Inheritance of oscillation in chemical reaction networks

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A B S T R A C T

Some results are presented on how oscillation is inherited by chemical reaction networks (CRNs) when they are built in natural ways from smaller oscillatory networks. The main results describe four important ways in which a CRN can be enlarged while preserving its capacity for oscillation. The results are for general CRNs, not necessarily fully open, but lead to an important corollary for fully open networks: if a fully open CRN $\mathcal{R}$ with mass action kinetics admits a nondegenerate (resp., linearly stable) periodic orbit, then so do all such CRNs which include $\mathcal{R}$ as an induced subnetwork. This claim holds for other classes of kinetics, but fails, in general, for CRNs which are not fully open. Where analogous results for multistationarity can be proved using the implicit function theorem alone, the results here call on regular and singular perturbation theory. Equipped with these results and with the help of some analysis and numerical simulation, lower bounds are put on the proportion of small fully open CRNs capable of stable oscillation under various assumptions on the kinetics. This exploration suggests that small oscillatory motifs are an important source of oscillation in CRNs.

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1. Introduction and context of the paper

At the heart of many biological systems are chemical reaction networks (CRNs), and the question of when these admit oscillation is of both theoretical and practical interest. Oscillation is known to occur – and play a key role – in a great variety of biological contexts. Examples include the natural rhythms of body clocks and ovulation, biochemical oscillations in cellular signalling, cyclic behaviour of various diseases, and periodic fluctuations in Lotka–Volterra-type models of interacting populations. Several chapters of [1] and [2] detail mathematical models of oscillation in biological settings. Some general biological principles underlying biological oscillation are discussed in [3]. Once a network admitting oscillation is identified, we might naturally wonder whether this network occurs as a "motif" in other larger networks and, if so, whether the larger networks must themselves admit oscillation. The desire to phrase this question precisely and provide some simple and partial answers motivates this work.

Several papers have treated analogous questions about the inheritance of multistationarity in CRNs [4–7]. In a recent contribution my coauthor and I showed that a great deal can be done in this direction using the implicit function theorem [8]. An (incomplete) list of network modifications proven to preserve the property of admitting nondegenerate multistationarity were listed; these collectively define a partial order $\preceq$ on the set of all CRNs such that if a CRN $\mathcal{R}$ admits nondegenerate multistationarity, then so do all CRNs $\succeq \mathcal{R}$ in this partial order. Although it is likely that most, if not all, of the results in [8] can be restated with "nondegenerate oscillation" replacing "nondegenerate multistationarity", only part of this task is undertaken here: we prove four results about general CRNs, Theorems 1 to 4, which are analogues of related results about

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multistationarity in [8], also numbered Theorems 1 to 4. An example of what these tell us is the following corollary about fully open CRNs:

Proposition 1.1. *If a fully open CRN $\mathcal{R}$ with mass action kinetics admits nondegenerate (resp., stable) oscillation, then so does any fully open CRN with mass action kinetics which includes $\mathcal{R}$ as an induced subnetwork.*

The definitions required to make this result precise will follow. Proposition 1.1 is the specialisation for mass action kinetics of a result with more general kinetic assumptions, Proposition 4.8, (see Remark 4.9) which is a natural starting point for some computational exploration on small fully open CRNs admitting oscillation. It is worth noting at the outset that Proposition 1.1 fails if the CRNs are not assumed to be fully open. An example is provided in the concluding section (Example 6.1).

Much of the mathematical literature on oscillation in CRNs has focussed on conditions which forbid oscillation, or forbid stable oscillation of the kind which might be observed in numerical simulations, or forbid bifurcations leading to oscillation. For CRNs with mass action kinetics, there are the original results of deficiency theory [9–12]; for CRNs with more general kinetics there are results based on the theory of monotone dynamical systems ([13–16] for example), and algebraic approaches ([17] for example). Various papers which do not directly treat CRNs also have natural applications to forbidding oscillation or stable oscillation in CRNs, including the work of Angeli, Hirsch and Sontag on "coherent" systems [18], and of Li and Muldowney on generalised Bendixson's criteria [19–21]. On the other hand oscillation has been shown to occur in numerical studies of various CRNs of interest (for example, [22–25]). Aside from numerical work, there exists an important strand of theory drawing on approaches in convex and toric geometry which provides *sufficient* conditions for Hopf bifurcations in CRNs with mass action and generalised mass action kinetics [26–29]. These approaches lead to algorithms for the determination of parameter regions where Hopf bifurcation occurs. Other papers treating the question of sufficient conditions for oscillation in chemical reaction networks include [30] and [31].

The work here is aimed at closing the gap between theory which forbids oscillation and examples of oscillatory networks or particular sufficient conditions for oscillation. It is likely that many examples of CRNs admitting oscillation in fact oscillate because they inherit this property from a smaller CRN which admits oscillation, and the goal is then to identify an appropriate notion of inheritance, and minimal oscillatory CRNs in some sense. The importance of inheritance is increasingly recognised. In [32], Conradi and Shiu pose a question closely related to the main question in this paper, namely whether Hopf bifurcation is preserved when CRNs are modified in natural ways. The problem of identifying a "minimal" oscillatory subnetwork was tackled for the biologically important MAPK cascade in [33].

Computational work on fully open CRNs towards the end of the paper confirms the practical usefulness of inheritance approaches. As oscillation may occur in very small regions of parameter space, it may be hard to find by brute force in numerical simulations, even where it is straightforward to predict its occurrence by inheritance results. Finding a single small oscillatory CRN on the other hand immediately gives us knowledge of a large number of CRNs which inherit this oscillation. Ultimately, the hope is that examining CRNs which can neither be proven to forbid oscillation nor be shown to oscillate (using numerics, known sufficient conditions for oscillation, or inheritance results such as here) may lead to new theorems about necessary conditions for oscillation.

1.1. Notational preliminaries

Notation 1.2 (Nonnegative and positive vectors). A real vector $x = (x_1, \ldots, x_n)^t$ is nonnegative (resp., positive) if $x_i \geq 0$ (resp., $x_i > 0$) for each i, and we refer to the nonnegative (resp., positive) orthant in $\mathbb{R}^n$ as $\mathbb{R}^n_{\geq 0}$ (resp., $\mathbb{R}^n_{\gg 0}$). Subsets of $\mathbb{R}^n_{\gg 0}$ are referred to as positive.

Notation 1.3 (Vector of ones). **1** denotes a vector of ones whose length is inferred from the context.

Notation 1.4 (Identity matrix). I_n is the $n \times n$ identity matrix.

Notation 1.5 (Set theoretic inverse). Given sets X, Y and a function $f : X \to Y$, not necessarily invertible, f^{-1} will generally refer to the set theoretic inverse, namely, given $Y_0 \subseteq Y$, $f^{-1}(Y_0) = \{x \in X : f(x) \in Y_0\}$.

Notation 1.6 (Monomials, vector of monomials). Given $x = (x_1, \ldots, x_n)^t$ and $a = (a_1, \ldots, a_n)$, x^a is an abbreviation for the (generalised) monomial $\prod_i x_i^{a_i}$. If A is an $m \times n$ matrix with rows $A_1, \ldots, A_m$, then x^A means the vector of (generalised) monomials $(x^{A_1}, x^{A_2}, \ldots, x^{A_m})^t$.

Notation 1.7 (Entrywise product). Given two matrices A and B with the same dimensions, $A \circ B$ will refer to the entrywise (or Hadamard) product of A and B, namely $(A \circ B)_{ij} = A_{ij}B_{ij}$.

2. Periodic orbits

We remind the reader of some standard results from Floquet theory (Chapters 3 and 4 of [34] for example) as needed here. Let $X \subseteq \mathbb{R}^r$ be open, $F : X \to \mathbb{R}^r$ be C^1, and consider the ODE

$$\dot{x} = F(x) \tag{2.1}$$