Model order reduction for Linear Noise Approximation using time-scale separation

Massachusetts Institute of Technology

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Narmada Herath[1] and Domitilla Del Vecchio[2]

Abstract— In this paper, we focus on model reduction of biomolecular systems with multiple time-scales, modeled using the Linear Noise Approximation. Considering systems where the Linear Noise Approximation can be written in singular perturbation form, with ϵ as the singular perturbation parameter, we obtain a reduced order model that approximates the slow variable dynamics of the original system. In particular, we show that, on a finite time-interval, the first and second moments of the reduced system are within an $O(\epsilon)$-neighborhood of the first and second moments of the slow variable dynamics of the original system. The approach is illustrated on an example of a biomolecular system that exhibits time-scale separation.

I. INTRODUCTION

Time-scale separation is a ubiquitous feature in biomolecular systems, which enables the separation of the system dynamics into 'slow' and 'fast'. This property is widely used in biological applications to reduce the complexity in dynamical models. In deterministic systems, where the dynamics are modeled using ordinary differential equations, the process of obtaining a reduced model is well defined by singular perturbation and averaging techniques [1], [2]. However, employing time-scale separation to obtain a reduced order model remains an ongoing area of research for stochastic models of biological systems [3].

Biological systems are inherently stochastic due to randomness in chemical reactions [4], [5]. Thus, different stochastic models have been developed to capture the randomness in the system dynamics, especially at low populations numbers. The chemical Master equation is a prominent stochastic model which considers the species counts as a set of discrete states and provides a description for the time-evolution of their probability density functions [6], [7]. However, analyzing the chemical Master equation directly proves to be a challenge due to the lack of analytical tools to analyze its behavior. Therefore, several approximations of the Master equation have been developed, which provide good descriptions of the system dynamics under certain assumptions. The chemical Langevin equation (CLE) is one such approximation, where the dynamics of the chemical species are described as a set of stochastic differential equations [8]. The Fokker-Plank equation is another method equivalent to the CLE, which considers the species counts as continuous variables and provides a description of the time evolution

of their probability density functions [6]. The Linear Noise Approximation (LNA) is another approximation, where the system dynamics are portrayed as stochastic fluctuations about a deterministic trajectory, assuming that the system volume is sufficiently large such that the fluctuations are small relative to the average species counts [7], [9].

In our previous work, we considered a class of stochastic differential equations in singular perturbation form, which captures the case of multiple scale chemical Langevin equation with linear propensity functions. We obtained a reduced order model for which the error between the moment dynamics were of $O(\epsilon)$, where ϵ is the singular perturbation parameter [10], [11]. In this work, we consider systems with nonlinear propensity functions, modeled using the Linear Noise Approximation.

There have been several works that obtain reduced order models for systems modeled using LNA, under different approaches for time-scale separation. One such model is derived by Pahlajani et. al, in [12], where the slow and fast species are identified by categorizing the chemical reactions as slow and fast. In [13], [14], Thomas et. al, derive a reduced order model by considering the case where the species are separated using the decay rate of their transients, according to the quasi-steady-state approximation for chemical kinetics. It is also shown that, imposing the time-scale separation conditions arising from slow and fast reactions, on their model, leads to the same reduced model obtained in [12]. In these previous works, the error between the original system and the reduced system has been studied numerically and has not been analytically quantified. The work by Sootla and Anderson in [15] gives a projection-based model order reduction method for systems modeled by Linear Noise Approximation. The authors extend this work in [16], where they also provide an error quantification in mean square sense for the reduced order model derived in [13] under quasi-steady state assumptions. However, to provide an error bound the authors explicitly use the Lipschitz continuity of the diffusion term, which is not Lipschitz continuous in general.

In this paper, we consider biomolecular systems modeled using the Linear Noise Approximation where system dynamics are represented by a set of ordinary differential equations that give the deterministic trajectory and a set of stochastic differential equations that describe the stochastic fluctuations about the deterministic trajectory. We consider the case where the system dynamics evolve on well separated time-scales with slow and fast reactions, and the LNA can be written in singular perturbation form with ϵ as the singular perturbation parameter, as in [12]. We define a reduced order

[1]Narmada Herath is with the Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology, 77 Mass. Ave, Cambridge MA nherath@mit.edu

[2]Domitilla Del Vecchio is with the Department of Mechanical Engineering, Massachusetts Institute of Technology, 77 Mass. Ave, Cambridge MA ddv@mit.edu

model and prove that the first and second moments of the reduced system are within an $O(\epsilon)$-neighborhood of the first and second moments of the original system. Our results do not rely on Lipschitz continuity assumptions on the diffusion term of the LNA.

This paper is organized as follows. In Section II, we describe the model considered. In Section III, we define the reduced system and derive the moment dynamics for the original and reduced systems. In Section IV, we prove the main convergence results. Section V illustrates our approach with an example and Section VI includes the concluding remarks.

II. System Model

A. Linear Noise Approximation

Consider a biomolecular system with n species interacting through m reactions in a given volume Ω. The Chemical Master Equation (CME) describes the evolution of the probability distribution for the species counts to be in state $Y = (Y_1, \ldots, Y_N)$, by the partial differential equation

$$\frac{\partial P(Y,t)}{\partial t} = \sum_{i=1}^{m} [a_i(Y - v_i, t)P(Y - v_i, t) - a_i(Y,t)P(Y,t)],$$
(1)

where $a_i(Y,t)$ is the microscopic reaction rate with $a_i(Y,t)dt$ being the probability that a reaction i will take place in an infinitesimal time step dt and v_i the change in state produced by reaction i for $i = 1, \ldots, m$ [17].

The Linear Noise Approximation (LNA) is an approximation to the CME obtained under the assumption that the system volume Ω and the number of molecules in the system are large [7]. To derive the LNA it is assumed that $Y = \Omega y + \sqrt{\Omega}\xi$, where y is a deterministic quantity and ξ is a stochastic variable accounting for the stochastic fluctuations. Then by expanding the chemical Master equation in a Taylor series and equating the terms of order $\Omega^{1/2}$ and Ω^0, it is shown that y is the macroscopic concentration and ξ is a Gaussian process whose dynamics are given by [7], [9]

$$\dot{y} = f(y,t),$$
(2)
$$\dot{\xi} = A(y,t)\xi + \sigma(y,t)\Gamma,$$
(3)

where Γ is an m-dimensional white noise process, $f(y,t) = \sum_{i=1}^{m} v_i \tilde{a}_i(y,t)$, $A(y,t) = \frac{\partial f(y,t)}{\partial y}$ and $\sigma(y,t) = [v_1 \sqrt{\tilde{a}_1(y,t)}, \ldots, v_m \sqrt{\tilde{a}_m(y,t)}]$. $\tilde{a}_i(y,t)$ is the macroscopic reaction rate which can be approximated by $\tilde{a}_i(y,t) = \frac{1}{\Omega}a_i(\Omega y, t)$ at the limit of $\Omega \to \infty$ and $Y \to \infty$ such that the concentration $y = Y/\Omega$ remains constant [18].

B. Singularly Perturbed System

We consider the case where the biomolecular system in (2) - (3) exhibits time-scale separation, with m_s slow reactions and m_f fast reactions where $m_s + m_f = m$. This allows the use of a small parameter ϵ to decompose the reaction rate vector as $\tilde{a}(y,t) = [\hat{a}_s(y,t), (1/\epsilon)\hat{a}_f(y,t)]^T$ where $\hat{a}_s(y,t) \in \mathbb{R}^{m_s}$ represents the reaction rates for the slow reactions and $(1/\epsilon)\hat{a}_f(y,t) \in \mathbb{R}^{m_f}$ represents the reaction

rates for the fast reactions. The corresponding v_i vectors representing the change of state by each reaction i could be represented as $v = [v_1, \ldots, v_{m_s}, v_{m_s+1}, \ldots, v_{m_s+m_f}]$ for m_s slow and m_f fast reactions. However, such a decomposition does not guarantee that the individual species in the system will evolve on well-separated time-scales. Therefore, a coordinate transformation may be necessary to identify the slow and fast variables in the system as seen in deterministic systems [19] and chemical Langevin models [20]. Thus, we make the following claim.

Claim 1: Assume there is an invertible matrix $A = [A_x, A_z]^T$ with $A_x \in \mathbb{R}^{n_s \times n}$ and $A_z \in \mathbb{R}^{n_f \times n}$, such that the change of variables $x = A_x y$, $z = A_z y$, allows the deterministic dynamics in (2) to be written in the singular perturbation form

$$\dot{x} = f_x(x,z,t),$$
(4)
$$\epsilon\dot{z} = f_z(x,z,t,\epsilon),$$
(5)

then, the change of variables $\psi_x = A_x\xi$, $\psi_z = A_z\xi$ takes the dynamics of the stochastic fluctuations given in (3), in to the singular perturbation form

$$\dot{\psi}_x = A_1(x,z,t)\psi_x + A_2(x,z,t)\psi_z + \sigma_x(x,z,t)\Gamma_x,$$
(6)
$$\epsilon\dot{\psi}_z = B_1(x,z,t,\epsilon)\psi_x + B_2(x,z,t,\epsilon)\psi_z + \sigma_z(x,z,t,\epsilon)\Gamma_z,$$
(7)

where Γ_x is an m_s-dimensional white noise process, $\Gamma_z = [\Gamma_x, \Gamma_f]^T$, where Γ_f is an m_f-dimensional white noise process and

$A_1(x,z,t) = \dfrac{\partial f_x(x,z,t)}{\partial x},$

$A_2(x,z,t) = \dfrac{\partial f_x(x,z,t)}{\partial z},$

$B_1(x,z,t,\epsilon) = \dfrac{\partial f_z(x,z,t,\epsilon)}{\partial x},$

$B_2(x,z,t,\epsilon) = \dfrac{\partial f_z(x,z,t,\epsilon)}{\partial z},$

$\sigma_x(x,z,t) =$

$A_x \left[v_1 \sqrt{\hat{a}_{s1}(A^{-1}[x,z]^T, t)}, \ldots, v_{m_s} \sqrt{\hat{a}_{sm_s}(A^{-1}[x,z]^T, t)} \right],$

$\sigma_z(x,z,t,\epsilon) =$

$\begin{bmatrix} \epsilon A_z \left[v_1 \sqrt{\hat{a}_{s1}(A^{-1}[x,z]^T, t)}, \ldots, v_{m_s} \sqrt{\hat{a}_{sm_s}(A^{-1}[x,z]^T, t)} \right] \\ A_z \left[v_{m_s+1} \sqrt{\epsilon\hat{a}_{f1}(A^{-1}[x,z]^T, t)}, \ldots, \right. \\ \left. v_{m_s+m_f} \sqrt{\epsilon\hat{a}_{fm_f}(A^{-1}[x,z]^T, t)} \right] \end{bmatrix}^T.$

Proof: See Appendix A-1. ∎

Based on the result of Claim 1, in this work, we consider the Linear Noise Approximation represented in the singular perturbation form:

$$\dot{x} = f_x(x,z,t), \qquad\qquad x(0) = x_0, \quad (8)$$
$$\epsilon\dot{z} = f_z(x,z,t,\epsilon), \qquad\qquad z(0) = z_0, \quad (9)$$
$$\dot{\psi}_x = A_1(x,z,t)\psi_x + A_2(x,z,t)\psi_z + \sigma_x(x,z,t)\Gamma_x,$$
$$\psi_x(0) = \psi_{x0}, \quad (10)$$

$$\epsilon\dot{\psi}_z = B_1(x,z,t,\epsilon)\psi_x + B_2(x,z,t,\epsilon)\psi_z + \sigma_z(x,z,t,\epsilon)\Gamma_z,$$
$$\psi_z(0) = \psi_{z0}, \quad (11)$$

where $x \in D_x \subset \mathbb{R}^{n_s}$, $\psi_x \in D_{\psi_x} \subset \mathbb{R}^{n_s}$ are the slow variables and $z \in D_z \subset \mathbb{R}^{n_f}$, $\psi_z \in D_{\psi_z} \subset \mathbb{R}^{n_f}$ are the fast variables. Γ_x is an m_s-dimensional white noise process. Then, $\Gamma_z = [\Gamma_x, \Gamma_f]^T$, where Γ_f to be a m_f-dimensional white noise process. We assume that the system (8) - (9) has a unique solution on a finite-time interval $t \in [0, t_1]$.

We refer to the system (8) - (11) as the original system and obtain a reduced order model when $\epsilon = 0$. To this end, we make the following assumptions on system (8) - (11) for $x \in D_x \subset \mathbb{R}^{n_s}$, $z \in D_z \subset \mathbb{R}^{n_f}$ and $t \in [0, t_1]$.

Assumption 1: The functions $f_x(x,z,t)$, $f_z(x,z,t,\epsilon)$ are twice continuously differentiable. The Jacobian $\frac{\partial f_z(x,z,t,0)}{\partial z}$ has continuous first and second partial derivatives with respect to its arguments.

Assumption 2: The matrix-valued functions $\sigma_x(x,z,t)\sigma_x(x,z,t)^T$, $\sigma_z(x,z,t,\epsilon)[\sigma_x(x,z,t) \quad 0]^T$ and $\sigma_z(x,z,t,\epsilon)\sigma_z(x,z,t,\epsilon)^T$ are continuously differentiable. Furthermore, we have that $\sigma_z(x,z,t,0) = 0$ and $\lim_{\epsilon\to0}\frac{\sigma_z(x,z,t,\epsilon)\sigma_z(x,z,t,\epsilon)^T}{\epsilon} = \sigma(x,z,t)$ where $\sigma(x,z,t)$ is bounded for given x, z, t and $\frac{\partial\sigma(x,z,t)}{\partial z}$ is continuous.

Assumption 3: There exists an isolated real root $z = \gamma_1(x,t)$, for the equation $f_z(x,z,t,0) = 0$, for which, the matrix $\frac{\partial f_z(x,z,t,0)}{\partial z}\big|_{z=\gamma_1(x,t)}$ is Hurwitz, uniformly in x and t. Furthermore, we have that the first partial derivative of $\gamma_1(x,t)$ is continuous with respect to its arguments. Also, the initial condition z_0 is in the region of attraction of the equilibrium point $z = \gamma_1(x_0, 0)$ for the system $\frac{dz}{d\tau} = f_z(x_0, z, 0, 0)$.

Assumption 4: The system $\dot{x} = f_x(x, \gamma_1(x,t), t)$ has a unique solution for $t \in [0, t_1]$.

III. PRELIMINARY RESULTS

A. Reduced System

The reduced system is defined by setting $\epsilon = 0$ in the original system (8) - (11), which yields

$$f_z(x,z,t,0) = 0, \quad (12)$$
$$B_1(x,z,t,0)\psi_x + B_2(x,z,t,\epsilon)\psi_z = 0. \quad (13)$$

Let $z = \gamma_1(x,t)$ be an isolated root of equation (12), which satisfies Assumption 3. Then, we have that $\psi_z = -B_2(x,\gamma_1(x,t),t,0)^{-1}B_1(x,\gamma_1(x,t),t,0)\psi_x$ is the unique solution of equation (13). Let $\gamma_2(x,t) = -B_2(x,\gamma_1(x,t),t,0)^{-1}B_1(x,\gamma_1(x,t),t,0)$. Then, substituting $z = \gamma_1(x,t)$ and $\psi_z = \gamma_2(x,t)\psi_x$ in equations (8) and (10), we obtain the reduced system

$$\dot{\bar{x}} = f_x(\bar{x},\gamma_1(\bar{x},t),t), \quad \bar{x}(0) = x_0, \quad (14)$$
$$\dot{\bar{\psi}}_x = A(\bar{x},t)\bar{\psi}_x + \sigma_x(\bar{x},\gamma_1(\bar{x},t),t)\Gamma_x, \quad \bar{\psi}_x(0) = \psi_{x0}, \quad (15)$$

where
$$A(\bar{x},t) = A_1(\bar{x},\gamma_1(\bar{x},t),t)\bar{\psi}_x + A_2(\bar{x},\gamma_1(\bar{x},t),t)\gamma_2(\bar{x},t).$$

Next, we derive the first and second moment dynamics of the variable $\bar{\psi}_x$ in the reduced system. To this end, we make the following claim:

Claim 2: The first and second moment dynamics for the variable $\bar{\psi}_x$ of the reduced system (14) - (15) can be written in the form

$$\frac{d\mathbb{E}[\bar{\psi}_x]}{dt} = A(\bar{x},t)\mathbb{E}[\bar{\psi}_x], \quad \mathbb{E}[\bar{\psi}_x(0)] = \psi_{x0}, \quad (16)$$

$$\frac{d\mathbb{E}[\bar{\psi}_x\bar{\psi}_x^T]}{dt} = A(\bar{x},t)\mathbb{E}[\bar{\psi}_x\bar{\psi}_x^T] + \mathbb{E}[\bar{\psi}_x\bar{\psi}_x^T]A(\bar{x},t)^T + \sigma_x(\bar{x},\gamma_1(\bar{x},t),t),t)\sigma_x(\bar{x},\gamma_1(\bar{x},t),t),t)^T,$$
$$\mathbb{E}[\bar{\psi}_x(0)\bar{\psi}_x(0)^T] = \psi_{x0}\psi_{x0}^T. \quad (17)$$

Proof: Similar to [21], the first and second moment dynamics of $\bar{\psi}_x$ in (15) can be written as

$$\frac{d\mathbb{E}[\bar{\psi}_x]}{dt} = \mathbb{E}[A(\bar{x},t)\bar{\psi}_x],$$

$$\frac{d\mathbb{E}[\bar{\psi}_x\bar{\psi}_x^T]}{dt} = \mathbb{E}[A(\bar{x},t)\bar{\psi}_x\bar{\psi}_x^T] + \mathbb{E}[\bar{\psi}_x(\bar{\psi}_x^T A(\bar{x},t)^T)] + \sigma_x(\bar{x},\gamma_1(\bar{x},t),t),t)\sigma_x(\bar{x},\gamma_1(\bar{x},t),t),t)^T.$$

Since the dynamics of $\bar{x}$ given by (14) is deterministic, using the linearity of the expectation operator we can write the moment dynamics of the reduced system as (16) - (17). ∎

Next, we proceed to derive the moment dynamics for ψ_x and ψ_z in the original system (8) - (11) given by the following claim.

Claim 3: The first and second moment dynamics for the variables ψ_x and ψ_z of the original system (8) - (11) can be written in the form

$$\frac{d\mathbb{E}[\psi_x]}{dt} = A_1(x,z,t)\mathbb{E}[\psi_x] + A_2(x,z,t)\mathbb{E}[\psi_z], \quad (18)$$

$$\frac{d\mathbb{E}[\psi_x\psi_x^T]}{dt} = A_1(x,z,t)\mathbb{E}[\psi_x\psi_x^T] + A_2(x,z,t)\mathbb{E}[\psi_z\psi_x^T] + \mathbb{E}[\psi_x\psi_x^T]A_1(x,z,t)^T + (\mathbb{E}[\psi_z\psi_x^T])^T A_2(x,z,t)^T + \sigma_x(x,z,t)\sigma_x(x,z,t)^T, \quad (19)$$

$$\epsilon\frac{d\mathbb{E}[\psi_z]}{dt} = B_1(x,z,t,\epsilon)\mathbb{E}[\psi_x] + B_2(x,z,t,\epsilon)\mathbb{E}[\psi_z], \quad (20)$$

$$\epsilon\frac{d\mathbb{E}[\psi_z\psi_x^T]}{dt} = \epsilon\mathbb{E}[\psi_z\psi_x^T]A_1(x,z,t)^T + \epsilon\mathbb{E}[\psi_z\psi_z^T]A_2(x,z,t)^T + B_1(x,z,t,\epsilon)\mathbb{E}[\psi_x\psi_x^T] + B_2(x,z,t,\epsilon)\mathbb{E}[\psi_z\psi_x^T] + \sigma_z(x,z,t,\epsilon)[\sigma_x(x,z,t) \quad 0]^T, \quad (21)$$

$$\epsilon\frac{d\mathbb{E}[\psi_z\psi_z^T]}{dt} = B_1(x,z,t,\epsilon)\mathbb{E}[\psi_x\psi_z^T] + B_2(x,z,t,\epsilon)\mathbb{E}[\psi_z\psi_z^T] + \mathbb{E}[\psi_z\psi_x^T]B_1(x,z,t,\epsilon)^T + \mathbb{E}[\psi_z\psi_z^T]B_2(x,z,t,\epsilon)^T + \frac{1}{\epsilon}\sigma_z(x,z,t,\epsilon)\sigma_z(x,z,t,\epsilon)^T, \quad (22)$$

where x and z are the solutions of the equations (8) - (9), and the initial conditions are given by $\mathbb{E}[\psi_x(0)] = \psi_{x0}$, $\mathbb{E}[\psi_x\psi_x^T(0)] = \psi_{x0}\psi_{x0}^T$, $\mathbb{E}[\psi_z(0)] = \psi_{z0}$, $\mathbb{E}[\psi_z\psi_x^T(0)] = \psi_{z0}\psi_{x0}^T$, $\mathbb{E}[\psi_z\psi_z^T(0)] = \psi_{z0}\psi_{z0}^T$.

Proof: The equations (10) - (11) can be written in the form

$$\dot{\psi}_x = A_1(x,z,t)\psi_x + A_2(x,z,t)\psi_z + [\sigma_x(x,z,t)\ 0]\Gamma_z,$$
$$\epsilon\dot{\psi}_z = B_1(x,z,t,\epsilon)\psi_x + B_2(x,z,t,\epsilon)\psi_z + \sigma_z(x,z,t,\epsilon)\Gamma_z,$$

where $[\ \sigma_x(x,z,t)\quad 0\ ] \in \mathbb{R}^{n\times(m_s+m_f)}$. Then, using the fact that the x and z are deterministic and the linearity of the expectation operator, the dynamics for the first moments can be written as

$$\frac{d\mathbb{E}[\psi_x]}{dt} = A_1(x,z,t)\mathbb{E}[\psi_x] + A_2(x,z,t)\mathbb{E}[\psi_z], \tag{23}$$

$$\frac{d\mathbb{E}[\psi_z]}{dt} = \frac{1}{\epsilon}B_1(x,z,t,\epsilon)\mathbb{E}[\psi_x] + \frac{1}{\epsilon}B_2(x,z,t,\epsilon)\mathbb{E}[\psi_z]. \tag{24}$$

Similarly, using Proposition III.1 in [21], the second moment dynamics can be written as

$$\frac{d}{dt}\mathbb{E}\left[\begin{array}{cc} \psi_x\psi_x^T & \psi_x\psi_z^T \\ \psi_z\psi_x^T & \psi_z\psi_z^T \end{array}\right] =$$

$$\left[\begin{array}{c} \psi_x(A_1(x,z,t)\psi_x + A_2(x,z,t)\psi_z)^T \\ \psi_z(A_1(x,z,t)\psi_x + A_2(x,z,t)\psi_z)^T \end{array}\right.$$

$$\left.\begin{array}{c} \frac{1}{\epsilon}\psi_x(B_1(x,z,t,\epsilon)\psi_x + B_2(x,z,t,\epsilon)\psi_z)^T \\ \frac{1}{\epsilon}\psi_z(B_1(x,z,t,\epsilon)\psi_x + B_2(x,z,t,\epsilon)\psi_z)^T \end{array}\right]$$

$$+\left[\begin{array}{c} (A_1(x,z,t)\psi_x + A_2(x,z,t)\psi_z)\psi_x^T \\ \frac{1}{\epsilon}(B_1(x,z,t,\epsilon)\psi_x + B_2(x,z,t,\epsilon)\psi_z)\psi_x^T \end{array}\right.$$

$$\left.\begin{array}{c} (A_1(x,z,t)\psi_x + A_2(x,z,t)\psi_z)\psi_z^T \\ \frac{1}{\epsilon}(B_1(x,z,t,\epsilon)\psi_x + B_2(x,z,t,\epsilon)\psi_z)\psi_z^T \end{array}\right]$$

$$+\left[\begin{array}{c} \sigma_x(x,z,t)\sigma_x(x,z,t)^T \\ \frac{1}{\epsilon}\sigma_z(x,z,t,\epsilon)[\ \sigma_x(x,z,t)\ \ 0\ ]^T \end{array}\right.$$

$$\left.\begin{array}{c} \frac{1}{\epsilon}[\ \sigma_x(x,z,t)\ \ 0\ ]\sigma_z(x,z,t,\epsilon)^T \\ \frac{1}{\epsilon^2}\sigma_z(x,z,t,\epsilon)\sigma_z(x,z,t,\epsilon)^T \end{array}\right]. \tag{25}$$

Employing the linearity of the expectation operator, we can sum the corresponding entries of the matrices in equation (25), and multiply by ϵ to write the moment equations (23) - (25) in the form of (18) - (22). Note that, since $\mathbb{E}[\psi_x\psi_z^T] = (\mathbb{E}[\psi_z\psi_x^T])^T$, we have eliminated the dynamics of the variable $\mathbb{E}[\psi_x\psi_z^T]$. ∎

Claim 4: Setting $\epsilon = 0$ in the system of moment dynamics (18) - (22) and the dynamics of x and z given by (8) - (9), yields the moment dynamics of the reduced system (16) - (17) where the dynamics of $\bar{x}$ are given by (14).

Proof: Setting $\epsilon = 0$ in the equations (8) - (9) and (19) - (20), yields

$$0 = f_z(x,z,t,0), \tag{26}$$
$$0 = B_1(x,z,t,0)\mathbb{E}[\psi_x] + B_2(x,z,t,0)\mathbb{E}[\psi_z], \tag{27}$$
$$0 = B_1(x,z,t,0)\mathbb{E}[\psi_x\psi_x^T] + B_2(x,z,t,0)\mathbb{E}[\psi_z\psi_x^T]. \tag{28}$$

By definition of the reduced system, we have that $z = \gamma_1(x,t)$ is an isolated root for equation (26). Then, under the Assumption 3, we have that the unique solutions for the equations (27) and (28) are given by

$$\mathbb{E}[\psi_z] = -B_2(x,\gamma_1(x,t),t,0)^{-1}(B_1(x,\gamma_1(x,t),t,0)\mathbb{E}[\psi_x])$$

$$= \gamma_2(x,t)\mathbb{E}[\psi_x], \tag{29}$$

$$\mathbb{E}[\psi_z\psi_x^T]$$
$$= -B_2(x,\gamma_1(x,t),t,0)^{-1}(B_1(x,\gamma_1(x,t),t,0)\mathbb{E}[\psi_x\psi_x^T])$$
$$= \gamma_2(x,t)\mathbb{E}[\psi_x\psi_x^T]. \tag{30}$$

Substituting $z = \gamma_1(x,t)$ and equations (29) - (30), in (8) and (18) - (22) results in

$$\dot{x} = f_x(x,\gamma_1(x,t),t), \tag{31}$$

$$\frac{d\mathbb{E}[\psi_x]}{dt} = A_1(x,\gamma_1(x,t),t)\mathbb{E}[\psi_x]$$
$$+ A_2(x,\gamma_1(x,t),t)\gamma_2(x,t)\mathbb{E}[\psi_x], \tag{32}$$

$$\frac{d\mathbb{E}[\psi_x\psi_x^T]}{dt} = A_1(x,\gamma_1(x,t),t)\mathbb{E}[\psi_x\psi_x^T]$$
$$+ A_2(x,\gamma_1(x,t),t)\gamma_2(x,t)\mathbb{E}[\psi_x\psi_x^T]$$
$$+ \mathbb{E}[\psi_x\psi_x^T]A_1(x,z,t)^T$$
$$+ (\gamma_2(x,t)\mathbb{E}[\psi_x\psi_x^T])^T A_2(x,\gamma_1(x,t),t)^T$$
$$+ \sigma_x(x,\gamma_1(x,t),t)\sigma_x(x,\gamma_1(x,t),t)^T. \tag{33}$$

It follows that equation (31) is equivalent to the reduced system given by (14) and since we have that $A(x,t) = A_1(x,\gamma_1(x,t),t)\bar{\psi}_x + A_2(x,\gamma_1(x,t),t)\gamma_2(x,t)$, the system (32) - (33) is equivalent to the moment dynamics of the reduced system given by (16) - (17). ∎

IV. MAIN RESULTS

Lemma 1: Consider the original system in (8) - (11), the reduced system in (14) - (15), and the moment dynamics for the original and reduced systems in (18) - (22), (16) - (17) respectively. We have that, under Assumptions 1 - 3, the commutative diagram in Fig. 1 holds.

Proof: The proof follows from Claim 1, Claim 2 and Claim 3. ∎

Theorem 1: Consider the original system (8) - (11), the reduced system in (14) - (15) and the moment dynamics for the original and reduced systems in (18) - (22), (16) - (17) respectively. Then, under Assumptions 1 - 4, there exists $\epsilon^* \geq 0$ such that for $0 < \epsilon < \epsilon^*$, we have

$$\|x(t) - \bar{x}(t)\| = O(\epsilon), \ t \in [0,t_1], \tag{34}$$
$$\|\mathbb{E}[\psi_x(t)] - \mathbb{E}[\bar{\psi}_x(t)]\| = O(\epsilon), \tag{35}$$
$$\|\mathbb{E}[\psi_x(t)\psi_x(t)^T] - \mathbb{E}[\bar{\psi}_x(t)\bar{\psi}_x(t)^T]\| = O(\epsilon). \tag{36}$$

Proof: From Lemma 1, we see that setting $\epsilon = 0$ in the moment dynamics of the original system (18) - (22) and in the dynamics of x and z given by (8) - (9), yields the moment dynamics of the reduced system (16) - (17) where the dynamics of $\bar{x}$ is given by (14). Therefore to prove Theorem 1, we apply Tikhonov's theorem [1] to the system of moment dynamics of the original system given by (18) - (22) together the dynamics of x and z given by (8) - (9). In order to apply Tikhonov's theorem, we first prove that the assumptions of the Tikhonov's theorem are satisfied. To this end, let us define the boundary layer variables

$$b_1 = z - \gamma_1(x,t), \tag{37}$$
$$b_2 = \mathbb{E}[\psi_z] - \gamma_2(x,t)\mathbb{E}[\psi_x], \tag{38}$$

Original System

$$\dot{x} = f_x(x,z,t),$$
$$\epsilon\dot{z} = f_z(x,z,t,\epsilon),$$
$$\dot{\psi}_x = A_1(x,z,t)\psi_x + A_2(x,z,t)\psi_z + \sigma_x(x,z,t)\Gamma_x,$$
$$\epsilon\dot{\psi}_z = B_1(x,z,t,\epsilon)\psi_x + B_2(x,z,t,\epsilon)\psi_z + \sigma_z(x,z,t,\epsilon)\Gamma_z.$$

Reduced System

$$\dot{\bar{x}} = f_x(\bar{x},\gamma_1(\bar{x},t),t),$$
$$\dot{\bar{\psi}}_x = A(\bar{x},t)\bar{\psi}_x + \sigma_x(\bar{x},\gamma_1(\bar{x},t),t)\Gamma_x.$$

Moments of the Original System

$$\dot{x} = f_x(x,z,t),$$
$$\epsilon\dot{z} = f_z(x,z,t,\epsilon),$$
$$\frac{d}{dt}\begin{pmatrix}\mathbb{E}[\psi_x]\\ \mathbb{E}[\psi_x\psi_x^T]\\ \epsilon\mathbb{E}[\psi_z]\\ \epsilon\mathbb{E}[\psi_z\psi_x^T]\\ \epsilon\mathbb{E}[\psi_z\psi_z^T]\end{pmatrix} = \ldots.$$

Moments of the Reduced System

$$\dot{\bar{x}} = f_x(\bar{x},\gamma_1(\bar{x},t),t),$$
$$\frac{d}{dt}\begin{pmatrix}\mathbb{E}[\bar{\psi}_x]\\ \mathbb{E}[\bar{\psi}_x\bar{\psi}_x^T]\end{pmatrix} = \ldots.$$
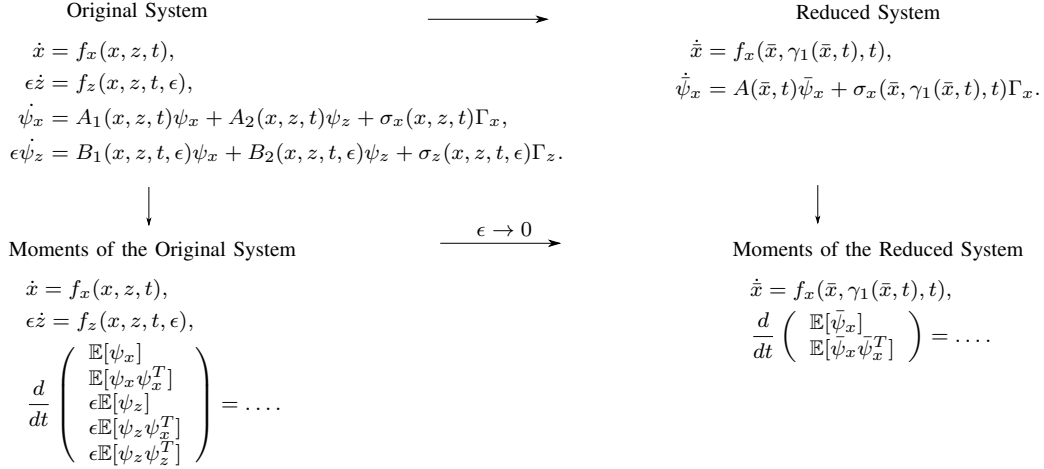
$\epsilon \to 0$

Fig. 1.   Commutative Diagram.

$$b_3 = \mathbb{E}[\psi_z\psi_x^T] - \gamma_2(x,t)\mathbb{E}[\psi_x\psi_x^T]. \tag{39}$$

The dynamics of the boundary layer variables are given by

$$\frac{db_1}{dt} = \frac{dz}{dt} - \frac{d\gamma_1(x,t)}{dt},$$
$$\frac{db_2}{dt} = \frac{d\mathbb{E}[\psi_z]}{dt} - \frac{d\gamma_2(x,t)\mathbb{E}[\psi_x]}{dt},$$
$$\frac{db_3}{dt} = \frac{d\mathbb{E}[\psi_z\psi_x]}{dt} - \frac{d\gamma_2(x,t)\mathbb{E}[\psi_x\psi_x^T]}{dt}.$$

Denote by $\tau = t/\epsilon$ the time variable in the fast time-scale. Then, expanding using the chain rule, we have

$$\frac{db_1}{d\tau} = \epsilon\frac{dz}{dt} - \epsilon\frac{\partial\gamma_1(x,t)}{\partial t} - \epsilon\frac{\partial\gamma_1(x,t)}{\partial x}\frac{dx}{dt},$$
$$\frac{db_2}{d\tau} = \epsilon\frac{d\mathbb{E}[\psi_z]}{dt} - \epsilon\mathbb{E}[\psi_x]\frac{\partial\gamma_2(x,t)}{\partial t} - \epsilon\mathbb{E}[\psi_x]\frac{\partial\gamma_2(x,t)}{\partial x}\frac{dx}{dt}$$
$$- \epsilon\gamma_2(x,t)\frac{d\mathbb{E}[\psi_x]}{dt},$$
$$\frac{db_3}{d\tau} = \epsilon\frac{d\mathbb{E}[\psi_z\psi_x^T]}{dt} - \epsilon\mathbb{E}[\psi_x\psi_x^T]\frac{\partial\gamma_2(x,t)}{\partial t}$$
$$- \epsilon\mathbb{E}[\psi_x\psi_x^T]\frac{\partial\gamma_2(x,t)}{\partial x}\frac{dx}{dt} - \epsilon\gamma_2(x,t)\frac{d\mathbb{E}[\psi_x\psi_x^T]}{dt}.$$

Substituting from equations (9), (20) and (22) yields

$$\frac{db_1}{d\tau} = f_z(x,z,t,\epsilon) - \epsilon\frac{\partial\gamma_1(x,t)}{\partial t} - \epsilon\frac{\partial\gamma_1(x,t)}{\partial x}\frac{dx}{dt}, \tag{40}$$

$$\frac{db_2}{d\tau} = B_1(x,z,t,\epsilon)\mathbb{E}[\psi_x] + B_2(x,z,t,\epsilon)\mathbb{E}[\psi_z]$$
$$- \epsilon\mathbb{E}[\psi_x]\frac{\partial\gamma_2(x,t)}{\partial t} - \epsilon\mathbb{E}[\psi_x]\frac{\partial\gamma_2(x,t)}{\partial x}\frac{dx}{dt}$$
$$- \epsilon\gamma_2(x,t)\frac{d\mathbb{E}[\psi_x]}{dt}, \tag{41}$$

$$\frac{db_3}{d\tau} = \epsilon\mathbb{E}[\psi_z\psi_x^T]A_1(x,z,t)^T + \epsilon\mathbb{E}[\psi_z\psi_z^T]A_2(x,z,t)^T$$
$$+ B_1(x,z,t,\epsilon)\mathbb{E}[\psi_x\psi_x^T] + B_2(x,z,t,\epsilon)\mathbb{E}[\psi_z\psi_x^T]$$
$$+ \sigma_z(x,z,t,\epsilon)[\sigma_x(x,z,t)\ 0]^T - \epsilon\mathbb{E}[\psi_x\psi_x^T]\frac{\partial\gamma_2(x,t)}{\partial t}$$
$$- \epsilon\mathbb{E}[\psi_x\psi_x^T]\frac{\partial\gamma_2(x,t)}{\partial x}\frac{dx}{dt} - \epsilon\gamma_2(x,t)\frac{d\mathbb{E}[\psi_x\psi_x^T]}{dt}. \tag{42}$$

where we take $z = b_1 + \gamma_1(x,t)$ and $\mathbb{E}[\psi_z] = b_2 + \gamma_2(x,t)\mathbb{E}[\psi_x]$, and $\mathbb{E}[\psi_z\psi_x^T] = b_3 + \gamma_2(x,t)\mathbb{E}[\psi_x\psi_x^T]$. Since, from Assumption 3, $\gamma_1(x,t)$ is a continuously differentiable functions in its arguments, we have that $\frac{\partial\gamma_1(x,t)}{\partial t}$, $\frac{\partial\gamma_1(x,t)}{dx}$ are bounded in a finite time interval $t \in [0,t_1]$. Since $\gamma_2(x,t) = -B_2(x,\gamma_1(x,t),t,0)^{-1}B_1(x,\gamma_1(x,t),t,0)$, and B_1 and B_2 are continuously differentiable from Assumption 1, we have that $\frac{\partial\gamma_2(x,t)}{\partial x}$ and $\frac{\partial\gamma_2(x,t)}{\partial t}$ are bounded in a finite time interval $t \in [0,t_1]$. Then, the boundary layer system obtained by setting $\epsilon = 0$ in (40) - (42) is given by

$$\frac{db_1}{d\tau} = f_z(x,b_1+\gamma_1(x,t),t,0), \tag{43}$$
$$\frac{db_2}{d\tau} = B_1(x,b_1+\gamma_1(x,t),t,0)\mathbb{E}[\psi_x]$$
$$+ B_2(x,b_1+\gamma_1(x,t),t,0)(b_2+\gamma_2(x,t)\mathbb{E}[\psi_x])$$
$$=: g_1(b_1,b_2,x,t), \tag{44}$$
$$\frac{db_3}{d\tau} = B_1(x,b_1+\gamma_1(x,t),t,0)\mathbb{E}[\psi_x\psi_x^T]$$
$$+ B_2(x,b_1+\gamma_1(x,t),t,0)(b_3+\gamma_2(x,t)\mathbb{E}[\psi_x\psi_x^T])$$
$$=: g_2(b_1,b_2,b_3,x,t). \tag{45}$$

To prove that the origin of the boundary layer system is exponentially stable, we consider the dynamics of the vector $b = [b_1,b_2,b_3]$. Linearizing the system (43) - (45) around the origin, we obtain the dynamics for $\tilde{b} = b - 0$ as

$$\frac{d\tilde{b}}{d\tau} = \begin{bmatrix} J_{11} & 0 & 0 \\ J_{21} & J_{22} & 0 \\ J_{31} & J_{32} & J_{33} \end{bmatrix}\tilde{b} \tag{46}$$

where $J_{11} = \frac{\partial f_z(x,b_1+\gamma_1(x,t),t,0)}{\partial b_1}\big|_{b_1=0}$, $J_{21} = \frac{\partial g_1(b_1,b_2,x,t)}{\partial b_1}$, $J_{22} = B_2(x,b_1+\gamma_1(x,t),t,0)\big|_{b_1=0}$, $J_{31} = \frac{\partial g_2(b_1,b_2,b_3,x,t)}{\partial b_1}$, $J_{32} = \frac{\partial g_2(b_1,b_2,b_3,x,t)}{\partial b_2}$, $J_{33} = B_2(x,b_1+\gamma_1(x,t),t,0)\big|_{b_1=0}$. Since the eigenvalues of a block triangular matrix are given by the union of eigenvalues of the diagonal blocks, we consider the eigenvalues of $\frac{\partial f_z(x,b_1+\gamma_1(x,t),t,0)}{\partial b_1}\big|_{b_1=0}$ and $B_2(x,b_1+\gamma_1(x,t),t,0)\big|_{b_1=0}$. Under Assumption 3,

we have that the matrix $\frac{\partial f_z(x,b_1+\gamma_1(x,t),t,0)}{\partial b_1}\Big|_{b_1=0} = \frac{\partial f_z(x,z,t,0)}{\partial z}\frac{dz}{db_1}\Big|_{z=\gamma_1(x,t)} = \frac{\partial f_z(x,z,t,0)}{\partial z}\Big|_{z=\gamma_1(x,t)}$ is Hurwitz. From the definition of the original system (8) - (11), we have that $B_2(x,z,t,\epsilon) = \frac{\partial f_z(x,z,t,\epsilon)}{\partial z}$. Therefore, $B_2(x,b_1+\gamma_1(x,t),t,0)\big|_{b_1=0} = \frac{\partial f_z(x,z,t,0)}{\partial z}\big|_{z=\gamma_1(x,t)}$. Under Assumption 3 we have that the matrix $\frac{\partial f_z(x,z,t,0)}{\partial z}\big|_{z=\gamma_1(x,t)}$ is Hurwitz, and thus, the boundary layer system is exponentially stable.

From Assumptions 1 and 2 we have that the functions $f_x(x,z,t)$, $f_z(x,z,t,\epsilon)$, $A_1(x,z,t)$, $A_2(x,z,t)$, $B_1(x,z,t,\epsilon)$, $B_2(x,z,t,\epsilon)$, $\sigma_x(x,z,t)\sigma_x(x,z,t)^T$, $\sigma_z(x,z,t,\epsilon)[\sigma_x(x,z,t)\ 0]^T$ and $\sigma_z(x,z,t,\epsilon)\sigma_z(x,z,t,\epsilon)^T$ and their first partial derivatives are continuously differentiable. From Assumption 1 we have that the $\frac{\partial f_z(x,z,t,0)}{\partial z}$, $\frac{\partial B_1(x,z,t,0)}{\partial z}$, $\frac{\partial B_2(x,z,t,0)}{\partial z}$ have continuous first partial derivatives with respect to their arguments. From Assumptions 1 and 3 we have that the $\gamma_1(x,t)$, $\gamma_2(x,t)\mathbb{E}[\psi_x]$, $\gamma_2(x,t)\mathbb{E}[\psi_x\psi_x^T]$ have continuous first partial derivatives with respect to their arguments. From Assumption 4 we have that the reduced system (14) has a unique bounded solution for $t \in [0,t_1]$. Since the moment equations (16) - (17), are linear in $\mathbb{E}[\bar\psi_x]$ and $\mathbb{E}[\bar\psi_x\bar\psi_x^T]$ there exists a unique solution to (16) - (17) in for $t \in [0,t_1]$. From Assumption 3 we have that the initial condition z_0 is in the region of attraction of the equilibrium point $\gamma_1(x_0,0)$, and thus the initial condition $z_0 - \gamma_1(x_0,0)$ for the boundary layer system b_1 is in the region of attraction of the equilibrium point $b_1 = 0$. Since the system (18) - (22) is linear in the moments, the system (20) - (22) has a unique equilibrium point for given x and thus the initial conditions ψ_{z0} and $\psi_{z0}\psi_{x0}^T$ are in the region of attraction of the equilibrium point for (20) - (22). Therefore, the initial conditions $\psi_{z0} - \gamma_2(x_0,0)\psi_{x0}$, $\psi_{z0}\psi_{x0}^T - \gamma_2(x_0,0)\psi_{x0}\psi_{x0}^T$ for the boundary layer variables b_2 and b_3 are in the region of attraction of the equilibrium point at $b_2 = 0$ and $b_3 = 0$. Thus, the assumptions of the Tikhonov's theorem on a finite time-interval [1] are satisfied and applying the theorem to the moment dynamics of the original system in (18) - (22) and the dynamics of x and z given by (8) - (9), we obtain the result (34) - (36). ∎

Remark: From [7], we have that the $\psi_x(t)$ and $\bar\psi_x(t)$ are multivariate Gaussian processes. Since a Gaussian distribution is fully characterized by their mean and the covariance, and from Theorem 1, we have that the

$$lim_{\epsilon\to0}\mathbb{E}[\psi_x(t)] = \mathbb{E}[\bar\psi_x(t)], \tag{47}$$

$$lim_{\epsilon\to0}\mathbb{E}[\psi_x(t)\psi_x(t)^T] = \mathbb{E}[\bar\psi_x(t)\bar\psi_x(t)^T]. \tag{48}$$

we have that for given $t \in [0,t_1]$, the vector $\psi_x(t)$ converges in distribution to the vector $\bar\psi_x(t)$ as $\epsilon \to 0$.

V. EXAMPLE

In this section we demostrate the application of the model reduction approach on an example of a biolomelcular system. Consider the system in Fig. 2, where a phosphorylated protein X*, binds to a downstream promoter site p which produces the protein G. Such a setup can be seen commonly occurring in natural biological systems, an example being the two component signalling systems in bacteria [22]. Moreover, similar setups are also used in synthetic biology to design biological circuits that are robust to the loading effects that appear due to the presence of downstream components [23], [24].
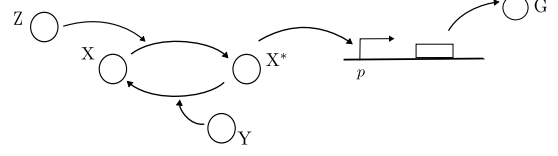

Fig. 2. Protein X is phosphorylated by kinase Z and dephosphorylated by phosphatase Y. Phosphorylated protein X* binds to the downstream promoter p.

The chemical reactions for the system are as follows: X + Z $\xrightarrow{k_1}$ X*+Z, X*+Y $\xrightarrow{k_2}$ X+Y, X*+p $\underset{k_{\text{off}}}{\overset{k_{\text{on}}}{\rightleftharpoons}}$ C, $C \xrightarrow{\beta} C+G$, $G \xrightarrow{\delta} \phi$. The protein X is phosphorylated by kinase Z and dephosphorylated by phosphatase Y with the rate constants k_1 and k_2, respectively. The binding between phosphorylated protein X* and promoter p produces a complex C, where k_{on} and k_{off} are the binding and unbinding rate constants. Protein G is produced at rate β, which encapsulates both transcription and translation processes and decayed at rate δ, which includes both degradation and dilution. We assume that the total concentration of protein X and promoter p are conserved, giving $X_{tot} = X + X^* + C$ and $p_{tot} = p + C$. Then, the dynamics for the macroscopic concentrations of X^*, C and G denoted by x^*, c and g, respectively, can be written as

$$\frac{dx^*}{dt} = k_1 Z(t)(X_{tot} - x^* - c) - k_2 Y x^*$$
$$- k_{\text{on}}x^*(p_{tot} - c) + k_{\text{off}}c, \tag{49}$$

$$\frac{dc}{dt} = k_{\text{on}}x^*(p_{tot} - c) - k_{\text{off}}c, \tag{50}$$

$$\frac{dg}{dt} = \beta c - \delta g. \tag{51}$$

Binding and unbinding reactions are much faster than phosphorylation/dephosphorylation, and therefore, we can write $k_2 Y/k_{\text{off}} = \epsilon \ll 1$. Taking $k_d = k_{\text{off}}/k_{\text{on}}$, we have

$$\frac{dx^*}{dt} = k_1 Z(t)(X_{tot} - x^* - c) - k_2 Y x^*$$
$$- \frac{k_2 Y}{\epsilon k_d}x^*(p_{tot} - c) + \frac{k_2 Y}{\epsilon}c, \tag{52}$$

$$\frac{dc}{dt} = \frac{k_2 Y}{\epsilon k_d}x^*(p_{tot} - c) - \frac{k_2 Y}{\epsilon}c, \tag{53}$$

$$\frac{dg}{dt} = \beta c - \delta g. \tag{54}$$

The system (52) - (54) is in the form of system (2), with $y = [x^*,\ c,\ g]^T$. To take the system in the singular perturbation form given in (8) - (9), we consider the change of variable $v = x^* + c$, which yields

$$\frac{dv}{dt} = k_1 Z(t)(X_{tot} - v) - k_2 Y(v - c), \tag{55}$$

$$\frac{dg}{dt} = \beta c - \delta g, \tag{56}$$

$$\epsilon \frac{dc}{dt} = \frac{k_2 Y}{k_d}(v-c)(p_{tot}-c) - k_2 Y c. \tag{57}$$

This change of coordinates corresponds to having $A_x = [1\ 1\ 0,\ 0\ 0\ 1]^T$, $A_z = [0\ 1\ 0]$, $x = [v,g]^T$ and $z = c$ in Claim 1. Then, the dynamics for the stochastic fluctuations can be written as

$$\frac{d\psi_v}{dt} = (-k_1 Z(t) - k_2 Y)\psi_v + k_2 Y \psi_c$$
$$+ \sqrt{k_1 Z(t)(X_{tot}-v)}\Gamma_1 - \sqrt{k_2 Y(v-c)}\Gamma_2, \tag{58}$$

$$\frac{d\psi_g}{dt} = \beta\psi_c - \delta\psi_g + \sqrt{\beta c}\Gamma_5 - \sqrt{\delta g}\Gamma_6, \tag{59}$$

$$\epsilon \frac{d\psi_c}{dt} = \frac{k_2 Y}{k_d}(p_{tot}-c)\psi_v$$
$$+ \left(-\frac{k_2 Y}{k_d}v - \frac{k_2 Y}{k_d}p_{tot} + 2\frac{k_2 Y}{k_d}c - k_2 Y\right)\psi_c$$
$$+ \sqrt{\frac{k_2 Y}{k_d}(v-c)(p_{tot}-c)}\Gamma_3 - \sqrt{\epsilon k_2 Y c}\Gamma_4. \tag{60}$$

with $\psi_x = [\psi_v, \psi_g]^T$ and $\psi_x = [\psi_v, \psi_g]^T$. Therefore, the equations (55) - (60) are in the form of the original system in (8) - (9) with $x = [v,g]^T$ and $z = c$. It follows that Assumptions 1 and 2 are satisfied since the system functions of (55) - (57) are polynomials of the state variables. We evaluate $f_z = \frac{k_2 Y}{k_d}(v-z)(p_{tot}-z) - k_2 Y z = 0$, which yields the unique solution $z(v) = \frac{1}{2}(v + p_{tot} + k_d) - \frac{1}{2}\sqrt{(v+p_{tot}+k_d)^2 - 4vp_{tot}}$, feasible under the physical constraints $0 \le c \le p_{tot}$. We have that Assumption 3 is satisfied since $\frac{\partial f_z}{\partial z}$ is negative. Thus, we obtain the reduced system

$$\frac{d\bar{v}}{dt} = k_1 Z(t)(X_{tot} - \bar{v}) - k_2 Y(\bar{v} - \bar{c}),$$
$$\frac{d\bar{g}}{dt} = \beta\bar{c} - \delta\bar{g},$$
$$\frac{d\bar{\psi}_v}{dt} = (-k_1 Z(t) - k_2 Y)\bar{\psi}_v + k_2 Y \bar{\psi}_c$$
$$+ \sqrt{k_1 Z(t)(X_{tot} - \bar{v})}\Gamma_1 - \sqrt{k_2 Y(\bar{v} - \bar{c})}\Gamma_2,$$
$$\frac{d\bar{\psi}_g}{dt} = \beta\bar{\psi}_c - \delta\bar{\psi}_g + \sqrt{\beta\bar{c}}\Gamma_5 - \sqrt{\delta\bar{g}}\Gamma_6,$$

where

$$\bar{c} = \frac{1}{2}(\bar{v} + p_{tot} + k_d) - \frac{1}{2}\sqrt{(\bar{v}+p_{tot}+k_d)^2 - 4\bar{v}p_{tot}},$$
$$\bar{\psi}_c = \frac{(p_{tot} - \bar{c})\bar{\psi}_v}{(\bar{v} + p_{tot} - 2\bar{c} + k_d Y)}.$$

Fig. 3 includes the simulation results for the error in second moments of the stochastic fluctuations of v and g. We use zero initial conditions for all variables and thus the first moment of the stochastic fluctuations remains zero at all times. The simulations are carried out with Euler-Maruyama method and the sample means are calculated using 3×10^6 realizations.

VI. CONCLUSION

In this work, we obtained a reduced order model for the Linear Noise Approximation of biomolecular systems with separation in time-scales. It was shown that, for a finite time-interval the first and second moments of the reduced system are within an $O(\epsilon)$-neighborhood of the first and second moments of the slow variable dynamics of the original
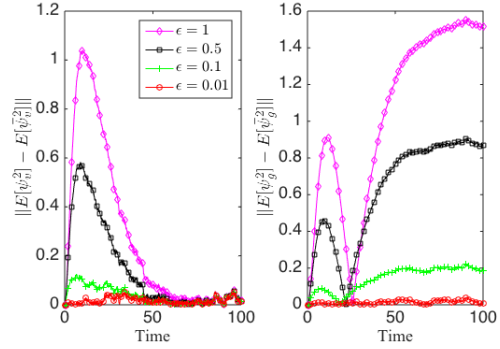

Fig. 3. Errors in the second moments decreases as ϵ decreases. The parameters used are $Z(t) = 1$, $k_1 = 0.01$, $k_2 = 0.01$, $k_d = 100$, $X_{tot} = 200$, $Y = 200$, $p_{tot} = 100$, $\delta = 0.1$, $\beta = 0.1$, $v(0) = 0$, $c(0) = 0$, $g(0) = 0$, $\psi_v(0) = 0$, $\psi_g(0) = 0$.

system. This result can be used to approximate the slow variable dynamics of the LNA with a system of reduced dimensions, which will be useful in analysis and simulations of biomolecular system especially when the system size is large. The reduced model that we obtain is equivalent to the reduced order model derived in [12]. Our results are also consistent with the error analysis that they have performed numerically, where it is approximated that the maximum errors in the mean and the variance over time are of $O(\epsilon)$.

In future work, we aim to extend this analysis to obtain an approximation for the fast variable dynamics.

APPENDIX

A-1: Applying the coordinate transformation $x = A_x y$, $z = A_z y$ to equation (2), with $\tilde{a}(y,t) = [\hat{a}_s(y,t), (1/\epsilon)\hat{a}_f(y,t)]^T$ and $v = [v_1, \ldots, v_{m_s}, v_{m_s+1}, \ldots, v_{m_s+m_f}]$, with $y = A^{-1}[x,z]^T$ we have

$$\dot{x} = A_x f(A^{-1}[x,z]^T, t)$$
$$= A_x \sum_{i=1}^{m_s} v_i \hat{a}_{si}(A^{-1}[x,z]^T, t)$$
$$+ A_x \sum_{i=v_{m_s}+1}^{m_s+m_f} v_i(1/\epsilon)\hat{a}_{fi}(A^{-1}[x,z]^T, t)$$
$$= f_x(x,z,t), \tag{61}$$
$$\dot{z} = A_z f(A^{-1}[x,z]^T, t)$$
$$= A_z \sum_{i=1}^{m_s} v_i \hat{a}_{si}(A^{-1}[x,z]^T, t)$$
$$+ A_z \sum_{i=v_{m_s}+1}^{m_s+m_f} v_i(1/\epsilon)\hat{a}_{fi}(A^{-1}[x,z]^T, t)$$
$$= \frac{1}{\epsilon} f_z(x,z,t,\epsilon). \tag{62}$$

Thus, from equation (61), if follows that $A_x v_i = 0$ for $i = m_s + 1, \ldots, m_s + m_f$.

Applying the coordinate transformation $\psi_x = A_x \xi$, $\psi_z = A_z \xi$, to equation (3), we have that

$$\dot{\psi}_x = A_x[A(y,t)\xi] + A_x \sigma(y,t)\Gamma,$$
$$\dot{\psi}_z = A_z[A(y,t)\xi] + A_z \sigma(y,t)\Gamma.$$

Since $A(y,t) = \frac{\partial f(y,t)}{\partial y}$ and we have that $y = A^{-1}[x,z]^T$, using the chain rule we can write

$$\dot{\psi}_x = A_x \left[\frac{\partial f(A^{-1}[x,z]^T,t)}{\partial x}\frac{\partial x}{\partial y} + \frac{\partial f(A^{-1}[x,z]^T,t)}{\partial z}\frac{\partial z}{\partial y} \right]\xi$$
$$+ A_x \left[v_1\sqrt{\tilde{a}_1(A^{-1}[x,z]^T,t)}, \ldots, v_m\sqrt{\tilde{a}_m(A^{-1}[x,z]^T,t)} \right]\Gamma,$$

$$\dot{\psi}_z = A_z \left[\frac{\partial f(A^{-1}[x,z]^T,t)}{\partial x}\frac{\partial x}{\partial y} + \frac{\partial f(A^{-1}[x,z]^T,t)}{\partial z}\frac{\partial z}{\partial y} \right]\xi$$
$$+ A_z \left[v_1\sqrt{\tilde{a}_1(A^{-1}[x,z]^T,t)}, \ldots, v_m\sqrt{\tilde{a}_m(A^{-1}[x,z]^T,t)} \right]\Gamma.$$

Using the linearity of the differentiation operator and the transformation $x = A_x y$, $z = A_z y$, we obtain

$$\dot{\psi}_x = \left[\frac{\partial A_x f(A^{-1}[x,z]^T,t)}{\partial x}A_x + \frac{\partial A_x f(A^{-1}[x,z]^T,t)}{\partial z}A_z \right]\xi$$
$$+ A_x \left[v_1\sqrt{\tilde{a}_1(A^{-1}[x,z]^T,t)}, \ldots, v_m\sqrt{\tilde{a}_m(A^{-1}[x,z]^T,t)} \right]\Gamma,$$

$$\dot{\psi}_z = \left[\frac{\partial A_z f(A^{-1}[x,z]^T,t)}{\partial x}A_x + \frac{\partial A_z f(A^{-1}[x,z]^T,t)}{\partial z}A_z \right]\xi$$
$$+ A_z \left[v_1\sqrt{\tilde{a}_1(A^{-1}[x,z]^T,t)}, \ldots, v_m\sqrt{\tilde{a}_m(A^{-1}[x,z]^T,t)} \right]\Gamma.$$

From (61) - (62), we have that $A_x f(A^{-1}[x,z]^T,t) = f_x(x,z,t)$ and $A_z f(A^{-1}[x,z]^T,t) = \frac{1}{\epsilon}f_z(x,z,t,\epsilon)$. Furthermore, substituting for $\tilde{a}(A^{-1}[x,z]^T,t) = [\hat{a}_s(A^{-1}[x,z]^T,t), (1/\epsilon)\hat{a}_f(A^{-1}[x,z]^T,t)]^T$, we have

$$\dot{\psi}_x = \frac{\partial f_x(x,z,t)}{\partial x}\psi_x + \frac{\partial f_x(x,z,t)}{\partial z}\psi_z +$$
$$A_x \left[v_1\sqrt{\hat{a}_{s1}(A^{-1}[x,z]^T,t)}, \ldots, v_{m_s}\sqrt{\hat{a}_{sm_s}(A^{-1}[x,z]^T,t)} \right]\Gamma_x$$
$$+ A_x \left[v_{m_s+1}\sqrt{\frac{1}{\epsilon}\hat{a}_{f1}(A^{-1}[x,z]^T,t)}, \ldots, \right.$$
$$\left. v_{m_s+m_f}\sqrt{\frac{1}{\epsilon}\hat{a}_{fm_f}(A^{-1}[x,z]^T,t)} \right]\Gamma_f,$$
(63)

$$\dot{\psi}_z = \frac{\partial \frac{1}{\epsilon}f_z(x,z,t,\epsilon)}{\partial x}\psi_x + \frac{\partial \frac{1}{\epsilon}f_z(x,z,t,\epsilon)}{\partial z}\psi_z +$$
$$A_z \left[v_1\sqrt{\hat{a}_{s1}(A^{-1}[x,z]^T,t)}, \ldots, v_{m_s}\sqrt{\hat{a}_{sm_s}(A^{-1}[x,z]^T,t)} \right]\Gamma_x$$
$$+ A_z \left[v_{m_s+1}\sqrt{\frac{1}{\epsilon}\hat{a}_{f1}(A^{-1}[x,z]^T,t)}, \ldots, \right.$$
$$\left. v_{m_s+m_f}\sqrt{\frac{1}{\epsilon}\hat{a}_{fm_f}(A^{-1}[x,z]^T,t)} \right]\Gamma_f,$$
(64)

where $\Gamma = [\Gamma_x, \Gamma_f]^T$. From (61) we have that, $A_x v_i = 0$ for $i = m_s+1, \ldots, m_s+m_f$. Then, multiplying (64) by ϵ, we can write the system (63) - (64), in the form of system (6) - (7), where $\Gamma_z = [\Gamma_x, \Gamma_f]^T$.

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