Analytical Solution of Steady-State Equations for Chemical Reaction Networks with Bilinear Rate Laws

Ádám M. Halász, Hong-Jian Lai, Meghan McCabe Pryor, Krishnan Radhakrishnan, and Jeremy S. Edwards

Abstract—True steady states are a rare occurrence in living organisms, yet their knowledge is essential for quasi-steady-state approximations, multistability analysis, and other important tools in the investigation of chemical reaction networks (CRN) used to describe molecular processes on the cellular level. Here, we present an approach that can provide closed form steady-state solutions to complex systems, resulting from CRN with binary reactions and mass-action rate laws. We map the nonlinear algebraic problem of finding steady states onto a linear problem in a higher-dimensional space. We show that the linearized version of the steady-state equations obeys the linear conservation laws of the original CRN. We identify two classes of problems for which complete, minimally parameterized solutions may be obtained using only the machinery of linear systems and a judicious choice of the variables used as free parameters. We exemplify our method, providing explicit formulae, on CRN describing signal initiation of two important types of RTK receptor-ligand systems, VEGF and EGF-ErbB1.

Index Terms—Chemical reaction networks, cell signaling, VEGF, EGF, linear conservation laws, analytical solution, bilinear systems, minimally parameterized solutions

1 INTRODUCTION

Chemical reaction networks (CRN) are a mainstay of mathematical modeling of molecular processes on the level of living cells. Much of the knowledge accumulated over the past half century on the detailed functionality of cells is naturally rendered in terms of elementary transformations of biomolecular species and their corresponding rate laws [1], [2], [3]. In the traditional CRN framework, the amounts of different substances are represented by continuous quantities (concentrations), and evolve according to deterministic rate laws, that define a set of ordinary differential equations (ODE). The applicability of ODE models is limited by two underlying assumptions [4], namely spatial homogeneity, and large numbers of molecules, allowing us to treat concentrations as continuous quantities.

By contrast, living cells exhibit a complex spatial structure, with length scales orders of magnitude smaller than the cells, and may contain few copies of important molecular entities. It is important to distinguish between employing CRN terminology as an empirical description, and using the well-mixed, continuum framework of chemical reaction networks as an exact, physical description of biomolecular processes.

With the appropriate caveats, ODE models provided much insight [5], [6], [7] and continue to be relevant at all levels of biological modeling [8], [9], [10], [11]. They naturally arise as effective models describing the dynamics of globally or locally averaged properties, such as the amount of a substance localized in a specific region of the cell (rather than actual concentrations). In addition, effective models based on simplified kinetics are crucial in interpreting experimental data and relating to the underlying processes. Effective kinetic parameters obtained experimentally may be all that is needed for a given application, or may serve as a starting point for analysis aimed at the true, molecular level kinetics [12], [13].

ODE models derived from biomolecular networks are often nonlinear and high dimensional, making simulation and analysis challenging. Steady-state analysis and approximations built on steady states are important means to reduce computational costs and to gain insight in the functionality of the system [8], [10], [14], [15]. Except for a few simple cases, analytical solutions to the corresponding nonlinear algebraic equations are thought of as hard to obtain and not worth the effort in comparison with widely available numerical tools. However, the advantages of an exact solution are numerous, ranging from easier parameter sensitivity and stability analysis, more efficient fitting procedures, to better insight into the role of different
processes or parameters. The widespread availability of computer algebra systems\(^1\) can make complex analytical calculations manageable. In this context, we believe that well thought out strategies to obtain analytical solutions may be valuable, and provide additional insight for systems such as signaling networks.

In this work, we identify a class of bimolecular chemical reaction networks for which a complete set of analytical solutions can be obtained, in a manner similar to systems of linear algebraic equations. The central idea is to linearize the system of equations by introducing a new variable for each bilinear term. The resulting system of linear equations is underdetermined by at least the number of new variables, and can be solved exactly using a subset of the variables as free parameters. We select the free variables in a way to implement the bilinear constraints,\(^2\) eliminate the dummy variables, and/or parameterize the set of solutions in terms of a minimal subset of the original variables. We identified two types of tractable problems, based on the number of variables, linear conservation laws (LCL), bilinera, and the number of variables that participate in bilinera. We describe solution strategies that can be applied to these types of systems without a limit to their dimensionality, and which may be useful in future applications based on automated analysis [16, 17, 18, 19, 20].

The remainder of the paper is organized as follows: In Section 2, we begin by defining the type of system we wish to investigate and illustrate the difficulty in solving the steady-state equations in a nonlinear context. We remind the reader about the terminology and role of conservation laws in the geometry of the solutions of a linear system. Section 3 presents our theoretical results. We first describe the linearization procedure and relate the rank deficiency of the linearized system to the size and number of conservation laws of the original, bilinear system. We then use a simple example to illustrate how the superfluous parameters may be eliminated, and the nonlinear constraints may be imposed by using only the machinery of linear systems. In Section 3.3, we generalize the method, and define two types of bilinear problems that can be solved, either directly or with a secondary procedure that has wider applicability. Sections 4 and 5 are devoted to examples from cell signaling that are solved using the secondary procedure. The final section summarizes our results, presents a more comprehensive description of the two versions of our method, and discusses possible applications and extensions of this work.

2 Problem Statement

We consider a system of \(N\) chemical species that participate in \(M\) chemical reactions. The state of the system is described by a vector of concentrations \(X = (X_1, \ldots, X_N)^T \in \mathbb{R}^N\), whose time evolution is determined by the stoichiometry coefficients \(\gamma_i\) and the rate laws \(\phi_j(X)\) of the reactions. A summary of definitions and basic relations is provided in Appendix A, which can be found on the Computer Society Digital Library at http://doi.ieeecomputersociety.org/10.1109/TCBB.2013.41. Formally,

\[ dX_i/dt = \sum_{j=1}^{M} \gamma_{ij} \phi_j(X) \equiv \psi_i(X_1, \ldots, X_N) \quad (\forall i \leq N). \]  

**Definition 1.** A chemical reaction network is a dynamical system with equations of motion

\[ \frac{dX_i}{dt} = \sum_{j=1}^{M} \gamma_{ij} \phi_j(X) \equiv \psi_i(X_1, \ldots, X_N) \quad (\forall i \leq N). \]  

The properties of the rate functions \(\psi_i(X)\) derive from the specific form of the rate laws.\(^3\) We focus on mass-action systems (see Appendix A (A.71) in the online supplemental material) that have first- and second-order processes, as exemplified by the forward \((\phi_{on})\) and backward \((\phi_{off})\) rates of the following reactions:

\[ \begin{align*}
R + L & \xrightarrow{\kappa_{on}} RL; \\
\phi_{on} &= \kappa_{on}[R][L]; \\
\phi_{off} &= \kappa_{off}[RL]; \\
\frac{d[R]}{dt} &= \frac{d[L]}{dt} = -\frac{d[RL]}{dt} = \phi_{off} - \phi_{on}.
\end{align*} \]

**Definition 2.** A CRN (1) is bilinear if its rate functions \(\psi_i()\) are bilinear:

\[ \frac{dX_i}{dt} = \psi_i(X_1, \ldots, X_N) = S_i + \sum_{j=1}^{N} a_{ij} X_j + \sum_{j,k=1}^{N} b_{ijk} X_j X_k \quad (\forall i \leq N). \]

In matrix notation, with \(S \in \mathbb{R}^N\), \(A \in \mathbb{R}^{N \times N}\), \(B_i \in \mathbb{R}^{N \times N}\), and \(e_i\) vectors in a standard basis,

\[ \frac{dX}{dt} = \Psi(X) = S + A \cdot X + \sum_{i=1}^{N} e_i (X^T \cdot B_i \cdot X). \]

Constant terms in \(S = (S_1, \ldots, S_N)^T\) may arise from external fluxes (e.g., \(\emptyset \rightarrow X_i\)). The entries of \(A = \{a_{ij}\}_{i,j=1}^{N}\) represent linear terms resulting from unimolecular reactions \((X_i \rightarrow X_i)\). The bilinear terms \(B_i = \{b_{ijk}\}_{i,j,k=1}^{N}\) result from bimolecular reactions \((X_j + X_k \rightarrow X_i)\).

**Remark 1.** In Definition 2, only the symmetric parts of \(B_i\) contribute to the equation of motion: \(X^T \cdot B_i \cdot X = (X^T \cdot B_i \cdot X)^T = X^T \cdot B_i^T \cdot X = \frac{1}{2} X^T \cdot (B_i + B_i^T) \cdot X\). Hereafter we assume, without loss of generality, that the coefficients are symmetric, \(B_i = B_i^T\).

We seek steady-state solutions \(X = (X_1, \ldots, X_N)^T\) to the equations of motion (3):

\[ \psi_i(X_1, \ldots, X_N) = 0 \quad (\forall i \leq N). \]

Some of the \(N\) equations in (5) may be functionally dependent on the others, in the sense that every \(X\) that satisfies a subset of equations \(\{\psi_i(X) = 0\}\) is also a solution of equation \(\psi_i(X) = 0\). This implies that there is a function \(F() : \mathbb{R}^{2N-1} \rightarrow \mathbb{R}\) such that:

\[ 3.\] Concentrations must be nonnegative; therefore, (1) should ensure that if \(X(0) \in \mathbb{R}^N_+\), then \(X(t) \in \mathbb{R}^N_+\). We will check that our arguments are consistent with physically meaningful states but will not use this property in our derivations.

4. The reader may note a superficial similarity with the continuous time Riccati equation [21] from optimal linear control with quadratic cost, \(P = -Q - PA - A^T P + PBB^T P\). Here, the unknown \(P\) as well as \(A, B, B^T, P\) are \(n \times n\) square matrices. The two problems coincide in the trivial case \((n = 1)\), but there is no obvious mapping between them for \(n > 1\).
\[ \psi_1(X) = F(X; \psi_2(X), \ldots, \psi_N(X)), \quad \text{and} \]
\[ F(X; 0_{N-1}) = 0, (\forall) X \in \mathbb{R}^N. \]

Each independent equation represents an algebraic constraint on the \( N \) variables. If \( N_D < N \) of the equations are independent, the set of solutions is infinite, parameterized by \( N_T = N - N_D \) variables. If all \( N \) equations are independent, the number of solutions is at most finite.

Linear functions of the form \( \psi_i(X) = F(X; \psi_2, \ldots, \psi_N) = \psi_2 \psi_3 + \cdots + \psi_N \) \( \in \mathbb{R}^N \) \((\text{where} \ d_i \text{are constants})\) are an important type of functional dependence, corresponding to linear conservation laws (to be introduced in (8)). Nonlinear equations may be linearly independent and imply one another. For instance, the equations \( \psi_1 = k[A] - \lambda[B] = 0 \) and \( \psi_2 = \alpha \lambda[A][B] - \alpha \lambda[A]^2 \) are linearly independent, yet they are not independent since \( \psi_2 = -\alpha[A] \psi_1 \) and \( \psi_1 = 0 \) imply \( \psi_2 = 0 \).

Nonlinear relations of this sort may be coincidental or may reflect deeper physical principles, and a general discussion is beyond the scope of the present work. Hereafter, we will assume that the only functional dependencies (6) among the equations of motion (3) are linear.

Obtaining solutions is not straightforward. A possible strategy is successive elimination. We solve an equation for one variable as a function of the others, and substitute into the remaining equations. The resulting system has one less equation and one less variable, and the reduction step may be repeated to arrive at a single equation in one variable. This approach works indefinitely for linear systems, but it can quickly become intractable if the rate functions \( \psi_i(X) \) are more complicated. Even with a single bilinear term in (3), solving for one variable may result in a second-order polynomial function, a rational function, or a more complicated expression involving radicals:

\[ S_i = \frac{a_{11}X_1 + a_{12}X_2 + \cdots + a_{1k}X_k}{a_{11}}. \]

Successive elimination steps typically lead to polynomials of increasing algebraic degrees.

**2.1 Linear Conservation Laws**

Linear conservation laws (LCLs) ensure that certain linear combinations of the concentrations remain constant during the evolution of a chemical reaction network. The number of independent variables in a CRN is constrained by that of independent LCL. We will show that, similarly to the linear case, the latter gives the number of free parameters in the set of steady states of (3).

**Definition 3.** A vector \( \mathbf{W} \in \mathbb{R}^N \) is a linear conservation law to the CRN (1) if it is nonzero, and is orthogonal to the rate functions \( \Psi(X) \) for all \( X \):

\[ \mathbf{W}^T \cdot \Psi(X) = 0 (\forall) X \in \mathbb{R}^N. \]

The name “conservation law” given to a vector \( \mathbf{W} \perp \Psi(X) \) refers to the following property.

**Remark 2.** Definition 3 implies that if \( X(t) \) is a solution of (1), the quantity \( \mathbf{W}^T \cdot X(t) \) is constant.

5. The solution of a linear equation is a linear function, as is the composition of two linear functions.

\[ \frac{d}{dt} (\mathbf{W}^T \cdot X(t)) = \mathbf{W}^T \cdot \frac{dX}{dt} = \mathbf{W}^T \cdot \Psi(X(t)) = 0. \]

We will denote by \( N_C \) the number of linearly independent LCL of the equations of motion (3). Conservation properties typically result from the stoichiometry of the system, rather than the specific form of the rate laws, and therefore apply to the equations of motion even if the rate laws are nonlinear. Next we will show that linear conservation laws that apply to a bilinear system are orthogonal to the constant, linear, and bilinear parts of \( \Psi(X) \) taken separately.

**Theorem 1.** Let \( \mathbf{W} \) be an LCL for the bilinear system (3), and let \( \Psi_A(X) = \mathbf{A} \cdot X \) and \( \Psi_B(X) = \sum_{i=1}^{N_c} \alpha_i \mathbf{X}^T \cdot B_i \cdot X \) denote the linear and bilinear parts of \( \Psi(X) \). Then, \( \mathbf{W} \) is orthogonal to each of \( \Psi_A(X) \) and \( \Psi_B(X) \), for any \( X \in \mathbb{R}^N \).

**Proof.** Consider a fixed \( X \in \mathbb{R}^N \). For \( V \in \mathbb{R}^N \) and \( a \in \mathbb{R} \), define \( U_a(V) = V^T \cdot \Psi(aX) \). For any fixed \( V \), \( U_a(V) \) is a real, quadratic polynomial in \( a \):

\[ U_a(V) = V^T \cdot \mathbf{S} + a(V^T \cdot \Psi_A(X)) + a^2(V^T \cdot \Psi_B(X)). \]

Since \( \mathbf{W} \perp \Psi(Y) (\forall) Y \in \mathbb{R}^N \), setting \( Y = aX \) we find that \( U_a(W) = 0 (\forall) a \in \mathbb{R} \). The three parts of the claim follow using linear combinations of \( U_a(W) = 0 \) for specific values of \( a \):}

\[ \mathbf{W}^T \cdot \mathbf{S} = \frac{1}{3} \left[ -6U_1(W) + U_2(W) + 8U_3(W) \right] = 0, \]
\[ \mathbf{W}^T \cdot \Psi_A(X) = 5U_1(W) - U_2(W) - 4U_3(W) = 0, \]
\[ \mathbf{W}^T \cdot \Psi_B(X) = \frac{2}{3} \left[ -3U_1(W) + U_2(W) + 2U_3(W) \right] = 0. \]

The above reasoning applies to any \( X \in \mathbb{R}^N \), since we made no additional assumptions.

Next, we will clarify the relation between the set of linearly independent LCL of (3) and the coefficient matrices. Recall [22] that for any \( N_{rows} \times N_{cols} \) matrix \( \mathbf{M} \), \( V \in \mathbb{R}^{N_{rows}} \) is a left null vector (LVN) of \( \mathbf{M} \) if \( \mathbf{V}^T \cdot \mathbf{M} = 0 \). The rank of a matrix is the number of linearly independent columns or rows. Each LVN represents a linear combination of the rows that is identically zero. Thus, the rank is the number of rows, less the number of linearly independent LVN:

\[ N_{LVN} + \text{rank}(\mathbf{M}) = N_{rows}. \]

**Remark 3.** If \( \mathbf{W} \) is an LCL to (3) then it is a LVN of \( \mathbf{A} \) and the extended matrix \( [\mathbf{S} | \mathbf{A}] \):

\[ \mathbf{W}^T \cdot \Psi_A(X) = \mathbf{W}^T \cdot \mathbf{A} \cdot X = 0 (\forall) X \in \mathbb{R}^N \Rightarrow \mathbf{W}^T \cdot \mathbf{A} = 0 \]
\[ \mathbf{W}^T \cdot [\mathbf{S} | \mathbf{A}] = [\mathbf{W}^T \cdot \mathbf{S} | \mathbf{W}^T \cdot \mathbf{A}] = [0 | 0_N] = 0_{N+1}. \]

The LCL of (3) are not LVN to the \( \mathbf{B}_i \) matrices; the relation with \( \Psi_B(X) \) is the following.

**Remark 4.** If \( \mathbf{W} \equiv (w_1, \ldots, w_N)^T \) is an LCL (3), then \( \sum_{i=1}^{N_c} w_i \mathbf{B}_i = 0_{N \times N} \).

**Proof.** Let \( \mathbf{Q} \equiv \sum_{i=1}^{N_c} w_i \mathbf{B}_i \). For \( X \in \mathbb{R}^N \), \( \mathbf{W}_i^T \mathbf{Q} = \sum_{i=1}^{N_c} w_i (X^T \cdot \mathbf{B}_i \cdot X) = X^T \cdot \mathbf{Q} \cdot X \). By Definition 2, \( \mathbf{B}_i = \mathbf{B}_i (\forall) 1 \leq i \leq N \); therefore, \( \mathbf{Q} = \mathbf{Q} \). By Theorem 1,
\[ W^T \Psi_B(X) = 0; \text{ therefore, } X^T \cdot Q \cdot X = 0 \text{ for all } X \in \mathbb{R}^N. \]

We can show that \( X^T \cdot Q \cdot Y = 0 \) for any \( X, Y \in \mathbb{R}^N \):

\[ 0 = (X^T + Y^T) \cdot Q \cdot (X + Y) = X^T Q X + Y^T Q Y + X^T Q Y + Y^T Q X = 2X^T \cdot Q \cdot Y, \]

implying that every entry of \( Q \) is zero.

We have shown that every LCL is an LNV to \( A \) and \( S \), but the reciprocal is not necessarily true.

**Remark 5.** If \( N_C \) is the number of linearly independent LCL of (3), then

\[ \text{rank}(A) \leq \text{rank}(S|A) \leq N - N_C. \quad (13) \]

A similar analysis can be done for the number of linearly independent vectors orthogonal to the bilinear part \( (\forall Y) \in \mathbb{R}^N \) such that \( W^T \cdot \Psi_B(X) = 0 \). By Theorem 1, an LCL to the complete system (3) must be a null vector to \( \Psi_B \), but the reciprocal is not necessarily true.

**Note:** Physically meaningful states in a CRN must be nonnegative, \( X \in \mathbb{R}^+ \). The proof of Theorem 1 would remain valid even with his restriction: \( W \in \mathbb{R}^N \), s.t. \( W \perp \Psi(X) \), \( (\forall X) \in \mathbb{R}^+ \) implies \( W \perp \{S, \Psi_A(X), \Psi_B(X)\} \), \( (\forall X) \in \mathbb{R}^N \), and Remarks 3 and 4 can still be easily proven. In turn, this would imply \( W \perp \Psi(X) \) for all \( X \in \mathbb{R}^N \), without the positivity restriction.

### 2.2 The Linear Case

Setting \( B_i = 0 \) \((\forall i) \leq N \), the equations of motion (3) and steady-state conditions (5) become

\[ \frac{dX_i}{dt} = \psi_i(X) = S_i + \sum_{j=1}^{N} a_{ij} X_j \quad (\forall 1 \leq i \leq N) \]

and \( S + A \cdot X = 0 \).

By Theorem 1, a linear conservation law to (14) will be orthogonal to \( S \) and \( A \); this is now also a sufficient condition for a LCL, changing the second inequality of (13). By the Kronecker-Capelli theorem [22], the linear system (14) has solutions if and only if rank \( (A) = \text{rank}(S|A) \).

**Remark 6.** A vector \( W \in \mathbb{R}^N \) is an LCL to the linear CRN (14), if and only if it is an LNV to the extended matrix \( [S|A] \). If \( N_C \) is the number of independent LCL, then

\[ \text{rank}(A) \leq \text{rank}(S|A) \leq N - N_C. \quad (15) \]

The inequality is replaced by equality if the equations of motion (14) have steady-state solution(s).

The rank of the linear system (14) is \( N_D = N - N_C \), allowing us to solve for \( N_D \) dependent variables as a function of the remaining \( N_F = N_C \) free variables. The calculation proceeds by moving the free variables to one side together with the constant terms, discarding \( N_F \) equations, and solving the resulting \( N_D \)-dimensional system using Cramer's rule. The choice of dependent variables and discarded equations must ensure that the remaining system matrix is nonsingular.

Our goal is to devise an analogous method for bilinear systems that provides 1) a direct estimation of the number of independent equations in terms of the rank of a matrix and 2) an explicit solution of the steady-state equations in terms of a minimal set of parameters, in terms of rational functions whose coefficients can be calculated directly from the model constants.

### 3 Steady States of Systems with Bilinear Dynamics

We denote the number of bilinears in the equations of motion (3) by \( N_B \), and the number of variables that appear in at least one bilinear, by \( N_P \). As before, \( N_C \) is the number of independent LCL. Given \( N \) species, there are \( \frac{N}{2} \) possible distinct bilinears. In networks where most species only interact with a handful of others, \( N_B \) will be generally much smaller than \( \frac{N}{2} \). If a significant subset of species only participate in simple transformations \( (A \rightarrow B) \), \( N_P \) will be significantly less than \( N \).

Note that \( N_B \) represents bilinear *types* defined by the identity of the two participating variables. We denote bilinears by \( \{Y_i\}_{i=1 \ldots N_B} \) and by \( \{a_{ij}, a_{il}\}_{i=1 \ldots N_B} \) the indices of the variables that form the bilinear:

\[ Y_i \equiv X_{a_{i}, a_{i}}; \quad 1 \leq a_i \leq b_i \leq N; \quad 1 \leq l \leq N_B. \quad (16) \]

For example, the following set of variables and bilinears

\[ X = \{X_1, X_2, X_3, X_4\}; \quad Y = \{X_{1,2}, X_{1,3}^2, X_{1,4}\}, \]

(17) corresponds to: \( N = 4 \), \( N_B = 3 \) (three distinct bilinears). \( N_P = 3 \) (three variables appearing in bilinears), \( (\alpha, \beta) = (1, 2) \) and the full set of \( \alpha, \beta \) coefficients is

\[ \{a_{ij}, a_{il}\}_{i=1 \ldots 3} = [(1, 2), (1, 1), (1, 4)]. \quad (18) \]

The relabeling of bilinears is similar to the representation of sparse matrices. For a given ordering \( (\alpha, \beta): \{1 \ldots N_B\} \rightarrow \mathbb{B} \) of the pairs of indices with nonzero bilinear terms in (3), \( \mathbb{B} = \{(\alpha, \beta) \mid \alpha \leq \beta, (\exists i \text{ s.t. } a_{\alpha \beta} \neq 0\} \), we define linearized coefficients \( c_{i\alpha} \) as follows:

\[ c_{i\alpha} = b_{i\alpha} = \psi_i(X) (\forall 1 \leq i \leq N; 1 \leq \alpha \leq N_B). \quad (19) \]

The factor \( 2 - \delta_{\alpha \beta} \) avoids the double counting of quadratic terms. Different choices of the ordering in (19) correspond to permutations of the nonzero bilinears; hereafter, we assume that one such mapping was selected and is used consistently. The linearized version of (3) is

\[ \frac{dX_i}{dt} = S_i + \sum_{j=1}^{N} a_{ij} X_j + \sum_{l=1}^{N_B} b_{i\alpha} X_{a_{i}, a_{i}} X_{a_{l}, a_{l}} \equiv \psi_i(X). \quad (20) \]

We can now analyze the bilinear part \( \psi_i(X) \) in terms of the \( N \times N_B \) bilinear matrix \( C \equiv \{c_{i\alpha}\} \).

**Remark 7.** For a bilinear CRN (3) and (20), a vector \( W \in \mathbb{R}^N \) is orthogonal to the bilinear part of the equation of motion \( \psi_B(X) = \sum_{i=1}^{N} \psi_i(X) \|\mathbf{S|B}, X \), if and only if \( W^T \cdot C = 0 \).

7. The bilinears are symmetric (i.e., \( X_j X_k = X_k X_j \)), so we adopt the convention that the smaller index is always first: \( \alpha_i \leq \beta_i \).

8. Recall that we defined the bilinear CRN with symmetric bilinear coefficients, \( b_{i\beta} = b_{ji} \).
Proof. If $W^T \cdot C = 0$, then $\sum_{i=1}^{N} w_i c_{i\ell} = 0 \ (\forall \ell)$; by (19) and the definition of $\Psi_B$ we have:

$$W^T \cdot \Psi_B(X) = \sum_{i=1}^{N} w_i \sum_{j=1}^{N} b_{i,j \alpha} X_j X_{\alpha} = \sum_{i=1}^{N} w_i \sum_{i=1}^{N} b_{i,0\alpha} X_{\alpha} X_{\beta} = \sum_{i=1}^{N} w_i c_{i\alpha} X_{\alpha} X_{\beta} = 0.$$

We have shown (see Remark 4) that $W^T \cdot \Psi_B(X) = 0 \ \ (\forall) X \in \mathbb{R}^N$ implies $\sum_{i=1}^{N} w_i b_{i,p \alpha} = 0$, which is equivalent to $\sum_{i=1}^{N} w_i b_{i,p \alpha} = 0$, $\ (\forall) p, q$. Choosing $(p, q) = (a, \beta)$, we have $\sum_{i=1}^{N} w_i b_{i, a \beta} = 0 \ (\forall) i$. By (19), this implies $\sum_{i=1}^{N} w_i c_{i\alpha} = 0 \ (\forall \alpha)$, i.e., $W^T \cdot C = 0$. □

This result allows us to characterize LCL as LNV of the matrix $C$, similarly to (13).

Remark 8. For the $N$-dimensional bilinear CRN (3) and (20),

1. If $\mathbf{W} \in \mathbb{R}^N$ is a LCL to (3), then $\mathbf{W}$ is a left null vector of the bilinear matrix $C$.

2. If the system (3) has $N_C$ linearly independent LCL, then $\text{rank}(C) \leq N - N_C$.

Our main theoretical result is that the linearized system matrix $\mathbf{S} | A | C$ relates to the linear conservation laws of the system (3) the same way as $\mathbf{S} | A$ does in the linear case (15).

Theorem 2. For a bilinear CRN (3) and (20),

1. A vector $\mathbf{W} \in \mathbb{R}^N$ is an LCL to the system (19) if and only if $W^T \cdot | S | A | C = 0$.

2. If $N_C$ is the number independent LCL, then $N_C + \text{rank}(S | A | C) = N$.

Proof. Any LCL $\mathbf{W}$ is a left null vector to (see Remark 3) $| S | A | C$ and (see Remark 8) $| S | A$; therefore, it is an LNV of the joint matrix, $W^T \cdot | S | A | C = 0$. Conversely, if $\mathbf{V}$ is an LNV to $| S | A | C$, it is an LNV to $| S | A | C$ and $| S | A$ to each of $\mathbf{S}, \mathbf{A}, \mathbf{C}$. Thus, $V^T \cdot S = 0$, $V^T \cdot | S | A | C = 0$; $V^T \cdot | S | A | C = 0$, and (see Remark 7) $V^T \cdot | S | A | C = 0$; since $\Psi(X) = S + \Psi_A(X) + \Psi_B(X)$, this implies $V^T \cdot \Psi(X) = 0 \ (\forall) X$. (2) by (1) $N_{\text{LCL}}(S | A | C) = N_C$, and the claim follows by (12). □

3.1 Linearization and Dummy Variables

We replace the $N_B$ bilinears with new variables (16) and (19) in the steady-state equations for (20):

$$S_i + \sum_{j=1}^{N} a_{ij} X_j + \sum_{i=1}^{N_B} c_{i\alpha} Y_{\alpha} = 0 \ \ (\forall \alpha \leq i \leq N) \quad \text{or}$$

$$\mathbf{S} + \mathbf{A} \cdot \mathbf{X} + \mathbf{C} \cdot \mathbf{Y} = 0.$$

and rewrite (21) in terms of an extended state vector and an $N \times (N + N_B)$ linear matrix:

$$\mathbf{S} + \mathbf{A}_E \cdot \mathbf{X}_E = 0, \ \text{where} \ \mathbf{A}_E \equiv | \mathbf{A} | \mathbf{C},$$

$$\mathbf{X}_E \equiv [X_1, \ldots, X_N, Y_1, \ldots, Y_{N_B}].$$

Remark 9. $\mathbf{X} \in \mathbb{R}^N$ is a steady-state solution of a bilinear CRN (3) linearized by (19) and (20), if the vector $\mathbf{Z} \in \mathbb{R}^{N + N_B}$, $\mathbf{Z} = [X_1, \ldots, X_N, X_{\alpha}, X_{\beta}, \ldots, X_{\alpha N_B}, X_{\beta_{N_B}}]$, satisfies (22).

Proof. By direct substitution: Given $\mathbf{X}$, the above-defined $\mathbf{Z}$ verifies (22). Given a solution $\mathbf{Z}$ of (22) that also verifies $Z_{N+1} = Z_{N} Z_{\beta} (\forall \alpha \leq l \leq N_B)$, we substitute the latter into the former and find that the first $N$ components of $\mathbf{Z}$ (i.e., $\mathbf{X}$) satisfy the steady-state equations of (3).

We have recast the problem of finding solutions $\mathbf{X} \in \mathbb{R}^N$ to the nonlinear steady-state equations (3) as finding $\mathbf{X}_E \in \mathbb{R}^{N + N_B}$ to satisfy (21), and then imposing $N_B$ constraints on the components:

$$\mathbf{Y}_i = \bar{X}_{\alpha_i \beta_i}, \ \ 1 \leq i \leq N_B. \quad (23)$$

Remark 10. If the bilinear CRN (3) has $N_C$ independent LCL and the system has at least one steady-state solution, then its linearized version (19) and (21) satisfies

$$\text{rank}(A_E) = \text{rank}(S | A | C) = N - N_C. \quad (24)$$

Proof. By Theorem 2 and (22), $\text{rank}(S | A | C) = N - N_C$. If the system (3) has a steady state, the linear system (21) must be consistent; therefore, $\text{rank}(S | A | C) = \text{rank}(A_E)$. □

This result is in complete analogy with the linear case (15). Therefore, we can solve (21) for $N_B = N - N_C$ of the variables, leaving $N_F = N_B + N_C$ as parameters. We will then attempt to use the $N_B$ constraints to eliminate $N_B$ of the parameters, leaving the complete set of steady-state solutions properly parameterized by $N_C$ free parameters.

3.2 A Simple Example

We first discuss a simple example to illustrate our method. Consider the system of reactions:

$$A + A \frac{1}{2} \mathbb{B}; \quad \mathbb{B} \rightarrow C + \mathbb{D}; \quad C \rightarrow A; \quad D \rightarrow A + E; \quad E \rightarrow \emptyset. \quad (25)$$

Denote the vector of concentrations by $\mathbf{X} = [A, B, C, D, E]^T$, the vector of reaction rates by $\mathbf{\Phi} = \phi(X) \ldots \phi(E)$ and the stoichiometry matrix by $\Gamma$. Assume that all reaction rates are mass-action with constants by $k_1, k_2, \ldots$. The rate of change for each species is determined by the reaction rates and the appropriate stoichiometric coefficients, $dX/dt = \Gamma \cdot \mathbf{\Phi}(X) = \Psi(X)$:

$$\begin{pmatrix} A \\ B \\ C \\ D \\ E \end{pmatrix} = \begin{pmatrix} -2 & 0 & 1 & -1 & 1 \\ 1 & -1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 1 & 0 & -1 \\ 0 & 0 & 0 & 0 & -1 \end{pmatrix} \begin{pmatrix} k_1 A^2 \\ k_2 B^3 \\ k_3 C^4 \\ k_4 D^5 \\ k_5 E^7 \end{pmatrix}. \quad (26)$$

The equations can be rearranged to separate the linear and bilinear dependence, as in (3).

9. The empty set (0) in a reaction equation stands for substances that are not accounted for explicitly in the model, either because their amount is irrelevant or can be assumed constant.
\[
\begin{bmatrix}
[A] \\
[B] \\
[C] \\
[D] \\
[E]
\end{bmatrix} = 
\begin{bmatrix}
-k_5 & 2k_2 & k_4 & k_6 & 0 \\
0 & -(k_2 + k_3) & 0 & 0 & 0 \\
k_5 & k_3 & -k_4 & 0 & 0 \\
0 & k_3 & 0 & -k_6 & 0 \\
0 & 0 & 0 & k_6 & -k_7
\end{bmatrix}
\]

\[
\frac{d}{dt} = 1 (77)
\]

We seek the steady states of this system, sets of concentration values \( \mathbf{X} = (A, B, C, D, E) \) for which the expression on the right-hand side of the equations of motion (26) and (27) is identically zero. We replace the quadratic term with a “dummy” variable \( [A]^2 \rightarrow Y \) in the steady-state equations, arriving at a linear system of five equations and six variables,

\[
\begin{bmatrix}
-k_5 & 2k_2 & k_4 & k_6 & 0 & -2k_1 \\
0 & -(k_2 + k_3) & 0 & 0 & 0 & k_1 \\
k_5 & k_3 & -k_4 & 0 & 0 & 0 \\
0 & k_3 & 0 & -k_6 & 0 & 0 \\
0 & 0 & 0 & k_6 & -k_7 & 0
\end{bmatrix}
\begin{bmatrix}
\mathbf{A} \\
\mathbf{B} \\
\mathbf{C} \\
\mathbf{D} \\
\mathbf{E}
\end{bmatrix} = 0.
\]

(28)

The five equations are not linearly independent, reflecting the existence of a single conservation law to the original system (26), \( W = (1, 2, 1, 0, 0) \). Consistently with this, the rank of the linear system (28) is 4 (if the kinetic constants are nonzero). We can discard any one of the equations, except for the last one, whose loss would reduce the rank. We discard the first equation. The remaining system is underdetermined by 2; we can choose two variables to treat as free parameters. Again, the choice is limited by the requirement that the remaining system must be full rank. This excludes the pairs \{B, Y\}, \{B, D\}, and \{D, E\}. However, we can select \{A, Y\}, which is helpful in the next step. After rewriting the system in this form:

\[
\begin{bmatrix}
-(k_2 + k_3) & 0 & 0 & 0 \\
k_5 & -k_4 & 0 & 0 \\
k_5 & 0 & -k_6 & 0 \\
0 & 0 & k_6 & -k_7
\end{bmatrix}
\begin{bmatrix}
\mathbf{B} \\
\mathbf{C} \\
\mathbf{D} \\
\mathbf{E}
\end{bmatrix} = k_5 \mathbf{A}
\]

we can apply Cramer’s rule and calculate the equilibrium values for \{B, C, D, E\}:

\[
\mathbf{B} = Y \cdot \frac{k_1}{k_2 + k_3}; \quad \mathbf{C} = \mathbf{A} \cdot \frac{k_5}{k_4} + Y \cdot \frac{k_1 k_3}{k_2 + k_3};
\]

\[
\mathbf{D} = Y \cdot \frac{k_1 k_3}{(k_2 + k_3)k_6}; \quad \mathbf{E} = \mathbf{Y} \cdot \frac{k_1 k_3}{(k_2 + k_3)k_7}.
\]

(30)

Thanks to the convenient choice of parameters, we can now simply replace \( Y \rightarrow \mathbf{Y} \) to retrieve the full set of solutions parameterized by \( \mathbf{A} \).

\[
\mathbf{B} = \mathbf{Y} \cdot \frac{k_1}{k_2 + k_3}; \quad \mathbf{C} = \mathbf{A} \cdot \frac{k_5}{k_4} + \mathbf{Y} \cdot \frac{k_1 k_3}{k_2 + k_3};
\]

\[
\mathbf{D} = \mathbf{Y} \cdot \frac{k_1 k_3}{(k_2 + k_3)k_6}; \quad \mathbf{E} = \mathbf{Y} \cdot \frac{k_1 k_3}{(k_2 + k_3)k_7}.
\]

(31)

The existence of multiple solutions does not reflect an ambiguity. The conservation law mentioned above guarantees that the combination \( A_{\text{total}} = [A] + 2[B] + [C] + [D] \) remains constant during the evolution of the system. This quantity can be expressed in terms of \( \mathbf{A} \), as follows:

\[
A_{\text{total}} = \mathbf{A} \left[ 1 + \frac{k_5}{k_4} + \frac{k_1 k_3}{k_2 + k_3} \left( \frac{2}{k_3} + \frac{1}{k_6 + k_7} \right) \right].
\]

(32)

The expression on the right-hand side is a monotonically increasing function of \( \mathbf{A} \) (for positive values of \( \mathbf{A} \) and of the \( k \) constants) and, therefore, there is a one-to-one correspondence between the positive values of the parameter \( \mathbf{A} \) and those of the conserved quantity \( A_{\text{total}} \). This guarantees that the system has exactly one steady-state consistent with any physically possible initial condition.

### 3.3 Classes of Exactly Solvable Bilinear Problems

We are interested in generalizing the ideas outlined above to a large class of systems. Depending on the number of species \( N \), conservation laws \( N_C \), bilinears \( N_B \), and species participating in bilinears \( N_P \), the steady-state equations may be amenable to a straightforward solution, with virtually no limitation on the size of the system. In the previous example, we were able to obtain a direct solution because the number of free variables in the expanded linear system was large enough, allowing us to use both the bilinear \( [A]^2 \) as well as the original variable \( [A] \) as free parameters. The goal of eliminating the dummy variable and reducing the number of free parameters to that dictated by the number of conservation laws was readily accomplished by direct substitution.

The set of solutions we obtained was complete, in the sense that for any solution of the original steady-state problem, there exists value of the parameter \( \mathbf{A} \) that reproduces the respective solution; conversely, any physically possible value of the parameter leads to a correct solution. The solutions are also unique, since there are no two \( \mathbf{A} \) values that lead to the same solution. Finally, the number of free parameters coincides with \( N_C = 1 \), the number of linearly independent conservation laws that apply to the complete system (27). We will refer to \( N_B = N - N_C \) as the (generalized) rank of the system and call a parametrization minimal if it uses exactly \( N_C \) of the original system variables.

We are interested in identifying bilinear systems for which complete, minimally parameterized sets of solutions can be obtained without directly solving nonlinear algebraic equations. Below we describe two such classes and outline the corresponding algorithms. We denote by \( \mathbf{X}_P \) the set of variables that participate in at least one bilinear and by \( \mathbf{X}_M \) those that do not; let \( \mathbf{A}_P \) and \( \mathbf{A}_M \) denote the analogous partition of \( \mathbf{A} \) (columns corresponding to \( \mathbf{X}_P \) and \( \mathbf{X}_M \)).
Type I systems. The straightforward calculation described in Section 3.2 is possible if the number of free parameters in the expanded system, \( N_F = N_C + N_B \), at least equals that of the bilinears, \( N_B \), plus the number of original variables that participate in them, \( N_P \). In a type I system, the column of constants \( S \), the dummy variables \( Y \), as well as the components of \( X_P \), are treated as free variables.

The conditions for a type I system are that 1) the number of linear conservation laws must at least equal that of original species involved in bilinears, and 2) the system matrix \( A_M \) left after removing the components of \( X_P \) must retain the full rank of the system, \( N - N_C \):

\[
1) N_P \leq N_C; \quad 2) \text{rank}(A_M) = N - N_C. \quad (33)
\]

Condition (2) is necessary and sufficient, and it implies the counting criterion (1).

Type II systems. A larger class of bilinear systems is amenable to minimally parameterized closed form solutions through a secondary procedure. The dimensionality requirement for this second approach is that the set of free variables is large enough to include the original variables that participate in bilinears,

\[
N_P \leq N_C + N_B. \quad (34)
\]

We assume that we can include some bilinears in the free set, leaving \( \Delta N \leq N_B \) of them.

The key element for type II is finding a clean set of at least \( \Delta N \) of the original variables. The clean set is a subset \( \Omega_X = \{X_{i,j}\} \leq \Delta N \) of \( X_P \) such that neither of the bilinears contains more than one of the \( X_{i,j} \) or are quadratic functions thereof. Given a clean set \( \Omega_X \), we proceed as follows: Select a set \( \Omega_Y \) of \( \Delta N \) representative bilinears so that each bilinear in \( \Omega_Y \) contains a different member of clean set \( \Omega_X \). The elements of \( \Omega_Y \) will be appended to \( X_M \) to form the dependent set of variables, \( X_{\text{dep}} \). The remaining bilinears, all the entries of \( X_P \), as well as \( S \) form the vector of free parameters, \( X_{\text{free}} \). The dependent system matrix \( A_D \) will consist of \( A_M \) and the part \( C_{ij} \) of \( C \) that corresponds to the chosen bilinears in \( \Omega_Y \). We can proceed to solve the linear system if

\[
\text{rank}(A_D) \equiv \text{rank}(A_M|C_{ij}) = N - N_C. \quad (35)
\]

With the solution of the linear system, we may readily substitute the definition of the bilinears that served as free parameters. We also proceed with the substitution in the \( \Delta N \) equations that involve bilinears as dependent variables. Because of the way we selected the dependent bilinears, we can treat the \( \Delta N \) resulting equations as a linear system in the \( \Delta N \) original variables of the clean set. Furthermore, since each member of \( \Omega_Y \) appears exactly once in the bilinear term, multiplied by a free parameter, this second linear system is full rank (\( \Delta N \)) and easily solved. The VEGF system (bivalent ligand, monovalent receptors that may dimerize) as well as the EGF system discussed in the next sections are members of this class.

4. STEADY STATES OF THE VEGF-VEGFR SYSTEM

Vascular endothelial growth factor [23] (VEGF) is a secreted protein, which binds to specific receptors that are located on the cell membrane and mediate signals related to angiogenesis (the growth of new blood vessels). VEGF is bivalent and its receptors are monovalent. VEGF receptors can dimerize directly or through cross-linking by ligand; a complex consisting of one VEGF ligand bound to two receptors is necessary for signal initiation. Several computational models of VEGF signal initiation were defined by MacGabhann et al. [24], [25], [26].

Here, we discuss a version with a single receptor type, based on [26]. We ignore internalization as well as de novo synthesis and insertion of receptors, and assume that the concentration \( V_0 \) of VEGF is kept constant. We denote the unbound (free) VEGF ligand by \( V \), and receptor monomers by \( R \). They may form the following combinations: RR (receptor dimer), VR (ligand-bound single receptor), VRR (ligand-bound receptor dimer), RVR (ligand bound to two unconnected receptors), and \( \Delta \) (fully bound complex of one ligand and two receptors). There are 14 separate (or seven reversible) reactions among these seven species:

\[
\begin{align*}
R + R & \rightleftharpoons \frac{1}{5} \text{RR}; \quad R + VR & \rightleftharpoons \frac{2}{9} \text{VRR}; \quad RR + V & \rightleftharpoons \frac{3}{10} \text{VRR}; \\
VRR & \rightleftharpoons \frac{4}{11} \Delta; \quad RVR & \rightleftharpoons \frac{5}{12} \Delta; \quad R + VR & \rightleftharpoons \frac{6}{15} \text{RVR}; \\
R + V & \rightleftharpoons \frac{7}{14} \text{VR}.
\end{align*}
\]

(36)

The reactions involve only two "rules" [3], the formation or dissociation of one of two types of bonds, \( R - R \) or \( V - R \). The corresponding rates in specific reactions may differ based on the molecular context, as follows: We denote by \( a \) the rate constant for \( V - R \) binding when the ligand \( V \) is in solution and the receptor \( R \) is membrane-bound (r3, r7). The constant for \( V - R \) binding when \( V \) is a part of another membrane surface-bound molecule is \( a_1 \) (r6), and \( a_1 \) when the process is internal, i.e., \( R \) and \( V \) are parts of the same molecule (r4). The constant for \( R - R \) binding from two separate molecules is \( b_2 \) (r1, r2), and \( b_1 \) when it is internal (r5). For dissociation constants, we distinguish between an internal breakup (which does not lead to the separation of the original molecule into two parts) and otherwise. For the \( V - R \) breakup, we have \( c \) with molecular separation (r10, r13, r14) and \( c_1 \) for internal (r11). Finally, the constant for \( R - R \) dissociation with separation is \( d \) (r8, r9) and \( d_1 \) when internal (r12). 10

Assuming the free VEGF concentration is kept constant at \( V_0 \), we have a 6D state vector \( X \equiv [R], [RR], [VR], [VRR], [RVR], [\Delta] \) and 14 (irreversible) reactions. It is convenient to group pairs of opposing reactions into single reversible reactions, 11 leaving us with seven reversible reactions. The stoichiometry matrix and the rate laws are as follows:

10. Further distinctions are possible and do not complicate the calculations. However, lacking reliable information on the actual molecular dynamics, these subtleties are not very useful.

11. For example, in the 14-reaction scheme (36), reaction 8 is the reverse of reaction 1, and in the seven-reaction scheme (37) both are represented by the reversible reaction 1. The label of the "new" joint reaction is that of the "old" forward reaction; the rate of the joint reaction is the algebraic sum of the corresponding forward and reverse rates, for example, \( \phi_1, \text{rev} \equiv \phi_1 - \phi_2 = b[R]^2 - d[R[R]]. \)
\[
\begin{pmatrix}
-2 & -1 & 0 & 0 & 0 & -1 & -1 \\
1 & 0 & -1 & 0 & 0 & 0 & 0 \\
0 & -1 & 0 & 0 & 0 & -1 & 1 \\
0 & 1 & 1 & -1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & -1 & 1 & 0 \\
0 & 0 & 0 & 1 & 1 & 0 & 0
\end{pmatrix}
\]

\[
\Phi(X) = b[\mathbf{R}]^2 + d[\mathbf{RR}] + b[\mathbf{R}] \cdot [\mathbf{VR}] - d[\mathbf{VRR}] + a_0[\mathbf{VRR}] - 2c[\Delta] + b_1[\mathbf{VR}] - b_1[\mathbf{V}] + a_1[\mathbf{VR}] - 2c[\mathbf{VR}] + a_0[\mathbf{V}] - 2c[\mathbf{V}] 
\]

In the resulting equations of motion \( \frac{d\mathbf{X}}{dt} = \Gamma \cdot \Phi(X) = \Psi(X) \), we formally rewrite the right-hand sides as linear combinations of an expanded vector \( \mathbf{X}_E \) that consists of the original variables of \( \mathbf{X} \), plus the binomials \([\mathbf{R}]^2\) and \([\mathbf{R}] \cdot [\mathbf{VR}]\):

\[
\mathbf{X}_E \equiv ([\mathbf{R}], [\mathbf{RR}], [\mathbf{VR}], [\mathbf{VRR}], [\mathbf{VRR}], [\Delta], [\mathbf{R}]^2, [\mathbf{R}] \cdot [\mathbf{VR}])^T.
\]

The resulting system is still 6D (six variables and six equations), but each equation of motion may contain the two possible bilinear terms

\[
\frac{d\mathbf{X}}{dt} = \begin{pmatrix}
-a_0 & 2d & c & d & 2c \\
0 & -(d + a_0) & 0 & c & 0 \\
a_0 & 0 & -c & d & 2c \\
0 & 2a_0 & 0 & -(d + c + a_0) & 0 \\
0 & 0 & 0 & 0 & -(b_1 + 2c_i) \\
0 & 0 & 0 & a_i & b_i \\
0 & -2b & -(b + a_s) & b & 0 \\
0 & 0 & -(b + a_s) & 0 & b \\
2c_i & 0 & b & 0 & 0 \\
d_i & 0 & a_s & 0 & 0 \\
-(2c_i + d_i) & 0 & 0 & 0
\end{pmatrix} \cdot \mathbf{X}_E = \mathbf{A}_E \cdot \mathbf{X}_E.
\]

We note that the system of equations has a single conservation law,

\[
\mathbf{W} = (1, 2, 1, 2, 2, 2)^T; \quad \mathbf{W}^T \cdot \Gamma = 0 \rightarrow \mathbf{W}^T \cdot \frac{d\mathbf{X}}{dt} = 0.
\]

As a result, the system matrix \( \mathbf{A}_E \) in the equations of motion (39) has rank 5 (\( N = 6, N_C = 1 \)).

To obtain the steady states, we set the l.h.s. of the equations of motion (39) to zero and define two "dummy" variables,

\[
Y_1 \equiv [\mathbf{R}]^2; \quad Y_2 \equiv [\mathbf{R}] \cdot [\mathbf{VR}].
\]

The resulting linear system, \( \mathbf{A}_E \cdot \mathbf{X}_E = 0 \), will have \( N = 6 \) equations and \( N + N_Y = 8 \) variables,

\[
\mathbf{X}_E = ([\mathbf{R}], [\mathbf{RR}], [\mathbf{VR}], [\mathbf{VRR}], [\mathbf{VRR}], [\Delta], Y_1, Y_2)^T.
\]

Since \( \text{rank}(\mathbf{A}_E) = N_D = 5 \), we can solve for a subset of 5 of these variables, leaving \( N_T = 3 \) as parameters. We cannot use both binomials \([\mathbf{R}]^2, [\mathbf{R}] \cdot [\mathbf{VR}]\) and their component variables \([\mathbf{R}], [\mathbf{VR}]\) as free parameters, only a subset of three of them.

This is a type II system, as defined in Section 3.3, with \( \Delta N = 1 \). The only possible choice for the clean set is \([\mathbf{VR}]\), because \([\mathbf{R}]^2\) is one of the second order terms. With \([\mathbf{R}], [\mathbf{VR}]\) and \( Y_1 = [\mathbf{R}]^2 \) as parameters and \( Y_2 = [\mathbf{R}] \cdot [\mathbf{VR}] \) as a dependent variable, the resulting constraint equation will be linear in the original variable \([\mathbf{VR}]\). The rearranged system, where we have discarded the last row of \( \mathbf{A}_E \), is

\[
\begin{pmatrix}
2d & d & 2c & 0 & -(a_s + b) \\
-(2d + a_0) & c & 0 & 0 & 0 \\
2a_0 & -(d + c + a_s) & 0 & 2c_i & b \\
0 & 0 & 0 & -(b_1 + 2c_i) & d_i & a_s \\
-a_0 & -c & 0 & 0 & -b & 2b \\
0 & 0 & 0 & 0 & 0 & [\mathbf{R}] \\
0 & 0 & 0 & 0 & 0 & [\mathbf{VR}] \\
0 & 0 & 0 & 0 & 0 & [\Delta]
\end{pmatrix} \cdot \mathbf{X}_E = \mathbf{A}_E \cdot \mathbf{X}_E.
\]

Solutions for the dependent variables are readily obtained as linear combinations of the three free variables. The coefficients are obtained via Cramer’s rule. In particular,

\[
Y_2 = A_y [\mathbf{R}] + B_y [\mathbf{VR}] + C_y Y_1,
\]

where

\[
A_y = \frac{D_{y_0}}{D_T}, \quad B_y = \frac{D_{y_0}}{D_T}, \quad C_y = \frac{D_{y_2}}{D_T},
\]

\( D_T \) is the determinant of the \( 5 \times 5 \) system matrix of (43), and \( D_{y_0, y_1, \ldots} \), are determinants of matrices formed from the system matrix and the \( 5 \times 3 \) parameter matrix on the right-hand side of the equation.

We eliminate \( Y_1 \) as before, by simply substituting \( Y_1 \rightarrow [\mathbf{R}]^2 \) into (44). The subsequent substitution \( Y_2 \rightarrow [\mathbf{R}] \cdot [\mathbf{VR}] \) yields a constraint linking the two remaining parameters \([\mathbf{R}]\) and \([\mathbf{VR}]\), which can be solved for \([\mathbf{VR}]\) as a linear equation

\[
[\mathbf{R}] \cdot [\mathbf{VR}] = A_y [\mathbf{R}] + B_y [\mathbf{VR}] + C_y [\mathbf{R}]^2 \rightarrow [\mathbf{VR}] = [\mathbf{R}] \frac{A_y + C_y [\mathbf{R}]}{[\mathbf{R}] - B_y}.
\]

Using positive combinations of the kinetic coefficients defined in Appendix B (B.75), which is available in the online supplemental material, the expression for \([\mathbf{VR}]\) at equilibrium becomes

\[
[\mathbf{VR}] = \frac{a_0 V_0}{c} \frac{2a_0 \rho^2 + d(P + Q) + bP[\mathbf{R}]}{2a_0 \rho^2 + d(P + Q) + dT[\mathbf{R}]} \equiv \varphi([\mathbf{R}]).
\]

We can now express the remaining four original variables \((A \in ([\mathbf{RR}], [\mathbf{VRR}],[\mathbf{VRR}], [\Delta])\) as

\[
\Lambda = A \cdot [\mathbf{R}] + B \cdot \varphi([\mathbf{R}]) + C \cdot [\mathbf{R}]^2,
\]

where the coefficients \( A, B, \ldots \) are algebraic expressions of the kinetic parameters, obtained as described in Appendix B, which is available in the online supplemental material.
Conservation of receptors and uniqueness of steady states. The fact that we arrived at a one-parameter set of solutions reflects the existence of a single conservation law (40). This law ensures the conservation of the total number of receptors, \( R_T = [R] + [VR] + 2([RR] + [VRR] + [RVR] + \Delta) \) in the system defined by (36) and (37). Using the analytical solutions (46) and (47), one may express \( R_T \) as a function of \([R]\). The resulting functional dependence is monotonic increasing, \( \frac{\partial R_T}{\partial [R]} > 0 \). This implies that there is only one value of \([R]\), therefore, one steady state, corresponding to a given total number of receptors \( R_T \) and external VEGF concentration \( V_0 \).

Checking for linear independence in the reduced system. When choosing the free parameters as well as deciding on which of the equations to discard, we have to make sure that the rank of the remaining linear system is not reduced. In this example, columns 1 and 3 of the \( 6 \times 8 \) system matrix in (39) are proportional to each other. This reflects an artificial coupling between \([R]\) and \([VR]\) which results if second-order terms are ignored. However, such couplings are likely to be present in other similar systems. An efficient approach to identifying such linear dependencies among columns is to perform Gaussian elimination or bring the system matrix to row-reduced echelon form. The choice of equations to be eliminated can be done after the column rearrangement.

A more complex version of the VEGF model. The full model of (26) has two VEGF receptor species. We describe the solution of the complete model in Appendix C, which is available in the online supplemental material. This system has 17 chemical species and 24 reactions. The equations of motion contain seven bilinear forms, formed by four of the original variables. This is an example of a Type II system with a clean set consisting of two variables.

5 STEADY STATES OF THE EGF-ERBB1 SYSTEM: SIGNAL INITIATION MODEL

Dysfunctionalities in signal transduction mediated by epidermal growth factor (EGF) are important factors in the pathogenesis of several cancers. Similarly to VEGF receptors, the ErbB family of EGF receptors (also known as EGFR) are receptor tyrosine kinases (RTK). ErbB1 undergoes ligand-induced dimerization. The corresponding signaling network has been studied extensively, and fully parameterized mathematical/computational models such as [7] have been assembled early on. Our group has performed several computational studies [27], [28], [29], [30], [31], [32], [33] aimed at elucidating the role of spatial inhomogeneity in EGF signal initiation. The complete Kholodenko model [7] has 23 distinct chemical species involved in 25 reversible or enzymatic reactions. The dimensionality of the system increases further by unpacking the enzymatic reactions.

We discuss a highly simplified version of the EGF model, defined in [33]. The concentration of EGF ligand is assumed fixed. Free receptors (denoted by \( R \)) may only bind to ligand; the resulting "bound" receptors (\( R_b \)) may form dimers (\( R_b^2 \)); bound receptor dimers may became active (\( R_a \)). Active receptors may deactivate spontaneously or through an enzymatic reaction

\[
\begin{align*}
R_b & \xrightarrow{\frac{1}{4}} R_b; \\
2R_b & \xrightarrow{\frac{2}{3}} R_b^2; \\
R_b^2 & \xrightarrow{\frac{3}{3}} R_b; \\
R_b & \xrightarrow{\frac{4}{4}} R_b.
\end{align*}
\]

The first three reactions are reversible and follow mass-action kinetics. We denote the kinetic constants as follows: There are two on-rates: \( a \) for ligand binding (reaction 1); the constant includes the fixed EGF concentration; \( b \) for the dimerization of ligand-bound receptors (reaction 2). The corresponding off-rates are \( c \) (ligand release, reaction 1) and \( d \) (dissociation, reaction 2). Spontaneous activation and deactivation of ligand-bound receptor dimers is characterized by rate constants \( f \) and \( g \), respectively. The enzymatic deactivation reaction 4 is irreversible, and follows Michaelis-Menten kinetics, characterized by a saturation constant \( K_M \) and a maximum rate \( V_{max} \).

\[
\Phi_4 = V_{max} \frac{[R_a]}{K_M + [R_a]}. \tag{49}
\]

Unpacking an enzymatic rate law. The Michaelis-Menten (MM) rate law (49) can be obtained from a mass-action reaction system where the enzyme \( Enz \) forms a complex \( EnzR \) with the substrate (the activated receptor complex \( Ra \)), and the complex may break up spontaneously or may proceed to release the deactivated receptor dimer \( R_b^2 \):

\[
\begin{align*}
Enz + Ra & \xrightarrow{\frac{a_1}{a_1}} EnzR \xrightarrow{\frac{a_2}{a_2}} R_b^2 + Enz.
\end{align*}
\]

The MM law may be reobtained as a quasi-steady-state approximation of the full mass-action rates under a number of assumptions, such as that the enzyme loading reactions 4.1 and 4.2 are fast compared to the forward reaction 4.3 or that the enzyme concentration is small compared to that of the substrate. The rate constants \( \lambda, \mu, \nu \) of the component reactions 4.1, 4.2, and 4.3 and the total enzyme concentration \( E_T = [EnzR] + [Enz] \) relate to the MM constants as follows:

\[
K_M = \frac{\mu + \nu}{\lambda}; \quad V_{max} = \nu E_T. \tag{51}
\]

The unpacking of the Michaelis-Menten reaction law introduces two additional species and increases the number of reactions by two. The resulting system has six species and five reactions (four reversible and one irreversible), and is described by the following state vector (\( X \)), flux vector (\( \Phi \)) and stoichiometry matrix (\( \Gamma \)):

\[
\begin{align*}
X &= ([Ru], [Rb], [Rb^2], [R_a], [Enz], [EnzR])^T, \\
\Phi &= 
\begin{pmatrix}
\Phi_1 \\
\Phi_2 \\
\Phi_3 \\
\Phi_{1,12} \\
\Phi_{4,3}
\end{pmatrix} = 
\begin{pmatrix}
a[Ru] - c[Rb] \\
b[Rb]^2 - d[Rb^2] \\
f[Rb^2] - g[R_a] \\
\lambda [Enz] \cdot [R_a] - \mu [EnzR] \\
\nu [EnzR]
\end{pmatrix}, \\
\Gamma &= 
\begin{pmatrix}
-1 & 0 & 0 & 0 & 0 \\
1 & -2 & 0 & 0 & 0 \\
0 & 1 & -1 & 0 & 1 \\
0 & 0 & 1 & -1 & 0 \\
0 & 0 & 1 & -1 & 1
\end{pmatrix}.
\end{align*}
\]

The Michaelis-Menten Reaction Law.

\[
\begin{align*}
Enz + R & \xrightarrow{a} EnzR \\
EnzR + R & \xrightarrow{b} EnzR \\
EnzR & \xrightarrow{c} Enz + R
\end{align*}
\]
There are two bilinear terms in the rate laws, \([\text{Rb}]^2\) and \([\text{Enz}] \cdot [\text{Ra}].\) With an expanded vector

\[
X_E \equiv ([\text{Ru}], [\text{Rb}], [\text{Rb}]^2, [\text{Ra}], [\text{Enz}], [\text{EnzR}], [\text{Rb}]^2, [\text{Enz}] \cdot [\text{Ra}])^T,
\]

(53)

the equations of motion resulting from (52) can be reobtained as a linear system

\[
\frac{dX}{dt} = \Gamma \cdot \Phi(X) = A_E \cdot X_E,
\]

(54)

where

\[
A_E = \begin{pmatrix}
-a & c & 0 & 0 & 0 & 0 & 0 & 0 \\
a & -c & 2d & 0 & 0 & 0 & -2b & 0 \\
0 & 0 & -d - f & g & 0 & \nu & b & 0 \\
0 & 0 & f & -g & 0 & \mu & 0 & -\lambda \\
0 & 0 & 0 & 0 & \mu + \nu & 0 & -\lambda & 0 \\
0 & 0 & 0 & 0 & 0 & -\mu - \nu & 0 & \lambda
\end{pmatrix}
\]

(55)

The solution of (58) yields

\[
[\text{Ru}] = \frac{c}{a} \cdot [\text{Rb}]; \quad [\text{Rb}] = \frac{b}{d} \cdot Y; \quad [\text{EnzR}] = \frac{fb}{\nu d} \cdot Y - \frac{g}{\nu} \cdot [\text{Ra}]; \quad Z = \frac{\mu + \nu}{\lambda} \left( \frac{fb}{\nu d} \cdot Y - \frac{g}{\nu} \cdot [\text{Ra}] \right).
\]

(59)

We can readily substitute \(Y = [\text{Rb}]^2\) in (59), eliminating the bilinear and leaving three free parameters. Notice that of these, \([\text{Enz}]\) does not explicitly appear in the equations. This reflects the fact that \([\text{Enz}]\) only enters the rate laws (52) through a bilinear term. Replacing \(Z = [\text{Enz}] \cdot [\text{Ra}]\) in the only equation where it appears yields

\[
[\text{Enz}] \cdot [\text{Ra}] = \frac{\mu + \nu}{\lambda} \left( \frac{fb}{\nu d} \cdot [\text{Rb}]^2 - \frac{g}{\nu} \cdot [\text{Ra}] \right).
\]

(60)

The above equation is linear in both \([\text{Enz}]\) and \([\text{Ra}],\) and is easily solved for either of them. Solving for \([\text{Enz}],\) we are left with a closed form solution in terms of \([\text{Ra}]\) and \([\text{Rb}]\):

\[
[\text{Ru}] = \frac{c}{a} \cdot [\text{Rb}]; \quad [\text{Rb}] = \frac{b}{d} \cdot [\text{Rb}]^2; \quad [\text{EnzR}] = \frac{fb}{\nu d} \cdot [\text{Rb}]^2 - \frac{g}{\nu} \cdot [\text{Ra}]; \quad [\text{Enz}] = \frac{K_M}{[\text{Ra}]} \cdot \left( \frac{fb}{\nu d} \cdot [\text{Rb}]^2 - \frac{g}{\nu} \cdot [\text{Ra}] \right).
\]

(61)

Parametrization in terms of conserved quantities. The solution (61) is a parametrization of all possible steady states of the system (54), using two of the original variables as free parameters. It is not coincidental that the number of free parameters matches that of the conservation laws. In practice, one would prefer to calculate the steady states as a function of the corresponding conserved quantities. A parametrization in terms of conserved quantities is especially useful in investigating multistability.\(^{12}\) At equilibrium, the total amount of enzyme \(E_T = \sum [\text{Enz}] + [\text{EnzR}]\) can be expressed using the two free variables, and recast into a useful identity (where we replaced \(E_T\) from (51)):

\[
E_T = \left(1 + \frac{K_M}{[\text{Ra}]}\right)^{-1} \frac{1}{\nu} \left(\frac{fb}{d} [\text{Rb}]^2 - g[\text{Ra}]\right) - \frac{fb}{d} [\text{Rb}]^2 - g[\text{Ra}] = V_{\text{max}} \cdot \frac{[\text{Ra}]}{[\text{Ra}] + K_M}.
\]

(62)

We may now use (62) to eliminate one of the free parameters. The equation is nonlinear, but it defines a one-to-one correspondence between nonnegative values of \([\text{Ra}], [\text{Rb}],\) through the function \(\varphi(\cdot)\) defined as follows:

\[
\varphi([\text{Ra}]) = \sqrt{\frac{d}{fb} \left( g[\text{Ra}] + V_{\text{max}} \cdot \frac{[\text{Ra}]}{[\text{Ra}] + K_M} \right)}.
\]

(63)

The function is monotonically increasing, \(\varphi(0) = 0\) and \(\lim_{x \to \infty} \varphi(x) = \infty\) for any set of positive parameter values; therefore, it is invertible on \([0, \infty)\). Thus, (61) and the identity (62) provide a parametrization of all possible

\(^{12}\) Actually, it would exclude it, since two different steady states could not possibly have the same conserved quantities; therefore, it would be impossible to have more than one steady state compatible with any given initial condition.
steady states in terms either one of [Ra] or [Rb]. For instance, in terms of [Ra] we have

\[
[Ra] = \frac{\mathcal{C}}{a} \varphi([Ra]), \quad [Rb] = \varphi([Ra]), 
\]

\[
[Rb] = \frac{1}{f} \left( g[Ra] + V_{\text{max}} \frac{[Ra]}{[Ra] + K_M} \right), 
\]

\[
[\text{Enz}] = \frac{V_{\text{max}}}{\nu} \frac{K_M}{[Ra] + K_M}, \quad [\text{EnzR}] = \frac{V_{\text{max}}}{\nu} \frac{[Ra]}{[Ra] + K_M}. 
\]

(64)

The total number of receptors \( R_T = \mathbf{W}^T \cdot \mathbf{X} = [Ra] + [Rb] + 2([Rb] + [Ra] + [\text{EnzR}]) \) can also be expressed in terms of [Ra]:

\[
R_T = \frac{c + a}{a} \varphi([Ra]) + 2 \cdot \frac{f + g}{f} [Ra] + 2 \cdot V_{\text{max}} \left( \frac{1 + 1}{\nu} \right) \frac{[Ra]}{[Ra] + K_M}. 
\]

(65)

Each term in the above expression is a monotonically increasing function of [Ra] and vanishes for [Ra] = 0. In addition, \( R_T \) is unbounded as [Ra] \( \rightarrow \infty \); therefore, (65) defines a one-to-one correspondence between [Ra] at equilibrium and the total amount of receptor, \( R_T \). Since \( R_T \) is conserved by the equations of motion, every initial state is consistent with exactly one value of [Ra] at equilibrium, hence a unique steady state. The analytical dependence in (65) can be easily inverted and used to calculate the equilibrium values of all variables. Steady states are not necessarily unique, of course. A nonmonotonic dependence of conserved quantities on parameters may result in multistability.

6 Discussion

6.1 Summary of the Method

Our primary goal is to obtain a minimal parametrization of the steady-state solutions of a bilinear system resulting from a chemical reaction network. We focus on the system of algebraic equations that results at steady state. Typically, for a system with \( N \) variables (species), only a subset of \( N_D \leq N \) of the equations of motion are independent. We assume that the deficiency results from \( N_F \equiv N - N_D = N_C \) linear conservation laws, which are generally a consequence of the stoichiometry of the underlying CRN. The minimal parametrization we seek is a set of closed form (explicit) algebraic expressions for \( N_F \) of the original variables, as functions of the other \( N_F \) variables, sometimes referred to as free parameters.

We linearize the algebraic system by introducing dummy variables for each of the \( N_F \) distinct bilinears that appear in the original equations of motion. The linear system has \( N + N_B \) variables and its rank is \( N_D \), the same as the number of independent equations in the nonlinear system. We can generally solve the linear system for a subset of \( N_D \) of its variables (original variables and/or dummies), as a function of the remaining \( N_F = N_F + N_B \); the only restriction to the choice of the “dependent” set is that the rank of the corresponding submatrix should be \( N_D \).

The feasibility of solving the system without dealing with higher order algebraic equations hinges on the possible choices of the free and dependent sets of variables, \( N_B \), and the number \( N_F \) of original variables that participate in at least one bilinear. In choosing the set of free parameters, we seek to include as many as possible of the \( N_B \) dummy variables, in addition to the \( N_F \) original variables that participate in bilinears.

**Type I systems.** If \( N_F \geq N_B + N_P \) (implying \( N_C \leq N_F \)) the set of free parameters may include every dummy variable as well as all the original variables participating in bilinears, as possible. If the rank of the system matrix restricted to the dependent variables is \( N_D \), we can proceed with Cramer’s Rule and obtain formulae for each one of the dependent variables as a linear combination of the independent set. We can then readily substitute the bilinears for the dummy variables, obtaining the closed form solution.

**Type II systems.** The favorable situation described above is not typical. However, the two examples discussed in Sections 4 and 5 were amenable to closed form solutions. For Type II systems, we assume \( N_F + N_B > N_P \) (implying \( N_C < N_F < N_C + N_D \)) so that we can include in the free set all the original variables that participate in bilinears. This will leave \( \Delta N \equiv N_F - N_C \) dummy variables in the dependent set. As in the previous case, we can solve the system and express the \( N - N_C \) original variables and \( \Delta N \) bilinears as linear combinations of \( N_F = N_F + \Delta N \) original variables (and bilinears formed by them). This is not a minimal parameterization. The key step is to use the expressions obtained for the \( \Delta N \) bilinears to eliminate the \( \Delta N \) superfluous parameters. This is feasible if we can find a clean set, a subset of \( \Delta N \) of the \( N_F \) original variables, for which the \( \Delta N \) constraint equations form a linear system. The requirement is that none of the bilinears in the original system contain two members of the clean set.

In the two examples discussed in the main text, we had \( \Delta N = 1 \), only one dummy variable treated as dependent ([R] \cdot [VR] in the VEGF example and [Enz] \cdot [Ra] in the simplified EGF model), and the choice of the clean set was trivial. In more complicated examples of Type II systems, the definition and possible variants of the clean set should be identified first, followed by a set of representative bilinears (one for each member of the clean set), which will be assigned to the dependent group.

We provided such an example in Appendix C, which is available in the online supplemental material, where we worked out the full VEGF model of [26] but did not analyze the solutions. The original system has 17 variables, which are augmented by seven dummy variables corresponding to bilinears. This system has \( \Delta N = 2 \). The choice of the clean set is unique, with some flexibility in the choice of the representative set of bilinears. After solving for a set of 15 variables, including the representative bilinears for the clean set, the explicit solutions provide a system of two equations (C.92) that are linear in the two members of the clean set.

6.2 Applicability

The examples discussed here were worked out analytically, using a computer algebra system (i.e., Maple). The extended EGF system and the “easy example” can be worked out manually with no significant difficulty. The VEGF example is somewhat more complex; it is not obvious beforehand that the steady state is unique or that detailed balance is satisfied. The approach described here can apply to much
larger systems, with tens or even hundreds of variables. For example, using Maple, we were able to find steady states for the full, two-receptor VEGF model with heterodimerization [26] (Appendix C, which is available in the online supplemental material), as well as for a large EGFR model [7]. Once the problem is properly coded, the most resource-intensive elements are the rank and determinant calculations, which took on the order of a few minutes in Maple on a generic PC.

If analytical expressions are not desired, the process can be easily automated to apply to a generic, mass-action CRN with uni- and bimolecular reactions. The prima facie applicability of the two cases simply requires counting the number of variables, bilinears, and conservation laws and checking $N_P \leq N_C$ for Type I and $N_P \leq N_C + N_R$ for Type II. For Type I, the most delicate step is the choice of free variables, which must be done in a way that ensures that the dependent part of the system matrix is full rank. For moderate sized systems, a simple enumeration of all possibilities is realistic. For Type II, the rank check can be done along with the identification of the clean set.

Unfortunately there is no guarantee that the rank of the system matrix remains $N_D$ for all possible choices of the dependent variables. This occurs for example, with variables that only participate in rate laws through bilinears (for example, $[Enz]_i$), leading to blank columns in the extended linear system matrix. However, these dependences ultimately reflect a reduction in the number of degrees of freedom, and could likely be resolved by a priori eliminating such variables, either from a conservation law ($[Enz] = E_T - [Enz]_R$) or by choosing one of their bilinears to represent the respective degree of freedom (i.e., using $Z = [Enz] - [Ia]_a$ as a parameter all the way to the end, and then calculating $[Enz] = Z/[Ia]_a$).

The restriction to bimolecular, mass-action systems does not significantly reduce the applicability of this method. Nonlinear rate laws can typically be obtained as quasi-steady-state approximations of a more complex mechanism, similarly to the way we unpacked the Michaelis-Menten law. Reactions involving more than two molecules can also be represented as sequences of several bimolecular reactions. These replacements involve increasing the dimensionality of the system by one or two additional species and the inclusion of "hidden" parameters. However, as in the reduced EGF example, the additional variables may be easily eliminated, and the hidden parameters generally appear only in combinations that are equivalent to the parameters of the original rate law.

6.3 Utility and Outlook

We are interested in developing computer code for a generic system of chemical reactions as described above. We are also investigating the mechanisms that may lead to rank loss, which can be likely avoided by a priori reducing the number of free parameters. Our approach applies to CRN that have a limited number of bimolecular terms. An explosion of such terms may result from combinatorial domain binding rules and decomposition of high-order reaction mechanisms. The proportion of bilinears may remain limited even in those cases. A survey of these situations would be useful.

The main utility of the approach described herein is in reducing the computational cost of parameter identification for moderately sized chemical reaction networks, such as those relevant to signaling. The lack of reliable information on reaction kinetics continues to be one of the major stumbling blocks to meaningful integration of modeling and experimental efforts. The fundamental (i.e., physically meaningful or microscopic) kinetic parameters are often deeply hidden behind layers of structure that cannot be included in a functional model, and thus parameter values determined in vitro may differ dramatically from the effective parameters that drive the behavior of the system of interest. However, even these effective parameters are hard to measure directly, even though excellent methods exist for the measurement of concentrations, molecule numbers, and other quantities that are part of the state of the system described by an ODE model. A direct method for obtaining steady state and quasi-steady-state values for all observables in the system allows for efficient methods of parameter fitting directly to the experimental data that is to be modeled ([34]). The key advantage is in the lower computational cost for evaluating model predictions using a formula versus a numerical procedure.

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Adám M. Halász (M'06) received the diploma de licenta degree in physics from the University of Bucharest, Romania, in 1989 and the MA and PhD degrees in physics from Stony Brook University, in 1995 and 1998, respectively. He is currently an assistant professor in the Department of Mathematics, West Virginia University. His current research interests include biomathematics, molecular systems biology, mesoscopic phenomena in cells, and swarm robotics.

Hong-Jian Lai received the PhD degree in mathematics from Wayne State University in 1989. He is a full professor in the Department of Mathematics at West Virginia University. His current research interests include discrete mathematics, algorithms, and optimizations.

Meghan McCabe Pryor received dual bachelor’s degrees in chemical engineering and quantitative biology from the University of Delaware in 2010. She is currently working toward the doctoral degree in the Chemical and Nuclear Engineering Department at the University of New Mexico. Her current research interests include investigating membrane protein kinetics and dynamics and their impact on signal initiation and propagation through rule-based modeling.

Krishnan Radhakrishnan received the BSc degree in mechanical engineering from the Imperial College London, the MS degree in mechanical engineering from Cornell University, the PhD degree in mechanical engineering from the Massachusetts Institute of Technology, and the MD degree from Case Western Reserve University. He is currently a resident physician in Preventive Medicine, American Cancer Society Fellow in the College of Public Health, and a lecturer in biomedical engineering and mechanical engineering.

Jeremy S. Edwards received the bachelor’s of Science degree in mechanical engineering from the Texas, in 1995, and the MS and PhD degrees in bioengineering from the University of California, San Diego, in 1997 and 1999, respectively. He is currently a professor with the Department of Molecular Genetics and Microbiology, University of New Mexico. His current research interests include biomathematics, molecular systems biology, bioinformatics, and DNA sequencing technology.