Published in final edited form as:

J Phys A Math Theor. 2017 October 20; 50(42): . doi:10.1088/1751-8121/aa89d0.

Solving moment hierarchies for chemical reaction networks

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Abstract

The study of chemical reaction networks (CRN's) is a very active field. Earlier well-known results (Feinberg 1987 *Chem. Enc. Sci.* **42** 2229, Anderson *et al* 2010 *Bull. Math. Biol.* **72** 1947) identify a topological quantity called deficiency, for any CRN, which, when exactly equal to zero, leads to a unique factorized steady-state for these networks. No results exist however for the steady states of non-zero-deficiency networks. In this paper, we show how to write the full moment-hierarchy for any non-zero-deficiency CRN obeying mass-action kinetics, in terms of equations for the factorial moments. Using these, we can recursively predict values for lower moments from higher moments, reversing the procedure usually used to solve moment hierarchies. We show, for nontrivial examples, that in this manner we can predict any moment of interest, for CRN's with non-zero deficiency and non-factorizable steady states.

Keywords

non-equilibrium steady states; chemical reaction networks; infinite moment hierarchies

1. Introduction

Models of chemical reaction networks (CRN's) are ubiquitous in the study of biochemistry, systems biology, ecology and epidemiology. They provide a framework within which even several models studied in physics, may be cast. CRN's are defined by a set of *species*, *complexes* and *reactions* which, when taken together, specify the system of interest (see figures 1 and 2). The mathematical modeling of CRN's is usually carried out either through the study of deterministic ODE's (or *rate equations*) which specify the mean behaviour of the concentrations of the different species, or by modeling the stochastic variability of species counts as a continuous-time Markov chain, where a transition occurs every time a

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reaction takes place. One of the major results pertaining to deterministic models of CRN's is the deficiency zero theorem [1, 3, 4]. This relates a topological quantity called the deficiency (a non-negative integer index, denoted by δ) to the existence, uniqueness, and stability of positive fixed points of the rate equations. In particular, when $\delta = 0$ for CRN's which are weakly reversible⁶, there is a unique, asymptotically stable equilibrium, for any choice of (positive) rate constants. A few theorems exist for deterministically-modeled CRN's with $\delta > 0$ as well [1, 5, 6], which either affirm that a given network is capable of multistationarity or can rule out this possibility (see [7] for a recent survey).

Modeling CRN's by ODE's is however expected to be accurate only when species concentrations are high. When this is not the case, such as in, for example, gene expression [8, 9], cell signaling [10] or enzymatic processes [11], then a stochastic modeling of CRN's is more appropriate. A major result for this class of models is the theorem by Anderson, Craciun and Kurtz (ACK) [2] (motivated by earlier work on queueing theory by Kelly [12]), who show that if the conditions of the deficiency zero theorem hold for a deterministically modeled CRN, then the corresponding stochastic system has a product-form steady state. There has also been work done [13] on the extinction time for certain reactions in stochastic models of CRN's of deficiency one. However, no general results exist for obtaining the steady-state behaviour of CRN's with $\delta > 0$.

This absence of general results reflects a deeper and more fundamental feature of CRN's: unlike simple random walks on ordinary graphs for which abundant results exist, the elementary reaction events in CRN's involve *concurrency* in the conversion of inputs to outputs [14, 15]. The underlying topology of a CRN is a *multihypergraph* rather than an ordinary graph [16, 17]; fewer results exist for hypergraphs because generic problems of search or optimization are computationally hard [18, 19]. The reflection of these difficulties in CRN moment hierarchies is that moment equations at any order couple to moments at higher order, leading to an infinite hierarchy of equations. The standard way to deal with these is via moment-closure schemes [20], which however are ad-hoc and sometimes give unphysical results [21]. In this paper, we take a different point of view. We show, for a generic mass-action CRN with arbitrary value of δ , that the equations for the *factorial moments* (FM), provide a better starting point for solving the infinite moment-hierarchy. The structure of these equations facilitates recursively writing FM ratios at lower-order in terms of FM ratios at higher order. The recursions can then be solved, exactly in some cases, to obtain any moment of interest. Our results are also applicable to any non-equilibrium process describable as a mass-action CRN, such as for example, the zero-range process [22]⁷.

⁶A weakly reversible CRN is one in which any complex can be transformed to any other, within one connected component of the network, via a directed path of reactions. A reversible network is one in which each reaction is accompanied by its reverse. Neither weakly reversible nor reversible networks need to be *time-reversible*.

So detailed balance does *not* generically hold.

⁷The zero range process, with periodic boundary conditions may be written as the following CRN $S_1 \rightarrow S_2 \rightarrow \dots \rightarrow S_N \rightarrow S_1$. Here the species and complexes are the same and correspond to all the particles sitting on a site. Particle flux into or out of the system may be easily accommodated by adding reactions of the type $S_j \rightleftharpoons \emptyset$.

2. Framework and results

In what follows, we develop a convenient formalism for describing CRN's, by combining a network decomposition made standard by CRN-theory [4, 23] with the well-known stochastic process formalism due to Doi [24]. To our knowledge, no one has combined these two methods earlier. The description of CRN's simplifies considerably within this framework. In addition this formalism is crucial to understanding why the equations for the FM have the structure they do. We hence utilize two simple examples of CRN's with non-zero deficiency, to explain both the formalism and our results. We also provide a definition for the very important concept of deficiency.

2.1. Two examples

Our first example is the following minimal model with just one species and $\delta = 1$, Its reaction scheme is

Another example is the following CRN with two species and $\delta = 2$:

Its reaction scheme is

In the description of CRN's two matrices conventionally appear [4, 23]. An *Adjacency matrix*, denoted by $\mathcal{A}$, is the matrix of transition rates among complexes. The matrix element $\mathcal{A}_{ij}$ for $i \rightarrow j$ denotes the transition (if any) that takes complex j to complex i , with $\mathcal{A}_{jj} \equiv -\sum_i \mathcal{A}_{ij}$. $\mathcal{A}$ has, by definition, a zero left eigenvector $[1, 1, \dots, 1]$.

For the network in figure 1 the adjacency matrix is

$$\mathcal{A} = \begin{bmatrix} -\alpha & \varepsilon & 0 \\ \alpha & -2\varepsilon & \beta \\ 0 & \varepsilon & -\beta \end{bmatrix}. \quad (3)$$

For the network in figure 2, $\mathcal{A}$ is a 6×6 matrix over the 6 complexes: $\emptyset$, A, B, A + B, 2A + B and A + 2B.

$$\mathcal{A} = \begin{bmatrix} -2\varepsilon & k_2 & k_2 & 0 & 0 & 0 \\ \varepsilon & -k_2 & 0 & 0 & 0 & 0 \\ \varepsilon & 0 & -k_2 & 0 & 0 & 0 \\ 0 & 0 & 0 & -2k_1 & \bar{k}_1 & \bar{k}_1 \\ 0 & 0 & 0 & k_1 & -\bar{k}_1 & 0 \\ 0 & 0 & 0 & k_1 & 0 & -\bar{k}_1 \end{bmatrix}. \quad (4)$$

We assume mass-action rates (as in earlier work [1, 2]): if n_a is the number of particles of species A, the rate at which complex A is converted to any other complex is the rate constant times n_a . Similarly the rate at which complex 2A takes part in any reaction is $n_a(n_a - 1)$, etc.

The other matrix which is useful to define is the stoichiometric matrix Y . An element $y_{p,i}$ of this matrix is the amount of species p in complex i . We denote by Y_p the p th row of this matrix.

For example, in the reaction scheme of equation (1), Y is a row vector given by

$$Y = [1 \ 2 \ 3]. \quad (5)$$

For the reaction scheme of equation (2), the Y matrix is

$$Y = \begin{bmatrix} 0 & 1 & 0 & 1 & 2 & 1 \\ 0 & 0 & 1 & 1 & 1 & 2 \end{bmatrix} \quad (6)$$

where the first row Y_1 refers to species A, the second row Y_2 to species B and the columns i refer to the complexes in the order mentioned above.

The time-evolution of the species in a CRN, is described by a master equation for the probability ρ_n , where $n \equiv [n_p]$ is a column vector, with components which are the instantaneous numbers of the different species p .

For example, for the CRN of equation (1), the master equation is

$$\dot{\rho}_n = \left\{ \left(e^{-\partial/\partial n} - 1 \right) [\alpha n + \varepsilon n(n-1)] + \left(e^{\partial/\partial n} - 1 \right) [\varepsilon n(n-1) + \beta n(n-1)(n-2)] \right\} \rho_n,$$

(7)

where the operators $e^{-\partial/\partial n}$ (or $e^{\partial/\partial n}$) act on any function $f(n)$ and convert it to $f(n)$ and convert it to $f(n-1)$ ($f(n+1)$ respectively) [25].

For the network of figure 2, n becomes a two-component index to ρ , which evolves under

$$\dot{\rho}_n = \left\{ \left(e^{-\partial/\partial n_a} - 1 \right) [\varepsilon + k_1 n_b n_a] + \left(e^{-\partial/\partial n_a} - 1 \right) [k_2 n_a + \bar{k}_1 n_b n_a (n_a - 1)] + \left(e^{-\partial/\partial n_b} - 1 \right) [\varepsilon + k_1 n_a n_b] + \left(e^{-\partial/\partial n_b} - 1 \right) [k_2 n_b + \bar{k}_1 n_a n_b (n_b - 1)] \right\} \rho_n \quad (8)$$

In general, for a CRN with P species, the master equation is more conveniently written in

terms of an equation for the generating function $\phi(z) \equiv \sum_n \left(\prod_{p=1}^P z_p^{n_p} \right) \rho_n$ where $z \equiv [z_p]$ is a vector. The generating function evolves under a *Liouville equation* of the form

$$\frac{\partial \phi}{\partial \tau} = -\mathcal{L} \phi$$

$$\text{shorthand ; for } \frac{\partial}{\partial \tau} \phi(z) = -\mathcal{L} \left(z, \frac{\partial}{\partial z} \right) \phi(z). \quad (9)$$

$\mathcal{L}$ is called the *Liouville operator*.

2.2. The Liouvillian

$\mathcal{L}$ has a well-known representation, due to Doi [24], in terms of raising and lowering operators $a^\dagger$ and a . We provide a brief introduction to the Doi algebra below⁸. The Doi algebra uses the following correspondence:

$$z_p \rightarrow a_p^\dagger \quad \frac{\partial}{\partial z_p} \rightarrow a_p. \quad (10)$$

It follows that the operators obey the conventional commutation algebra

$$[a_p, a_p^\dagger] = \delta_{pq}, \quad (11)$$

where δ_{pq} is the Kronecker δ .

Defining formal *right-hand and left-hand null states*,

$$1 \rightarrow |0\rangle \quad \int d^P z \delta^P(z) \rightarrow \langle 0| \quad (12)$$

⁸Much more comprehensive treatments are to be found in [26, 27]. Interpretations of terms in the Doi algebra in the language of conventional generating functions is elaborated on in detail in [28].

(where $\delta^P(z)$ is the Dirac δ in P dimensions, and the inner product of the null states is normalized: $\langle 0|0\rangle = 1$), for any vector $n \equiv [n_p]$,

$$\prod_{p=1}^P a_p^{\dagger n_p} |0\rangle \equiv |n\rangle. \quad (13)$$

With these steps, the generating function ϕ becomes⁹

$$\phi(z) = \sum_n \prod_{p=1}^P z_p^{n_p} \rho_n \rightarrow \sum_n \rho_n |n\rangle \equiv |\phi\rangle. \quad (14)$$

The Liouville equation in this language takes the form

$$\frac{\partial |\phi\rangle}{\partial \tau} = -\mathcal{L}(a_p, a_p^\dagger) |\phi\rangle. \quad (15)$$

For example, the Liouville operator $\mathcal{L}$ for the network of figure 1 (and equation (1)) is

$$\mathcal{L} = (1 - a^\dagger) \left[\alpha a^\dagger a - \varepsilon (1 - a^\dagger) a^\dagger a^2 - \beta a^{\dagger 2} a^3 \right] = (1 - a^\dagger) (a^\dagger a) [(\alpha - \varepsilon a) + (a^\dagger a - 1)(\varepsilon - \beta a)]. \quad (16)$$

The Liouville operator corresponding to the two-species network (figure 2) is

$$\mathcal{L} = (1 - a^\dagger) [(\varepsilon - k_2 a) + (b^\dagger b) (a^\dagger a) (k_1 - \bar{k}_1 a)] + (1 - b^\dagger) [(\varepsilon - k_2 b) + (a^\dagger a) (b^\dagger b) (k_1 - \bar{k}_1 b)], \quad (17)$$

where $(a^\dagger, a)$ and $(b^\dagger, b)$, are creation and annihilation operators for the number components n_a and n_b , respectively.

The Liouvillian may be written more compactly in terms of the matrices $\mathcal{A}$ and Y . To accomplish this, we need to introduce a little more notation. Define a column vector,

$$\psi_Y^i(a) \equiv \prod_p (a_p)^{y_{p,i}} \quad (18)$$

⁹Note that though the generating function ϕ is explicitly an analytic function of z , while the state $|\phi\rangle$ is not, the information they carry as a power series is exactly the same. Hence, for the purpose of generating moments, the fact that both are formal power series, of z in one case and of $a^\dagger$ in the other, suffices without worrying about convergence properties [29].

$\psi_Y^\dagger \equiv [\psi_Y^{\dagger i}]^T$ is then a row vector of components defined on the indices i^{10} ,

$$\psi_Y^{\dagger i}(a^\dagger) \equiv \prod_p (a^\dagger_p)^{y_{p,i}}. \quad (19)$$

For example, for the two-species network, these are simply

$$\psi^\dagger = [1 \ a^\dagger \ b^\dagger \ a^\dagger b^\dagger \ a^{\dagger 2} b^\dagger \ a^\dagger b^{\dagger 2}]$$

$$(\psi)^T = [1 \ a \ b \ ab \ a^2 b \ ab^2]. \quad (20)$$

In this formalism, the Liouville operator takes on the simple form,

$$-\mathcal{L} = \psi_Y^\dagger \mathcal{A} \psi_Y. \quad (21)$$

2.3. The moment hierarchy

Entirely equivalent to solving the master equation or the Liouville equation, is to solve the *moment hierarchy*, namely to compute the time-dependent values of *all* the relevant moments in the problem. The set of equations for all these moments, obtained directly from the master equation or the Liouville equation, is referred to as the moment hierarchy, because usually lower-order moments couple to higher-order ones, resulting in an infinite hierarchy of equations. Solving the moment hierarchy is hence by no means a simple task and often involves making approximations. In what follows, we demonstrate that for any mass-action CRN, the equations for the *factorial moments* (rather than the equations for ordinary moments) take on a particularly tractable form. For the examples we consider, we show how this tractability helps in solving the entire moment hierarchy in the steady state.

In order to see this, we first need to write down the equations for the moments. The time dependence of arbitrary moments is easily extracted from the Liouville equation via the Glauber inner product, which is a standard construction [26, 27]. In the interest of completeness, we provide all relevant details in what follows. As mentioned earlier, we will prefer instead to look at the *factorial moments* (FM). In order to define these, consider, for a single component n_p and power k_p , the quantity

$$\begin{aligned} n_p^{k_p} &\equiv \frac{n_p!}{(n_p - k_p)!} && ; k_p \leq n_p \\ &\equiv 0 && ; k_p > n_p. \end{aligned} \quad (22)$$

¹⁰The index i on the LHS indicates a component of the row vector and not a power.

For a vector $k \equiv [k_p]$ of powers and a vector n of instantaneous numbers of the species, we introduce the *factorial moment* indexed by k , as the expectation

$$\langle n^k \rangle \equiv \left\langle \prod_p n_p^{k_p} \right\rangle. \quad (23)$$

The FM are generated by the action of the lowering operator on the number state. In particular, for any non-negative integer k_p

$$a_p^{k_p} |n\rangle = n_p^{k_p} |n - k_p\rangle$$

$$a_p^{\dagger k_p} a_p^{k_p} |n\rangle = n_p^{k_p} |n\rangle, \quad (24)$$

where $|n - k_p\rangle$ is the number state with k_p subtracted from n_p and all n_q for $q \neq p$ unchanged.

The time dependence of the FM is then simply given by

$$\frac{\partial}{\partial \tau} \left\langle \prod_p n_p^{k_p} \right\rangle \equiv \frac{\partial}{\partial \tau} \langle n^k \rangle = \langle 0 | e^{\sum_q a_q} \prod_p (a_p)^{k_p} (-\mathcal{L}) | \phi \rangle = \langle 0 | e^{\sum_q a_q} \prod_p (a_p)^{k_p} \psi_Y^\dagger(a^\dagger) \mathcal{A} \psi_Y(a) | \phi \rangle. \quad (25)$$

In writing equation (25), the fact that all number states are normalized with respect to the *Glauber inner product*, defined by

$$\langle 0 | e^{\sum_p a_p} | n \rangle = 1, \quad \forall n \quad (26)$$

is used.

The Glauber inner product with a generating function is simply the trace of the underlying probability density:

$$\langle 0 | e^{\sum_p a_p} | \phi \rangle = \sum_n \rho_n = 1. \quad (27)$$

Equation (25) denotes the time-evolution of a generic FM for a CRN with an arbitrary number of species. In particular, the equation for the first moment takes on a simple form. Note that a first moment, for a CRN of P species, is specified by a vector $k \equiv [k_p]$, with only

one of the k_p 's being non-zero (and having the value 1). This corresponds to computing the average value of the number of one specific species p . In this case, from equation (25), we need only to commute a_p through $\psi_Y^\dagger(a^\dagger)^{11}$ to obtain,

$$\frac{\partial}{\partial \tau} \langle n_p \rangle = Y_{p,\mathcal{A}}(0) e^{\sum_q a_q} \psi_Y(a) |\phi\rangle. \quad (28)$$

In what follows, we refer to the inner product in equation (28) as $E[\psi_Y(a)]$ to simplify notation. Note that, using the above definitions, $E[a_p^{k_p}] \equiv \langle \frac{k_p}{n_p} \rangle$: the FM of order k_p .

2.4. Deficiency

It is useful at this stage to understand the relations between the dimensions of the matrix $\mathcal{A}$ and the matrix $Y\mathcal{A}$ (or the row vector $Y_{p,\mathcal{A}}$). The reason for considering these is that, as we see from equation (28), all steady states must lie in $\ker(Y\mathcal{A})$ (since the steady state condition implies that the LHS of equation (28) must vanish). This can happen either because the steady state lies in $\ker \mathcal{A}$ (and so vanishes directly by the action of $\mathcal{A}$) or because the steady state *does not* lie in $\ker \mathcal{A}$ but nevertheless lies in $\ker(Y\mathcal{A})$. The difference between these two situations, as we will see, summarises the difference between $\delta = 0$ and $\delta > 0$ networks.

By definition, since the number of columns (and rows) in the matrix $\mathcal{A}$ is equal to the number of complexes $\mathcal{C}$, matrix $\mathcal{A}$ has dimension $\mathcal{C}$. Then from elementary considerations,

$$\dim(\mathcal{A}) = \dim(\text{im}(\mathcal{A})) + \dim(\ker(\mathcal{A})) = \dim(\text{im}(Y\mathcal{A})) + \dim(\ker Y \cap \text{im}(\mathcal{A})) + l \equiv s + \delta + l.$$

(29)

Here $\dim(\ker(\mathcal{A})) \equiv l$ where l is the number of linkage classes¹². In equation (29), the $\dim(\text{im}(\mathcal{A}))$ is further split into those vectors that either lie *both* in the $\text{im}(\mathcal{A})$ and $\ker(Y)$ or lie in the $\text{im}(Y\mathcal{A})$.

Equation (29) provides a definition for the parameter s and deficiency $\delta = \mathcal{C} - s - l$ [1]. For the CRN in figure 1, $\mathcal{C}=3$, $l=1$, $s=1$ giving $\delta=1$. For the CRN in figure 2, $\mathcal{C}=6$, $l=2$, $s=2$ giving $\delta=2$.

For $\delta=0$ networks, all steady states lie simultaneously in $\ker \mathcal{A}$ and in $\ker(Y\mathcal{A})$ and are termed *complex-balanced*. If $\delta > 0$, this is no longer true. In what follows, we derive some new results for CRN's in this category.

¹¹The general closed form expression for the commutation of $a_p^{k_p}$ through any power of $a^\dagger$ is given in equation (31).

¹²A linkage class is a connected component of the directed graph representing the CRN; $l=1$ for the CRN described by equation (1) and $l=2$ for the CRN described by equation (2).

From the above discussion, it follows that we can define basis vectors $\{e_i\}_{i=1}^s$ for $\ker(Y\mathcal{A})^\perp$, the space of vectors perpendicular to those lying in $\ker(Y\mathcal{A})$.

Let also $\{\tilde{e}_j\}_{j=1}^\delta$ be a basis for $\ker(Y\mathcal{A})/\ker(\mathcal{A})$, the space of vectors lying in $\ker(Y\mathcal{A})$ but *not* in $\ker(\mathcal{A})$.

It follows that jointly $\{\{e_i\}_{i=1}^s, \{\tilde{e}_j\}_{j=1}^\delta\}$ form a basis for $\ker(\mathcal{A})^\perp$.

Then from equation (21),

$$-\mathcal{L} = \psi_Y^\dagger \mathcal{A} \left\{ \sum_{i=1}^s e_i e_i^T + \sum_{j=1}^\delta \tilde{e}_j \tilde{e}_j^T \right\} \psi_Y. \quad (30)$$

That the second sum does not play a role for $\delta = 0$ networks, has implications for the steady state, as we will see in section 2.6. It is easy to explicitly work out these basis vectors for specific examples (such as the networks of figures 1 and 2) [30].

2.5. Equation for the factorial moments

Equation (25) is valid for a generic FM, but may be simplified further by writing the RHS in terms of the matrices Y and $\mathcal{A}$, in correspondence to the equation for the first moment equation (28). In order to see this, we need to understand what terms we get when we commute $a_p^{k_p}$ through $\psi_Y^\dagger(a^\dagger)$ which contains terms like $a_p^{\dagger y}$. For non-negative integers k_p and y , we can use the relation

$$(a_p^{k_p} a_p^{\dagger y}) = \sum_{j=0}^{k_p} \binom{k_p}{j} y^j - a_p^{\dagger y-j} a_p^{k_p-j} \quad (31)$$

where $y^0=1$. For $j=0$, $y^j=(y)(y-1)\cdots(y-j+1)$ for $j=1, \dots, y$ and $y^j=0$ otherwise. It is now easily seen that,

$$(0|e^a(a_p)^{k_p}\psi_Y^\dagger(a^\dagger)=(0|\sum_{j=0}^{k_p} \binom{k_p}{j} (Y_p)^j - e^a(a_p)^{k_p-j} \quad (32)$$

where $(Y_p)^j$ is the matrix Y with the elements in the p th row modified to $y_{p,i}^j$, $\psi(a^\dagger=1)=1$, because $(0|e^a a^{\dagger y}=(0|(1+a^\dagger)^y e^a=(0|e^a$.

The equation for the time-dependence of $n_p^{k_p}$ may hence be compactly written as

$$\frac{\partial}{\partial \tau} \left\langle n_p^{k_p} \right\rangle = \sum_{j=0}^{k_p} \binom{k_p}{j} (Y_p)^j \mathcal{A} E \left[a_p^{k_p-j} \psi_Y(a) \right]. \quad (33)$$

Note that in equation (33), $j=0$, does not contribute since this multiplies $\mathcal{A}$ by a row vector of 1's, which is a zero left eigenvector. Hence for $k_p = 1$, only the $j = 1$ term contributes.

This gives $(Y_p)^1 = Y_p$, resulting in the RHS of equation (28).

Equation (33) may also be easily generalized in order to calculate mixed moments as in equation (23). For this we need to consider the action of the lowering operators $\prod_p a_p^{k_p}$ (as in equation (25)) which, by their action on $|\phi\rangle$ result in mixed moments $\left\langle \prod_p n_p^{k_p} \right\rangle$. By considering the generalisation of equation (31), the equation for the time derivative of such a mixed moment is seen to be,

$$\frac{\partial}{\partial \tau} \left\langle \prod_p n_p^{k_p} \right\rangle = \sum_{j_1=0}^{k_1} \binom{k_1}{j_1} \cdots \sum_{j_p=0}^{k_p} \binom{k_p}{j_p} \left[\prod_p Y_p^{j_p} \right] \mathcal{A} E[\Psi_{Y+(k-j)}(n)]. \quad (34)$$

The notation $\prod_p$ denotes a product over species p within each index i of the row vectors $Y_p^{j_p}$. Note that in the sums over j_p , we must now retain the $j_p = 0$ entries, because even if one index $Y_p^{j_p} = [1]^T$, there may be others in the sum where $j_{p'} \neq 0$, and the product $\left(\prod_p Y_p^{j_p} \right) \mathcal{A}$ is only assured to vanish when all $j_p = 0$. The term $E[\Psi_{Y+(k-j)}(n)]$ is a shorthand notation for $E \left[\prod_p a_p^{k_p-j_p} \psi_Y(a) \right]$.

Note that though equations (33) and (34) may be derived directly from the master equation (without going through the Doi algebra), the simplification that comes from noting the relation of the coefficients to the matrices Y and $\mathcal{A}$ is only possible within the formalism we introduce here. This in turn helps in writing and solving recursion relations to solve the entire moment hierarchy as we demonstrate in section 2.7.

2.6. A one-line proof of the ACK theorem

We explain how the ACK theorem follows very simply from the considerations above. Without loss of generality we limit this discussion to equation (33), for ease of presentation.

From the considerations in section 2.4, equation (33) may be re-written as,

$$\frac{\partial}{\partial \tau} \langle n_p^{k_p} \rangle = \sum_{j=0}^{k_p} \binom{k_p}{j} (Y_p)^j \mathcal{A} \left\{ \sum_{i=1}^s e_i e_i^T + \sum_{j=1}^{\delta} \tilde{e}_j \tilde{e}_j^T \right\} \times E \left[a_p^{k_p-j} \psi_Y(a) \right]. \quad (35)$$

In particular, the equation for the first moment equation (28), can be written as

$$\frac{\partial}{\partial \tau} \langle n_p \rangle = Y_p \mathcal{A} \sum_{i=1}^s e_i e_i^T E[\psi_Y(a)] \quad (36)$$

where we have used the fact that all other basis vectors are projected to zero by $Y_p \mathcal{A}$.

Hence for $\delta = 0$ networks with mass-action rates, the entire hierarchy of moments, equation (35) for any value of k_p , is satisfied if

$$e_i^T E[\psi_Y(a)] = 0 \quad (37)$$

for every $i = 1, \dots, s$. The notation $E[\]$ denotes now an average over a specific distribution: a Poisson distribution. Note that for a Poisson distribution, an equation for the first moment is the same as a *rate equation* (since $\langle n^k \rangle = \langle n^k \rangle$). Hence, for $\delta = 0$ networks, the condition that the rate equation has a unique solution also guarantees that the entire moment hierarchy is solved, whereby follows the ACK theorem [2].

2.7. Steady-state recursions

For CRN's for which $\delta = 0$, there is no general way to satisfy the full moment-hierarchy of equation (34) by demanding that any combination of e and $\tilde{e}$ vanish.

Note though that the sums Σ_j in equation (34), only extend from $j = 0$ to $j = j_{\max}$ with the latter determined by when row $Y_p^{j_{\max}}$ vanishes. For the CRN in figure 1, $j_{\max} = 4$, while for the CRN in figure 2, there are two sums over j in equation (34), both with $j_{\max} = 3$.

This helps us write equation (33) (or equation (34) in the general case), as a recursion relation for the ratios of FM's in the steady state. We demonstrate this for the two examples

introduced above. For the CRN of figure 1 if we define $R_k \equiv \frac{\langle n^k \rangle}{\langle n^{k-1} \rangle}$ ¹³, then equation (33) may be rewritten *exactly* as the following recursion relation for $k > 1$ ¹⁴,

¹³For one species $k = k_p$

¹⁴The moment recursions for this CRN leave $k = 1$ undetermined. However this does *not* mean that R_1 is free to take any value. Moments of a probability distribution satisfy inequalities [31] such as the elementary relation $R_2 \geq (R_1 - 1)$. These presumably constrain the first moment to its actual value.

$$R_k = \frac{(k-1) \left(\frac{\alpha}{\beta} + \frac{\varepsilon}{\beta} (k-2) \right)}{(k-1) \left(2R_{k+1} + (k-2) \frac{\varepsilon}{\beta} \right) + R_{k+2} R_{k+1} - \frac{\alpha}{\beta}}. \quad (38)$$

We have written the recursion for R_k for descending k because, while we do not know the value of R_k for small k , we do know it for large k , where $R_k \sim \varepsilon/\beta$ (as evident from equation (38)). If we begin from this ‘asymptotic’ value at arbitrarily large k , we have a procedure to obtain the value of R_k all the way down to $k=2$, for any choice of parameters¹⁵ The result is shown in figure 3. Equation (38) being *exact*, the results of the recursions and the Monte-Carlo simulations agree to arbitrary accuracy, limited only by the amount of averaging done in the simulations (and we expect this to be the case for any set of parameters)¹⁶.

The one-species case we have considered is an example of a birth-death process [31] for which many results are known, including the steady state. The recursions equation (38) however, give us a particularly easy way, albeit numerical, to obtain this steady state. In addition, while there exists no general formalism to obtain the steady state for CRN’s which are *not* birth-death processes, the above procedure is, in principle, applicable to any CRN, such as the two-species CRN of figure 2, as we show below.

The moment hierarchy for the two-species case consists of mixed moments such as

$\langle n_a^k n_b^{k'} \rangle$. This CRN has no conservation law, so solving the full moment hierarchy is equivalent to solving for the full probability distribution $P(n_a, n_b)$ which is, in addition, *not* factorized. In analogy with the one-species case, we can write a coupled set of recursions for

the quantities $T_k \equiv \frac{\langle n_a^k n_b^k \rangle}{\langle n_a^{k-1} n_b^{k-1} \rangle}$ and $S_k \equiv \frac{\langle n_a^k n_b^{k-1} \rangle}{\langle n_a^{k-1} n_b^{k-1} \rangle}$. For large k , the equations for the FM predict that $T_k \sim (k_1/\bar{k}_1)^2$ and $S_k \sim (k_1/\bar{k}_1)$.

Using the symmetries of this CRN (in the exchangeability of the species A and B; hence

$\langle n_a^k n_b^{k'} \rangle = \langle n_a^{k'} n_b^k \rangle$, and approximating $\frac{\langle n_a^{k-2} n_b^k \rangle}{\langle n_a^{k-1} n_b^{k-1} \rangle} \sim 1$ ¹⁷, we obtain two coupled recursions,

¹⁵We often want to obtain the actual moments and not just their ratios. Note that this is possible since $R_1 \equiv \langle n \rangle$. Hence,

$\langle n^2 \rangle = R_2 R_1$, $\langle n^3 \rangle = R_3 R_2 R_1$ etc.

¹⁶The downward recursion equation (38) may however not converge below k -values much smaller than $\langle n \rangle$ for parameter values which make the latter large. In this case, an *upward* recursion, for larger k in terms of smaller k can be written and both upward and downward recursions solved simultaneously. In [30], we elaborate on this further.

¹⁷We have verified this numerically. A theoretical justification comes from looking at the analytic form of the FM in the large- k , k' limit [30]. We can show that to leading order the FM are only functions of $k + k'$ thus validating this approximation.

$$T_k = \frac{2\varepsilon k - \varepsilon + k k_1 (k-1)(2k-3)}{S_{k+1}C + T_{k+1}D + E} \quad (39)$$

$$S_k = T_k (S_{k+1}C_1 + T_{k+1}D_1 + E_1)$$

where C, D etc are functions of k as well as the rate constants $k_1, \bar{k}_1$ etc in the problem. Again, for large k , it is easy to see from the recursions (after putting in the expressions for C, D etc), that $T_k \sim \left(\frac{k_1}{\bar{k}_1}\right)^2$ and $S_k \sim \frac{k_1}{\bar{k}_1}$ as required by the equations for the FM. Beginning from this value at some arbitrarily large value of k , we can predict values for T_k all the way down to $k = 2$ as shown in figure 4.

Note that R_k saturating to a constant value independent of k in the one-species case is as if the large- k moments obey a Poisson distribution with parameter ε/β ¹⁸. Similarly T_k and S_k saturating to constant values is equivalent to the large- k behaviour of the two-species system being describable by a factorised Poisson distribution with parameter $(k_1/\bar{k}_1)$. From the form of equation (33) in the steady state, it is evident that, even with an arbitrary number of species, there will always be a limited number of terms which will dominate for large moments. Demanding that these terms vanish will hence always lead to a factorized Poisson distribution which will approximately (up to corrections of order $1/k$) solve the moment hierarchy. On the other side, at $k = 1$, the equation for the first moment can also be solved by postulating a factorized Poisson distribution with the parameter of the Poisson determined by the rate equation of the problem. These two Poisson distributions have different parameters and are both, for a $\delta = 0$ - network, only approximations for the true distribution. Nevertheless, they are helpful in implementing a systematic approximation procedure to solve the moment hierarchy as we elaborate in a following paper [30].

2.8. Quasi steady states

The CRN's we have considered so far have been *reversible* in the sense that every reaction is accompanied by its reverse. We now consider a CRN which is neither reversible nor even weakly reversible:

¹⁸ R_k could also be a constant if the distribution was a delta function around ε/β . This can however not happen when fluctuations in the number are possible.

This CRN has been considered in [13] in the context of understanding properties of the quasi-stationary distribution. The true steady state of this model is an absorbing state with $n_b = 0$. However when $n_a + n_b = M$, and M is large, the system could take a very long time to reach this absorbing state, and reach instead a quasi-stationary distribution. All properties of the quasi-stationary distribution are easily derivable for this model [13] and it is seen that as $M \rightarrow \infty$, this distribution is a Poisson with parameter β/α [13]. The equations for the FM,

give this result very easily as well. If we define $X_k \equiv \frac{\langle n_a^k n_b^{k'-1} \rangle}{\langle n_a^{k-1} n_b^{k'-1} \rangle}$, then it is easily seen that the CRN of equation (40) leads to the recursions

$$X_k = \frac{k\beta M^2}{k\alpha M^2 + A + X_{k+1}B + X_{k+1}X_{k+2}\alpha(k+k')}. \quad (41)$$

A and B are linear in M , and hence for large M and $k' = 1$, $X_k \sim \frac{\beta}{\alpha}$ for any k , as expected for the ratios of the FM of a Poisson distribution¹⁹.

3. Conclusion

To conclude, the structure of the equations for the FM help us write them as recursions for ratios of FM, which then can be solved numerically, beginning from an asymptotic estimate (predicted by the equations themselves). The equations for the FM (equations (33) or (34)) are exact and given any CRN, are easy to write down. In this paper, we have illustrated this procedure for two toy models. However, there are several physically relevant model-CRN's in the biochemistry, systems-biology, ecology and epidemiology contexts, to which we expect to be able to apply our methods.

It should be noted however, that except in the case of very few species, or very simple stoichiometry, the recursions obtained from these equations could get complicated to solve. It would hence be very useful if this procedure could be systematised in some way independent of the particular CRN under study, perhaps with the help of some of the techniques available in the large body of work that exists on efficient ways to truncate the moment hierarchy in CRN's [20]. In [30], we have provided alternate approximation schemes (differing from moment-closure schemes) for the FM equations, related to asymptotic expansions in the low- k and large- k limit. These methods might be applicable, even in the case when recursions like equations (38) and (39) are hard to obtain for CRN's with many species.

CRN's with non-mass-action kinetics could also be interesting to look at [32]. Finally, though we have only concentrated on the static properties here, the Liouvillian contains all information on the dynamics as well, which can be investigated further, in the spirit of [33].

¹⁹Note that $X_k = M$ is also a solution for $k' = 1$. This is the absorbing state.

Acknowledgments

SK would like to thank Artur Wachtel for very useful discussions during the Nordita program ‘Stochastic thermodynamics in biology’ (2015). DES thanks Nathaniel Virgo for discussions and the Stockholm University Physics Department for hospitality while this work was being carried out. DES also acknowledges support from the NASA Astrobiology Institute Cycle 7 Cooperative Agreement Notice (CAN-7) award: Reliving the History of Life: Experimental Evolution of Major Transitions.

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Figure 1.

A compact graphical representation for a CRN: the filled circle with label *A* represents the *species A* while each open circle represents a *complex*, such as $2A$. The number of solid lines connecting each species to each complex, represents the *stoichiometry* of the complex. Each dashed line connecting two complexes represents a *reaction*.

Figure 2.
A CRN involving two species A and B. The complex with no solid lines attached to it is the null node $\emptyset$.

Figure 3. Numerical evaluation of the recursions of equation (38) (line) compared to values from Monte-Carlo simulations (symbols) for $\alpha = 100$, $\beta = 10$ and $\varepsilon = 70$. For large k , R_k saturates to $\varepsilon/\beta = 7$ as explained in the text.

Figure 4. Numerical evaluation of the recursions of equation (39) (line) compared to values from Monte-Carlo simulations (symbols) for $k_1 = 1$, $\bar{k}_1 = 1$, $\varepsilon = 36$ and $k_2 = 49$. For large k , T_k saturates to $(k_1/\bar{k}_1)^2 = 196$. The values obtained from the recursions and simulations agree upto the first decimal place for any k .