Hybrid Master Equation for Jump-Diffusion Approximation of Biomolecular Reaction Networks

Derya Altıntan 1,∗, Heinz Koeppl2,†

Abstract

Cellular reactions have multi-scale nature in the sense that the abundance of molecular species and the magnitude of reaction rates can vary in a wide range. This diversity leads to hybrid models that combine deterministic and stochastic modeling approaches. To reveal this multi-scale nature, we proposed jump-diffusion approximation in a previous study. The key idea behind the model was to partition reactions into fast and slow groups, and then to combine Markov chain updating scheme for the slow set with diffusion (Langevin) approach updating scheme for the fast set. Then, the state vector of the model was defined as the summation of the random time change model and the solution of the Langevin equation. In this study, we have proved that the joint probability density function of the jump-diffusion approximation over the reaction counting process satisfies the hybrid master equation, which is the summation of the chemical master equation and the Fokker-Planck equation. To solve the hybrid master equation, we propose an algorithm using the moments of reaction counters of fast reactions given the reaction counters of slow reactions. Then, we solve a constrained optimization problem for each conditional probability density at the time point of interest utilizing the maximum entropy approach. Based on the multiplication rule for joint probability density functions, we construct the solution of the hybrid master equation. To show the efficiency of the method, we implement it to a canonical model of gene regulation.

Keywords: jump-diffusion approximation, chemical master equation, Fokker-Planck equation, maximum entropy approach

1 Introduction

Reaction networks in systems of biology have discrete and stochastic nature [11,14,15]. Ignoring the randomness of the stochastic fluctuations and the discreteness of the number of molecules of species result in inappropriate models which cannot correctly describe the dynamics of the whole cell. Stochastic modeling approach explains the dynamics of these systems using discrete-state continuous-time Markov chains and describes the state of the system by integer-valued number of molecules of species. In this approach, the state vector of the system satisfies the random time change model (RTCM), which defines the reaction counting processes using Poisson processes [2]. Also, the probability mass function of these systems satisfies a set of differential equations referred to as the chemical master equation (CME) in the literature [18]. When the number of molecules of the species in the system of interest is very high, the state vector of the system can be defined by real-valued concentrations instead of integer-valued particle numbers. Dynamics of such systems can be modeled through diffusion approximation, and the state vector of the system satisfies an Itô stochastic differential equation (SDE) known as the chemical Langevin equation (CLE). Similarly, probability density function of these systems suffices the Fokker-Planck equation (FPE) [20,21]. In the thermodynamic limit, in which the number of molecules of species and the system volume both approach to infinity while the concentrations of species stay constant, the state of the system is given by the reaction rate equation (RRE) of the traditional deterministic modeling approach.

Cellular reaction systems involve reactions with very different rates and species with very different abundances. Models only based on the traditional deterministic modeling approach fail to account for this nature. Therefore,
different hybrid methods that couple the stochastic and deterministic modeling approaches are needed. In general, hybrid methods separate reactions and/or species into different groups of reactions and/or species, and they use the diffusion or the deterministic modeling approach to describe the dynamics of fast reactions and/or species with high copy numbers, while Markov chain representation is utilized for slow reactions and/or species with low copy numbers \cite{6,7,8,10,13,27}.

A major challenge of modeling the reaction networks using the CME is the curse of dimensionality. Each state of the system under consideration adds one dimension to the corresponding CME. Therefore, when the number of reachable states is very high, it is very difficult to obtain the numerical solution of the CME. To avoid this drawback, different simulation algorithms, such as Gillespie’s stochastic simulation algorithms (SSAs) and their versions, were proposed to obtain the trajectories of the biochemical system of interest \cite{17,22}. The computational cost of these algorithms increases with the size of the model; therefore, it is not appropriate to use them for very complicated systems involving many reactions and reactants.

Moment approximations that analyze the dynamics of the reaction network under consideration using moments of the probability distribution satisfying the corresponding CME are considered as an alternative. In \cite{12}, the author proposed the method of moments that computes the moments for any reaction network from the corresponding CME. In \cite{30}, a moment closure approximation that obtains finite dimensional ordinary differential equation (ODE) system for the mean and the central moments by truncating the moment equations at a certain order and using the Taylor series is introduced. Another moment closure method that approximates the moments with higher order, compared to the order of truncation, utilizing nonlinear functions of the lower order moments is introduced in \cite{33}.

In \cite{26}, the authors introduced the method of conditional moments (MCM) that can be considered as the combination of a hybrid method and a moment approximation method. The MCM separates species into two different classes involving species with high copy number of molecules and species with low copy number of molecules. Based on this decomposition, the joint probability density function satisfying the corresponding CME is also represented as a product of the marginal probabilities of species with low copy number of molecules and the conditional probabilities of species with high copy number of molecules conditioned on the remaining species with low copy numbers of molecules. To describe the dynamics of species with low copy number of molecules, the authors used marginal probabilities, while the conditional means and the centered conditional moments are used to model the dynamics of species with high copy numbers. In comparison to \cite{26}, in \cite{3}, the authors obtained moments of the system of interest directly from the corresponding CME without using any partitioning of the species, and the maximum entropy approach is used to construct the corresponding probability distribution.

In \cite{16}, we developed a jump-diffusion approximation to model multi-scale behavior of cellular reactions. Based on an error bound, we separated reactions into fast and slow groups. We employed diffusion approximation for the fast reactions, while Markov jump process was kept for the slow ones. As a result, the state of the system was defined as the summation of the RTCM and the solution of the corresponding CLE. In this paper, based on this representation, we present the hybrid master equation (HME), which is the evolution equation for the joint probability density function of the jump diffusion approximation over the reaction counting process. We prove that the HME is the summation of the corresponding CME and the corresponding FPE \cite{32}. To solve the HME, we obtain the evolution equation for the marginal probability of slow reactions and the evolution equations for the conditional moments of the fast reactions given slow reactions \cite{26}. Using the maximum entropy approach, we construct the corresponding conditional probability at the time point of interest, which in turn gives the approximate solution of the corresponding HME.

The rest of the paper is organized as follows: In Section \cite{2} we describe the basic concepts of the stochastic modeling approach. In Section \cite{3} we give a brief summary of the jump-diffusion approximation. We introduce the HME in Section \cite{4}. In Section \cite{5} we construct an ODE system that will be used to obtain the approximate solution of the HME. In Section \cite{6} we introduce the maximum entropy approach. In Section \cite{7} we present numerical results and also explain the details of how we use the maximum entropy approach to construct the joint probability density function describing the HME. Section \cite{8} concludes the paper.

Notation
Before we give the details of the mathematical derivations, we present the basic notations used through the present paper. We represent all random variables and their realizations by upper-case (i.e. $A$) and lower case (i.e. $a$) symbols, respectively, and we use bold symbols to represent the support of a random variable (i.e. $\mathbf{A}$). Also, $e_j$, $\bar{e}_j$ denote $(R - L) \times 1$, $L \times 1$, unit vectors with 1 in the $j-$th component and 0 in other coordinates.
2 Stochastic Modeling of Chemical Kinetics

In this study, we consider a well-mixed reaction system of $M$ species, $S_1, S_2, \ldots, S_M$, interacting through $R \geq 1$ reaction channels $R_1, R_2, \ldots, R_R$ inside the reaction compartment with volume $V$. The $k$–th reaction channel of the system is described as follows:

$$r_{1k}S_1 + r_{2k}S_2 + r_{3k}S_3 + \ldots + r_{Mk}S_M \rightarrow p_{1k}S_1 + p_{2k}S_2 + p_{3k}S_3 + \ldots + p_{Mk}S_M,$$

where $r_{jk}, p_{jk} \in \mathbb{N}$, $j = 1, 2, \ldots, M$, represent the number of molecules of species $S_j$ consumed and produced with a single occurrence of the reaction $R_k$, respectively, and $\ell_k$ is the real-valued stochastic reaction rate constant. Let $X_i(t) \in \mathbb{N}_0$ denote the number of molecules of species $S_i$, $i = 1, 2, \ldots, M$, at time $t \geq 0$. Then, the state of the system at time $t$ is $X(t) = (X_1(t), X_2(t), \ldots, X_M(t))^T \in \mathbb{N}_0^M$.

The classical stochastic modeling of biochemical networks assumes that the process of $X$ is a continuous time Markov chain (CTMC). In this approach, the state vector, $X(t)$, is defined as a random variable of the Markov jump process. Each reaction channel $R_k$, $k = 1, 2, \ldots, R$, is specified by its stoichiometric vector (state-change vector) and its propensity function. The stoichiometric vector $\nu_k = (\nu_{1k}, \nu_{2k}, \ldots, \nu_{Mk}) \in \mathbb{Z}^M$ with $\nu_{jk} = p_{jk} - r_{jk}$, $j = 1, 2, \ldots, M$, represents the change in the state of the system after one occurrence of the reaction $R_k$. In other words, when the reaction $R_k$ fires, the system state $X(t) = x$ jumps to a new state $x + \nu_k$. Given $X(t) = x$, the probability that one $R_k$ reaction takes place in the time interval $[t, t + h]$ is $a_k(x)h + o(h)$ where $a_k(x) : \mathbb{N}_0^M \rightarrow \mathbb{R}_+$ represents the propensity function calculated by the law of mass action kinetics, i.e., $a_k(x) = \ell_k \prod_{i=1}^M \frac{x_i}{r_{ik}}$. Let $Z_k(t)$ denote the number of occurrence of the reaction $R_k$ by the time $t$, then the state of the system at time $t$ can be obtained as follows:

$$X(t) = X(0) + \sum_{k=1}^R Z_k(t)\nu_k.$$

If we represent the counting process $Z_k(t)$ in terms of the independent Poisson process denoted by $\xi_k$, such that $Z_k(t) = \xi_k \left( \int_0^t a_k(X(s))ds \right)$, then the state vector of the above CTMC satisfies the following RTCM [2]

$$X(t) = X(0) + \sum_{k=1}^R \xi_k \left( \int_0^t a_k(X(s))ds \right)\nu_k. \quad (2.1)$$

Let define the following probability mass function

$$p_t(x) = P(X(t) = x).$$

Another way of analyzing this CTMC process is to consider the time evolution of the probability function $p_t(x)$. This probability mass function is the solution of the following Kolmogorov’s forward equation, which is known as the CME [23]

$$\frac{\partial p_t(x)}{\partial t} = \sum_{k=1}^R [a_k(x - \nu_k)p_t(x - \nu_k) - a_k(x)p_t(x)]. \quad (2.2)$$

When the number of molecules in the system is very high, then the abundance of the species at time $t$ can be represented by the real valued concentrations of the form $U(t) = V^{-1}X(t) \in \mathbb{R}_+^M$. In most cases, reaction channels in biochemical systems are bimolecular or monomolecular. If the $k$–th reaction channel $R_k$ is bimolecular or monomolecular, then its propensity function satisfies the equality $a_k(x) = V\bar{a}_k(u)$ where $\bar{a}_k$ is the propensity function obtained using the deterministic reaction rate $\ell_k$ [36].

It is well known that the centered version of each Poisson process, $\xi_k$, in Equation (2.1) can be approximated through the independent Brownian motions $W_k(t)$ [2] [29]. Considering the fact that $(\xi_k(Vt) - Vt)/\sqrt{V}$ converges in distribution to the Brownian motion $W_k(t)$ for large $V$, we obtain the diffusion approximation of Equation (2.1) as given below:

$$U(t) = U(0) + \sum_{k=1}^R \nu_k \int_0^t \bar{a}_k(U(s))ds + \frac{1}{\sqrt{V}} \sum_{k=1}^R \nu_k W_k(\int_0^t \bar{a}_k(U(s))ds). \quad (2.3)$$
The first and the second summand in the right hand-side of Equation (2.3) are called drift and diffusion terms, respectively. The time derivative of the state vector \( U(t) \) satisfies an SDE, namely the CLE.

Let define the following probability density function

\[
q_{\ell}(u)du = P(U(t) \in [u, u + du]).
\]

Then, analog of the CME for this continuous process is represented by the following FPE [20]

\[
\frac{\partial q_{\ell}(u)}{\partial t} = -\sum_{i=1}^{M} \frac{\partial}{\partial u_i} \left( \sum_{k=1}^{R} \nu_{ik} \bar{a}_{k}(u) q_{\ell}(u) \right) + \frac{1}{2} \sum_{i,i'=1}^{M} \frac{\partial^2}{\partial u_i \partial u_{i'}} \left[ \sum_{k=1}^{R} \nu_{ik} \nu_{i'k} \bar{a}_{k}(u) q_{\ell}(u) \right].
\]

Cellular processes consist of bimolecular reactions of very different speeds involving reactants of largely different abundances. Therefore, the models based only on the RTCM or only the diffusion approximation may be inappropriate to dynamics of such multi-scale processes. In [16], we developed a jump-diffusion approximation to model such processes. In the following section, we will give a summary of this approximation.

### 3 Jump Diffusion Approximation

In jump-diffusion approximation [16], we partition the reactions into the fast subgroup, \( C \), and the slow subgroup, \( D \), and model the fast group using a diffusion process, while Markov chain representation is kept for the slow group.

In this approach instead of the CTMC process represented by \( X \), we focus on the scaled abundances \( X^{N}_{t} = X_{t}/N_{t}^{\gamma}, i = 1, 2, \ldots, M \), and the scaled stochastic reaction rates \( \kappa_{j} = \ell_{j}/N_{t}^{\gamma}, j = 1, 2, \ldots, R \), such that \( X^{N}_{t} = O(1), \kappa_{j} = O(1) \). Naturally, these scaled quantities will produce new scaled propensity functions as follows

\[
a_{k}(X(t)) = N^{\gamma_{k}+\gamma_{\ell}} \bar{a}_{k}(X^{N}(t)),
\]

where \( r_{k} = (r_{1k}, r_{2k}, \ldots, r_{Mk}) \) and \( \zeta = (\zeta_{1}, \zeta_{2}, \ldots, \zeta_{M}) \). It must be noted that \( \bar{a}_{k}(\cdot) \) functions are also \( O(1) \). Finally, scaling the time \( t \to tN^{\theta} \) and defining \( X^{N}(t) = X^{N}(tN^{\theta}) \), we transform the state vector, \( X(t) \), given by Equation (2.1) into the following scaled state vector

\[
X^{N}(t) = X^{N}(0) + \sum_{k=1}^{R} \xi_{k} \left( \int_{0}^{t} \alpha_{k}(X^{N}(s))ds \right) \mu_{k}, \tag{3.4}
\]

where \( \alpha_{k}(X^{N}(t)) = N^{\gamma_{k}} \bar{a}_{k}(X^{N}(t)), \rho_{k} = \theta + \eta_{k} + r_{k} \cdot \zeta \) and \( \mu_{ik} = \nu_{ik}/N_{t}^{\gamma_{i}}, i = 1, 2, \ldots, M \).

Modeling the fast reactions through diffusion approximation and modeling the slow reactions through Markov chains give the state vector of the jump diffusion approximation as follows:

\[
Y(t) = Y(0) + \sum_{i \in D} \xi_{i} \left( \int_{0}^{t} \alpha_{i}(Y(s))ds \right) \mu_{i} + \sum_{j \in C} \int_{0}^{t} \alpha_{j}(Y(s))ds \mu_{j} + \sum_{j \in C} W_{j} \left( \int_{0}^{t} \alpha_{j}(Y(s))ds \right) \mu_{j}, \tag{3.5}
\]

where \( Y(0) = X^{N}(0) \), and \( W_{j} \) is a standard Brownian motion. If \( \tau_{1}, \tau_{2} \) denote the successive firing times of reactions from the slow group, then for \( \tau_{1} < t < \tau_{2} \), only reactions from the fast group can fire. Therefore, in this time interval, the state vector of the system is given by

\[
Y(t) = Y(\tau_{1}) + \sum_{j \in C} \int_{\tau_{1}}^{t} \alpha_{j}(Y(s))ds \mu_{j} + \sum_{j \in C} W_{j} \left( \int_{\tau_{1}}^{t} \alpha_{j}(Y(s))ds \right) \mu_{j}. \tag{3.6}
\]

The main contribution of this study is the derivation of an error bound for the mean \( e(t) = E \mid X^{N}(t) - Y(t) \mid \), which is used to partition the reaction set into fast and slow subgroups. Based on this error bound, we construct a dynamic partitioning algorithm that takes into account the fact that a fast reaction can return to a slow reaction or vice versa during the course of time.

By describing the state vector of the system as the summation of purely discrete and purely continuous components, we can introduce the HME, which defines the joint probability density function of the jump diffusion approximation over the reaction counting process. In the following section, we will obtain the HME.
4 Hybrid Master Equation

In jump diffusion approximation, we partition the reaction set into two subsets. As mentioned before, the first subset \( C \) involves reactions modeled by diffusion approximation, while the rest of the reactions constituting the slow set \( D \) are modeled by Markov chains. In the rest of the study, we will consider that there are \( L \) slow reactions, i.e., \(| D | = L\), and \( R - L \) fast reactions in the system, i.e., \(| C | = R - L\).

Let \( Z(t) = (Z_1(t), Z_2(t), \ldots, Z_R(t))^T \) be a vector of reaction counters such that \( Z_i(t) \) denotes the number of occurrences of the reaction \( R_i \), \( i = 1, 2, \ldots, R \), during the time of the process until time \( t > 0 \). Similar to the idea of splitting the state vector of the system into purely discrete and purely continuous parts, we also separate \( Z(t) = (D(t), C(t))^T \) into purely discrete and continuous parts corresponding to the reaction counters of the slow, \( D(t) \in \mathbb{N}^L \), and the fast reaction set, \( C(t) \in \mathbb{R}^{R-L}_\geq \) such that \( D_i(t) = Z_i(t), i \in D \), and \( C_j(t) = Z_j(t), j \in C \). We also separate the stoichiometric vectors such that \( \mu_i^D = \mu_i, i \in D \), and \( \mu_j^C = \mu_j, j \in C \).

By using Equation (3.5), we will define reaction counters as follows:

\[
D_i(t) = \xi_i \left( \int_0^t \alpha_i(Y(s)) ds \right) = \xi_i \left( \int_0^t \alpha_i(D(s), C(s)) ds \right), \quad i \in D,
\]
\[
C_j(t) = \int_0^t \alpha_j(Y(s)) ds + W_j \left( \int_0^t \alpha_j(Y(s)) ds \right) = \int_0^t \tilde{\alpha}_j(D(s), C(s)) ds + W_j \left( \int_0^t \tilde{\alpha}_j(D(s), C(s)) ds \right), \quad j \in C,
\]

where

\[
\alpha_k(y) = \alpha_k(y(0)) + \sum_{i \in D} d_i \mu_i^D + \sum_{j \in C} c_j \mu_j^C = \tilde{\alpha}_k(d, c), \quad k = 1, 2, \ldots, R.
\]

It must be noted that if \( \tau_1, \tau_2 \) denote the successive firing times of reactions from the slow group, then for \( \tau_1 < t < \tau_2 \), \( C(t) \) satisfies the following equation

\[
C(t) = C(\tau_1) + \sum_{j \in C} \left( \int_{\tau_1}^t \tilde{\alpha}_j(d, C(s)) ds \right) e_j + \sum_{j \in C} W_j \left( \int_{\tau_1}^t \tilde{\alpha}_j(d, C(s)) ds \right) e_j,
\]

where \( d \) denotes the number of slow reactions fired until time \( \tau_1 > 0 \).

The HME is the time derivative of the joint probability density function \( p_t : \mathbb{N}^L \times \mathbb{R}^{R-L}_\geq \rightarrow \mathbb{R}_\geq \)

\[
p_t(d, c) dc = P(D(t) = d, C(t) \in [c, c + dc]).
\]

Then, we can write

\[
p_t(d, c) = p_t(c \mid d) p_t(d),
\]

where

\[
p_t(c \mid d) \ dc = P(C(t) \in [c, c + dc] \mid D(t) = d) \quad \text{and} \quad p_t(d) = P(D(t) = d).
\]

To obtain the evolution equation for \( p_t(d, c) \), which is called the HME, we need the following result whose details can be found in [32].

**Result:** Let \( D(t) \in D \subset \mathbb{N}^L \) be a discrete process and \( C(t) \in \mathbb{R}^{R-L}_\geq \) be a continuous process. Define the joint probability density function as follows:

\[
p_t(d, c) = p_t(c \mid d) p_t(d).
\]

Then, the time derivative of this joint probability function, which is referred to as generalized Fokker-Planck equation (GFPE), has the following form

\[
\frac{\partial}{\partial t} p_t(d, c) = \sum_{d' \in D} a_{dd'} p_t(d', c) + \sum_{n_1, n_2, \ldots, n_{R-L}=1}^\infty \left( \prod_{i=1}^{R-L} \frac{(-1)^{n_i} \partial^n_{n_i}}{n_i!} \right) \left[ A_{n_1, n_2, \ldots, n_{R-L}} p_t(d, c) \right],
\]

(4.10)
By using Equation (4.10) and Equation (4.13), we obtain

\[ A_{n_1, n_2, \ldots, n_{R-L}} = \lim_{h \to 0} \frac{1}{h} \mathbb{E} \left[ \prod_{i=1}^{R-L} \{C_i(t + h) - C_i(t)\}^{n_i} \mid D(t) = d, C(t), D(t + h) = d \right], \]

and

\[ a_{dd'} = \lim_{h \to 0} \frac{1}{h} \left[ \mathbb{P}(D(t + h) = d \mid D(t) = d', C(t)) - \delta_{dd'} \right]. \quad (4.11) \]

where

\[ \mathbb{E}[C(t) \mid d] = \int_{\mathbb{R}^{R-L}} e_{n}(c \mid d) dc. \]

It is also proved that \( A_{n_1, n_2, \ldots, n_{R-L}} = 0 \) for all \( \sum_{i=1}^{R-L} n_i \geq 3 \). This gives us

\[ \sum_{n_1, n_2, \ldots, n_{R-L} = 1}^{\infty} \left( \prod_{i=1}^{R-L} \frac{(-1)^{n_i} \frac{\partial^n}{\partial c_i^n}}{n_i!} \right) [A_{n_1, n_2, \ldots, n_{R-L}} p_t(d, c)] = - \sum_{j=1}^{R-L} \frac{\partial}{\partial c_j} [B_j p_t(d, c)] + \frac{1}{2} \sum_{i,j=1}^{R-L} \frac{\partial^2}{\partial c_i \partial c_j} [B_{ij} p_t(d, c)]. \quad (4.12) \]

Theorem 4.1. Let \( Z(t) = \{D(t), C(t)\} \) be a joint reaction counting process where \( D(t) \) is a discrete random process with states \( d \in \mathbb{D} \subset \mathbb{N}_L, L > 0 \), and \( C(t) \) is a continuous random process with states \( c \in \mathbb{R}^{R-L}, R - L > 0 \). Define \( Y \) as a multi-scale process whose state vector is given in Equation (3.5). Then, the joint counting probability density function given in Equation (4.9) satisfies the following GFPE, which is referred to as the HME in the present paper.

\[ \frac{\partial}{\partial t} p_t(d, c) = \sum_{i \in \mathbb{D}} \left( \bar{\alpha}_i (d - \bar{e}_i, c) p_t(d - \bar{e}_i, c) - \bar{\alpha}_i(d, c) p_t(d, c) \right) \]

\[ + \sum_{j \in \mathbb{C}} \frac{\partial}{\partial c_j} (\bar{\alpha}_j (d, c) p_t(d, c)) + \frac{1}{2} \sum_{j \in \mathbb{C}} \frac{\partial^2}{\partial c_j^2} (\bar{\alpha}_j (d, c) p_t(d, c)). \quad (4.13) \]

Proof. By using Equation (4.10) and Equation (4.13), we obtain

\[ \frac{\partial}{\partial t} p_t(d, c) = \sum_{d' \in \mathbb{D}} a_{dd'} p_t(d', c) - \sum_{j \in \mathbb{C}} \frac{\partial}{\partial c_j} (B_j p_t(d, c)) + \frac{1}{2} \sum_{i,j \in \mathbb{C}} \frac{\partial^2}{\partial c_i \partial c_j} (B_{ij} p_t(d, c)). \quad (4.14) \]

Now, let’s focus on the first summand on the right hand-side of Equation (4.14), which can be rewritten as follows:

\[ \sum_{d' \in \mathbb{D}} a_{dd'} p_t(d', c) = \sum_{d' \in \mathbb{D}} p_t(d', c) + a_{dd} p_t(d, c). \quad (4.15) \]

Using Equation (4.11) gives

\[ a_{dd} = \lim_{h \to 0} \frac{1}{h} \mathbb{P}(D(t + h) = d \mid D(t) = d, C(t)) - 1, \]

which can be reformulated as follows

\[ a_{dd} = \lim_{h \to 0} \frac{1}{h} \left[ \mathbb{P}(D(t + h) = d' \mid D(t) = d, C(t)) - 1 \right]. \]
By using this representation, we can rewrite Equation (4.15) in the following form
\[ \sum_{d' \in D} a_{dd'} p_t(d', c) = \sum_{d' \in D, d \neq d'} \left( a_{dd'} p_t(d', c) - a_{d'd} p_t(d, c) \right). \]

In our multi-scale process, we have \( L \) slow reactions, and one firing of the reaction \( R_j \) in this set updates \( d \) to \( d + \varepsilon_j \). Starting from \( d \), the system can jump to \( d' = d + \varepsilon_j \), meaning that \( a_{d+d\varepsilon_j} = \alpha_j(d, c) \). In the same vein, to reach \( d \), the system must supervise on \( d - \varepsilon_j \), by definition \( a_{d-d\varepsilon_j} = \bar{\alpha}_j(d - \varepsilon_j, c) \). As a result, we obtain the desired summand as follows:
\[ \sum_{d' \in D} a_{dd'} p_t(d', c) = \sum_{i \in D} \left( \bar{\alpha}_i(d - \varepsilon_i, c) p_t(d - \varepsilon_i, c) - \alpha_i(d, c) p_t(d, c) \right). \quad (4.16) \]

Now, we can concentrate on the second and the third summands of Equation (4.14). Jump diffusion approximation is based on the idea that between two successive firing times of the slow reactions, the fast reactions continue to fire. Hence, the state vector and also the reaction counting process of the fast reaction set will satisfy diffusion processes (see Equation [3.6] [4.8]). Therefore, \( B_j \) and \( B_{ij} \) values have the forms [19, 21, 28]
\[ B_j = \sum_{k \in C} e_{jk} \bar{\alpha}_k(d, c), \quad B_{ij} = \sum_{k \in C} e_{ik} e_{jk} \bar{\alpha}_k(d, c). \]

Substitution of \( B_j \) and \( B_{ij} \) values and Equation (4.16) into Equation (4.14) gives
\[
\frac{\partial}{\partial t} p_t(d, c) = \sum_{i \in D} \left( \bar{\alpha}_i(d - \varepsilon_i, c) p_t(d - \varepsilon_i, c) - \alpha_i(d, c) p_t(d, c) \right) \\
- \sum_{j \in C} \frac{\partial}{\partial c_j} \left( \sum_{k \in C} e_{jk} \bar{\alpha}_k(d, c) \right) + \frac{1}{2} \sum_{i,j \in C} \frac{\partial^2}{\partial c_i \partial c_j} \left( \sum_{k \in C} e_{ik} e_{jk} \bar{\alpha}_k(d, c) p_t(d, c) \right) \\
= \sum_{i \in D} \left( \bar{\alpha}_i(d - \varepsilon_i, c) p_t(d - \varepsilon_i, c) - \alpha_i(d, c) p_t(d, c) \right) - \sum_{j \in C} \frac{\partial}{\partial c_j} \left( \bar{\alpha}_j(d, c) p_t(d, c) \right) + \frac{1}{2} \sum_{j \in C} \frac{\partial^2}{\partial c_j^2} \left( \bar{\alpha}_j(d, c) p_t(d, c) \right),
\]
which completes the proof.

Based on the properties of the joint counting probability density function, we can write
\[ p_t(d, c) = p_t(c \mid d) p_t(d). \]

Since we partition reaction counters into two subsets, we will also decompose the propensity functions. Using mass action kinetics to compute propensities is very popular, and for this large class we partition the propensity function of the reaction \( R_k, \bar{\alpha}_k(d, c), k = 1, 2, \ldots, R \), as follows:
\[
\bar{\alpha}_k(d, c) = \alpha_k(y(0) + \sum_{i \in D} d_i \mu_i^D + \sum_{j \in C} c_j \mu_j^C) = \kappa_k \prod_{s=1}^{M} \left( y_s(0) + \sum_{i \in D} d_i \mu_i^{D,s} + \sum_{j \in C} c_j \mu_j^{C,s} \right)^{r_{sk}} \\
= \kappa_k \prod_{s=1}^{M} \left( \beta_s(d) + \gamma_s(c) \right)^{r_{sk}} = \kappa_k \prod_{s=1}^{M} \prod_{n=0}^{r_{sk}} \left( \frac{r_{sk}}{n} \beta_s^n(d) \gamma_s^{r_{sk}-n}(c) \right) = K \kappa_k \prod_{s=1}^{M} \prod_{n=0}^{r_{sk}} \beta_s^n(d) \gamma_s^{r_{sk}-n}(c),
\]
where \( \beta_s(d) = y_s(0) + \sum_{i \in D} d_i \mu_i^{D,s}, \gamma_s(c) = \sum_{j \in C} c_j \mu_j^{C,s} \) and \( K \) is a real constant that will be ignored to simplify the notation for the reader. Based on this representation, the HME given in Equation (4.13) can be rewritten in the following form
\[
\frac{\partial}{\partial t} p_t(d, c) = \sum_{i \in D} \prod_{s=1}^{M} \sum_{n=0}^{r_{si}} \kappa_i \left( \beta_s^n(d - \varepsilon_i) \gamma_s^{r_{si}-n}(c) p_t(d - \varepsilon_i, c) - \beta_s^n(d) \gamma_s^{r_{si}-n}(c) p_t(d, c) \right) \\
- \sum_{j \in C} \frac{\partial}{\partial c_j} \left( \kappa_j \prod_{s=1}^{M} \sum_{n=0}^{r_{sj}} \beta_s^n(d) \gamma_s^{r_{sj}-n}(c) p_t(d, c) \right) + \frac{1}{2} \sum_{j \in C} \frac{\partial^2}{\partial c_j^2} \left( \kappa_j \prod_{s=1}^{M} \sum_{n=0}^{r_{sj}} \beta_s^n(d) \gamma_s^{r_{sj}-n}(c) p_t(d, c) \right), \quad (4.17)
\]
Let $f(d) : \mathbb{D} \rightarrow \mathbb{R}$ and $g(c) : \mathbb{R}^{R-L}_{\geq 0} \rightarrow \mathbb{R}$ be any functions of $d$ and $c$ variables, respectively. To simplify the notation, we introduce one step operator in the following form

$$F^{ar{e}_i} (f(d)g(c)) = f(d + \bar{e}_i)g(c), i \in \mathbb{D}.$$ 

Based on this representation, we define

$$\Gamma(\beta(d), \gamma(c)) = \sum_{i \in \mathbb{D}} (F^{-\bar{e}_i} - I) \left( \kappa_i \prod_{s=1}^{M} \sum_{n=0}^{r_{si}} \beta^n_s (d) \gamma^{r_{si} - n}_s (c) \right)$$

$$- \sum_{j \in \mathbb{C}} \frac{\partial}{\partial c_j} \left( \kappa_j \prod_{s=1}^{M} \sum_{n=0}^{r_{sj}} \beta^n_s (d) \gamma^{r_{sj} - n}_s (c) \right) + \frac{1}{2} \sum_{j \in \mathbb{C}} \frac{\partial^2}{\partial c_j^2} \left( \kappa_j \prod_{s=1}^{M} \sum_{n=0}^{r_{sj}} \beta^n_s (d) \gamma^{r_{sj} - n}_s (c) \right).$$

Then, we can write Equation (4.17) in the following form

$$\frac{\partial}{\partial t} p_t(d, c) = \Gamma(\beta(d), \gamma(c)) p_t(d, c).$$

In the rest of the study, we will assume that $p_t(d, c)$ is zero at $c = 0$, $c = \infty$ [25][33]. In the following section, we will explain how we obtain the solution of this HME.

## 5 Solution of the Hybrid Master Equation

To obtain the joint counting probability density function, $p_t(d, c)$, described by the HME given in Equation (4.18), we will approximate the process $C(t) \mid D(t)$ using its moments. Solving a maximum entropy problem for each conditional moment will produce the conditional probability function, $p_t(c \mid d)$. The multiplication of $p_t(c \mid d)$ with the marginal probabilities of the remaining discrete states, i.e.,

$$p_t(d) = \int_{\mathbb{R}^{R-L}} p_t(d, c) \, dc,$$ 

will give us the desired joint probability density function $p_t(d, c)$.

In the rest of the study, time dependent conditional means and the centered conditional moments of the process $C(t) \mid D(t)$ will be denoted by

$$\mathbb{E}_t[C_m \mid d] = \int_{\mathbb{R}^{R-L}} c_m p_t(c \mid d) \, dc, \quad m \in \mathbb{C},$$

$$\mathbb{E}_t[\bar{C}^M \mid d] = \int_{\mathbb{R}^{R-L}} \prod_{j=1}^{M} \bar{c}_j^{M_j} p_t(c \mid d) dc,$$

where $\bar{c} = c - \mathbb{E}_t[C \mid d]$, $M = (M_1, M_2, \ldots, M_{R-L}) \in \mathbb{N}^{R-L}$. Now, based on the study [20], we want to construct a differential equation system to obtain $p_t(d)$, $\mathbb{E}_t[C_m \mid d]$, $\mathbb{E}_t[\bar{C}^M \mid d]$. To construct this system, we will need the following Lemma [12][26].

**Lemma 5.1.** Let $F_t : \mathbb{R}^{R-L}_{\geq 0} \rightarrow \mathbb{R}$ be a polynomial function of $c$, and $p_t(d, c)$ satisfy differential Equation (4.18). Assume that sufficiently many moments of $p_t(d, c)$ with respect to $c$ exist, and the joint counting probability density vanishes at $c = 0$ and $c = \infty$. Define the following conditional mean

$$\mathbb{E}_t[F_t(C) \mid d] = \int_{\mathbb{R}^{R-L}} F_t(c) p_t(c \mid d) \, dc.$$

Then,

$$\frac{\partial}{\partial t} (\mathbb{E}_t[F_t(C) \mid d] p_t(d)) = \bar{\Gamma}(\beta(d), F_t(c) \gamma(c)) p_t(d) + \mathbb{E}_t[\frac{\partial}{\partial t} F_t(C) \mid d] p_t(d),$$

where

$$\bar{\Gamma}(\beta(d), F_t(c) \gamma(c)) = \sum_{i \in \mathbb{D}} (F^{-\bar{e}_i} - I) \left( \kappa_i \prod_{s=1}^{M} \sum_{n=0}^{r_{si}} \beta^n_s (d) \mathbb{E}_t[F_t(C) \gamma^{r_{si} - n}_s (C) \mid d] \right)$$

$$+ \sum_{j \in \mathbb{C}} \kappa_j \prod_{s=1}^{M} \sum_{n=0}^{r_{sj}} \beta^n_s (d) \mathbb{E}_t[\gamma^{r_{sj} - n}_s (C) \frac{\partial}{\partial c_j} F_t(C) \mid d] + \frac{1}{2} \sum_{j \in \mathbb{C}} \kappa_j \prod_{s=1}^{M} \sum_{n=0}^{r_{sj}} \mathbb{E}_t[\gamma^{r_{sj} - n}_s (C) \frac{\partial^2}{\partial c_j^2} F_t(C) \mid d].$$
Proof. The proof of the Lemma can be found in Appendix A.1.

When \( F_t(e) = 1 \) in Lemma 5.1 we obtain the time derivative of the marginal probability \( p_t(d) \), which is given in the following proposition.

**Proposition 5.2.**

\[
\frac{\partial}{\partial t} p_t(d) = \sum_{i \in D} (\mathcal{F}^{-\tilde{e}_i} - I) \left( \kappa_i \prod_{s=1}^{M} \sum_{n=0}^{r_x} \beta^n_s(d) \mathcal{E}_t[\gamma_s^{r_x-n}(C) \mid d] p_t(d) \right)
\]  

(5.19)

The strategy of our method is to obtain \( p_t(d) \) and \( p_t(c \mid d) \) separately and construct the joint probability function using the equality \( p_t(d, c) = p_t(c \mid d) p_t(d) \). To obtain the conditional probability \( p_t(c \mid d) \), we will use evolution equations of the conditional means \( \mathcal{E}_t[C_m \mid d] \), \( m \in \mathcal{C} \), and the centered conditional moments \( \mathcal{E}_t[\tilde{C}^M \mid d] \), \( M \in \mathbb{N}^{R-L} \), which are the functions of \( p_t(d) \), \( \mathcal{E}_t[C_m \mid d] \), \( \mathcal{E}_t[\tilde{C}^M \mid d] \). Equation (5.19) will be the first equation of our system. It must be noted that differential equation defining the marginal probability only depends on the slow reactions. To solve this differential equation, we need to reformulate the unknown conditional means \( \mathcal{E}_t[\gamma_s^{r_x-n}(C) \mid d] \) through the known \( \mathcal{E}_t[C_m \mid d] \), \( \mathcal{E}_t[\tilde{C}^M \mid d] \). The details of this transformation can be found in Appendix A.2.

In the following proposition, we will obtain the time evolution equation for the conditional means \( \mathcal{E}_t[C_m \mid d] \), \( m \in \mathcal{C} \).

**Proposition 5.3.**

\[
p_t(d) \frac{\partial}{\partial t} \mathcal{E}_t[C_m \mid d] = \sum_{i \in D} (\mathcal{F}^{-\tilde{e}_i} - I) \left( \kappa_i \prod_{s=1}^{M} \sum_{n=0}^{r_x} \beta^n_s(d) \mathcal{E}_t[C_m \gamma_s^{r_x-n}(C) \mid d] p_t(d) \right)  
\]  

(5.20)

where \( \delta_{jm} \) is the Kronecker delta function.

Proof. The proof of the proposition can be found in Appendix A.3.

In the following proposition, we will obtain \( p_t(d) \frac{\partial}{\partial t} \mathcal{E}_t[\tilde{C}^M \mid d] \).

**Proposition 5.4.**

\[
p_t(d) \frac{\partial}{\partial t} \mathcal{E}_t[\tilde{C}^M \mid d] = \sum_{i \in D} (\mathcal{F}^{-\tilde{e}_i} - I) \left( \kappa_i \prod_{s=1}^{M} \sum_{n=0}^{r_x} \beta^n_s(d) \mathcal{E}_t[\tilde{C}^M \gamma_s^{r_x-n}(C) \mid d] p_t(d) \right) 
\]  

(5.21)

Proof. The proof of the theorem can be found in Appendix Section A.4.

Up to this section, we have obtained the time derivatives of the marginal probabilities as well as those of the conditional means and the centered conditional moments. These three equations will give us the following differential equation system.
Theorem 5.5. Let $p_t(d, c) = p_t(c \mid d)p_t(d)$ satisfy Equation (4.13). Then, the time derivative of $p_t(d)$, $E_t[C_m \mid d]$, $m \in C$ and $E_t[C^M \mid d]$, $M = (M_1, M_2, \ldots, M_{R-L})$, satisfies the following system

$$
\frac{\partial}{\partial t} p_t(d) = \sum_{i \in D} (F^e_t - I) \left( \kappa_i \prod_{s=1}^{M} \beta^R_s(d) E_t[\gamma^R_s - n(C) \mid d] p_t(d) \right)
$$

$$
p_t(d) \frac{\partial}{\partial t} E_t[C_m \mid d] = \sum_{i \in D} (F^e_t - I) \left( \kappa_i \prod_{s=1}^{M} \beta^R_s(d) E_t[C_m \gamma^R_s - n(C) \mid d] p_t(d) \right)
$$

$$
+ \sum_{j \in C} \kappa_j \prod_{s=1}^{M} \beta^R_s(d) E_t[M_j \gamma^R_s - n(C) \mid d] p_t(d) - E_t[C_m \mid d] \frac{\partial}{\partial t} p_t(d)
$$

$$
p_t(d) \frac{\partial}{\partial t} E_t[C^M \mid d] = \sum_{i \in D} (F^e_t - I) \left( \kappa_i \prod_{s=1}^{M} \beta^R_s(d) E_t[C^M \gamma^R_s - n(C) \mid d] p_t(d) \right)
$$

$$
+ \sum_{j \in C} \kappa_j \prod_{s=1}^{M} \beta^R_s(d) E_t[M_j (M_j - 1) \gamma^R_s - n(C) \mid d] p_t(d)
$$

$$
- \sum_{j \in C} M_j E_t[C^M - e_j \mid d] p_t(d) \frac{\partial}{\partial t} E_t[C_j \mid d] - E_t[C^M \mid d] \frac{\partial}{\partial t} p_t(d),
$$

where $\delta_{jm}$ is kronecker delta function. Also, $F^e_t$ is a one step operator as follows:

$$
F^e_t \left( f(d) g(c) \right) = f(d + e_t) g(c), i \in D.
$$

where $f(d) : D \to \mathbb{R}$ and $g(c) : \mathbb{R}^{R-L} \to \mathbb{R}$ be any functions of $d$ and $c$ variables, respectively.

In the following section, we will explain the details of the maximum entropy method which will be used to construct the conditional probability distribution $p_t(c \mid d)$.

6 Maximum Entropy

Assume that we want to obtain the solution of the HME under consideration at a specific time point $\tau > 0$. Solving the ODE system in (5.22) gives $p_\tau(d)$, $E_\tau[C_m \mid d], E_\tau[C^M \mid d]$, $m \in C$, $M = (M_1, M_2, \ldots, M_{R-L})^T \in \mathbb{R}^{R-L}$ values for the system of interest. Although the marginal probabilities, $p_\tau(d)$, can directly be obtained from the ODE system, we still do not know the corresponding conditional probability density function, $p_\tau(c \mid d)$, which will be used to construct the joint probability, $p_\tau(d, c)$, solving the corresponding HME.

To estimate the unknown conditional probability density functions using its moments, we will use the maximum entropy approach proposed by Shannon [24]. Assume that we have a state space $\Omega = D \times \mathbb{R}^{R-L}$ and our goal is to estimate the unknown probability density function $p_\tau : \Omega \to \mathbb{R}_{\geq 0}$. Let

$$
S^M_{\tau} = \int_{\mathbb{R}^{R-L}} \prod_{j \in C} c_j^{M_j} p_\tau(c \mid d) dc, \quad M = (M_1, M_2, \ldots, M_{R-L}) \in \mathbb{N}^{R-L},
$$

denote the moments of the joint probability density function at time point $\tau$. It must be noted that when $M = e_m$, we obtain $E_\tau[C_m \mid d]$. To guarantee that $p_\tau(c \mid d)$ is a probability function, we must impose the condition $S^0_{\tau} = 1$. Then, the approximation for the conditional probability density function $p_\tau(c \mid d)$ will be obtained solving the following constrained convex optimization problem
following Lagrange function

\[
\begin{align*}
\min & \quad \int_{R_{R-L}} p_r(c \mid d) \ln(p_r(c \mid d)) dc \\
\text{subject to} & \quad S^0_r = \int_{R_{R-L}} p_r(c \mid d) = 1 \\
& \quad S^m_r = \mathbb{E}_r[C_m \mid d] = \int_{R_{R-L}} c_m p_r(c \mid d) \\
& \quad S^M_r = \mathbb{E}_r[C^M \mid d] = \int_{R_{R-L}} \prod_j c_j^{M_j} p_r(c \mid d) dc
\end{align*}
\]

Let \( N \) be the number of moment constraints and \( M^k, k = 0, 1, \ldots, N, \) denote different choices of vectors \( M^k = (M^k_1, M^k_2, \ldots, M^k_{R-L}) \in \mathbb{N}^{R-L}. \) To impose the conditions given above, we will have \( M^0 = 0, M^j = e_j, \) \( j = 1, 2, \ldots, R-L. \) Then, the solution of this constrained optimization problem can be obtained maximizing the following Lagrange function

\[
\mathcal{L}(p_r(c \mid d), \lambda(\tau)) = -\int_{R_{R-L}} p_r(c \mid d) \ln(p_r(c \mid d)) dc + \sum_{k=0}^N \lambda_k(\tau) \left( \int_{R_{R-L}} \prod_{j \in \mathcal{C}} c_j^{M_j} p_r(c \mid d) dc - S^M_r \right),
\]

where \( \lambda_k \in \mathbb{R}, k = 1, 2, \ldots, N \) are referred to as Lagrange multipliers. Taking the derivative of \( \mathcal{L}(p_r(c \mid d), \lambda(\tau)) \) with respect to \( p_r(c \mid d) \) will give the approximate solution of the conditional probability density for \( p_r(c \mid d) \) in the following form

\[
p^*_r(c \mid d) = \arg\max \left( \frac{1}{Z(N, \lambda(\tau))} \exp \left( -\sum_{k=0}^N \lambda_k(\tau) \prod_{j \in \mathcal{C}} c_j^{M_j} \right) \right),
\]

where \( Z(N, \lambda(\tau)) \) is a normalization constant \([1, 4, 5]\). Now, we can obtain the approximate solution of the joint probability density function which solves the HME under consideration by multiplying the obtained conditional probability function \( p^*_r(c \mid d) \) with the marginal probability function \( p_r(d) \).

7 Application

In this section of the present study, we will implement our proposed method to the following reaction system

\[
R_1 : 2S_1 \xrightarrow{\kappa_1} 2S_2, \quad R_2 : S_2 \xrightarrow{\kappa_2} S_1.
\]

The state vector of the system at time \( t \geq 0 \) is defined by \( Y(t) = (Y_1(t), Y_2(t))^T \in \mathbb{Z}_{\geq 0}^2, \) where \( Y_i(t) \) denote the number of molecules of species \( S_i, i = 1, 2. \)

The joint probability density function, \( p_t(d, c) \), satisfies the following CME

\[
\frac{\partial}{\partial t} p_t(d, c) = \kappa_1(y_1(0) - 2(d - 1) + c) p_t(d - 1, c) - \kappa_1(y_1(0) - 2d + c) p_t(d, c) - \kappa_2(y_2(0) + 2d - (c - 1)) p_t(d, c) + \kappa_2(y_2(0) + 2d - c) p_t(d, c).
\]

We separate reactions and stoichiometric vectors as follows:

\[
\mathcal{D} = \{1\}, \quad \mathcal{C} = \{2\}, \quad \mu^D_1 = (-2, 2)^T, \quad \mu^C_2 = (1, -1)^T.
\]

Propensity functions of the reactions are assumed to be

\[
\bar{\alpha}_1(d, c) = \kappa_1(\beta_1(d) + \gamma_1(c)), \quad \bar{\alpha}_2(d, c) = \kappa_2(\beta_2(d) + \gamma_2(c)),
\]

where

\[
\beta_1(d) = y_1(0) - 2d, \quad \gamma_1(c) = c, \quad \beta_2(d) = y_2(0) + 2d, \quad \gamma_2(c) = -c.
\]
Then, the HME for the joint probability density function, \( p_t(d, c) \), is defined as given below:

\[
\frac{\partial}{\partial t} p_t(d, c) = \kappa_1(y_1(0) - 2(d - 1) + c)p_t(d - 1, c) - \kappa_1(y_1(0) - 2d + c)p_t(d, c) - \frac{\partial}{\partial c} \left( \kappa_2(y_2(0) + 2d - c)p_t(d, c) \right) + \frac{1}{2} \frac{\partial^2}{\partial c^2} \left( \kappa_2(y_2(0) + 2d - c)p_t(d, c) \right)
\]  

(7.24)

The system of differential equation defining the marginal probabilities, the conditional means and the centered conditional moments has the following form

\[
\begin{align*}
\frac{\partial}{\partial t} p_t(d) &= \left( \kappa_1(y_1(0) - 2(d - 1)) + \kappa_1 E_t[C \mid d - 1] \right) p_t(d - 1) - \left( \kappa_1(y_1(0) - 2d) - \kappa_1 E_t[C \mid d] \right) p_t(d) \\
p_t(d) \frac{\partial}{\partial t} E_t[C \mid d] &= \kappa_1(y_1(0) - 2(d - 1))E_t[C \mid d - 1]p_t(d - 1) - \kappa_1(y_1(0) - 2d)E_t[C \mid d]p_t(d) + \kappa_1 E_t[C^2 \mid d - 1]p_t(d) + \kappa_2(y_2(0) + 2d)p_t(d) - \kappa_2 E_t[C \mid d]p_t(d) \\
p_t(d) \frac{\partial}{\partial t} E_t[C^2 \mid d] &= \kappa_1(y_1(0) - 2(d - 1))E_t[C^2 \mid d - 1]p_t(d - 1) - \kappa_1(y_1(0) - 2d)E_t[C^2 \mid d]p_t(d) + \kappa_1 E_t[C \mid d - 1]E_t[C]p_t(d) + \kappa_2(y_2(0) + 2d)p_t(d) - \kappa_2 E_t[C \mid d]E_t[C]p_t(d) \\
&- 2 \kappa_2 E_t[C^2 \mid d]p_t(d) - E_t[C^2 \mid d] \frac{\partial}{\partial t} p_t(d).
\end{align*}
\]  

(7.25)

Based on our previous discussions, we get the following system of differential equation which will be referred to as the moment equation system of the HME in the rest of the study

\[
\begin{align*}
\frac{\partial}{\partial t} p_t(d) &= \left( \kappa_1(y_1(0) - 2(d - 1)) + \kappa_1 E_t[C \mid d - 1] \right) p_t(d - 1) - \left( \kappa_1(y_1(0) - 2d) - \kappa_1 E_t[C \mid d] \right) p_t(d) \\
p_t(d) \frac{\partial}{\partial t} E_t[C \mid d] &= \kappa_1(y_1(0) - 2(d - 1))E_t[C \mid d - 1]p_t(d - 1) - \kappa_1(y_1(0) - 2d)E_t[C \mid d]p_t(d) + \kappa_1 E_t[C^2 \mid d - 1]p_t(d) + \kappa_2(y_2(0) + 2d)p_t(d) - \kappa_2 E_t[C \mid d]p_t(d) - E_t[C] \frac{\partial}{\partial t} p_t(d) \\
p_t(d) \frac{\partial}{\partial t} E_t[C^2 \mid d] &= \left( \kappa_1 E_t[C^2 \mid d - 1] + \kappa_2(y_2(0) + 2d)p_t(d) - \kappa_2 E_t[C \mid d]E_t[C]p_t(d) - E_t[C^2 \mid d] \frac{\partial}{\partial t} p_t(d) + \kappa_1 E_t[C \mid d - 1]E_t[C]p_t(d) + \kappa_2(y_2(0) + 2d)p_t(d) - \kappa_2 E_t[C \mid d]E_t[C^2 \mid d]p_t(d) \\
&- \kappa_1 E_t[C^2 \mid d - 1]E_t[C]p_t(d) + \kappa_1 E_t[C \mid d - 1]E_t[C]p_t(d) - \kappa_2 E_t[C \mid d]E_t[C^2 \mid d]p_t(d) \\
&+ \kappa_1 E_t[C^2 \mid d - 1]E_t[C]p_t(d) - \kappa_2 E_t[C \mid d]E_t[C^2 \mid d]p_t(d) + \kappa_2(y_2(0) + 2d)p_t(d) - \kappa_2 E_t[C \mid d]E_t[C^2 \mid d]p_t(d) \\
&- 2 \kappa_2 E_t[C^2 \mid d]p_t(d) - \kappa_2 E_t[C \mid d] \frac{\partial}{\partial t} p_t(d),
\end{align*}
\]

Substitution \( \frac{\partial}{\partial t} p_t(d) \) into \( p_t(d) \frac{\partial}{\partial t} E_t[C \mid d] \) will give a system of differential equations that is expressed only in terms of the marginal probabilities, the conditional means and the second centered moments. In our application, we close moment equations setting the third and the higher moments to zero. If \( p_t(d) = 0 \), then we will not be able to obtain \( E_t[C \mid d], E_t[C^2 \mid d] \). To avoid this drawback, in [20], the authors proposed a successful initialization procedure.

Based on the fact that propensity functions must be non negative, we define the state space of the system as follows:

\[ \Omega = D \times C = \{(d, c) \in D \times \mathbb{R}_{\geq 0} : y_1(0) - 2d + c \geq 0, y_2(0) + 2d - c \geq 0, D \subset \mathbb{N} \}. \]

To obtain each conditional probability density function by solving the corresponding convex optimization problem on the state space of interest, we use the CVX toolbox of the MATLAB [24]. When the size of \( \Omega \) is very high, the dimensionality of the optimization problem increases. Therefore, the CVX cannot produce accurate results.
To keep the dimension of the optimization problems small for the CVX, we construct state space iteratively using a similar strategy to the sliding window method \([37]\). In summary, our strategy is to solve the moment equation system of the HME using an appropriate discretization method. At each discretization step, we check the marginal probabilities. If they are higher than a given threshold, then we extend the state space of the variable \(d\). This procedure continues until the time point of the interest is reached. Finally, depending on the state space of the variable \(d\), we construct a state space for the variable \(c\). Now, we can explain the details of the method.

In the first step of this construction, we define a feasible subset \(\Omega^0\) of \(\Omega\), \(\Omega^0 = D^0 \times C^0\), in which the dimension of the optimization problem is acceptable for the CVX. To avoid the problem of having \(p_0(d) = 0\), we choose an initial Poisson distribution, \(p_0(d, c)\), in the state space \(\Omega^0\) and compute the corresponding \(p_0(d), E_0[C \mid d], E_0[C^2 \mid d]\), which will be considered as the initial conditions for the moment equation of the system of the HME.

Assume that we want to obtain the conditional counting probability density at time point \(\tau > 0\). Then, we approximate the solution of the moment equation system of the HME on \([0, \tau]\) time interval using a numerical method.

We choose a discretization time step \(\Delta\) and define \(t_j = j\Delta, j = 0, 1, \ldots, J\) such that \(t_0 = 0, t_J = \tau\). As a result, we obtain subintervals \([t_j, t_{j+1})\), \(j = 0, 1, \ldots, J - 1\). Let \(p^1(d), E^1[C \mid d], E^1[C^2 \mid d]\) represent the approximate solution of the ODE system given in Equation (7.26) and \(D^0\) represents the state space of \(d\) at time point \(t_j\). To construct \(D^1\), we will solve the moment equation system of the HME using initial conditions \(p^0(d) = p_0(d), E^0[C \mid d] = E_0[C \mid d], E^0[C^2 \mid d] = E_0[C^2 \mid d]\). Then, we will obtain \(p^1(d), E^1[C \mid d], E^1[C^2 \mid d]\) values for each \(d\) variable in the state space \(D^0 = \{d : \min(D^0) \leq d \leq \max(D^0)\}\).

To extend \(D^0\), we define a threshold \(\varepsilon > 0\) and check the marginal probability \(p^1_{\max} = \max(D^0)\). If \(p^1_{\max} > \varepsilon\), then we extend \(D^0\) as follows:

\[
D^1 = \{d : \min(D^0) \leq d \leq \max(D^0) + 1\}.
\]

To approximate the solution of Equation (7.26) at time point \(t_2\), we need to initialize the system on \(D^1\). Although we know \(p^1(d), E^1[C \mid d], E^1[C^2 \mid d]\) for \(d \in D^0\), we have to impose initial conditions for \(d = \max(D^0) + 1\)

\[
p^1(\max(D^0)+1) = \frac{\sum_{d \in D^0} p^1(d)}{|D^0| + 1}, \quad E^1[C \mid \max(D^0)+1] = E^1[C \mid \max(D^0)], \quad E^1[C^2 \mid \max(D^0)+1] = E^1[C^2 \mid \max(D^0)],
\]

where \(|D^0|\) denotes the cardinality of the subset \(D^0\). We employ this procedure successively until the desired time point \(\tau\) is reached. Let \(D^*\) denote the state space of \(d\) at time point \(\tau\). Here, we must choose \(\varepsilon > 0\) such that, \(D^*\) must also be in the feasible region of the CVX. Now, we can construct the feasible state space for \(c\) denoted by \(C^*\). Since we know initial domain \(\Omega^0 = D^0 \times C^0\), we only need to obtain \((d, c)\) pairs for \(d \in D^* \setminus D^0\). Then, for a given \(\varepsilon > 0\), we construct the feasible region \(C^*\) for variable \(c\) as follows:

\[
C^* = C^0 \cup C \quad \text{with} \quad C = \bigcup_{d \in D^* \setminus D^0} C_d,
\]

where

\[
C_d = \{c : max(min(C^0) - c\sigma, 0) \leq c \leq max(C^0) + c\sigma) \land y_1(0) - 2d + c \geq 0 \land y_2(0) + 2d - c \geq 0 \land d \in D^* \setminus D^0\},
\]

where \(\sigma = \sqrt{E^1[C^2 \mid d]}\). Here \(max(C^0)\) and \(min(C^0)\) denote the maximum and the minimum values of \(c\) of pairs \((c, max(D^0))\) \(\in \Omega^0\), respectively. As a result, we have a feasible region \(\Omega^* = D^* \times C^*\) for the CVX. Then, we can solve the corresponding convex optimization problems for each conditional counting probability density \(p_r(c \mid d), d \in D^*\) using the CVX. Finally, we can compute the approximate solution of \(p_r(d, c)\). The resulting algorithm is presented in Algorithm 4.

In our numerical simulation study, the state of the system is initialized \(y(0) = (50, 0)^T\) and the reaction rate constants of \(R_1, R_2\) are given by \(k_1 = 0.2s^{-1}, k_2 = 0.4s^{-1}\), respectively. We define

\[
\Omega = \{((d, c) : 50 - 2d + c \geq 0, 2d - c \geq 0, d, c \in \{0, 1, 2, \ldots, 30\}\}. \]

The initial state space \(\Omega^0\) is

\[
\Omega^0 = \{(d, c) \in \Omega : (d, c) \in \{0, 1, 2, \ldots, 8\}\}.
\]
AlGORITHM 1: Constructing feasible region for the CVX

Input: The state vector $Y$, the error bound $\varepsilon$, a discretization time step $\Delta$, stoichiometric vectors $\mu_1^D$, $\mu_2^C$, the initial domain $\Omega^0 = D^0 \times C^0, D^0, C^0 \subset \mathbb{N}_0$, end of the simulation time $\tau > 0$.

Output: The conditional probability at time point $\tau$, $p_\tau(c \mid d)$.

1. Set $t = 0$.
2. Calculate $p_0(d), E_0[C \mid d], E_0[C^2 \mid d]$ on domain $\Omega^0$ by using a Poisson distribution.
3. Set $J = \frac{\tau}{\Delta}$ and define $t_j = j\Delta$, $j = 0, 1, \ldots, J$.
4. Set $p_0(d) \equiv p_0(d), E_0[C \mid d] \equiv E_0[C \mid d], E_0[C^2 \mid d] \equiv E_0[C^2 \mid d]$.
5. for $j = 1, 2, \ldots, J$ do
   6. Solve moment equation of the HME by using any discretization based numerical method and obtain $p^j(d)$, $E^j[C \mid d], E^j[C^2 \mid d]$ for $d \in D^j$.
   7. if $p^j(\max(D^j)) > \varepsilon$ then
      8. Set $D^{j+1} = D^j \cup \{\max(D^j) + 1\}$
      9. Set $p^j(d) = p^j(d)$ for $d \in D^j$.
      10. Define $p^j(\max(D^j) + 1) = \frac{\sum_{d \in D^{j+1}} p^j(d)}{\sum_{d \in D^j} p^j(d)}$, $E^j[C \mid \max(D^j) + 1] = E^j[C \mid \max(D^j)]$, $E^j[C^2 \mid \max(D^j) + 1] = E^j[C^2 \mid \max(D^j)]$.
   11. end
12. Set $D^* = D^J$.
13. Set $C^* = C^0$.
14. for $d \in D^* \setminus D^0$ do
   15. Obtain
      \[ C_d = \left\{ c : \max(\min(C^0) - \varepsilon, 0) \leq c \leq \max(C^0) + \varepsilon \right\} \]
   16. $C^* = C^* \cup C_d$
17. end
18. For each $d \in D^*$ obtain $p_\tau(c \mid d)$ using the CVX.

In Figures 1a and 2a, one can see the state space $\Omega$ shown by the points with only green markers and $\Omega^0$ shown by the points with black edged markers. The threshold for extending the region of the variable $d$ is $\varepsilon = 10^{-6}$, and $\varepsilon = 2$. We obtain joint counting probability density function at time points $\tau = 0.5$ and $\tau = 1$. We have used the Euler method with fixed time step $\Delta = 10^{-4}$. Figures 1a and 2a also show the $\Omega^*$ at time points $\tau = 0.5$ and $\tau = 1$, respectively. In both figures, the state space $\Omega^*$ is the union of the points denoted by markers with black and red edges. Figures 1b and 2b show the joint counting probability satisfying the CME given in Equation 7.23 at time points $\tau = 0.5$ and $\tau = 1$, respectively. Figures 1c and 2c indicate the approximate solution of the $p_\tau(d, c)$ satisfying Equation 7.24 obtained with Algorithm1 at time points $\tau = 0.5$ and $\tau = 1$, respectively.

8 Conclusion

In this study, we present the hybrid master equation for jump-diffusion approximation, which models systems with multi-scale nature. The idea of jump diffusion approximation is to separate reactions into fast and slow groups based on an obtained error bound. Fast reactions are modeled using diffusion approximation, while Markov chain representation is employed for slow reactions. As a result, the state vector of the system is defined as the summation of the random time change model and the solution of the Langevin equation. In this study, based on the study of Pawula [32], we prove that joint probability density of this hybrid model over reaction counting process satisfies the hybrid master equation, which is the summation of the corresponding chemical master equation and the Fokker-Planck equation. It can be said that while [16] presents a state vector representation for reaction networks with multi-scale nature, the
current study complements it by obtaining evolution equation for the corresponding joint probability density over reaction counting process. To solve this equation, we use the same strategy with [26]. We write the joint probability density function as the product of the conditional counting probability density of the fast reactions conditioned on the counting process of the slow reactions and the marginal probability of the counting process of the slow reactions. To construct the conditional probability density functions at a specific time point, we used the maximum entropy approach. We use the CVX toolbox of the MATLAB to solve the constrained optimization problems. Based on restrictions of the CVX on the dimensionality of the optimization problems, we present a method which constructs feasible regions for the CVX. We apply the method to a gene model.

A Appendix

A.1 Proof of Lemma 5.1

Proof. Using Leibniz integral rule and the boundary conditions gives

$$\frac{\partial}{\partial t}(E_t[F_i(C) \mid d]p_t(d)) = \frac{\partial}{\partial t}\left( \int_{R^R_{\geq 0}} F_t(c)p_t(c \mid d)p_t(d) dc \right) = \int_{R^R_{\geq 0}} F_t(c) \frac{\partial}{\partial t}p_t(d,c) dc + \int_{R^R_{\geq 0}} p_t(d,c) \frac{\partial}{\partial t}F_t(c) dc$$
Inserting Equation (4.17) into the first integral yields
\[
\frac{\partial}{\partial t}(E_t[F_t(C) \ | \ d]p_t(d)) = \int_{\mathbb{R}_{>0}^L} F_t(c) \sum_{i \in D} \kappa_i \prod_{s=1}^{M} \beta_s^n(d - \bar{c}_i) \gamma^{\tau_{s_i-n}(c)} p_t(d - \bar{c}_i, c) - \beta^n_s(d) \gamma^{\tau_{s_i-n}(c)} p_t(d, c) \, dc \\
- \int_{\mathbb{R}_{>0}^L} F_t(c) \sum_{j \in C} \frac{\partial}{\partial c_j} \left( \kappa_j \prod_{s=1}^{M} \beta_s^n(d) \gamma^{\tau_{s_j-n}(c)} p_t(d, c) \right) \, dc \\
+ \frac{1}{2} \sum_{j \in C} \kappa_j \prod_{s=1}^{M} \beta_s^n(d) \gamma^{\tau_{s_j-n}(c)} p_t(d, c) \, dc \\
+ \int_{\mathbb{R}_{>0}^L} p_t(d, c) \frac{\partial}{\partial t} F_t(c) \, dc.
\]

Since \( F_t(c) \) is a polynomial function and sufficiently many moments of \( p_t(d, c) \) with respect to \( c \) exist, we can manipulate the integral as follows:
\[
\frac{\partial}{\partial t}(E_t[F_t(C) \ | \ d]p_t(d)) = \sum_{i \in D} \kappa_i \prod_{s=1}^{M} \beta_s^n(d - \bar{c}_i) \gamma^{\tau_{s_i-n}(c)} p_t(d - \bar{c}_i, c) - \beta^n_s(d) \gamma^{\tau_{s_i-n}(c)} p_t(d, c) \, dc \\
- \sum_{j \in C} \kappa_j \prod_{s=1}^{M} \beta_s^n(d) \gamma^{\tau_{s_j-n}(c)} p_t(d, c) \, dc \\
+ \frac{1}{2} \sum_{j \in C} \kappa_j \prod_{s=1}^{M} \beta_s^n(d) \gamma^{\tau_{s_j-n}(c)} p_t(d, c) \, dc \\
+ \int_{\mathbb{R}_{>0}^L} p_t(d, c) \frac{\partial}{\partial t} F_t(c) \, dc.
\]

Here, we want to draw the attention of the reader to the following mean which is used in our equations
\[
E_t[F_t(C) \gamma^{\tau_{s_j-n}(C)} \beta_s(d) \ | \ d] = \int_{\mathbb{R}_{>0}^L} F_t(c) \gamma^{\tau_{s_j-n}(C)} \beta_s(d) p_t(c \ | \ d) \, dc = \beta_s(d) E_t[F_t(C) \gamma^{\tau_{s_j-n}(C)} \beta_s(d) \ | \ d].
\]

Using this equality and the properties of the FPE will give us the following equation [33]:
\[
\frac{\partial}{\partial t}(E_t[F_t(C) \ | \ d]p_t(d)) = \sum_{i \in D} \kappa_i \prod_{s=1}^{M} E_t[F_t(C) \gamma^{\tau_{s_i-n}(C)} \ | \ d - \bar{c}_i] \beta_s^n(d - \bar{c}_i) p_t(d - \bar{c}_i) - E_t[F_t(C) \gamma^{\tau_{s_i-n}(C)} \ | \ d] \beta^n_s(d) p_t(d) \\
+ \sum_{j \in C} \kappa_j \prod_{s=1}^{M} E_t[\gamma^{\tau_{s_j-n}(C)} \frac{\partial}{\partial c_j} F_t(C) \ | \ d] p_t(d) \\
+ \frac{1}{2} \sum_{j \in C} \kappa_j \prod_{s=1}^{M} E_t[\gamma^{\tau_{s_j-n}(C)} \frac{\partial^2}{\partial c_j^2} F_t(C) \ | \ d] p_t(d) \\
+ E_t[\frac{\partial}{\partial t} F_t(C) \ | \ d] p_t(d).
\]

Define
\[
\bar{\Gamma}(\beta(d), F_t(c) \gamma(c)) = \sum_{i \in D} (F^{-\bar{c}_i} - I) \left( \kappa_i \prod_{s=1}^{M} \beta_s^n(d) E_t[F_t(C) \gamma^{\tau_{s_i-n}(C)} \ | \ d] \right) \\
+ \sum_{j \in C} \kappa_j \prod_{s=1}^{M} \beta_s^n(d) E_t[\gamma^{\tau_{s_j-n}(C)} \frac{\partial}{\partial c_j} F_t(C) \ | \ d] + \frac{1}{2} \sum_{j \in C} \kappa_j \prod_{s=1}^{M} E_t[\gamma^{\tau_{s_j-n}(C)} \frac{\partial^2}{\partial c_j^2} F_t(C) \ | \ d] \\
+ E_t[\frac{\partial}{\partial t} F_t(C) \ | \ d] p_t(d).
\]

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Then, we obtain
\[
\frac{\partial}{\partial t} \left( E_t[F_t(C) \mid d]p_t(d) \right) = \tilde{\Gamma}(\beta(d), F_t(c)\gamma(c))p_t(d) + E_t\left[ \frac{\partial}{\partial t} F_t(C) \mid d \right]p_t(d)
\]
which completes the proof.

\[\]

### A.2 Mean of the propensity functions

To express \( E_t[\gamma_{s^i}^{\gamma_{s^j}}(C) \mid d] \) in terms of \( E_t[C_m \mid d], E_t[\tilde{C}^{M} \mid d] \), we will use the Taylor series expansion of \( \gamma_{s^i}^{\gamma_{s^j}}(C) \) around \( E_t[C \mid d] \). The Taylor polynomial of degree \( q \) for \( \gamma_{s^i}^{\gamma_{s^j}}(C) \) around \( E_t[C \mid d] \) has the following form
\[
G_q(c) = \sum_{k_1, \ldots, k_R \leq q} \frac{\partial^{k_1} \cdots \partial^{k_R-L}}{k_1! \cdots k_R!} \gamma_{s^i}^{\gamma_{s^j}}(E_t[C \mid d]) (c_{k_1} - E_t[C_{k_1} \mid d])^{k_1} \cdots (c_{k_R-L} - E_t[C_{k_R-L} \mid d])^{k_R-L},
\]
where \( \partial^j = \frac{\partial}{\partial c_j} \), \( e_{k, \ell} \in \{1, \ldots, k_R - L \} \). In general cellular reactions are unimolecular or bimolecular. Therefore, the third and the higher order derivatives will be zero, meaning that the conditional mean of the function \( \gamma_{s^i}^{\gamma_{s^j}}(C) \) satisfies \[26\]
\[
E_t[\gamma_{s^i}^{\gamma_{s^j}}(C) \mid d] = \gamma_{s^i}^{\gamma_{s^j}}(E_t[C \mid d]) + \frac{1}{2} \sum_{k_1, \ldots, k_R \leq q} \frac{\partial^{2}}{\partial c_k \partial c_{\ell}} \gamma_{s^i}^{\gamma_{s^j}}(E_t[C \mid d]) E_t[\tilde{C}^{\kappa + \epsilon_k} \mid d].
\]
(1.28)

Here, we use the fact that \( E_t[C_{s_i} - E_t[C_i] \mid d] = 0 \), \( i \in C \). As a result, if we have a reaction with linear propensity, the second term in Equation (1.28) will also be zero and we will get \( E_t[\gamma_{s^i}^{\gamma_{s^j}}(C) \mid d] = \gamma_{s^i}^{\gamma_{s^j}}(E_t[C \mid d]) \).

### A.3 Proof of Proposition 5.3

**Proof.** We will use the product rule for derivatives as follows:
\[
p_t(d) \frac{\partial}{\partial t} E_t[C_m \mid d] = \frac{\partial}{\partial t} \left( E_t[C_m \mid d]p_t(d) \right) - E_t[C_m \mid d] \frac{\partial}{\partial t} p_t(d).
\]
(1.29)

By setting \( F_t(c) = c_m \) in Lemma 5.1, we can obtain the first derivative on the right hand-side of Equation (1.29) as follows:
\[
\frac{\partial}{\partial t} \left( E_t[C_m \mid d]p_t(d) \right) = \tilde{\Gamma}(\beta(d), c_m \gamma(c))p_t(d) + E_t\left[ \frac{\partial}{\partial t} C_m \mid d \right]p_t(d).
\]

By using equalities \( \frac{\partial}{\partial C_j} C_m = 0 \), \( \frac{\partial^2}{\partial c_j^2} C_m = 0 \), we get
\[
p_t(d) \frac{\partial}{\partial t} E_t[C_m \mid d] = \sum_{i \in D} (\mathcal{F}^{-\tilde{E}_i} - I) \left( \kappa_i \prod_{s=1}^M \sum_{n=0}^{r_s} \beta^s_n(d) E_t[C_m \gamma_{s^i}^{\gamma_{s^j}}(C) \mid d]p_t(d) \right)
\]
\[
+ \sum_{j \in C} \kappa_j \prod_{s=1}^M \sum_{n=0}^{r_s} \beta^s_n(d) E_t[\gamma_{s^j}^{\gamma_{s^j}}(C) \delta_{jm} \mid d]p_t(d) = E_t[C_m \mid d] \frac{\partial}{\partial t} p_t(d),
\]
where \( \delta_{jm} \) is the Kronecker delta function.

In Equation (5.20), we have the conditional mean \( E_t[\gamma_{s^j}^{\gamma_{s^j}}(C) \mid d] \) term to and from \( E_t[C_m \gamma_{s^i}^{\gamma_{s^j}}(C) \mid d] \), which must also be formulated in terms of the conditional means \( E_t[C_m \mid d], m \in C \), and the centered conditional moments \( E_t[\tilde{C}^{M} \mid d] \). To achieve this goal, we will add and subtract \( E_t[C_m \mid d] \) term to and from \( E_t[C_m \gamma_{s^i}^{\gamma_{s^j}}(C) \mid d] \) as follows [26]:
\[
E_t[C_m \gamma_{s^i}^{\gamma_{s^j}}(C) \mid d] = E_t[(C_m - E_t[C_m \mid d]) \gamma_{s^i}^{\gamma_{s^j}}(C) \mid d] + E_t[C_m \mid d] \gamma_{s^i}^{\gamma_{s^j}}(C) \mid d] = E_t[\tilde{C}^{\kappa m} \gamma_{s^i}^{\gamma_{s^j}}(C) \mid d] + E_t[C_m \mid d] E_t[\gamma_{s^i}^{\gamma_{s^j}}(C) \mid d].
\]
Similarly, adding and subtracting \( E_t[c_m \mid d - \bar{e}_i] \) terms to and from \( E_t[C_m\gamma_s^{r_{si} - n}(C) \mid d - \bar{e}_i] \) will produce
\[
E_t[C_m\gamma_s^{r_{si} - n}(C) \mid d - \bar{e}_i] = E_t[(C_m - E_t[C_m \mid d - \bar{e}_i])\gamma_s^{r_{si} - n}(C) \mid d - \bar{e}_i]
\]
\[
= E_t[\tilde{\Psi} \gamma_s^{r_{si} - n}(C) \mid d - \bar{e}_i] + E_t[(C_m - \bar{e}_i)\gamma_s^{r_{si} - n}(C) \mid d - \bar{e}_i],
\]
where \( \tilde{\Psi} = c - E_t[C \mid d - \bar{e}_i] \) and for \( M \in \mathbb{N}^{R-L} \), \( \tilde{\Psi}^M = \prod_{j \in C} \tilde{\Psi}_j^M \). Inserting the obtained \( E_t[C_m\gamma_s^{r_{si} - n}(C) \mid d] \) and \( E_t[C_m\gamma_s^{r_{si} - n}(C) \mid d - \bar{e}_i] \) values into Equation (5.20) will give us the following equation
\[
p_t(d) \frac{\partial}{\partial t} E_t[C_m \mid d] = \sum_{j \in D} \sum_{s=1}^{M_r} \sum_{n=0}^{r_s} \kappa_j \left( E_t[\tilde{\Psi} \gamma_s^{r_{si} - n}(C) \mid d - \bar{e}_i] + E_t[C_m \mid d - \bar{e}_i]E_t[\gamma_s^{r_{si} - n}(C) \mid d - \bar{e}_i] \right) \beta_s^n (d - \bar{e}_i) p_t(d - \bar{e}_i)
\]
\[
- \sum_{j \in D} \sum_{s=1}^{M_r} \sum_{n=0}^{r_s} \kappa_j \left( E_t[\tilde{\Psi} \gamma_s^{r_{si} - n}(C) \mid d] + E_t[C_m \mid d]E_t[\gamma_s^{r_{si} - n}(C) \mid d] \right) \beta_s^n (d) p_t(d)
\]
\[
+ \sum_{j \in D} \sum_{s=1}^{M_r} \sum_{n=0}^{r_s} \left( E_t[\gamma_s^{r_{si} - n}(C) \mid d] \right) \delta_{jm} \left( d \right) \beta_s^n (d) p_t(d) - E_t[C_m \mid d] \frac{\partial}{\partial t} p_t(d).
\]

As mentioned before, the Taylor series expansion of \( \gamma_s^{r_{si} - n}(C) \) around \( E_t[C \mid d] \) will give us the possibility to reformulate \( E_t[\tilde{\Psi} \gamma_s^{r_{si} - n}(C) \mid d] \) using the conditional means and the centered conditional moments. Here, we must reformulate \( E_t[\tilde{\Psi} \gamma_s^{r_{si} - n}(C) \mid d] \) and \( E_t[\tilde{\Psi} \gamma_s^{r_{si} - n}(C) \mid d - \bar{e}_i] \) using the corresponding conditional means and the centered moments. To do this, we will use the Taylor expansion given in Equation (1.27) as follows:
\[
E_t[\tilde{\Psi} \gamma_s^{r_{si} - n}(C) \mid d] = \gamma_s^{r_{si} - n}(E_t[C \mid d])E_t[\tilde{\Psi} M \mid d] + \sum_{k \in c} \frac{\partial}{\partial c_k} \gamma_s^{r_{si} - n}(E_t[C \mid d])E_t[\tilde{\Psi} M + e_k \mid d]
\]
\[
+ \frac{1}{2} \sum_{k \in c} \frac{\partial^2}{\partial c_k \partial c_k} \gamma_s^{r_{si} - n}(E_t[C \mid d])E_t[\tilde{\Psi} M + e_k + e_k \mid d],
\]
where \( M = (M_1, M_2, \ldots, M_{R-L})^T \in \mathbb{N}^{R-L} \). It is clear that \( E_t[\tilde{\Psi} \gamma_s^{r_{si} - n}(C) \mid d - \bar{e}_i] \) can also be reformulated by using the Taylor expansion of \( \gamma_s^{r_{si} - n}(C) \) around \( E_t[C \mid d - \bar{e}_i] \). Substitution of the new representations of \( E_t[\tilde{\Psi} \gamma_s^{r_{si} - n}(C) \mid d] \) and \( E_t[\tilde{\Psi} \gamma_s^{r_{si} - n}(C) \mid d - \bar{e}_i] \), which only depend on the conditional means and the centered conditional moments conditioned on the corresponding discrete variable into Equation (5.20) will produce
\[
p_t(d) \frac{\partial}{\partial t} E_t[C_m \mid d] \]
in terms of the marginal probabilities, the conditional means and the centered conditional moments.

### A.4 Proof of Proposition 5.4

**Proof.** Similar to our previous proofs, again we will use the product rule for derivatives as follows:
\[
p_t(d) \frac{\partial}{\partial t} E_t[\tilde{\Psi} M \mid d] = \frac{\partial}{\partial t} \left( E_t[\tilde{\Psi} M \mid d]p_t(d) \right) - E_t[\tilde{\Psi} M \mid d] \frac{\partial}{\partial t} p_t(d).
\]
The first term in the right-hand-side of the equation above can be obtained from Lemma 5.1 choosing \( F(c) = \tilde{\Psi} M \).
Then, we obtain
\[
\frac{\partial}{\partial t} \left( E_t[\tilde{\Psi} M \mid d]p_t(d) \right) = \tilde{\Gamma} (\beta(d), \tilde{\Psi} M, \gamma(c)) p_t(d) + E_t[\frac{\partial}{\partial t} \tilde{\Psi} M \mid d] p_t(d).
\]
Since, we have
\[
\frac{\partial}{\partial c_i} \tilde{\Psi} M = \frac{\partial}{\partial c_i} \left( \prod_{k \in C} (c_k - E_t[C_k \mid d])^M_k \right) = M_i \tilde{\Psi} M - e_i
\]
\[
\frac{\partial^2}{\partial c_i \partial c_j} \tilde{\Psi} M = \frac{\partial^2}{\partial c_i \partial c_j} \left( \prod_{k \in C} (c_k - E_t[C_k])^M_k \right) = M_j (M_j - 1) \tilde{\Psi} M - 2\epsilon_j
\]
\[
E_t[\frac{\partial}{\partial t} \tilde{\Psi} M \mid d] = - \sum_{j \in C} M_j E_t[\tilde{\Psi} M - e_j \mid d] p_t(d) \frac{\partial}{\partial t} E_t[C_j \mid d].
\]
We get
\[ p_t(d) \frac{\partial}{\partial t} E_t[\widetilde{C}^M | d] = \sum_{\iota \in D} \kappa_\iota \prod_{s=1}^M \sum_{n=0}^{r_{s\iota}} \left( \beta^n_t(d - \bar{e}_i) E_t[\widetilde{C}^M \gamma_{s\iota}^{r_{s\iota}-n}(C) | d - \bar{e}_i] p_t(d - \bar{e}_i) - \beta^n_t(d) E_t[\widetilde{C}^M \gamma_{s\iota}^{r_{s\iota}-n}(C) | d] p_t(d) \right) \]
\[ + \sum_{j \in C} \kappa_j \prod_{s=1}^M \sum_{n=0}^{r_{s\iota}} \beta^n_t(d) E_t[M_j \gamma_{s\iota}^{r_{s\iota}-n}(C) \widetilde{C}^M-e_j | d] p_t(d) \]
\[ + \frac{1}{2} \sum_{j \in C} \kappa_j \prod_{s=1}^M \sum_{n=0}^{r_{s\iota}} \beta^n_t(d) E_t[M_j (M_j - 1) \gamma_{s\iota}^{r_{s\iota}-n}(C) \widetilde{C}^M-2e_j | d] p_t(d) \]
\[ - \sum_{j \in C} M_j E_t[\widetilde{C}^M-e_j | d] p_t(d) \frac{\partial}{\partial t} E_t[C_j | d] - E_t[\widetilde{C}^M | d] \frac{\partial}{\partial t} p_t(d). \]

As a result, we obtain
\[ p_t(d) \frac{\partial}{\partial t} E_t[\widetilde{C}^M | d] = \sum_{\iota \in D} (\mathcal{F} - \bar{e}_i - I) \left( \kappa_\iota \prod_{s=1}^M \sum_{n=0}^{r_{s\iota}} \beta^n_t(d) E_t[\widetilde{C}^M \gamma_{s\iota}^{r_{s\iota}-n}(C) | d] p_t(d) \right) \]
\[ + \sum_{j \in C} \kappa_j \prod_{s=1}^M \sum_{n=0}^{r_{s\iota}} \beta^n_t(d) E_t[M_j \gamma_{s\iota}^{r_{s\iota}-n}(C) \widetilde{C}^M-e_j | d] p_t(d) \]
\[ + \frac{1}{2} \sum_{j \in C} \kappa_j \prod_{s=1}^M \sum_{n=0}^{r_{s\iota}} \beta^n_t(d) E_t[M_j (M_j - 1) \gamma_{s\iota}^{r_{s\iota}-n}(C) \widetilde{C}^M-2e_j | d] p_t(d) \]
\[ - \sum_{j \in C} M_j E_t[\widetilde{C}^M-e_j | d] p_t(d) \frac{\partial}{\partial t} E_t[C_j | d] - E_t[\widetilde{C}^M | d] \frac{\partial}{\partial t} p_t(d), \]
which completes our proof. \( \square \)

To formulate the right hand-side of Equation (5.21) in terms of the marginal probabilities, the conditional means and the centered conditional moments, we must restate \( E_t[\widetilde{C}^M \gamma_{s\iota}^{r_{s\iota}-n}(C) | d - \bar{e}_i] \), \( E_t[\widetilde{C}^M \gamma_{s\iota}^{r_{s\iota}-n}(C) | d] \) terms using these terms. \( E_t[\widetilde{C}^M \gamma_{s\iota}^{r_{s\iota}-n}(C) | d] \), \( E_t[M_j \gamma_{s\iota}^{r_{s\iota}-n}(C) \widetilde{C}^M-e_j | d] \), \( E_t[M_j (M_j - 1) \gamma_{s\iota}^{r_{s\iota}-n}(C) \widetilde{C}^M-2e_j | d] \) can be expressed utilizing the corresponding Taylor series expansion given in Equation (1.31). To express \( E_t[\widetilde{C}^M \gamma_{s\iota}^{r_{s\iota}-n}(C) | d - \bar{e}_i] \) in terms of the marginal probabilities, the conditional means and the centered conditional moments, we will add and subtract \( E_t[C | d - \bar{e}_i] \) to and from \( \widetilde{C}^M \) as follows:
\[ \widetilde{C}^M = (c - E_t[C | d])^M = (c - E_t[C | d - \bar{e}_i] + E_t[C | d - \bar{e}_i] - E_t[C | d])^M \]
\[ = \sum_{0 \leq k \leq M} \binom{M}{k} (E_t[C | d - \bar{e}_i] - E_t[C | d])^{M-k} \bar{\psi}^k. \]

Then, we obtain
\[ E[\widetilde{C}^M \gamma_{s\iota}^{r_{s\iota}-n}(C) | d - \bar{e}_i] = \sum_{0 \leq k \leq M} \binom{M}{k} (E_t[C | d - \bar{e}_i] - E_t[C | d])^{M-k} E[\bar{\psi}^k \gamma_{s\iota}^{r_{s\iota}-n}(C) | d - \bar{e}_i]. \]

Using the Taylor series expansion of \( \gamma_{s\iota}^{r_{s\iota}-n}(C) \) around \( E_t[C | d - \bar{e}_i] \) gives us the corresponding Taylor series representation for \( E_t[\bar{\psi}^k \gamma_{s\iota}^{r_{s\iota}-n}(C) | d - \bar{e}_i] \). As a result, we can obtain the right hand-side of Equation (5.21) in terms of the marginal probabilities, the conditional means and the centered moments.

References

[1] R. V. Abramov. The multidimensional maximum entropy moment problem: a review of numerical methods. Communications in Mathematical Sciences, 8(2):377–392, 2010.
[2] D. F. Anderson and T. G. Kurtz. Continuous time Markov chain models for chemical reaction networks. In H. Koeppl, Gianluca Setti, Mario di Bernardo, and Douglas Densmore, editors, Design and Analysis of Biomolecular Circuits. Springer-Verlag, 2011.

[3] A. Andreychenko, L. Mikeev, and V. Wolf. Model reconstruction for moment-based stochastic chemical kinetics. ACM Trans. Model. Comput. Simul., 25(2), 2015.

[4] S. Boyd and L. Vandenberghe. Convex Optimization. Cambridge University Press, 2004.

[5] G. L. Bretthorst. The maximum entropy method of moments and bayesian probability theory. AIP Conf. Proc., 1553:3–15, 2013.

[6] L. Cardelli, M. Kwiatkowska, and L. Laurenti. A stochastic hybrid approximation for chemical kinetics based on the linear noise approximation. In CMSB, Lecture Notes in Computer Science, pages 147–167. Springer, 2016.

[7] A. Chevallier and S. Engblom. Pathwise error bounds in multiscale variable splitting methods for spatial stochastic kinetics. SIAM J. NUMER. ANAL., 58(1):469–498, 2018.

[8] A. Crudu, A. Debussche, and O. Radulescu. Hybrid stochastic simplifications for multiscale gene networks. BMC Systems Biology, 3(89), 2009.

[9] B. Cseke, D. Schnoerr, M. Opper, and G. Sanguinetti. Expectation propagation for continuous time stochastic processes. Journal of Physics A: Mathematical and Theoretical, 49(49), 2016.

[10] A. Duncan, R. Erban, and K. Zygalakis. Hybrid framework for the simulation of stochastic chemical kinetics. Journal of Computational Physics, 326, 2016.

[11] A. Eldar and M. B. Elowitz. Functional roles for noise in genetic circuits. Nature, 467:167–173, 2010.

[12] S. Engblom. Computing the moments of high dimensional solutions of the master equation. Applied Mathematics and Computation, 180:498–515, 2006.

[13] S. Engblom, A. Hellander, and P. Lötstedt. Multiscale Simulation of Stochastic Reaction-Diffusion Networks, pages 55–79. Stochastic Processes, Multiscale Modeling, and Numerical Methods for Computational Cellular Biology. Springer, 2017.

[14] N. Fedoroff and W. Fontana. Small numbers of big molecules. Science, 297, 2002.

[15] N. Friedman, L. Cai, and X.S. Xie. Stochasticity in gene expression as observed by single-molecule experiments in live cells. Israel Journal of Chemistry, 49:333–342, 2010.

[16] A. Ganguly, D. Altintan, and H. Koeppl. Jump-diffusion approximation of stochastic reaction dynamics: Error bounds and algorithms. Multiscale Model. Simul., 13(4):1390–1419, 2015.

[17] M.A. Gibson and J. Bruck. Efficient exact stochastic simulation of chemical systems with many species and many channels. The Journal of Physical Chemistry A, 104(9):1876–1889, 2000.

[18] D. T. Gillespie. A general method for numerically simulating the stochastic time evolution of coupled chemical reactions. J. Comput. Phys., 22:403–434, 1976.

[19] D. T. Gillespie. Approximating the master equation by Fokker-Planck type equations for singlevariable chemical systems. The Journal of Chemical Physics, 72(5363), 1980.

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

[21] D. T. Gillespie. The chemical Langevin and Fokker-Planck equations for the reversible isomerization reaction. J. Phys. Chem. A, 106:5063–5071, 2002.

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

[23] D.T. Gillespie. A rigorous derivation of the chemical master equation. Physica A, 188:404–425, 1992.

20
[24] M. Grant and S. Boyd. CVX: Matlab software for disciplined convex programming, version 2.1, March 2014.

[25] R. Grima, P. Thomas, and A. V. Straube. How accurate are the nonlinear chemical Fokker-Planck and chemical Langevin equations? *Journal of Chemical Physics*, 135(8), 2011.

[26] J. Hasenauer, V. Wolf, A. Kazeroonian, and F. J. Theis. Method of conditional moments (MCM) for the chemical master equation : A unified framework for the method of moments and hybrid stochastic-deterministic models. *J. Math. Biol.*, 69(3):687–735, 2014.

[27] T. Jahnke. On reduced models for the chemical master equation. *Multiscale Model. Simul.*, 9(4):1646–1676, 2011.

[28] N. G. van Kampen. The diffusion approximation for Markov process. In *Thermodynamics and Kinetics of Biological Processes*, pages 185–195. Walter de Gruyter and Co., 1982.

[29] Thomas G. Kurtz. Strong approximation theorems for density dependent Markov chains. *Stochast. Process. Appl.*, 6(3):177–191, 1978.

[30] C. H. Lee, K. H. Kim, and P. Kim. A moment closure method for stochastic reaction networks. *The Journal of Chemical Physics*, 130:134107, 2009.

[31] D. L. Otten and P. Vedula. A quadrature based method of moments for nonlinear Fokker-Planck equations. *Journal of Statistical Mechanics: Theory and Experiment*, 2011(9), 2011.

[32] R. F. Pawula. Generalizations and extensions of the Fokker-Planck Kolmogorov equations. *IEEE Transactions on Information Theory*, 13(1), 1967.

[33] H. Risken and H. Haken. *The Fokker-Planck Equation: Methods of Solution and Applications Second Edition*. Springer, 1989.

[34] C. E. Shannon. A mathematical theory of communication. *The Bell System Technical Journal*, 27:379–423, 1948.

[35] A. Singh and J. P. Hespanha. Approximate moment dynamics for chemically reacting systems. *IEEE Trans. on Automat. Contr.*, 56(2):414–418, 2011.

[36] D.J. Wilkinson. *Stochastic modelling for systems biology*. Chapman & Hall/CRC mathematical and computational biology series. Boca Raton, FL : Taylor & Francis, 2006.

[37] V. Wolf, R. Goel, M. Mateescu, and T. A. Henzinger. Solving the chemical master equation using sliding windows. *BMC Systems Biology*, 4, 2010.