



Sharper graph-theoretical conditions for the stabilization of complex reaction networks



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ABSTRACT

Across the landscape of all possible chemical reaction networks there is a surprising degree of stable behavior, despite what might be substantial complexity and nonlinearity in the governing differential equations. At the same time there are reaction networks, in particular those that arise in biology, for which richer behavior is exhibited. Thus, it is of interest to understand network-structural features whose presence enforces dull, stable behavior and whose absence permits the dynamical richness that might be necessary for life. We present conditions on a network's *Species-Reaction Graph* that ensure a high degree of stable behavior, so long as the kinetic rate functions satisfy certain weak and natural constraints. These graph-theoretical conditions are considerably more incisive than those reported earlier.

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1. Introduction

In two recent articles [1,2] we described a subtle structural attribute, *concordance* (Definition 6.5), that enforces a degree of stable behavior for all chemical reaction networks having that attribute, so long as the kinetic rate functions satisfy certain mild constraints (e.g., weak monotonicity [1]). In some respects, the concordance condition captures completely a network's capacity for particular kinds of behavior.

For example, it is *precisely* the concordant reaction networks for which the species-formation-rate function is injective for *all* choices of weakly monotonic kinetics.³ (Among other things, injectivity precludes the possibility of two distinct stoichiometrically compatible

positive equilibria.⁴) Moreover, among the fully open reaction networks that have the capacity to admit a positive equilibrium, it is *precisely* the concordant ones for which no differentially monotonic kinetics can give rise to an instability resulting from a positive real eigenvalue. In addition, for every discordant weakly reversible [3] network there invariably exists a differentially monotonic kinetics—in fact a polynomial kinetics—that engenders an unstable positive equilibrium having a positive real eigenvalue. It was in [1] that we discussed the stability-enforcing properties of concordant networks and also the consequences of discordance.

In [2] we connected concordance of a network with properties of the network's *Species-Reaction Graph* (SR Graph), which resembles the diagram often used for the depiction of biochemical pathways. In particular, we showed that, when a nondegenerate⁵ network's SR Graph satisfies fairly weak conditions, concordance of the network is ensured. Consequently, one can deduce directly from properties of a network's SR Graph the regular, stable behavior that derives from concordance, even in the absence of finely detailed information about the kinetics. Although the concordance of a reaction network can be decided computationally by means of easy-to-use freely available software [4,5], the SR Graph theorems in [2] have the added virtue of

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² This work was initiated while G.S. was in the Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot 76100, Israel.

³ Appendix A provides a brief review of some vocabulary from [1,2]. For the purposes of this article, however, the most essential terminology is introduced in the main text.

⁴ In fact, in the class of networks with positively dependent reaction vectors, it is precisely the discordant ones for which there exists a weakly monotonic kinetics that admits two distinct stoichiometrically compatible positive equilibria. See Appendix B.

⁵ See Section 2 and Appendix C.

providing insight into the extremely subtle network-structural features that make for concordance or discordance.

The SR Graph theorems in [2] are quite robust in the networks for which they affirm concordance. There are, however, many examples of networks for which computations, via [5], establish concordance but for which the graphical theorems in [2] are silent. (All of the examples in Section 4 are of this kind.) These examples point to the existence of graph-theoretical theorems more incisive than those provided in [2].

It is the purpose of this article to provide SR Graph theorems that subsume the earlier ones and that give concordance information about networks for which the theorems in [2] say nothing. Proofs of the broader theorems presented here turn out to be considerably simpler than the proofs of the narrower ones given in [2].

Readers interested only in the rich dynamical information carried by a network's SR Graph can proceed directly to Theorems 4.1 and 5.1 after reading Section 3 and, to a lesser extent, Section 2. Although network concordance underlies their proofs, those theorem statements make no reference to the concordance idea.

Remark 1.1. See [1] and [2] for a discussion of earlier work [6–12] that connects properties of the Species-Reaction Graph (or the Species-Complex-Linkage Graph) to qualitative dynamics, in particular to the preclusion of multiple equilibria. Here it is worth pointing out once again that the earlier SR Graph results were confined to mass action kinetics until the surprising papers of Banaji and Craciun [11,12].

Remark 1.2. In this paper we will impose a fairly inconsequential restriction that was also imposed in [2,12]: It will be understood that, in connection with the SR Graph theorems, we consider only networks in which no species appears as both a reactant and a product in the same reaction. For example, we preclude from consideration a network containing the reaction $A + B \rightarrow 2A$, but we do not preclude a network containing the reactions $A + B \rightarrow C \rightarrow 2A$.

Remark 1.3. A formal definition of a *weakly monotonic kinetics* [1] for a network is provided in Appendix A. In less formal terms, weak monotonicity reflects a natural restriction on the relationship between mixture composition and the rates of a network's various reactions: For each reaction, an increase in its occurrence rate requires an increase in the concentration of at least one of its *reactant* species. Mass action kinetics provides an example of a weakly monotonic kinetics, but the weakly monotonic class is far wider. For example, the reaction $A + B \rightarrow C$ might be governed by a rate function such as

$$\frac{\alpha c_A c_B}{\beta + \gamma c_A + \delta c_B},$$

where α , β , γ , and δ are positive.

In Section 5, we will also make reference to *two-way weakly monotonic kinetics*, which is defined formally in [1] and which is similar to what Banaji and Craciun [11,12] call NAC kinetics. The two-way weakly monotonic class of kinetics extends the weakly monotonic class to admit reaction-rate functions consistent with the possibility of product inhibition: For each reaction, an increase in its rate requires an increase in the concentration of at least one of its reactant species or a decrease in the concentration of at least one of its product species. Thus, for example, the reaction $A \rightarrow B$ might be governed by a rate function such as

$$\frac{\alpha c_A}{\beta + \gamma c_B}.$$

2. Prelude: Fully open and nondegenerate networks

A reaction network is *fully open* if, for each species s in the network, there is a reaction of the form $s \rightarrow 0$ (s reacts to zero). Such a reaction is often introduced to model either the degradation of species s to inconsequential products or the physical effusion of s from the reacting

mixture. (The network might also contain reactions of the form $0 \rightarrow s$ to model the synthesis or infusion of species s .)

Fully open reaction networks are, in some respects, easier to study than other networks. They have certain features that make for some simplicity in the mathematics; in particular, constraints imposed by stoichiometry become less consequential. The *fully open extension* of a given reaction network is the network obtained by adding all reactions of the form $s \rightarrow 0$ that are not already present. In some instances, properties of a network's fully open extension are inherited by the network itself.

In fact, apart from certain degenerate networks discussed below (and more fully in Appendix C), a network is concordant if the network's fully open extension is concordant. For this reason, it is of interest to determine whether a network's fully open extension is concordant. This is so not only because fully open networks are easier to study but also because concordance of the network's fully open extension actually gives important dynamical information beyond that given by concordance of the network itself. In particular, when a network's fully open extension is concordant and when the kinetics is differentially monotonic, not only are multiple positive stoichiometrically compatible equilibria impossible for the original network, but also all real eigenvalues at any positive equilibrium are strictly negative [1].

We say that a network is *nondegenerate* if, for the network, there is *even one* choice of a differentially monotonic kinetics such that there exists *some* positive composition (*not necessarily an equilibrium*) at which the derivative of the species-formation rate function is nonsingular [2]. Otherwise, we say that the network is *degenerate*. Note that in this context nondegeneracy (or degeneracy) is a property of a *network*.

Degenerate networks make for poor models of real behavior, for they typically lack robustness. For example, a mass action model derived from a degenerate network might admit multiple stoichiometrically compatible equilibria, but the multiplicity of equilibria can disappear if the model is perturbed just slightly, say by adding the reverse of an existing reaction and assigning to it a *vanishingly small* rate constant.⁶ An example is provided in Appendix C.

The nondegenerate networks are *precisely* the ones for which concordance of the fully open extension ensures concordance of the network itself. Especially among networks that have the capacity to admit a positive equilibrium, degeneracy is rare. In fact, *every reversible network is nondegenerate* (as is every weakly reversible network), but reversibility (or, more generally, weak reversibility) is far from necessary for nondegeneracy.

Because chemists often insist that every naturally occurring network of chemical reactions is reversible, if only to a small extent,⁷ they might regard degeneracy of a particular reaction network model to have roots in the improper neglect of reverse reactions that should have, in fact, been taken into account. Indeed, any degenerate reaction network model becomes nondegenerate when it is perturbed by the addition of sufficiently many reverse reactions, usually few in number.⁸ Moreover, *every fully open network is nondegenerate, regardless of what the reactions are* (Remark C.6).

In Appendix C we provide a fuller discussion of network nondegeneracy, including characterizations of nondegeneracy in terms of network structure alone. In [5] we provide a tool to decide a network's

⁶ Perverse mathematical phenomena of this kind should not be confused with other model perturbations involving the addition of a reverse reaction but in which changes of behavior require a substantial rate constant for the reaction added. Perturbations of this second kind appear in Section 4.

⁷ With mass action kinetics, for example, the reverse rate constant might be extremely small.

⁸ It is sufficient for nondegeneracy, but certainly not necessary, that there be r linearly independent reactions that are reversible, where r is the rank of the network (Definition 6.3). See Proposition C.22 in Appendix C.

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