IOP Publishing Phys. Biol. 14 (2017) 04LT01 https://doi.org/10.1088/1478-3975/aa75c6

Physical Biology

LETTER

Exact lower and upper bounds on stationary moments in stochastic biochemical systems

RECEIVED
21 February 2017

REVISED
16 May 2017

ACCEPTED FOR PUBLICATION
30 May 2017

PUBLISHED
29 June 2017

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Keywords: stationary moments, moment approximations, biochemical systems

Abstract

In the stochastic description of biochemical reaction systems, the time evolution of statistical moments for species population counts is described by a linear dynamical system. However, except for some ideal cases (such as zero- and first-order reaction kinetics), the moment dynamics is underdetermined as lower-order moments depend upon higher-order moments. Here, we propose a novel method to find exact lower and upper bounds on stationary moments for a given arbitrary system of biochemical reactions. The method exploits the fact that statistical moments of any positive-valued random variable must satisfy some constraints that are compactly represented through the positive semidefiniteness of moment matrices. Our analysis shows that solving moment equations at steady state in conjunction with constraints on moment matrices provides exact lower and upper bounds on the moments. These results are illustrated by three different examples—the commonly used logistic growth model, stochastic gene expression with auto-regulation and an activator–repressor gene network motif. Interestingly, in all cases the accuracy of the bounds is shown to improve as moment equations are expanded to include higher-order moments. Our results provide avenues for development of approximation methods that provide explicit bounds on moments for nonlinear stochastic systems that are otherwise analytically intractable.

1. Introduction

Stochasticity is an integral aspect of biochemical systems, in which different species are often present at low counts. Mathematical characterization of such systems is done by employing the chemical master equation (CME) [1–3]. However, the CME is analytically intractable except for few special cases, and generally requires considerable computation effort if solved numerically [4–13]. The computational cost tends to become prohibitive if one is interested in studying the long-time (i.e. stationary or steady-state) behavior of the system. Perhaps a reasonable goal is to determine a few lower-order moments (such as mean, variance, etc) of different species in the stationary state. Not only is moment computation of primary importance for many purposes, it can also be used to infer useful information about the probability density function using tools such as the Chebyshev's inequality [14], moment-based reconstruction of the probability density function [15], etc.

The time evolution of moments of a biochemical system is governed by a system of differential equations which can be obtained from the CME [16–18]. Consider a system of n species $X_j, j = \{1, 2, \ldots, n\}$ and denote the state of the system by a vector $\boldsymbol{x}(t) = [x_1(t) \quad x_2(t) \ldots x_n(t)]^\top$, where $x_j(t)$ represents the population of X_j at time t. Given a vector $\boldsymbol{m} = [m_1 \quad m_2 \quad \ldots m_n]^\top$ of n non-negative integers, a statistical moment of $\boldsymbol{x}$ is defined as $\langle x_1^{m_1} x_2^{m_2} \cdots x_n^{m_n} \rangle$, where the sum $\sum_{j=1}^{n} m_j$ is referred to as the order of the moment. Using a short-hand notation $\boldsymbol{x}^{[m]} := x_1^{m_1} x_2^{m_2} \cdots x_n^{m_n}$, the time derivative of $\langle \boldsymbol{x}^{[m]} \rangle$ obtained from the CME is given by [16–18]

$$\frac{\mathrm{d}\langle \boldsymbol{x}^{[m]} \rangle}{\mathrm{d}t} = \left\langle \sum_{i=1}^{S} f_i(\boldsymbol{x})((\boldsymbol{x} + \boldsymbol{\alpha}_i)^{[m]} - \boldsymbol{x}^{[m]}) \right\rangle, \qquad (1)$$

where S represents the number of reactions $\mathcal{R}_i$, $i \in \{1, 2, \ldots, S\}$ through which the species interact. The term $f_i(\boldsymbol{x}(t))$ denotes the propensity of the ith reaction $\mathcal{R}_i$ in the sense that the probability that it occurs in an infinitesimal small time interval $[t, t + \mathrm{d}t)$ is given by $f_i(\boldsymbol{x}(t))\mathrm{d}t$. Upon occurrence of $\mathcal{R}_i$, the state of the system is transitioned to $\boldsymbol{x} + \boldsymbol{\alpha}_i$, where $\boldsymbol{\alpha}_i$ is the stoichiometry vector that describes the change in population.

Typically the propensity functions $f_i(\boldsymbol{x})$ for mass action kinetics are taken as polynomials in $\boldsymbol{x}$ [1–3]. In that case, it follows from equation (1) that if all moments up to order M are stacked in a vector $\boldsymbol{\mu}$, then the time evolution of $\boldsymbol{\mu}$ is given by

$$\frac{\mathrm{d}\boldsymbol{\mu}}{\mathrm{d}t} = \boldsymbol{a} + A\boldsymbol{\mu} + B\overline{\boldsymbol{\mu}}. \tag{2}$$

Here $\overline{\boldsymbol{\mu}}$ consists of moments of order higher than M [17]. The elements of the vector $\boldsymbol{a}$ and the matrices A and B depend upon the reaction parameters. Assuming that a stationary distribution (not necessarily unique) with valid moments exists, equation (2) implies that the stationary moments must satisfy the following:

$$\boldsymbol{a} + A\boldsymbol{\mu} + B\overline{\boldsymbol{\mu}} = \boldsymbol{0}. \tag{3}$$

When the reaction propensities are constants (zero-order reactions), linear (first-order reactions) or the system has some special structure [19], then $B = \boldsymbol{0}$ and the steady-state moments in $\boldsymbol{\mu}$ can be determined exactly by solving equation (3). However, in general the matrix $B \neq \boldsymbol{0}$, which implies that equation (3) represents an underdetermined system of equations. One widely used approach for handling such cases is to employ an appropriate moment closure technique. Based on different assumptions, these techniques approximate the vector $\overline{\boldsymbol{\mu}}$ as a, possibly nonlinear, function of $\boldsymbol{\mu}$ [20–44]. Although presumed to be reasonably accurate, moment closure schemes typically do not provide any mathematical guarantee on the accuracy of the approximation.

In this paper we present an alternative method that provides both upper and lower bounds on the stationary moments. Instead of finding an approximation of $\overline{\boldsymbol{\mu}}$, we use the fact that the elements of $\boldsymbol{\mu}$ and $\overline{\boldsymbol{\mu}}$ are moments of some probability distribution. Therefore these elements cannot take arbitrary values and must satisfy some constraints (e.g. variance is non-negative). These constraints are compactly represented in terms of positive semidefiniteness of moment matrices [45]. We show that solving the moment equations in equation (3) along with the positive semidefiniteness of moment matrices results in the lower and upper bounds on elements of $\boldsymbol{\mu}$. Furthermore, increasing the order of truncation, i.e. the size of $\boldsymbol{\mu}$, and correspondingly increasing the number of moment constraints often results in improvement in these bounds. We describe the constraints on moments of a random variable in the following.

2. Constraints on moments

In the proposed method, our aim is to exploit the constraints satisfied by moments of any random variable [45]. For simplicity, let us first consider the case of a scalar random variable x. Suppose we construct a vector $\boldsymbol{v} = \begin{bmatrix} 1 & x & x^2 & \ldots x^d \end{bmatrix}^\top$ that consists of monomials up to degree d of x. Then the outer product $\boldsymbol{v}\boldsymbol{v}^\top$ is positive semidefinite (denoted by $\succeq 0$), and the semidefiniteness is preserved if expectation is taken (see appendix A). That is, we have

$$\langle \boldsymbol{v}\boldsymbol{v}^\top \rangle = \begin{bmatrix} 1 & \langle x \rangle & \ldots & \langle x^d \rangle \\ \langle x \rangle & \langle x^2 \rangle & \ldots & \langle x^{d+1} \rangle \\ \vdots & \vdots & \ldots & \vdots \\ \langle x^d \rangle & \langle x^{d+1} \rangle & \ldots & \langle x^{2d} \rangle \end{bmatrix} \succeq 0, \tag{4}$$

for all $d = \{1, 2, \ldots\}$. Furthermore, if the random variable x is non-negative, which is the case when x represents the level of some biochemical species, another semidefinite constraint can be obtained as

$$\langle x\boldsymbol{v}\boldsymbol{v}^\top \rangle = \begin{bmatrix} \langle x \rangle & \langle x^2 \rangle & \ldots & \langle x^{d+1} \rangle \\ \langle x^2 \rangle & \langle x^3 \rangle & \ldots & \langle x^{d+2} \rangle \\ \vdots & \vdots & \ldots & \vdots \\ \langle x^{d+1} \rangle & \langle x^{d+2} \rangle & \ldots & \langle x^{2d+1} \rangle \end{bmatrix} \succeq 0, \tag{5}$$

for all $d = \{1, 2, \ldots\}$. More generally, any matrix of the form $\langle g(x)\boldsymbol{v}\boldsymbol{v}^\top \rangle$, where g is a non-negative polynomial function of x, is positive semidefinite. This fact can be further exploited if x has bounded support. For example, if $x \in [L, U]$ then $\langle (x - L)\boldsymbol{v}\boldsymbol{v}^\top \rangle \succeq 0$ and $\langle (U - x)\boldsymbol{v}\boldsymbol{v}^\top \rangle \succeq 0$.

These constraints can be generalized to multivariate random variables. For example, for an n-dimensional random variable $\boldsymbol{x} = \begin{bmatrix} x_1 & x_2 & \ldots & x_n \end{bmatrix}^\top$, a matrix analogous to the one in equation (4) can be constructed by taking the expectation of the outer product $\boldsymbol{v}\boldsymbol{v}^\top$ where the vector $\boldsymbol{v}$ (with slight abuse of the notation) consists of all monomials of $\boldsymbol{x}$ up to order d

$$\boldsymbol{v} = \begin{bmatrix} 1 & x_1 \ldots x_n & x_1^2 & x_1x_2 \ldots x_1x_n \ldots x_n^2 \ldots x_n^d \end{bmatrix}^\top. \tag{6}$$

Furthermore, n matrices analogous to equation (5) can be generated as $\langle x_i\boldsymbol{v}\boldsymbol{v}^\top \rangle \succeq 0$ for $i = 1, 2, \ldots, n$. Additional constraints can also be encoded via $\langle g(\boldsymbol{x})\boldsymbol{v}\boldsymbol{v}^\top \rangle \succeq 0$.

The constraints described by equations (4)–(5) and their multivariate analogues essentially ensure that the higher-order moments appearing in equation (3) do not take arbitrary values. To see this, we can use the fact that a matrix is positive semidefinite if and only if all of its principal minors are non-negative (this is known as the Sylvester criterion [46]). Therefore, for $d = 1$, the non-negative determinants of the matrices in equation (4) and equation (5) result in

$$\langle x^2 \rangle \geq \langle x \rangle^2, \quad \langle x^3 \rangle \geq \frac{\langle x^2 \rangle^2}{\langle x \rangle}, \tag{7}$$

respectively. Note that the first inequality above is nothing but the well-known inequality representing non-negativity of variance. Similarly, for $d = 2$, the determinant of the matrix in equation (4) yields

$$\langle x^4\rangle \geqslant \frac{\langle x^3\rangle^2 + \langle x^2\rangle^3 - 2\langle x^3\rangle\langle x^2\rangle\langle x\rangle}{\langle x^2\rangle - \langle x\rangle^2}. \quad (8)$$

In essence, these determinants for varying d allow higher-order moments to be bounded from below by nonlinear functions of the lower-order moments.

Another point to note is that the matrix $\langle \boldsymbol{v}\boldsymbol{v}^\top\rangle$ generates inequalities for even-order moments whereas $\langle \boldsymbol{x}\boldsymbol{v}\boldsymbol{v}^\top\rangle$ generates inequalities for odd-order moments. Likewise, for the multivariate random variable $\boldsymbol{x}$, non-negativity of the principal minors of matrix $\langle \boldsymbol{v}\boldsymbol{v}^\top\rangle$ gives bound on the moments $\left\langle x_i^{2d}\right\rangle, i = \{1, 2, \ldots, n\}$. As an example, for $\boldsymbol{x} = \begin{bmatrix} x_1 & x_2 \end{bmatrix}^\top$, the following is obtained for $d = 1$

$$\left\langle \begin{bmatrix} 1 & x_1 & x_2 \\ x_1 & x_1^2 & x_1x_2 \\ x_2 & x_1x_2 & x_2^2 \end{bmatrix} \right\rangle \succeq 0, \quad (9)$$

which results in $\left\langle x_1^2\right\rangle \geqslant \langle x_1\rangle^2$, and the following inequality bounding $\left\langle x_2^2\right\rangle$

$$\left\langle x_2^2\right\rangle \geqslant \frac{\langle x_1x_2\rangle^2 + \left\langle x_1^2\right\rangle\langle x_2\rangle - 2\langle x_1\rangle\langle x_2\rangle\langle x_1x_2\rangle}{\left\langle x_1^2\right\rangle - \langle x_1\rangle^2}. \quad (10)$$

The moments whose form is different from $\left\langle x_i^{2d}\right\rangle$ can be bounded by taking expectation of $\langle g(\boldsymbol{x})\boldsymbol{v}\boldsymbol{v}^\top\rangle$ with an appropriately chosen g. For instance, when $\boldsymbol{x}$ takes positive values, $g(\boldsymbol{x}) = x_1$ gives the constraint

$$\left\langle x_1 \begin{bmatrix} 1 & x_1 & x_2 \\ x_1 & x_1^2 & x_1x_2 \\ x_2 & x_1x_2 & x_2^2 \end{bmatrix} \right\rangle \succeq 0, \quad (11)$$

which can be used to find a lower bound on $\left\langle x_1x_2^2\right\rangle$.

It should also be noted that the univariate inequalities obtained from equations (4)–(5) are valid for both x_1 and x_2. Furthermore, as x_1 and x_2 are positive random variables, additional inequalities as follows can also be written

$$\left\langle x_1 \begin{bmatrix} 1 & x_2 \\ x_2 & x_2^2 \end{bmatrix} \right\rangle \succeq 0, \quad \left\langle x_2 \begin{bmatrix} 1 & x_1 \\ x_1 & x_1^2 \end{bmatrix} \right\rangle \succeq 0. \quad (12)$$

These inequalities translate to lower bounds on moments $\left\langle x_1^2x_2\right\rangle$ and $\left\langle x_1x_2^2\right\rangle$. To sum up, one can write a multitude of positive semidefinite matrix constraints satisfied by the moments. In the following section, we discuss how these constraints can be used to find bounds on moments.

3. Bounds on steady-state moments

In this section, we provide a general methodology to obtain bounds on stationary moments of a biochemical system, and illustrate it using examples.

3.1. Method

Broadly speaking, the method utilizes the linear equations in equation (3) and constraints on the higher-order moments discussed in the previous section. The key steps are enumerated below.

(i) Obtain the system of linear equations $\boldsymbol{a} + \boldsymbol{A}\boldsymbol{\mu} + \boldsymbol{B}\overline{\boldsymbol{\mu}} = \boldsymbol{0}$ for the stationary moments.
(ii) Solve $\boldsymbol{a} + \boldsymbol{A}\boldsymbol{\mu} + \boldsymbol{B}\overline{\boldsymbol{\mu}} = \boldsymbol{0}$ for the elements of $\boldsymbol{\mu}$ in terms of the elements of $\overline{\boldsymbol{\mu}}$.
(iii) Use inequalities which bound the elements of $\overline{\boldsymbol{\mu}}$ in terms of elements of $\boldsymbol{\mu}$ in conjugation with equations in step (ii). This yields inequalities for the elements of $\overline{\boldsymbol{\mu}}$.
(iv) Usually, there are multiple solutions; the spurious solutions can be discarded based on moment inequalities satisfied by the lower-order moments.
(v) Reverting to step (ii), the bound on elements of $\boldsymbol{\mu}$ are readily obtained by substituting the corresponding bounds on $\overline{\boldsymbol{\mu}}$.

These steps can be easily implemented in a computational tool such as Mathematica or Matlab, and can even give analytical bounds if the problem at hand is small enough. However, it turns out that as the size of the problem grows, solving the inequalities becomes difficult for these off-the-shelf tools. A more specialized approach is to recognize the fact that we are essentially looking for a minimum or maximum value taken by a moment of interest, subject to linear constraints arising from the moment equations in equation (3) and the semidefinite constraints in equations (4)–(5) (or their multivariate analogues). Thus, the problem could be posed as a semidefinite program whereby maximizing (minimizing) a moment gives upper (lower) bound [47, 48], and these programs could be solved using specialized algorithms [49]. In what follows, we will illustrate the proposed method via examples.

3.2. Example 1: stochastic logistic growth with a constant immigration rate

Consider the following biochemical system, where a species X arrives in the system via two modes, a constant immigration rate k and a species-dependent rate r, and each species degrades or leaves the system with a rate rx/C

$$\varnothing \xrightarrow{k} X, \quad X \xrightarrow{r} X + 1, \quad X \xrightarrow{rx/C} X - 1, \quad (13)$$

where x denotes the population level of the species. With $k = 0$, this model essentially represents a logistic growth model which is widely used to model the growth of populations in ecology and virus dynamics [28, 50–52]. In the deterministic sense, the population grows with a rate r and saturates once it reaches a finite carrying capacity C due to resource limitations. The

term k here represents a constant rate of immigration so as to avoid the extinction of the population.

In this example, there are three reactions with propensity functions and stoichiometric vectors tabulated in table 1. Using equation (1), we can write the moment dynamics for a mth-order moment as

$$\frac{\mathrm{d}\langle x^m\rangle}{\mathrm{d}t} = \left\langle (k+rx)((x+1)^m - x^m) + \frac{r}{C}x^2((x-1)^m - x^m)\right\rangle. \tag{14}$$

Note that these equations are not closed because of the quadratic propensity function, and time evolution of an mth-order moment depends upon a moment of $(m+1)$th order. Thus, if we construct a vector $\boldsymbol{\mu}$ consisting of the first M moments, then $\overline{\boldsymbol{\mu}} = [\langle x^{M+1}\rangle]$.

To see how the moment inequalities lead to bounds, we start with the simplest case of $M = 1$. From equation (14), the steady-state moment satisfies

$$\langle \dot{x}\rangle = k + r\langle x\rangle - \frac{r}{C}\langle x^2\rangle = 0. \tag{15}$$

Solving the above equation gives

$$\langle x\rangle = \frac{r\langle x^2\rangle - kC}{rC}. \tag{16}$$

Using this with the non-negative variance inequality $\langle x^2\rangle \geqslant \langle x\rangle^2$ gives a quadratic inequality in $\langle x^2\rangle$

$$r^2\langle x^2\rangle^2 - (2krC + r^2C^2)\langle x^2\rangle + k^2C^2 \geqslant 0, \tag{17}$$

whose solution can be used in equation (16) to obtain bounds on $\langle x\rangle$

$$\frac{C}{2} - \frac{1}{2}\sqrt{\frac{4kC + C^2r}{r}} \leqslant \langle x\rangle \leqslant \frac{1}{2}\sqrt{\frac{4kC + C^2r}{r}} + \frac{C}{2}. \tag{18}$$

The lower bound on $\langle x\rangle$ can be discarded from the fact that $\langle x\rangle \geqslant 0$. Thus, we have the following lower and upper bounds on $\langle x\rangle$

$$0 \leqslant \langle x\rangle \leqslant \frac{1}{2}\sqrt{\frac{4kC + C^2r}{r}} + \frac{C}{2}. \tag{19}$$

Next, consider the case of $M = 2$. In this case, the steady-state moment equations are given by

$$\langle \dot{x}\rangle = k + r\langle x\rangle - \frac{r}{C}\langle x^2\rangle = 0, \tag{20}$$

$$\langle \dot{x^2}\rangle = k + \left(2k + \frac{r}{C}\right)\langle x\rangle + \left(2r + \frac{r}{C}\right)\langle x^2\rangle - \frac{2r}{C}\langle x^3\rangle = 0. \tag{21}$$

Solving these equations results in

$$\langle x\rangle = -\frac{kC^2 + kC - r\langle x^3\rangle}{C(k + Cr + r)}, \quad \langle x^2\rangle = \frac{k^2C + r^2\langle x^3\rangle}{r(k + Cr + r)}. \tag{22}$$

Using the above expressions in the second inequality from (7) leads to a quadratic inequality in $\langle x^3\rangle$. Substituting the solution back to expressions of $\langle x\rangle$ and $\langle x^2\rangle$ results in bounds on them. Upon rejecting the spurious solutions by using inequalities $\langle x^2\rangle \geqslant \langle x\rangle$ and $\langle x\rangle \geqslant 0$, a more useful lower bound for $\langle x\rangle$ is found compared with the $M = 1$ case

$$\frac{1}{2}\sqrt{\frac{4k^3C + k^2C^2r + 2k^2Cr + k^2r}{r(k+r)^2}} + \frac{k(C-1)}{2(k+r)} \leqslant \langle x\rangle \leqslant \frac{1}{2}\sqrt{\frac{4kC + C^2r}{r}} + \frac{C}{2}. \tag{23}$$

As the order of truncation M is increased, the same approach can be used: take steady-state equations of first M moments, use the inequality bounding the $(M+1)$th moment and apply the inequalities for lower-order moments to prune solutions. Though the resulting expressions do not lead to closed-form analytical bounds, numerical solutions are still possible. Interestingly, the solutions for odd values of M improve the upper bounds on the average population level whereas the solutions for even values of M improve the lower bounds (figure 1(Left)). At $M = 9$, the lower and upper bounds obtained are respectively given by 18.9711 and 19.1635. The exact average population level obtained from Monte Carlo simulations of the process is 19.1495.

Although we have so far discussed the bounds only on $\langle x\rangle$, this approach yields bounds on all moments up to order M. These bounds can be straightforwardly used to infer the bounds on other statistical quantities of interest, for example coefficient of variation, skewness, etc. In particular, the coefficient of variation squared is equal to $(\langle x^2\rangle/\langle x\rangle^2) - 1$. Thus, a lower (upper) bound on the coefficient of variation can be computed by using the lower (upper) bound of $\langle x^2\rangle$ and the upper (lower) bound of $\langle x\rangle$.

To illustrate this point, we compute the bounds on the coefficient of variation squared as k/r is varied. It is worth noting that both the upper and lower bounds on $\langle x\rangle$ in equation (23) depend only on k/r and not on individual values of k and r. This holds true for all bounds obtained here, as evident from the steady state of the moment equation in equation (14). We call the ratio k/r the relative immigration rate and show its effect on the coefficient of variation in figure 1(Right). It is seen that both the upper and lower bounds on the coefficient of variation decrease with increase in k/r, thus suggesting that the coefficient of variation decreases. Interestingly, the difference between the bounds is large for small values of k/r and it becomes negligible for high values of k/r. Thus, depending upon the parameter regime,

Table 1. Description of reactions for the logistic growth model.

Reaction, $\mathcal{R}_i$	Stoichiometric vector, $\boldsymbol{\alpha}_i$	Propensity function, $f_i(x)$
$\varnothing \xrightarrow{k} X+1$	$\begin{bmatrix}1\end{bmatrix}^\top$	k
$X \xrightarrow{r} X+1$	$\begin{bmatrix}1\end{bmatrix}^\top$	rx
$X \xrightarrow{rx/C} X-1$	$\begin{bmatrix}-1\end{bmatrix}^\top$	$(r/C)x^2$

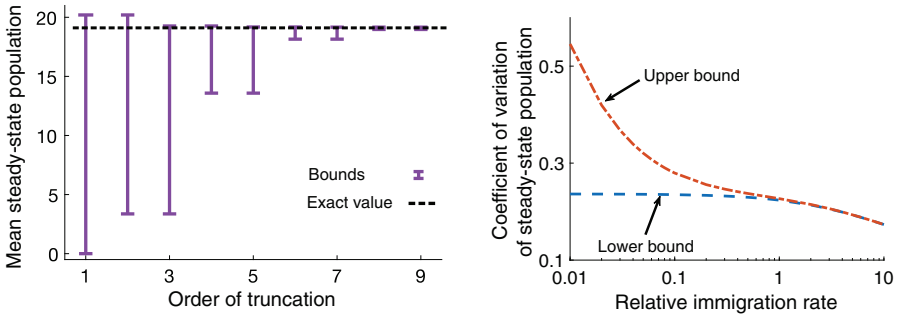

Figure 1. *Estimated bounds on steady-state moments for the logistic growth model.* Left: upper and lower bounds on the second moment of the population level are shown for different orders of truncation M. As M is increased, the bounds obtained get tighter. The exact mean value of 19.149 is obtained by averaging 100 000 MC simulations performed using the stochastic simulation algorithm (SSA) [53]. Parameters in (13) are taken as $k = 1$, $r = 5$ and $C = 20$. Right: the bounds on the coefficient of variation (standard deviation/mean) of the steady-state population level are shown as the relative immigration rate k/r is changed. Both lower and upper bounds decrease as the relative immigration rate increases. These bounds are obtained via a fifth-order truncation.

a lower- or higher-order truncation might be used to obtain bounds within a desired accuracy.

3.3. Example 2: stochastic gene expression with negative auto-regulation

Consider stochastic expression of an auto-regulating gene represented by the following reactions:

$$\begin{aligned}&\mathrm{Gene_{OFF}} \underset{k_{\mathrm{off}}x_2}{\overset{k_{\mathrm{on}}}{\rightleftharpoons}} \mathrm{Gene_{ON}},\\ &\mathrm{Gene_{ON}} \xrightarrow{k_{\mathrm{p}}} B \times \mathrm{Protein} \xrightarrow{\gamma_{\mathrm{p}}} \varnothing.\end{aligned} \tag{24}$$

Here the gene is assumed to reside in one of the two states: ON (active) and OFF (inactive). The protein is produced at a rate k_{p} from the ON state whereas there is no protein production when the gene is in the OFF state. Each production event produces B protein molecules where B follows a geometric distribution. The gene state is represented by x_1, which is a Bernoulli random variable ($x_1 = 1(0)$ for the ON (OFF) state), and the protein level is represented by x_2. The gene negatively regulates itself by switching to the OFF state in a protein copy number-dependent fashion with a rate $k_{\mathrm{off}}x_2$. Finally, the protein molecules can degrade with a rate γ_{p}. This gene expression model has been studied previously [34, 54–56]; exact solutions to its moments are available which allows us to validate the bounds obtained using our method.

In this example, the state of the system is $\boldsymbol{x} = \begin{bmatrix} x_1 & x_2 \end{bmatrix}^\top$. There are four reactions whose propensity functions and stoichiometric vectors are described in table 2. Using equation (1), the time evolution of a moment $\langle x_1^{m_1} x_2^{m_2} \rangle$ is given as

$$\begin{aligned}\frac{\mathrm{d}\langle x_1^{m_1}x_2^{m_2}\rangle}{\mathrm{d}t} = \big\langle & k_{\mathrm{on}}(1-x_1)((x_1+1)^{m_1} - x_1^{m_1})x_2^{m_2}\\ &+ k_{\mathrm{off}}x_1x_2((x_1-1)^{m_1} - x_1^{m_1})x_2^{m_2}\\ &+ k_{\mathrm{p}}x_1^{m_1}((x_2+B)^{m} - x_2^{m_2})\\ &+ \gamma_{\mathrm{p}}x_2x_1^{m_1}((x_2-1)^{m} - x_2^{m_2})\big\rangle.\end{aligned} \tag{25}$$

Table 2. Description of reactions for an auto-regulating gene.

Reaction, $\mathcal{R}_i$	Stoichiometric vector, $\boldsymbol{\alpha}_i$	Propensity function, $f_i(\boldsymbol{x})$
$\mathrm{Gene_{OFF}} \xrightarrow{k_{\mathrm{on}}} \mathrm{Gene_{ON}}$	$\begin{bmatrix} 1 & 0 \end{bmatrix}^\top$	$k_{\mathrm{on}}(1-x_1)$
$\mathrm{Gene_{ON}} \xrightarrow{k_{\mathrm{off}}\,x_2} \mathrm{Gene_{OFF}}$	$\begin{bmatrix} -1 & 0 \end{bmatrix}^\top$	$k_{\mathrm{off}}x_1x_2$
$\mathrm{Gene_{ON}} \xrightarrow{k_{\mathrm{p}}} \mathrm{Gene_{ON}} + B \times \mathit{Protein}$	$\begin{bmatrix} 0 & B \end{bmatrix}^\top$	$k_{\mathrm{p}}x_1$
$\mathrm{Protein} \xrightarrow{\gamma_{\mathrm{p}}} \varnothing$	$\begin{bmatrix} 0 & -1 \end{bmatrix}^\top$	γx_2

Note that dynamics is unclosed due to the nonlinearity arising from the negative feedback: a moment $\langle x_1^{m_1}x_2^{m_2}\rangle$ depends upon $\langle x_1^{m_1}x_2^{m_2+1}\rangle$. Furthermore, $x_1 \in \{0, 1\}$ is a binary random variable for which the following relations hold

$$\begin{aligned}&\langle x_1^{m_1}x_2^{m_2}\rangle = \langle x_1x_2^{m_2}\rangle, m_1 \in \{1, 2, 3, \ldots\},\\ &\qquad m_2 \in \{0, 1, 2, 3, \ldots\}.\end{aligned} \tag{26}$$

The above relations imply that the moment vector $\boldsymbol{\mu}$ does not need to contain all cross moments. For example, the moments up to order 3 can be stacked as $\boldsymbol{\mu} = \begin{bmatrix} \langle x_1\rangle & \langle x_2\rangle & \langle x_1x_2\rangle & \langle x_2^2\rangle & \langle x_1x_2^2\rangle & \langle x_2^3\rangle \end{bmatrix}^\top$. In this case, the corresponding $\overline{\boldsymbol{\mu}}$ is given by $\overline{\boldsymbol{\mu}} = [\langle x_1x_2^3\rangle]$.

As with the one-dimensional example, here too we are interested in obtaining bounds on moments of the state $\boldsymbol{x}$. Towards this end, we begin by writing the first-order moment equations in steady state

$$\langle \dot{x_1}\rangle = k_{\mathrm{on}} - k_{\mathrm{on}}\langle x_1\rangle - k_{\mathrm{off}}\langle x_1x_2\rangle = 0, \tag{27}$$

$$\langle \dot{x_2}\rangle = k_{\mathrm{p}}\langle B\rangle\langle x_1\rangle - \gamma_{\mathrm{p}}\langle x_2\rangle = 0. \tag{28}$$

To obtain a bound on $\langle x_1\rangle$ and $\langle x_2\rangle$, we require a bound on the second-order moment $\langle x_1x_2\rangle$. Generally, the only bound that we can use is $\langle x_1x_2\rangle \geqslant 0$. However, because x_1 is a binary random variable, we have that $\langle x_1^2x_2\rangle = \langle x_1x_2\rangle$. Thus, using the inequality obtained from

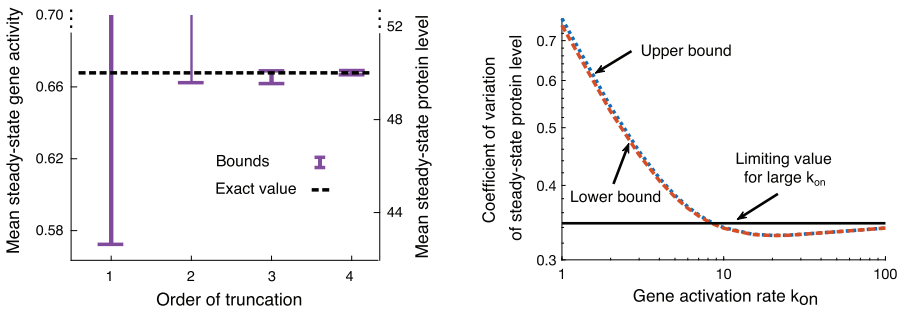

Figure 2. *Estimated bounds on moments for a stochastic gene expression model.* Left: the lower and upper bounds for the average gene activity (left axis)/protein level (right axis) for different orders of truncation M is shown. The bound for $M = 1$ corresponds to equation (29). As M is increased, the bounds obtained get tighter. The exact mean values are obtained from the analytical solution of the system from [56]. Parameters in equation (24) taken as $k_{on} = 10, k_{off} = 0.1, k_p = 15, \langle B\rangle = 5$, and $\gamma_p = 1$. Right: the coefficient of variation (standard deviation/mean) of the steady-state protein level as a function of the gene activation rate k_{on} is plotted. The steady-state protein level in the deterministic sense is kept constant at 50 molecules by varying k_p with k_{on} such that $k_p = 50\gamma_p(50k_{off} + k_{on})/(k_{on}\langle B\rangle)$. The lower and upper bounds on the coefficient of variation are obtained for $M = 5$ and they exhibit U-shaped profiles, thus showing that the noise is minimizing at a specific value of k_{on}. Other parameters are taken as $k_{off} = 0.1, \langle B\rangle = 5$ and $\gamma_p = 1$.

first matrix of equation (12), a bound $\langle x_1x_2\rangle \leqslant \langle x_2\rangle$ can be found. Plugging this in the moment equations yields

$$\frac{k_{on}\gamma_p}{k_{on}\gamma_p + k_{off}k_p\langle B\rangle} \leqslant \langle x_1\rangle \leqslant 1,$$
$$\frac{k_p\langle B\rangle}{\gamma_p}\frac{k_{on}\gamma_p}{k_{on}\gamma_p + k_{off}k_p\langle B\rangle} \leqslant \langle x_2\rangle \leqslant \frac{k_p\langle B\rangle}{\gamma_p}. \quad (29)$$

In the similar fashion to the above, we can write moment equations up to order two and use the inequality for $\langle x_1x_2^2\rangle$ obtained from the second matrix of equation (12). This eventually leads to an improvement in the lower bounds on both $\langle x_1\rangle$ and $\langle x_2\rangle$.

Continuing in similar way, we obtain improvements in the lower bounds for $M = 4$ and $M = 6$, and improvements in the upper bounds for $M = 3$, $M = 5$ and $M = 7$. The bounds up to $M = 4$ are shown in figure 2(Left). The lower and upper bounds obtained for $\langle x_1\rangle$ via seventh-order truncation are 0.667 463 and 0.667 465 respectively. These are quite precise, as the exact solution for $\langle x_1\rangle$ is 0.667 464 obtained using the exact solution from [56]. It is worth noting that as discussed below equation (5), we can also use additional bounds arising from the fact that $x_1 \in [0, 1]$, so x_1 and $1 - x_1$ both would be positive. However, in this particular example, they do not lead to significant improvements in the bounds.

As done in the logistic growth example, we also obtain the bounds on the second-order moment and compute the bounds on coefficient of variation. In particular, we study the effect of varying the parameter k_{on} (gene activation rate). Our results show that there is a U-shaped curve, and the noise is minimized at an optimal value of k_{on} (figure 2(Right)). Furthermore, the coefficient of variation approaches a limiting value for large values of k_{on} (i.e. the gene is always ON). Similar results were obtained in [34] for an autoregulating gene expression model using the moment closure techniques. Notably, here the lower and upper bounds remain reasonably close to each other for the range of k_{on} considered as opposed to the logistic growth example.

3.4. Example 3: activator–repressor gene motif

Next we apply the proposed method to estimate bounds on moments of a slightly more complicated example of a gene network motif that consists of two genes as described by the following reactions:

$$\text{Gene}_{A_{OFF}} \underset{k_{off_A}x_4}{\overset{k_{on_A}}{\rightleftharpoons}} \text{Gene}_{A_{ON}},$$
$$\text{Gene}_{A_{ON}} \xrightarrow{k_A} B_A \times \text{Protein}_A \xrightarrow{\gamma_A} \varnothing \quad (30)$$

$$\text{Gene}_{R_{OFF}} \underset{k_{off_R}}{\overset{k_{on_R}x_2}{\rightleftharpoons}} \text{Gene}_{R_{ON}},$$
$$\text{Gene}_{R_{ON}} \xrightarrow{k_R} B_R \times \text{Protein}_R \xrightarrow{\gamma_R} \varnothing \quad (31)$$

Here the notations with subscript A denote the activator whereas those with subscript R represent the repressor. The state of the system is represented by the vector $\boldsymbol{x} = \begin{bmatrix} x_1 & x_2 & x_3 & x_4 \end{bmatrix}^\top$, where x_1 and x_3, respectively, represent the activator and repressor gene state. The corresponding proteins are represented by x_2 and x_4. As with the previous example, the genes are assumed to reside in two states: OFF and ON. The activator turns the repressor gene ON whereas the repressor turns the activator gene OFF, thereby creating a feedback loop. There are eight reactions in this example. The corresponding stoichiometric vectors and propensity functions are given in table 3.

The time evolution of a moment $\langle x_1^{m_1}x_2^{m_2}x_3^{m_3}x_4^{m_4}\rangle$ can be computed using equation (1). For example, the first-order moment equations in the steady state are given by

$$\dot{\langle x_1\rangle} = k_{on_A} - k_{on_A}\langle x_1\rangle - k_{off_A}\langle x_1x_4\rangle = 0, \quad (32)$$

Table 3. Description of reactions for the activator repressor motif.

Reaction, $\mathcal{R}_i$	Stoichiometric vector, $\boldsymbol{\alpha}_i$	Propensity function, $f_i(\boldsymbol{x})$
$\text{Gene}_{\text{A}_{\text{OFF}}} \xrightarrow{k_{\text{on}_\text{A}}} \text{Gene}_{\text{A}_{\text{ON}}}$	$\begin{bmatrix}1 & 0 & 0 & 0\end{bmatrix}^\top$	$k_{\text{on}_\text{A}}(1-x_1)$
$\text{Gene}_{\text{A}_{\text{ON}}} \xrightarrow{k_{\text{off}_\text{A}} x_4} \text{Gene}_{\text{A}_{\text{OFF}}}$	$\begin{bmatrix}-1 & 0 & 0 & 0\end{bmatrix}^\top$	$k_{\text{off}_\text{A}}x_1x_4$
$\text{Gene}_{\text{A}_{\text{ON}}} \xrightarrow{k_\text{A}} \text{Gene}_{\text{A}_{\text{ON}}} + B_\text{A} \times \text{Protein}_\text{A}$	$\begin{bmatrix}0 & B_\text{A} & 0 & 0\end{bmatrix}^\top$	$k_\text{A}x_1$
$\text{Protein}_\text{A} \xrightarrow{\gamma_\text{A}} \varnothing$	$\begin{bmatrix}0 & -1 & 0 & 0\end{bmatrix}^\top$	$\gamma_\text{A}x_2$
$\text{Gene}_{\text{R}_{\text{OFF}}} \xrightarrow{k_{\text{on}_\text{R}} x_2} \text{Gene}_{\text{R}_{\text{ON}}}$	$\begin{bmatrix}0 & 0 & 1 & 0\end{bmatrix}^\top$	$k_{\text{on}_\text{R}}x_2(1-x_3)$
$\text{Gene}_{\text{R}_{\text{ON}}} \xrightarrow{k_{\text{off}_\text{R}}} \text{Gene}_{\text{R}_{\text{OFF}}}$	$\begin{bmatrix}0 & 0 & -1 & 0\end{bmatrix}^\top$	$k_{\text{off}_\text{R}}x_3$
$\text{Gene}_{\text{R}_{\text{ON}}} \xrightarrow{k_\text{R}} \text{Gene}_{\text{R}_{\text{ON}}} + B_\text{R} \times \text{Protein}_\text{R}$	$\begin{bmatrix}0 & 0 & 0 & B_\text{R}\end{bmatrix}^\top$	$k_\text{R}x_3$
$\text{Protein}_\text{R} \xrightarrow{\gamma_\text{R}} \varnothing$	$\begin{bmatrix}0 & 0 & 0 & -1\end{bmatrix}^\top$	$\gamma_\text{R}x_4$

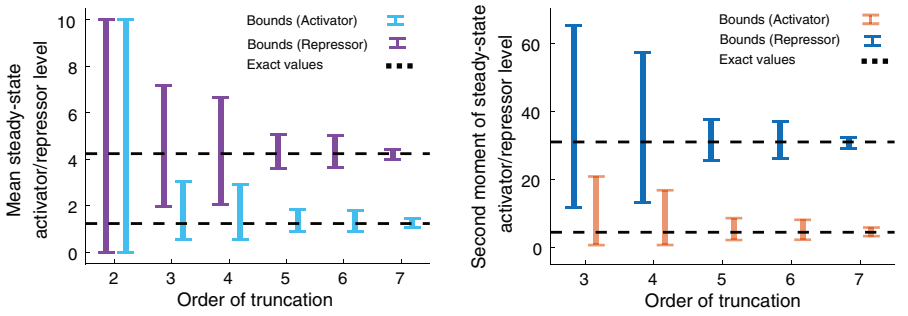

Figure 3. *Estimated bounds on steady-state moments for the activator–repressor motif.* Left: upper and lower bounds on the mean of both the activator and repressor are shown for different orders of truncation M. As M is increased, the bounds obtained get tighter. The exact mean values of 1.23 for the activator and 4.24 for the repressor are obtained by averaging 30 000 Monte Carlo simulations performed using SSA [53]. Parameters are taken as $k_{\text{on}_\text{A}} = k_{\text{on}_\text{R}} = 1, k_{\text{off}_\text{A}} = 5, k_{\text{off}_\text{R}} = 1, k_\text{A} = k_\text{R} = 10, \gamma_\text{A} = \gamma_\text{R} = 1$, and $B_\text{A} = B_\text{R} = 1$ with probability one. Right: the bounds on the second-order moments of the steady-state activator/repressor levels are shown for different orders of truncation. The bounds improve with increase in the order of truncation. The exact second-order moments of 4.48 for the activator and 30.98 for the repressor are shown as obtained from 30 000 Monte Carlo simulations. The parameters are taken to be same as those for the left part.

$$\langle \dot{x_2} \rangle = k_\text{A}\langle B_\text{A}\rangle\langle x_1\rangle - \gamma_\text{A}\langle x_2\rangle = 0, \tag{33}$$

$$\langle \dot{x_3} \rangle = k_{\text{on}_\text{R}}\langle x_2\rangle - k_{\text{on}_\text{R}}\langle x_2x_3\rangle - k_{\text{off}_\text{R}}\langle x_3\rangle = 0, \tag{34}$$

$$\langle \dot{x_4} \rangle = k_\text{R}\langle B_\text{R}\rangle\langle x_3\rangle - \gamma_\text{R}\langle x_4\rangle = 0. \tag{35}$$

These equations are not closed as the first-order moments depend upon the second-order moments $\langle x_1x_4\rangle$ and $\langle x_2x_3\rangle$. Solving the first-order moments gives

$$\langle x_1\rangle = 1 - \frac{k_{\text{off}_\text{A}}}{k_{\text{on}_\text{A}}}\langle x_1x_4\rangle, \tag{36}$$

$$\langle x_2\rangle = \frac{k_\text{A}\langle B_\text{A}\rangle}{\gamma_\text{A}}\left(1 - \frac{k_{\text{off}_\text{A}}}{k_{\text{on}_\text{A}}}\langle x_1x_4\rangle\right) \tag{37}$$

$$\langle x_3\rangle = \frac{k_{\text{on}_\text{R}}}{k_{\text{off}_\text{R}}}\left(\frac{k_\text{A}\langle B_\text{A}\rangle}{\gamma_\text{A}}\left(1 - \frac{k_{\text{off}_\text{A}}}{k_{\text{on}_\text{A}}}\langle x_1x_4\rangle\right) - \langle x_2x_3\rangle\right), \tag{38}$$

$$\langle x_4\rangle = \frac{k_\text{R}\langle B_\text{R}\rangle}{\gamma_\text{R}}\frac{k_{\text{on}_\text{R}}}{k_{\text{off}_\text{R}}}\left(\frac{k_\text{A}\langle B_\text{A}\rangle}{\gamma_\text{A}}\left(1 - \frac{k_{\text{off}_\text{A}}}{k_{\text{on}_\text{A}}}\langle x_1x_4\rangle\right) - \langle x_2x_3\rangle\right). \tag{39}$$

Using the property mentioned in (26) of Bernoulli random variables x_1 and x_3, we have that $0 \leqslant \langle x_1x_4\rangle \leqslant \langle x_4\rangle$ and $0 \leqslant \langle x_2x_3\rangle \leqslant \langle x_2\rangle$. Applying these inequalities in the moment equations yields the trivial bounds, such as $0 \leqslant \langle x_1\rangle \leqslant 1$. As the order of truncation is increased, the number of moment equations and corresponding inequalities grows significantly such that the bounds cannot be obtained with off-the-shelf tools. We therefore employ the semidefinite programming based optimization to obtain lower and upper bounds on moments of interest. As expected, these bounds improve as more moment equations and subsequently semidefinite matrices with higher-order moments are used (figure 3). For $M = 7$, the bounds for both mean and second-order moments of the activator and repressor are fairly close to each other.

4. Discussion

Biochemical systems are inherently stochastic owing to random motion of particles, coupled with the low copy number of species. Mathematical description of these systems is usually based on CME; however,

solving a CME is usually not possible, particularly if the system contains nonlinearities. Another possible mathematical characterization involves computing statistical moments of the species counts, although the moment computations for systems with nonlinearities require solving a system of infinite-hierarchical coupled differential equations. Computing, or even estimating, moments of species level in such systems has implications not only for quantitative understanding of such systems but also for parameter inference [30, 57–60]. Furthermore, accurate estimation of moments is desirable for identification of the molecular underpinnings of biochemical processes [61]. Whereas current methods to approximate moments are based on ad-hoc assumptions, here we proposed a method to obtain both lower and upper bounds on stationary moments of a biochemical system without any assumption. The method uses the steady-state moment equations obtained from the CME along with semidefinite constraints that are required to be satisfied by moments of a random variable. These inequalities are constructed from positive semidefinite constraints on moments of a positive random variable. Using three examples of biochemical reaction systems, we show that not only can one obtain upper and lower bounds on a given stationary moment, but also both upper and lower bounds improve considerably as one uses more moment equations. Thus, there is a trade-off between the computational cost and the accuracy of bounds.

An explanation is warranted for why we obtain bounds by using inequalities, and why these bounds improve with the order of truncation and use of corresponding inequalities for higher-order moments. The moment equations in equation (3) can be viewed as values assigned to elements of $\boldsymbol{\mu}$ in terms of elements of $\overline{\boldsymbol{\mu}}$. Therefore, if the higher-order moments in $\overline{\boldsymbol{\mu}}$ are allowed to take arbitrary values, the elements of $\boldsymbol{\mu}$ also take arbitrary values. However, the moment inequalities restrict the values that can be taken by the higher-order moments. As a result, the values taken by the lower-order moments are restricted as well, and we get a range of feasible values with lower and upper bounds. Now suppose that we increase the order of truncation, i.e. we add more moment equations (equality constraints) and use more inequalities. By adding more constraints, the feasible values taken by the lower-order moments cannot get worse; they would be at least as large as they were earlier. However, as illustrated by the examples, the feasible range often gets smaller and we would expect to obtain exact moments as the order of truncation $M \to \infty$.

The examples also illustrate that whether the use of a certain inequality improves a lower bound or an upper bound depends upon the structure of the problem. For example, in the one-dimensional example of stochastic logistic growth, the truncations at $M = 1$ and $M = 2$, respectively, yield upper and lower bounds. On the other hand, in the two-dimensional example of gene expression with feedback regulation, the truncations at $M = 1$ and $M = 2$ both result in lower bounds. Future work will systematically address the effect of structures of the vector $\boldsymbol{a}$, and the matrices $\boldsymbol{A}$ and $\boldsymbol{B}$ on the nature of bound that is improved by increasing the order of truncation and the rate at which the bounds converge.

Another open issue is the scalability of the approach. Theoretically speaking, obtaining the bounds on moments in a transient state can be done in the same manner. However, the problem size often gets out of hand even if it is solved at some sampled time points because the semidefinite inequalities are to be satisfied at all times. Future work will develop specialized optimization tools for stochastic chemical kinetics. This would enable the species-level moment estimates to be used to compute moments of other statistical quantities such as first-passage times [62] and also to study interesting phenomena such as the apparent Poissonization of the kinetics [63, 64].

Acknowledgments

AS acknowledges funding support from NSF DMS-1312926. The authors thank Mohammad Soltani for discussions on some of the ideas contained herein.

Appendix A. Semidefiniteness of the outer product

A symmetric $n \times n$ matrix $\boldsymbol{M}$ is said to be positive semidefinite if

$$z^\top M z \geqslant 0 \tag{A.1}$$

for any $n \times 1$ vector $\boldsymbol{z}$. Let $\boldsymbol{M} = \boldsymbol{v}\boldsymbol{v}^\top$ for a $n \times 1$ vector $\boldsymbol{v}$. We have

$$z^\top \boldsymbol{v}\boldsymbol{v}^\top z = (z^\top \boldsymbol{v})(z^\top \boldsymbol{v})^\top = \|z^\top \boldsymbol{v}\|^2 \geqslant 0. \tag{A.2}$$

Therefore, the outer product $\boldsymbol{v}\boldsymbol{v}^\top$ is always positive semidefinite. Recall that the moment matrix is generated by taking expectation of the outer product. Its positive semidefiniteness can be proved as follows

$$z^\top \langle \boldsymbol{v}\boldsymbol{v}^\top \rangle z = \left\langle (z^\top \boldsymbol{v})(z^\top \boldsymbol{v})^\top \right\rangle = \left\langle \|z^\top \boldsymbol{v}\|^2 \right\rangle \geqslant 0. \tag{A.3}$$

Appendix B. Numerical implementation

For the first two examples in the paper, the proposed method was implemented in Mathematica. For the third example, the moment equations for the first order of truncation were solved in Mathematica. For higher orders, the problem was solved as a semidefinite program in MATLAB. To this end, the YALMIP wrapper [65] was used with SDPA-GMP as the solver [66].

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