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A mathematical approach to emergent properties of metabolic networks: Partial coupling relations, hyperarcs and flux ratios

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HIGHLIGHTS

- We introduce some of the emergent properties of metabolic networks.
- These properties generally emerge because of hyperarcs and irreversible reactions.
- Graph-based models are not suitable for the analysis of such networks.

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ABSTRACT

Emergent properties in systems biology are those which arise only when the biological system passes a certain level of complexity. In this study, we introduce some of the emergent properties which appear in the constraint-based analysis of metabolic networks. These properties generally appear as a result of existence of hfdeyperarcs and irreversible reactions in networks. Here, we present examples of metabolic networks in which there exist at least two reactions whose fluxes cannot be written as products and/or ratios of the stoichiometric coefficients of the network. We show that any such network contains at least one hyperarc. Additionally, we prove that partial coupling cannot appear in consistent metabolic networks with less than four reactions, or with less than three irreversible reactions, or without hyperarc(s).

1. Introduction

1.1. Emergent properties in systems biology

Aristotle (384-322 BC) was probably the first person to describe the concept of *emergence* in his famous statement: “the whole is more than the sum of its parts” (Mazzocchi, 2008). It is now widely accepted that biological systems cannot be fully understood merely on a molecular level (Powell and Dupre, 2009). Emergent properties in systems biology are those which arise only when the system passes a certain level of complexity (Ferrell, 2009).

Example 1. As a concrete example of emergence, we show how the number of components in a gene regulatory network can determine its oscillatory behavior. In a gene regulatory network, a negative feedback loop is a feedback loop which includes an odd number of inhibitory interactions. In Fig. 1 two examples of negative feedback loops are presented. If there is no time delay, it can be shown that a network with two components may only show damped (and not sustained) oscillation. In contrast, a network with three genes can function as a sustained oscillator (Ferrell et al., 2011). Therefore, oscillatory behavior emerges at the level of a three gene system (Ferrell, 2009).

Typically, emergence appears as a result of non-linear interactions among the components of system. Therefore, reductionist and deterministic attempts fail to explain it (Powell and Dupre, 2009; Mazzocchi, 2011).

Emergent properties are commonly observed in systems biology. There are several instances of emergent properties reported in signalling networks (Bhalla and Iyengar, 1999; Papin and Palsson, 2004; Liu et al., 2013; Appleton and Luttrell, 2013), gene regulatory networks (Barberis et al., 2007; Ferrell et al., 2011; Torres-Sosa et al., 2012), immune systems (De Boer and Perelson, 1991; Nardai et al., 2006), metabolic systems (Boogerd et al., 2005; Palumbo et al., 2007), and even cell-to-cell communication networks in bacteria (Wintermute and Silver, 2010).

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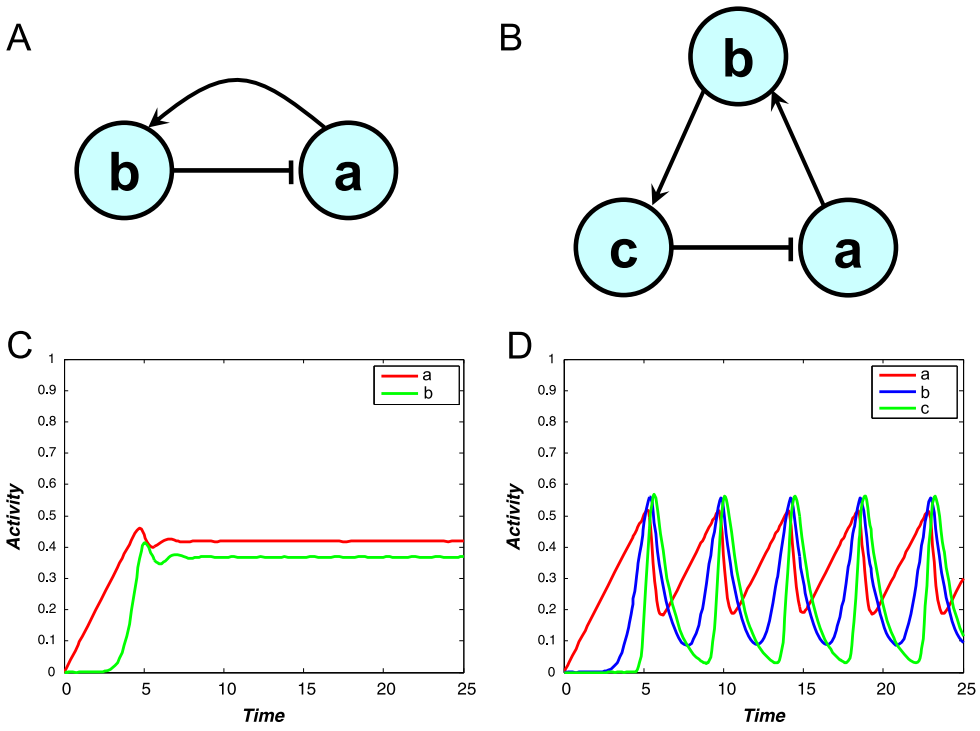

Fig. 1. An example of emergent properties in gene regulatory networks. (A) Two genes connected in a negative feedback loop are not able to show sustained oscillatory behavior; (B) three genes connected in a negative feedback loop are able to show sustained limit cycle oscillations. In this figure, normal arrows indicate activation, while blunt-end arrows indicate inhibition and negative regulation. (C,D) Damped oscillation and sustained oscillation as the expected behaviors of examples A and B, respectively. This example is adopted from Ferrell (2009). Panels C and D are re-drawn from the equations presented in Ferrell et al. (2011).

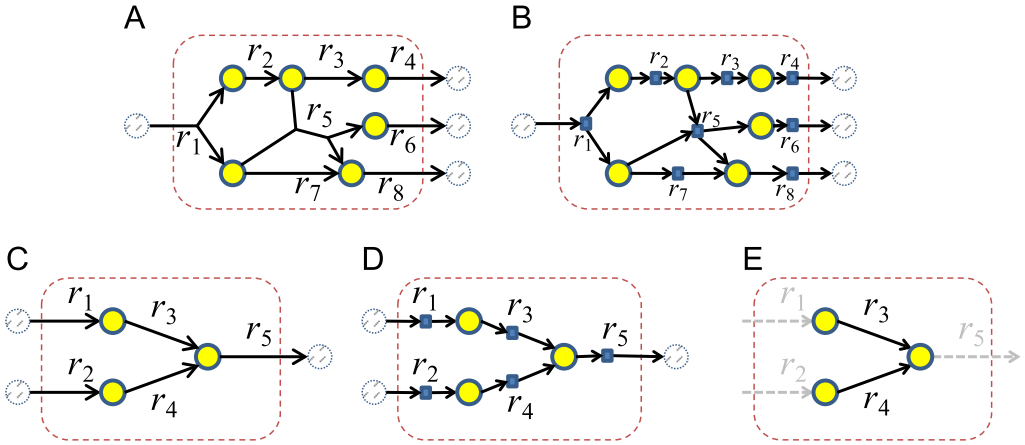

Fig. 2. (A) Hypergraph illustration of a small metabolic network. Internal metabolites are shown by yellow circles. Reactions r_3 and r_4 are examples of arcs, while reactions r_1 and r_5 are examples of hyperarcs; (B) bipartite graph illustration of the same network. "Reaction nodes" are shown by squares; (C–E) a simple network with five reactions illustrated as hypergraph, bipartite graph and directed graph representations, respectively. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

1.2. Modeling metabolic networks

Metabolic networks are certainly among the best studied biological systems (Pfeiffer et al., 2005; Soh and Hatzimanikatis, 2010). Models of metabolic networks have been widely used in a wide range of studies, from biotechnology to evolution (Price et al., 2003; Wagner, 2012; McCloskey et al., 2013).

Metabolic networks are typically viewed as hypergraphs (Klamt et al., 2009; Carbonell et al., 2012) or equivalently, as bipartite graphs (Warren et al., 2009). In the hypergraph representation, every reaction is shown either by an *arc* or a *hyperarc*, which connects a set of *reactants* to a set of *products* (Fig. 2A). On the other hand, when a metabolic network is represented as a bipartite graph, each reaction is shown by a *reaction node*, which connects the set of reactants and the set of products (Fig. 2B).

There are different strategies to model metabolic fluxes in these networks, including constraint-based modeling (Covert et al., 2001; Price et al., 2003) and Petri net modeling of metabolic networks (Voss et al., 2003). However, simple modeling frameworks like "flow networks" (Schrijver, 2002) are not used in modeling metabolic fluxes. This might be related to the fact that modeling fluxes in metabolic networks by flow networks is possible only when the network merely includes *simple* reactions (i.e., either in the form $\mu_i \rightarrow \mu_j$ or in the form $\mu_i \rightleftharpoons \mu_j$). De Figueiredo