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

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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 $\epsilon$ 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.

1 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 population 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

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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 \(\epsilon\) 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 variables 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 the 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 \(\epsilon\) as the singular perturbation parameter, as in \[12\]. We define a reduced order 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 2 we describe the model considered. In Section 3 we define the reduced system and derive the moment dynamics for the original and reduced systems. In Section 4 we prove the main convergence results. Section 5 illustrates our approach with an example and Section 6 includes the concluding remarks.

2 System Model

2.1 Linear Noise Approximation

Consider a biomolecular system with \( n \) species interacting through \( m \) reactions in a given volume \( \Omega \). 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

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

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 \( \Omega \) and the number of molecules in the system are large [7, 6]. To derive the LNA it is assumed that \( Y = \Omega y + \sqrt{\Omega} \xi \), where \( y \) is a deterministic quantity and \( \xi \) 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 \( \Omega^0 \), it is shown that \( y \) is the macroscopic concentration and \( \xi \) is a Gaussian process whose dynamics are given by [7, 9]

\[
\dot{y} = f(y,t),
\]

\[
\dot{\xi} = A(y,t)\xi + \sigma(y,t)\Gamma,
\]

where \( \Gamma \) 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].

2.2 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 \( \epsilon \) to decompose the reaction rate vector as \( \tilde{a}(y,t) = \epsilon a_i(y,t) \).
\[ \hat{a}_s(y, t), (1/\epsilon)\hat{a}_f(y, t) \] 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 \( A_x \in \mathbb{R}^{n_s \times n} \), \( A_z \in \mathbb{R}^{n_f \times n} \), 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

\[
\dot{x} = f_x(x, z, t),
\]

\[
\epsilon \dot{z} = f_z(x, z, t, \epsilon).
\]

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), into the singular perturbation form

\[
\dot{\psi}_x = A_1(x, z, t) \psi_x + A_2(x, z, t) \psi_z + \sigma_x(x, z, t) \Gamma_x,
\]

\[
\epsilon \dot{\psi}_z = B_1(x, z, t, \epsilon) \psi_x + B_2(x, z, t, \epsilon) \psi_z + \sigma_z(x, z, t, \epsilon) \Gamma_z,
\]

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

\[
A_1(x, z, t) = \frac{\partial f_x(x, z, t)}{\partial x},
\]

\[
A_2(x, z, t) = \frac{\partial f_x(x, z, t)}{\partial z},
\]

\[
B_1(x, z, t, \epsilon) = \frac{\partial f_z(x, z, t, \epsilon)}{\partial x},
\]

\[
B_2(x, z, t, \epsilon) = \frac{\partial f_z(x, z, t, \epsilon)}{\partial z},
\]

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

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

Proof. See Appendix A-1. \qed

4
Based on the result of Claim 1, in this work we consider the Linear Noise Approximation represented in the singular perturbation form:

\[
\begin{align*}
\dot{x} &= f_x(x, z, t), & x(0) &= x_0, \\
\epsilon \dot{z} &= f_z(x, z, t, \epsilon), & z(0) &= z_0, \\
\dot{\psi}_x &= A_1(x, z, t)\psi_x + A_2(x, z, t)\psi_z + \sigma_x(x, z, t)\Gamma_x, & \psi_x(0) &= \psi_{x0}, \\
\epsilon \dot{\psi}_z &= B_1(x, z, t, \epsilon)\psi_x + B_2(x, z, t, \epsilon)\psi_z + \sigma_z(x, z, t, \epsilon)\Gamma_z, & \psi_z(0) &= \psi_{z0},
\end{align*}
\]

where \( x \in D_x \subset \mathbb{R}^{n_x}, \psi_x \in D_{\psi_x} \subset \mathbb{R}^{n_x} \) 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. \( \Gamma_x \) is an \( m_x \)-dimensional white noise process. Then, \( \Gamma_z = [\Gamma_x, \Gamma_f]^T \), where \( \Gamma_f \) is an \( m_f \)-dimensional white noise process. We assume that the system (8) - (11) 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 \( x \in D_x \subset \mathbb{R}^{n_x}, z \in D_z \subset \mathbb{R}^{n_f} \) 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 \( \sigma_x(x, z, t)\sigma_x(x, z, t)^T, \sigma_z(x, z, t, \epsilon)[\sigma_x(x, z, t) 0]^T \) 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 \( \lim_{\epsilon \to 0} \frac{\sigma(x, z, t, \epsilon)}{\epsilon} = \sigma(x, z, t) \) 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 \( \frac{\partial f_z(x, z, t, 0)}{\partial z} \bigg|_{z=\gamma_1(x,t)} \) 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 \( \frac{dz}{dt} = f_z(x_0, z, 0, 0) \).

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

### 3 Preliminary Results

#### 3.1 Reduced System

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

\[
\begin{align*}
f_z(x, z, t, 0) &= 0, \quad (12) \\
B_1(x, z, t, 0)\psi_x + B_2(x, z, t, \epsilon)\psi_z &= 0. \quad (13)
\end{align*}
\]
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
\[
\dot{\bar{x}} = f_x(\bar{x}, \gamma_1(\bar{x},t), t), \quad \bar{x}(0) = x_0, \tag{14}
\]
\[
\dot{\bar{\psi}}_x = A(\bar{x},t)\bar{\psi}_x + \sigma_x(\bar{x}, \gamma_1(\bar{x},t), t)\Gamma_x, \quad \bar{\psi}_x(0) = \psi_{x0}, \tag{15}
\]
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
\[
\frac{dE[\bar{\psi}_x]}{dt} = A(\bar{x},t)E[\bar{\psi}_x], \quad E[\bar{\psi}_x(0)] = \psi_{x0}, \tag{16}
\]
\[
\frac{dE[\bar{\psi}_x \bar{\psi}_x^T]}{dt} = A(\bar{x},t)E[\bar{\psi}_x \bar{\psi}_x^T] + E[\bar{\psi}_x \bar{\psi}_x^T]A(\bar{x},t)^T
+ \sigma_x(\bar{x}, \gamma_1(\bar{x},t), t)\sigma_x(\bar{x}, \gamma_1(\bar{x},t), t)^T, \quad E[\bar{\psi}_x(0)\bar{\psi}_x(0)^T] = \psi_{x0}\psi_{x0}^T. \tag{17}
\]

**Proof.** Similar to [21], the first and second moment dynamics of \( \bar{\psi}_x \) in (15) can be written as
\[
\frac{dE[\bar{\psi}_x]}{dt} = E[A(\bar{x},t)\bar{\psi}_x],
\]
\[
\frac{dE[\bar{\psi}_x \bar{\psi}_x^T]}{dt} = E[A(\bar{x},t)\bar{\psi}_x \bar{\psi}_x^T] + E[\bar{\psi}_x (\bar{\psi}_x^T A(\bar{x},t)^T)] + \sigma_x(\bar{x}, \gamma_1(\bar{x},t), t)\sigma_x(\bar{x}, \gamma_1(\bar{x},t), t)^T.
\]
Since the dynamics of \( \bar{x} \) given by (14) are 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 \( \psi_x \) and \( \psi_z \) in the original system (8) - (11) given by the following claim.

**Claim 3.** The first and second moment dynamics for the variables \( \psi_x \) and \( \psi_z \) of the original
system (8) - (11) can be written in the form

$$\frac{dE[\psi_x]}{dt} = A_1(x, z, t)E[\psi_x] + A_2(x, z, t)E[\psi_z],$$  \hspace{1cm} (18)

$$\frac{dE[\psi_x^T\psi_x^T]}{dt} = A_1(x, z, t)E[\psi_x\psi_x^T] + A_2(x, z, t)E[\psi_z\psi_z^T] + \frac{E[\psi_x\psi_z^T]A_1(x, z, t)^T}{(x, z, t)^T} + \sigma_z(x, z, t)\sigma_z(x, z, t)^T,$$  \hspace{1cm} (19)

$$\epsilon \frac{dE[\psi_z]}{dt} = B_1(x, z, t, \epsilon)E[\psi_x] + B_2(x, z, t, \epsilon)E[\psi_z],$$  \hspace{1cm} (20)

$$\epsilon \frac{dE[\psi_z^T\psi_z^T]}{dt} = B_1(x, z, t, \epsilon)E[\psi_x^T\psi_x^T] + B_2(x, z, t, \epsilon)E[\psi_z^T\psi_z^T] + \frac{E[\psi_z^T]B_1(x, z, t, \epsilon)}{y(x, z, t, \epsilon)} + \frac{1}{\epsilon} \sigma_z(x, z, t, \epsilon)\sigma_z(x, z, t, \epsilon)^T,$$  \hspace{1cm} (21)

where $x$ and $z$ are the solutions of the equations (8) - (9), and the initial conditions are given by $E[\psi_x(0)] = \psi_0$, $E[\psi_x^T(0)] = \psi_0^T$, $E[\psi_z(0)] = \psi_0$, $E[\psi_z^T(0)] = \psi_0^T$. 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

$$\frac{dE[\psi_x]}{dt} = A_1(x, z, t)E[\psi_x] + A_2(x, z, t)E[\psi_z],$$  \hspace{1cm} (23)

$$\frac{dE[\psi_z]}{dt} = \frac{1}{\epsilon} B_1(x, z, t, \epsilon)E[\psi_x] + \frac{1}{\epsilon} B_2(x, z, t, \epsilon)E[\psi_z].$$  \hspace{1cm} (24)
Similarly, using Proposition III.1 in [21], the second moment dynamics can be written as

\[
\frac{d}{dt} \mathbb{E} \begin{bmatrix} \psi_x \psi_x^T & \psi_x \psi_z^T & \psi_z \psi_z^T \end{bmatrix} = \\
\psi_x (A_1(x, z, t) \psi_x + A_2(x, z, t) \psi_z)^T + \frac{1}{\epsilon} \psi_x (B_1(x, z, t, \epsilon) \psi_x + B_2(x, z, t, \epsilon) \psi_z)^T \\
\psi_z (A_1(x, z, t) \psi_x + A_2(x, z, t) \psi_z)^T + \frac{1}{\epsilon} \psi_z (B_1(x, z, t, \epsilon) \psi_x + B_2(x, z, t, \epsilon) \psi_z)^T \\
+ \begin{bmatrix}
\frac{1}{\epsilon} \sigma_x(x, z, t) \sigma_x(x, z, t)^T & \frac{1}{\epsilon} \sigma_x(x, z, t)^T \sigma_z(x, z, t, \epsilon) \\
\frac{1}{\epsilon} \sigma_z(x, z, t, \epsilon) \sigma_x(x, z, t) & \frac{1}{\epsilon} \sigma_z(x, z, t, \epsilon) \sigma_z(x, z, t, \epsilon)^T
\end{bmatrix}
\]

(25)

Employing the linearity of the expectation operator, we can sum the corresponding entries of the matrices in equation (25), and multiply by \( \epsilon \) to write the moment equations (23) - (25) in the form of (18) - (22). Note that, since \( \mathbb{E}[\psi_x \psi_z^T] = (\mathbb{E}[(\psi_x \psi_z^T)^T])^T \), 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 \( x \) are given by (14).

**Proof.** Setting \( \epsilon = 0 \) in equations (8) - (9) and (19) - (20), yields

\[
0 = f_x(x, z, t, 0), \\
0 = B_1(x, z, t, 0) \mathbb{E}[\psi_x] + B_2(x, z, t, 0) \mathbb{E}[\psi_z], \\
0 = B_1(x, z, t, 0) \mathbb{E}[\psi_x \psi_x^T] + B_2(x, z, t, 0) \mathbb{E}[\psi_z \psi_x^T].
\]

(26) (27) (28)

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

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

(29) (30)
\[ \dot{x} = f_x(x, z, t), \]
\[ \dot{\epsilon} = f_x(x, z, t, \epsilon), \]
\[ \psi_x = A_1(x, z, t) \psi_x + A_2(x, z, t) \psi_z + \sigma_x(x, z, t) \Gamma_x, \]
\[ \epsilon \dot{\psi}_z = B_1(x, z, t, \epsilon) \psi_x + B_2(x, z, t, \epsilon) \psi_z + \sigma_z(x, z, t, \epsilon) \Gamma_z. \]

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

Moments of the Original System \[ \text{Moments of the Reduced System} \]
\[ \dot{\bar{x}} = f_x(\bar{x}, \gamma_1(\bar{x}, t), t), \]
\[ \frac{d}{dt} \left( \begin{array}{c} E[\psi_x] \\ E[\psi_x \psi_x^T] \\ eE[\psi_x] \\ eE[\psi_x \psi_x^T] \\ eE[\psi_z \psi_z^T] \\ eE[\psi_z \psi_z^T] \end{array} \right) = \ldots. \]

Figure 1: Commutative Diagram.

Substituting \( z = \gamma_1(x, t) \) and equations (29) - (30), in (8) and (18) - (22) results in
\[ \dot{x} = f_x(x, \gamma_1(x, t), t), \]
\[ \frac{d}{dt} E[\psi_x] = A_1(x, \gamma_1(x, t), t) E[\psi_x] + A_2(x, \gamma_1(x, t), t) \gamma_2(x, t) E[\psi_x], \]
\[ \frac{d}{dt} E[\psi_x \psi_x^T] = A_1(x, \gamma_1(x, t), t) E[\psi_x \psi_x^T] + A_2(x, \gamma_1(x, t), t) \gamma_2(x, t) E[\psi_x \psi_x^T] 
+ E[\psi_x \psi_x^T] A_1(x, z, t)^T + (\gamma_2(x, t) E[\psi_x \psi_x^T])^T A_2(x, \gamma_1(x, t), t)^T 
+ \sigma_x(x, \gamma_1(x, t), t) \sigma_x(x, \gamma_1(x, t), t)^T. \]

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

4 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

\begin{align*}
\|x(t) - \bar{x}(t)\| &= O(\epsilon), \quad t \in [0, t_1], \\
\|E[\psi_x(t)] - E[\bar{\psi}_x(t)]\| &= O(\epsilon), \\
\|E[\psi_x(t)\psi_x(t)^T] - E[\bar{\psi}_x(t)\bar{\psi}_x(t)^T]\| &= O(\epsilon).
\end{align*}

(34) \hspace{1cm} (35) \hspace{1cm} (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 $\bar{x}$ are 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 with 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

\begin{align*}
b_1 &= z - \gamma_1(x, t), \\
b_2 &= E[\psi_z] - \gamma_2(x, t)E[\psi_x], \\
b_3 &= E[\psi_z\psi_x^T] - \gamma_2(x, t)E[\psi_x\psi_x^T].
\end{align*}

(37) \hspace{1cm} (38) \hspace{1cm} (39)

The dynamics of the boundary layer variables are given by

\begin{align*}
\frac{db_1}{dt} &= \frac{dz}{dt} - \frac{d\gamma_1(x, t)}{dt}, \\
\frac{db_2}{dt} &= \frac{dE[\psi_z]}{dt} - \frac{d\gamma_2(x, t)E[\psi_x]}{dt}, \\
\frac{db_3}{dt} &= \frac{dE[\psi_z\psi_x^T]}{dt} - \frac{d\gamma_2(x, t)E[\psi_x\psi_x^T]}{dt}.
\end{align*}

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

\begin{align*}
\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} dx, \\
\frac{db_2}{d\tau} &= \epsilon \frac{dE[\psi_z]}{dt} - \epsilon \frac{E[\psi_x]}{\partial t} \frac{\partial \gamma_2(x, t)}{\partial x} dx - \epsilon \frac{E[\psi_x]}{\partial x} \frac{\partial \gamma_2(x, t)}{\partial t} dx - \epsilon \frac{\gamma_2(x, t)}{dt} dE[\psi_x], \\
\frac{db_3}{d\tau} &= \epsilon \frac{dE[\psi_z\psi_x^T]}{dt} - \epsilon \frac{E[\psi_x\psi_x^T]}{\partial t} \frac{\partial \gamma_2(x, t)}{\partial x} dx - \epsilon \frac{E[\psi_x\psi_x^T]}{\partial x} \frac{\partial \gamma_2(x, t)}{\partial t} dx - \epsilon \frac{\gamma_2(x, t)}{dt} dE[\psi_x\psi_x^T].
\end{align*}

(10)
Substituting from equations (9), (20) and (22) yields

\[
\frac{db_1}{d\tau} = f_z(x, b_1 + \gamma_1(x, t), t, 0),
\]

\[
\frac{db_2}{d\tau} = B_1(x, b_1 + \gamma_1(x, t), t, 0)\mathbb{E}[\psi_x] + B_2(x, b_1 + \gamma_1(x, t), t, 0)(b_2 + \gamma_2(x, t)\mathbb{E}[\psi_x])
\]

\[
=: g_1(b_1, b_2, x, t),
\]

\[
\frac{db_3}{d\tau} = B_1(x, b_1 + \gamma_1(x, t), t, 0)\mathbb{E}[\psi_x^T\psi_x] + B_2(x, b_1 + \gamma_1(x, t), t, 0)(b_3 + \gamma_2(x, t)\mathbb{E}[\psi_x^T\psi_x])
\]

\[
=: g_2(b_1, b_2, b_3, x, t).
\]

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 \( \ddot{b} = b - \dot{b} \) as

\[
\frac{\ddot{b}}{d\tau} = \begin{bmatrix}
J_{11} & 0 & 0 \\
J_{21} & J_{22} & 0 \\
J_{31} & J_{32} & J_{33}
\end{bmatrix} \ddot{b}
\]

where \( J_{11} = \frac{\partial f_z(x, b_1 + \gamma_1(x, t), t, 0)}{\partial b_1} |_{b_1 = 0} \), \( J_{21} = \frac{\partial g_1(b_1, b_2, x, t)}{\partial b_1} |_{b_1 = 0, b_2 = 0} \), \( J_{22} = B_2(x, b_1 + \gamma_1(x, t), t, 0) |_{b_1 = 0} \), \( J_{31} = \frac{\partial g_2(b_1, b_2, b_3, x, t)}{\partial b_1} |_{b_1 = 0, b_2 = 0, b_3 = 0} \), \( J_{32} = \frac{\partial g_2(b_1, b_2, b_3, x, t)}{\partial b_2} |_{b_1 = 0, b_2 = 0, b_3 = 0} \), \( J_{33} = B_2(x, b_1 + \gamma_1(x, t), t, 0) |_{b_1 = 0} \).
Since the eigenvalues of a block triangular matrix are given by the union of eigenvalues of the diagonal blocks, we consider the eigenvalues of \( \frac{\partial f_1(x,b_1+\gamma_1(x,t),t,0)}{\partial b_1} |_{b_1=0} \) and \( B_2(x,b_1+\gamma_1(x,t),t,0) |_{b_1=0} \).

Under Assumption 3, we have that the matrix \( \frac{\partial f_1(x,b_1+\gamma_1(x,t),t,0)}{\partial b_1} |_{b_1=0} \) and \( B_2(x,b_1+\gamma_1(x,t),t,0) |_{b_1=0} \) is Hurwitz. From the definition of the original system (8) - (11), we have \( B_2(x,z,t,\epsilon) = \frac{\partial f_1(x,z,t,\epsilon)}{\partial z} \). Therefore, \( B_2(x,b_1+\gamma_1(x,t),t,0) |_{b_1=0} = \frac{\partial f_1(x,z,t,\epsilon)}{\partial z} |_{z=\gamma_1(x,t)} \), which is Hurwitz under Assumption 3.

Thus, the boundary layer system is exponentially stable.

From Assumptions 1 and 2, we have that the functions \( f_1(x,z,t) \), \( f_2(x,z,t,\epsilon) \), \( A_1(x,z,t) \), \( A_2(x,z,t) \), \( B_1(x,z,t,\epsilon) \), \( B_2(x,z,t,\epsilon) \), \( \sigma_1(x,z,t) \), \( \sigma_2(x,z,t,\epsilon) \), \( \sigma_3(x,z,t,\epsilon) \), \( \sigma_4(x,z,t) \), and their first partial derivatives are continuously differentiable.

From Assumption 1, we have that the \( \frac{\partial f_1(x,z,t,\epsilon)}{\partial z} \), \( \frac{\partial B_1(x,z,t,\epsilon)}{\partial z} \), and \( \frac{\partial B_2(x,z,t,\epsilon)}{\partial z} \) have continuous first partial derivatives with respect to their arguments. From Assumptions 1 and 3, we have that the \( \gamma_1(x,t) \), \( \gamma_2(x,t) \), \( \gamma_3(x,t) \), \( \gamma_4(x,t) \), \( \gamma_5(x,t) \), \( \gamma_6(x,t) \), and \( \gamma_7(x,t) \) have continuous first partial derivatives with respect to their arguments.

From Assumption 1, 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 \( \bar{\psi}_x \) and \( \bar{\psi}_z \), there exists a unique solution to (16) - (17) for \( t \in [0,t_1] \).

From Assumption 3, we have that the initial condition \( z_0 = 0 \) is in the region of attraction of the equilibrium point \( \gamma_1(x_0,0) \), and thus the initial condition \( z_0 = 0 \) for the boundary layer system 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) in the fast time-scale \( \tau \), has a unique equilibrium point for given \( x \) and \( t \), and thus the initial conditions \( \psi_{z0} \) and \( \psi_{z0} \psi_{x0}^T \) are in the region of attraction of the equilibrium point. Therefore, the initial conditions \( \psi_{z0} - \gamma_2(x_0,0) \psi_{x0} \), \( \psi_{z0} \psi_{x0}^T - \gamma_2(x_0,0) \psi_{z0} \psi_{x0}^T \) 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 \( \psi_x(t) \) and \( \bar{\psi}_x(t) \) are multivariate Gaussian processes. Since a Gaussian distribution is fully characterized by their mean and the covariance, and Theorem 1 gives

\[
\lim_{t \to 0} E[\psi_x(t)] = E[\bar{\psi}_x(t)],
\]

\[
\lim_{t \to 0} E[\psi_x(t)\psi_x(t)^T] = E[\bar{\psi}_x(t)\bar{\psi}_x(t)^T],
\]

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 \( \epsilon \to 0 \).
5 Example

In this section we demonstrate 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].

![Figure 2](image)

Figure 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: $X + Z \xrightarrow{k_1} X^* + Z$, $X^* + Y \xrightarrow{k_2} X + Y$, $X^* + p \xrightarrow{k_{on}} C$, $C \xrightarrow{\beta} C + G$, $G \xrightarrow{\delta} \phi$. 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 $\beta$, which encapsulates both transcription and translation processes and decays at rate $\delta$, which includes both degradation and dilution. We assume that the total amounts of protein X and promoter p are conserved, and thus we can write $X + X^* + C = \Omega X_{tot}$ and $p + C = \Omega p_{tot}$, where $\Omega$ is the system volume, $X_{tot}$ denotes the total concentration of protein X and $p_{tot}$ denotes the total concentration of promoter p. Then, the dynamics for the macroscopic concentrations of $X^*$, C and G denoted by $x^*$, $c$ and $g$, respectively, can be written as

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

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

$$\frac{dg}{dt} = \beta c - \delta g.$$  \hfill (51)

Binding and unbinding reactions are much faster than phosphorylation/dephosphorylation, and therefore, we can write $k_2 Y / k_{off} = \epsilon \ll 1$. Taking $k_d = k_{off} / k_{on}$, we have
\[ \frac{dx^*}{dt} = k_1 Z(t)(X_{tot} - x^* - c) - k_2 Y x^* - \frac{k_2 Y}{\epsilon d} x^*(p_{tot} - c) + \frac{k_2 Y}{\epsilon} c, \] (52)

\[ \frac{dc}{dt} = \frac{k_2 Y}{\epsilon d} x^*(p_{tot} - c) - \frac{k_2 Y}{\epsilon} c, \] (53)

\[ \frac{dg}{dt} = \beta c - \delta g. \] (54)

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

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

\[ \frac{dg}{dt} = \beta c - \delta g, \] (56)

\[ \frac{dc}{dt} = \frac{k_2 Y}{k_d} (p_{tot} - c)(v - c) - k_2 Y c. \] (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

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

\[ \frac{d\psi_g}{dt} = \beta \psi_c - \delta \psi_g + \sqrt{\beta c}\Gamma_5 - \sqrt{\delta g}\Gamma_6, \] (59)

\[ \epsilon \frac{d\psi_c}{dt} = \frac{k_2 Y}{k_d} (p_{tot} - c)\psi_v + \left( -\frac{k_2 Y}{k_d} v - \frac{k_2 Y}{k_d} p_{tot} + 2\frac{k_2 Y}{k_d} c - k_2 Y \right)\psi_c \]

\[ + \sqrt{\epsilon\frac{k_2 Y}{k_d} (v - c)(p_{tot} - c)}\Gamma_3 - \sqrt{\epsilon k_2 Y c}\Gamma_4. \] (60)

with \( \psi_x = [\psi_v, \psi_g]^T \) and \( \psi_z = [\psi_v, \psi_g]^T \). Therefore, the equations (55) - (60) are in the form of the original system in (5) - (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 \( 0 \leq c \leq p_{tot} \). We have that Assumption 3 is satisfied since \( \frac{\partial f_z}{\partial z} \) is negative. Thus, we obtain the reduced system

\[ \frac{d\tilde{v}}{dt} = k_1 Z(t)(X_{tot} - \tilde{v}) - k_2 Y(\tilde{v} - \tilde{c}), \]

\[ \frac{d\tilde{g}}{dt} = \beta \tilde{c} - \delta \tilde{g}, \]

\[ \frac{d\tilde{\psi}_v}{dt} = (-k_1 Z(t) - k_2 Y)\tilde{\psi}_v + k_2 Y\tilde{\psi}_c + \sqrt{k_1 Z(t)(X_{tot} - \tilde{v})}\Gamma_1 - \sqrt{k_2 Y(\tilde{v} - \tilde{c})}\Gamma_2, \]

\[ \frac{d\tilde{\psi}_g}{dt} = \beta \tilde{\psi}_c - \delta \tilde{\psi}_g + \sqrt{\beta c}\Gamma_5 - \sqrt{\delta g}\Gamma_6, \]
where
\[ \bar{c} = \frac{1}{2} (\bar{v} + p_{tot} + k_d) - \frac{1}{2} \sqrt{(\bar{v} + p_{tot} + k_d)^2 - 4\bar{v}p_{tot}}, \]
\[ \bar{\psi}_c = \frac{(p_{tot} - \bar{c})\bar{\psi}_v}{(\bar{v} + p_{tot} - 2\bar{c} + k_dY)}. \]

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 the Euler-Maruyama method and the sample means are calculated using \( 3 \times 10^6 \) realizations.

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

6 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 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 systems especially when the system has high dimension. 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.

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Appendix

**A-1:** Applying the coordinate transformation $x = A_x y$, $z = A_z y$ to equation (2), with $\tilde{a}(y, t) = [\tilde{a}_s(y, t), (1/\epsilon)\tilde{a}_f(y, t)]^T$ 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

$$
\frac{dx}{dt} = A_x f(A^{-1}[x, z]^T, t)
$$

$$
= A_x \sum_{i=1}^{m_s} v_i \tilde{a}_{si}(A^{-1}[x, z]^T, t) + A_x \sum_{i=m_s+1}^{m_s+m_f} v_i (1/\epsilon) \tilde{a}_{fi}(A^{-1}[x, z]^T, t)
$$

$$
= f_x(x, z, t), \tag{61}
$$

$$
\frac{dz}{dt} = A_z f(A^{-1}[x, z]^T, t)
$$

$$
= A_z \sum_{i=1}^{m_s} v_i \tilde{a}_{zi}(A^{-1}[x, z]^T, t) + A_z \sum_{i=m_s+1}^{m_s+m_f} v_i (1/\epsilon) \tilde{a}_{zi}(A^{-1}[x, z]^T, t)
$$

$$
= \frac{1}{\epsilon} f_z(x, z, t, \epsilon). \tag{62}
$$

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 $y = A^{-1}[x, z]^T$, using the chain rule we can write

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

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

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

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

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

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 $\hat{a}(A^{-1}[x, z]^T, t) = [\hat{a}_s(A^{-1}[x, z]^T, t), (1/\epsilon)\hat{a}_f(A^{-1}[x, z]^T, t)]^T$, we have

\[
\dot{\psi}_x = \frac{\partial f_x(x, z, t)}{\partial x} \psi_x + \frac{\partial f_z(x, z, t)}{\partial z} \psi_z + A_x \left[ v_1 \sqrt{\hat{a}_1(A^{-1}[x, z]^T, t)} \ldots v_m \sqrt{\hat{a}_s(A^{-1}[x, z]^T, t)} \right] \Gamma_x + A_x \left[ v_{m+1} \sqrt{\frac{1}{\epsilon} \hat{a}_f_1(A^{-1}[x, z]^T, t)} \ldots v_{m+m_f} \sqrt{\frac{1}{\epsilon} \hat{a}_f_m(A^{-1}[x, z]^T, t)} \right] \Gamma_f,
\]

\[
\dot{\psi}_z = \frac{\partial f_x(x, z, t)}{\partial x} \psi_x + \frac{\partial f_z(x, z, t)}{\partial z} \psi_z + A_z \left[ v_1 \sqrt{\hat{a}_1(A^{-1}[x, z]^T, t)} \ldots v_m \sqrt{\hat{a}_s(A^{-1}[x, z]^T, t)} \right] \Gamma_x + A_z \left[ v_{m+1} \sqrt{\frac{1}{\epsilon} \hat{a}_f_1(A^{-1}[x, z]^T, t)} \ldots v_{m+m_f} \sqrt{\frac{1}{\epsilon} \hat{a}_f_m(A^{-1}[x, z]^T, t)} \right] \Gamma_f,
\]

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

17
References

[1] H. K. Khalil. *Nonlinear systems*, volume 3. Prentice hall Upper Saddle River, 2002.

[2] G. Pavliotis and A. Stuart. *Multiscale methods: averaging and homogenization*, volume 53. Springer Science & Business Media, 2008.

[3] J. K. Kim, K. Josić, and M. R. Bennett. The validity of quasi-steady-state approximations in discrete stochastic simulations. *Biophysical journal*, 107(3):783–793, 2014.

[4] S. S. Andrews, T. Dinh, and A. P. Arkin. Stochastic models of biological processes. In *Encyclopedia of Complexity and Systems Science*, pages 8730–8749. Springer, 2009.

[5] D. A. McQuarrie. Stochastic approach to chemical kinetics. *Journal of applied probability*, 4(3):413–478, 1967.

[6] C. W. Gardiner. *Handbook of stochastic methods*, volume 4. Springer Berlin, 1985.

[7] N. G. Van Kampen. *Stochastic processes in physics and chemistry*, volume 1. Elsevier, 1992.

[8] D. T. Gillespie. The chemical langevin equation. *The Journal of Chemical Physics*, 113(1):297–306, 2000.

[9] J. Elf and M. Ehrenberg. Fast evaluation of fluctuations in biochemical networks with the linear noise approximation. *Genome research*, 13(11):2475–2484, 2003.

[10] N. Herath, A. Hamadeh, and D. Del Vecchio. Model reduction for a class of singularly perturbed stochastic differential equations. In *American Control Conference (ACC), 2015*.

[11] N. Herath and D. Del Vecchio. Moment convergence in a class of singularly perturbed stochastic differential equations. In *Control Conference (AUCC), 2015 5th Australian*, pages 43–48. IEEE, 2015.

[12] C. D. Pahlajani, P. J. Atzberger, and M. Khammash. Stochastic reduction method for biological chemical kinetics using time-scale separation. *Journal of theoretical biology*, 272(1):96–112, 2011.

[13] P. Thomas, R. Grima, and A. V. Straube. Rigorous elimination of fast stochastic variables from the linear noise approximation using projection operators. *Physical Review E*, 86(4):041110, 2012.

[14] P. Thomas, A. V Straube, and R. Grima. The slow-scale linear noise approximation: an accurate, reduced stochastic description of biochemical networks under timescale separation conditions. *BMC systems biology*, 6(1):39, 2012.
[15] A. Sootla and J. Anderson. On projection-based model reduction of biochemical networks part ii: The stochastic case. In Decision and Control (CDC), 2014 IEEE 53rd Annual Conference on, pages 3621–3626, Dec 2014.

[16] A. Sootla and J. Anderson. Structured projection-based model reduction with application to stochastic biochemical networks. arXiv preprint arXiv:1510.05784, 2015.

[17] D. T Gillespie. Stochastic simulation of chemical kinetics. Annu. Rev. Phys. Chem., 58:35–55, 2007.

[18] D. T. Gillespie. Deterministic limit of stochastic chemical kinetics. The Journal of Physical Chemistry B, 113(6):1640–1644, 2009.

[19] S. Jayanthi and D. Del Vecchio. Retroactivity attenuation in bio-molecular systems based on timescale separation. Automatic Control, IEEE Transactions on, 56(4):748–761, 2011.

[20] M. Contou-Carrere, V. Sotiropoulos, Y. N. Kaznessis, and P. Daoutidis. Model reduction of multi-scale chemical langevin equations. Systems & Control Letters, 60(1):75–86, 2011.

[21] B. Mélykúti, K. Burrage, and K. C. Zygalakis. Fast stochastic simulation of biochemical reaction systems by alternative formulations of the chemical langevin equation. The Journal of chemical physics, 132(16):164109, 2010.

[22] K. K. Koretke, A. N. Lupas, P. V. Warren, M. Rosenberg, and J. R. Brown. Evolution of two-component signal transduction. Molecular Biology and Evolution, 17(12):1956–1970, 2000.

[23] D. Del Vecchio, A. J. Ninfa, and E. D. Sontag. Modular cell biology: retroactivity and insulation. Molecular systems biology, 4(1), 2008.

[24] S. Jayanthi and D. Del Vecchio. Retroactivity attenuation in bio-molecular systems based on timescale separation. Automatic Control, IEEE Transactions on, 56(4):748–761, 2011.