Moment closure for biochemical networks

João Hespanha
Department of Electrical and Computer Engineering
University of California, Santa Barbara 93106-9560
email: hespanha@ece.ucsb.edu

***Abstract*—Moment closure is a technique used to construct systems of differential equations to approximately compute means, standard deviations, and correlations between molecule counts of species involved in chemical reactions. These techniques are especially useful when the number of molecules exhibit large stochasticity, which is not uncommon in bio-chemical reactions. We discuss several approaches to moment closure that have been proposed in the literature and that have been recently implemented in a Matlab toolbox.**

I. Introduction to Moment Closure

Consider a set of chemical species $X_1, X_2, \ldots, X_n$ involved in a set of chemical reactions and let us denote by $x := (x_1, x_2, \ldots, x_n)$ a vector containing their molecule counts. Given a vector of integers $m := (m_1, m_2, \ldots, m_n)$, we use the notation $\mu^{(m)}$ to denote the following uncentered moment of x:

$$\mu^{(m)} := \mathrm{E}[x_1^{m_1} x_2^{m_2} \cdots x_n^{m_n}].$$

Such moment if said to be of order $\sum_i m_i$. With n species there are exactly n first order moments $\mathrm{E}[x_i]$, $\forall i \in \{1,2,\ldots,n\}$, which are just the means; $n(n-1)/2$ second order moments $\mathrm{E}[x_i^2]$, $\forall i$ and $\mathrm{E}[x_i x_j]$, $\forall i \neq j$, which can be used to compute variances and covariance; $n(n-1)(n-2)/6$ third order moments; and so on.

It was show in [4], that if we construct a vector μ containing all the uncentered moments of x up to some order k, the evolution of μ is determined by a differential equation of the form

$$\dot{\mu} = A\mu + B\bar{\mu}, \quad \mu \in \mathbb{R}^K, \, \bar{\mu} \in \mathbb{R}^{\bar{K}} \tag{1}$$

where A and B are appropriately defined matrices and $\bar{\mu}$ is a vector containing moments of order larger[1] than k. The equation (1) is exact and we call it the *(exact) k-order moment dynamics* and the integer k is called the *order of truncation*. Note that the dimension K of (1) is always larger than k since there are many moments of each order. In fact, in general K is of order n^k.

When all chemical reactions have only one reactant, the term $B\bar{\mu}$ does not appear in (1) and we say that the exact moment dynamics are *closed*. However, when at least one chemical reaction has 2 or more reactants, then the term $B\bar{\mu}$ appears and we say that the moment dynamics are *open* since (1) depends on the moments in $\bar{\mu}$, which are not part of the state μ. When all chemical reactions are elementary (i.e., with at most 2 reactants), then all moments in $\bar{\mu}$ are exactly of order $k+1$.

Moment closure is a procedure by which one approximates the exact (but open) moment dynamics (1) by an approximate (but now closed) equation of the form

$$\dot{\nu} = A\nu + B\varphi(\nu), \quad \nu \in \mathbb{R}^K \tag{2}$$

where $\varphi(\nu)$ is a column vector that approximates the moments in $\bar{\mu}$. The function $\varphi(\nu)$ is called the moment closure function and (2) is called the *approximate kth order moment dynamics*. The goal of any moment closure method is to construct $\varphi(\nu)$ so that the solution ν to (2) is close to the solution μ to (1).

Some moment closure methods approximate the exact moments dynamics (1) by a closed equation of larger order, such as in

$$\dot{\phi} = \psi(\phi), \quad \phi \in \mathbb{R}^N, \tag{3a}$$

$$\dot{\nu} = A\nu + B\varphi(\phi, \nu), \quad \nu \in \mathbb{R}^K, \tag{3b}$$

where one now approximates $\bar{\mu}$ by the function $\varphi(\phi, \nu)$ that is allowed to also depend on the state ϕ of an additional dynamic system. Often $\varphi(\phi, \nu)$ can be made linear in ν. In this case, once ϕ reaches a steady state, the ν dynamics became linear and time-invariant.

There are three main approaches to construct the moment closure function $\varphi(\cdot)$:

1) *Matching-based methods* directly attempt to match the solutions to (1) and (2) [or (3)].
2) *Distribution-based methods* construct $\varphi(\cdot)$ by making "reasonable" assumptions on the statistical distribution of the molecule counts vector x.
3) *Large volume methods* construct $\varphi(\cdot)$ by assuming that reactions take place on a large volume.

It is important to emphasize that this classification is about methods to *construct* moment closure. It turns out that sometimes different methods lead to the same moment closure function $\varphi(\cdot)$.

II. Methods for Moment Closure

In this section we discuss several methods to construct the moment closure function. We shall see that the choice of which method to use depends on the type of system

This research was supported by the NSF.

[1] When one does not include in μ the zero-order moment $\mu^{(0)} = 1$, this term will appear in $\bar{\mu}$.

TABLE I
WHICH MOMENT CLOSURE TO USE?

	distributions have low variability (i.e., low standard deviations when compared to the mean) or are fairly symmetric	distributions have large standard deviations when compared to the mean, but populations do not become zero with high probability	populations can become zero with high probability
accuracy	zero cumulant closure	derivative matching closure	no good solution (yet)
simple dynamics	quasi-deterministic closure or Van Kampen's linear noise approximation	derivative matching closure (but will not be very simple)	no good solution (yet)

(e.g., how population means compare with standard deviations for the system considered) and also on the primary goal in constructing the approximate moment dynamics (e.g., how important is accuracy versus simplicity of the equations). Table I summarizes some rules of thumb on the choice of which approximation to use.

A. Derivative Matching

Derivative matching is a matching-based method for moment closure described in [4]. It uses moment closure functions $\varphi(\cdot)$ in (2) whose entries are *separable*, i.e., of the form $v_1^{\gamma_1} v_2^{\gamma_2} \cdots v_n^{\gamma_n}$. The coefficients $\gamma_i \in \mathbb{R}$ are then computed to make the relative error

$$\frac{\left\| \frac{\mathrm{d}^\ell \nu}{\mathrm{d}t^\ell} - \frac{\mathrm{d}^\ell \mu}{\mathrm{d}t^\ell} \right\|}{\left\| \frac{\mathrm{d}^\ell \mu}{\mathrm{d}t^\ell} \right\|}$$

as small as possible for molecule counts larger than one. Somewhat surprisingly, this minimization leads to explicit formulas for the moment closure functions $\varphi(\cdot)$ that do not depend on the reaction parameters [4].

B. Zero Cumulants

Zero cumulants is a distribution-based method for moment closure that finds the kth order moment closure function $\varphi(\cdot)$ in (2) by assuming that all multi-variable cumulants of the population x with order larger than k are negligible [2]. This makes the distribution of x "as close as possible" to a Gaussian distribution, which has all cumulants of order higher than two equal to zero.

To construct zero cumulant closures, one uses the fact that the cumulant $\kappa^{(m)}$ can be expressed as

$$\kappa^{(m)} = \mu^{(m)} + \sum_{\sum \bar{m}_i < \sum m_i} \alpha_{\bar{m}} \mu^{(\bar{m})}, \tag{4}$$

where the summation is over moments $\mu^{(\bar{m})}$ of order strictly smaller than $\sum m_i$ and the $\alpha_{\bar{m}}$ are appropriately selected constants [3]. This shows that the cumulant $\kappa^{(m)}$ depends only on the moment $\mu^{(m)}$ and lower-order moments $\mu^{(\bar{m})}$, so setting $\kappa^{(m)} = 0$ one obtains an expression for $\mu^{(m)}$ as a function of lower-order moments.

The procedure to compute the *zero-cumulants* moment closure function $\varphi(\cdot)$ consists of setting to zero all cumulants corresponding to the moments that do not appear in μ and then solving the equations (4) for the moments in $\bar{\mu}$.

C. Low Dispersion

Low dispersion is a distribution-based method for moment closure that finds the moment closure function $\varphi(\cdot)$ in (2) by assuming that the distributions of the populations are tightly clustered around their means, with standard deviations much smaller than the means. Specifically, for the kth order moment closure one assumes that the normalized centered moments of order larger than k are much smaller than one. We recall that given a vector of integers $m := (m_1, m_2, \ldots, m_n)$, the corresponding *normalized centered moment* is defined by

$$\eta^{(m)} := \mathrm{E}\left[\left(\frac{x_1 - \mathrm{E}[x_1]}{\mathrm{E}[x_1]} \right)^{m_1} \left(\frac{x_2 - \mathrm{E}[x_2]}{\mathrm{E}[x_2]} \right)^{m_2} \cdots \right].$$

Such moment if said to be of order $\sum_i m_i$. For fairly symmetric distributions the odd-order moments can be quite small and therefore this technique is especially useful for even-order moment closures for which the odd-order higher moments can be safely neglected.

To construct low dispersion closures, one uses the fact that an uncentered moment $\mu^{(m)}$ can be expressed in terms of the normalized centered moment as follows

$$\mu^{(m)} = \mathrm{E}[x_1]^{m_1} \mathrm{E}[x_2]^{m_2} \cdots \mathrm{E}[x_n]^{m_n} \left(1 + \eta^{(m)} + \sum_{2 \le \sum \bar{m}_i < \sum m_i} \beta_{\bar{m}} \eta^{(\bar{m})} \right),$$

where the summation is over moments $\eta^{(\bar{m})}$ of order two or larger and strictly smaller than $\sum m_i$, and the $\beta_{\bar{m}}$ are appropriately selected nonnegative constants [3]. When a particular normalized centered moment $\eta^{(m)}$ is much smaller than one, we have that

$$\mu^{(m)} \approx \mathrm{E}[x_1]^{m_1} \mathrm{E}[x_2]^{m_2} \cdots \mathrm{E}[x_n]^{m_n} \left(1 + \sum_{2 \le \sum \bar{m}_i < \sum m_i} \beta_{\bar{m}} \eta^{(\bar{m})} \right), \tag{5}$$

which allows one to express the uncentered moment $\mu^{(m)}$ solely in terms of normalized centered moments $\eta^{(\bar{m})}$ of order strictly smaller than $\sum m_i$. On the other hand, we can express all these normalized centered moments as linear combinations of the uncentered moments of order strictly smaller than $\sum m_i$ as follows

$$\eta^{(\bar{m})} = \frac{\mu^{(\bar{m})}}{\mathrm{E}[x_1]^{\bar{m}_1} \mathrm{E}[x_2]^{\bar{m}_2} \cdots \mathrm{E}[x_n]^{\bar{m}_n}} + \sum_{\sum \tilde{m}_i < \sum m_i} \gamma_{\tilde{m}} \frac{\mu^{(\tilde{m})}}{\mathrm{E}[x_1]^{\tilde{m}_1} \mathrm{E}[x_2]^{\tilde{m}_2} \cdots \mathrm{E}[x_n]^{\tilde{m}_n}}, \tag{6}$$

where the summation is over uncentered moments $\mu^{(\tilde{m})}$ of order strictly smaller than $\sum \bar{m}_i$ and the $\gamma_{\tilde{m}}$ are appropriately selected constants [3].

The procedure to compute the *low dispersions* moment closure function $\varphi(\cdot)$ in (2) thus consists of using (5) and (6) to approximate any moment that does not appear in μ as a linear combination of the moments in μ. Note however that the coefficients of these linear combinations will depend on monomials of the form $\mathrm{E}[x_1]^{\hat{m}_1}\mathrm{E}[x_2]^{\hat{m}_2}\cdots\mathrm{E}[x_n]^{\hat{m}_n}$, with all the $\hat{m}_i \geq 0$ and therefore the moment closure function $\phi(\cdot)$ will be polynomial but nonlinear on μ.

Relationship with zero-cumulants closure: For second order moment closure ($k=2$) one sets to zero 3th-order normalized centered moments, which is equivalent to setting to zero the 3th-order cumulants. Therefore for 2nd-order closures, zero cumulant and low dispersion coincide.

D. Quasi Deterministic

Quasi-deterministic is a distribution-based method for moment closure that finds the moment closure function $\varphi(\cdot)$ in (3) by assuming that the distributions of the populations are tightly clustered around the solution ϕ to the deterministic dynamics

$$\dot{\phi} = A_{\mathrm{det}}\phi + B_{\mathrm{det}}\psi(\phi), \qquad \phi := (\phi_1, \phi_2, \ldots, \phi_n) \in \mathbb{R}^n, \tag{7}$$

which are obtained by assuming that each $\phi_i := x_i$ is deterministic and therefore

$$\mathrm{E}[\phi_i\phi_j] = \mathrm{E}[\phi_i]\,\mathrm{E}[\phi_j] = \phi_i\phi_j.$$

Specifically, for the kth order moment closure one assumes that the quasi-deterministic normalized centered moments of order larger than k are much smaller than one. Given a vector of integers $m := (m_1, m_2, \ldots, m_n)$, the corresponding *quasi-deterministic normalized centered moment* is defined by

$$\hat{\eta}^{(m)} := \mathrm{E}\left[\left(\frac{x_1-\phi_1}{\phi_1}\right)^{m_1}\left(\frac{x_2-\phi_2}{\phi_2}\right)^{m_2}\cdots\left(\frac{x_n-\phi_n}{\phi_n}\right)^{m_n}\right].$$

Such moment if said to be of order $\sum_i m_i$.

To construct quasi-deterministic closures, one uses the fact that an uncentered moment $\mu^{(m)}$ can be expressed in terms of the quasi-deterministic normalized centered moment as follows

$$\mu^{(m)} = \phi_1^{m_1}\phi_2^{m_2}\cdots\phi_n^{m_n}\Big(1 + \hat{\eta}^{(m)} + \sum_{1\leq\sum\bar{m}_i<\sum m_i}\beta_{\bar{m}}\hat{\eta}^{(\bar{m})}\Big),$$

where the summation is over moments $\eta^{(\bar{m})}$ of order one or larger and strictly smaller than $\sum m_i$, and the $\beta_{\bar{m}}$ are appropriately selected nonnegative constants [3]. When a particular quasi-deterministic normalized centered moment $\hat{\eta}^{(m)}$ is much smaller than one, we have that

$$\mu^{(m)} \approx \phi_1^{m_1}\phi_2^{m_2}\cdots\phi_n^{m_n}\Big(1 + \sum_{2\leq\sum\bar{m}_i<\sum m_i}\beta_{\bar{m}}\hat{\eta}^{(\bar{m})}\Big), \tag{8}$$

which allows one to express the uncentered moment $\mu^{(m)}$ solely in terms of quasi-deterministic normalized centered moments $\hat{\eta}^{(\bar{m})}$ of order strictly smaller than $\sum m_i$. On the other hand, we can express all these quasi-deterministic normalized centered moments as linear combinations of the uncentered moments of order strictly smaller than $\sum m_i$ as follows

$$\hat{\eta}^{(\bar{m})} = \frac{\mu^{(\bar{m})}}{\phi_1^{m_1}\phi_2^{m_2}\cdots\phi_n^{\bar{m}_n}} + \sum_{\sum\tilde{m}_i<\sum m_i}\gamma_{\tilde{m}}\frac{\mu^{(\tilde{m})}}{\phi_1^{\tilde{m}_1}\phi_2^{\tilde{m}_2}\cdots\phi_n^{\tilde{m}_n}}, \tag{9}$$

where the summation is over uncentered moments $\mu^{(\tilde{m})}$ of order strictly smaller than $\sum \bar{m}_i$ and the $\gamma_{\tilde{m}}$ are appropriately selected constants [3].

The procedure to compute the *quasi-deterministic* moment closure function $\varphi(\cdot)$ in (3) thus consists of using (5) and (6) to approximate any moment that does not appear in μ as a linear combination of the moments in μ. The coefficients of these linear combinations will depend on monomials of the form $\phi_1^{\hat{m}_1}\phi_2^{\hat{m}_2}\cdots\phi_n^{\hat{m}_n}$, with all the $\hat{m}_i \geq 0$ and therefore the moment closure function will be linear on μ for a fixed ϕ. This means that the approximate dynamics in (3) are of the form

$$\dot{\phi} = A_{\mathrm{det}}\phi + B_{\mathrm{det}}\psi(\phi), \quad \phi \in \mathbb{R}^n, \tag{10a}$$

$$\dot{\nu} = A_\nu(\phi)\nu + c_\nu(\phi), \quad \nu \in \mathbb{R}^K, \tag{10b}$$

and, when ϕ reaches a steady state value, the ν dynamics become linear.

Relationship with low dispersion closure: In general the normalized centered moment are smaller than their quasi-deterministic version and therefore whenever quasi-deterministic moment closure provides a good approximation, one should expect low-dispersion moment closure to do at least as well. However, quasi-deterministic moment closure has the advantage that it results in moment dynamics that are "almost" linear and therefore generally easier to analyze.

E. Van Kampen's Linear Noise Approximation

Van Kampen's *Linear Noise Approximation* is developed in [5, Chapter X] and can be applied when the matrices A, B in (1) depend on some parameter V that can be assumed large, i.e., when we have

$$\dot{\mu} = A(V)\mu + B(V)\bar{\mu}, \quad \mu \in \mathbb{R}^K,$$

with V large. This form of moment closure results in a system of the form (3) and is exact in the limit as $V \to \infty$. Typically, V is the volume on which the chemical reactions take place.

To construct (3), one starts by choosing $\bar{\phi}$ to satisfy the *deterministic large-volume dynamics*

$$\dot{\bar{\phi}} = A_{\mathrm{det}}\bar{\phi} + B_{\mathrm{det}}\psi(\bar{\phi}), \bar{\phi} := (\bar{\phi}_1, \bar{\phi}_2, \ldots, \bar{\phi}_n) \in \mathbb{R}^n, \tag{11}$$

which are obtained by assuming that each $\bar{\phi}_i := x_i/V$ is deterministic and therefore

$$\mathrm{E}[\bar{\phi}_i\bar{\phi}_j] = \mathrm{E}[\bar{\phi}_i]\,\mathrm{E}[\bar{\phi}_j] = \bar{\phi}_i\bar{\phi}_j$$

and also by making $V \to \infty$.

Regarding the vector $\bar{\phi}$ in (11) as a deterministic approximation to the stochastic vector x/V, motivates defining the

following stochastic perturbation vector $\chi := (\chi_1, \chi_2, \ldots, \chi_n)$, with

$$\chi_i := \frac{x_i - V\bar{\phi}_i}{V^{\frac{1}{2}}} \quad \Leftrightarrow \quad x_i = V\bar{\phi}_i + V^{\frac{1}{2}}\chi_i, \tag{12}$$

where the normalization by $V^{\frac{1}{2}}$ will be needed to keep the moments of χ bounded as $V \to \infty$. Given a vector of integers $m := (m_1, m_2, \ldots, m_n)$, we use the notation $\xi^{(m)}$ to denote the following uncentered moment of χ:

$$\xi^{(m)} := \mathrm{E}[\chi_1^{m_1}\chi_2^{m_2}\cdots\chi_n^{m_n}].$$

The moments of x and χ are related by

$$\begin{aligned}\mu^{(m)} &= \mathrm{E}[(V\bar{\phi}_1 + V^{\frac{1}{2}}\chi_1)^{m_1}\cdots(V\bar{\phi}_n + V^{\frac{1}{2}}\chi_n)^{m_n}] \\ &= V^{\sum_i m_i} \sum_{\sum\bar{m}_i \le \sum m_i} \frac{\alpha_{\bar{m}}}{V^{\frac{\bar{m}}{2}}}\xi^{(\bar{m})}\end{aligned} \tag{13}$$

where the summation is over moments $\xi^{(\bar{m})}$ of order up to $\sum m_i$ and the $\alpha_{\bar{m}}$ are appropriately selected constants.

Computing the (exact) moment dynamics for ξ, one obtains

$$\dot{\xi} = A_\xi(V,\bar{\phi})\xi + B_\xi(V,\bar{\phi})\bar{\xi}, \quad \xi \in \mathbb{R}^K, \tag{14}$$

where ξ and $\bar{\xi}$ contain the moments of χ corresponding to the moments of x in μ and $\bar{\mu}$, respectively. For elementary reactions with reaction rates that depend on the volume as follows:

$$\emptyset \xrightarrow{\text{rate}=cV} * \qquad X \xrightarrow{\text{rate}=cX} *$$

$$2X \xrightarrow{\text{rate}=c\frac{X(X-1)}{V}} * \qquad X+Y \xrightarrow{\text{rate}=c\frac{XY}{V}} *$$

the open system (14) converges as $V \to \infty$ to a closed system of the form

$$\dot{\xi} = A_\xi(V,\bar{\phi})\xi + B_\xi(V,\bar{\phi})\bar{\xi} \xrightarrow{V\to\infty} A_\xi(\infty,\bar{\phi})\xi, \quad \xi \in \mathbb{R}^K. \tag{15}$$

Since the moments μ and ξ are related through (13), one can use (15) to obtain a closed equation for μ as in (3). Moreover, this equation will be linear in μ, leading to approximate dynamics similar to (10).

Relationship with quasi-deterministic closure: The deterministic equations (7) and (11) differ by two facts: (i) the state in (11) was normalized through a division by the volume, and (ii) in (11) we took the limit as $V \to \infty$. For elementary reactions with molecule counts much larger than one, taking the limit as $V \to \infty$ has almost no effect and we essentially have $\phi = V\bar{\phi}$. In this case,

$$\xi^{(m)} \approx \frac{\phi_1^{m_1}\phi_2^{m_2}\cdots\phi_n^{m_n}}{V^{\frac{\sum_i m_i}{2}}}\hat{\eta}^{(m)}.$$

In view of this, setting a quasi-deterministic moment $\hat{\eta}^{(m)}$ to zero is equivalent to setting to zero the corresponding uncentered moment $\xi^{(m)}$ of χ. This means that we can view the quasi-deterministic closure as taking the Van Kampen equations (11) and (15) and simply setting $\bar{\xi}$ in (15) to zero, without ignoring other terms that would also disappear as $V \to \infty$. Since we are keeping more terms of the exact equations, with quasi-deterministic closure one often obtains more accurate results then with Van Kampen's linear noise approximation.

III. StochDynTools Toolbox

In this section we illustrate how to use the `StochDynTools` Matlab toolbox to compute different moment closure dynamics for the network of chemical reactions considered in [5, p. 263]:

$$A \xrightarrow{\alpha V\phi_A} X, \qquad 2X \xrightarrow{\gamma X(X-1)/V} Y, \qquad Y \xrightarrow{\beta Y} B, \tag{16}$$

where the population of A is assumed constant with a concentration ϕ_A, V is the volume on which the reactions take place, and the expressions above the arrows in (16) correspond to the rates at which the different reactions take place. With some abuse of notation we will use the symbols X and Y to denote both the names of the species and their molecular counts. Within `StochDynTools`, this network of chemical reactions is described by the following "`.net` file:"

```
species:
   X stochastic;        % number of X molecules
   Y stochastic;        % number of Y molecules
parameters:
   V              = 20; % volume
   phiA "\phi_A"= 5;    % concentration     of A (fixed )
   al "\alpha"    = 10;
   be "\beta"     = 20;
   ga "\gamma"    = 30;
reactions:
   rate = al*phiA*V;     {X}   >{X+1};     % A -> X
   rate = ga*X*(X-1)/V; {X,Y}>{X-2,Y+1};%2X -> Y
   rate = be*Y;          {Y}   >{Y-1};     % Y -> B
```

Providing a detailed discussion of `.net` files syntax is beyond the scope of this paper and the reader is referred to [3] for details. Assuming that the above file is called `VKp263.net`, the exact 2nd-order moment dynamics for this system can be computed using the following Matlab commands:

```
net=readNet('VKp263.net');
mdyn=momentDynamics(net,2);
```

from which one obtains (after conversion to LaTeX):

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{bmatrix}\mathrm{E}[X]\\ \mathrm{E}[Y]\\ \mathrm{E}[X^2]\\ \mathrm{E}[XY]\\ \mathrm{E}[Y^2]\end{bmatrix} = \begin{bmatrix} 2\frac{\gamma}{V} & 0 & -2\frac{\gamma}{V} & 0 & 0\\ -\frac{\gamma}{V} & -\beta & \frac{\gamma}{V} & 0 & 0\\ 2\alpha\phi_A V - 4\frac{\gamma}{V} & 0 & 8\frac{\gamma}{V} & 0 & 0\\ 2\frac{\gamma}{V} & \alpha\phi_A V & -3\frac{\gamma}{V} & -\beta+2\frac{\gamma}{V} & 0\\ -\frac{\gamma}{V} & \beta & \frac{\gamma}{V} & -2\frac{\gamma}{V} & -2\beta \end{bmatrix}\begin{bmatrix}\mathrm{E}[X]\\ \mathrm{E}[Y]\\ \mathrm{E}[X^2]\\ \mathrm{E}[XY]\\ \mathrm{E}[Y^2]\end{bmatrix} + \begin{bmatrix}\alpha\phi_A V & 0 & 0\\ 0 & 0 & 0\\ \alpha\phi_A V & -4\frac{\gamma}{V} & 0\\ 0 & \frac{\gamma}{V} & -2\frac{\gamma}{V}\\ 0 & 0 & 2\frac{\gamma}{V}\end{bmatrix}\begin{bmatrix}1\\ \mathrm{E}[X^3]\\ \mathrm{E}[X^2Y]\end{bmatrix}.$$

The different moment closure approximations could then be obtained using the following Matlab commands:

```
mdyn_dm =momentClosure(net,mdyn,'derivativeMatching');
mdyn_zc =momentClosure(net,mdyn,'zeroCumulants');
mdyn_ld =momentClosure(net,mdyn,'lowDispersion');
mdyn_qd =momentClosure(net,mdyn,'quasiDeterministic');
mdyn_lna=momentClosure(net,mdyn,{'VanKampen','V'});
```

From these commands we would obtain the different approximate moment dynamics listed below.
Derivative matching:

$$\begin{bmatrix} \mathrm{E}[X^3] \\ \mathrm{E}[X^2Y] \end{bmatrix} \approx \begin{bmatrix} \frac{\mathrm{E}[X^2]^3}{\mathrm{E}[X]^3} \\ \frac{\mathrm{E}[X^2]\mathrm{E}[XY]^2}{\mathrm{E}[X]^2\,\mathrm{E}[Y]} \end{bmatrix}$$

Zero cumulants and *low dispersion*:

$$\begin{bmatrix} \mathrm{E}[X^3] \\ \mathrm{E}[X^2Y] \end{bmatrix} \approx \begin{bmatrix} 3\,\mathrm{E}[X^2]\,\mathrm{E}[X]-2\mathrm{E}[X]^3 \\ \mathrm{E}[X^2]\,\mathrm{E}[Y]+2\,\mathrm{E}[X]\,\mathrm{E}[XY]-2\mathrm{E}[X]^2\,\mathrm{E}[Y] \end{bmatrix}$$

Quasi deterministic:

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{bmatrix} \phi_X \\ \phi_Y \end{bmatrix} = \begin{bmatrix} 2\frac{\gamma\phi_X}{V}-2\frac{\gamma{\phi_X}^2}{V}+\alpha\phi_A V \\ -\frac{\gamma\phi_X}{V}-\beta\phi_Y+\frac{\gamma{\phi_X}^2}{V} \end{bmatrix}$$

$$\begin{bmatrix} \mathrm{E}[X^3] \\ \mathrm{E}[X^2Y] \end{bmatrix} \approx \begin{bmatrix} {\phi_X}^3-3{\phi_X}^2\,\mathrm{E}[X]+3\phi_X\,\mathrm{E}[X^2] \\ {\phi_X}^2\phi_Y+\phi_Y\,\mathrm{E}[X^2]-2\phi_X\phi_Y\,\mathrm{E}[X]-{\phi_X}^2\,\mathrm{E}[Y]+2\phi_X\,\mathrm{E}[XY] \end{bmatrix}$$

Van Kampen's linear noise approximation:

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{bmatrix} \phi_X \\ \phi_Y \end{bmatrix} = \begin{bmatrix} -2\gamma{\phi_X}^2+\alpha\phi_A \\ -\beta\phi_Y+\gamma{\phi_X}^2 \end{bmatrix}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{bmatrix} \mathrm{E}[X] \\ \mathrm{E}[Y] \\ \mathrm{E}[X^2] \\ \mathrm{E}[XY] \\ \mathrm{E}[Y^2] \end{bmatrix} \approx \begin{bmatrix} -4\gamma\phi_X & 0 & 0 & 0 & 0 \\ 2\gamma\phi_X & -\beta & 0 & 0 & 0 \\ 4\gamma V{\phi_X}^2+2\alpha\phi_A V & 0 & -8\gamma\phi_X & 0 & 0 \\ -\gamma V{\phi_X}^2 & 2\gamma V{\phi_X}^2+\alpha\phi_A V & 2\gamma\phi_X & -\beta-4\gamma\phi_X & 0 \\ 0 & -2\gamma V{\phi_X}^2 & 0 & 4\gamma\phi_X & -2\beta \end{bmatrix}\begin{bmatrix} \mathrm{E}[X] \\ \mathrm{E}[Y] \\ \mathrm{E}[X^2] \\ \mathrm{E}[XY] \\ \mathrm{E}[Y^2] \end{bmatrix} + \begin{bmatrix} 2\gamma V{\phi_X}^2+\alpha\phi_A V \\ -\gamma V{\phi_X}^2 \\ 4\gamma V{\phi_X}^2+\alpha\phi_A V \\ -2\gamma V{\phi_X}^2 \\ \gamma V{\phi_X}^2+\beta V\phi_Y \end{bmatrix}$$

Figure 1 compares the accuracy of the different moment closure methods for a low volume ($V = 2$) and a high volume ($V = 20$). For the larger volume all moment closure techniques provide a very good match with Monte Carlo results, but for the smaller volume derivative matching produces the most accurate results even with only a second order truncation. These results are fairly typical.

ACKNOWLEDGMENT

The author would like to thanks Mustafa Khammash and Abhyudai Singh for several discussions that motivated this paper.

REFERENCES

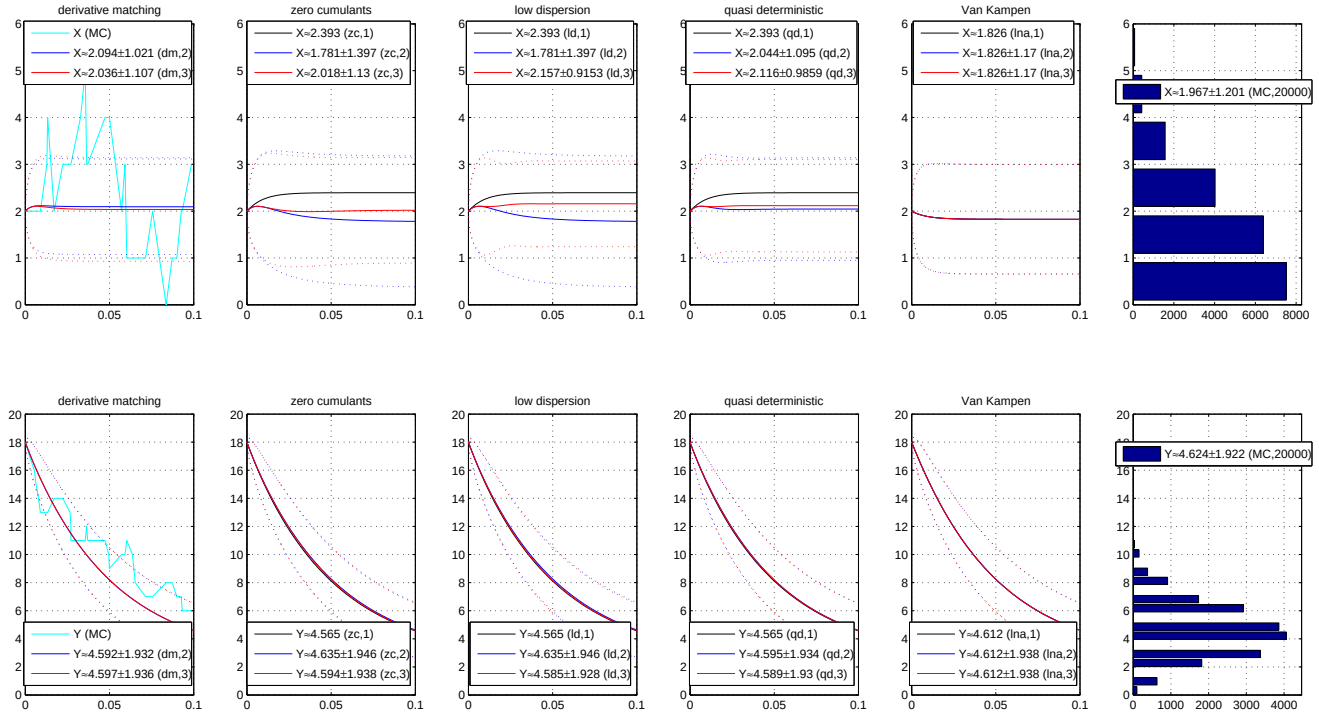
[1] Y. Cao, A. Hall, H. Li, and S. Lampoudi. *User's Guide for* STOCHKIT. University of California, Santa Barbara. Available at http://www.engineering.ucsb.edu/~cse/StochKit.

[2] C. A. Gomez-Uribe and G. C. Verghese. Mass fluctuation kinetics: Capturing stochastic effects in systems of chemical reactions through coupled mean-variance computations. *J. of Chemical Physics*, 126(2):024109–024109–12, 2007.

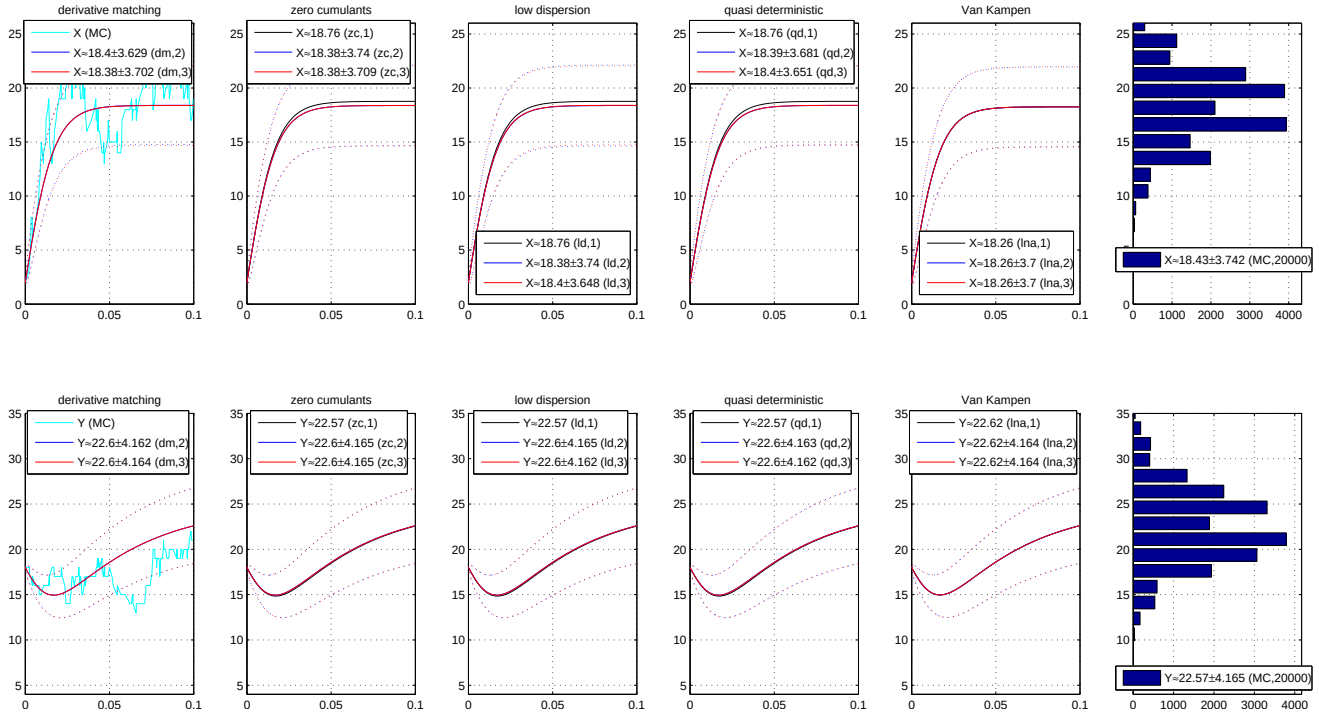
[3] J. P. Hespanha. `StochDynTools` — a MATLAB toolbox to compute moment dynamics for stochastic networks of bio-chemical reactions. Available at http://www.ece.ucsb.edu/~hespanha/software, Dec. 2006.

[4] A. Singh and J. P. Hespanha. Lognormal moment closures for biochemical reactions. In *Proc. of the 45th Conf. on Decision and Contr.*, Dec. 2006.

[5] N. G. Van Kampen. *Stochastic Processes in Physics and Chemistry*. Elsevier Science, 2001.



(a) volume $V = 2$



(b) volume $V = 20$

Fig. 1. Comparison of accuracy between different moment closure methods for the example described in Section III with two different volumes. The legends show (i) the values of the mean $\pm$ one standard deviation at the final time (ii) a two-character string indicating the moment closure method, and (iii) an integer indicating the order of truncation. The distributions, means and standard deviations in the right-most plots were obtained using 20,000 Monte Carlo simulations produced by [1]. The left-most plots include a typical Monte Carlo run.