Bounding Transient Moments of Stochastic Chemical Reactions

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Abstract

The predictive ability of stochastic chemical reactions is currently limited by the lack of closed form solutions to the governing chemical master equation. To overcome this limitation, this paper proposes a computational method capable of predicting mathematically rigorous upper and lower bounds of transient moments for reactions governed by the law of mass action. We first derive an equation that transient moments must satisfy based on the moment equation. Although this equation is underdetermined, we introduce a set of semidefinite constraints known as moment condition to narrow the feasible set of the variables in the equation. Using these conditions, we formulate a semidefinite program that efficiently and rigorously computes the bounds of transient moment dynamics. The proposed method is demonstrated with illustrative numerical examples and is compared with related works to discuss advantages and limitations.

1 Introduction

Chemical processes in living cells are highly stochastic unlike those in engineered batch reactors because of the low abundance of reacting molecules in a cell. The stochastic reactions result in large cell-to-cell variations of molecular copy numbers and lead to phenotypic diversity, which is often considered to be beneficial for bet hedging against perturbations. Thus, in biology, the dynamics of cellular reactions are often measured as the snapshots of population distributions rather than a trajectory of a single representative cell (see [1–5] for example).

The dynamics of stochastic chemical reactions are modeled by a discrete state Markov process, where the state represents the copy number of molecules. The evolution of the stochastic process is, thus, characterized by Kolmogorov forward equation, also known as the chemical master equation (CME) [6]. Unfortunately, an exact analytic solution to the CME is not known except for some simple reactions due to the fact that the state of the Markov chain is semi-infinite, i.e. a set of non-negative integers. Consequently, the stochastic chemical reactions are currently analyzed by time consuming sample-path simulations [7] or approximation based techniques such as the finite state projection [8,9], linear noise approximation [10] and Langevin equations [11–14].

Other approaches attempt to directly compute the moments of the stochastic process based on moment equation, the governing equation of moment kinetics derived from the CME. This approach enables a direct characterization of the statistics of stochastic chemical reactions such as the mean and the covariance of molecular abundance. However, the moment equation essentially faces the same problem as the CME — the equation forms an infinite chain of ODEs, and the solution is analytically intractable for most stochastic reactions of interest. To deal with this issue, moment closure [15–17] is widely used to obtain a (truncated) finite order equation by approximately expressing high order moments with low order moments at the cost of accuracy.

On the other hand, computing moments with guaranteed precision remains an active research topic. In [18], a recursive algorithm was proposed to obtain bounds of moments based on concentration inequalities. More recently, a semidefinite program (SDP) [19] was formulated to compute guaranteed upper/lower bounds of steady state moments based on the moment equation [20–25]. These works also used the

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truncated moment equation used in the moment closure, but they compensated for the truncated moments based on a relaxation that a moment matrix, a matrix defined by a product of monomial vectors, is positive semidefinite. The use of the semidefinite relaxation was motivated by its close connection with a so-called moment condition, a necessary and sufficient condition for a given sequence of real numbers to be moments of some non-negative measure (probability distribution) under some assumptions [20]. Although complete understanding the underlying mechanism requires further study, the previous works demonstrated that this approach could give surprisingly tight bounds of steady state moments only with a small number of moments [20] [25].

Building upon the idea for the steady state moment computation [20] [24], this paper presents a semidefinite program capable of computing the upper and lower bounds of transient, or dynamic, moments for stochastic reactions consisting of elementary reactions. An obvious requirement for this extension is the introduction of new variables and constraints for the transient moments. For this purpose, we introduce “temporal moments”, the moments of state variables and time. Conceptually, this means that we regard the time variable $t$ as part of random variables and attempt to compute the moments of a measure supported on the state space of the Markov chain and a real number. This leads to a new equality constraint that replaces the steady state moment equation used in the previous study [20, 24] and introduces additional semidefinite conditions that correspond to moment conditions. Consequently, we obtain a semidefinite program for computing the transient statistics of molecular abundance.

It should be noted that, recently, a similar approach was developed in parallel by Dowdy and Barton [27]. A main difference from the proposed method is that a moment generating function of $t$ is considered instead of a moment itself to constrain the values of transient moments. This results in different semidefinite conditions from the proposed method, and the computed bounds are indeed different. Here we also discuss how these different formulations affect the tightness of the bounds by comparing the results for multiple reaction examples.

This paper is organized as follows. In Section II.A, we introduce the moment equation. Then, in Section II.B, we define the temporal moment and formulate the optimization problem. Illustrative numerical examples are provided in Section III, and the results are compared between the proposed approach and the one in [27]. Finally, Section IV concludes this paper.

The following notations are used in this paper. $\mathbb{N} := \{1, 2, 3, \cdots \}$. $\mathbb{N}_0 := \mathbb{N} \cup \{0\}$. $\mathbb{Z}$ is a set of all integers. $\mathbb{R}_+ := \{x \in \mathbb{R} \mid x \geq 0\}$. $\mathbb{R}[\mathbf{x}]$ is the set of all polynomials with real coefficients. $\text{deg}(p(\mathbf{x})) := \sum_{j=1}^{n} p_j$ is the degree of a monomial $p(\mathbf{x}) = \prod_{j=1}^{n} x_j^{p_j}$.

## 2 Computation of moment dynamics of stochastic chemical reactions

### 2.1 Moment dynamics of stochastic chemical reactions

In this section, we introduce a general mathematical model of stochastic chemical reactions and review an ordinary differential equation (ODE) model of moment dynamics. Consider a chemical reaction system that consists of $n \in \mathbb{N}$ species of molecules and $r$ types of reactions. The copy numbers of the $n$ molecules are denoted by $\mathbf{x} := [x_1, x_2, \cdots, x_n]^T \in \mathbb{K}$, where $\mathbb{K} \subseteq \mathbb{N}_0^r$ represents a set of all possible combinations of copy numbers. The copy numbers $\mathbf{x}$ specify the state of the reaction system and fluctuate in time due to stochastic chemical reactions. The stochastic fluctuation of the copy numbers $\mathbf{x}$ can be modeled by a Markov process. Specifically, we define $P_{\mathbf{x}}(t)$ as the probability that there are $\mathbf{x}$ molecules at time $t$. Then the dynamics of $P_{\mathbf{x}}(t)$ follows the following Chemical Master Equation (CME) [6],

$$\frac{dP_{\mathbf{x}}(t)}{dt} = \sum_{i=1}^{r} \{ w_i(\mathbf{x} - \mathbf{s}_i)P_{\mathbf{x}-\mathbf{s}_i}(t) - w_i(\mathbf{x})P_{\mathbf{x}}(t) \},$$

(1)

where $w_i(\mathbf{x})$ is the propensity function (reaction rate) of the $i$-th reaction ($i = 1, 2, \cdots, r$), and $\mathbf{s}_i = [s_{i1}, s_{i2}, \cdots, s_{im}]^T \in \mathbb{Z}^n$ is the stoichiometry of the $i$-th reaction. We assume that all reactions are elementary. That is, each reaction is either a unimolecular or a bimolecular reaction, and the propensity function $w_i(\cdot)$ is a polynomial of $x_j$ ($j = 1, 2, \cdots, n$) [28].
To derive an ODE model of moment dynamics based on the CME \([1]\), we define a raw moment of a probability distribution \(P_x(t)\) by

\[
m_\alpha(t) := E_t \left[ \prod_{j=1}^{n} x_j^{\alpha_j} \right] = \sum_{x \in \mathbb{K}} \prod_{j=1}^{n} x_j^{\alpha_j} P_x(t),
\]

where \(\alpha := [\alpha_1, \alpha_2, \ldots, \alpha_n] \in \mathbb{N}_0^n\). We then multiply \(\prod_{j=1}^{n} x_j^{\alpha_j}\) to both sides of the CME \([1]\) and take sum over \(\mathbb{K}\) to obtain an ODE of moments known as moment equation

\[
\frac{d}{dt} m(t) = Am(t) + Bu(t),
\]

where \(A\) and \(B\) are constant matrices whose entries are linear combinations of the rate constants of the propensity functions \(w_i(\cdot)\), and \(m(t)\) and \(u(t)\) are vectors of raw moments up to the \(\mu\)-th order and those of the \(\mu + 1\)-th order, respectively (see Section 2.2 and S.3 of \([24]\) for derivation). The moment equation \([3]\) implies that the raw moments of the \(\mu + 1\)-th order, i.e., the entries of \(u(t)\), are required for computing the moments up to the \(\mu\)-th order, i.e., the entries of \(m(t)\). Thus, we need to estimate \(u(t)\) to obtain the solution \(m(t)\) of the moment equation.

In the next section, we present an approach to solving the equation \([3]\) without explicitly computing \(u(t)\). The proposed approach utilizes a so-called moment condition to find the lower and upper bounds of the moments \(m(t)\) of molecular copy numbers \(x\) at time \(t\). This allows us to rigorously bound the transient statistics of the copy numbers \(x\) over time.

### 2.2 Semidefinite programming for transient moment analysis

In this section, we present a mathematical optimization problem for rigorously bounding the transient moments. Our derivation is based on the recently proposed method for computing the steady state moments \([20, 25]\).

Let \(\hat{m}_s(T_1, T_2)\) and \(\hat{u}_s(T_1, T_2)\) be defined by

\[
\hat{m}_s(T_1, T_2) := \int_{T_1}^{T_2} t^s m(t) dt,
\]

\[
\hat{u}_s(T_1, T_2) := \int_{T_1}^{T_2} t^s u(t) dt,
\]

where \(s \in \mathbb{N}_0\). We derive an equation of these vectors by multiplying \(t^s\) to both sides of the moment equation \([3]\) and taking the integral of time \(t\) as

\[
\int_{T_1}^{T_2} t^s \frac{d}{dt} m(t) dt = \int_{T_1}^{T_2} t^s m(t) dt + \int_{T_1}^{T_2} t^s u(t) dt.
\]

Using integration by parts, this equation can be calculated as

\[
T_2^s m(T_2) - T_1^s m(T_1) - s \hat{m}_{s-1}(T_1, T_2)
= A \hat{m}_s(T_1, T_2) + B \hat{u}_s(T_1, T_2),
\]

where we define \(\theta^0 = 1\) in the case of \(T_i = 0\) \((i = 1, 2)\) and \(s = 0\).

The transient values of raw moments at time \(T_1\) and \(T_2\) could be obtained if we could solve the linear equation \([6]\). In particular, if we have a priori knowledge of the moments at the initial time, say \(T_1 = 0\), the transient moment computation reduces to finding \(m(T_2)\) for the given initial moment \(m(T_1)\). In general, however, the equation \([6]\) is underdetermined, and the solution is given only as a certain linear subspace.

Thus, we need more conditions to further specify the solution space of the moments \(m(T_2)\), \(u(T_2)\), \(\hat{m}_s(T_1, T_2)\) and \(\hat{u}_s(T_1, T_2)\). Here, we use the fact that the entries of these vectors must be moments of some non-negative measure. It should be noted that \(\hat{m}_s(T_1, T_2)\) and \(\hat{u}_s(T_1, T_2)\) can be viewed as moments of a non-negative measure defined on \(\mathbb{K} \times [T_1, T_2]\).
To this end, we start by introducing conditions for \( m(T_2) \) and \( u(T_2) \) to be moments. Let \( X := [(x^0)^T, (x^1)^T, \ldots, (x^n)^T]^T \) with \( x^p \) being a vector of monomial bases satisfying \( \deg(\prod_j x_j^p) = p \). It then follows that the entries of the matrix

\[
H_0([m_{\alpha}]) := \mathbb{E}_t[XX^T] = \sum_{x \in \mathbb{K}} XX^T P_x(t)
\]

(7)

consist of the moments \( m_{\alpha}(t) \), which are the entries of \( m \) and \( u \). Moreover, \( H_0([m_{\alpha}]) \geq O \) holds due to its definition (7). Thus, \( H_0([m_{\alpha}]) \) constitutes a linear matrix inequality (LMI) condition that the entries of \( m \) and \( u \) must satisfy.

The moment values can further be constrained by using the fact that the moments are defined for the measure \( P_x(t) \) on \( \mathbb{K} \). Let \( \mathbb{K} \) denote a semi-algebraic set specified by real polynomials \( g_k(x) \), i.e.,

\[
\mathbb{K} := \{ x \in \mathbb{R}^n \mid g_k(x) \geq 0, g_k \in \mathbb{R}[x] (k = 1, 2, \ldots, \ell) \}
\]

and satisfying \( \mathbb{K} \subseteq \mathbb{R}(\subseteq \mathbb{R}^n) \). We can then obtain a condition \( H([m_{\alpha}], g_k) \geq O \), which \( m \) and \( u \) must satisfy, where

\[
H([m_{\alpha}], g_k) := \mathbb{E}_t[g_k(x)XX^T] = \sum_{x \in \mathbb{K}} g_k(x)XX^T P_x(t).
\]

(8)

**Example.** When the state space of the Markov chain in (11) is \( n = 1 \) dimension and non-negative integers, i.e., \( \mathbb{K} = \mathbb{N}_0 \), we can define \( \mathbb{K} = \mathbb{R}_+ \) with \( g_1(x) = x \). Then, the moments of the probability distribution \( P_x(t) \) must satisfy

\[
\begin{bmatrix}
m_0(t) & m_1(t) \\
m_1(t) & m_2(t)
\end{bmatrix} \geq O,
\]

(7)

\[
\begin{bmatrix}
m_1(t) & m_2(t) \\
m_2(t) & m_3(t)
\end{bmatrix} \geq O
\]

(8)

for each \( t \), where \( \gamma_1 = 1 \) in this example. Since principal minors of a positive semidefinite matrix are non-negative, the second inequality implies non-negativity of the mean \( m_1(t) \geq 0 \), which indeed constrains the moment value.

In summary, we have the following proposition.

**Proposition 1.** Consider \( m_{\alpha}(t) (\alpha \in \mathbb{N}_0^n) \) defined by (2), which are the moments of the probability measure \( P_x(t) \) defined on \( \mathbb{K} \). Then, the following LMIs hold.

\[
H_0([m_{\alpha}]) \geq O,
\]

(9)

\[
H([m_{\alpha}], g_k) \geq O \quad (k = 1, 2, \ldots, \ell),
\]

(10)

where \( H_0([m_{\alpha}]) \) and \( H([m_{\alpha}], g_k) \) are defined in (7) and (8), respectively.

These LMIs serve as additional convex constraints to restrict the possible values of the moments \( m(\cdot) \) and \( u(\cdot) \) in the linear equation (6). Thus, combining the LMIs (9) and (10) with (6), we can formulate a semidefinite program (SDP) that computes upper and lower bounds of moment values, which will be seen in detail at the end of this section. In general, we can obtain progressively tighter bounds by increasing the order of the moments \( \mu \) of the vector \( m \) and the associated LMI conditions, i.e., \( \gamma_1 \) in (7) and (8) since it increases the number of equalities (6) and associated inequality conditions.

**Remark 1.** The LMIs (9) and (10) can be viewed as a necessary condition for a given sequence \( \{m_{\alpha}\} \) to be moments of some positive measure supported on \( \mathbb{K} \). It is known that, in some cases, the LMIs are also sufficient. In fact, the semidefinite conditions are known as moment condition and have been studied for more than a century (see [26] for example). For instance, for \( n = 1 \) (univariate moments), the LMIs (9) and (10) with \( g_1(x) = x \) and \( \gamma_1 \to \infty \) become a necessary and sufficient condition for the existence of a positive measure supported on \( \mathbb{R}_+ ^{\ell} \). A similar LMI based sufficient condition is known when \( n \geq 1 \) and \( \mathbb{K} \) is compact (K-moment condition) [26]. The use of the moment conditions in our work is motivated by these necessary and sufficient conditions, though there remain many open problems regarding the sufficiency.
Using the same approach, we derive conditions that constrain possible values of $\hat{m}_{\alpha, s}(T, 2)$ and $\hat{u}_s(T_1, T_2)$. Each entry of these vectors is represented by

$$\hat{m}_{\alpha, s}(T, 2) = \int_{T_1}^{T_2} t^s \sum_{x \in \mathbb{K}} \prod_{j=1}^{n} x_j^\alpha_j P_x(t) dt.$$  \hfill (11)

This can be viewed as a moment of a measure defined on $\mathbb{K} \times [T_1, T_2]$. Thus, it is possible to derive a similar condition to Proposition 1. We define a vector $\hat{X}$ by $\hat{X} := [X^T t^0, X^T t^1, \ldots, X^T t^{\ell}]^T$, and real polynomials $\hat{g}_k(x, t)$ ($k = 1, 2, \ldots, \ell'$) that specify a semi-algebraic set

$$\mathbb{K} \times [T_1, T_2] = \{(x, t) \in \mathbb{R}^n \times \mathbb{R} | \hat{g}_k(x, t) \geq 0, \hat{g}_k \in \mathbb{R}[x, t] \ (k = 1, 2, \ldots, \ell')\}. \hfill (12)$$

Then the following proposition holds.

**Proposition 2.** Consider $\hat{m}_{\alpha, s}(T, 2)$ ($\alpha \in \mathbb{N}_0^n$, $s \in \mathbb{N}_0$) defined by (11). Let $\hat{H}_0(\hat{\alpha}, s)$ and $\hat{H}(\hat{m}_{\alpha, s}, \hat{g}_k)$ be

$$\hat{H}_0(\hat{\alpha}, s) := \int_{T_1}^{T_2} \mathbb{E}[\hat{X} \hat{X}^T] dt$$

$$= \int_{T_1}^{T_2} \sum_{x \in \mathbb{K}} \hat{X} \hat{X}^T P_x(t) dt, \hfill (13)$$

$$\hat{H}(\hat{\alpha}, s, \hat{g}_k) := \int_{T_1}^{T_2} \mathbb{E}[\hat{g}_k(x, t) \hat{X} \hat{X}^T] dt$$

$$= \int_{T_1}^{T_2} \sum_{x \in \mathbb{K}} \hat{g}_k(x, t) \hat{X} \hat{X}^T P_x(t) dt. \hfill (14)$$

Then, the following LMIs hold.

$$\hat{H}_0(\hat{\alpha}, s) \succeq O, \hfill (15)$$

$$\hat{H}(\hat{\alpha}, s, \hat{g}_k) \succeq O \ (k = 1, 2, \ldots, \ell'). \hfill (16)$$

The proof is clear from the definitions (13) and (14). Similar to Proposition 1, the LMIs (15) and (16) become constraints for the values of the moments $\hat{m}_{\alpha, s}(T_1, T_2)$ and $\hat{u}_s(T_1, T_2)$. In the case of $\mathbb{K} = \mathbb{R}_+^n$, the function $\hat{g}_k(x, t)$ can, for example, be defined as

$$\hat{g}_k(x, t) = \begin{cases} x_k & (k = 1, 2, \ldots, n) \\ t - T_1 & (k = n + 1) \\ T_2 - t & (k = n + 2) \end{cases}. \hfill (17)$$

**Remark 2.** There can be many possible choices of polynomials $g_k(x)$ and $\hat{g}_k(x, t)$ to represent $\mathbb{K}$ and $\mathbb{K} \times [T_1, T_2]$, respectively. The choice of the polynomials may affect the tightness of the bounds of the moments, but it is left open to explore what choices give tighter bounds in general.

**Optimization problem** Finally, we combine the equation (6) and the LMIs (9), (10), (15) and (16) to formulate an optimization problem that computes the bounds of the statistics of the copy numbers $x$. Consider the stochastic chemical reaction modeled by the equation (1). The following optimization problem gives the lower bound of a statistics $f(m(t), u(t))$ or the upper bound of $-f(m(t), u(t))$.

$$\min \ f(m(t), u(t))$$

s.t. \hspace{1cm} (6), (9), (10), (15) and (16).

The matrices $H_0(\hat{\alpha}, s)$, $H(\hat{m}_{\alpha, s}, \hat{g}_k)$, $H_0(\hat{\alpha}, s)$, and $H(\hat{m}_{\alpha, s}, \hat{g}_k)$ should contain all the moments that appear in the equation (6). Thus, $\gamma_1$ and $\gamma_2$, which determines the size of the vectors $X$ and $\hat{X}$ should be defined depending on $\mu$, the highest order of the moments in $m$, and $\nu$, the highest exponent of
Table 1: List of reactions and associated definitions

| Index | Reaction          | Propensity | Stoichiometry $s_i$ of P |
|-------|-------------------|------------|--------------------------|
| 1     | $D \rightarrow P$ | $k_1 D$    | 1                        |
| 2     | $P \rightarrow \phi$ | $k_2 x$   | -1                       |
| 3     | $P + P \rightarrow P:P$ | $k_3 x(x - 1)$ | -2                       |

Figure 1: Bounds of the statistics of monomer protein P using the proposed approach with $\mu = 7$. The SSA simulation [7] is based on 50,000 sample paths. (A) the mean copy number (B) the variance of the copy number.

In what follows, we analyze the mean and the variance of the monomer protein P at the transient state. To this end, we consider a truncated moment equation (3) with $\mu = 7$, where the moment vectors are $\mathbf{m}(t) = [m_0(t), m_1(t), \ldots, m_7(t)]^T$ and $u(t) = m_8(t)$. Note that, by definition (2), $m_0(t) = 1$, and the mean and the variance of the copy number $x$ are $m_1(t)$ and $m_2(t) - m_1(t)$, respectively. To compute the transient values of the moments, we define the vectors of moments $\hat{\mathbf{m}}_s(0, T)$ and $\hat{u}_s(0, T)$ by (4) and (5).

We assume the initial state is $x(0) = 0$ for all the cells (samples), that is, $P_0(0) = 1$. Then, we obtain
the equality constraints \(\{6\}\), which can be represented by

\[
\begin{bmatrix}
  m(T) \\
  Tm(T)
\end{bmatrix} - \begin{bmatrix}
  I \\
  O
\end{bmatrix} m(0) = \begin{bmatrix}
  A & O \\
  I & A
\end{bmatrix} \begin{bmatrix}
  \hat{m}_0(0,T) \\
  \hat{m}_1(0,T)
\end{bmatrix} + \begin{bmatrix}
  b & O \\
  O & b
\end{bmatrix} \begin{bmatrix}
  \hat{u}_0(0,T) \\
  \hat{u}_1(0,T)
\end{bmatrix}
\]

where \(m(0) = [1, 0, 0, \ldots, 0]^T \in \mathbb{R}^8\), and the highest exponent of time is set as \(\nu = 1\) for an illustration purpose. This equation is underdetermined as the low order moments \(m(T), \hat{m}_0(0,T)\) and \(\hat{m}_1(0,T)\) are dependent on the high order moments \(\hat{u}_0(0,T)\) and \(\hat{u}_1(0,T)\). Thus, it is impossible to uniquely determine the solution only from the equality constraint. Hence, we consider the moment conditions \(\{9\}, \{10\}, \{15\}\) and \(\{16\}\) to narrow the solution space. In this example, we used \(g_1(x) = x\) and \(\hat{g}_k(x,t)\) shown in \(\{17\}\) to represent \(K = \mathbb{R}_+(\geq K)\) and \(\mathbb{R}_+ \times [T_1, T_2]\), respectively.

Based on this formulation, the bounds of the mean and the variance were computed by solving the optimization problem \(\{18\}\) with MATLAB 2016b and SeDuMi 1.32 solver \([30]\). Specifically, we solved the optimization problem for \(T = 0.25, 0.50, 0.75, \ldots, 5.0\). The parameters were set as \(k_1 = 0.1\) min\(^{-1}\), \(k_2 = \ln(2)/20\) min\(^{-1}\), \(k_3 = 0.02\) min\(^{-1}\), \(D_T = 50\). To avoid numerical instability, the variables were normalized by constants (see Implementation Details in Supplementary Material). Figure 1(A) and (B) illustrate the bounds of the mean and the variance of the monomer copy number \(x\) for different values of \(\nu\), the highest exponent of time in \(\{6\}\). We observe that the upper and lower bounds approach to each other as we increase \(\nu\). We can also confirm that they are indeed upper/lower bounds of the statistics by comparing with the sample path simulations of stochastic simulation algorithm (SSA) \([7]\).

Regarding computational efforts, it took 0.580 s (CPU time) in average to solve a single optimization with a fixed \(T\) for \(\mu = 7\) and \(\nu = 1\) and 4.45 s for \(\mu = 7\) and \(\nu = 4\) (see Fig. S1 for more data). Since the number of decision variables increases combinatorially with the number of chemical species, \(n\), the proposed approach is currently limited in terms of the size of the reaction networks.

### 3.2 Bounds with different temporal moments

Recently, Dowdy and Barton \([27]\) independently developed a similar optimization-based approach to obtaining the bounds of moments. Therein, the following moment generating function was used instead of the temporal moment

\[
\hat{m}_{\alpha,\rho}(0,T) := \int_0^T e^{\rho(T-t)} \sum_{x \in K} \prod_{j=1}^n x_j^{\alpha_j} P_x(t) dt,
\]

where \(\rho \in \mathbb{R}\) is a tuning constant. Although the definition of \(\hat{m}_{\alpha,\rho}\) loses the apparent connection with the necessary and sufficient moment condition unlike \(m_{\alpha,s}(t)\) (see Remark 1), the non-negativity of
the exponential function still allows for the same argument that leads to a necessary condition for the existence of a positive measure supported on \( K \) (see Proposition 1 for comparison). Thus, it is possible to obtain a semidefinite program of the form (18). In what follows, we use shorthands GRD-SDP and YS-SDP to refer to their approach and the proposed approach, respectively.

Here we discuss how the different definitions of the moments affects the tightness of bounds by comparing the results of the two optimization methods. Specifically, we analyzed the stochastic dimerization process in Table 1 and a dynamic equilibrium reaction

\[
A + B \overset{c_1}{\underset{c_3}{\rightleftharpoons}} C
\]

taken from [27]. To make the comparison as fair as possible, the number of decision variables was set equal to each other. To be more specific, the dimensions of the vectors \( m \) and \( u \) were set equal between both methods. This means that we used the same value of \( \mu \), the highest order of moments in \( m \). The number of temporal moments was also set equal, that is, \( \hat{m}_{\alpha,0}, \hat{m}_{\alpha,1}, \ldots, \hat{m}_{\alpha,\nu} \) was used for YS-SDP and \( \tilde{m}_{\alpha,\rho_0}, \tilde{m}_{\alpha,\rho_1}, \ldots, \tilde{m}_{\alpha,\rho_\nu} \) for GRD-SDP. For GRD-SDP, the constants \( \rho_i \) were determined as described in [27]. As a result, we obtained the same number of equality constraints corresponding to (6).

Fig. 2 illustrates the bounds of the mean and the variance of \( x \) for the dimerization process. We observed that initially YS-SDP (proposed) computes tighter bounds around \( t = 0 \), but the bounds tend to be loose as the reaction approaches to the steady state, at which point GRD-SDP gives better bounds (Fig. 2(A), (B)). This trend hold for different choices of \( \mu \) and \( \nu \) (Fig. S2). These observations suggest that the difference of the temporal moments may affect the frequency band of the dynamic moments at which the bounds are tight, though the rationale needs further study in future. Specifically, YS-SDP tends to give tighter bounds when the system evolves at relatively high frequency (at the beginning of the reaction) compared with GRD-SDP.

We observed the same trend for most of the reaction examples presented in [27] (Fig. S3-S7). The only exception was the reaction system that involves only unimolecular reactions, that is, the cases where \( w_i(x) \) is linear in \( x \), in which case GRD-SDP computed tight bounds as explained in [27] (Fig. S5). As an example, we show the results of the dynamic equilibrium reaction in Fig. 3(A), (B). In this figure, we deliberately picked \( \mu \) and \( \nu \) to be small so that the difference between YS-SDP and GRD-SDP becomes clear, but we also confirmed that the bounds tend to be tighter by making these parameters large (Fig. S8).

4 Conclusion

This paper has proposed an optimization algorithm for computing the transient statistics of stochastic chemical reactions. We have first introduced the concept of temporal moments. This has enabled the derivation of an equality constraint that the transient moments must satisfy. Although this equation is
underdetermined, the possible solutions can be drastically narrowed by employing the moment conditions. Combining these equality and semidefinite conditions, we have obtained the SDP for computing the bounds of transient moments. Finally, the proposed optimization has been compared with a similar formulation proposed in [27] to discuss the advantages and limitations.

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**Appendix**

The size of the moment matrices in the optimization problem is defined as follows. For $H_0(\{m_\alpha\})$,

$$\gamma_1 = \begin{cases} (\mu - 1)/2 & \text{(if } \mu \text{ is odd)} \\ \mu/2 & \text{(if } \mu \text{ is even)} \end{cases}.$$

(20)

For $H(\{m_\alpha\}, g_k)$,

$$\gamma_1 = \begin{cases} (\mu - 1)/2 & \text{(if } \mu \text{ is odd)} \\ \mu/2 - 1 & \text{(if } \mu \text{ is even)} \end{cases}.$$

(21)

For $\hat{H}_0(\{\hat{m}_{\alpha,s}\}, \hat{g}_k)$,

$$\gamma_1 = \begin{cases} (\nu + 1)/2 & \text{(if } \mu \text{ is odd)} \\ \mu/2 + 1 & \text{(if } \mu \text{ is even and } \nu \text{ is odd)} \\ \mu/2 & \text{(if } \mu \text{ is even and } \nu \text{ is even)} \end{cases}.$$

(22)

For $\hat{H}(\{\hat{m}_{\alpha,s}\}, \hat{g}_k)$ with $k = 1, 2, \ldots, n$, $\gamma_1$ is defined by (20). For $\hat{H}(\{\hat{m}_{\alpha,s}\}, \hat{g}_{k+n+1})$ with $k = n+1, n+2$, $\gamma_1$ is defined by (22). For $\hat{H}_0(\{\hat{m}_{\alpha,s}\}, \hat{g}_k)$, $\gamma_2$ is defined by

$$\gamma_2 = \begin{cases} (\nu - 1)/2 & \text{(if } \nu \text{ is odd)} \\ \nu/2 & \text{(if } \nu \text{ is even)} \end{cases}.$$

(23)
For $\hat{H}([\hat{m}_{\alpha,s}, \hat{g}_k])$ with $k = 1, 2, \cdots, n$, $\gamma_2$ is defined by (23). For $\hat{H}([\hat{m}_{\alpha,s}, \hat{g}_k])$ with $k = n + 1, n + 2$,

$$\gamma_2 = \begin{cases} 
(\nu - 1)/2 & \text{(if \( \nu \) is odd)} \\
\nu/2 - 1 & \text{(if \( \nu \) is even)}
\end{cases} \quad (24)$$
Implementation details

The implementation of the code was with MATLAB 2016b and SeDuMi 1.32\cite{30}. Optimization programs were run on HP Z440 workstation with Intel Xeon E5-1650v4 processor (6 cores, 3.60 GHz, 15 MB) and 96 GB of DDR SDRAM (2400 MHz, ECC, Registered).

In the implementation, the variables \(m, u, \hat{m}_s\) and \(\hat{u}_s\) were normalized by constants to avoid numerical instability. In other words, coefficients in the constraints were multiplied by normalization constants. For the dimerization process, the value of the mean \(m_1(t)\) was normalized by 20, and the other moments in \(m\) and \(u\) were normalized as appropriate \((m_i(t)/20^i\) for the \(i\)-th moment). This normalization was applied to both YS-SDP (proposed) and GRD-SDP\cite{27}. The temporal moments \(\hat{m}_{\alpha,s}\) were further normalized by \(T\), that is, \(\hat{m}_{\alpha,s}(t)/(20^i \times T^s)\). For the dynamic equilibrium reactions, \(m\) and \(u\) were not normalized. \(\hat{m}\) and \(\hat{u}\) were normalized by \(T\).

CPU time to solve a single optimization problem

![Figure S4: Average CPU time for solving a single optimization problem for a given \(T\). (A) Dimerization reaction in Table I. \(\mu = 7\) and \(n = 1\). (B) Dynamic equilibrium reaction \(A + B \overset{c_1}{\rightarrow} C \overset{c_2}{\rightarrow} D\) with the set of parameters and initial conditions used in Fig. 3. \(\mu = 3\) and \(n = 2\).](image-url)
Supplementary numerical examples for Fig. 2(A) and (B)

| Time (min) | Mean copy number of monomer | Variance of monomer copy number |
|------------|----------------------------|--------------------------------|
|            | Lower bound (GRD-SDP)      | Upper bound (GRD-SDP)          |
|            | Lower bound (YS-SDP)       | Upper bound (YS-SDP)           |
| SSA simula/g415 on |                         |                                |

Figure S5: Bounds of the statistics of monomer protein P for different choices of $\mu$ and $\nu$. The model of the reaction is based on Table I. (A), (B): $\mu = 3, \nu = 1$ and $\rho = \{0, -0.8844\}$. (C), (D): $\mu = 3, \nu = 7$ and $\rho = \{0, -0.8844, -1.7481, -2.5902, -3.4099, -4.2062, -4.9778, -5.7231\}$. (E), (F): $\mu = 7, \nu = 1$ and $\rho = \{0, -0.8844\}$. The bounds are computed for $t = 0.25, 0.5, \cdots , 5$. 
A simple irreversible reaction $A + B \rightarrow C$

(A) (B) (C) (D)

Figure S6: Bounds of the statistics of molecule $A$ for different choices of $\mu$ and $\nu$. The reaction model is $A + B \rightarrow C$, and the parameters and the initial values are set as specified in Fig. 1 and 2 of [27]. (A), (B): $\mu = 3, \nu = 1$ and $\rho = \{0, -2\}$. (C), (D): $\mu = 3, \nu = 2$ and $\rho = \{0, -2, -6\}$. The bounds are computed for $t = 0.05, 0.10, \cdots, 4$. 
**A cyclic reaction system** $A + B \rightarrow C$, $C \rightarrow D$ and $D \rightarrow A + B$

Figure S7: Bounds of the statistics of molecule $A$. The reaction model is $A + B \overset{c_1}{\rightarrow} C, C \overset{c_2}{\rightarrow} D$ and $D \overset{c_3}{\rightarrow} A + B$. The parameters and the initial values are set as specified in Fig. 7 of [27]. (A), (B): $\mu = 3, \nu = 2$ and $\rho = \{0, -2.1322, -4.1637\}$. The bounds are computed for $t = 0.05, 0.10, \cdots , 4$.

**Unimolecular reactions** $A \rightarrow B \rightarrow C$

Figure S8: Bounds of the statistics of molecule $B$. The reaction model is $A \overset{c_1}{\rightarrow} B$ and $B \overset{c_2}{\rightarrow} C$. The parameters are set as specified in Fig. 8 of [27]. The initial values are set $[A, B, C] = [1, 0, 0]$. (A), (B): $\mu = 3, \nu = 2$ and $\rho = \{0, -1, -3\}$. The bounds are computed for $t = 0.05, 0.10, \cdots , 4$.
Supplementary numerical examples for Fig. 3(A), (B)

Figure S9: Bounds of the statistics of molecule B. The reaction model is \( A + B \xrightarrow{c_1} C \xrightarrow{c_2} D \). The parameter values and initial conditions are set as specified in Fig. 4 and 6 of [27]. (A), (B) : \( \mu = 3, \nu = 3 \) and \( \rho = \{0, -2, -2.4, -4.4\} \) (see Fig. 4 of [27]). (C), (D) : \( \mu = 3, \nu = 3 \) and \( \rho = \{0, -6, -12, -18\} \) (see Fig. 6 of [27]). The bounds are computed for \( t = 0.05, 0.10, \cdots, 4 \). Note that the upper bounds of the variance with GRD-SDP is slightly different from those shown in [27] despite our best efforts.
Figure S10: Bounds of the statistics of molecule B. The reaction model is $A + B \xrightarrow{c_1} C \xleftarrow{c_2} D$. The parameter values and initial conditions are set as specified in Fig. 9 of [27]. (A), (B): $\mu = 3, \nu = 3$ and $\rho = \{0, -2, -2.4, -4.4\}$. The initial values are set $P_{[3,4,0,0]} = 1/4, P_{[1,2,2,0]} = 1/2, P_{[0,1,0,3]} = 1/4$ and $P_x(0) = 0$ for all the other possible states. The bounds are computed for $t = 0.05, 0.10, \cdots, 4$.

Figure S11: Tight bounds are obtained for the example shown in Fig. 3 by using larger values of $\mu$ and $\nu$ ($\mu = 7$ and $\nu = 6$). The reaction model is $A + B \xrightarrow{c_1} C \xleftarrow{c_2} D$. The parameter values and initial conditions are set equal to those in Fig. 3. The bounds are computed for $t = 0.05, 0.10, \cdots, 4$. For all $t \in [0, 4]$, the gap between the upper/lower bounds and the analytic solution is within $\pm 0.0015$ for the mean and $\pm 0.0045$ for the variance, implying that the bounds become sufficiently tight for practical use by increasing $\mu$ and $\nu$. 