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Quantifying the effects of the division of labor in metabolic pathways

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HIGHLIGHTS

- We investigate the division of labor (metabolic function) in microbial systems.
- We compare a syntrophic consortia to a monoculture with equivalent metabolic capability.
- Consortia biomass is always lower than a monoculture with the same metabolic dynamics.
- Increasing the growth rate or substrate affinity does not explain the observed consortial advantage.
- Increased metabolic pathway efficiency (yield) provides the observed increase in productivity.

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ABSTRACT

Division of labor is commonly observed in nature. There are several theories that suggest diversification in a microbial community may enhance stability and robustness, decrease concentration of inhibitory intermediates, and increase efficiency. Theoretical studies to date have focused on proving when the stable co-existence of multiple strains occurs, but have not investigated the productivity or biomass production of these systems when compared to a single 'super microbe' which has the same metabolic capacity. In this work we prove that if there is no change in the growth kinetics or yield of the metabolic pathways when the metabolism is specialized into two separate microbes, the biomass (and productivity) of a binary consortia system is always less than that of the equivalent monoculture. Using a specific example of *Escherichia coli* growing on a glucose substrate, we find that increasing the growth rates or substrate affinities of the pathways is not sufficient to explain the experimentally observed productivity increase in a community. An increase in pathway efficiency (yield) in specialized organisms provides the best explanation of the observed increase in productivity.

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1. Introduction

From the earliest observations of microbial organisms, it has been apparent that microbial consortia are ubiquitous in nature. In fact, naturally occurring ecosystems are almost exclusively organized as consortia. Recent metagenomic studies from the soil (Fierer and Jackson, 2006), to the ocean (Venter et al., 2004), to the human gut (Gill et al., 2006), have found that microbial communities are incredibly diverse, often consisting of thousands of interacting species. Subsets of these communities form *consortia* that act together to enhance their capabilities and survival (Eiteman et al., 2008).

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Early theoretical ecology studies led to the development of the *competitive exclusion principle* (CEP), which states that the maximum number of species that can coexist in a system is equal to the total number of limiting (essential) resources (Hardin, 1960; MacArthur and Levins, 1964; Rescigno and Richardson, 1965). However, in nature we see many examples of multiple microbial species stably coexisting. Frequent explanations for coexistence in a natural population can be categorized into three main types: the development of multiple niches due to spatial heterogeneity or self-organized segregation, the system not being in equilibrium due to environmental fluctuations or external forcing, and the presence of inter- and intra-species interactions. Despite the limited direct applicability of CEP to natural systems, the clear mathematical formulation of CEP allows for significant insight by identifying which conditions of the CEP have been violated to lead to the observed coexistence of species. For example, by applying the CEP to the dynamics in a chemostat, we see that due to the consistent flow of nutrients and continuous mixing, the environment is kept constant and the development of different niches due

to spatial heterogeneity is not possible; therefore, it must be some form of inter- or intra-species interactions such as crowding, chemical signaling, cooperativity, or mutual inhibition that lead to any observed coexistence. Studying these interactions in simple chemostat systems gives us a better understanding of the factors that maintain the diversity in naturally occurring microbial consortia.

Natural consortia are often found to form *syntrophic* systems, where the microbes depend on each other for survival, either by the production of required metabolic substrates or by the maintenance of chemically advantageous conditions (Schink, 2002). It is often observed that this syntrophic cooperation within microbial consortia increases their productivity and can allow the consortia to perform advanced functions that the microbial species are not capable of individually. These microbial interactions are known to be important in diverse areas including chronic medical infections (e.g. diabetic ulcers, Gardner et al., 2013; James et al., 2008), biofuel synthesis (e.g. biodiesel production, Peralta-Yahya et al., 2012; Zuroff and Curtis, 2012), environmental nutrient cycling (e.g. CO₂ sequestering, nitrification, Costa et al., 2006), bioprocessing (Shong et al., 2012), and wastewater treatment (Schink, 1997; Seitz et al., 1990a, 1990).

A frequently observed syntrophic system is a *cross-feeding* chain where microbes work together to perform the sequential degradation of complex compounds like lignocellulosic material (Schink, 2002). In these syntrophic cross-feeding systems a single substrate must be broken down in many steps, with one species catabolizing the available substrate and oxidizing it to produce a byproduct that the next species in the chain can consume. The intermediate byproducts in these systems are often found to be inhibitory. In this work we will consider the case where the intermediate byproduct inhibits growth. However, this more complicated system can be reduced to the case where there is no inhibition by taking the appropriate limit.

It has been observed experimentally that these syntrophic chain systems where the metabolic pathways are split among separate organisms (known as ‘*microbial specialization*’ or a ‘*division of labor*’) are more productive than a single organism with the equivalent metabolic capabilities (Bernstein et al., 2012; Wintermute and Silver, 2010). For example, if we compare a single organism that metabolizes $A \rightarrow B \rightarrow C$ to a pair of organisms that metabolize $A \rightarrow B$ (organism 1) and $B \rightarrow C$ (organism 2), experimental observation has found the pair of organisms to be more productive than the single organism. Productivity is defined here as total biomass production per unit of input A .

An example of this division of labor that has been found to evolve repeatedly in different experiments occurs when *E. coli* is grown on a glucose substrate. The original population of *E. coli* can fully metabolize glucose (glucose \rightarrow acetate \rightarrow CO₂ (TCA cycle)), but when grown on glucose for many generations the population splits into two main subpopulations: microbes that preferentially consume glucose and produce acetate (glucose \rightarrow acetate) and microbes that preferentially consume acetate (acetate \rightarrow CO₂) (Rosenzweig et al., 1994; Rozen and Lenski, 2000; Treves et al., 1998).

In this paper we use standard chemostat modeling techniques to investigate whether the division of labor (splitting the pathways into two separate organisms) alone is sufficient to explain the observed increase in biomass, and if not, what other changes may be required. It is important to note that in contrast to the past work which has investigated the evolution of such cross-feeding systems, we will not consider the two systems in direct competition, instead comparing the maximum biomass (productivity) of the systems in isolation. This is motivated by industrial applications where the total productivity of the consortia, which is usually proportional to the biomass, is of primary interest.

This type of system has been studied mathematically, and it can be shown that for n species in a simple syntrophic cross-feeding chain, there is a stable coexistence steady state (Kreikenbohm and Bohl, 1986; Powell, 1985, 1986; Reilly, 1974). This simple system has been modified to include other forms of inhibition, external toxins, multiple substrates, and other forms of mutualism; in all cases, a stable, stationary, coexistence steady state is found (Aota and Nakajima, 2001; Burchard, 1994; Elkhader, 1991; Katsuyama et al., 2009; Sari et al., 2012). Previous research has focused on proving the existence and stability of coexistence steady-states. There has been no investigation of the productivity of these syntrophic chain systems. Some recent work (Doebeli, 2002; Estrela and Gudejl, 2010; Pfeiffer and Bonhoeffer, 2004) investigated the evolution of cross-feeding in microbial populations and found that there are a wide range of parameter values for which cross-feeding is seen to evolve. The aim of these evolution studies was to identify conditions for stable coexisting syntrophic chain systems to evolve and outcompete equivalent monocultures. They did not explicitly investigate the productivity of the systems that are found to evolve.

In our initial model, we assume that the metabolic dynamics of the pathways do not change when being split into separate microbes. In addition, we initially assume that the growth rate for the monoculture is a linear combination of the growth rates of the two pathways. This formulation allows us to obtain theoretical results and is effectively an upper bound on the growth rate of the monoculture microbe. Realistically, there are costs to utilizing both pathways at once for the monoculture, and there are changes that are known to occur to the metabolic pathway dynamics when the microbes specialize to a single substrate. For example, Pfeiffer and Bonhoeffer (2004) theorize that the evolution of cross-feeding could be due to the system minimizing the concentration of inhibitory intermediates and minimizing the concentration of enzymes it must produce, while maximizing the rate of ATP-production. Another explanation comes from Johnson et al. (2012) who find, by considering the biochemical conflicts which constrain the relationships between two metabolic processes that the division of metabolic pathways could be advantageous as it allows microbes to focus on producing a smaller number of enzymes and optimizing a smaller subset of pathways.

By starting with the assumption of no adaptation for the specialists and the maximal growth rate for the monoculture, we get a strong theoretical result. Then, by varying the growth kinetics (growth rates and substrate affinities) and yields between the monoculture and the binary culture systems, we are able to use our model to test possible explanations for the observed increase in productivity and to quantitatively investigate what changes are required for the division of labor to be advantageous (increased biomass). Considering the specific example of *E. coli* grown on a glucose substrate (Rosenzweig et al., 1994; Rozen and Lenski, 2000; Treves et al., 1998), we use standard Monod kinetics and measured experimental parameters to determine the conditions under which the model results match the experimentally observed increase in biomass.

The main result of this work is a comparison of the biomass production of a single microbe with full metabolic capacity to a syntrophic consortium of two specialized microbes each with a unique subset of the full metabolic chain, where the intermediate byproduct may be inhibitory. We prove that the monoculture system will always have higher biomass production (i.e., higher productivity) if there are no changes to the growth kinetics or yield of the pathways between the two systems. In a specific example, we show that increasing the growth rates or substrate affinities of the consortial pathways, a change that might be expected due to specialization, is not sufficient to generate the observed higher biomass production in the binary consortia.

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