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An age-dependent model to analyse the evolutionary stability of bacterial quorum sensing

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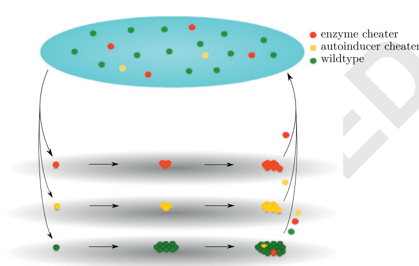
HIGHLIGHTS

- We model quorum sensing in bacteria switching between plankton and biofilm.
- We assess the evolutionary stability against different types of cheaters.
- The long-term outcome depends on nonlinear parameter combinations.
- Growth in colonies can stabilize cooperation in plankton.
- Intermediary colony death rates promote cooperators.

GRAPHICAL ABSTRACT



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ABSTRACT

Bacterial communication is enabled through the collective release and sensing of signalling molecules in a process called quorum sensing. Cooperative processes can easily be destabilized by the appearance of cheaters, who contribute little or nothing at all to the production of common goods. This especially applies for planktonic cultures. In this study, we analyse the dynamics of bacterial quorum sensing and its evolutionary stability under two levels of cooperation, namely signal and enzyme production. The model accounts for mutation rates and switches between planktonic and biofilm state of growth. We present a mathematical approach to model these dynamics using age-dependent colony models. We explore the conditions under which cooperation is stable and find that spatial structuring can lead to long-term scenarios such as coexistence or bistability, depending on the non-linear combination of different parameters like death rates and production costs.

1. Introduction

Cooperation between bacterial cells seems to be the rule rather than the exception, which has led to the development of a field of research called sociomicrobiology (Parsek and Greenberg, 2005). Forms of cooperation often include the release of public goods, i.e., extracellular molecules that benefit all neighbouring cells (such as antibiotica, sidephores or certain virulence factors). Some of these molecules play a crucial role for bacterial nutrition (e.g. exoglycosidase, exoprotease). Production and release of public goods is often regulated by bacterial cell–cell communication (usually termed quorum sensing, QS) using released signals (autoinducers) (Fuqua et al., 1994). Once a certain environmental concentration of autoinducers is reached, which is usually associated with a certain cell density or number of cells, the population starts a coordinated release of public goods. The evolutionary purpose of such a control has been described as guaranteeing a reasonable cost/benefit ratio or efficiency (Hense et al., 2007; Hense and Schuster, 2015; Darch et al., 2012).

Understanding the evolutionary stability of bacterial cooperation is challenging (Keller and Surette, 2006; West et al., 2007a; Ghoul et al., 2014; Leggett et al., 2014; Harrington and Sanchez, 2014). “Cheater” mutants (also called “defectors” or “free riders”),

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which do not contribute to the cooperation, e.g. which do not release public goods, are assumed to save costs, although they do benefit from the public goods provided by cooperators. This theoretically predicted fitness advantage of cheaters has been confirmed with and without QS regulation in vitro and in vivo (Diggle et al., 2007; Sandoz et al., 2007; Köhler et al., 2009; Rumbaugh et al., 2009; Popat et al., 2012; Pollitt et al., 2014). In terms of game theory, such a behaviour is usually described as prisoners dilemma, where the non-cooperative behaviour is the dominant strategy (Archetti et al., 2011). This raises the question, why bacterial cooperation nevertheless exists, i.e., why in the long term cheaters do not outcompete honest cooperators in nature.

With respect to evolutionary stability, QS represents a specific situation as it involves two levels of cooperation: (a) cooperation at the signalling level, as autoinducers themselves are public goods, (b) cooperation on the level of QS-controlled target genes. Both are prone to cheater mutants.

Several mechanisms explaining evolutionary stability of cooperation and QS have been described (for a recent overview see Ross-Gillespie and Kümmerli, 2014). The concepts of kin selection and multi-level selection provide additional approaches from evolutionary theory (Lehmann et al., 2007). In short, these concepts require assortment by a privileged allocation of the benefits of public goods to cooperative producers (Damore and Gore, 2012).

Spatial structuring of populations is a fundamental principle allowing for assortment in bacteria. Such separation could serve to stabilize cooperation in combination with population bottlenecks (Brockhurst, 2007). Spatial structuring can be caused by environmental heterogeneities, but also by self-organization via bacterial interactions (Frey and Reichenbach, 2011). In biofilms, for example, cells and cheaters tend to grow in clusters (Nadell et al., 2010). Both theoretical and experimental studies (Cremer et al., 2012; Chuang et al., 2009; Melke et al., 2010; Rumbaugh et al., 2012) showed that under certain conditions, cyclic separations of the whole population into small subpopulations and subsequent remixing events can protect cooperative behaviour from being completely outcompeted.

Studies analysing the influence of fragmentation/re-assortment processes usually do not discuss specifically how these processes may be realized in nature. Most bacteria live as free-floating single cells (plankton) or in aggregates, most frequently attached to surfaces (colonies or biofilms). Fragmentation in colonies usually works as follows: Aggregates normally start with cells that attach to a surface and divide while staying together, if the conditions fit. From a growing colony, eventually cells leave, disperse and found new colonies. Initiating usually from single cells, such a lifestyle presents an extreme form of fragmentation, providing in this respect optimal conditions for the maintenance of cooperation.

In contrast, the realization of fragmentation in plankton is more challenging as cyclic spatial structuring will probably only exceptionally occur (e.g. in cases of growth to flocs). Nevertheless, although a number of genes are differentially expressed under planktonic and attached conditions, QS has been described for both, meaning QS is not switched off in plankton. Values of quorum sensing parameters have even been reported to be almost identical both under planktonic and attached conditions (Meyer et al., 2012; Fekete et al., 2010; Buddrus-Schiemann et al., 2014).

QS signalling within microcolonies seems to be isolated to a certain degree towards signals in the surrounding fluid, which strengthens the degree of separation (Meyer et al., 2012). Although the amount of production can be assumed to vary quantitatively depending on the environmental conditions, QS-controlled public goods as nutritional exoenzymes and siderophores are released in both life styles (Evans et al., 1994). Accordingly, a number of QS-regulated genes are expressed both under planktonic and biofilm conditions (Waite et al., 2006).

There have been different theoretical (modelling) approaches to investigate evolutionary stability of cooperation, using a broad spectrum of analytical tools. For an illustrative review on the evolution of cooperation see West et al. (2007b). Czárán and Hoekstra (2009) modelled cooperation through cellular automata, investigating the spatial aspects of cooperation. Since bacteria procreate through cell division, cells in the vicinity tend to be closely related. In this way, the results could also be explained by Hamilton's Rule, which has been used in (Chuang et al., 2010).

Cremer et al. (2012) presented an individual-based model of cooperation in microbial populations, following the experimental results of Chuang et al. (2009).

Garcia et al. (2014) addressed the evolutionary dynamics of attachment and group cohesion. Frank (2010) presented an ODE model which suggests that it is the combination of mutation and demographic processes (such as local density, colony survival and dispersal) which determines the relative fitness of cooperators versus cheaters. In his model, cheaters are just the endpoint of a continuum of secretion rates capability.

As mentioned, most bacteria switch between two states: attached to surfaces, which actually represents the main life style of bacteria, and plankton, which allows to disperse to new niches. A theoretical analysis about evolutionary stability of (QS regulated) cooperation regarding explicitly the biphasic life style of these bacteria is missing yet. In this paper, we thus investigate stability of QS controlled cooperation under such conditions, including mutation rates which are ignored in most similar models. Our aim is the identification of critical factors for cooperation and an analysis of the conditions for domination of wildtype or cheater mutants, or coexistence of both. We hypothesize that cooperative behaviours like the production of exoenzymes or siderophores, which are expressed both in plankton and in colonies/biofilms, can be evolutionarily stabilized for both conditions through inter-subpopulation selection in the colony state.

In a generic modelling approach, we will analyse whether and under which conditions this hypothesis holds. For that purpose we use differential equations, as in Frank (2010). The model includes a switch between habitation in separated colonies and in plankton, growth and death, QS-controlled release of a nutritional exoenzyme, and mutations toward both signal and exoenzyme cheaters. In a first step, we will analyse the model with respect to which parameter sets promote the long term dominance of honest cells, cheater cells of both types or the co-existence of both. We first build up our model in Section 2 and analyse it mathematically in Section 3. As a second step, we investigate the behaviour of the model through numerical simulations, using experimentally derived parameters when known. In particular, the influence of key parameters (such as cooperation costs, number of colonies and colony death rate) on the stability of the system are tested. The results are shown in Section 4.

2. The basic age-dependent model

As we want to analyse the effect of repeated mixing and separating, our model will be composed by two parts, namely population dynamics and lifestyle switch: *plankton*, where the bacteria are well mixed and from which they can separate to continue growing in *colonies*, the second lifestyle. Every bacterium in the plankton has an equally distributed chance to do so. Entire colonies can die out due to external influences, e.g. grasers, while the plankton cannot die out at once. Additionally, we assume that there are only a limited number of colony places that are fit for settlements, due to space restrictions. We consider the important processes in plankton and colonies as similar enough to assign

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