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Estimating the probability of coexistence in cross-feeding communities

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HIGHLIGHTS

- This manuscript investigates the likelihood of coexistent triplets of cross-feeding species, based on the species' pair-wise interactions.
- The analysis is based on qualitative information about the pair-wise interactions between the species.
- The analysis shows that three species that coexist pair-wise and intransitive triplets of species are likely to exhibit coexistence.
- This information could be valuable when synthetic microbial communities are to be constructed.

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ABSTRACT

The dynamics of many microbial ecosystems are driven by cross-feeding interactions, in which metabolites excreted by some species are metabolised further by others. The population dynamics of such ecosystems are governed by frequency-dependent selection, which allows for stable coexistence of two or more species. We have analysed a model of cross-feeding based on the replicator equation, with the aim of establishing criteria for coexistence in ecosystems containing three species, given the information of the three species' ability to coexist in their three separate pairs, i.e. the long term dynamics in the three two-species component systems. The triple-system is studied statistically and the probability of coexistence in the species triplet is computed for two models of species interactions. The interaction parameters are modelled either as stochastically independent or organised in a hierarchy where any derived metabolite carries less energy than previous nutrients in the metabolic chain. We differentiate between different modes of coexistence with respect to the pair-wise dynamics of the species, and find that the probability of coexistence is close to $\frac{1}{2}$ for triplet systems with three pair-wise coexistent pairs and for the so-called intransitive systems. Systems with two and one pair-wise coexistent pairs are more likely to exist for random interaction parameters, but are on the other hand much less likely to exhibit triplet coexistence. Hence we conclude that certain species triplets are, from a statistical point of view, rare, but if allowed to interact are likely to coexist. This knowledge might be helpful when constructing synthetic microbial communities for industrial purposes.

1. Introduction

In recent years it has become increasingly clear that microbial species form complex communities, and rarely exist in isolation from each other (Zelezniak et al., 2016). A common form of interaction occurs via the exchange of nutrients that are released by one species and absorbed and further metabolised by other species in the community. This phenomenon is known as cross-feeding or syntrophy and has been observed in a wide range of systems such as the human gut flora (Belenguer et al., 2006), the interactions of sulfate-reducers and methane oxidisers in the deep sea (Hallam et al., 2004; Pernthaler, 2008), the degradation of pesticides (Katsuyama et al., 2009), methanogenic environments (Stams, 1994), and in soil nitrification (Costa et al., 2006).

Note that cross-feeding can come in different degrees of complexity and interdependence. For example, when studying a system of *Escherichia coli* strains feeding off an inflow of glucose, one strain is known to partially degrade the glucose to acetate, which would then be consumed by a second strain. Thus, the second strain will be affected by a negative frequency-dependent selection, as it needs the primary degrader. Furthermore, it has been put forward that the primary strain is dependent on the second one, as the secondary metabolite could be toxic at high concentrations, see for example Pelz et al. (1999).

Since the growth rate of a species within the community depends on the metabolites produced by other species, it indirectly depends on the frequency of other species. This implies that

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systems where cross-feeding is dominant are governed by frequency-dependent selection, which allows for both dominance and coexistence depending on the strength and sign of the interactions between the species (Bomze, 1983).

Frequency-dependent selection (together with other mechanisms such as spatial structure, Kerr et al., 2002) is the most likely explanation for the stability of natural microbial ecosystems, such as the gut microbiota. Although we have mapped out a large number of microbial communities, we still lack a definite understanding of their dynamics and cannot explain why they are stable (Harcombe et al., 2014). This lack of knowledge becomes evident when it comes to assembling or constructing artificial communities that are stably maintained (Jagmann and Philipp, 2014), and the need for understanding has become even more pressing now that the potential for engineering microbial communities for specific industrial purposes has been unravelled (Großkopf and Soyer, 2014).

In order to build efficient microbial communities we could like to know if a given collection of species can form a stable ecosystem in which no species are outcompeted and driven to extinction. This question can be approached either from a top-down perspective using flux-balance analysis and co-occurrence data (Zelezniak et al., 2016; van Hoek and Merks, 2016), or from a detailed understanding of the population dynamics of cross-feeding systems. We take the latter approach and address the following straightforward and concrete question: if we have qualitative information about the pair-wise dynamics of three species, what can be said about the likelihood of coexistence in the three-species community?

Thus, this paper strives to outline what configurations of species triplets that are likely to form coexistent populations. More specifically, we would like to know the coexistence properties of a triplet based on known pair-wise interactions between the constituent species. Ideally we would like to have quantitative information about the interactions of the different species, but for many practical purposes this is too much to ask. We therefore settle for qualitative information, and assume that for each pair of species we know if they coexist or if one species outcompetes the other. However, this poses a problem since it is known that systems that are identical on the pair-wise level (in the above qualitative sense) might behave differently when all three species are present (Bomze, 1983). This implies that triplet coexistence cannot be determined from the three pairs in isolation, but is a property of the interactions in the complete triplet. But all is not lost, since we may still be able to say something about the probability of coexistence. With this in mind we set out to study cross-feeding systems in which one, two or three pairs of species (out of the three) co-exist in isolation, and also intransitive systems where no dominant species exists (like rock-scissors-paper), and we do this from a statistical point of view to estimate the probability of coexistence in triplets of species.

1.1. *Mathematical modelling of cross-feeding*

The dynamics of large — consisting of some billion cells or more — and well-mixed populations of cross-feeding bacteria can be described by a system of coupled non-linear autonomous ordinary differential equations known as the replicator system of equations (Lundh and Gerlee, 2013). The assumption of well-mixedness allows us to disregard spatial effects in the system and in a large population, we may safely discard any stochastic individual interactions. The replicator system of equations has its origin in game theory (Hofbauer and Sigmund, 2002) where it describes an evolutionary game of n strategies and d players (Gokhale and Traulsen, 2010), which corresponds to n species and d steps in the metabolic process in the cross-feeding framework. This correspondence is due to the fact that each metabolic step considered introduces a coupled interaction between the species that take part in the metabolic chain.

Replicator systems have been studied extensively (Bomze, 1983; Hofbauer and Sigmund, 2002; Gokhale and Traulsen, 2010; Lundh and Gerlee, 2013) in relation to game theory and population dynamics, and we apply this theory to the present problem in order to find how pair-wise dynamics influence triplet coexistence.

In the present setting, the fitness of a species is given by the amount of energy that the species can extract from the available nutrients excreted by another species. Here we interpret “energy” in a somewhat loose and abstract meaning. In this general setting the total energy is modelled as a sum over all possible metabolic interactions, represented as a series expansion of the fitness function. The model has been studied for two species by Lundh and Gerlee (2013), under the assumption that metabolites are only utilised by at most two species. In the same paper, the authors derived conditions for coexistence in a two-species population and the case of intransitive three-species populations.

The dynamics of a cross-feeding ecosystem need not be modelled in the game-theoretical framework of the replicator system described by Lundh and Gerlee (2013). Other ODE-systems have described cross-feeding as a direct interaction between the involved species (Bull and Harcombe, 2009; Estrela and Gudelj, 2010), by explicitly modelling nutrient uptake and mortality (Katsuyama et al., 2009), and by using adaptive dynamics (Doebeli, 2002). Agent-based models have also been used by Gerlee and Lundh (2010) and Crombach and Hogeweg (2009), whereas Pfeiffer and Bonhoeffer (2004) have studied the evolution of cross-feeding as a result of optimal ATP energy production in cells. In a recent study by Gedeon and Murphy (2015) cross-feeding in a chemostat environment was analysed. Under fairly general assumptions on the structure of the cross-feeding network they could show that there is a unique stable equilibrium that corresponds to the largest community of species that can be supported by the available resources, and that biomass production is maximised at this equilibrium point.

In this paper we take as a starting point the work of Lundh and Gerlee (2013) and derive conditions for coexistence. Although we are able to derive analytical expressions for the conditions of coexistence, the large number of parameters in the model makes it difficult to draw any direct conclusions. Instead we approach the problem from a statistical point of view and randomly generate a large number of three species systems. The interaction parameters that model the energy uptake of a species are modelled in two ways: either as independent random variables or according to a hierarchical model where energy gains further down in the metabolic chain are lower than energy gains from primary metabolites. For a given parameter model, interaction parameters are drawn randomly from certain probability distributions to estimate the likelihood of permanence from the coexistence criteria. Then, the relevant statistics of the sampled systems are computed and compared to the derived coexistence criteria.

2. Preliminaries

The replicator system of equations for a population of species $i = 1, 2, \ldots, n$ with individual frequencies $\mathbf{x} = (x_1, x_2, \ldots, x_n)$ is defined as

$$\begin{cases} \dot{x}_i &= (\phi_i(\mathbf{x}) - \bar{\phi}(\mathbf{x}))x_i, \\ \bar{\phi}(\mathbf{x}) &= \sum_{k=1}^{n} x_k \phi_k(\mathbf{x}), \end{cases} \tag{1}$$