Stochastic filters based on hybrid approximations of multiscale stochastic reaction networks

Zhou Fang, Ankit Gupta, and Mustafa Khammash

Abstract—We consider the problem of estimating the dynamic latent states of an intracellular multiscale stochastic reaction network from time-course measurements of fluorescent reporters. We first prove that accurate solutions to the filtering problem can be constructed by solving the filtering problem for a reduced model that represents the dynamics as a hybrid process. The model reduction is based on exploiting the time-scale separations in the original network, and it can greatly reduce the computational effort required to simulate the dynamics. This enables us to develop efficient particle filters to solve the filtering problem for the original model by applying particle filters to the reduced model. We illustrate the accuracy and the computational efficiency of our approach using a numerical example.

I. INTRODUCTION

In the past few decades, scientists’ ability to look into the dynamic behaviors of a living cell has been greatly improved by the fast development of fluorescent technologies and advances in microscopic techniques. Despite this big success, light intensity signals observed in a microscope can only report the dynamics of a small number of key components in a cell, such as fluorescent proteins and mRNAs, and, therefore, leave other dynamic states of interest, e.g., gene (on/off) state, indirectly observable. As a result, it is urgent to build efficient stochastic filters to estimate latent states of intracellular biochemical reaction systems from these partial observations.

Although it is possible to solve the filtering (and inference) problem accurately for intracellular systems with particle filters (see [1] for particle filters), the required computational effort to simulate the system in the sampling step usually prevents it from being used on-line due to the high complexity of practical models. Motivated by this obstacle, some methods are proposed to obtain computationally efficient filters by approximating the underlying Markov jump process by a diffusion process [2], [3], [4] or a block model [5]. All these methods are shown to be efficient for broad classes of bio-chemical reaction systems, however, their drawbacks are also clear — the diffusion process strategy loses its validity in low copy number scenarios, and the block model methodology may not work well for highly interconnected nonlinear biological circuits. Unfortunately, some reaction systems involve species with low copy numbers and densely interconnected biological circuits, which precludes the utilization of previous methods to these systems and require researchers to build new solutions.

In this paper, we propose another strategy to obtain efficient particle filters based on hybrid approximations of multiscale stochastic reaction networks. Specifically, the model reduction technique introduced in [6] is applied to approximating the underlying stochastic reaction system by a piecewise deterministic model, which can greatly reduce the computational effort required to simulate the system. Also, we prove that the solution to the filtering problem for the original system can be constructed by solving the filtering problem for the reduced model if some mild conditions are satisfied. Both of these facts enable us to develop efficient particle filters to solve the filtering problem for the original model by applying particle filters to the reduced model.

It is worth noting that the idea of applying time-scale separation techniques to reduce underlying models to make particle filters computationally feasible has already been proposed in [7], [8], [9] for diffusion type stochastic models, and its efficiency is proven in the literature [10]. Compared with these works, our paper considers a different type of underlying model, the Markov jump process, and provides a much-simplified proof for the convergence of the approximate filters. All these references and our paper show the efficiency of applying the time-scale separation technique to the filtering problem for multiscale systems.

The rest of this paper is organized as follows. In Section II we introduce some basic notations and review the chemical reaction network theory and the filtering theory. In Section III we present our main results. We first prove that the accurate solution to the filtering problem can be accurately approximated by the solution to the filtering problem for the reduced model under some mild condition. Then, based on this result, we establish an efficient particle filter to solve the filtering problem for the original model by applying the particle filter to the reduced model. For the sake of readability, we put the proof of our main result in the appendix. In Section IV a numerical example is presented to illustrate our approach. Finally, Section V concludes this paper.

II. PRELIMINARY

A. Notations

We first denote a natural filtered probability space by \((\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t \geq 0}, P)\), where \(\Omega\) is the sample space, \(\mathcal{F}\) is the \(\sigma\)-algebra, \(\{\mathcal{F}_t\}_{t \geq 0}\) is the filtration, and \(P\) is the natural probability. Also, we term \(\mathbb{N}_{>0}\) as the set of positive integers,
\( \mathbb{R}^n \) with \( n \) being a positive integer as the space of \( n \)-dimensional real vectors, \( \| \cdot \| \) as the Euclidean norm, \( \| \cdot \| \) as the absolute value notation, \( s \wedge t \) (for any \( s, t \in \mathbb{R} \)) as \( \min(s, t) \), and \( s \vee t \) as \( \max(s, t) \). For any positive integer \( n \) and any \( t > 0 \), we term \( \mathbb{D}_n^{n,0} = ]0, t[ \) as the Skorokhod space that consists of all \( \mathbb{R}^n \) valued cadlag functions on \( [0, t] \) and \( \mathbb{D}_n^{n, \infty} = ]0, \infty[ \) as the Skorokhod space that consists of all \( \mathbb{R}^n \) valued cadlag functions on \( [0, \infty) \).

### B. Stochastic chemical reaction networks

We consider an intracellular system undergoing reactions

\[
v_{1,j}S_1 + \cdots + v_{n,j}S_n \xrightarrow{k_j} v'_{1,j}S_1 + \cdots + v'_{n,j}S_n, \quad j = 1, \ldots, r,
\]

where \( S_i (i = 1, \ldots, n) \) are distinguished species in the systems, \( v_{i,j} \) and \( v'_{i,j} \) are non-negative integers, called stoichiometric coefficients, \( k_j \) are the reaction constants, and \( r \) is the number of reactions. Also, we name the linear combination above reaction equations can be fully represented by a triplet \( \{S, C, \mathcal{R}\} \), called a chemical reaction network [11], where

- \( S \) is the species set \( \{S_1, S_2, \ldots, S_n\} \) whose elements represent distinct substances,
- \( C \) is the complex set \( \bigcup_{j=1}^r \{v_j, v'_j\} \), where \( v_j \triangleq (v_{1,j}, \ldots, v_{n,j})^\top \) and \( v'_j \triangleq (v'_{1,j}, \ldots, v'_{n,j})^\top \), indicating substrate complexes and product complexes,
- \( \mathcal{R} \) is the reaction set \( \{v_1 \rightarrow v'_1, \ldots, v_r \rightarrow v'_r\} \) showing the connections between the complexes.

Let \( X(t) = (X_1(t), X_2(t), \ldots, X_n(t))^\top \) be the numbers of molecules of these species at time \( t \), then the system’s dynamics following mass-action kinetics can be expressed as [12]

\[
X(t) = X(0) + \sum_{j=1}^r (v'_j - v_j) R_j \left( \int_0^t \lambda_j(X(s)) ds \right)
\]

where \( R_j(t) \) (\( j = 1, \ldots, r \)) are mutually independent unit rate Poison random processes, \( \lambda_j(x) \triangleq k_j \prod_{i=1}^n \frac{x_i^{s_i}}{(x_i - v_{i,j})^{\alpha_i}} 1_{\{x \geq v_{i,j}\}} \) with \( 1\{\} \) the indicator function, and the initial condition \( X(0) \) is subject to a particular known distribution.

### C. Model reduction via the time scale separation

In a practical bio-chemical reaction system, different species can vary a lot in abundance, and rate constants can also vary over several orders of magnitude. To normalize the quantities, we term \( N \) as a scaling factor, \( \alpha_i \) (for \( i = 1, \ldots, n \)) as the magnitude of the \( i \)-th species such that \( X_i(t) \triangleq N^{-\alpha_i}X_i(t) = O(1) \), \( \beta_j \) (for \( j = 1, \ldots, r \)) as the magnitude of the reaction constant \( k_j \) such that \( k_j \triangleq k_j N^{-\beta_j} = O(1) \), \( \gamma \) as the time scale parameter, and \( X_N(t) \triangleq X(tN^\gamma) \). Then, in the new coordinate, the dynamic equation can be expressed as \[ \text{Proposition 1 (Adapted from [6]): On any finite time interval} [0, t], \text{if } X_N(t) \text{ and } X_N(t) \text{ hold, then } X_N(t) \Rightarrow X(t) \text{ in the sense of the Skorokhod topology.}

\[
X_N(t) = X_N(0) + \sum_{j=1}^r N^{-\alpha_i} (v'_j - v_j) R_j \left( \int_0^t N^{-\gamma} \lambda_j(X_N(s)) ds \right)
\]

where \( \Lambda^N = \text{diag}(N^{-\alpha_1}, \ldots, N^{-\alpha_n}) \), \( \alpha = (\alpha_1, \ldots, \alpha_n) \), \( \lambda_j^N(x) \triangleq k_j^N \prod_{i=1}^n (x_i - tN^{-\alpha_i})^{\alpha_i} \{x_i \geq N^{-\gamma} x_{i,j}\} \) are of order \( O(1) \), and \( \tilde{\beta}_j = \beta_j + v^T_j \alpha \). For this system, we denote its transition kernel by \( K_N^\gamma(x, A) \triangleq \mathbb{P}(X_N^\gamma(t) \in A | X_N^\gamma(0) = x) \).

Following the notations in [6], we further term \( \Gamma^+ \triangleq \{j | v'_{i,j} > v_{i,j}\} \) as the set of reactions that result in an increase of the \( i \)-th species, \( \Gamma^- \triangleq \{j | v'_{i,j} < v_{i,j}\} \) as the set of reactions that result in a decrease of the \( i \)-th species. Then, the constant \( \alpha_i - \max_{j \in \Gamma^-} v_{i,j}^T \alpha \) is the time scale of the \( i \)-th substance, i.e., the time scale where \( X_N^\gamma(t) \) evolves at the rate of \( O(1) \). Moreover, we term \( \gamma_1 \triangleq \min_i (\alpha_i - \max_{j \in \Gamma^-} v_{i,j}^T \alpha) \) as the parameter of the fastest time scale of the system and \( \Gamma^0 \triangleq \text{diag}(\ldots, 1_{\{\alpha_i = \gamma_1\}}, \ldots) \) as a diagonal matrix indicating whether a species is at the scale of \( N^\gamma \). In the rest of this paper, we focus on the dynamic behaviors of a reaction system at the fastest time scale \( \gamma_1 \).

For a large scaling factor \( N \), by neglecting all slow reactions \( (\gamma_1 + \tilde{\beta}_j < 0) \) and approximating fast reactions \( (\gamma_1 + \tilde{\beta}_j > 0) \) by a continuous process, we can arrive at a simplified piecewise deterministic process as follows.

\[
X(t) = \lim_{N \to \infty} X_N(t) = \lim_{N \to \infty} \left( \sum_{j \in \Gamma^+} \int_0^t N^{-\gamma} \lambda_j^N(X_N(s)) ds \right) + \sum_{j \in \Gamma^-} R_j \left( \int_0^t N^{-\gamma} \lambda_j^N(X_N(s)) ds \right) D^0 (v'_j - v_j).
\]

We denote the transition kernel of the above process by \( K^{\gamma_1}(x, A) \triangleq \mathbb{P}(X^{\gamma_1}(t) \in A | X^{\gamma_1}(0) = x) \). If we further assume the initial conditions to satisfy that

\[
\lim_{N \to \infty} X_N(0) \text{ exists,}
\]

and that the above systems are non-explosive, i.e.,

\[
\lim_{c \to \infty} c^{-\gamma_1}X^\gamma_1 = \infty, \quad \text{and} \quad \lim_{c \to \infty} \tau^\gamma_1 c = \infty, \quad \text{a.s.},
\]

where \( \tau^\gamma_1 c = \inf \{t | \| X^{\gamma_1}(t) \| \geq c \} \) and \( \tau^\gamma_1 c = \inf \{t | \| X^{\gamma_1}(t) \| \geq c \} \), then the original model \( X_N^{\gamma_1}(\cdot) \) converges in distribution to the reduced model \( X^{\gamma_1}(\cdot) \) on any finite time interval.

\[
\text{Proposition 1 (Adapted from [6]): On any finite time interval} [0, t], \text{if } [\text{Proposition 1}] \text{ and } \text{Proposition 2}, \text{then } X_N^{\gamma_1}(\cdot) \Rightarrow X^{\gamma_1}(\cdot) \text{ in the sense of the Skorokhod topology.}
\]

\[
\text{Proof: It follows from [6, Theorem 4.1] and the portmanteau lemma.}
\]

Also, the finite-dimensional distribution of \( X_N^{\gamma_1}(\cdot) \) converges to the finite-dimensional distribution of \( X^{\gamma_1}(\cdot) \).

\[
\text{Corollary 1: Let } i \text{ be a positive integer and } \{t_j\}_{0 \leq j \leq i} \text{ be a sequence of scalars. If } [\text{Proposition 1}] \text{ and } \text{Proposition 2}, \text{then } X^{\gamma_1}_{t_1:t_i} \Rightarrow X^{\gamma_1}_{t_1:t_i} \text{ where } X^{\gamma_1}_{t_1:t_i} \triangleq \{X^{\gamma_1}(t_1), \ldots, X^{\gamma_1}(t_i)\} \text{ and } X^{\gamma_1}_{t_1:t_i} \triangleq \{X^{\gamma_1}(t_1), \ldots, X^{\gamma_1}(t_i)\}.
\]

\[
\text{Proof: It follows immediately from Proposition [1] and [13, Theorem 7.8 in Chapter 3].}
\]

Note that the convergence result does not always hold on the infinite time horizon, because the limit model may miss...
bi-stability or some other phenomenon that the full model has (see [14, Section VI]).

In the above results, the non-explosivity condition is not a very strong condition; there exist checkable sufficient conditions to ensure non-explosivity (see [15, 16]) that can deal with it efficiently. In this paper, we do not provide specific conditions for non-explosivity in order to make the result general and avoid the deviation from this paper’s main concern.

Remark 1: The computational complexity to simulate $X^N,\gamma(t)$ can be greatly lower than the complexity to simulate $X^{N,\gamma}(t)$, because the former avoids the exact simulation of fast reactions ($\gamma + \rho_j > 0$), which consume a lot of computational resources to update the system at a rate proportional to $N^{-1}$.\hfill \\

D. Filtering problems, the change of measure method, and the particle filter

In this paper, we assume that $m$ channels of light intensity signals of fluorescent reporters in a single cell can be observed discretely in time from a microscopy platform (e.g., the one in [17]). The discrete-time property is mainly caused by the cell segmentation and tracking, which is required prior to the measuring step and can be time-consuming. Suppose that $\{t_i\}_{i \in \mathbb{N}_0}$ are time points when the observation comes, and the value of each observation, $Y^{N,\gamma}(t_i)$, satisfies

$$Y^{N,\gamma}(t_i) = h_\ell \left( X^{N,\gamma}(t_i) \right) + W_\ell(t_i), \quad \ell = 1, \ldots, m,$$

where $h_\ell$ are bounded Lipschitz continuous functions indicating the relation between the observation and the reaction process, and $W_\ell(t_i)$ ($\ell = 1, \ldots, m$ and $i \in \mathbb{N}_0$) are mutually independent standard Gaussian random variables which are also independent of $R_j(\cdot)$ ($j = 1, \ldots, r$).

Our task is to provide optimal estimates to latent states of the system, e.g., $\phi(X^{N,\gamma}(t_i))$ where $\phi$ is a known measurable function, in the sense of mean square error based on observations up to the time $t_i$; in other words, we are going to calculate the conditional expectation $\pi^{N,\gamma}(\cdot)$ of $\phi(X^{N,\gamma}(t_i)) | Y^{N,\gamma}_t$, where $Y^{N,\gamma}_t$ is the filtration generated by the process $\{Y^{N,\gamma}(t_i)\}_{0 \leq t \leq t_i}$.

Similarly, we can define artificial readouts for the reduced model by

$$Y^{\gamma}(t_i) = h_\ell \left( X^{\gamma}(t_i) \right) + W_\ell(t_i), \quad \ell = 1, \ldots, m,$$

and attempt to solve the corresponding filtering problem, i.e., calculating the conditional expectation $\pi^{\gamma}(\cdot) \equiv \mathbb{E}_P \left[ \phi(X^{\gamma}(t_i)) | Y^{\gamma}_t \right]$, where $Y^{\gamma}_t$ is the filtration generated by the process $\{Y^{\gamma}(t_i)\}_{0 \leq t \leq t_i}$. Note that in practical experiments, one can only observe $\{Y^{\gamma}(t_i)\}_{t \in \mathbb{N}_0}$ but never get $\{Y^{\gamma}(t_i)\}_{t \in \mathbb{N}_0}$.

The change of measure method is a powerful tool to deal with filtering problems, whose core idea lies in constructing a reference probability measure that orthogonalizes the underlying process and the observation. For our problem, we construct an auxiliary random process $Z^{N,\gamma}(t_i) = \prod_{j=1}^m g \left( X^{N,\gamma}(j), Y^{N,\gamma}(j) \right)$, where $g(x, y) = \exp \left( \sum_{i=1}^m h_i(x) y_i - h_i^2(x)/2 \right)$, and whose reciprocal is a martingale with respect to the filtration $F_{t_i}$ under $P$. Based on this martingale, we define a reference probability measure, $\mathbb{P}^{N,\gamma}$, by the Radon-Nikodym derivation $\frac{d\mathbb{P}^{N,\gamma}}{d\mathbb{P}}|_{F_{t_i}} = \left( Z^{N,\gamma}(t_i) \right)^{-1}$, under which $\{Y^{N,\gamma}(t_i)\}_{t \in \mathbb{N}_0}$ are mutually independent standard $m$-dimensional Gaussian random variables, the law of the process $X^{N,\gamma}(t)$ is the same as its law under $P$, and the process $X^{N,\gamma}(t)$ and observation $Y^{N,\gamma}(t)$ are independent of each other. (These results can be easily shown by checking the joint characteristic function of these processes.) Furthermore, by the Kallianpur-Striebel formula [18, Theorem 3], for any measurable function $\phi$ such that $\phi(X^{N,\gamma}(t_i))$ is integrable under $P$, there holds

$$\pi^{N,\gamma}(\phi) = \mathbb{E}_{\mathbb{P}^{N,\gamma}} \left[ \frac{Z^{N,\gamma}(t_i) \phi \left( X^{N,\gamma}(t_i) \right)}{Z^{N,\gamma}(t_i)} \right]$$

$\mathbb{P}$-a.s. and $\mathbb{P}^{N,\gamma}$-a.s.. Recall that $\pi^{N,\gamma}(\phi)$ is the notation for $\mathbb{E}_P \left[ \phi(X^{N,\gamma}(t_i)) | Y^{N,\gamma}_t \right]$. We, here, name $\pi^{N,\gamma}(\phi) \equiv \mathbb{E}_{\mathbb{P}^{N,\gamma}} \left[ Z^{N,\gamma}(t_i) \phi \left( X^{N,\gamma}(t_i) \right) | Y^{N,\gamma}_t \right]$ as the unnormalized conditional expectation and $\pi^{N,\gamma}(\phi)$ as the normalization factor. Note that both $\pi^{N,\gamma}(\phi)$ and $\pi^{N,\gamma}(\phi)$ are $Y^{N,\gamma}_t$-measurable. Therefore, for any bounded $\phi$, there exist measurable functions, $\hat{\phi}_{t_i}^{\gamma}(\cdot)$, and $\hat{\phi}_{t_i}^{\gamma}(\cdot)$, from the domain of the observations to $\mathbb{R}$ such that $\hat{\phi}_{t_i}^{\gamma}(Y^{\gamma}(t_i)) = \pi^{N,\gamma}(\phi)$ and $\hat{\phi}_{t_i}^{\gamma}(Y^{\gamma}(t_i)) = \pi^{N,\gamma}(\phi)$, where $Y^{\gamma}_t \equiv \left(Y^{N,\gamma}(t_1), \ldots, Y^{N,\gamma}(t_i)\right)$ is the observation process up to the time $t_i$.

Based on [3], an algorithm called the particle filter (also known as sequential Monte Carlo method) can be constructed as Algorithm 1 to numerically solve the filtering problem. In Algorithm 1, the particles $x_j(\cdot)$ mimic the dynamic state $X^{N,\gamma}(\cdot)$, and the weights $w_j(\cdot)$ mimic the normalized $Z^{N,\gamma}(\cdot)$; therefore, the computed filter can approximate the true filter by [3]. A resampling step is executed in each iteration to remove non-significant particles so that sample impoverishment can be avoided [1].

Algorithm 1: The particle filter [1]

Input a kernel function $K(t, \cdot)$ and observations $Y(\cdot)$;
Initialize $M$ particles $x_1(0), \ldots, x_M(0)$ to $X^0(0)$ and weights $w_1(0), \ldots, w_M(0)$ to $1/M$. Set $t_0 = 0$;
for each time point $t_i$ ($i \in \mathbb{N}_0$) do
For $j = 1, \ldots, M$, sample $x_j(t_i)$ from $K(t_{i-1}, t_i)$, and compute weights $w_j(t_i) \propto w_j(t_{i-1}) g(x_j(t_i), Y(t_i))$;
Compute filter $\tilde{\pi}_{t_i}(\phi) = \sum_{j=1}^M w_j(t_i) \phi(x_j(t_i))$;
Resample $\{w_j(t_i), x_j(t_i)\}$ to obtain $M$ equally weighted particles $\{1/M, \tilde{x}_i(t_i)\}$ and set $\{w_j(t_i), x_j(t_i)\} \leftarrow \{1/M, \tilde{x}_i(t_i)\}$;
end
Similarly, for the filtering problem of the reduced model, we can define another auxiliary function \( Z^{\gamma_i}(t_i) = \prod_{j=1}^{i} g(X^{\gamma_i}(t_j), Y^{\gamma_i}(t_j)) \) and a reference probability \( P^{\gamma_i} \) by \( \frac{\partial P^{\gamma_i}}{\partial r_{\gamma_i}} |_{r_{\gamma_i}} = (Z^{\gamma_i}(t_i))^{-1} \), under which \( \{Y^{\gamma_i}(t_i)\}_{i \in \mathbb{N}_{>0}} \) are mutually independent standard m-dimensional Gaussian random variables, the law of the process \( X^{\gamma_i}() \) is the same as its law under \( P \), and the process \( X^{\gamma_i}() \) and observation \( Y^{\gamma_i}() \) are independent of each other. By the Kallianpur-Striebel formula, for any measurable function \( \phi() \) such that \( \phi(X^{\gamma_i}(t_i)) \) is integrable under \( P \), there holds

\[
\pi^{\gamma_i}_t(\phi) = \frac{\mathbb{E}_{P^{\gamma_i}} \left[ Z^{\gamma_i}(t_i) \phi(X^{\gamma_i}(t_i)) | Y^{\gamma_i}_t \right]}{\mathbb{E}_{P^{\gamma_i}} \left[ Z^{\gamma_i}(t_i) \right]} \tag{6}
\]

\( \mathbb{P} \)-a.s. and \( \mathbb{P}^{\gamma_i} \)-a.s., in which we further denote the numerator by \( \rho^{\gamma_i}_t(\phi) \) and the denominator by \( \rho^{\gamma_i}_0(\phi) \). (1) Note that both \( \pi^{\gamma_i}_t(\phi) \) and \( \rho^{\gamma_i}_t(\phi) \) are \( Y^{\gamma_i} \)-measurable. Therefore, for any bounded \( \phi() \), there exist measurable functions, \( f_{\phi,t}^{\gamma_i}(\cdot) \) and \( g_{\phi,t}^{\gamma_i}(\cdot) \), from the domain of the observations to \( \mathbb{R} \), such that

\[
f_{\phi,t}^{\gamma_i}(Y_{t_1:t_i}) = \pi^{\gamma_i}_t(\phi) \quad \text{and} \quad g_{\phi,t}^{\gamma_i}(Y_{t_1:t_i}) = \rho^{\gamma_i}_t(\phi), \quad \text{where} \quad Y_{t_1:t_i} \triangleq (Y^{\gamma_i}(t_1), \ldots, Y^{\gamma_i}(t_i)) \quad \text{is the observation process up to the time} \ t_i.
\]

III. MAIN RESULTS

Recall that our task is to accurately and computationally efficiently solve the filtering problem for the multi-scale system (1), i.e., to calculate \( \{\pi^{M,\gamma}_t(\phi)\}_{i \in \mathbb{N}_{>0}} \). A straightforward idea to solve this problem is to use the particle filter where the transition kernel of the full model (i.e., \( K^{N,\gamma} \)) and observations \( Y^{N,\gamma}() \) are inserted. We denote this particle filter by \( \tilde{\pi}^{M,\gamma}_t(\phi) \). Although it can accurately solve the filtering problem if the resampling method is properly chosen (see [19, Corollary 2.4.4]), this algorithm involves the simulation of the full model and, therefore, can be computationally expensive (see Remark 1). Consequently, we need to figure out a smarter way to approach this problem.

We first show that the exact solution to the filtering problem of the original model can be constructed by solving the filtering problem for the reduced model.

**Theorem 1:** Assume that (3) and (4) are satisfied. Then, for any \( i \in \mathbb{N}_{>0} \) and any bounded continuous function \( \phi() \), there holds \( \pi^{N,\gamma}_t(\phi) = \tilde{\pi}^{N,\gamma}_t(\phi) \triangleq \int f_{\phi,t}^{N,\gamma}(Y_{t_1:t_i}) - \int g_{\phi,t}^{N,\gamma}(Y_{t_1:t_i}) \) to \( N \to \infty \), in \( \mathbb{P} \)-probability.

**Proof:** The proof is in the appendix.

Recall that \( f_{\phi,t}^{\gamma_i}(\cdot) \) is a mapping that maps the observation to the solution of the filtering problem for the reduced model. The above theorem suggests that the probability of the error of these filters below a given threshold is very close to 1 if the scaling factor, \( N \), is large, and, therefore, that \( \tilde{\pi}^{N,\gamma}_t(\phi) \triangleq \int f_{\phi,t}^{N,\gamma}(Y_{t_1:t_i}) \) is a good approximation to the exact filter \( \pi^{N,\gamma}_t(\phi) \).

Let us construct a particle filter \( \tilde{\pi}^{M,\gamma}_t(\phi) \) where the transition kernel of the reduced model (i.e., \( K^{\gamma_i}() \)) and observations \( Y^{N,\gamma}() \) are inserted. Clearly, this particle filter is an approximation of the filter \( f_{\phi,t}^{\gamma_i}(Y_{t_1:t_i}) \). Based on Theorem 1, we can further show that this particle filter \( \tilde{\pi}^{M,\gamma}_t(\phi) \) can also accurately approximate the true filter \( \pi^{N,\gamma}_t(\phi) \) with high probability.

**Corollary 2:** Assume that (3) and (4) are satisfied, and the resampling step in the particle filter (Algorithm 1) adopts the multinomial branching method. Then for any \( i \in \mathbb{N}_{>0} \), any positive \( \delta \), and any bounded continuous function \( \phi() \), there holds

\[
\lim_{N \to \infty} \lim_{M \to \infty} \mathbb{P} \left( \left| \tilde{\pi}^{M,\gamma}_t(\phi) - \pi^{N,\gamma}_t(\phi) \right| > \delta \right) = 0.
\]

**Proof:** It is a direct consequence of Corollary 2.4.4 in the literature [19] and Theorem 1.

Recall that the required computational effort to simulate the reduced model \( X^{\gamma_i}() \) is much lower than the effort to simulate \( X^{N,\gamma}() \) (see Remark 1). As a consequence, particle filter \( \pi^{M,\gamma}_t(\phi) \), which applies the kernel function \( K^{\gamma_i}() \) and, therefore, is required to simulate the reduced model \( X^{\gamma_i}() \) in the sampling step, has a much lower computational cost compared with the particle filter \( \tilde{\pi}^{M,\gamma}_t(\phi) \), which applies kernel function \( K^{N,\gamma}() \) and is required to simulate the full model. This fact, together with the accuracy result Corollary 2, indicates that the filter \( \tilde{\pi}^{M,\gamma}_t(\phi) \) based on the reduced model is a better candidate than \( \pi^{M,\gamma}_t(\phi) \) for solving a practical filtering problem for multiscale intracellular reaction systems.

We need to emphasize that the boundedness condition of \( \phi() \) is not generally satisfied in biological applications, where concentrations of most target species have no theoretical upper bounds apart from some exceptions, e.g., gene copies. To tackle this problem, we can truncate a target quantity by a large number beyond which the conditional probability is comparatively low, and the tail event contributes little to the conditional expectation. Then, an estimation of the truncated quantity generated by the particle filtering applying the reduced model can provide an accurate approximation to the conditional expectation of the target quantity.

IV. NUMERICAL EXAMPLE

In this section, we illustrate our approach using a numerical example. We consider a gene expression model involving four species: a gene having on and off states (denoted respectively as \( S_2 \) and \( S_1 \)), the mRNA it transcribes (denoted as \( S_3 \)), and a fluorescent protein it expresses (denoted as \( S_4 \)), and six reactions: \( S_1 \rightarrow S_2 \) (gene activation), \( S_2 \rightarrow S_1 \) (gene deactivation), \( S_2 \rightarrow S_3 \) (gene transcription), \( S_3 \rightarrow S_4 \) (translation), \( S_3 \rightarrow \emptyset \) (mRNA degradation), and \( S_4 \rightarrow \emptyset \) (protein degradation).

For this system, we take \( N = 100 \), \( \alpha_3 = 1 \), and \( \alpha_1 = 0 \) for \( 1 \leq i \leq 3 \), i.e., the cellular system consists of hundreds of fluorescent protein molecules but very few copies of other molecules. The values of reaction constants and their scaling exponents are shown in Table I, where the unit of both reaction constants and scale rates is "minute". Also, we assume \( X^{N,\gamma}_1(0) \) to have a binary distribution with mean 1/3, \( X^{N,\gamma}_2(0) \) to satisfy \( X^{N,\gamma}_2(0) = 1 - X^{N,\gamma}_1(0) \), \( X^{N,\gamma}_3(0) \) to have a Poisson distribution with mean 2, and \( X^{N,\gamma}_4(0) \) to also have a Poisson distribution with mean 2. Moreover, we assume that initial conditions except \( X_2(0) \) are independent of each other. With this setting, we can easily calculate that \( \gamma_1 = 0 \).
i.e., the fastest time scale is 0, and the full dynamic model satisfies

\[ X^{N,\gamma_1}(t) = X^{N,\gamma_1}(0) + \zeta_1 R_1 \left( k'_1 \int^t_0 X_1^{N,\gamma_1}(s) ds \right) \]

\[ + \zeta_2 R_2 \left( k'_2 \int^t_0 X_2^{N,\gamma_1}(s) ds \right) + \zeta_3 R_3 \left( k'_3 \int^t_0 X_2^{N,\gamma_1}(s) ds \right) \]

\[ + \zeta_4 R_4 \left( k'_4 \int^t_0 X_3^{N,\gamma_1}(s) ds \right) + \zeta_5 R_5 \left( k'_5 \int^t_0 X_3^{N,\gamma_1}(s) ds \right) \]

\[ + \zeta_6 R_6 \left( k'_6 \int^t_0 X_4^{N,\gamma_1}(s) ds \right) \]

where \( \zeta_1 = (-1, 1, 0, 0)^T \), \( \zeta_2 = (1, -1, 0, 0)^T \), \( \zeta_3 = (0, 0, 1, 0)^T \), \( \zeta_4 = (0, 0, 0, 1)^T \), \( \zeta_5 = (0, 0, -1, 0)^T \), and \( \zeta_6 = (0, 0, 0, -1)^T \); the reduced dynamics satisfies

\[ X^{\gamma_1}(t) = \lim_{N \to \infty} X^{N,\gamma_1}(t) + R_1 \left( k'_1 \int^t_0 X_1^{N,\gamma_1}(s) ds \right) \]

\[ + \zeta_2 R_2 \left( k'_2 \int^t_0 X_2^{N,\gamma_1}(s) ds \right) + \zeta_3 R_3 \left( k'_3 \int^t_0 X_2^{N,\gamma_1}(s) ds \right) \]

\[ + \zeta_4 R_4 \left( k'_4 \int^t_0 X_3^{N,\gamma_1}(s) ds \right) + \zeta_5 R_5 \left( k'_5 \int^t_0 X_3^{N,\gamma_1}(s) ds \right) \]

\[ + \zeta_6 R_6 \left( k'_6 \int^t_0 X_4^{N,\gamma_1}(s) ds \right). \]

We simulate the full dynamics by a modified next reaction method [20] and the reduced model by Algorithm 2 in [21].

We assume that light intensity signals can be observed every 2 minutes from a fluorescent microscope and satisfy

\[ Y^{N,\gamma_1}(t) = h \left( X^{N,\gamma_1}(t) \right) + W(t) \]

where \( h(x) = (10 \times x) \land 10^3 \) with \( 10^3 \) being the measurement range, and \( W(t) \) is a sequence of mutually independent standard Gaussian random variables. Our goal is to provide estimates of latent dynamic states, including DNA copies, mRNA copies, and protein concentrations, based on readouts.

A numerical simulation is shown in Fig. 1, where we first simulated the full dynamic system and observations, which were taken as true signals, and then applied two different types of particle filters to estimate the system. Here, we set the particle population to be 5000. From the results, we can observe that both filters can follow the behavior of the true signal, and the particle filter applying the reduced model is within the credible interval (light red region) most of the time. In the meanwhile, the particle filter applying the original model took 9.44 seconds in average to output the estimation in each iteration, whereas the particle filter applying the reduced model took only 0.95 seconds in each iteration, 10 times faster than its opponent. These results indicate that the proposed particle filter applying the reduced model is both accurate and computationally efficient in solving filtering problems for multi-scale stochastic chemical reaction network systems.

V. CONCLUSION

In this paper, we provide efficient particle filters to solve the filtering problem for multiscale stochastic reaction network systems, based on a time-scale separation technique. We first show that the solution of the filtering problem for the original systems can be well approximated by the solution of the filtering problem for a reduced model that represents the dynamics as a hybrid process. Since the reduced model is based on exploiting the time-scale separation in the original network, the reduced model can greatly reduce the computational complexity to simulate the dynamics. This enables us to develop efficient particle filters to solve the filtering problems.
problem for the original model by applying the particle filter to the reduced model. Finally, a numerical example is presented to illustrate our approach.

There are a few topics deserving further investigation in future work. First, since the variability of model parameters can greatly influence the performance of a filter, it is worth investigating if we can put parameter inference and latent state estimation into the same framework to improve the performance of the proposed particle filter. Second, it is worth extending the convergence result of the particle filter (see Corollary 2) to unbounded function scenarios, as many biological states are not necessarily bounded. Third, we will also apply the proposed filter to the optimal control problem for an intracellular system.

APPENDIX

In this section, we give the outline of the proof of theorem 1. Here, we utilize a framework proposed in [22], which requires us to construct random variables $X_{t_{1};j; t}$, $\tilde{X}_{t_{1};j; t}$, $Y_{t_{1};j; t}$, $\tilde{Y}_{t_{1};j; t}$, $Z_{N;\gamma}(t_{j})$ and $\tilde{Z}_{\gamma}(t_{j})$ on a common probability space $(\tilde{\Omega}_{\gamma}, \tilde{F}_{\gamma}, \tilde{Q}_{\gamma})$ at each time point $t_{j}$ such that

(A.1) random variables $\bigl(\tilde{X}_{t_{1};j; t}, \tilde{Y}_{t_{1};j; t}, \tilde{Z}_{N;\gamma}(t_{j})\bigr)$ take values in $\mathbb{R}^{n \times i} \times \mathbb{R}^{m \times i} \times \mathbb{R}$ and have the same law as $(X_{t_{1};j; t}, Y_{t_{1};j; t}, Z_{N;\gamma}(t_{j}))$ on $(\Omega, F, P_{N;\gamma})$.

(A.2) the random variable $(\tilde{X}_{t_{1};j, t}, \tilde{Y}_{t_{1};j; t}, \tilde{Z}_{\gamma}(t_{j}))$ takes values in $\mathbb{R}^{n \times i} \times \mathbb{R}^{m \times i} \times \mathbb{R}$ and has the same law as $(X_{t_{1};j, t}, Y_{t_{1};j; t}, Z_{\gamma}(t_{j}))$ on $(\Omega, F, P_{\gamma})$.

(A.3) \( f_{\gamma,t_{j}}(Y_{t_{1};j; t}) \to f_{\gamma,t_{j}}(Y_{t_{1};j; t}) \) in $\tilde{Q}_{\gamma}$-probability.

(A.4) \( \lim_{N \to \infty} \mathbb{E}_{\tilde{Q}_{\gamma}} \left[ \tilde{Z}_{N;\gamma}(t_{j}) - \tilde{Z}_{\gamma}(t_{j}) \right] = 0 \).

If we succeed in finding the above random variables, then the convergence result is guaranteed by the following theorem.

**Theorem 2 (Adapted from [22]):** For any $i > 0$ and any measurable function $\phi(\cdot)$, if (A.1) (A.2) (A.3) and (A.4) are satisfied, then $\pi^{N;\gamma}_{t_{1};j; t}(\phi) \to \pi^{\gamma}_{t_{1};j; t}(\phi)$ in $\mathbb{P}$-probability. We can construct such random variables and the common probability space as follows. First, for any $i \in \mathbb{N}_{>0}$, we can apply the Skorokhod representation theorem to constructing a common probability space $(\tilde{\Omega}_{\gamma}, \tilde{F}_{\gamma}, \tilde{Q}_{\gamma})$ on which are defined $\mathbb{R}^{n \times i}$-valued random variables $\tilde{X}_{t_{1};j; t}$ and $\tilde{X}_{t_{1};j; t}$, with the laws of $X_{t_{1};j; t}$ and $X_{t_{1};j; t}$, respectively, such that $\lim_{N \to \infty} \tilde{X}_{t_{1};j; t} = X_{t_{1};j; t}$ in this probability space. Moreover, we define $\tilde{Z}_{N;\gamma}(t_{j}) \triangleq \prod_{j=1}^{i} g \left( X_{N;\gamma}(t_{j}), Y_{\gamma}(t_{j}) \right)$ and $\tilde{Z}_{\gamma}(t_{j}) \triangleq \prod_{j=1}^{i} g \left( \tilde{X}_{t_{1};j; t}, \tilde{Y}_{t_{1};j; t} \right)$ on the product probability space $(\tilde{\Omega}_{\gamma}, \tilde{F}_{\gamma}, \tilde{Q}_{\gamma}) \triangleq \left( \tilde{\Omega}_{\gamma} \times \tilde{\Omega}_{\gamma} \times \tilde{\Omega}_{\gamma} \times \tilde{\Omega}_{\gamma} \times \tilde{\Omega}_{\gamma} \right)$, where $X_{N;\gamma}(t_{j})$ is the $j$-th column of $\tilde{X}_{t_{1};j; t}$, $\tilde{X}_{t_{1};j; t}$ is the $j$-th column of $\tilde{Y}_{t_{1};j; t}$, and $\tilde{Y}_{t_{1};j; t}$ is the $j$-th column of $\tilde{Y}_{t_{1};j; t}$.

Obviously, such defined random variables and the common probability space satisfy (A.1) and (A.2). The condition (A.4) can be proven straightforwardly by the fact that $\lim_{N \to \infty} \tilde{X}_{t_{1};j; t} = X_{t_{1};j; t}$ almost surely. Similarly, we can also show (A.3) by using (5) and (6). Consequently, Theorem 1 is proven.

REFERENCES

[1] A. Doucet and A. M. Johansen, “A tutorial on particle filtering and smoothing: Fifteen years later,” Handbook of nonlinear filtering, vol. 12, no. 656-704, p. 3, 2009.

[2] C.-L. Lin, et al., “Robust estimation of stochastic gene-network systems,” Journal of Biomedical Science and Engineering, vol. 6, no. 02, p. 213, 2013.

[3] A. Golightly and D. J. Wilkinson, “Bayesian sequential inference for stochastic kinetic biochemical network models,” Journal of Computational Biology, vol. 13, no. 3, pp. 838–851, 2006.

[4] S. Calderazzo, M. Brancaccio, and B. Finkenstein, “Filtering and inference for stochastic oscillators with distributed delays,” Bioinformatics, vol. 35, no. 8, pp. 1380–1387, 2019.

[5] R. J. Boys, D. J. Wilkinson, and T. B. Kirkwood, “Bayesian inference for a discretely observed stochastic kinetic model,” Statistics and Computing, vol. 18, no. 02, pp. 125–135, 2008.

[6] W.-K. Kang, T. G. Kurtz, “Separation of time-scales and model reduction for stochastic reaction networks,” The Annals of Applied Probability, vol. 23, no. 2, pp. 529–583, 2013.

[7] J. H. Park, N. S. Namachchivaya, and R. B. Sowers, “A problem in stochastic averaging of nonlinear filters,” Stochastics and Dynamics, vol. 8, no. 03, pp. 543–560, 2008.

[8] J. H. Park, R. B. Sowers, and N. S. Namachchivaya, “Dimensional reduction in nonlinear filtering,” Nonlinearity, vol. 23, no. 2, p. 305, 2010.

[9] J. H. Park, N. Namachchivaya, and H. C. Yeong, “Particle filters in a multiscale environment: homogenized hybrid particle filter,” Journal of Applied Mechanics, vol. 78, no. 6, 2011.

[10] P. Imkeller, N. S. Namachchivaya, N. Perkowski, H. C. Yeong, et al., “Dimensional reduction in nonlinear filtering: a homogenization approach,” The Annals of Applied Probability, vol. 23, no. 6, pp. 2290–2326, 2013.

[11] M. Feinberg, Foundations of Chemical Reaction Network Theory. Springer, 2019.

[12] D. F. Anderson and T. G. Kurtz, “Continuous time markov chain models for chemical reaction networks,” in Design and analysis of biomolecular circuits, pp. 3–42, Springer, 2011.

[13] S. N. Ethier and T. G. Kurtz, “Markov processes: Characterization and convergence,” 1986.

[14] D. T. Gillespie, “The chemical langevin equation,” The Journal of Chemical Physics, vol. 113, no. 1, pp. 297–306, 2000.

[15] A. Gupta, C. Briat, and M. Khammash, “A scalable computational framework for establishing long-term behavior of stochastic reaction networks,” PLoS Comput Biol, vol. 10, no. 6, e1003669, 2014.

[16] D. F. Anderson, D. Cappelletti, M. Koyama, and T. G. Kurtz, “Non-explosivity of stochastically modeled reaction networks that are complex balanced,” Bulletin of mathematical biology, vol. 80, no. 10, pp. 2561–2579, 2018.

[17] M. Rullan, D. Benzing, G. W. Schmidt, A. Milias-Argeitis, and M. Khammash, “An optogenetic platform for real-time, single-cell interrogation of stochastic transcriptional regulation,” Molecular cell, vol. 70, no. 4, pp. 745–756, 2018.

[18] G. Kallianpur and C. Striebel, “Estimation of stochastic systems: Arbitrary system process with additive white noise observation errors,” The Annals of Mathematical Statistics, vol. 39, no. 3, pp. 785–801, 1968.

[19] D. Crisan, “Particle filters—a theoretical perspective,” in Sequential Monte Carlo methods in practice, pp. 17–41, Springer, 2001.

[20] A. Duncan, R. Erban, and K. Zygalakis, “Hybrid framework for the simulation of stochastic chemical kinetics,” Journal of Computational Physics, vol. 326, pp. 398–419, 2016.