

Notes on the ordering of the concentrations of chemical species

Motivation:

There is experimental evidence supporting an order relation on the concentration of certain pairs of metabolites, when the system is at steady-state and which is conserved across experimental conditions [1,2]. That is, denoting the concentrations a pair of metabolites by the symbols x_i, x_j , we find that they satisfy $x_i \geq x_j$ under different experimental conditions. We aim at explaining these relations with a mathematical model of a chemical system.

Approach:

Consider the chemical dynamical system:

$$\frac{dx_i}{dt} = \sum_j S_{ij} v_j(\theta, x) \quad (1)$$

where the rate of change of x_i is expressed as the sum over all fluxes v_j of the reactions r_j which produce or consume m_i , which are weighted by their corresponding stoichiometric coefficients, S_{ij} . Furthermore, we follow mass action kinetics, in which the flux of a reaction r_j is modelled following

$$v_j = \theta_j \prod_{i \in \text{Subs}} x_i^{s_{ij}}, \quad (2)$$

in which the parameter θ_j represents the reaction rate constant, the product is taken over the concentrations x_i of the metabolites acting as substrates in the reaction, and the stoichiometric coefficients s_{ij} correspond to the number of molecules of each substrate. We will denote the monomial $\prod_{i \in \text{Subs}} x_i^{s_{ij}}$ the substrate complex of reaction r_j .

We are interested in finding pairs of species that satisfy an order relation at any positive steady-state of the chemical system (with fixed parameters, θ). That is, we search for pairs $x_i, x_j \in \{\chi: Sv(\theta, \chi) = 0, x_i \geq x_j\}$. In the following, we discuss a sufficient condition to search for such pairs of species.

Suppose that we find a pair of reactions, r_k, r_l which differ only in n molecules of species x_i in their substrate complexes, then, under mass-action, we have $\frac{v_k}{v_l} = \frac{\theta_k}{\theta_l} x_i^n$ and $x_i^n = \frac{\theta_l}{\theta_k} \frac{v_k}{v_l}$. Let's assume that we find a second pair of reactions, r_p, r_q also differing in n molecules of a different species x_j . Then taking the concentration ratio of the two species we obtain,

$$\frac{x_i}{x_j} = \left(\frac{\theta_l}{\theta_k} \frac{\theta_q}{\theta_p} \frac{v_k}{v_l} \frac{v_p}{v_q} \right)^{\frac{1}{n}}. \quad (3)$$

Since we are interested in finding $x_i \geq x_j$, we need $\frac{\theta_l}{\theta_k} \frac{\theta_q}{\theta_p} \frac{v_k}{v_l} \frac{v_p}{v_q} \geq 1$, and provided that the system is parameterized such that $\frac{\theta_l}{\theta_k} \frac{\theta_q}{\theta_p} \geq 1$, then this condition reduces to

$$\frac{v_k v_p}{v_l v_q} \geq 1. \quad (4)$$

The last condition is satisfied if $v_k \geq v_l$ and $v_p \geq v_q$ or if $v_k \geq v_q$ and $v_p \geq v_l$, for any steady-state of the system. Furthermore, we can use convex optimization tools to determine whether the reaction quadruples satisfy this property, and hence, to identify pairs of chemical species satisfying $x_i \geq x_j$ at steady-state. To see this, let us select the reaction pair r_k, r_l , we can determine the bounds of the flux ratio $\rho_{kl} = v_k/v_l$ by solving the two linear-fractional programs

$$\begin{aligned} \rho_{\min}, \rho_{\max} &= \min, \max \frac{v_k}{v_l} \\ \text{s.t.} \\ Sv &= 0 \\ v_{\min} &\leq v \leq v_{\max}, \end{aligned} \quad (5)$$

which, by the Charnes-Cooper transformation [3] are equivalent to the linear programs

$$\begin{aligned} \rho_{\min}, \rho_{\max} &= \min, \max v_k \\ \text{s.t.} \\ Sv &= 0 \\ v_l &= 1 \\ v_{\min} &\leq v \leq v_{\max}. \end{aligned} \quad (6)$$

The reaction pair, r_k, r_l then satisfies $v_k \geq v_l$ if $\rho_{\min} \geq 1$, and $\rho_{\max} > 1$. Note that $\rho_{\min} = \rho_{\max}$ implies that reactions r_k, r_l are fully coupled [4], that is, there exist $\alpha \in \mathbb{R}$ such that $v_k = \alpha v_l, \forall v: Sv = 0$. So we can also exploit efficient algorithms to find fully coupled reaction pairs [5] with $\alpha \geq 1$, as a means to reduce the number of reaction pairs to be evaluated with (6).

Finally, we can relax the steady-state condition $Sv = 0$, and search for order relations between reaction fluxes that are still valid outside of steady-state. We just need to substitute the constraint $Sv = 0$ in (6) by $-\epsilon \leq Sv \leq \epsilon$, where ϵ corresponds to the maximum allowed absolute deviation from steady-state where ϵ corresponds to the maximum allowed absolute deviation from steady-state. This modification would ultimately allow us to find order relations among metabolite concentration values that are preserved even outside steady-state—an interesting approach considering that metabolism is rarely exactly at steady-state, and so are the experimental measurements.

Open questions:

There are several questions that should be addressed in this project. The first one, perhaps, is to evaluate whether such quadruples of reactions exist at all in extant metabolic models. Second, it would be interesting to explore whether such order relation in the concentrations can be found with a different method, or even under a different reaction rate formalism. Third, since we need $\frac{\theta_l}{\theta_k} \frac{\theta_q}{\theta_p} \geq 1$, it would be required to check if this condition is actually satisfied by measured kinetic parameters, *i.e.*, proxies of rate constants. Or, given measured metabolite concentration ratios, to evaluate if one can predict rate constant ratios. Lastly, analyzing pairs

of chemical species with ordered concentrations outside steady-state is worth exploring. This would mean that entire trajectories of concentrations—*i.e.*, provided that $-\epsilon \leq Sv \leq \epsilon$ —would follow the order relation.

References:

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