each pathogen, $\lambda > 0$, and the mutation probability $r \in (0, 1]$. So, λr is the mutation rate of our system, that is, the rate at which each pathogen introduces new types of pathogens in the system.
We start with a single pathogen of type 1 at time zero. Each pathogen gives birth independently at rate λ. When a new pathogen is born, with probability $1-r$, it has the same type of its parent, and with probability r, a mutation occurs, and the new born pathogen has a new type that has never appeared previously in the system. Furthermore, we assume that each new type that enters the system has a fitness higher than its ancestor type. So, the immune system only can get rid of a certain type of pathogen after it has already managed to eliminate its ancestor type. For this, when each type first appears in the system, it receives an independent 'clock' distributed as an Exponential random variable with mean 1. However, the 'clock' of each type only starts ticking after its ancestor type has been eliminated. When the 'clock' of a type rings, all pathogens of that type are eliminated simultaneously by the immune system.
These 'clocks' can be thought as the incremental time (or the processing time) that the immune system needs to recognize a new pathogen type after it has already managed to eliminate its ancestor type. Once a type is recognized the immune system is able to eliminate all pathogens of that type very effectively. Our main result concerning this model is the following.

Theorem 2.1 *Let $\lambda > 0$ and $r \in (0, 1]$.*

i. *If $\lambda \leq \frac{1}{4}$, then the pathogens die out with probability 1 for all $r \in (0,1]$.*

ii. *If $1/4 < \lambda < 1$, then the pathogens die out with probability 1 for $r \leq (1-\sqrt{\lambda})^2/\lambda$, and survive with positive probability for $r > (1-\sqrt{\lambda})^2/\lambda$*

iii. *If $\lambda \geq 1$, then the pathogens survive with positive probability for all $r \in (0,1]$.*

By Theorem 2.1 we can represent the survival and extinction of the model in function of its parameters as in Figure 1.

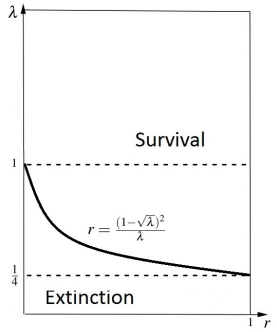


Figura 1: Survival and extinction of non-spatial model

2.2. Spatial Model

Let's introduce a spatial version on the lattice $\mathbb{Z}^d$, denoted by $\mathcal{B}(r,d)$, of the $\mathcal{B}(r)$ model. Every vertex of $\mathbb{Z}^d$ is either occupied by a pathogen or empty. At time $t=0$ there is a lonely pathogen of type 1 at the origin of $\mathbb{Z}^d$. The dynamics of the model are as follows. For x a vertex occupied by a pathogen and y one of its nearest neighbors, the pathogen on x, after an exponential time of rate λ, gives birth to a pathogen on y, provided it is empty. If y is occupied, nothing happens. This new pathogen, will be of the same type as the pathogen of x with probability $1-r$. On the other hand, with probability r a mutation will occur and the new pathogen will be of a different type, a type which is different from all that have appeared so far. We consider that the pathogen present at time zero has type 1, and the $k-th$ type to appear will be called type k. To each new type we associate an exponential clock of rate 1, which will start to tick only when its progenitor dies.

Theorem 2.2 *Consider $\lambda \leq 1/(8d)$. For all $r \in [0,1]$ the pathogens die out with probability 1.*

Theorem 2.3 *Let $\lambda > 0$ and $r \in [0,1]$. Let $\lambda_c := \lambda_c(d)$ be the critical parameter for the contact process.*

(i) *For any $\lambda > \lambda_c$, there is $r_1 \in (0,1)$ such that if $r < r_1$, then the pathogens die out.*

(ii) *For any $\lambda > \lambda_c$, there is $r_2 \in (0,1)$ such that if $r > r_2$, then the pathogens survive with positive probability.*

From Theorems 2.2 and 2.3 on sees that there exists a function $\lambda_*(\cdot,d) : (0,1] \to \mathbb{R}^+$ such that the extinction and survival can be schematically represented as in Figure 2. Besides, we have that $1/(8d) \leq \lambda_*(1,d) \leq \lambda_c(d)$. Observe that differently than what happens in the spacial case, here for every $\lambda > 0$ there is an $r > 0$ such that the process gets extinct.

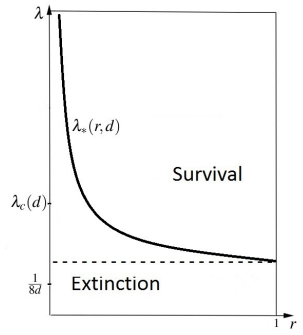


Figura 2: Survival and extinction of model on $\mathbb{Z}^d$

3. Model with beneficial and deleterious mutations

Next, we introduce the non-spatial version of our which considers beneficial and deleterious mutations. It is similar to the model in section 2, but it has an additional parameter which determines whether or not a mutation is deleterious. Again, we have the reproduction rate of each pathogen, $\lambda > 0$, the mutation probability, $r \in (0, 1]$. So, λr is the mutation rate of our system, that is, the rate at which each pathogen introduces new types of pathogens in the system, and the probability that a mutation is deleterious (lethal) $1 - p$, $p \in (0, 1]$. So, the effective rate at which each pathogen introduces new types of pathogens in the system is λrp.

Let $\lambda > 0$ and $r, p \in (0, 1]$. We start our model with a single pathogen of type 1 at time zero. Any pathogen born without lethal mutations reproduces independently at rate λ. Each newborn pathogen is independently labelled as a clone with probability $1 - r$, and it has the same type of its parent, or a mutation occurs with probability r. Such mutations are lethal with probability $1 - p$, and non-lethal with probability p. Non-lethal mutations originate new pathogens types which have never appeared previously in the system. Furthermore, we assume that each new type that enters the system has a fitness higher than its ancestor type. So, the immune system only can get rid of a certain type of pathogen after it has already managed to eliminate its ancestor type. For this, when each type first appears in the system, it receives an independent 'clock' distributed as an Exponential random variable with mean 1. However, the 'clock' of each type only starts ticking after its ancestor type has been eliminated. When the 'clock' of a type rings, all pathogens of that type are eliminated simultaneously by the immune system.
Our main result concerning this model is the following.

Theorem 3.1 *Let $\lambda > 0$ and $r, p \in (0, 1]$. Define*

$$r_1 := r_1(\lambda, p) := 1 - \frac{1 - 2p}{\lambda} - \frac{2\sqrt{p(\lambda + p - 1)}}{\lambda}$$

$$r_2 := r_1(\lambda, p) := 1 - \frac{1 - 2p}{\lambda} + \frac{2\sqrt{p(\lambda + p - 1)}}{\lambda}$$

i) For all $\lambda \leq \frac{1}{4}$. The pathogens die out with probability 1 for all $r, p \in (0, 1]$.

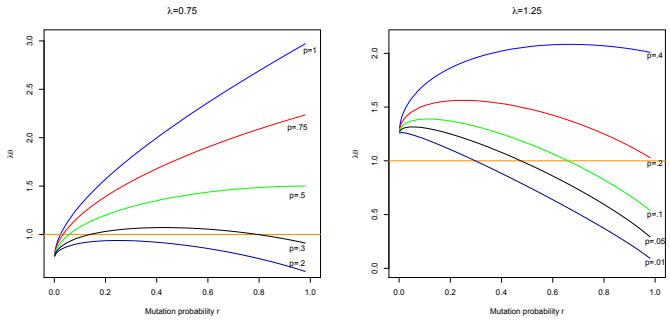
ii) For $\frac{1}{4} < \lambda \leq \frac{1}{2}$. The pathogens survive with positive probability if and only if $p > \frac{1}{4\lambda}$ and $r > r_1$.

iii) *For* $\frac{1}{2} < \lambda < 1$. *The pathogens survive with positive probability if and only if one of the following conditions holds:*
(a) $p > \frac{1}{4\lambda}$ *and* $r > r_1$
(b) $p \leq \frac{1}{4r}$ *and* $r \in (r_1, r_2)$

iv) *For* $\lambda \geq 1$. *The pathogens survive with positive probability if and only if one of the following conditions holds:*
(a) $p > \frac{r}{4}$
(b) $p \leq \frac{r}{4}$ *and* $r < r_2$.

Note that the model including deleterious mutations has a more interesting behavior, for instance, it also includes a parameter phase which behaves similarly to the models introduced by Sasaki [6].

It is more difficult to illustrate the results given in Theorem 3.1. However, we illustrate it for some choices of parameters in Figure 3. Note that, for instance, that when $\lambda = 0{,}75$ and $p = 0{,}3$, the pathogen population only can survive for intermediate values of the mutation probability. Also, we can observe that lethal mutagenesis is only possible when the probability of deleterious mutation is above a certain threshold.



Referencias

[1] Aldous, D.; Krebs, W. (1990) *The birth-and-assassination process.* Statistics and Probability Letters, **10**, 427-430.

[2] Bordenave, C. (2014) *Extinction probability and total progeny of predator-prey dynamics on infinite trees.* Electronic Journal of Probability, **19**, paper no. 20, 1-33.

[3] Iwasa, Y; Michor, F; Nowak, M. A. (1990) *Some basic properties of immune selection.* Journal of Theoretical Biology, **229**, 179-188.

[4] Liggett, T.; Schinazi, R.; Schweinsberg, J. (2009).A contact process with mutations on a tree. Stochastic Processes and their Applications, **118**, 319-332.

[5] Nowak, M. A.; May, R. M. (2000) *Virus Dynamics, Mathematical Principles of Immunology and virolgy.* Oxford University Press, Oxford.

[6] Sasaki, A. (1994) *Evolution of antigen drift/switching continuously evading pathogens.* Journal of Theoretical Bioology **168**, 291-308.

[7] Schinazi, R; Schweinsberg, J. (2008) *Spatial and non-spatial stochastic models for immune response.* Markov Processes and Related Fields, **14** (2), 255-276.