Decomposition of kinetically feasible metabolic flux distributions onto elementary modes

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1 Introduction

As genome-scale metabolic networks are being reconstructed with increasing accuracy, new methods are needed to understand the systemic biochemical properties of these large networks. The behaviour of complex systems of interacting components cannot be comprehended by the sole characterization of their individual components or pair-wise relations, because new properties emerge from the interaction of larger numbers of components. Systems-based approaches are needed to gain knowledge about complex cellular processes, and may allow in a further future to provide an integrated and predictive description of a complete organism.

Metabolic pathways are an essential key to the systemic behaviour of a biological cell. Accurate dynamical modelling of cellular processes is in most cases impossible because the required kinetic data are missing. Therefore alternative network-based approaches have been developed and have found much interest recently. In contrast to dynamical simulation, these descriptions only require the knowledge of network topology and stoichiometry, which are well known is many cases.

In network-based pathway analysis, a biological network of interacting components is represented by a stoichiometric matrix that relates reactions and metabolites. This matrix is analyzed by an algorithm that computes a set of routes satisfying specified conditions. Two very similar concepts called *elementary flux modes* and *extreme pathways* have been introduced recently [1]. An elementary mode is a minimal set of reactions that can operate at steady state, and the set of extreme pathways is the systemically independent subset of the elementary modes. In a mathematical multidimensional representation where each axis corresponds to a reaction flux, all possible steady-state flux distributions lie within a multidimensional flux cone. Extreme pathways form the edges of this cone, and the additional elementary modes may lie on the surface or in the interior of the cone.

2 Decomposition of flux distributions

Although the space generated by the extreme pathways contains all possible steady-state flux distributions, not necessarily all these states may actually be reached in a real biological organism. Several attempts to further characterize the space of allowable states, and to understand how it is affected by regulatory mechanisms or environmental conditions, have already been published.

Our aim is to understand how kinetics influences the extent of the space of allowable states in a biological system. Our approach starts with decomposing steady-state flux distributions onto the set of elementary modes. Any flux distribution can be described as a non-negative linear combination of elementary modes, however this decomposition is generally not unique. The concept of *α-spectrum* has been introduced previously as an attempt to understand how extreme pathways contribute to the construction of physiological steady-states [2]. The α-spectrum describes the range of possible weightings a particular mode can reach in the decomposition. The drawback of this description is that possible relations between modes do not appear. For example, two elementary modes EM1 and EM2 may have an α-spectrum ranging from 0 to 1, but if the α-value of EM1 is set to 0.5, the allowable range for EM2 may shrink to the interval 0.3 to 0.7.

We here introduce a different description, which consists in selecting, among the possible sets of weightings, the particular set that minimizes the distance between the flux vector and the elementary modes

used in the decomposition. For a steady-state flux vector **v** and a set of elementary modes $\mathbf{v}_1$, $\mathbf{v}_2$ … $\mathbf{v}_m$, this implies finding a set of values α_1, α_2 … α_m sharing the following three properties:
(1) $\mathbf{v} = \alpha_1 \mathbf{v}_1 + \alpha_2 \mathbf{v}_2 + \ldots + \alpha_m \mathbf{v}_m$
(2) $\alpha_i \geq 0$ for $i = 1,\ldots, m$
(3) $\alpha_1^2 + \alpha_2^2 + \ldots + \alpha_m^2$ is minimal
The problem defined by these conditions belongs to a class of optimization problems called "Quadratic Programming", and can be solved using the Active Set algorithm [3].

3 Influence of kinetics

It then becomes possible to study the range of kinetically feasible steady-states, and to observe how the contribution of particular elementary modes is affected by the uncertainty of kinetic parameter values. A simple example using a theoretical network is presented below. Figure 1a) shows a simple network built of four metabolites, two irreversible reactions, and one reversible reaction. All reactions are assumed to follow mass-action kinetics. This network has three elementary modes, which are shown in Figure 1b). Steady states were computed using the Gepasi software [4], and were decomposed onto the set of elementary modes using our Active Set based algorithm. Figure 1c) shows the normalized α rates obtained for the three elementary modes as a function of the variable kinetic parameter k_{12}.

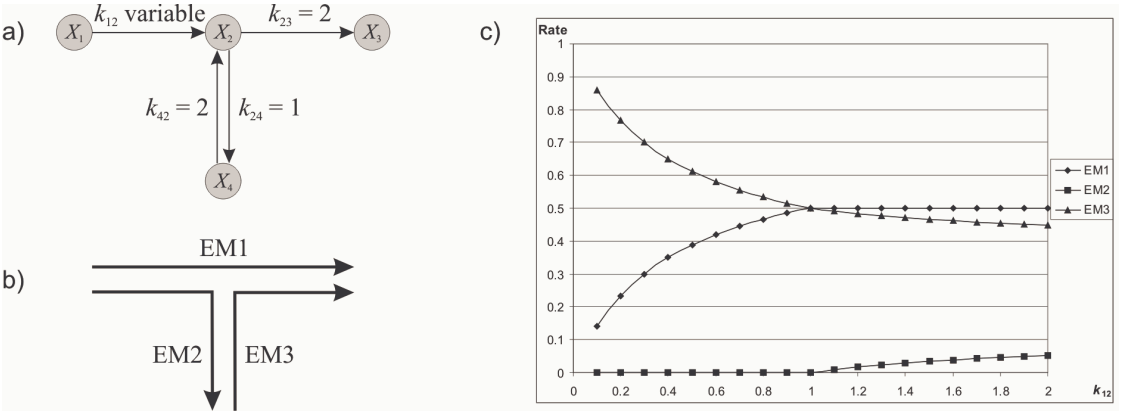

Figure 1: Decomposition of flux distributions onto elementary modes in a simple network.

It can be observed that elementary mode EM2 has very little influence whatever the value of k_{12}. This result is consistent with the model, since kinetics of the reversible reaction between X_2 and X_4 forces the network to operate predominantly in the direction of EM3, and inhibits the operation of EM2.

Although this example is too simple to draw biochemically relevant conclusions, it nevertheless shows that partial knowledge of kinetic data, combined with network-based pathway analysis, can lead to clues about the dominant modes in a biochemical network, or allow to eliminate other modes which are unable to make any significant contribution under given conditions. The next step of this project will consist in applying the same kind of analysis to more complex examples and to real biochemical networks.

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