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A numerical approach to determine mutant invasion fitness and evolutionary singular strategies

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ABSTRACT

We propose a numerical approach to study the invasion fitness of a mutant and to determine evolutionary singular strategies in evolutionary structured models in which the competitive exclusion principle holds. Our approach is based on a dual representation, which consists of the modeling of the small size mutant population by a stochastic model and the computation of its corresponding deterministic model. The use of the deterministic model greatly facilitates the numerical determination of the feasibility of invasion as well as the convergence-stability of the evolutionary singular strategy. Our approach combines standard adaptive dynamics with the link between the mutant survival criterion in the stochastic model and the sign of the eigenvalue in the corresponding deterministic model. We present our method in the context of a mass-structured individual-based chemostat model. We exploit a previously derived mathematical relationship between stochastic and deterministic representations of the mutant population in the chemostat model to derive a general numerical method for analyzing the invasion fitness in the stochastic models. Our method can be applied to the broad class of evolutionary models for which a link between the stochastic and deterministic invasion fitnesses can be established.

1. Introduction

Bacterial ecosystems are subject to mutations and natural selection. When a mutation occurs, a natural question is to determine the capability of the mutation to be fixed in the population. Adaptive dynamics theory proposes mathematical tools to tackle this question (Metz et al., 1996; Dieckmann and Law, 1996; Geritz et al., 1998). Among these tools, invasion fitness is a selective value which allows to determine if a mutant population can invade a resident one. The definition of the invasion fitness depends on the model under consideration (Metz et al., 1992; Metz, 2008): usually for deterministic models, it is the asymptotic growth rate of the population, for stochastic models we choose to define it as the survival probability of the mutant population, though we note that this is not a standard definition (Campillo et al., 2016, in press).

Here, we propose a general numerical approach to study the invasion capacity of a mutant population and to determine the evolutionary singular strategies when the competitive exclusion principle holds. The method is applied to a mass-structured chemostat model, for which we have obtained previous mathematical results which provide the necessary background information for developing our numerical approach. First developed by Monod (1950) and Novick and Szilard (1950), the chemostat is a culture method for maintaining a bacterial ecosystem in continuous growth. Adaptive dynamics in chemostat were studied for unstructured models in a deterministic context by Doebeli (2002) and Mirrahimi et al. (2012) and in a stochastic context by Champagnat et al. (2014).

The choice between stochastic and deterministic models usually depends on the context of the study: the latter for homo-

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geneous large size populations, the former for small size populations where randomness cannot be neglected (Fritsch et al., 2015; Campillo and Fritsch, 2015). The numerical inference of adaptive dynamics for deterministic models is straightforward compared to that of stochastic models. For example, for the stochastic mass-structured chemostat model, the invasion fitness is defined as the survival probability which is the solution of a functional equation. The mutant population can invade the resident one if and only if this survival probability is strictly positive. It is usually difficult to decide whether a numerical approximation of a survival probability is different from zero or not. For the corresponding deterministic model, the mutant population dynamics can be modeled as a population balance equation (Fredrickson et al., 1967; Ramkrishna, 1979; Doumic, 2007; Doumic Jauffret and Gabriel, 2010), and the feasibility of invasion depends on the sign of the principal eigenvalue of the operator associated to this equation. The latter approach is more straightforward to apply, compared to evaluating the positiveness of the survival probability. Campillo et al. (2016, in press) established a mathematical link between the two invasion criteria for mass-structured growth–fragmentation–death models, that link considerably simplifies the numerical analysis of the stochastic version.

In this article, we focus on mutations which affect the division mechanism of a bacterial population; mutations can affect the mean proportion of the smallest daughter cell during the division and/or the minimal mass required for bacterial division. We apply an evolutionary analysis to determine the best cytokinesis strategy that the population should adopt in terms of mass division. The optimal division strategy has been previously studied by Michel (2005, 2006), in a deterministic context without interactions between bacteria (through the substrate in our model) and for strategies focusing only on the proportion of division.

In Section 2, we introduce the models which are considered for the numerical simulations as well as a model reduction approach, based on Campillo and Fritsch (2015) and Campillo et al. (2016). In Section 2.1, we introduce the mass-structured chemostat model where mutations affect the division parameters, namely the minimal mass for division and the mean proportion of the smallest daughter cell. In Section 2.2, we reduce the chemostat model for the mutant population by assuming that the mutations are rare and the resident population is large. In Section 2.2.1, we introduce deterministic and stochastic representations for the reduced model of the mutant population. We present two definitions of the invasion fitness: the principal eigenvalue of a growth–fragmentation–death operator in the deterministic case, and the survival probability of the mutant population in the stochastic case. We also present the link between the invasion criteria derived from these two definitions, established by Campillo et al. (2016). Section 3 presents the numerical methods that we use for the simulations. We present numerical tests in Section 4. In Section 4.1, we compare the different models, full chemostat model *vs* reduced model and deterministic reduced model *vs* stochastic reduced model, in order to numerically justify the model reduction of the mutant population and to present the difference between the deterministic and stochastic models. In Section 4.2, we study the evolution of the one-dimensional trait representing the mean proportion of the smallest daughter cell in the division mechanism. In Section 4.3, we extend the approach presented in the previous section to the case where both the mean proportion of the smallest daughter cell in the division mechanism and the minimal mass of division evolve simultaneously. We conclude this article by a discussion in Section 5.

2. The models

This section details a numerical approach, based on common adaptive dynamics methods as well as mathematical results of Campillo and Fritsch (2015) and Campillo et al. (2016), which allows one to analyze evolutionary dynamics in a relatively complex chemostat model.

Our approach is based on the following models that we will detail in this section:

- *IBM: individual-based model of resident and mutant populations.* This is the full chemostat model in which both resident and mutant populations are described by a stochastic individual-based model.
- *PDE: deterministic approximation of the IBM.* Under a rare mutation assumption, between mutation times, the populations follow a system of integro-differential equations. This model is useful when populations are large, which is however not the case for the mutant population at a mutation time. A challenge associated with this model is to determine when a mutation occurs as the mutations are supposed to be rare.
- *r-IBM: reduced individual-based model for the mutant population.* The resident population is assumed to stay at its stationary state, whereas the mutant population is described by an individual-based model. This model is realistic if the mutations are sufficiently rare in order for the resident population to reach its stationary state before the mutation and as long as the mutant population remains sufficiently small to have a neglectable effect on the stationary state of the resident population.
- *r-PDE: reduced deterministic model for the mutant population.* This model is a deterministic approximation of the r-IBM model: the resident population is assumed to stay at its stationary state and the mutant population evolves according to an integro-differential equation. This model may appear to be unrealistic due to opposing assumptions: the deterministic approximation is valid in large populations while the reduced model (constant resident population) is valid for a small mutant population. However, this model will prove to be very useful in the numerical study.

2.1. The chemostat model with mutations

We are interested to study numerically the evolution of a mass-structured population in a chemostat. We suppose that individuals grow by consuming a resource and divide after reaching a sufficiently large size. Individuals are also removed from the system due to the output flow of the chemostat. We also assume that during the division, mutations can appear in a gene that affects the minimal mass for division y and/or the mean proportion c of the smallest daughter bacteria after division (that is the expectation of the ratio of the size of the smaller of the two daughter cells over the size of the mother cell before division). A population will then be characterized by a trait $\xi = (y, c) \in \Xi$ which will evolve through mutations.

The model was originally introduced by Fritsch (2014) and Campillo et al. (2016). In this model, each individual is characterized by its trait $\xi = (y, c)$ and its mass x. The model consists of the following stochastic events.

(i) *Each individual divides* at rate $b(y, x)$ into two individuals with respective masses $\alpha\, x$ and $(1-\alpha)\, x$, where the proportion α is distributed according to a distribution $Q(c, \mathrm{d}\alpha) = q(c, \alpha)\, \mathrm{d}\alpha$, and
   - with probability $\gamma \in [0, 1]$, the daughter cell with mass $\alpha\, x$ is a mutant, with trait $\xi + h \in \Xi$, where h is distributed according to a distribution $\kappa(\xi, h)\, \mathrm{d}h$ and the daughter cell with mass $(1-\alpha)\, x$ inherits the trait ξ of its mother.