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Reaction-centric modeling of microbial ecosystems

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ABSTRACT

The growth of microbial populations catalyzing biochemical reactions leads to positive feedback loops and self-amplifying process dynamics at ecosystem scales. Hence, the state of a biocatalyzed process is not completely determined by its physicochemical state, but also depends on current cell or enzyme concentrations that are often unknown. Here we propose a generic approach to modeling reaction networks of natural and engineered microbial ecosystems, that is able to capture the self-amplifying nature of biochemical reactions without explicit reference to the underlying microbial populations. This is achieved by keeping track of a system's "capacity" to perform particular reactions, rather than the cell populations actually catalyzing them. Our reaction-centric approach minimizes the need for cell-physiological parameters such as yield factors and provides a suitable framework for describing a system's dynamics purely in terms of chemical concentrations and fluxes. We demonstrate our approach using data from an incubation experiment involving urea hydrolysis and nitrification, as well as time series from a long-term nitrifying bioreactor experiment. We show that reaction-centric models can capture the dynamical character of microbially catalyzed reaction kinetics and enable the reconstruction of bioprocess states using solely chemical data, hence reducing the need for laborious biotic measurements in environmental and industrial process monitoring.

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1. Introduction

Microbial metabolism powers biochemical fluxes in natural and engineered ecosystems (Falkowski et al., 2008; McDuffie, 1991). Reciprocally, biochemical fluxes sustain biosynthesis and thus drive microbial population dynamics (Jin and Bethke, 2007). Changes in the microbial populations, in turn, influence the reaction kinetics at ecosystem scales because system-wide reaction rates depend not only on substrate concentrations but also on the density of catalyzing cells or of extracellular enzymes (Simkins and Alexander, 1984). Thus, the dynamics of microbial communities emerge from the continuous interplay between metabolic activity, changes in the extracellular metabolite pool and microbial population growth (Song et al., 2014). In particular, and in contrast to purely abiotic chemical processes (Marjanovic et al., 2006), the state and future trajectory of a biocatalyzed process cannot be determined solely based on the system's chemical state (Simkins and Alexander, 1984; Jin and Bethke, 2007). For example, empirical mineralization curves that describe the degradation rate of organic matter as a function of substrate density can vary strongly in shape, and this variation historically resulted partly from the interaction of substrate concentrations and cell population densities in experiments (Simkins and Alexander, 1984).

In deterministic or stochastic differential equation models (Resat et al., 2009; Khatri et al., 2012; Song et al., 2014), the dynamical character of microbially catalyzed reaction kinetics is typically incorporated by including additional variables representing cell densities, whose growth is proportional to the rates of the processes that they catalyze and determined by cell-per-substrate (or sometimes biomass-per-substrate) yield factors (Jin and Bethke, 2007). In turn, system-wide reaction kinetics are modulated by current cell densities and extracellular metabolite concentrations. Such cell-centric models are widely used and can capture the typical self-amplifying character of biocatalyzed processes (Cheyns et al., 2010). Likewise, deterministic as well as stochastic individual-based models, which keep track of multiple individual organisms and their metabolic activity, can also capture the feedback loops within microbial metabolic networks because the metabolic or trophic activity of each organism eventually

Abbreviations: AOB, ammonium oxidizing bacteria; NOB, nitrite oxidizing bacteria; *ure*, urea hydrolysis (gene or pathway); *amo*, aerobic ammonium oxidation (gene or pathway); *nxr*, aerobic nitrite oxidation (gene or pathway).

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leads to the production of new copies of that organism (Ferrer et al., 2008; Larsen et al., 2012). All of these cell-centric models, however, depend on physiological parameters such as yield factors, cell masses or maximum cell-specific reaction rates, and require knowledge of cell or enzyme concentrations (in addition to physicochemical variables) for describing a system's current state. As we explain below, some of these parameters also introduce redundancies from a reaction kinetic point of view that can lead to strong uncertainties in parameter estimation (Simkins and Alexander, 1984; Knightes and Peters, 2000).

Flux-balance models, a popular alternative to dynamical models (Orth et al., 2010), reduce the number of required parameters by ignoring cell population dynamics and by assuming that metabolite concentrations are constant through time (i.e. metabolite fluxes are "balanced"). In these models, reaction rates (and sometimes metabolite turnover rates; Chung and Lee, 2009) are the only independent variables, and their values are calculated by optimizing some objective function (e.g. ATP production) in the presence of constraints (e.g. on maximum reaction rates). Flux balance models have been very successful in elucidating metabolic network properties such as the feasibility of certain reactions or the prediction of metabolic interactions between species (Stolyar et al., 2007; Zomorrodi and Maranas, 2012; Klitgord and Segrè, 2010) but – being steady-state models – they fail to capture the dynamical nature of microbial communities. Hence, current model frameworks either ignore the temporal and self-amplifying character of biocatalyzed processes or require an extensive set of – often poorly estimated – physiological parameters.

To address the above limitations, here we develop a new framework for dynamical bioprocess modeling with a focus on system-wide reaction kinetics. Our objective was to reduce the reliance on physiological parameters and to reduce the need for biotic measurements for state reconstruction and model calibration, while still accounting for the self-amplifying character of metabolic reactions at the ecosystem level. Such a "reaction-centric" model would ideally make predictions purely in terms of metabolite concentrations and reaction rates at the ecosystem level, without the need to consider the underlying cell populations. As we show below, this can be achieved by keeping track of a system's "capacity" to perform particular reactions (or pathways), rather than the cell populations actually catalyzing them. Microbial ecosystem metabolism can then be described similarly to abiotic reaction networks, with the addition of so-called self- and cross-amplification factors between reactions. These amplification factors are specific to a particular microbial community and translate the system's metabolic fluxes into changes of the system's reaction capacities. Hence, a system's state and dynamics can be inferred using solely physicochemical measurements, bypassing laborious biotic measurements for example in environmental and industrial process monitoring. Furthermore, reaction-centric models minimize the reliance on cell-physiological parameters, allowing for model calibration even when biotic data are scarce. Reaction-centric models thus provide an elegant alternative to many conventional cell-centric models, particularly when the ultimate focus is on a system's reaction kinetics.

We begin with a derivation of the reaction-centric framework and show how it relates to conventional, cell-centric models. We focus on differential equation models, however we note that our reasoning can also be applied to other cell-centric frameworks. We demonstrate the potential of reaction-centric models using data from a previous short-term incubation experiment with a ureolytic and nitrifying microbial community (de Boer and Laanbroek, 1989), as well as long-term time series from a flow-through nitrifying bioreactor (Dumont et al., 2009). Bioreactors provide ideal model ecosystems for testing new theories for microbial ecology, due to their higher controllability and measurability when compared to natural ecosystems. Ureolysis and nitrification were chosen as examples because of their conceptual simplicity as well as their great relevance to ecosystem productivity, industry and agriculture (Wiesmann, 1994; Prosser, 2005). Our entire analysis was performed with a recently published computational tool for modeling microbial ecosystems (Louca and Doebeli, 2015a), which we extended to accommodate reaction-centric models.

2. Methods

2.1. Derivation of reaction-centric models: one reaction per cell

Conventional cell-centric microbial ecosystem models consider the extracellular concentrations of metabolites as well as the cell densities of microbial populations catalyzing various reactions. In the simplest and most common case each reaction is catalyzed by a distinct microbial population, the growth of which is proportional to the rate of the reaction (Simkins and Alexander, 1984; Larsen et al., 2012; Jin and Bethke, 2007). More precisely, the population density of cells catalyzing reaction r (N_r, cells per volume) and the concentration (C_m) of each metabolite m are described by differential equations similar to the following:

$$\frac{dN_r}{dt} = N_r Y_r V_r h_r(\mathbf{C}) - \lambda_r N_r, \tag{1}$$

$$\frac{dC_m}{dt} = F_m(t, \mathbf{C}) + \sum_r S_{mr} N_r V_r h_r(\mathbf{C}). \tag{2}$$

In Eq. (1), Y_r is a cell yield factor (cells produced per substrate used), V_r is the maximum cell-specific reaction rate (flux per cell per time) and $\mathbf{C}$ is the vector representing all metabolite concentrations (overview of symbols in Table 1). We note that in models where N_r is alternatively measured in biomass (rather than cells) per volume, Y_r is typically a biomass yield factor and V_r is a maximum biomass-specific reaction rate. The dependence of cell-specific reaction kinetics on $\mathbf{C}$ is encoded by the unitless function $h_r(\mathbf{C})$, which is normalized to unity at those $\mathbf{C}$ that maximize the cell-specific reaction rate. The last term in Eq. (1) corresponds to the decay of biomass at an exponential rate λ_r (with units time^{-1}), for example due to cell death. Alternatively, λ_r can account for reduced biosynthesis due to maintenance energy requirements, in which case it is sometimes called the "specific maintenance rate" (Jin and Bethke, 2007). In Eq. (2), F_m accounts for abiotic metabolite fluxes, such as substrate supply in a bioreactor, and S_{mr} is the stoichiometric coefficient of metabolite m in reaction r. The sum in Eq. (2) iterates through all reactions and accounts for microbial metabolic fluxes.

In the above cell-centric model the system's state depends on the current metabolite concentrations (C_m) as well as the current cell densities (N_r), the prediction of which, in turn, requires knowledge of physiological parameters such as Y_r and V_r. As we show below, this focus on cell populations can be avoided if one is solely interested in the system's reaction kinetics. Observe that the product $M_r = N_r V_r$, henceforth referred to as the system's current "reaction capacity", is the maximum system-wide rate of reaction r (flux per volume per time) that could possibly be attained at favorable metabolite concentrations (i.e. when $h_r(\mathbf{C}) = 1$). On the other hand, the product $H_r = N_r V_r h_r = M_r h_r$ is the actual system-wide rate of reaction r. Note that H_r depends both on the reaction capacity M_r as well as the normalized kinetics $h_r(\mathbf{C})$, which encodes the dependence of the reaction rate on the system's chemical state. Rewriting Eqs. (1) and (2) in terms of the reaction capacities M_r yields the reaction-centric model

$$\frac{dM_r}{dt} = A_r M_r h_r(\mathbf{C}) - M_r \lambda_r, \tag{3}$$

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