Dynamic Independence and Modularity in Graphs of Large Biochemical Reaction Networks

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An ultimate aim of Systems Biology is to understand the dynamic properties of large, interconnected biochemical reaction networks at different levels of organisation. A principal challenge is thus to map from fine level descriptions – such as network reconstructions listing the myriad component reactions – to higher level, coarse-grained descriptions of the dynamic properties. I introduce a rigorous graphical representation of the Markov pure jump process (or 'stochastic kinetic model') implied by stochastic biochemical kinetics for the concentrations of the different biochemical species (or biomolecules) present in the cell. These Kinetic Independence Graphs (KIGs) provide a conceptually powerful and computationally feasible tool for understanding and deriving the dynamic independence properties of large reaction networks. Graphical decompositions are used to provide new automated and semi-automated methods for modularising such networks on the basis of these dynamic independences. The methods identify biologically interesting modules and network architecture using publicly available network reconstructions, including the example of human red blood cell metabolism discussed below.

As input, the techniques merely require for each reaction in the network a list of its reactants and some limited information about the stoichiometry – namely a list of those reactants and products whose level is changed by the reaction. In particular, known rate parameters are not required. The first output is a cyclic, directed graph (the KIG) that encodes the local independence structure of the dynamics of any group of biochemical species, enabling one to read off those species that are irrelevant for the conditional intensity governing the group's instantaneous dynamic evolution. Methods are provided to derive from the KIG the implied global conditional independencies between the evolution of groups of biochemical species over time. These appear to be the first methods, graphical or otherwise, for analysis of the dynamic independence structure of stochastic kinetic models. Furthermore, their applicability is not limited to networks of modest size.

Modularity has emerged in biology as an important property of biochemical networks and, loosely speaking, refers to the separability of the design into units that perform relatively independently of one another. An approach to module definition and identification is proposed that, unlike others, is explicitly based on the dynamics implied by the stochastic kinetic model. Here a modularisation is defined as a collection of modules (i.e., of groups of biochemical species) each of whose dynamic evolution is conditionally independent of that of all the other modules, given information on the history of jumps of the species present in the module's intersection with the rest of the network. It is shown that such modularisations may be obtained by decomposition of the undirected version of the KIG, and their properties usefully conveyed by the junction tree used in their computation. Both the maximal prime subgraph decomposition (MPD) and related methods that allow some incomplete separators are considered.

The MPD has the advantage of being unique and can be fully automated, but appears in some of the network reconstructions examined to unduly limit the richness of the modularisation obtained. In the case of the red blood cell metabolic network a finer decomposition is shown to identify, inter alia, the following modules: interaction of pentose phosphate cycle and early glycolysis components, NAPDH/ glutathione management of oxidative stress, and phosphoglycerate metabolism/ magnesium complex formation. This modularisation also reveals interesting conditioning sets (module intersections) associated with the various dynamic independencies. Application of the methods to very large network reconstructions is currently underway.