

2 **Supplementary Information for**

3 **Advanced methods for gene network identification and noise decomposition from single-cell** 4 **data**

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S1. Stochastic intracellular reaction systems, the chemical master equation (CME), and the associated stochastic filtering problem

In this work, we focus on an intracellular reaction system that has r reactions:



where $S_1, \dots, S_n$ are n different chemical species, and $\nu_{i,j}$ and $\nu'_{i,j}$ are the stoichiometric coefficients indicating the number of molecules consumed or produced for S_i in the j -th reaction. Due to the low molecular counts, an intracellular reaction system is inevitably random, and, therefore, its dynamics is usually modeled by a stochastic process called the continuous time Markov chain. Following [1], the dynamical equation can be written by

$$X(t) = X(0) + \sum_{j=1}^r \zeta_j R_j \left(\int_0^t \lambda_j(X(s)) ds \right) \quad (2)$$

where $X(t)$ is an n -dimensional vector representing the molecular count for each species at time t , the vector ζ_j equals to $(\nu'_{1,j} - \nu_{1,j}, \dots, \nu'_{n,j} - \nu_{n,j})^\top$ indicating the state change after a firing of the j -th reaction, $R_j(t)$ are independent unit rate Poisson processes, and $\lambda_j(\cdot)$ are the propensities indicating the rates of these reactions. To avoid negative molecular counts, the propensities should satisfy the condition $\lambda_j(x) = 0$ for all $x + \zeta_j \notin \mathbb{Z}_{\geq 0}^n$. For rigorousness, we only consider the processes that satisfy the condition

$$\sum_{j=1}^n \mathbb{E} [\lambda_j^2(X(t))] \text{ is uniformly bounded on any time interval } [0, T], \quad (3)$$

which means the system state will almost surely not grow to infinity in finite time. What's more, this condition also implies that the random variables $\{\lambda_j(X(t))\}_{t \in [0, T]}$ are uniformly integrable. Also, for simplicity, we assume that the initial conditions for different species are independent, i.e.,

$$X_1(0), \dots, X_n(0) \text{ are independent.} \quad (4)$$

Alternative to (2), one can also model the intracellular reaction system by the chemical master equation (CME) [1]:

$$\frac{dp(t, x)}{dt} = \sum_{j=1}^r \lambda_j(x - \zeta_j) p(t, x - \zeta_j) - \sum_{j=1}^r \lambda_j(x) p(t, x), \quad \forall x \in \mathbb{Z}_{\geq 0}^n,$$

where $p(t, x) \triangleq \mathbb{P}(X(t) = x)$. Provided with the condition (3), these two dynamical presentations are equivalent [1].

In the lab, scientists can directly measure fluorescent reporters and use these measurements to infer the dynamical states of unobserved species. This is called stochastic filtering for intracellular reaction systems. Mathematically, we can model the observations by

$$Y(t_i) = h(X(t_i)) + \Sigma W_i \quad (5)$$

where t_i are the observation time points, $Y(t_i)$ is a vector of observations with each element corresponding to a particular light frequency, $h(\cdot)$ is a vector-valued function indicating the ideal relation between the measurement and the system state, W_i are vectors of independent standard Gaussian noise, and Σ is a diagonal matrix indicating observation noise intensities. When the observations $Y(t_i)$ are one dimensional, we denote the 1×1 matrix Σ as σ . The goal of the stochastic filtering is to compute the conditional expectation $\pi_{t_i}(x) \triangleq \mathbb{P}(X(t_i) = x | Y(t_s), 1 \leq s \leq i)$. By Bayes' rule, the solution of the filtering problem satisfies the following recursive formulas [2]

$$\rho_{t_{i+1}}(x) = \sum_{x' \in \mathbb{Z}_{\geq 0}^n} \mathbb{P}(X(t_{i+1}) = x | X(t_i) = x') \pi_{t_i}(x') \quad (6)$$

$$\pi_{t_{i+1}}(x) \propto L(Y(t_{i+1}) | x) \rho_{t_{i+1}}(x) \quad (7)$$

where $\rho_{t_{i+1}}(x) \triangleq \mathbb{P}(X(t_{i+1}) = x | Y(t_s), 1 \leq s \leq i)$ and $L(y|x)$ is the density function of $\mathbb{P}(Y(t_{i+1}) \in \cdot | X(t_{i+1}) = x)$ (usually called the likelihood function). We can interpret (6) as the prediction of the state at the next time point t_{i+1} using the observation up to the current time t_i , and we interpret (7) as the adjustment of the predication according to the new observations. Note that the prediction step (6) is actually solving a CME with $\pi_{t_i}(\cdot)$ being the initial probability and $\rho_{t_{i+1}}(\cdot)$ being the final solution. Consequently, the filtering problem can be seen as a combination of the CME and an adjustment step.

S2. Error analysis of the Monte-Carlo method and the particle filter

One popular method to solve the CME is the Monte-Carlo method, which utilizes stochastic simulations to approximate the exact probability. Since the stochastic filtering problem can be seen as a combination of the CME and an adjustment step, one can also solve the filtering problem by using Monte Carlo for the CME step. In the literature, this Monte-Carlo method for the filtering problem is called the particle filter or the sequential Monte-Carlo method.

In this section, we perform the error analysis of these Monte-Carlo methods and show that their error tends to grow exponentially with the system dimension. Moreover, we also show that both approaches have relatively the same performance when solving their associated problems.

A. Error analysis of the Monte-Carlo method for CMEs. To solve a CME, the Monte-Carlo method first simulates N trajectories of the system (2), denoted by $x_1(t), \dots, x_N(t)$, and then uses the empirical distribution $p_{MC}(t, x) \triangleq \sum_{j=1}^N \mathbb{1}(x_1(t) = x)$ to approximate the exact probability. Here, $\mathbb{1}(\cdot)$ is the indicator function whose value equals to 1 if its argument is true, otherwise 0. Also, for simplicity, we only use the exact simulation method (e.g., Gillespie method) to generate the trajectories.

We now analyze the L_1 error of the Monte-Carlo method, defined by $\|\hat{p}_{MC}(t, \cdot) - p(t, \cdot)\|_1 \triangleq \sum_{x \in \mathbb{Z}_{\geq 0}^n} |\hat{p}_{MC}(t, x) - p(t, x)|$. By the law of the central limit theorem, we have that for each $x \in \mathbb{Z}_{\geq 0}^n$,

$$\sqrt{N} (\hat{p}_{MC}(t, x) - p(t, x)) \xrightarrow{d} \mathcal{N}(0, \text{Var}(\mathbb{1}(x_1(t) = x))), \quad \text{as } N \rightarrow \infty.$$

Notice that $\mathbb{1}(x_1(t) = x)$ has the Bernoulli distribution, so $\text{Var}(\mathbb{1}(x_1(t) = x)) = p(t, x)(1 - p(t, x))$ for every $x \in \mathbb{Z}_{\geq 0}^n$. Therefore, if the sum $\sum_{x \in \mathbb{Z}_{\geq 0}^n} \sqrt{p(t, x)}$ is convergent, we have that

$$\lim_{N \rightarrow \infty} \sqrt{N} \mathbb{E} [\|\hat{p}_{MC}(t, \cdot) - p(t, \cdot)\|_1] = \lim_{N \rightarrow \infty} \sqrt{N} \sum_{x \in \mathbb{Z}_{\geq 0}^n} \mathbb{E} [\|\hat{p}_{MC}(t, x) - p(t, x)\|] = \sqrt{\frac{2}{\pi}} \sum_{x \in \mathbb{Z}_{\geq 0}^n} \sqrt{p(t, x)(1 - p(t, x))}. \quad (8)$$

Finally, by the relation $\sqrt{a - b} \geq \sqrt{a} - \sqrt{b}$ for any $0 \leq b \leq a$, we can conclude

$$\lim_{N \rightarrow \infty} \sqrt{N} \mathbb{E} [\|\hat{p}_{MC}(t, \cdot) - p(t, \cdot)\|_1] = \sqrt{\frac{2}{\pi}} \left[\left(\sum_{x \in \mathbb{Z}_{\geq 0}^n} \sqrt{p(t, x)} \right) \pm 1 \right], \quad (9)$$

which provides upper and lower bounds for the error.

The formula (9) tells that when the sample size N is large and fixed, the error of the Monte-Carlo method largely depends on the value of $\sum_{x \in \mathbb{Z}_{\geq 0}^n} \sqrt{p(t, x)}$. This value tends to scale poorly with the size of the state space containing most of the probability mass. Particularly, when the probability mass is uniformly distributed on T states, this quantity equals $\sqrt{T}$, which can be very large when T is big. Also, since this state size often grows exponentially with the number of species, this quantity $\sum_{x \in \mathbb{Z}_{\geq 0}^n} \sqrt{p(t, x)}$ tends to scale poorly with the system dimension n . When the molecular counts of different chemical species are independent, this sum does grow exponentially with n , as its value equals to $\prod_{i=1}^n \left(\sum_{x_i \in \mathbb{Z}_{\geq 0}} \sqrt{p_i(t, x_i)} \right)$ with $p_i(t, \cdot)$ the marginal distribution for the i -th species. In summary, the error of a Monte-Carlo method tends to scale unfavorably with the size of state space and system dimension, and, thus, this method usually performs poorly in high-dimensional problems.

Next, we show that if the state variables are independent and their marginal distributions are estimated separately, then the errors in estimating these marginal distributions additively contribute to the error in the joint probability estimate. Again, let us denote $p_i(t, x_i)$ the marginal distribution for the i -th species, and $\hat{p}_i(t, x)$ be an estimate of this marginal distribution by the Monte-Carlo method. Here, we consider that these marginal distributions are estimated separately, using different sets of

119 samples. Therefore, these estimates are probabilistically independent, and we can get

$$\begin{aligned}
120 \quad & \underbrace{\sum_{x_1 \in \mathbb{Z}_{\geq 0}} \cdots \sum_{x_n \in \mathbb{Z}_{\geq 0}} \mathbb{E} \left[\left| \prod_{i=1}^n \hat{p}_i(t, x_i) - \prod_{i=1}^n p_i(t, x_i) \right| \right]}_{\text{Error in estimating the joint distribution}} \\
121 \quad & \leq \sum_{x_1 \in \mathbb{Z}_{\geq 0}} \cdots \sum_{x_n \in \mathbb{Z}_{\geq 0}} \mathbb{E} \left[\left| \hat{p}_1(t, x_1) \prod_{i=2}^n \hat{p}_i(t, x_i) - \prod_{i=2}^n p_i(t, x_i) \right| + \left| \hat{p}_1(t, x_1) - p_1(t, x_1) \right| \prod_{i=2}^n p_i(t, x_i) \right] \\
122 \quad & = \sum_{x_2 \in \mathbb{Z}_{\geq 0}} \cdots \sum_{x_n \in \mathbb{Z}_{\geq 0}} \mathbb{E} \left[\left| \prod_{i=2}^n \hat{p}_i(t, x_i) - \prod_{i=2}^n p_i(t, x_i) \right| \right] + \sum_{x_1 \in \mathbb{Z}_{\geq 0}} \mathbb{E} \left[\left| \hat{p}_1(t, x_1) - p_1(t, x_1) \right| \right] \quad (\text{by independence}) \\
123 \quad & \dots \dots \dots \\
124 \quad & \leq \sum_{i=1}^n \underbrace{\left[\sum_{x_i \in \mathbb{Z}_{\geq 0}} \mathbb{E} \left[\left| \hat{p}_i(t, x_i) - p_i(t, x_i) \right| \right] \right]}_{\text{Error in estimating each marginal distribution}}.
\end{aligned}$$

125 This result suggests that the error in estimating the joint distribution is no greater than the sum of the errors in estimating
126 marginal distributions.

127 **B. Error analysis of the particle filter.** Recall that the filtering problem can be seen as a combination of the CME and the
128 adjustment step. Therefore, one idea to solve this problem is using the Monte-Carlo method for the CME step. In the literature,
129 this method is called the particle filter, whose detailed algorithm is summarized in Algorithm 1. Specifically, the particle filter
130 first generates equally weighted particles $(x_1(0), \dots, x_N(0))$ from the initial probability so that their empirical distribution
131 approximates the initial distribution. Then, in each iteration, the algorithm simulates the particles to solve the CME in the
132 prediction step and then correct their weights according to the new observations. Based on the prediction and the correction steps,
133 a numerical filter is constructed by the empirical distribution of the particles, i.e., $\hat{\pi}_{t_{i+1}}^{\text{PF}}(x) = \sum_{j=1}^N w_j(t_{i+1}) \mathbb{1}(x_j(t_{i+1}) = x)$.
Finally, the algorithm resamples particles to delete non-significant particles.

Algorithm 1 Particle filter (adapted from [3])

- 1: Generate N particle $(x_1(0), \dots, x_N(0))$ from the initial probability, and give them equal weights $(w_j(0) = \frac{1}{N}, j = 1, \dots, N)$.
▷ Initialization
 - 2: $i \leftarrow 0$ and $t_0 \leftarrow 0$.
 - 3: **while** t_i is not the final observation time **do**
 - 4: Simulate every particle from time t_i to t_{i+1} according to (2). ▷ Prediction (see (6))
 - 5: Update weights $w_j(t_{i+1}) \propto w_j(t_i) L(Y(t_{i+1}) | x_j(t_{i+1}))$. ▷ Adjustment (see (7))
 - 6: Compute the filter $\hat{\pi}_{t_{i+1}}^{\text{PF}}(x) = \sum_{j=1}^N w_j(t_{i+1}) \mathbb{1}(x_j(t_{i+1}) = x)$ ▷ Compute the filter
 - 7: Resample $\{w_j(t_{i+1}), x_j(t_{i+1})\}$ to obtain equally weighted particles $\{1/N, x_j(t_{i+1})\}$ ▷ Delete non-significant particles
 - 8: $i \leftarrow i + 1$.
 - 9: **end while**
-

134 Now, we analyze the error of the particle filter $\hat{\pi}_{t_i}^{\text{PF}}(x)$. We first look at the L_1 error of this filter at the first observation
135 time point t_1 . (Readers who are not interested in the mathematical derivation can directly go to (13).) Given a fixed $Y(t_i)$,
136 the literature [4, Theorem 1] tells that for any $x \in \mathbb{Z}^n$, there is the central limit result

$$138 \quad \sqrt{N} (\hat{\pi}_{t_1}^{\text{PF}}(x) - \pi_{t_1}(x)) \xrightarrow{\text{in distribution}} \mathcal{N} \left(0, \text{Var} \left[\frac{\pi_{t_1}(x_1(t_1))}{\rho_{t_1}(x_1(t_1))} [\mathbb{1}(x_1(t_1) = x) - \pi_{t_1}(x)] \middle| Y(t_1) \right] \right), \quad \text{as } N \rightarrow \infty,$$

139 where $\pi_{t_1}(\cdot)$ is the exact filter at t_1 , the letter $\mathcal{N}$ is the notation for the Gaussian distribution, the term $x_1(t_1)$ is the value of
140 the first particle at time t_1 before the resampling step, the term $\rho_{t_1}(x)$ is the prediction probability $\mathbb{P}(X(t_1) = x)$, and $\mathbb{1}(\cdot)$ is
141 the indicator function. Based on this formula, we can conclude that

$$142 \quad \lim_{N \rightarrow \infty} \sqrt{N} \mathbb{E} \left[\left| \hat{\pi}_{t_1}^{\text{PF}}(x) - \pi_{t_1}(x) \right| \middle| Y(t_1) \right] = \sqrt{\frac{2}{\pi}} \sqrt{\text{Var} \left[\frac{\pi_{t_1}(x_1(t_1))}{\rho_{t_1}(x_1(t_1))} [\mathbb{1}(x_1(t_1) = x) - \pi_{t_1}(x)] \middle| Y(t_1) \right]}. \quad (10)$$

143 To further investigate (10), we simplify the variance in this formula as follows. We first term $\rho_{t_1}^Y(y) \triangleq \sum_{x \in \mathbb{R}^n} L(y|x) \rho_{t_1}(x)$ as
144 the density of $Y(t_1)$. Using this notation, we can write $\pi_{t_1}(x_1(t_1)) / \rho_{t_1}(x_1(t_1)) = L(Y(t_1) | x_1(t_1)) / \rho_{t_1}^Y(Y(t_1))$. Since $x_1(t_1)$

has the distribution ρ_{t_1} , we can easily check that given $Y(t_1)$, the random variable $\frac{\pi_{t_1}(x_1(t_1))}{\rho_{t_1}(x_1(t_1))} [\mathbb{1}(x_1(t_1) = x) - \pi_{t_1}(x)]$ has zero conditional mean, and its conditional variance satisfies

$$\mathbb{V}ar \left[\frac{\pi_{t_1}(x_1(t_1))}{\rho_{t_1}(x_1(t_1))} [\mathbb{1}(x_1(t_1) = x) - \pi_{t_1}(x)] \middle| Y(t_1) \right] \leq \left(\frac{L(Y(t_1)|x)}{\rho_{t_1}^Y(Y(t_1))} \right)^2 \rho_{t_1}(x) + \pi_{t_1}^2(x) \sum_{x' \in \mathbb{R}^n} \left(\frac{L(Y(t_1)|x')}{\rho_{t_1}^Y(Y(t_1))} \right) \pi_{t_1}(x')$$

and

$$\mathbb{V}ar \left[\frac{\pi_{t_1}(x_1(t_1))}{\rho_{t_1}(x_1(t_1))} [\mathbb{1}(x_1(t_1) = x) - \pi_{t_1}(x)] \middle| Y(t_1) \right] \geq \left(\frac{L(Y(t_1)|x)}{\rho_{t_1}^Y(Y(t_1))} \right)^2 \rho_{t_1}(x) (1 - \pi_{t_1}(x))^2.$$

Moreover, by applying $\sqrt{a+b} \leq \sqrt{a} + \sqrt{b}$ and $L(y|x) \leq \det(\sqrt{2\pi}\Sigma)^{-1}$ ($\det$ is the determinant notation) to the above equations, we can further obtain

$$\sqrt{\mathbb{V}ar \left[\frac{\pi_{t_1}(x_1(t_1))}{\rho_{t_1}(x_1(t_1))} [\mathbb{1}(x_1(t_1) = x) - \pi_{t_1}(x)] \middle| Y(t_1) \right]} \leq \left(\frac{L(Y(t_1)|x)}{\rho_{t_1}^Y(Y(t_1))} \right) \sqrt{\rho_{t_1}(x)} + \pi_{t_1}(x) \sqrt{\frac{\det(\sqrt{2\pi}\Sigma)^{-1}}{\rho_{t_1}^Y(Y(t_1))}} \quad (11)$$

and

$$\begin{aligned} \sqrt{\mathbb{V}ar \left[\frac{\pi_{t_1}(x_1(t_1))}{\rho_{t_1}(x_1(t_1))} [\mathbb{1}(x_1(t_1) = x) - \pi_{t_1}(x)] \middle| Y(t_1) \right]} &\geq \left(\frac{L(Y(t_1)|x)}{\rho_{t_1}^Y(Y(t_1))} \right) \sqrt{\rho_{t_1}(x)} (1 - \pi_{t_1}(x)) \\ &= \left(\frac{L(Y(t_1)|x)}{\rho_{t_1}^Y(Y(t_1))} \right) \sqrt{\rho_{t_1}(x)} \left(1 - \sqrt{\rho_{t_1}(x)} \sqrt{\pi_{t_1}(x)} \sqrt{\frac{L(Y(t_1)|x)}{\rho_{t_1}^Y(Y(t_1))}} \right) \\ &\geq \left(\frac{L(Y(t_1)|x)}{\rho_{t_1}^Y(Y(t_1))} \right) \left(\sqrt{\rho_{t_1}(x)} - \rho_{t_1}(x) \sqrt{\frac{\det(\sqrt{2\pi}\Sigma)^{-1}}{\rho_{t_1}^Y(Y(t_1))}} \right). \end{aligned} \quad (12)$$

Finally, by plugging (11) and (12) into (10), we can estimate the L_1 error of the particle filter by

$$\begin{aligned} \lim_{N \rightarrow \infty} \sqrt{N} \mathbb{E} [\|\hat{\pi}_{t_1}^{\text{PF}} - \pi_{t_1}\|_1] &\triangleq \lim_{N \rightarrow \infty} \sqrt{N} \sum_{x \in \mathbb{Z}^n} \mathbb{E} [\|\hat{\pi}_{t_1}^{\text{PF}}(x) - \pi_{t_1}(x)\|] \\ &= \sqrt{\frac{2}{\pi}} \left[\left(\sum_{x \in \mathbb{Z}_{\geq 0}^n} \sqrt{\rho_{t_1}(x)} \right) \pm \det(\sqrt{2\pi}\Sigma)^{-1/2} \int_{y \in \mathbb{R}^m} \sqrt{\rho_{t_1}^Y(y)} dy \right], \end{aligned} \quad (13)$$

provided that the quantities $\sum_{x \in \mathbb{Z}_{\geq 0}^n} \sqrt{\rho_{t_1}(x)}$ and $\int_{y \in \mathbb{R}^m} \sqrt{\rho_{t_1}^Y(y)} dy$ are convergent. Here, m is the dimension of $Y(t_1)$.

The formula (13) tells that for a large but fixed sample size N , the error of the particle filter at time t_1 largely depends on the quantities $\sum_{x \in \mathbb{Z}_{\geq 0}^n} \sqrt{\rho_{t_1}(x)}$ and $\det(\sqrt{2\pi}\Sigma)^{-1/2} \int_{y \in \mathbb{R}^m} \sqrt{\rho_{t_1}^Y(y)} dy$. Similar to the analysis in the previous subsection, these two terms tend to grow exponentially with the system dimension and the observation dimension, respectively. Note that the system dimension is usually much larger than the observation dimension, and the observation noise is usually not negligible. So, we can conclude that the quantity $\sum_{x \in \mathbb{Z}_{\geq 0}^n} \sqrt{\rho_{t_1}(x)}$ dominates in (13), and, therefore, the L_1 error of $\pi_{t_1}^{\text{PF}}$ tend to scale exponentially with the system dimension n . Moreover, this also suggests that the particle filter for the filtering problem has relatively the same performance as the Monte-Carlo method for solving the CME. Particularly, their performance are the same when the observation noise intensity is sufficiently large, i.e., the observation does not provide any information of the system.

Remark 1. For other observation time points, we conjecture that the same results should also hold true. A theoretical analysis can be performed in the same way as we presented above, with the exception that the particles $x_1(t_i), \dots, x_N(t_i)$ do not have the distribution ρ_{t_i} before the adjustment step. Instead, the particles converges to the distribution ρ_{t_i} in the limit of large sample size [4], which definitely complicates the analysis. However, we conjecture that this discrepancy should not affect the performance of the particle filter too much, and, therefore, the results obtained for time t_1 should also apply to other time points. Our numerical studies also support this point (see Fig. 6G–H in the main text). Since this theoretical analysis can be very long, we leave it for further work.

S3. Rao-Blackwellized CME solver (RB-CME solver): derivation, error analysis, and the optimal lead-follower decomposition.

A. Leader-follower decomposition and the conditional independence among follower subsystems. The Rao-Blackwellized CME solver (RB-CME solver) is established based on a decomposition of the system. We first divide the system state $X(t)$ into a leader system $\tilde{X}(t)$ and a follower subsystem $Z(t)$. Furthermore, we decompose each reaction vector ζ_j into $\zeta_j^{\tilde{X}}$ and ζ_j^Z , where $\zeta_j^{\tilde{X}}$ indicates the state change of the leader system, and ζ_j^Z indicates the state change of the follower system. For the follower system, we further decompose it into several subsystems, $Z_1(t), \dots, Z_l(t)$, such that the following topological conditions are satisfied.

C1 Each reaction involves a maximum of one follower subsystem (meaning that at most one follower subsystem can influence the reaction's propensity or have its state altered by the reaction).

C2 The reactions with the same non-zero $\zeta_j^{\tilde{X}}$ involve a maximum of one follower subsystem (meaning that at most one follower subsystem can influence the propensities of these reactions or have its state altered by these reactions).

For the ease of notations, we rearrange the order of species such that $X(t) = (\tilde{X}(t), Z_1(t), \dots, Z_l(t))$; also, for every state x , we write $x = (\tilde{x}, z_1, \dots, z_l)$, where $\tilde{x}$ is the state of the leader system, and z_i ($i = 1, \dots, l$) is the state of the follower system. We denote the dimension of the leader system by $n_{\tilde{X}}$ and the dimension of the follower system by n_Z . An automated algorithm for this leader-follower decomposition is presented in Section S3.D.

One key ingredient in our new method is computing the conditional distribution of the follower system given the trajectory of the leader one, i.e., $\mathbb{P}(Z(t) = z | \tilde{X}(s), 0 \leq s \leq t)$. Mathematically, this conditional probability is not uniquely defined for each $t > 0$; it can be any $\tilde{X}_t$ -measurable* random variable $\mathcal{P}(z)$ satisfying

$$\mathbb{E}[\mathcal{P}(z)A] = \mathbb{E}[\mathbb{1}(Z(t) = z)A] \quad \forall \tilde{X}_t\text{-measurable random variable } A \text{ with finite expectation.}$$

Therefore, $\mathbb{P}(Z(t) = z | \tilde{X}(s), 0 \leq s \leq t)$ viewed as a continuous-time process is not uniquely defined either, and some of them can be non-cadlag. ("Cadlag" means right continuous and having a left limit). Fortunately, [5, Theorem 2.24] and the right continuity of $X(t)$ guarantee that for each $z \in \mathbb{Z}_{\geq 0}^{n_Z}$, there exists a $\tilde{X}_t$ -adaptive cadlag process $\pi_{Z|\tilde{X}}(t, z)$ satisfying $\pi_{Z|\tilde{X}}(t, z) = \mathbb{P}(Z(t) = z | \tilde{X}(s), 0 \leq s \leq t)$ almost surely for every t . Moreover, since the propensities are uniformly integrable due to (3), the conditional expectation $\pi_{Z|\tilde{X}}(t, \lambda_j) \triangleq \sum_{z' \in \mathbb{Z}_{\geq 0}^{n_Z}} \lambda_j(\tilde{X}(t), z') \pi_{Z|\tilde{X}}(t, z')$ is also cadlag for each $j = 1, \dots, r$ [5, Remark 2.27]. In the following, we only consider this cadlag conditional probability $\pi_{Z|\tilde{X}}(t, \cdot)$ for the follower system. Also, when discussing other conditional probability, we are referring to a distribution that is cadlag.

Before introducing the equation characterizing the conditional probability $\pi_{Z|\tilde{X}}(t, \cdot)$, we list a few necessary notations. Following [6], we term $\mathcal{O} \triangleq \{j | \zeta_j^{\tilde{X}} \neq \mathbf{0}_{n_{\tilde{X}}}\}$ as the leader-level reactions, where $\mathbf{0}_{n_{\tilde{X}}}$ is the $n_{\tilde{X}}$ -dimensional zero vector. Here, we use the notation $\mathcal{O}$ to indicate that these reactions are 'observable' given the trajectory of $\tilde{X}(\cdot)$. Similarly, we term $\mathcal{U} \triangleq \{j | j \notin \mathcal{O}\}$ as the follower-level reactions, where the notation $\mathcal{U}$ indicates that these reactions are 'unobservable' given the trajectory of $\tilde{X}(t)$. Note that for these leader-level reactions, some $\zeta_j^{\tilde{X}}$ might have the same value. To consider this issue, we term

- $\{\xi_1, \dots, \xi_{r_1}\}$ as the set of non-zero and distinct $\zeta_j^{\tilde{X}}$,
- $\mathcal{O}_{\xi_k} \triangleq \{j | \zeta_j^{\tilde{X}} = \xi_k\}$ ($k = 1, \dots, r_1$) as the set in which non-zero $\zeta_j^{\tilde{X}}$ are identical to ξ_k ,
- $\tilde{R}_{\xi_k}(t) \triangleq \sum_{j \in \mathcal{O}_{\xi_k}} R_j \left(\int_0^t \lambda_j(\tilde{X}(s), Z(s)) ds \right)$ as the total firing number of the reactions in $\mathcal{O}_{\xi_k}$ up to time t ,
- $\lambda^{\mathcal{O}_{\xi_k}}(\tilde{X}(s), Z(s)) \triangleq \sum_{j \in \mathcal{O}_{\xi_k}} \lambda_j(\tilde{X}(s), Z(s))$ as the rate of the process $\tilde{R}_{\xi_k}(t)$,
- $\lambda^{\mathcal{O}}(\tilde{X}(s), Z(s)) \triangleq \sum_{j \in \mathcal{O}} \lambda_j(\tilde{X}(s), Z(s))$.

Note that processes $\tilde{R}_{\xi_1}(t), \dots, \tilde{R}_{\xi_{r_1}}(t)$ contain the same information as the leader system $\tilde{X}(t)$, meaning that we can construct the former given the trajectory of the latter and vice versa.

Then, under the condition (3), the conditional probability $\pi_{Z|\tilde{X}}(t, z)$ (for any $z \in \mathbb{Z}_{\geq 0}^{n_Z}$), is almost surely characterized by

* $\tilde{X}_t$ is the filtration generated by the process $X(t)$.

[heuristically derived in [6–9] and rigorously verified in [10]]

$$\begin{aligned} \pi_{Z|\tilde{X}}(t, z) = & \pi_{Z|\tilde{X}}(0, z) + \int_0^t \sum_{j \in \mathcal{U}} \lambda_j(\tilde{X}(s), z - \zeta_j^Z) \pi_{Z|\tilde{X}}(s, z - \zeta_j^Z) - \sum_{j \in \mathcal{U}} \lambda_j(\tilde{X}(s), z) \pi_{Z|\tilde{X}}(s, z) ds \\ & - \int_0^t \pi_{Z|\tilde{X}}(s, z) \left(\lambda^\circ(\tilde{X}(s), z) - \sum_{z' \in \mathbb{Z}_{\geq 0}^n} \lambda^\circ(\tilde{X}(s), z') \pi_{Z|\tilde{X}}(s, z') \right) ds \\ & + \sum_{k=1}^{r_1} \int_0^t \left(\frac{\sum_{j \in \mathcal{O}_{\xi_k}} \lambda_j(\tilde{X}(s^-), z - \zeta_j^Z) \pi_{Z|\tilde{X}}(s^-, z - \zeta_j^Z)}{\sum_{z' \in \mathbb{Z}_{\geq 0}^n} \lambda^{\mathcal{O}_{\xi_k}}(\tilde{X}(s^-), z') \pi_{Z|\tilde{X}}(s^-, z')} - \pi_{Z|\tilde{X}}(s^-, z) \right) d\tilde{R}_{\xi_k}(s), \end{aligned} \quad (14)$$

and

$$\int_0^t \sum_{z \in \mathbb{Z}_{\geq 0}^n} \sum_{j=1}^r \lambda_j(\tilde{X}(s), z) \pi_{Z|\tilde{X}}(s, z) ds < \infty \text{ almost surely, } \quad \forall t \geq 0. \quad (15)$$

Here, we call (14) the filtered CME for $Z(t)$. The integral in the first line of (14) represents the contributions from the unobserved reactions. Notably, the terms in this integral are very similar to the terms in the CME. Particularly, when all the reactions are unobservable, the subsequent components in (14) will be zero, reducing the filtered CME to the classical CME. This fact is logical, as the CME describes the unconditioned distribution of the reaction system in scenarios where no reaction or species is observable. The second and third lines of (14) represent the adjustment to the conditional distribution based on the exact firing time of the observable reactions. Moreover, (15) indicates that the conditional expectations of the propensities are non-explosive. To enhance the understanding of the filtered CME, we present here an example adapted from [6].

Example 1. Let's consider a gene-expression system consisting of two species (S_1 : Protein; S_2 : mRNA) and three reactions



All the reactions have mass-action kinetics. In this system, we classify the protein (S_1) as the leader species and mRNA (S_2) as the follower species. In other words, we term $\tilde{X}(t)$ as the copy number of the Protein and $Z(s)$ as the copy number of the mRNA. Then, there is only one non-zero $\zeta_j^{\tilde{X}}$, which is 1 resulting from the first reaction. We denote this as ξ_1 . By definition, the set of observable reactions associated with ξ_1 is $\mathcal{O}_{\xi_1} = \{1\}$, and the set of unobservable reactions is $\mathcal{U} = \{2, 3\}$. Moreover, we have the jump process $\tilde{R}_{\xi_k}(t) = R_1 \left(\int_0^t k_1 Z(s) ds \right)$, and $\lambda^{\mathcal{O}_{\xi_1}}(\tilde{X}(t), Z(t)) = \lambda^\circ(\tilde{X}(t), Z(t)) = k_1 Z(t)$. Then, by (14), the conditional distribution of the follower species (mRNA), denoted by $\pi_{Z|\tilde{X}}(t, z) \triangleq \mathbb{P}(Z(t) = z | \tilde{X}(s), 0 \leq s \leq t)$, satisfies the equation

$$\begin{aligned} \pi_{Z|\tilde{X}}(t, z) = & \pi_{Z|\tilde{X}}(0, z) + \int_0^t k_2 \pi_{Z|\tilde{X}}(s, z - 1) + k_3(z + 1) \pi_{Z|\tilde{X}}(s, z + 1) - [k_2 + K_3(z + 1)] \pi_{Z|\tilde{X}}(s, z) ds \\ & - \int_0^t \pi_{Z|\tilde{X}}(s, z) \left(k_1 z - \sum_{z'} k_1 z' \pi_{Z|\tilde{X}}(s, z') \right) ds \\ & + \int_0^t \left(\frac{k_1 z \pi_{Z|\tilde{X}}(s^-, z)}{\sum_{z'} k_1 z' \pi_{Z|\tilde{X}}(s^-, z')} - \pi_{Z|\tilde{X}}(s^-, z) \right) d\tilde{R}_{\xi_1}(s). \end{aligned}$$

Here, the integral in the first line represents the contribution by the unobservable reactions, and the subsequent terms represent the contributions by the observable reactions.

Now, we show that the follower subsystems $Z_1(t), \dots, Z_l(t)$ are conditionally independent given the trajectory of the leader system, and the filtered CME (14) can be divided into several lower dimensional, independent equations. We first introduce some notations. For each vector ζ_j^Z ($j = 1, \dots, r$), we decompose it into $\zeta_j^{Z_1}, \dots, \zeta_j^{Z_l}$, where $\zeta_j^{Z_i}$ corresponds to the state change of $Z_i(t)$ after the firing of the j -th reaction. Also, we denote the dimension of $Z_i(t)$ ($i = 1, \dots, l$) by n_{Z_i} . For each follower subsystem $Z_i(t)$, we term $\mathcal{U}_i \triangleq \{j \in \mathcal{U} | \zeta_j^{Z_i} \neq \mathbf{0}_{n_{Z_i}} \text{ or } \lambda_j(\tilde{x}, z_1, \dots, z_l) \text{ depends on } z_i\}$ as the follower-level reactions involving $Z_i(t)$, and we term

$$\begin{aligned} \mathcal{O}_i &\triangleq \bigcup_{k: \lambda^{\mathcal{O}_{\xi_k}}(\tilde{x}, z_1, \dots, z_l) \text{ depends on } z_i, \\ &\quad \text{or } \zeta_j^{Z_i} \neq \mathbf{0}_{n_{Z_i}} \text{ for some } j \in \mathcal{O}_{\xi_k}} \mathcal{O}_{\xi_k} \end{aligned}$$

as the leader-level reactions that involves $Z_i(t)$. According to the conditions C1 and C2, we can easily conclude that

254 Conclusion 1 The sets $\mathcal{U}_1, \dots, \mathcal{U}_l$ are disjoint, and $\mathcal{U} = \bigcup_{i=1}^l \mathcal{U}_i$. (By C1 and the definition of $\mathcal{U}_i$)

255 Conclusion 2 For any $i \in \{1, \dots, l\}$ and $k \in \{1, \dots, r_1\}$, there is either $\mathcal{O}_{\xi_k} \subset \mathcal{O}_i$ or $\mathcal{O}_{\xi_k} \cap \mathcal{O}_i = \emptyset$. (By definition)

256 Conclusion 3 The sets $\mathcal{O}_1, \dots, \mathcal{O}_l$ are disjoint. (By Conclusion 2 and C2)

257 Conclusion 4 If $j \in \mathcal{O}/\mathcal{O}_i$, then $\zeta_j^{Z_i} = 0_{n_{Z_i}}$. (By definition).

258 Then, the conditional independence of the follower subsystems are guaranteed by the following theorem.

259 **Theorem 1.** Assume that condition (3) holds, the follower subsystems $Z_1(t), \dots, Z_l(t)$ satisfy C1 and C2, and $Z_1(0), \dots, Z_l(0)$
 260 are conditionally independent given $\tilde{X}(0)$. Then, for any $t > 0$, the follower subsystems $Z_1(t), \dots, Z_l(t)$ are conditionally
 261 independent given the trajectory of $\tilde{X}(\cdot)$ up to time t . Their marginal conditional probability defined by $\pi_{Z_i|\tilde{X}}(t, z_i) \triangleq$
 262 $\mathbb{P}(Z_i(t) = z_i | \tilde{X}(s), 0 \leq s \leq t)$ is almost surely characterized by

$$\begin{aligned} \pi_{Z_i|\tilde{X}}(t, z_i) &= \pi_{Z_i|\tilde{X}}(0, z_i) + \int_0^t \sum_{j \in \mathcal{U}_i} \lambda_j(\tilde{X}(s), z_i - \zeta_j^{Z_i}) \pi_{Z_i|\tilde{X}}(s, z_i - \zeta_j^{Z_i}) - \sum_{j \in \mathcal{U}_i} \lambda_j(\tilde{X}(s), z_i) \pi_{Z_i|\tilde{X}}(s, z_i) ds \\ &\quad - \int_0^t \pi_{Z_i|\tilde{X}}(s, z_i) \left(\lambda^{\mathcal{O}_i}(\tilde{X}(s), z_i) - \sum_{z'_i \in \mathbb{Z}_{\geq 0}^{n_{Z_i}}} \lambda^{\mathcal{O}_i}(\tilde{X}(s), z'_i) \pi_{Z_i|\tilde{X}}(s, z'_i) \right) ds \\ &\quad + \sum_{k: \mathcal{O}_{\xi_k} \subset \mathcal{O}_i} \int_0^t \left(\frac{\sum_{j \in \mathcal{O}_{\xi_k}} \lambda_j(\tilde{X}(s^-), z_i - \zeta_j^{Z_i}) \pi_{Z_i|\tilde{X}}(s^-, z_i - \zeta_j^{Z_i})}{\sum_{z'_i \in \mathbb{Z}_{\geq 0}^{n_{Z_i}}} \lambda^{\mathcal{O}_{\xi_k}}(\tilde{X}(s^-), z'_i) \pi_{Z_i|\tilde{X}}(s^-, z'_i)} - \pi_{Z_i|\tilde{X}}(s^-, z_i) \right) d\tilde{R}_{\xi_k}(s), \end{aligned} \quad (16)$$

266 and

$$\int_0^t \sum_{z_i \in \mathbb{Z}_{\geq 0}^{n_{Z_i}}} \sum_{j \in \mathcal{U}_i \cup \mathcal{O}_i} \lambda_j(\tilde{X}(s), z_i) \pi_{Z_i|\tilde{X}}(s, z_i) ds < \infty \text{ almost surely, } \quad \forall t \geq 0.$$

268 where $\lambda_j(\tilde{X}(t), z_i)$ (for $j \in \mathcal{U}_i \cup \mathcal{O}_i$) is the abbreviation of the propensity $\lambda_j(\tilde{X}(t), z_1, \dots, z_l)$ (which does not depend on
 269 variables other than $\tilde{X}(t)$ and z_i due to the definition of $\mathcal{O}_i$ and Conclusion 1), $\lambda^{\mathcal{O}_i}(\tilde{X}(s), z') \triangleq \sum_{j \in \mathcal{O}_i} \lambda_j(\tilde{X}(s), Z_i(s))$, and
 270 n_{Z_i} is the dimension of $Z_i(t)$.

Proof. To prove the result, we only need to calculate the conditional probability

$$\pi_{Z_i|\tilde{X}_{Z_i}}(t, z_i) \triangleq \mathbb{P}(Z_i(t) = z_i | \tilde{X}(s), Z_1(s), \dots, Z_{i-1}(s), Z_{i+1}(s), \dots, Z_l(s) \ 0 \leq s \leq t)$$

271 (for $i = 1, \dots, l$) and show it is irrelevant to the trajectory of other follower subsystems, i.e., $Z_1(\cdot), \dots, Z_{i-1}(\cdot), Z_{i+1}(\cdot), \dots, Z_l(\cdot)$.
 272 Here, we present the proof for the case $i = 1$; the rest results can be shown in the same way.

273 To compute $\pi_{Z_i|\tilde{X}_{Z_i}}(t, z_i)$, we can view $\mathcal{U}_1$ as the unobservable reactions given the trajectory of $\tilde{X}(\cdot), Z_2(\cdot), \dots, Z_l(\cdot)$ and
 274 the reactions in $\mathcal{O} \cup_{i=2}^l \mathcal{U}_i$ as observable reactions given these trajectories. We term

- 275 • $\tilde{\mathcal{O}} = \mathcal{O} \cup_{i=2}^l \mathcal{U}_i$ as the set of ‘observable’ reactions in this case,
- 276 • $\lambda^{\tilde{\mathcal{O}}/\mathcal{O}_1}(\tilde{x}, z_1, \dots, z_l) \triangleq \sum_{j \in \tilde{\mathcal{O}}/\mathcal{O}_1} \lambda_j(\tilde{x}, z_1, \dots, z_l)$ as the total propensity for the reaction in $\tilde{\mathcal{O}}/\mathcal{O}_1$,
- 277 • $\{\eta_1, \dots, \eta_{r_2}\}$ as the set of non-zero and distinct $(\zeta_j^{\tilde{X}}, \zeta_j^{Z_2}, \dots, \zeta_j^l)$ for $j \in \mathcal{O} \cup_{i=2}^l \mathcal{U}_i$,
- 278 • $\tilde{\mathcal{O}}_{\eta_k} \triangleq \left\{ j \in \mathcal{O} \cup_{i=2}^l \mathcal{U}_i \mid (\zeta_j^{\tilde{X}}, \zeta_j^{Z_2}, \dots, \zeta_j^l) = \eta_k \right\}$ for $k = 1, \dots, r_2$,
- 279 • $\tilde{R}_{\eta_k}(t) \triangleq \sum_{j \in \tilde{\mathcal{O}}_{\eta_k}} R_j \left(\int_0^t \lambda_j(\tilde{X}(s), Z_1(s), \dots, Z_l(s)) ds \right)$ as the total firing number of the reactions in $\tilde{\mathcal{O}}_{\eta_k}$ up to time t ,
- 280 • $\lambda^{\mathcal{O}_{\eta_k}}(\tilde{X}(s), Z_1(s), \dots, Z_l(s)) \triangleq \sum_{j \in \mathcal{O}_{\eta_k}} \lambda_j(\tilde{X}(s), Z_1(s), \dots, Z_l(s))$ as the rate of the process $\tilde{R}_{\eta_k}(t)$,

Consequently, by (14), we conclude that $\pi_{Z_1|\tilde{X}Z/1}(t, z_1)$ is characterized by

$$\begin{aligned}
& \pi_{Z_1|\tilde{X}Z/1}(t, z_1) \\
&= \pi_{Z_1|\tilde{X}Z/1}(0, z_1) \\
&+ \int_0^t \sum_{j \in \mathcal{U}_1} \lambda_j(\tilde{X}(s), z_1 - \zeta_j^{Z_1}, Z_2(s), \dots, Z_l(s)) \pi_{Z_1|\tilde{X}Z/1}(s, z_1 - \zeta_j^{Z_1}) ds \\
&- \int_0^t \sum_{j \in \mathcal{U}_1} \lambda_j(\tilde{X}(s), z_1, Z_2(s), \dots, Z_l(s)) \pi_{Z_1|\tilde{X}Z/1}(s, z_1) ds \\
&- \int_0^t \pi_{Z_1|\tilde{X}Z/1}(s, z_1) \left(\lambda^{\mathcal{O}_1}(\tilde{X}(s), z_1, Z_2(s), \dots, Z_l(s)) - \sum_{z'_1 \in \mathbb{Z}_{\geq 0}^{n_{Z_1}}} \lambda^{\mathcal{O}_1}(\tilde{X}(s), z'_1, Z_2(s), \dots, Z_l(s)) \pi_{Z_1|\tilde{X}Z/1}(s, z'_1) \right) ds \\
&- \int_0^t \pi_{Z_1|\tilde{X}Z/1}(s, z_1) \left(\lambda^{\tilde{\mathcal{O}}/\mathcal{O}_1}(\tilde{X}(s), z_1, Z_2(s), \dots, Z_l(s)) - \sum_{z'_1 \in \mathbb{Z}_{\geq 0}^{n_{Z_1}}} \lambda^{\tilde{\mathcal{O}}/\mathcal{O}_1}(\tilde{X}(s), z'_1, Z_2(s), \dots, Z_l(s)) \pi_{Z_1|\tilde{X}Z/1}(s, z'_1) \right) ds \\
&+ \sum_{k: \tilde{\mathcal{O}}_{\eta_k} \cap \mathcal{O}_1 \neq \emptyset} \int_0^t \left(\frac{\sum_{j \in \tilde{\mathcal{O}}_{\eta_k}} \lambda_j(\tilde{X}(s^-), z_1 - \zeta_j^{Z_1}, Z_2(s), \dots, Z_l(s)) \pi_{Z_1|\tilde{X}Z/1}(s^-, z_1 - \zeta_j^{Z_1})}{\sum_{z'_1 \in \mathbb{Z}_{\geq 0}^{n_{Z_1}}} \lambda^{\tilde{\mathcal{O}}_{\eta_k}}(\tilde{X}(s^-), z'_1, Z_2(s), \dots, Z_l(s)) \pi_{Z_1|\tilde{X}Z/1}(s^-, z'_1)} - \pi_{Z_1|\tilde{X}Z/1}(s^-, z_1) \right) d\tilde{R}_{\eta_k}(s) \\
&+ \sum_{k: \tilde{\mathcal{O}}_{\eta_k} \cap \mathcal{O}_1 = \emptyset} \int_0^t \left(\frac{\sum_{j \in \tilde{\mathcal{O}}_{\eta_k}} \lambda_j(\tilde{X}(s^-), z_1 - \zeta_j^{Z_1}, Z_2(s), \dots, Z_l(s)) \pi_{Z_1|\tilde{X}Z/1}(s^-, z_1 - \zeta_j^{Z_1})}{\sum_{z'_1 \in \mathbb{Z}_{\geq 0}^{n_{Z_1}}} \lambda^{\tilde{\mathcal{O}}_{\eta_k}}(\tilde{X}(s^-), z'_1, Z_2(s), \dots, Z_l(s)) \pi_{Z_1|\tilde{X}Z/1}(s^-, z'_1)} - \pi_{Z_1|\tilde{X}Z/1}(s^-, z_1) \right) d\tilde{R}_{\eta_k}(s),
\end{aligned}$$

which holds almost surely. By the independence condition (4), we can write $\pi_{Z_1|\tilde{X}Z/1}(0, z_1) = \pi_{Z_1|\tilde{X}}(0, z_1)$. Moreover, By Conclusion 1 and Conclusion 3, the propensities in 3rd to 5th line only depend on the first two arguments. With the same reason, the propensities $\lambda_j(\tilde{x}, z_1, \dots, z_l)$ (for every $j \in \tilde{\mathcal{O}}/\mathcal{O}_1$) depend on z_1 , and, therefore, the 6th line is zero. Moreover, by Conclusion 2, we can conclude that $\tilde{\mathcal{O}}_{\eta_k} \cap \mathcal{O}_1 \neq \emptyset$ holds only if $\tilde{\mathcal{O}}_{\eta_k} \subset \mathcal{O}_1$; consequently, by Conclusion 4 and the definition of $\mathcal{O}_1$, we can rewrite the 7th line by

$$\sum_{k: \tilde{\mathcal{O}}_{\xi_k} \subset \mathcal{O}_1} \int_0^t \left(\frac{\sum_{j \in \tilde{\mathcal{O}}_{\xi_k}} \lambda_j(\tilde{X}(s^-), z_1 - \zeta_j^{Z_1}) \pi_{Z_1|\tilde{X}Z/1}(s^-, z_1 - \zeta_j^{Z_1})}{\sum_{z'_1 \in \mathbb{Z}_{\geq 0}^{n_{Z_1}}} \lambda^{\tilde{\mathcal{O}}_{\xi_k}}(\tilde{X}(s^-), z'_1) \pi_{Z_1|\tilde{X}Z/1}(s^-, z'_1)} - \pi_{Z_1|\tilde{X}Z/1}(s^-, z_1) \right) d\tilde{R}_{\xi_k}(s).$$

By Conclusion 1, Conclusion 3, and Conclusion 4, the propensities in the 8th line does not depend on the second argument, and the vectors $\zeta_j^{Z_1}$ in this line are always zero. Consequently, the 8th line is zero. Finally, by combining all these results, we can rewrite the dynamics of $\pi_{Z_1|\tilde{X}Z/1}(t, z_1)$ (which satisfies (16)) and find that it is almost surely irrelevant to the trajectory of $Z_2(\cdot), \dots, Z_l(\cdot)$. Moreover, by (3), $\pi_{Z_1|\tilde{X}Z/1}(t, z_1)$ also satisfies

$$\int_0^t \sum_{z_i \in \mathbb{Z}_{\geq 0}^{n_{Z_i}}} \sum_{j=1}^r \lambda_j(\tilde{X}(s), Z_1(s), \dots, Z_{i-1}(s), z_i, Z_{i+1}(s), \dots, Z_l(s)) \pi_{Z_1|\tilde{X}Z/1}(s, z_1) ds < \infty \text{ almost surely, } \quad \forall t \geq 0$$

or equivalently (by (3))

$$\int_0^t \sum_{z_i \in \mathbb{Z}_{\geq 0}^{n_{Z_i}}} \sum_{j \in \mathcal{U}_i \cup \mathcal{O}_i} \lambda_j(\tilde{X}(s), z_i) \pi_{Z_i|\tilde{X}}(s, z_i) ds < \infty \text{ almost surely, } \quad \forall t \geq 0.$$

Note that the solution of this equation and this inequality is unique, so we can further conclude that $\pi_{Z_1|\tilde{X}Z/1}(t, z_1)$ is also almost surely irrelevant to the trajectory of $Z_2(\cdot), \dots, Z_l(\cdot)$. This implies that the conditional probability $\pi_{Z_1|\tilde{X}}(t, z_1) \triangleq \mathbb{E}[\pi_{Z_1|\tilde{X}Z/1}(t, z_1) | \tilde{X}(s), 0 \leq s \leq t]$ equals to $\pi_{Z_1|\tilde{X}Z/1}(t, z_1)$ almost surely and, therefore, satisfies (16) and the inequality in this theorem with $i = 1$. $\square$

We call (16) the filtered CME for the follower subsystem $Z_i(t)$. Also, we can rewrite (16) into a differential form

$$\begin{aligned}
d\pi_{Z_i|\tilde{X}}(t, z_i) &= f_1(\tilde{X}(t), z_i, \pi_{Z_i|\tilde{X}}(t, \cdot)) dt + f_2(\tilde{X}(t), z_i, \pi_{Z_i|\tilde{X}}(t, \cdot)) dt \\
&+ \sum_{j=1}^r \mathbb{1}(\tilde{X}(t) - \tilde{X}(t^-) = \zeta_j^{\tilde{X}}) g_j(\tilde{X}(t^-), z_i, \pi_{Z_i|\tilde{X}}(t^-, \cdot))
\end{aligned} \tag{17}$$

310 where

$$311 \quad f_1(\tilde{X}(t), z_i, \pi_{Z_i|\tilde{X}}(t, \cdot)) = \sum_{j \in \mathcal{U}_i} \lambda_j(\tilde{X}(s), z_i - \zeta_j^{Z_i}) \pi_{Z_i|\tilde{X}}(s, z_i - \zeta_j^{Z_i}) - \sum_{j \in \mathcal{U}_i} \lambda_j(\tilde{X}(s), z_i) \pi_{Z_i|\tilde{X}}(s, z_i),$$

$$312 \quad f_2(\tilde{X}(t), z_i, \pi_{Z_i|\tilde{X}}(t, \cdot)) = -\pi_{Z_i|\tilde{X}}(s, z_i) \left(\lambda^{\mathcal{O}_i}(\tilde{X}(s), z_i) - \sum_{z'_i \in \mathbb{Z}_{\geq 0}^{n_{Z_i}}} \lambda^{\mathcal{O}_i}(\tilde{X}(s), z'_i) \pi_{Z_i|\tilde{X}}(s, z'_i) \right),$$

313 and

$$314 \quad g_j(\tilde{X}(t^-), z_i, \pi_{Z_i|\tilde{X}}(t^-, \cdot)) = \frac{1}{|\mathcal{O}_{\zeta_j^{\tilde{X}}}|} \mathbb{1}(j \in \mathcal{O}_i) \sum_{k: \xi_k = \zeta_j^{\tilde{X}}} \left(\frac{\sum_{j' \in \mathcal{O}_{\xi_k}} \lambda_{j'}(\tilde{X}(s^-), z_i - \zeta_{j'}^{Z_i}) \pi_{Z_i|\tilde{X}}(s^-, z_i - \zeta_{j'}^{Z_i})}{\sum_{z'_i \in \mathbb{Z}_{\geq 0}^{n_{Z_i}}} \lambda^{\mathcal{O}_{\xi_k}}(\tilde{X}(s^-), z'_i) \pi_{Z_i|\tilde{X}}(s^-, z'_i)} - \pi_{Z_i|\tilde{X}}(s^-, z_i) \right)$$

315 with $|\mathcal{O}_{\zeta_j^{\tilde{X}}}|$ the size of $\mathcal{O}_{\zeta_j^{\tilde{X}}}$. In (17), f_1 represents the prediction of the conditional distribution based on the dynamical model,
 316 and the remaining terms correspond to the corrections to the estimates in accordance with the dynamics of the observable
 317 species.

318 **B. Derivation of the Rao-Blackwellized CME solver.** We note that for any state $x = (\tilde{x}, z) = (\tilde{x}, z_1, \dots, z_l)$, the probability
 319 $p(t, x)$ can be written by

$$320 \quad p(t, x) = \mathbb{E}[\mathbb{1}(\tilde{X}(t) = \tilde{x}) \pi_{Z|\tilde{X}}(z)] = \mathbb{E}\left[\mathbb{1}(\tilde{X}(t) = \tilde{x}) \prod_{i=1}^l \pi_{Z_i|\tilde{X}}(z_i)\right]$$

321 where the first equality follows from the law of total expectation, and the second follows from Theorem 1. Consequently, we
 322 can use the following algorithm to solve the CME master equation.

- 323 • Generate N simulations of the system (2) and denote their leader-system parts by $\tilde{x}_1(t), \dots, \tilde{x}_N(t)$.
- 324 • For each $\tilde{x}_j(t)$ and each $Z_i(t)$, we calculate the conditional probability $q_j^i(t, z_i) \triangleq \mathbb{P}(Z_i(t) = z_i | \tilde{X}(s) = \tilde{x}_j(s), 0 \leq s \leq t)$
 325 using a filtering approach (e.g., the filtered FSP [10])
- 326 • Approximate the exact probability by the quantity $\hat{p}_{\text{RB}}(t, x) = \frac{1}{N} \sum_{j=1}^N \left[\mathbb{1}(\tilde{x}_j(t) = \tilde{x}) \prod_{i=1}^l q_j^i(t, z_i) \right]$.

327 We name this algorithm the Rao-Blackwellized CME solver (RB-CME solver).

328 In this paper's examples, we choose the filtered FSP [10] to solve the filtered CMEs. Specifically, this method approaches
 329 the unnormalized version of the filtered CME, which is linear between two neighboring jump time points. This method
 330 straightforwardly solves this unnormalized version on a large but finite state space and obtains the filter by normalization. We
 331 refer readers to the literature [10] for more details.

332 **C. Error analysis of the RB-CME solver.** Now, we analyze the error of the RB-CME solver and show that it is more accurate
 333 than the Monte-Carlo method given the same sample size N . Here, we assume that the error caused by the filtering approach
 334 applied to the filtered CME is negligible.

335 We focus on the L_1 error of the RB-CME solver, defined by $\|\hat{p}_{\text{RB}}(t, \cdot) - p(t, \cdot)\|_1 \triangleq \sum_{x \in \mathbb{Z}_{\geq 0}^n} |\hat{p}_{\text{RB}}(t, x) - p(t, x)|$. For every
 336 $j \in \{1, \dots, N\}$, $t > 0$, and $z = (z_1, \dots, z_l)$, we term $q_j(t, z) = \prod_{i=1}^l q_j^i(t, z_i)$ as the conditional probability of the whole
 337 follower system given the trajectory $\tilde{x}_j(\cdot)$ from 0 to t . Notice that $\{(\tilde{x}_j(t), q_j(t, z))\}_{j=1, \dots, N}$ are independently sampled from
 338 the distribution of $(\tilde{X}(t), \pi_{Z|\tilde{X}}(t, z))$; therefore, by the law of large numbers, we can conclude

$$339 \quad \sqrt{N}(\hat{p}_{\text{RB}}(t, x) - p(t, x)) \xrightarrow{d} \mathcal{N}\left(0, \text{Var}\left(\mathbb{1}(\tilde{X}(t) = \tilde{x}) \pi_{Z|\tilde{X}}(t, z)\right)\right) \quad \forall x \in \mathbb{Z}_{\geq 0}^n.$$

340 We can rewrite the variance by $\text{Var}\left(\mathbb{1}(\tilde{X}(t) = \tilde{x}) \pi_{Z|\tilde{X}}(t, z)\right) = \mathbb{E}\left[\pi_{Z|\tilde{X}}^2(t, z) | \tilde{X}(t) = \tilde{x}\right] p^{\tilde{X}}(t, \tilde{x}) - p^2(t, x)$ where $x = (\tilde{x}, z)$,
 341 and $p^{\tilde{X}}(t, \tilde{x}) = \mathbb{P}(\tilde{X}(t) = \tilde{x})$ is the marginal probability of the leader system. Consequently, the error of the RB-CME solver
 342 can be written by

$$343 \quad \lim_{N \rightarrow \infty} \sqrt{N} \mathbb{E}[\|\hat{p}_{\text{RB}}(t, \cdot) - p(t, \cdot)\|_1] = \sqrt{\frac{2}{\pi}} \sum_{x \in \mathbb{Z}_{\geq 0}^n} \sqrt{\mathbb{E}\left[\pi_{Z|\tilde{X}}^2(t, z) | \tilde{X}(t) = \tilde{x}\right] p^{\tilde{X}}(t, \tilde{x}) - p^2(t, x)}. \quad (18)$$

344 and

$$345 \quad \lim_{N \rightarrow \infty} \sqrt{N} \mathbb{E} [\|\hat{p}_{\text{RB}}(t, \cdot) - p(t, \cdot)\|_1] = \sqrt{\frac{2}{\pi}} \left[\left(\sum_{x \in \mathbb{Z}_{\geq 0}^n} \sqrt{\mathbb{E} [\pi_{Z|\tilde{X}}^2(t, z) | \tilde{X}(t) = \tilde{x}] p^{\tilde{X}}(t, \tilde{x})} \right) \pm 1 \right]. \quad (19)$$

346 Notice that $\pi_{Z|\tilde{X}}(t, z) \in [0, 1]$, so we can further conclude

$$347 \quad \lim_{N \rightarrow \infty} \sqrt{N} \mathbb{E} [\|\hat{p}_{\text{RB}}(t, \cdot) - p(t, \cdot)\|_1] \leq \sqrt{\frac{2}{\pi}} \sum_{x \in \mathbb{Z}_{\geq 0}^n} \sqrt{\mathbb{E} [\pi_{Z|\tilde{X}}(t, z) | \tilde{X}(t) = \tilde{x}] p^{\tilde{X}}(t, \tilde{x}) - p^2(t, x)}$$

$$348 \quad \stackrel{(8)}{=} \lim_{N \rightarrow \infty} \sqrt{N} \mathbb{E} [\|\hat{p}_{\text{MC}}(t, \cdot) - p(t, \cdot)\|_1]$$

349 which suggests that the RB-CME solver is no worse than the Monte-Carlo method given a large sample size N . In one
 350 extreme case where $\pi_{Z|\tilde{X}}(t, z)$ only depends on the final state of $\tilde{X}(\cdot)$ and is irrelevant to its historical information (i.e.,
 351 $\text{Var} [\pi_{Z|\tilde{X}}(t, z) | \tilde{X}(t) = \tilde{x}] = 0$), we can get

$$352 \quad \lim_{N \rightarrow \infty} \sqrt{N} \mathbb{E} [\|\hat{p}_{\text{RB}}(t, \cdot) - p(t, \cdot)\|_1] = \sqrt{\frac{2}{\pi}} \sum_{x \in \mathbb{Z}_{\geq 0}^n} \sqrt{(\mathbb{E} [\pi_{Z|\tilde{X}}(t, z) | \tilde{X}(t) = \tilde{x}])^2 p^{\tilde{X}}(t, \tilde{x}) - p^2(t, x)}$$

$$353 \quad = \sqrt{\frac{2}{\pi}} \sum_{\tilde{x} \in \mathbb{Z}_{\geq 0}^{n_2}} \sqrt{p^{\tilde{X}}(t, \tilde{x}) (1 - p^{\tilde{X}}(t, \tilde{x}))}.$$

354 where the last line is the error of the Monte-Carlo method in estimating the leader system (adapted from (8)). This formula
 355 means that in this extreme case, the RB-CME solver is equivalent to the model reduction method that eliminates all the
 356 follower-level species using stochastic averaging; moreover, the RB-CME solver tends to be far more accurate than the
 357 Monte-Carlo method in this case, as the leader system usually has a much lower dimension than the whole system by our
 358 system decomposition algorithm (see the next subsection). This gives a clue that the RB-CME solvers can be far more accurate
 359 than the Monte-Carlo method in general high-dimensional problems.

360 **D. Automated algorithm for the leader-follower decomposition.** Notice that the decomposition introduced in Section S3.A
 361 consists of two parts, where the first one decomposes the system into a leader system and a follower system, and the second
 362 part further divides the follower system into several subsystems. Here, we establish the algorithm according to this two-level
 363 decomposition strategy.

364 We first establish the second-level decomposition, i.e., decomposing the whole follower system into several follower subsystems.
 365 Notice that this decomposition needs to satisfy C1 and C2, and the maximum size of the follower subsystems should be as
 366 small as possible so that the filtering method applied to the filtered CME (see the algorithm of the RB-CME solver) is more
 367 efficient. Following these ideas, we propose Algorithm 2 for this decomposition. Specifically, the algorithm first treats each
 368 follower-level species as an individual group and then merges them according to the topological conditions C1 and C2. Finally,
 369 each group left corresponds to a follower subsystem. One can easily check that this bottom-up algorithm provides the most
 370 sparse follower-subsystem decomposition, meaning that any other second-level decomposition satisfying C1 and C2 can only
 371 lead to subsystems that are the union of those provided by Algorithm 2. Moreover, this algorithm has a polynomial complexity
 372 with respect to the system size (the species number n and the number of reactions r). In general, Algorithm 2 can do the
 373 second-level decomposition efficiently and effectively.

374 We now consider the first-level decomposition, which classifies species into the leader and the follower systems. Since every
 375 species can be either a leader-level species or a follower-level one, we have 2^n choices in total. Among them, we hope to
 376 choose the one that leads to the most accurate RB-CME solver while keeping the solver's time cost below some threshold.
 377 As mentioned in the main text, we can interpret this optimal decomposition as the one that maximizes the size of the whole
 378 follower system while keeping the size of each individual follower subsystem below a given threshold. Following this idea, we
 379 propose Algorithm 3 for the first-level decomposition. Specifically, we first insert a threshold for the maximum size of follower
 380 subsystems and provide a truncated state space that contains most probability. After that, we exhaustively search for the
 381 optimal decomposition among all the candidates, and finally we use the obtained optimal decomposition to construct the
 382 RB-CME solver. Though Algorithm 3 uses the brute-force method, its computational time is acceptable: for the linear network
 383 presented in the main text, the algorithm consumes only 3 seconds when nine species are present.

384 **E. The connection between the RB-CME solver and the time-scale separation approach.** The time-scale separation approach
 385 ([11–16]) and our RB-CME solver share many similarities. Both methods use the Monte-Carlo samples to estimate a part
 386 of the species (the slow species or the leader species) and combine these estimates with conditional distributions (by the
 387 quasi-stationary assumption or filtered FSP) to estimate the remaining species. In the extreme case when all the leader species
 388 (in our framework) are slow and the follower species are very fast, the conditional distributions of the follower species are

Algorithm 2 Second-level decomposition for the RB-CME solver and RB-PF

```
1: Input the set of leader-level species and the set of follower-level species. ▷ Input
2: Classify each follower-level species as an individual group. ▷ Initialization
3: for  $j = 1, \dots, r$  do
4:   Merge the groups that involves in the  $j$ -th reaction. (Denote the merged group by  $\mathcal{G}_j$ ) ▷ For C1
5: end for
6: for  $k = 1, \dots, r_1$  do ▷ For C2
7:   Merge the groups that have species influencing  $\lambda^{\mathcal{O}_{\xi_k}}(x)$ . (Denote the merged group by  $\tilde{G}_k$ )
8:   for  $j = 1, \dots, r$  do
9:     if  $j \in \mathcal{O}_{\xi_k}$  then
10:      Merge  $\tilde{G}_k$  with the groups that have species influenced by the  $j$ -th reaction.
11:       $\tilde{G}_k \leftarrow$  the group merged in the previous step.
12:    end if
13:  end for
14: end for
15: if this is the decomposition for the RB-PF then
16:   Merge the groups that have the same color fluorescent reporters. ▷ For C3
17: end if
18: Each group is a follower subsystem. ▷ Output
```

Algorithm 3 Leader-follower decomposition for the RB-CME solver and the RB-PF

```
1: Input the threshold  $T$  for the maximum size of follower subsystems.
2: Input a truncated state space  $\{0, \dots, TS_1 - 1\} \times \dots \times \{0, \dots, TS_n - 1\}$  that contains most probability  $p(t, x)$ . ▷ Input
3: Largest_size  $\leftarrow 0$ . ▷ Initialization
4: Figure out the  $2^n$  choices of the first-level decomposition and give each an index.
5: for  $j = 1, \dots, 2^n$  do ▷ Search for the optimum
6:   Use Algorithm 2 to obtain follower subsystems for the  $j$ -th first-level decomposition candidate.
7:    $l \leftarrow$  the number of follower subsystems.
8:   Evaluate the size of each follower subsystem:  $SS_i = \prod_{i': \text{species } S_{i'} \text{ belongs to the } Z_i} TS_{i'}$ .
9:   if  $SS_i \leq T$  (for all  $i \in \{1, \dots, l\}$ ) and  $\prod_{i=1}^l SS_i > \text{Largest\_size}$  then ▷ Check optimality
10:    Replace the optimal decomposition with the current one.
11:    Largest_size  $\leftarrow \prod_{i=1}^l SS_i$ .
12:   end if
13: end for
14: Output the optimal decomposition. ▷ Output
```

approximately the quasi-stationary distribution, and, therefore, the RB-CME solver provides the same estimate as that of the time-scale separation approach. This point has been observed in Section S3.C when analyzing the estimation error of the RB-CME solver. Also, in this extreme case, our method is applicable for computing steady-state solutions of CMEs. Specifically, the conditional independence of follower subsystems is then established based on the current state of the leader system (rather than its historical trajectory), and, therefore, the steady-state CME can be divided into several sub-problems for the leader system and follower subsystems, which can be computationally more efficient.

Despite these similarities, the RB-CME solver and the time-scale separation approach are developed based on different motivations. The time-scale separation approach is designed to simplify the analysis and simulation of multi-scale systems. In contrast, the RB-CME solver aims to improve the estimation methods for systems whose species are at similar time scales. The current system decomposition algorithm is also developed based on the same-time-scale setting. When facing a multi-scale system, it is reasonable to first decompose the system based on the time scales and then apply the RB-CME solver to the reduced system.

In scenarios where the species are at similar time scales but exhibit non-negligible fast-slow behaviors, the system decomposition algorithm needs to be re-designed accordingly. Intuitively, the dynamics of a fast species (as it contains many jumps) have much information about the remaining species. In other words, the conditioned distribution of the slow species, given the dynamics of the fast species, can be very narrow. Consequently, if the fast species are classified as the leader species and the slow ones as the follower species, the error of the RB-CME solver can be large (see (18)). Therefore, a more effective decomposition could be the one classifying the slow species as the leader species and the faster ones as the follower species. However, we need to point out that in this case, the optimal decomposition should also consider other factors such as the size of the leader system, the stiffness and the size of the filtered CME of each follower subsystem, etc. In general, extending the RB-CME solver to (relatively) multi-scale systems is a challenging problem. We leave it for future work.

S4. Rao-Blackwellized particle filter (RB-PF): derivation and error analysis.

A. Modified leader-follower decomposition for the filtering problem. Recall that the filtering problem for intracellular reaction systems can be solved by recursively computing (6) and (7), which correspond to prediction and correction, respectively. Following this idea, we propose the Rao-Blackwellized particle filter (RB-PF), which uses the RB-CME solver for the prediction step (6) and standard techniques for the adjustment step (7). Note that the RB-CME solver is established based on the conditional independence among follower subsystems. So, for the RB-PF, this conditional independence needs to be preserved in both the prediction and correction steps. This actually means that the follower subsystems are conditionally independent given the trajectories of both the leader system and the observation process. To this end, we require the following condition for the system decomposition in addition to C1 and C2.

C3 Each observation channel cannot be affected by more than one follower subsystem. In other words, each entry of $h(\cdot)$ can depend on one follower subsystem at most (besides the leader system).

The theoretical verification is as follows. Let $h_j(\tilde{x}, z_1, \dots, z_l)$ be the j -th element of the function $h(x)$. We first term $\mathcal{M}_k \triangleq \{j | h_j(\tilde{x}, z_1, \dots, z_l) \text{ depends on } z_k\}$ as the set of observation channels that measures follower subsystem Z_k . By C3, the sets $\mathcal{M}_1, \dots, \mathcal{M}_l$ are disjoint, and the likelihood function can be decomposed by

$$L(y|x) = L_0(y, \tilde{x}) \prod_{k=1}^l L_k(y, \tilde{x}, z_k); \quad (20)$$

here, $L_0(y, \tilde{x})$ is the density function of the probability $\prod_{j \notin \bigcup_{k=1}^l \mathcal{M}_k} \mathbb{P}(Y_j(t_i) \in \cdot | \tilde{X}(t_i) = \tilde{x})$ which can be interpreted as the part of the likelihood irrelevant to the follower subsystems, and $L_k(y, \tilde{x}, z_k)$ is the density function of the probability $\prod_{j \in \mathcal{M}_k} \mathbb{P}(Y_j(t_i) \in \cdot | \tilde{X}(t_i) = \tilde{x}, Z_k(t_i) = z_k)$ which can be viewed as the part of the likelihood function relevant to the follower subsystem Z_k . With these notations, we can prove the following theorem which guarantees the conditional independence result.

Theorem 2. Under conditions (3) and (4), the follower subsystems $Z_1(t), \dots, Z_l(t)$ satisfying C1, C2, and C3 are conditionally independent given the trajectories of $\tilde{X}(\cdot)$ and $Y(\cdot)$ up to time t . Moreover, for every $i \in \{0, 1, 2, \dots\}$ and every $t \in (t_i, t_{i+1}]$, the conditional probability $\pi_{Z_k | \tilde{X}Y}(t, z_k) \triangleq \mathbb{P}(Z_k(t) = z_k | \tilde{X}(s), 0 \leq s \leq t, \text{ and } Y(t_j), 0 \leq j \leq i)$ is almost surely characterized by (16) with the initial condition $\mathbb{P}(Z_k(t_i) = z_k | \tilde{X}(s), 0 \leq s \leq t_i, \text{ and } Y(t_j), 0 \leq j \leq i)$ and

$$\int_0^t \sum_{z_k \in \mathbb{Z}_{\geq 0}^{n_{Z_k}}} \sum_{j \in \mathcal{U}_i \cup \mathcal{O}_i} \lambda_j(\tilde{X}(s), z_k) \pi_{Z_k | \tilde{X}Y}(t, z_k) ds < \infty \text{ almost surely,} \quad \forall t \geq 0.$$

Proof. We prove the result by mathematical induction. For $t = 0$, the result holds immediately from Theorem 1. Then, we assume that the theorem holds for $t \in [0, t_i]$ and check whether it holds for $t \in [t_i, t_{i+1}]$.

Now, we show that for all $t \in (t_i, t_{i+1}]$, the process $\pi_{Z_k | \tilde{X}Y}(t, z_k) \triangleq \mathbb{P}(Z_k(t) = z_k | \tilde{X}(s), 0 \leq s \leq t, \text{ and } Y(t_j), 0 \leq j \leq i)$ is almost surely characterized by (16) with the initial condition $\mathbb{P}(Z_k(t_i) = z_k | \tilde{X}(s), 0 \leq s \leq t_i, \text{ and } Y(t_j), 0 \leq j \leq i)$. Note that $\pi_{Z_k | \tilde{X}Y}(t, z_k) = \mathbb{E}[\pi_{Z_k | \tilde{X}}(t, z_k) | \tilde{X}(s), 0 \leq s \leq t, \text{ and } Y(t_j), 0 \leq j \leq i]$. By applying this relation to Theorem 1, we can show that for all $t \in [t_i, t_{i+1}]$, the conditional probability $\pi_{Z_k | \tilde{X}Y}(t, z_k)$ almost surely satisfies (16) with the initial condition $\mathbb{P}(Z_k(t_i) = z_k | \tilde{X}(s), 0 \leq s \leq t_i, \text{ and } Y(t_j), 0 \leq j \leq i)$. Also, note that the solution is unique given the inequality in the theorem (see Theorem 1).

By this characterization equation and the conditional independence of $Z_1(t_i), \dots, Z_l(t_i)$ given $\{\tilde{X}(s), 0 \leq s \leq t_i\}$ and $\{Y(t_j), 0 \leq j \leq i\}$, we can say that the conditional probability $\pi_{Z_k | \tilde{X}Y}(t, z_k)$ (for every $k = 1, \dots, l$ and $t \in [t_i, t_{i+1}]$) is almost surely irrelevant to the trajectories of the follower subsystems other than Z_k . Therefore, for $t \in [t_i, t_{i+1}]$, the follower subsystems $Z_1(t), \dots, Z_l(t)$ are conditionally independent given $\{\tilde{X}(s), 0 \leq s \leq t\}$ and $\{Y(t_j), 0 \leq j \leq i\}$.

Finally, we prove that the follower subsystem are still conditionally independent after the collection of the observation at time t_{i+1} . By Bayes' rule and (20), we have

$$\begin{aligned} & \mathbb{P}(Z_1(t_{i+1}) = z_1, \dots, Z_l(t_{i+1}) = z_l | \tilde{X}(s), 0 \leq s \leq t_{i+1}, \text{ and } Y(t_j), 0 \leq j \leq i+1) \\ & \propto \prod_{k=1}^l L_k(Y(t_{i+1}), \tilde{X}(t_{i+1}), z_k) \mathbb{P}(Z_k(t_{i+1}) = z_k | \tilde{X}(s), 0 \leq s \leq t_{i+1}, \text{ and } Y(t_j), 0 \leq j \leq i) \\ & = \prod_{k=1}^l \mathbb{P}(Z_k(t_{i+1}) = z_k | \tilde{X}(s), 0 \leq s \leq t_{i+1}, \text{ and } Y(t_j), 0 \leq j \leq i+1) \end{aligned}$$

where the last line follows from the definition of the conditional marginal distribution. This suggests that $Z_1(t_{i+1}), \dots, Z_l(t_{i+1})$ are conditionally independent given $\{\tilde{X}(s), 0 \leq s \leq t_{i+1}\}$ and $\{Y(t_j), j = 1, \dots, i+1\}$.

Combining all the above results, we show the theorem for $t \in [t_i, t_{i+1}]$. Moreover, by the principle of mathematical induction, we prove the result. $\square$

Now, we modify the leader-follower decomposition algorithm according to C3. Note that this additional requirement only affects the second-level decomposition, which divides the follower system into subsystems, and does not affect the first-level decomposition, which classifies species into the leader and follower systems according to an optimization rule. Following this idea, we propose a modified second-level decomposition algorithm by adding a step to put fluorescent reporters of the same color into the same subsystem (see Line 15–17 Algorithm 2). The first-level decomposition is the same as that for the RB-CME solver (see Algorithm 3).

B. Algorithm of the RB-PF. By Theorem 2, we can rewrite the prediction probability $\rho_{t_{i+1}}(\cdot)$ and the filter $\pi_{t_{i+1}}(\cdot)$ by

$$\rho_{t_{i+1}}(\tilde{x}, z_1, \dots, z_l) = \mathbb{E} \left[\mathbb{1}(\tilde{X}(t_{i+1}) = \tilde{x}) \prod_{k=1}^l \pi_{Z_k|\tilde{X}Y}(t_{i+1}, z_k) \middle| Y(t_j), 0 \leq j \leq i \right] \quad (21)$$

$$\pi_{t_{i+1}}(\tilde{x}, z_1, \dots, z_l) = \mathbb{E} \left[\mathbb{1}(\tilde{X}(t_{i+1}) = \tilde{x}) \prod_{k=1}^l \bar{\pi}_{Z_k|\tilde{X}Y}(t_{i+1}, z_k) \middle| Y(t_j), 0 \leq j \leq i+1 \right] \quad (22)$$

where $\pi_{Z_k|\tilde{X}Y}(t_{i+1}, z_k) \triangleq \mathbb{P}(Z_k(t_{i+1}) = z_k | \tilde{X}(s), 0 \leq s \leq t_{i+1}, \text{ and } Y(t_j), 0 \leq j \leq i)$ and

$$\begin{aligned} \bar{\pi}_{Z_k|\tilde{X}Y}(t_{i+1}, z_k) &\triangleq \mathbb{P}(Z_k(t_{i+1}) = z_k | \tilde{X}(s), 0 \leq s \leq t_{i+1}, \text{ and } Y(t_j), 0 \leq j \leq i+1) \\ &\propto L_k(Y(t_{i+1}), \tilde{X}(t_{i+1}), z_k) \pi_{Z_k|\tilde{X}Y}(t_{i+1}, z_k). \end{aligned} \quad (\text{by Bayes' rule and (20)})$$

Theorem 2 also states that the conditional probability $\pi_{Z_k|\tilde{X}Y}(t, z_k)$ (for $t \in (t_i, t_{i+1}]$) satisfies the filtered CME (16) with the initial probability $\bar{\pi}_{Z_k|\tilde{X}Y}(t_i, z_k)$. Consequently, we can solve the filtering problem by applying the RB-CME solver to the prediction probability $\rho_{t_{i+1}}(\cdot)$ in (21) (or equivalently (6)).

Following this idea, we provide the detailed algorithm of the RB-PF in Algorithm 4. Specifically, this algorithm first decomposes the system into a leader system and several follower subsystems using Algorithm 3. Then, in each iteration, the algorithm computes the prediction probability $\rho_{t_{i+1}}(\cdot)$ by the RB-CME solver (see line 6–10). The prediction probability is approximated by $\hat{\rho}_{t_{i+1}}^{\text{RB}}(x) = \sum_{j=1}^N w_j(t) \mathbb{1}(\tilde{x}_j(t_{i+1}) = \tilde{x}) \prod_{k=1}^l \bar{q}_j^k(t_{i+1}, z_k)$ where $w_j(t)$ is the weight of the j -th particle, $\tilde{x}_j(t_{i+1})$ is the leader part of the j -th particle (simulated in Line 6–8), and $\bar{q}_j^k(t_{i+1}, z_k)$ is the conditional probability of the subsystem Z_k given $\tilde{x}_j(\cdot)$ and $Y(\cdot)$ up to time t_{i+1} . Here, $\hat{\rho}_{t_{i+1}}^{\text{RB}}(x)$ is not explicitly given in the algorithm because it is not necessary. After the prediction step, the RB-PF updates the weights for each $\tilde{x}_j(t_{i+1})$ according to the adjustment step (7) and reevaluates the conditional probability of follower subsystems by including new observations (line 11–12). Finally, Algorithm 4 computes the filter according to (22) (line 13) and resamples the particles to delete non-significant ones (line 14).

Algorithm 4 Rao-Blackwellized particle filter (RB-PF)

- 1: Decompose the systems using Algorithm 3. ▷ System decomposition
 - 2: Generate N samples $(x_1(0), \dots, x_N(0))$ from the initial probability and give them equal weights $(w_j(0) = \frac{1}{N}, j = 1, \dots, N)$.
 - 3: Denote the leader parts of these particles by $(\tilde{x}_1(0), \dots, \tilde{x}_N(0))$. For each $\tilde{x}_j(0)$, each subsystem Z_k , and each z_k in a finite state space, set $\bar{q}_j^k(0, z_k) \triangleq \mathbb{P}(Z_k(0) = z_k | \tilde{X}(0) = \tilde{x}_k(0))$. ▷ Initialization
 - 4: $i \leftarrow 0$ and $t_0 \leftarrow 0$.
 - 5: **while** t_i is not the final observation time **do**
 - 6: Construct particles: for each $j \in \{1, \dots, N\}$ and each subsystems Z_k , sample a $\tilde{z}_k(t_i)$ from the distribution $\bar{q}_j^k(t_i, \cdot)$;
 - 7: then the j -th particle becomes $(\tilde{x}_j(t_i), \tilde{z}_1^j(t_i), \dots, \tilde{z}_\ell^j(t_i))$
 - 8: Simulate every particle $x_j(t)$ from time t_i to t_{i+1} according to (2) and denote their leader parts by $\tilde{x}_1(\cdot), \dots, \tilde{x}_N(\cdot)$.
 - 9: For each $\tilde{x}_j(\cdot)$ and Z_k , use a filtering approach (i.e., the filtered FSP [10]) to solve (16) from time t_i to t_{i+1} with the initial probability $\bar{q}_j^k(t_i, z_k)$.
 - 10: Denote the solution at t_{i+1} by $q_j^k(t_{i+1}, z_k)$ ▷ Prediction ((6) and (21))
 - 11: Update weights $w_j(t_{i+1}) \propto w_j(t_i) L_0(Y(t_{i+1}), \tilde{x}_j(t_{i+1})) \prod_{k=1}^l \left(\sum_{z_k} L_k(Y(t_{i+1}), \tilde{x}_j(t_{i+1}), z_k) q_j^k(t_{i+1}, z_k) \right)$.
 - 12: $\bar{q}_j^k(t_{i+1}, z_k) \propto L_k(Y(t_{i+1}), \tilde{x}_j(t_{i+1}), z_k) q_j^k(t_{i+1}, z_k)$. ▷ Adjustment ((7) and (22))
 - 13: Compute the filter $\hat{\pi}_{t_{i+1}}^{\text{RB}}(x) = \sum_{j=1}^N w_j(t_{i+1}) \mathbb{1}(\tilde{x}_j(t_{i+1}) = \tilde{x}) \prod_{k=1}^l \bar{q}_j^k(t_{i+1}, z_k)$.
 - 14: Resample $\{w_j(t_{i+1}), (\tilde{x}_j(t_{i+1}), \bar{q}_j^1(t_{i+1}, \cdot), \dots, \bar{q}_j^\ell(t_{i+1}, \cdot))\}$ to obtain N equally weighted particles
 - 15: $i \leftarrow i + 1$.
 - 16: **end while**
-

C. Error analysis of the RB-PF. Now, we analyze the error of the RB-PF. First, we investigate the error at the first observation time point t_1 and show that its performance (for the filtering problem) is similar to that of the RB-CME solver (for solving the CME). Again, we assume that the error of the filtering approach applied to the filtered CME is negligible. Readers who are not interested in the detailed derivation can directly go to (24).

For the j -th particle, we term $q_j(t_1, z) \triangleq \prod_{i=1}^l q_j^i(t_1, z_i)$ as the conditional distribution of $Z(t_1)$ given the trajectory of the leader system $\tilde{x}_j(\cdot)$. Then, we can rewrite the RB-PF filter at t_1 by

$$\hat{\pi}_{t_1}^{\text{RB}}(x) = \frac{\frac{1}{N} \sum_{j=1}^N \left(\frac{L(Y(t_1)|(\tilde{x}_j(t_1), z))}{\rho_{t_1}^Y(Y(t_1))} \right) \mathbb{1}(\tilde{x}_j(t_1) = \tilde{x}) q_j(t_1, z)}{\frac{1}{N} \sum_{j=1}^N \sum_{z'} \left(\frac{L(Y(t_1)|(\tilde{x}_j(t_1), z'))}{\rho_{t_1}^Y(Y(t_1))} \right) q_j(t_1, z')} = \frac{\frac{1}{N} \sum_{j=1}^N \left(\frac{L(Y(t_1)|(\tilde{x}_j(t_1), z))}{\rho_{t_1}^Y(Y(t_1))} \right) \mathbb{1}(\tilde{x}_j(t_1) = \tilde{x}) q_j(t_1, z)}{\frac{1}{N} \sum_{j=1}^N \left(\frac{q_j^Y(t_1, Y(t_1))}{\rho_{t_1}^Y(Y(t_1))} \right) q_j(t_1, z)}$$

where $\rho_{t_1}^Y(y) \triangleq \sum_{\tilde{x}} L(y|\tilde{x}) \rho_{t_1}(x)$ is the probability density of $Y(t_1)$, and $q_j^Y(t_1, y) \triangleq \sum_{z'} L(y|\tilde{x}_j(t_1), z') q_j(t_1, z')$ is the estimate of $Y(t_1)$'s probability density by the j -th particle. By applying the delta method to this formula, we have

$$\sqrt{N} [\hat{\pi}_{t_1}^{\text{RB}}(\tilde{x}, z) - \pi_{t_1}(\tilde{x}, z)] \xrightarrow{d} \mathcal{N} \left(0, \text{Var} \left(\frac{L(Y(t_1)|(\tilde{x}_1(t_1), z))}{\rho_{t_1}^Y(Y(t_1))} \mathbb{1}(\tilde{x}_1(t_1) = \tilde{x}) q_1(t_1, z) - \frac{q_1^Y(t_1, Y(t_1))}{\rho_{t_1}^Y(Y(t_1))} \pi_{t_1}(\tilde{x}, z) \middle| Y(t_1) \right) \right).$$

given $Y(t_1)$ and, therefore,

$$\begin{aligned} & \lim_{N \rightarrow \infty} \sqrt{N} \mathbb{E} \left[\left| \hat{\pi}_{t_1}^{\text{RB}}(\tilde{x}, z) - \pi_{t_1}(\tilde{x}, z) \right| \middle| Y(t_1) \right] \\ &= \sqrt{\frac{2}{\pi}} \sqrt{\text{Var} \left(\frac{L(Y(t_1)|(\tilde{x}_1(t_1), z))}{\rho_{t_1}^Y(Y(t_1))} \mathbb{1}(\tilde{x}_1(t_1) = \tilde{x}) q_1(t_1, z) - \frac{q_1^Y(t_1, Y(t_1))}{\rho_{t_1}^Y(Y(t_1))} \pi_{t_1}(\tilde{x}, z) \middle| Y(t_1) \right)}. \end{aligned} \quad (23)$$

Since the particle $(\tilde{x}_1(t_1), q_1(t_1, z))$ has the same distribution as $(\tilde{X}(t_1), \pi_{Z|\tilde{X}}(t_1, z))$ and is independent of $Y(t_1)$, the conditional variance in (23) satisfies

$$\begin{aligned} & \text{Var} \left(\frac{L(Y(t_1)|(\tilde{x}_1(t_1), z))}{\rho_{t_1}^Y(Y(t_1))} \mathbb{1}(\tilde{x}_1(t_1) = \tilde{x}) q_1(t_1, z) - \frac{q_1^Y(t_1, Y(t_1))}{\rho_{t_1}^Y(Y(t_1))} \pi_{t_1}(\tilde{x}, z) \middle| Y(t_1) \right) \\ & \leq \left(\frac{L(Y(t_1)|(\tilde{x}, z))}{\rho_{t_1}^Y(Y(t_1))} \right)^2 \rho_{t_1}^{\tilde{X}}(\tilde{x}) \mathbb{E} \left[\pi_{Z|\tilde{X}}^2(t_1, z) \middle| \tilde{X}(t_1) = \tilde{x} \right] + \frac{\mathbb{E} \left[(q_1^Y(t_1, Y(t_1)))^2 \middle| Y(t_1) \right]}{(\rho_{t_1}^Y(Y(t_1)))^2} \pi_{t_1}^2(\tilde{x}, z) \\ & \leq \left(\frac{L(Y(t_1)|(\tilde{x}, z))}{\rho_{t_1}^Y(Y(t_1))} \right)^2 \rho_{t_1}^{\tilde{X}}(\tilde{x}) \mathbb{E} \left[\pi_{Z|\tilde{X}}^2(t_1, z) \middle| \tilde{X}(t_1) = \tilde{x} \right] \\ & \quad + \frac{\mathbb{E} \left[\sum_{z'} L^2(y|\tilde{x}_j(t_1), z') q_j(t_1, z') \middle| Y(t_1) \right]}{(\rho_{t_1}^Y(Y(t_1)))^2} \pi_{t_1}^2(\tilde{x}, z) \quad (\text{Jensen's inequality}) \\ & \leq \left(\frac{L(Y(t_1)|(\tilde{x}, z))}{\rho_{t_1}^Y(Y(t_1))} \right)^2 \rho_{t_1}^{\tilde{X}}(\tilde{x}) \mathbb{E} \left[\pi_{Z|\tilde{X}}^2(t_1, z) \middle| \tilde{X}(t_1) = \tilde{x} \right] + \left(\frac{\det(\sqrt{2\pi\sigma})^{-1/2}}{\rho_{t_1}^Y(Y(t_1))} \right) \pi_{t_1}^2(\tilde{x}, z) \quad (L(y|x) \leq \det(\sqrt{2\pi\sigma})^{-1/2}) \end{aligned}$$

where $\rho_{t_1}^{\tilde{X}}(\tilde{x}) \triangleq \sum_z \rho_{t_1}(\tilde{x}, z)$ is the marginal distribution of $\tilde{X}(t_1)$, and

$$\begin{aligned} & \text{Var} \left(\frac{L(Y(t_1)|(\tilde{x}_1(t_1), z))}{\rho_{t_1}^Y(Y(t_1))} \mathbb{1}(\tilde{x}_1(t_1) = \tilde{x}) q_1(t_1, z) - \frac{q_1^Y(t_1, Y(t_1))}{\rho_{t_1}^Y(Y(t_1))} \pi_{t_1}(\tilde{x}, z) \middle| Y(t_1) \right) \\ & \geq \mathbb{E} \left[\left(\frac{L(Y(t_1)|(\tilde{x}_1(t_1), z))}{\rho_{t_1}^Y(Y(t_1))} \right)^2 \mathbb{1}(\tilde{x}_1(t_1) = \tilde{x}) q_1^2(t_1, z) - 2 \times \mathbb{1}(\tilde{x}_1(t_1) = \tilde{x}) \frac{L(Y(t_1)|(\tilde{x}_1(t_1), z)) q_1(t_1, z)}{\rho_{t_1}^Y(Y(t_1))} \frac{q_1^Y(t_1, Y(t_1))}{\rho_{t_1}^Y(Y(t_1))} \pi_{t_1}(\tilde{x}, z) \middle| Y(t_1) \right] \\ & \geq \mathbb{E} \left[\left(\frac{L(Y(t_1)|(\tilde{x}_1(t_1), z))}{\rho_{t_1}^Y(Y(t_1))} \right)^2 \mathbb{1}(\tilde{x}_1(t_1) = \tilde{x}) q_1^2(t_1, z) - 2 \times \mathbb{1}(\tilde{x}_1(t_1) = \tilde{x}) \frac{\pi_{t_1}(\tilde{x}, z) q_1(t_1, z)}{\rho_{t_1}(\tilde{x}, z)} \frac{\det(\sqrt{2\pi\sigma})^{-1/2}}{\rho_{t_1}^Y(Y(t_1))} \pi_{t_1}(\tilde{x}, z) \middle| Y(t_1) \right] \\ & = \left(\frac{L(Y(t_1)|(\tilde{x}, z))}{\rho_{t_1}^Y(Y(t_1))} \right)^2 \rho_{t_1}^{\tilde{X}}(\tilde{x}) \mathbb{E} \left[\pi_{Z|\tilde{X}}^2(t_1, z) \middle| \tilde{X}(t_1) = \tilde{x} \right] - 2 \left(\frac{\det(\sqrt{2\pi\sigma})^{-1/2}}{\rho_{t_1}^Y(Y(t_1))} \right) \pi_{t_1}^2(\tilde{x}, z). \end{aligned}$$

By applying these results together with the relation $\sqrt{a+b} \leq \sqrt{a} + \sqrt{b}$ to the formula (23), we can estimate the L_1 error of the RB-PF filter by

$$\begin{aligned} & \lim_{N \rightarrow \infty} \sqrt{N} \mathbb{E} \left[\left\| \hat{\pi}_{t_1}^{\text{RB}}(\cdot) - \pi_{t_1}(\cdot) \right\|_1 \right] \\ & \triangleq \lim_{N \rightarrow \infty} \sum_{(\tilde{x}, z) \in \mathbb{Z}_{\geq 0}^n} \sqrt{N} \mathbb{E} \left[\left| \hat{\pi}_{t_1}^{\text{RB}}(\tilde{x}, z) - \pi_{t_1}(\tilde{x}, z) \right| \right] \\ & = \sqrt{\frac{2}{\pi}} \left[\left(\sum_{x \in \mathbb{Z}_{\geq 0}^n} \sqrt{\rho_{t_1}^{\tilde{X}}(\tilde{x}) \mathbb{E} \left[\pi_{Z|\tilde{X}}^2(t_1, z) \middle| \tilde{X}(t_1) = \tilde{x} \right]} \right) \pm 2 \det(\sqrt{2\pi\sigma})^{-1/4} \int_{y \in \mathbb{R}^m} \sqrt{\rho_{t_1}^Y(y)} dy \right] \end{aligned} \quad (24)$$

provided that both terms in the last line are convergent. Here, m is the dimension of $Y(t_1)$.

The formula (24) tells that the error of the RB-PF at time t_1 largely depends on the two quantities in the square brackets. The first term in this bracket represents the error of the RB-CME solver in estimating the prediction probability $\rho_{t_1}(\cdot)$ (see (19)), and the second term shows the dispersion of $\rho_{t_1}^Y(\cdot)$ which tends to grow exponentially with m . Note that the observation dimension m is usually very low, and the observation noise is not negligible. So, we can conclude that the term

$\sum_{x \in \mathbb{Z}_{\geq 0}^n} \sqrt{\rho_{t_1}^{\tilde{X}}(\tilde{x}) \mathbb{E} \left[\pi_{Z|\tilde{X}}^2(t_1, z) \middle| \tilde{X}(t_1) = \tilde{x} \right]}$ usually dominates in (24); in other words, the performance of the RB-PF (for the filtering problem) is similar to that of the RB-CME solver (for solving CMEs). This result suggests that if one system's CME can be accurately solved by the RB-CME solver, then its filtering problem can also be accurately solved by the RB-PF and vice versa. Also, since the RB-CME solver scales favorably with the system dimension (as discussed in the main text), the RB-PF should also scale favorably with the system dimension.

From (13) and the discussion after that, we can observe that this performance consistency also applies to the Monte-Carlo method (for solving the CME) and the particle filter (for the filtering problem). Therefore, we conjecture that this consistency is a universal property for CME solvers and their associated filters.

For observation time points other than t_1 , we conjecture that the same results should also hold. The theoretical analysis can be performed in the same way as we presented above, except that the particles $(\tilde{x}_j(t_i), q_j^1(t_i, \cdot), \dots, q_j^l(t_i, \cdot))$ have a slightly different distribution from that of $(\tilde{X}(t_i), \pi_{Z_1|\tilde{X}Y}(t_i, \cdot), \dots, \pi_{Z_l|\tilde{X}Y}(t_i, \cdot))$ due to the adjustment step and resampling. A rigorous analysis for that requires more sophisticated techniques in [4], which we leave for future work. However, we conjecture that this discrepancy should not affect the performance of the RB-PF too much, and, therefore, the results obtained for time t_1 should also apply to other time points. Our numerical studies also support this point (see Fig. 6G–H in the main text). We leave the theoretical verification for further work.

S5. Rao-Blackwell method for cell-specific parameter identification: derivation and algorithms.

A. Problem statement. Now, we introduce the mathematics for parameter identification, whose main difference from before is the incorporation of parameter uncertainty. We still consider a chemical reaction network (1), which consists of all possible reactions in the considered cell. Similar to (2), the dynamical equation can be written by

$$X(t) = X(0) + \sum_{j=1}^r \zeta_j R_j \left(\int_0^t \lambda_j(\Theta, X(s)) ds \right) \quad (25)$$

where Θ is an $\tilde{r}$ -vector of model parameters (e.g., reaction constant and hill coefficients) taking values in a discrete state space $\Theta \subset \mathbb{R}_{\geq 0}^{\tilde{r}}$, and the remaining terms have the same meaning as the ones in (2). Compared with (2), the propensity function $\lambda_j(\cdot)$ in (25) has an additional dependence on model parameters, thereby accounting for parameter uncertainty. Similar to (3), we consider a non-explosivity condition:

$$\sum_{j=1}^n \mathbb{E} [\lambda_j^2(\Theta, X(t))] \text{ is uniformly bounded on any time interval } [0, T], \quad (26)$$

This condition also implies that the random variables $\{\lambda_j(\Theta, X(t))\}_{t \in [0, T]}$ are uniformly integrable. Moreover, similar to (4), we assume that all the parameters and the initial conditions for different species are independent, i.e.,

$$\text{all the elements in } \Theta \text{ and } X(0) \text{ are independent} \quad (27)$$

We still considered the experiments under fluorescent microscope platforms as in the filtering case, where a cell is measured at different time points $\{t_1, \dots, t_{n_f}\}$ with measurements $Y(t_i)$ satisfying (5). Parameter identification aims to calculate the conditional distribution of Θ given all the measurements, i.e., $\mathbb{P}(\Theta = \cdot | Y(t_s), 1 \leq s \leq t_{n_f})$. By Bayes' rule, the solution of this identification problem can be solved by a series of recursive formulas:

$$\rho_{t_{i+1}}(\theta, x) = \sum_{x \in \mathbb{Z}_{\geq 0}^n} \mathbb{P}(X(t_{i+1}) = x | \Theta = \theta, X(t_i) = x') \pi_{t_i}(\theta, x') \quad \text{for } i = 0, 1, \dots, n_f - 1 \quad (28)$$

$$\pi_{t_{i+1}}(\theta, x) \propto L(Y(t_{i+1}) | x) \rho_{t_{i+1}}(\theta, x) \quad \text{for } i = 0, 1, \dots, n_f - 1 \quad (29)$$

$$\mathbb{P}(\Theta = \theta | Y(t_s), 1 \leq s \leq t_{n_f}) = \sum_{x \in \mathbb{Z}_{\geq 0}^n} \pi_{t_{n_f}}(\theta, x) \quad (30)$$

where $\pi_{t_i}(\theta, x) \triangleq \mathbb{P}(\Theta = \theta, X(t_i) = x | Y(t_s), 1 \leq s \leq i)$ and $\rho_{t_{i+1}}(\theta, x) \triangleq \mathbb{P}(\Theta = \theta, X(t_{i+1}) = x | Y(t_s), 1 \leq s \leq i)$.

B. Connection between parameter identification and stochastic filtering. Essentially, we can view $(\Theta, X(t))$ as a state of an expanded chemical reaction network, where Θ represents some additional special chemical species that can take non-integer values and remain constant over time. From this viewpoint, the probability distribution of $(\Theta, X(t))$ (denoted by $p(t, \theta, x) \triangleq \mathbb{P}(\Theta = \theta, X(t) = x)$) follows an augmented CME:

$$\frac{dp(t, \theta, x)}{dt} = \sum_{j=1}^r \lambda_j(\theta, x - \zeta_j) p(t, \theta, x - \zeta_j) - \sum_{j=1}^r \lambda_j(\theta, x) p(t, \theta, x), \quad \forall \theta \in \Theta, \text{ and } \forall x \in \mathbb{Z}_{\geq 0}^n.$$

Moreover, parameter identification can be viewed as a type of filtering problem that aims to infer the additional hidden states Θ . This point is also reflected in the formulas (28) and (29), where (28) solves an augmented CME with the initial condition $\pi_{t_i}(\cdot)$, and (29) adjusts the prediction $\rho_{t_{i+1}}(\cdot)$ according to the new observation $Y(t_{i+1})$.

C. Rao-Blackwell method for parameter identification. Due to the similarities between parameter identification and stochastic filtering, the RB-PF introduced earlier can be adapted to address parameter identification challenges. The RB-PF consists of two fundamental components: 1) leader-follower decomposition and 2) the Rao-Blackwell algorithm for calculating the conditional distribution. In the subsequent discussion, we will explore how to modify these components for the use in parameter identification context.

C.1. Modification of the leader-follower decomposition. The RB-PF (introduced earlier) utilizes a hybrid approach to infer different components of the system, where the leader part is inferred using particle filtering, and the follower part is inferred with the assistance of a filtering approach. In this paper, we particularly choose the filtered FSP [10] as the filtering approach. Classical particle filtering is known to be inefficient for inferring static hidden variables (e.g., model parameters) due to sample degeneracy, where the efficient sample size for the inference of these static variables drops dramatically over time [17]. Though several modification methods have been developed to address this issue (such as the resample-move method [18, 19], regularized particle filtering [17, 20, 21] and nested particle filtering [22, 23]), they all introduce extra noise into the inference algorithm, necessitating fine-tuning to strike a balance between sample degeneracy and the added noise, which can be extremely time-consuming [21]. Consequently, we choose to classify all the parameters as part of the follower component of the system to circumvent sample degeneracy and avoid additional noise.

573 C4 All the model parameters Θ are classified as follower components of the system.

574 Following C4, we can decompose the whole system state $(\Theta, X(t))$ into a leader system $\tilde{X}(t)$, and several follower subsystems
 575 $(\Theta_1, Z_1(t)), \dots, (\Theta_\ell, Z_\ell(t))$, where the dimension of a particular Θ_i or $Z_i(t)$ ($i = 1, \dots, \ell$) can be zero, but the dimensions of
 576 Θ_i and $Z_i(t)$ cannot be zero simultaneously. We term $\mathcal{O}_i$ as the feasible region of Θ_i . To indicate the contribution of model
 577 parameters to the propensity function, we redefine $\mathcal{U}_i \triangleq \{j \in \mathcal{U} | \zeta_j^{Z_i} \neq 0_{n_{Z_i}} \text{ or } \lambda_j(\theta_1, \dots, \theta_\ell, \tilde{x}, z_1, \dots, z_\ell) \text{ depends on } (\theta_i, z_i)\}$,
 578 which represents follower-level reactions involving $(\Theta_i, Z_i(t))$, and

$$579 \quad \mathcal{O}_i \triangleq \bigcup_{k: \begin{array}{l} \lambda^{\mathcal{O}_{\xi_k}}(\theta_1, \dots, \theta_\ell, \tilde{x}, z_1, \dots, z_\ell) \text{ has dependence on } \theta_i \text{ or } z_i, \\ \text{or } \zeta_j^{Z_i} \neq 0_{n_{Z_i}} \text{ for some } j \in \mathcal{O}_{\xi_k} \end{array}} \mathcal{O}_{\xi_k}$$

580 which represents the leader-level reactions that involves $(\Theta_i, Z_i(t))$. All other notations introduced previously are kept
 581 unchanged.

582 Recall that the model parameters can be viewed as static chemical species (see S5.C); therefore, we can get a result similar
 583 to Theorem 2 based on Conditions C1 — C3. Specifically, if the follower subsystems satisfy these conditions, then they are
 584 conditionally independent given the trajectory of the leader system and observations, and the dynamics of their conditional
 585 probability distributions have expressions similar to (16). More details are given in the following theorem.

Theorem 3 (Adapted from Theorem 2). *Under conditions (26) and (27), the follower subsystems $(\Theta_1, Z_1(t)), \dots, (\Theta_\ell, Z_\ell(t))$ satisfying C1, C2, and C3 are conditionally independent given the trajectory of $\tilde{X}(\cdot)$ and $Y(\cdot)$ up to time t . Moreover, for every $k \in \{0, 1, 2, n_f - 1\}$ and every $t \in (t_k, t_{k+1}]$, the conditional probability*

$$\pi_{\Theta_i Z_i | \tilde{X} Y}(t, \theta_i, z_i) \triangleq \mathbb{P}(\Theta_i = \theta_i, Z_i(t) = z_i | \tilde{X}(s), 0 \leq s \leq t, \text{ and } Y(t_j), 0 \leq j \leq \tilde{k})$$

586 is almost surely characterized by

$$\begin{aligned} 587 \quad & \pi_{\Theta_i Z_i | \tilde{X} Y}(t, \theta_i, z_i) \\ 588 \quad & = \mathbb{P}(\Theta_i = \theta_i, Z_i(t_i) = z_i | \tilde{X}(s), 0 \leq s \leq t_i, \text{ and } Y(t_j), 0 \leq j \leq i) \\ 589 \quad & + \int_{t_k}^t \sum_{j \in \mathcal{U}_i} \lambda_j(\theta_i, \tilde{X}(s), z_i - \zeta_j^{Z_i}) \pi_{\Theta_i Z_i | \tilde{X} Y}(s, \theta_i, z_i - \zeta_j^{Z_i}) - \sum_{j \in \mathcal{U}_i} \lambda_j(\theta_i, \tilde{X}(s), z_i) \pi_{\Theta_i Z_i | \tilde{X} Y}(s, \theta_i, z_i) ds \\ 590 \quad & - \int_{t_k}^t \pi_{\Theta_i Z_i | \tilde{X} Y}(s, \theta_i, z_i) \left(\lambda^{\mathcal{O}_i}(\theta_i, \tilde{X}(s), z_i) - \sum_{(\theta'_i, z'_i) \in \Theta_i \times \mathbb{Z}_{\geq 0}^{n_{Z_i}}} \lambda^{\mathcal{O}_i}(\theta'_i, \tilde{X}(s), z'_i) \pi_{\Theta_i Z_i | \tilde{X} Y}(s, \theta'_i, z'_i) \right) ds \\ 591 \quad & + \sum_{k: \mathcal{O}_{\xi_k} \subset \mathcal{O}_i} \int_0^t \left(\frac{\sum_{j \in \mathcal{O}_{\xi_k}} \lambda_j(\theta_i, \tilde{X}(s^-), z_i - \zeta_j^{Z_i}) \pi_{\Theta_i Z_i | \tilde{X} Y}(s^-, \theta_i, z_i - \zeta_j^{Z_i})}{\sum_{(\theta'_i, z'_i) \in \Theta_i \times \mathbb{Z}_{\geq 0}^{n_{Z_i}}} \lambda^{\mathcal{O}_{\xi_k}}(\theta'_i, \tilde{X}(s^-), z'_i) \pi_{\Theta_i Z_i | \tilde{X} Y}(s^-, \theta'_i, z'_i)} - \pi_{\Theta_i Z_i | \tilde{X} Y}(s^-, \theta_i, z_i) \right) d\tilde{R}_{\xi_k}(s), \end{aligned} \quad (31)$$

592 and

$$593 \quad \int_0^t \sum_{(\theta'_i, z'_i) \in \Theta_i \times \mathbb{Z}_{\geq 0}^{n_{Z_i}}} \sum_{j \in \mathcal{U}_i \cup \mathcal{O}_i} \lambda_j(\theta_i, \tilde{X}(s), z_i) \pi_{\Theta_i Z_i | \tilde{X} Y}(s, \theta_i, z_i) ds < \infty \text{ a.s. for all } t \in [t_k, t_{k+1}].$$

594 *Proof.* Note that the model parameters can be viewed as static chemical species (see S5.C). Therefore, this theorem is a
 595 straightforward consequence of Theorem 2. $\square$

596 This theorem together with Theorem 2 demonstrates that the leader-follower decompositions for stochastic filtering and
 597 parameter identification bear a considerable resemblance to each other. The leader-follower decomposition for parameter
 598 identification requires further consideration only of the involvement of parameters in each reaction and the fulfillment of
 599 condition C4, which stipulates that the parameters should be classified as follower components. From this perspective, we
 600 modify the two-level decomposition algorithms (Algorithm 2 and Algorithm 3) to obtain new ones for parameter identification
 601 (see Algorithm 5 and Algorithm 6). Specifically, the second-level decomposition additionally considers the involvement of
 602 model parameters (see Lines 2, 4, and 7 in Algorithm 5); meanwhile, the first-level decomposition classify only species as
 603 leader components (see Line 5 in Algorithm 6) and include the size of parameter space when calculating the size of follower
 604 subsystems (see Line 9 in Algorithm 6).

Algorithm 5 Second-level decomposition in the Rao-Blackwell method for parameter identification

```
1: Input the set of leader-level species and the set of follower-level species. ▷ Input
2: Classify each follower-level species and model parameter as an individual group. ▷ Initialization
3: for  $j = 1, \dots, r$  do
4:   Merge the groups that are involved in the  $j$ -th reaction. (Denote the merged group by  $\mathbf{G}_j$ ) ▷ For C1
5: end for
6: for  $k = 1, \dots, r_1$  do ▷ For C2
7:   Merge the groups that have species and parameters influencing  $\lambda^{\mathcal{O}_{\epsilon_k}}(\theta, x)$ . (Denote the merged group by  $\tilde{G}_k$ )
8:   for  $j = 1, \dots, r$  do
9:     if  $j \in \mathcal{O}_{\epsilon_k}$  then
10:      Merge  $\tilde{G}_k$  with the groups that have species influenced by the  $j$ -th reaction.
11:       $\tilde{G}_k \leftarrow$  the group merged in the previous step.
12:    end if
13:  end for
14: end for
15: Merge the groups that have the same color fluorescent reporters. ▷ For C3
16: Each group is a follower subsystem. ▷ Output
```

Algorithm 6 Leader-follower decomposition for parameter identification

```
1: Input the threshold  $T$  for the maximum size of follower subsystems.
2: Input a truncated state space for species  $\{0, \dots, \mathbf{TS}_1 - 1\} \times \dots \times \{0, \dots, \mathbf{TS}_n - 1\}$  that contains most probability.
3: Input the number of admissible values for each model parameter, represented by  $\mathbf{S}_1^\theta, \dots, \mathbf{S}_r^\theta$  ▷ Input
4: Largest_size  $\leftarrow 0$ . ▷ Initialization
5: Figure out the  $2^n$  choices of the first-level decomposition and give each an index.
6: for  $j = 1, \dots, 2^n$  do ▷ Search for the optimum
7:   Use Algorithm 5 to obtain follower subsystems for the  $j$ -th first-level decomposition candidate.
8:    $l \leftarrow$  the number of follower subsystems.
9:   Evaluate the size of each follower subsystem:  $\mathbf{SS}_i = \left( \prod_{i': i' \text{-th parameter belongs to } \Theta_i} \mathbf{S}_{i'}^\theta \right) \left( \prod_{i': \text{species } S_{i'} \text{ belongs to the } Z_i} \mathbf{TS}_{i'} \right)$ .
10:  if  $\mathbf{SS}_i \leq T$  (for all  $i \in \{1, \dots, l\}$ ) and  $\prod_{i=1}^l \mathbf{SS}_i > \mathbf{Largest\_size}$  then ▷ Check optimality
11:    Replace the optimal decomposition with the current one.
12:    Largest_size  $\leftarrow \prod_{i=1}^l \mathbf{SS}_i$ .
13:  end if
14: end for
15: Output the optimal decomposition. ▷ Output
```

C.2. Rao-Blackwell algorithm for parameter identification. Now, we present the detailed algorithm applying Rao-Blackwell method to parameter identification. Similar to the filtering problem, the key of the algorithm is to represent the prediction and correction steps ((28) and (29)) in a Rao-Blackwell format. By Theorem 3, the prediction probability $\rho_{t_{i+1}}(\cdot)$ can be re-written by

$$\rho_{t_{i+1}}(\theta_1, \dots, \theta_\ell, \tilde{x}, z_1, \dots, z_\ell) = \mathbb{E} \left[\mathbb{1} \left(\tilde{X}(t_{i+1}) = \tilde{x} \right) \prod_{k=1}^{\ell} \pi_{\Theta_k Z_k | \tilde{X} Y}(t_{i+1}, \theta_k, z_k) \middle| Y(t_j), 0 \leq j \leq i \right] \quad (32)$$

where $\pi_{\Theta_k Z_k | \tilde{X} Y}(t_{i+1}, \theta_k, z_k)$ is given in Theorem 3, and the adjusted probability $\pi_{t_{i+1}}(\cdot)$ can be rewritten by

$$\pi_{t_{i+1}}(\theta_1, \dots, \theta_\ell, \tilde{x}, z_1, \dots, z_\ell) = \mathbb{E} \left[\mathbb{1} \left(\tilde{X}(t_{i+1}) = \tilde{x} \right) \prod_{k=1}^{\ell} \bar{\pi}_{\Theta_k Z_k | \tilde{X} Y}(t_{i+1}, \theta_k, z_k) \middle| Y(t_j), 0 \leq j \leq i+1 \right] \quad (33)$$

where $\bar{\pi}_{\Theta_k Z_k | \tilde{X} Y}(t_{i+1}, \theta_k, z_k) \triangleq \mathbb{P}(\Theta_k = \theta_k, Z_k(t_{i+1}) = z_k | \tilde{X}(s), 0 \leq s \leq t_{i+1}, \text{ and } Y(t_j), 0 \leq j \leq i+1)$ and satisfies

$$\bar{\pi}_{\Theta_k Z_k | \tilde{X} Y}(t_{i+1}, \theta_k, z_k) \propto L_k(Y(t_{i+1}), \tilde{X}(t_{i+1}), z_k) \pi_{\Theta_k Z_k | \tilde{X} Y}(t_{i+1}, \theta_k, z_k) \quad (\text{by Bayes' rule and (20)}).$$

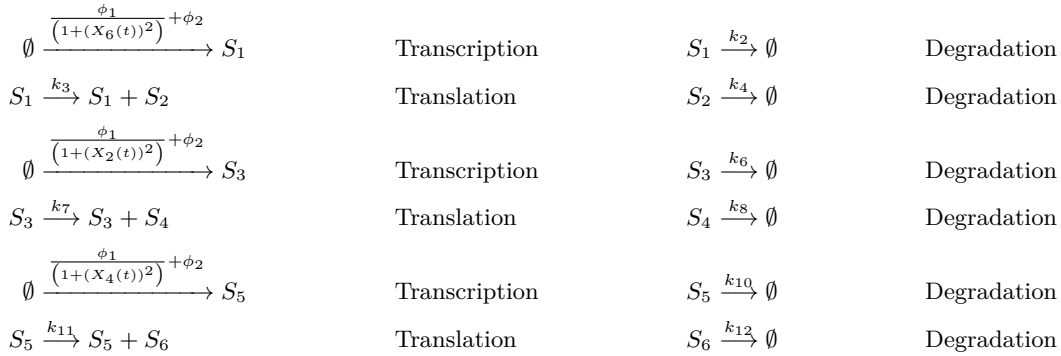
Also, Theorem 3 states that the term $\pi_{\Theta_k Z_k | \tilde{X} Y}(t, \theta_k, z_k)$ (for $t \in (t_i, t_{i+1})$) satisfies (31) with the initial condition $\bar{\pi}_{\Theta_k Z_k | \tilde{X} Y}(t_i, \theta_k, z_k)$. With these formulas, we can construct a Rao-Blackwell method for parameter identification (see Algorithm 7). Essentially, this algorithm for parameter identification follows the same structure as the RB-PF (refer to Algorithm 4), but it also takes model parameters into account. Again, this is not surprising as the model parameters can be viewed as static chemical species, and the parameter identification problem with time-course data has a strong resemblance to the stochastic filtering problem (see S5.C).

Algorithm 7 Rao-Blackwell method for parameter identification (with time-course data)

- 1: Decompose the systems using Algorithm 6. ▷ System decomposition
 - 2: Sample N species state $x_1(0), \dots, x_N(0)$ from the initial probability and give them equal weights ($w_j(0) = \frac{1}{N}$, $j = 1, \dots, N$).
 - 3: Denote the leader parts of these samples by $(\tilde{x}_1(0), \dots, \tilde{x}_N(0))$. For each $\tilde{x}_j(0)$, each subsystem (Θ_k, Z_k) , and each pair (θ_k, z_k) , set $\bar{q}_j^k(0, \theta_k, z_k) \triangleq \mathbb{P} \left(\Theta_k = \theta_k, Z_k(0) = z_k \mid \tilde{X}(0) = \tilde{x}_k(0) \right)$. ▷ Initialization
 - 4: $i \leftarrow 0$ and $t_0 \leftarrow 0$.
 - 5: **while** t_i is not the final observation time **do**
 - 6: Construct particles: for each $j \in \{1, \dots, N\}$ and each subsystems (θ_k, z_k) , sample a pair $(\tilde{\theta}_j, \tilde{z}_j(t_i))$ from the
 - 7: distribution $\bar{q}_j^k(t_i, \cdot)$; then the j -th particle becomes $(\tilde{\theta}_1, \dots, \tilde{\theta}_\ell, \tilde{x}_j(t_i), \tilde{z}_1(t_i), \dots, \tilde{z}_\ell(t_i))$
 - 8: Simulate every particle from time t_i to t_{i+1} according to (25) and denote the leader parts by $\tilde{x}_1(\cdot), \dots, \tilde{x}_N(\cdot)$.
 - 9: For each $\tilde{x}_j(\cdot)$ and each subsystem $(\Theta_k, Z_k(t))$, use the filtered FSP to solve (31) in $[t_i, t_{i+1}]$ with the initial
 - 10: condition $\bar{q}_j^k(t_i, \theta_k, z_k)$. Denote the solution at t_{i+1} by $q_j^k(t_{i+1}, \theta_k, z_k)$ ▷ Prediction ((6) and (32))
 - 11: Update weights $w_j(t_{i+1}) \propto w_j(t_i) L_0(Y(t_{i+1}), \tilde{x}_j(t_{i+1})) \prod_{k=1}^\ell \left(\sum_{z_k} L_k(Y(t_{i+1}), \tilde{x}_j(t_{i+1}), z_k) q_j^k(t_{i+1}, \theta_k, z_k) \right)$.
 - 12: $\bar{q}_j^k(t_{i+1}, \theta_k, z_k) \propto L_k(Y(t_{i+1}), \tilde{x}_j(t_{i+1}), z_k) q_j^k(t_{i+1}, \theta_k, z_k)$. ▷ Adjustment ((7) and (33))
 - 13: Compute the filter $\hat{\pi}_{t_{i+1}}^{\text{RB}}(\theta, x) = \sum_{j=1}^N w_j(t_{i+1}) \mathbb{1}(\tilde{x}_j(t_{i+1}) = \tilde{x}) \prod_{k=1}^\ell \bar{q}_j^k(t_{i+1}, \theta_k, z_k)$.
 - 14: Resample $\{w_j(t_{i+1}), (\tilde{x}_j(t_{i+1}), \bar{q}_j^1(t_{i+1}, \cdot), \dots, \bar{q}_j^\ell(t_{i+1}, \cdot))\}$ to obtain N equally weighted particles
 - 15: $i = i + 1$
 - 16: **end while**
-

S6. Modeling of the genetic circuits in cases studies

A. Modeling of the repressilator. Here, we introduce the details of the repressilator model presented in the main text. First, we build the model according to the literature [24]. Specifically, this model consists of three gene expression systems producing cI, lacI, and tetR, respectively, and the protein products cyclically repress each other's expression. The involved chemical reactions are listed as follows, where $S_1, S_2, \dots, S_6$ represents the cI mRNA, cI, lacI mRNA, lacI, tetR mRNA, and tetR, respectively.



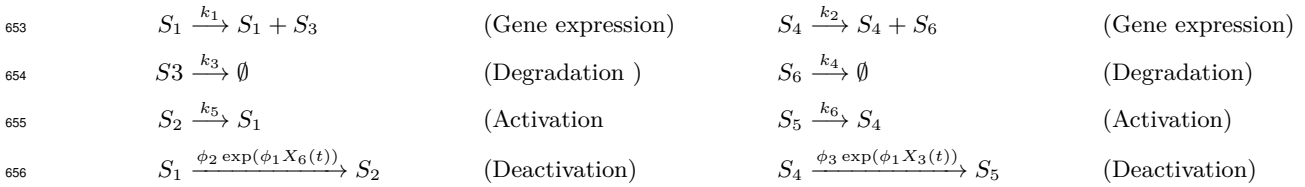
In these reactions, the first two lines correspond to the gene expression system of cI, the third and fourth lines correspond to the gene expression system of lacI, and the last two lines correspond to the gene expression system of tetR. The values of model parameters and the initial conditions are listed in Table S1.

Model parameter (min^{-1})	Initial condition
$k_2 = 0.3$	$X_1(0) = 1$
$k_3 = 2$	$X_2(0) = 50$
$k_4 = 0.07$	$X_3(0) = 0$
$k_6 = 0.3$	$X_4(0) = 0$
$k_7 = 2$	$X_5(0) = 0$
$k_8 = 0.07$	$X_6(0) = 0$
$k_{10} = 0.3$	
$k_{11} = 2$	
$k_{12} = 0.07$	
$\phi_1 = 0.5$	
$\phi_2 = 0.5 \times 10^{-4}$	

Table S1. Performance of

In this example, we solve the associated CME at time 500, before which a few oscillations have taken place. Through a few simulations, we found that most of the probability is contained in the state space where each mRNA has fewer than 20 copies, and each protein has fewer than 200 copies. (The simulations are not shown in the paper.) Note that this state space contains 64 billion states, and storing a probability on this state space requires 476.8 GB (8 bytes for each state). Consequently, the FSP is impractical for this problem. To have an accurate approximation of the exact probability, we simulated 3×10^9 trajectories of the system and viewed the empirical distribution as the exact probability. The whole procedure took 10 GPUs (3×10^8 simulations for each) about 24 hours! Recall that storing the whole probability is impractical, so we only stored the marginal distribution of the mRNAs and the marginal distribution of the proteins. We also applied the RB-CME solver and the Monte-Carlo method to this example, and all the results are shown in the main text. The performance of the RB-CME solver and Monte-Carlo method is evaluated by the sum of the L_1 errors in estimating the marginal distributions of the mRNAs and proteins.

B. Modeling of the genetic toggle switch. Here, we introduce the details of the genetic toggle switch presented in the main text. This circuit consists of two gene expression systems whose protein products repress each other's expression. Following the literature [25], we model the genetic toggle switch by the following reactions, where S_1 is the activated state of the first gene, S_2 is the deactivated state of the first gene, S_3 is the protein product of the first gene, S_4 is the activated state of the second gene, S_5 is the deactivated state of the second gene, and S_6 is the protein product of the second gene.



In these reactions, the first column corresponds to the first gene expression system, and the second column corresponds to the second gene expression system. The model parameters and initial conditions are presented in Table S2. Moreover, we assume

Model parameter (min^{-1})	Initial condition
$k_1 = 60$	$X_1(0) = 0$
$k_2 = 60$	$X_2(0) = 1$
$k_3 = 0.5$	$X_3(0) = 0$
$k_4 = 0.5$	$X_4(0) = 1$
$k_5 = 0.3$	$X_5(0) = 0$
$k_6 = 0.3$	$X_6(0) = 20$
$\phi_1 = 0.05$	
$\phi_2 = 0.1$	
$\phi_3 = 0.1$	

Table S2. Model parameters and initial conditions of the genetic toggle switch

that the first protein is fluorescent and measured by a microscope every 20 minutes. Moreover, we assume the observation to satisfy

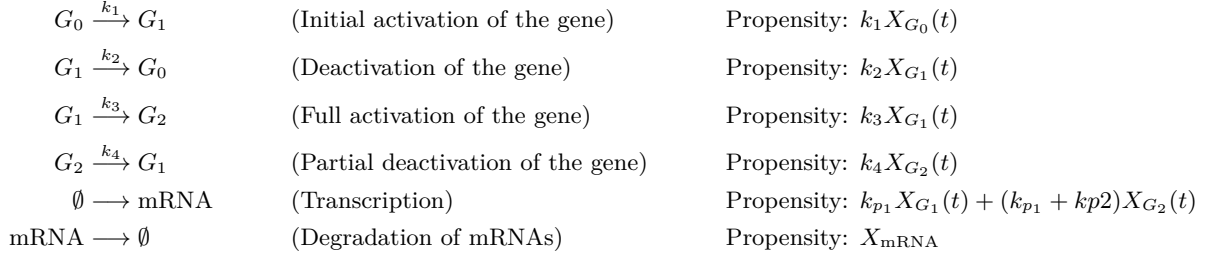
$$Y(t_i) = X_3(t_i) + \sigma W_i, \quad \forall t_i \in \{20, 40, \dots, 200\}, \quad (34)$$

where $\{t_i\}$ are the observation time points, σ is the observation noise intensity, and $\{W_i\}$ is a sequence of independent standard Gaussian white noise.

In this example, our goal is to estimate the hidden dynamical state based on these partial observations. Through a few simulations, we found that most of the probability is contained in the state space where each protein has fewer than 200 copies. Then, we applied the FSP with this specific state space to the associated filtering problem and viewed its solution as the ground truth. Also, we applied both the RB-PF and the PF to the problem and depicted their errors by the distances between their solutions and the exact filter. The numerical results are presented in the main text.

S7. Modeling and analysis of the transcription system in yeast cells

A. Reaction network model for this transcription system. The transcription system consists of four species: G_0 (inactive gene), G_1 (active gene), G_2 (gene in an advanced active state), and mRNA (messenger RNA). We represent their respective molecular counts by X_{G_0} , X_{G_1} , X_{G_2} , and X_{mRNA} . Then, the chemical reactions occurring within this system are modeled as follows.



Here, the gene transitions among three gene states G_0 , G_1 , and G_2 , and the mRNA are transcribed when the gene is in either of the two active states, G_1 and G_2 . At the initial time point, the gene is in the state G_0 , and the mRNA count equals zero.

Moreover, the cell is measured under a microscope at different time points $\{t_1, \dots, t_{n_f}\}$, and the measurements satisfy the relation

$$Y(t_i) = X_{\text{mRNA}}(t_i) + \sigma W_i$$

where σ is the noise intensity, and $\{W_i\}_{i=1, \dots, n_f}$ are independent standard Gaussian random variables.

For the ease of notation, let us denote G_0 , G_1 , G_2 , and mRNA as S_1 , S_2 , S_3 , and S_4 , respectively. Similarly, we denote X_{G_0} , X_{G_1} , X_{G_2} , and X_{mRNA} as X_1 , X_2 , X_3 , and X_4 .

B. Ergodicity of the system. Now, we show that the system exhibits ergodicity in some invariant state space when reasonable parameters are chosen. Recall that given an invariant space, ergodicity means the occupation time distribution $\mathbb{P}_{oc}(T, x) \triangleq \frac{1}{T} \int_0^T \mathbb{1}(X(t) = x) dt$ almost surely converges to the stationary distribution on this space as $T \rightarrow \infty$. The following analysis are based on the method in [26].

First, we consider the case where all the parameters are positive. In this case, we can observe that the system state $(X_1(t), X_2(t), X_3(t), X_4(t))$ evolves in an invariant space $\mathcal{IS} \triangleq \{x \in \mathbb{Z}_{\geq 0}^4 | x_1 + x_2 + x_3 = 1\}$, and the stochastic system is irreducible on this state space. Furthermore, by denoting $v = (1, 1, 1, 1)^\top$, we have that

$$\begin{aligned} \sum_{j=1}^6 \lambda_j(\theta, x) \langle v, \zeta_j \rangle &= k_{p_1} x_2 + (k_{p_1} + k_{p_2}) x_3 - x_4 \leq (k_{p_1} + k_{p_2}) + 1 - \langle v, x \rangle \quad \forall x \in \mathcal{IS} \\ \sum_{j=1}^6 \lambda_j(\theta, x) \langle v, \zeta_j \rangle^2 &= k_{p_1} x_2 + (k_{p_1} + k_{p_2}) x_3 + x_4 \leq (k_{p_1} + k_{p_2}) + \langle v, x \rangle \quad \forall x \in \mathcal{IS}. \end{aligned}$$

Therefore, according to [26, Proposition 4], the system has a unique stationary distribution on $\mathcal{IS}$ for any positive parameters, and the system also exhibits ergodicity.

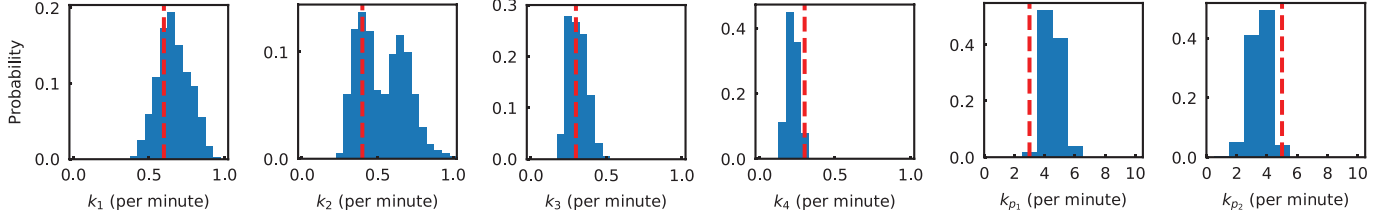
Second, we consider the scenario where the system has only one active gene state, meaning that k_1 , k_2 , and k_{p_1} are positive, but $k_3 = 0$. In this case, we can also find an invariant measure $\mathcal{IS}_{x_3=0} \triangleq \{x \in \mathbb{Z}_{\geq 0}^4 | x_1 + x_2 = 1, x_3 = 0\}$, and the stochastic system is irreducible on this state space. Moreover, by denoting $v = (1, 1, 1, 1)^\top$, we have that

$$\begin{aligned} \sum_{j=1}^6 \lambda_j(\theta, x) \langle v, \zeta_j \rangle &= k_{p_1} x_2 - x_4 \leq k_{p_1} + 1 - \langle v, x \rangle \quad \forall x \in \mathcal{IS}_{x_3=0} \\ \sum_{j=1}^6 \lambda_j(\theta, x) \langle v, \zeta_j \rangle^2 &= k_{p_1} x_2 + x_4 \leq k_{p_1} + \langle v, x \rangle \quad \forall x \in \mathcal{IS}_{x_3=0}. \end{aligned}$$

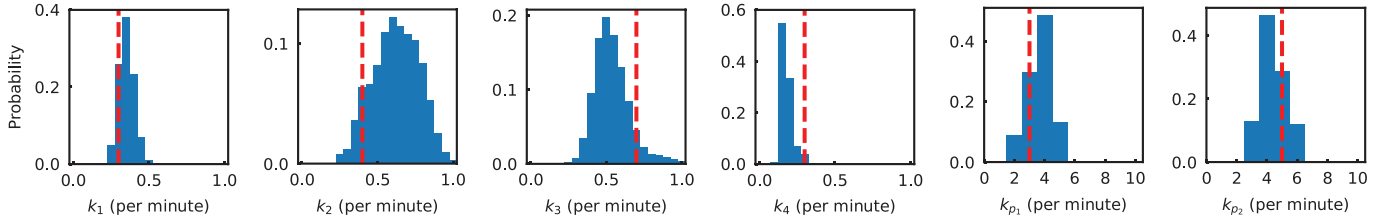
Consequently, according to [26, Proposition 4], the system is also ergodic when $k_1, k_2, k_{p_1} > 0$ but $k_3 = 0$.

C. More simulation results. In the main text, we presented two simulation examples to illustrate our identification algorithm. Here, we present additional simulation results to further demonstrate the effectiveness of our approach. For these simulations, we first generated 1000-minute observation trajectories using specific sets of parameters and then applied our method to infer these model parameters. These parameters were properly chosen to represent several different scenarios: (1) strong initial gene activation (characterized by a large k_1), (2) strong second-step gene activation (large k_3), (3) strong basal transcription (large k_{p_1}), and (4) strong transcription due to a large k_{p_2} . These simulation examples complement the numerical example in the main text well, where all the parameters took medium or relatively small values. All the other settings for these numerical examples were kept the same as those in the main text. The numerical results are presented in Figure S1.

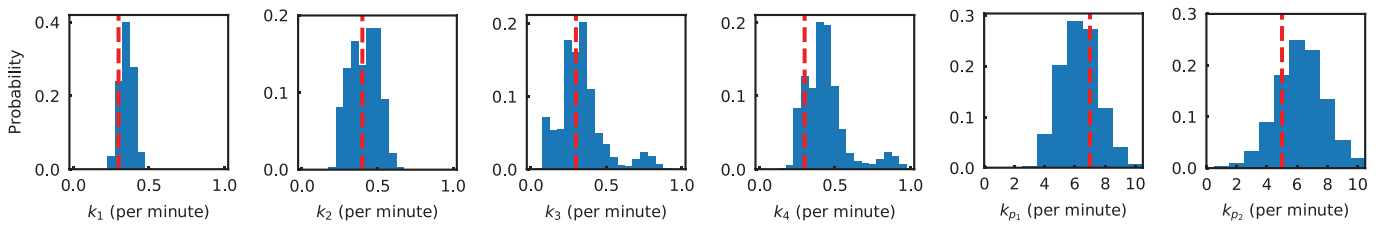
A Strong initial gene activation (large k_1)



B Strong second-step gene activation (large k_3)



C Strong basal transcription rate (large k_{p1})



D Strong transcription due to a large k_{p2}

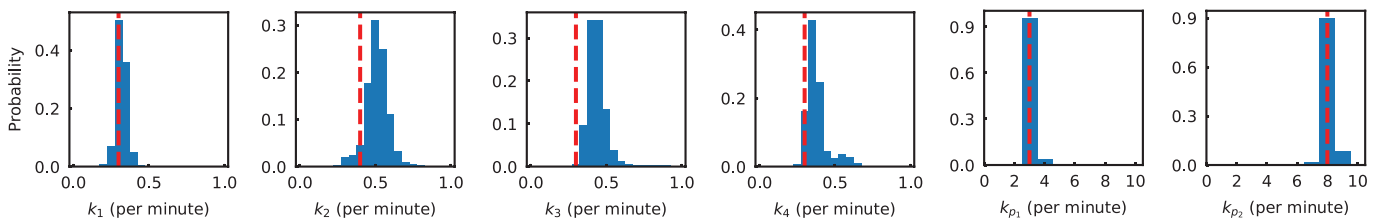


Fig. S1. Performance of the Rao-Blackwell identification algorithm across several numerical examples. The sample size of the algorithm was 10,000. (A) to (D) represent the inference results in four different scenarios: (A) strong initial gene activation (characterized by a large k_1), (B) strong second-step gene activation (large k_3), (C) strong basal transcription (large k_{p1}), and (D) strong transcription due to a large k_{p2} . In these panels, the blue bar plots represent the conditional distribution of the parameters, and the red dashed line represents the actual value of these parameters. Source data are provided as a Source Data file.

The results in Figure S1 show that in different scenarios, our method can provide sharp estimates of the parameters, with most of the maximum a posteriori (MAP) estimates being close to or identical to the actual values. In Figure S1.B, the MAP estimates of k_2 and k_3 are a bit deviated from the actual values. These discrepancies are mainly attributed to the insufficient information in the measurements for highly precise estimation, as evidenced by the wide shapes of the conditional distributions. Even in this case, our method still successfully provided conditional distributions with much probability mass distributed around the actual values. In conclusion, all these results indicate that our identification method is effective across various scenarios where actual parameters are chosen differently.

D. Parameter identification when the measurement noise intensity (σ) is unknown. In many biological experiments, the measurement noise intensity (represented by σ) is often difficult to determine. Therefore, many parameter identification problems also require inferring the value of the measurement noise intensity along with the other model parameters. In this subsection, we demonstrate by several numerical examples that our approach can effectively solve the associated identification problem with the presence of σ uncertainty.

Essentially, in the considered system, we can view σ as an additional model parameter and treat it the same as other parameters. From this perspective, our method can be directly applied to this inference problem. To test our method's performance in this context, we used the same settings as those in the numerical experiments presented in the main text. Specifically, we assumed that $k_1, \dots, k_4$ were within the set $\{0, 0.05, \dots, 1\}$, the parameters k_{p1} and k_{p2} were within the set $\{1, 2, \dots, 10\}$, and σ was within the set $\{0.1, 0.2, \dots, 1\}$. All these parameters were in units of minute^{-1} and had uniform

prior distributions, with the exception of k_3 . For k_3 , half of its initial probability mass was allocated at zero to indicate the uncertainty of whether the number of active gene states is one or two, and the rest of the probability was uniformly distributed over states $0.05, 0.1, \dots, 1$. Also, we truncated the space for the mRNA count to be $\{0, 1, \dots, 20\}$ and that for each gene to be $\{0, 1\}$. At the initial time, we set the gene state to G_0 and the mRNA count to zero. Moreover, the mRNA count was measured every minute.

In this numerical experiment, we generated several observation trajectories based on different choices of σ values. Our aim was to test whether our method can accurately infer the real value of σ along with other parameters. The numerical results are shown in Figure S2. In these numerical experiments, we set the sample size in our algorithm to 3,000. Also, we required the size of the maximum follower subsystem to be less than 30,000. Consequently, our algorithm classified G_1 and G_2 as the leader species and assigned the remaining components into four follower subsystems. The follower species forms four conditionally independent subgroups. The first consists of G_0 , k_1 , and k_2 , the second contains k_3 , the third contains k_4 , and the fourth consists of k_{p_1} , k_{p_2} , mRNA, and σ .

Figure S2.A shows the estimation results when the observation noise intensity σ has a value of 0.1. It shows that the proposed algorithm can accurately identify the parameter σ as well as other parameters in this case. Particularly, the algorithm very confidently identifies the observation noise intensity σ with almost all the probability mass located at the value of 0.1. For the remaining parameters, the MAP (maximum a posteriori) estimates are all close to or equal to the real values. The plots (B) – (K) in Figure S2 show the convergence of the σ estimate over time when the real σ value is chosen differently in the system. We can observe that under all situations, the estimate of σ converges fast to the real value. When the observation noise intensity is small ($\sigma \leq 0.2$), the estimate is almost the same as the real value after 20 minutes. In all the situations, the algorithm consistently provides a very confident and accurate estimate for the parameter σ at the final observation time, as shown in (B) – (K) of Figure S2. All the above results indicate that our algorithm can accurately estimate the observation noise intensity σ as well as other parameters with the presence of σ uncertainty.

E. RB-PF based on grid refinement. When analyzing the experimental data, we initially selected a very coarse discretization scheme for the parameter spaces, especially for the parameters k_{p_1} and k_{p_2} . This can potentially lead to less accurate estimates of the model parameters and be a source of the discrepancy between the stationary distributions of the inferred model and the actual cell system.

In this subsection, we introduce an improved RB-PF based on grid refinement. In the inference problem, we initially choose a very large region for the parameters to make sure that their actual values are within these regions. However, this choice of large regions is not necessary if we have more accurate information about the parameter values. After applying the inference algorithm based on the coarse discretization scheme, we gain more precise estimates of the parameters; particularly, we can identify regions where the conditional distribution mass is sparse or even nonexistent. Based on such information, we can shrink the parameter space, set a finer discretization scheme, and re-apply the inference algorithm. This procedure can be repeated many times until a good resolution of the parameter spaces is reached.

Essentially, this grid refinement procedure reuses data to inform a prior distribution for the next refinement stage. Consequently, the inference result obtained in the last stage may not necessarily align with the target of the original inference problem, and their difference could be significant. Therefore, the refinement method should be used with care; otherwise, data reuse (also known as double-dipping or double-counting) can lead to severe problems [27]. To avoid this issue, this algorithm in each refinement stage should be conservative, only discarding the parameter regions containing extremely low posteriors, for the following reason. Let us denote Ω_i ($i = 1, 2, \dots$) as the parameter region used for the i -th stage inference. The first stage aims at the original inference problem with no refinement. Then, given the uniform prior distribution on Ω_i , the target posterior in the i -th stage is proportional to the likelihood, i.e.,

$$P_i(\theta|Y_{0:T}) \propto L(Y_{0:T}|\theta)P_{\text{prior}}(\theta) \propto L(Y_{0:T}|\theta) \quad \forall \theta \in \Omega_i$$

where $Y_{0:T}$ denotes the measurements from time zero to T , the notation $L(Y_{0:T}|\theta)$ is the likelihood of observing $Y_{0:T}$ with the parameter θ , and $P_{\text{prior}}(\cdot)$ is the uniform prior distribution. This formula demonstrates that regardless of the selected region, the inference result in each stage provides the correct likelihoods at different parameter points up to a constant proportionality. As long as the selected region Ω_i contains most of the parameters with large likelihoods, the distribution $P_i(\theta|Y_{0:T})$ will closely approximate the target posterior distribution $P_1(\theta|Y_{0:T})$. This requires the grid refinement procedure to eliminate only the regions with negligible likelihoods (i.e., small posterior) in each stage for accurate inference results.

We applied this grid refinement strategy to the inference problem of cell #78. From the inference result based on the coarse grid (Fig. 9A in the main text), we observed that all the conditional probability mass for k_{p_1} and k_{p_2} are within the regions of $[20, 40]$ and $[40, 80]$, respectively. Also, the result suggested that k_3 was positive, i.e., the system had three gene states. Based on these observations, we adjusted the parameter spaces as follows. The parameters k_1 , k_2 , and k_3 were within the set $\{0, 0.05, \dots, 1\}$, k_4 was within the set $\{0, 0.1, \dots, 2\}$, k_{p_1} was within $\{20, 22, 24, \dots, 40\}$, and k_{p_2} was within $\{40, 44, 48, \dots, 80\}$. This refined grid scheme offered an acceptable resolution. Moreover, all the parameters were assumed to have uniform distributions on these sets. We again applied our Rao-Blackwell method to this inference problem on the finer discretization scheme. The result is shown in Figure S3.

The inference results obtained under the coarse grid scheme and the refined one are quite consistent. Comparing Figure S3 and Fig. 9A (in the main text), we can find that the conditional distributions for each parameter (k_1 , k_2 , k_3 , and k_4) have the same shape and similar peak values in both inference results. Also, in both results, the conditional distributions for k_{p_1} are

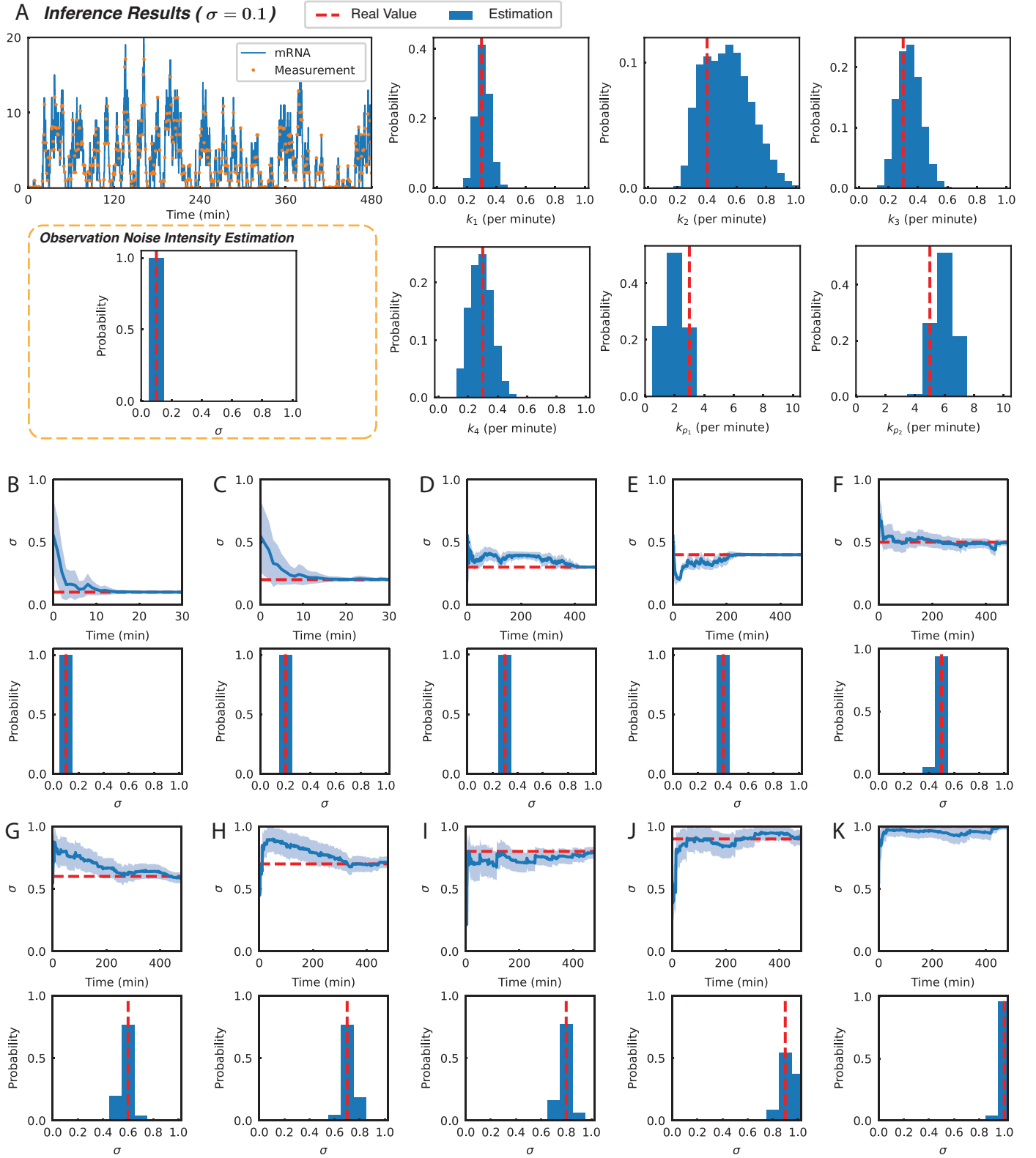


Fig. S2. Performance of the Rao-Blackwell identification algorithm in the numerical transcription example with σ uncertainty. The sample size of the algorithm was 3,000. (A) The estimation result when σ has a real value of 0.1. The top left panel shows the dynamics of the mRNA together with the time-course measurements. The other panels show the estimates of the observation noise intensity and other parameters. These results indicate that our algorithm can accurately identify the observation noise intensity (σ) simultaneously with other parameters. (B) – (K) The convergence of σ estimates over time in systems with different real σ values. These plots also provide the final-time estimate of σ in the lower panel. Source data are provided as a Source Data file.

both concentrated around the value of 30, and the conditional distributions for k_{p_2} are both concentrated around the value of 70. These consistencies underscores the robustness of our method, demonstrating its good reproducibility whether applied on a coarse or a refined grid scheme.

After the grid refinement, we obtained potentially more accurate estimates of k_{p_1} and k_{p_2} . To test their accuracy, we again compared the stationary distributions of the inferred model (with the MAP estimates) and the actual cell system (see Figure S3B). They matched closely. This time, the KL divergence between these two distributions is 0.020, one-third less than the values obtained when inferring the system under a coarse grid. Additionally, the L_1 distance between the distributions dropped from 0.19 (under the coarse grid) to 0.11 (under this refined grid). All these results suggest that our identification method, based on grid refinement, provided more accurate parameter estimates.

All these improved results of the grid refinement strategy demonstrate that this strategy should be employed whenever a large region of low posterior is observed. Compared with results obtained at a finer scale, the algorithm based on a coarse grid cannot provide much detailed information, thereby leading to biased estimates. For instance, the conditional distribution of k_{p_1} exhibits a bimodal structure (Figure S3C), which is absent when using a coarse grid (see the results in the main text). Moreover, the determination of grid fineness should be based on the ability to capture peaks and valleys within the posterior distribution, rather than merely on the ratio between the step size and the parameter interval.

A Refinement of the grid scheme

$k_1 : \{0, 0.05, 0.10, \dots, 1\}$ $k_2 : \{0, 0.05, 0.10, \dots, 1\}$ $k_3 : \{0, 0.05, 0.10, \dots, 1\}$ $k_4 : \{0, 0.1, 0.2, \dots, 2\}$

$k_{p_1} : \{0, 8, 16, \dots, 80\}$ $\xrightarrow{\text{refine}}$ $k_{p_1} : \{20, 22, 24, \dots, 40\}$
 $k_{p_2} : \{20, 30, 40, \dots, 120\}$ $\xrightarrow{\text{refine}}$ $k_{p_2} : \{40, 44, 48, \dots, 80\}$

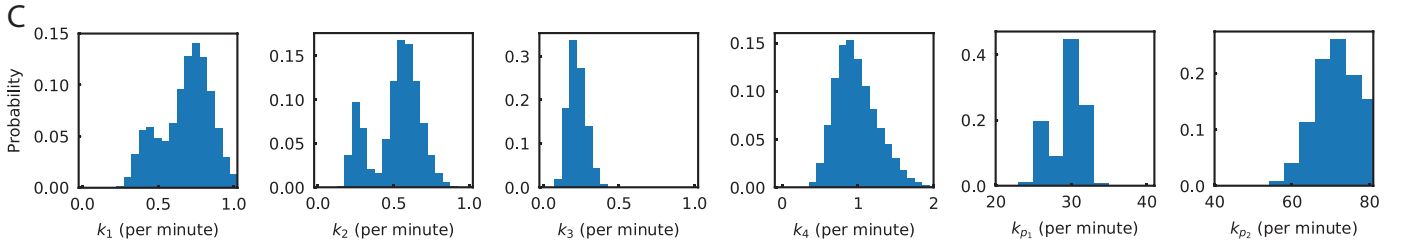
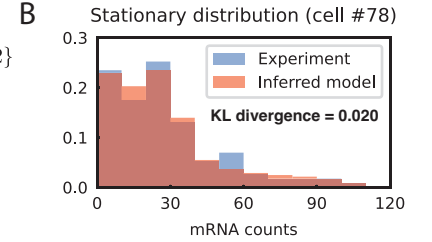


Fig. S3. Inference result of cell #78 based on a refined discretization scheme. The sample size of the algorithm was 3,000. (A) Refinement of the grid scheme. For parameters $k_1, \dots, k_4$, the grid schemes are unchanged. The scheme for k_{p_1} is refined to $\{20, 22, 24, \dots, 40\}$ with a discretization size of 2. The scheme for k_{p_2} is refined to $\{40, 44, 48, \dots, 80\}$ with a discretization size of 4. (B) Stationary distributions of the inferred model (using the MAP estimates) and the actual cell system. They have a KL divergence of 0.020. (C) Parameter estimation result. Source data are provided as a Source Data file.

F. Estimation of the observation noise intensity σ from the experimental data. In this biological experiment, the observation noise intensity σ has not been exactly quantified. Here, we intend to estimate this parameter σ , along with others, using the RB-PF with the grid-refinement strategy.

The basic setup of this Bayesian analysis is as follows. First, we view σ as an additional model parameter and treat it the same as other parameters. Since the measurement is thought to be quite accurate [28], we assumed that σ was within the narrow set $\{0.2, 0.4, \dots, 2\}$. For other parameters, we adopt the refined setting in the previous subsection. Specifically, the parameters k_1, k_2 , and k_3 were within the set $\{0, 0.05, \dots, 1\}$, k_4 was within the set $\{0, 0.1, \dots, 2\}$, k_{p_1} was within $\{20, 22, 24, \dots, 40\}$, and k_{p_2} was within $\{40, 44, 48, \dots, 80\}$. All the parameters were assumed to have uniform prior distributions over their specified sets. Moreover, for the system decomposition, we required the size of the maximum follower subsystem to be less than 300,000, and we set the sample size in our algorithm to 3,000. Consequently, our algorithm still classified G_1 and G_2 as the leader species and assigned the remaining components into four follower subsystems. The first follower subsystem consists of G_0, k_1 , and k_2 , the second contains k_3 , the third contains k_4 , and the fourth consists of k_{p_1}, k_{p_2} , mRNA, and σ .

The inference results are shown in Figure S4. Our algorithm confidently estimated the parameter σ to be 0.4 (Figure S4B), demonstrating a high degree of accuracy in the mRNA measurements. This inference result also indicates that the observation noise intensity is even much less than what we assumed previously (i.e., $\sigma = 1$). We also compared the stationary distributions of the inferred model (with the MAP estimates) and the actual cell system (Figure S4D). These two distributions matched closely, with the KL divergence being 0.021, indicating the accuracy of the inference result. In addition, this KL divergence is similar to that obtained from the grid-refinement strategy based on assuming $\sigma = 1$ (Figure S3B). Furthermore, the inference results for parameters other than σ are similar in both settings (see Figure S4C and Figure S3C). This demonstrates that in this inference problem, the precise estimation of σ does not lead to a significant improvement in the inference results.

In conclusion, our method can accurately estimate the observation noise intensity σ in this problem. However, this accurate estimation of σ does not significantly impact the inference results for the other parameters.

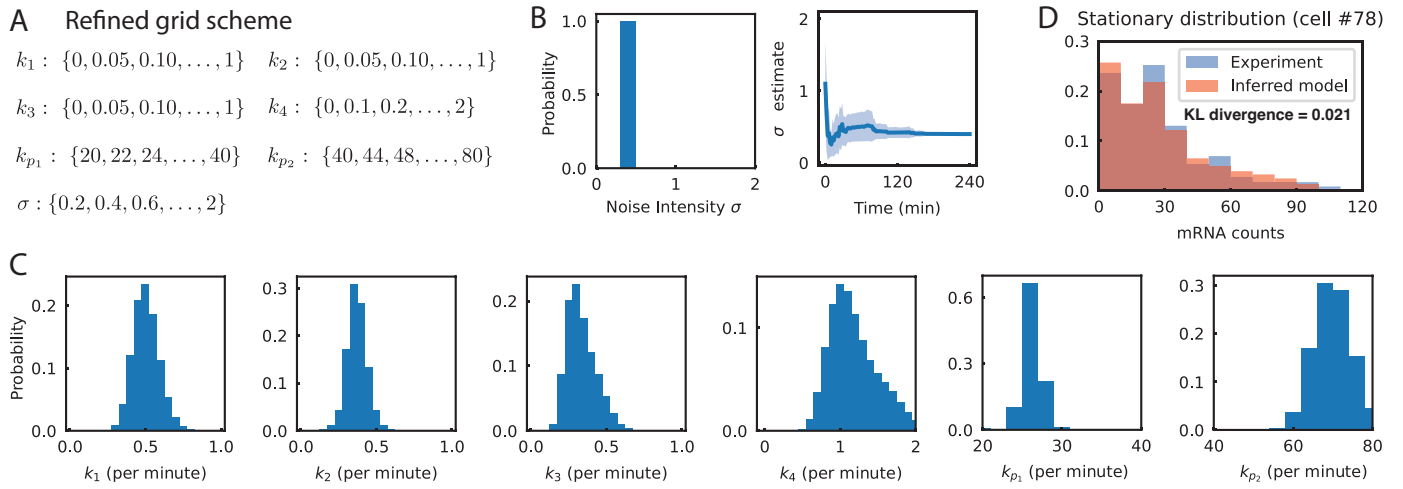


Fig. S4. Inference of the observation noise intensity σ from the experimental data of cell #78. The sample size in our algorithm was 3,000. (A) The grid for parameter inference. We selected the refined grid obtained from the grid refinement strategy, and we set σ within the set $\{0.2, 0.4, \dots, 2\}$. (B) Inference results of σ at the final time and its estimate over time. (C) Estimation of other parameters. (D) Stationary distributions of the inferred model (using the MAP estimates) and the actual cell system. They have a KL divergence of 0.021. Source data are provided as a Source Data file.

S8. Noise decomposition based on ergodicity

Now, we utilize the stability of the underlying continuous-time Markov chain, i.e. ergodicity, to propose a method for noise decomposition from single-cell time-lapse microscopy data. We consider that a microscopic platform can record the dynamics of a particular chemical species in individual cells. This dynamics is denoted by $\{X_\theta(t)\}_{t \geq 0}$ with θ the system parameters that can be different from cell-to-cell due to *extrinsic variability*. Also, We assume that for each cell the value of θ is constant and unchanging with time. Furthermore we assume that for each θ fixed, the dynamics $(X_\theta(t))_{t \geq 0}$ is ergodic and therefore (see [26]) we have

$$\frac{1}{T} \int_0^T X_\theta(t) dt \longrightarrow \mathbb{E}[X_\theta^* | \theta] \quad \text{as } T \rightarrow \infty \quad (35)$$

$$\frac{1}{T} \int_0^T (X_\theta(t))^2 dt \longrightarrow \mathbb{E}[(X_\theta^*)^2 | \theta] \quad \text{as } T \rightarrow \infty \quad (36)$$

where X_θ^* is the copy number of the measured species at the stationary probability distribution (or equivalently at a sufficiently large time point).

The total cell-to-cell variability at the stationary probability distribution is $\text{Var}(X_\theta^*)$. The law of total variance stipulates that

$$\text{Var}(X_\theta^*) = \text{Var}(\mathbb{E}[X_\theta^* | \theta]) + \mathbb{E}[\text{Var}(X_\theta^* | \theta)] \quad (37)$$

where the quantity $\text{Var}(X_\theta^* | \theta)$ is the conditional variance defined by

$$\text{Var}(X_\theta^* | \theta) = \mathbb{E}[(X_\theta^*)^2 | \theta] - \mathbb{E}[X_\theta^* | \theta]^2$$

and it measures the variation in X_θ^* when the parameter θ is fixed. Hence the only contribution to $\text{Var}(X_\theta^* | \theta)$ comes from sources other than θ , and in this setup the only such source is the *intrinsic noise* introduced by the random timing of reactions. Therefore we term the second term $\mathbb{E}[\text{Var}(X_\theta^* | \theta)]$ on the r.h.s of (37) as the aggregate/bulk/population-level measure of the total intrinsic noise in the system.

On the other hand, the first term $\text{Var}(\mathbb{E}[X_\theta^* | \theta])$ on the r.h.s of (37) measures all the noise due to the randomness in the parameters θ . This is because when we take the conditional expectation $\mathbb{E}[X_\theta^* | \theta]$ we are averaging-out noise from all other sources except the parameters θ . Due to this reason we term $\text{Var}(\mathbb{E}[X_\theta^* | \theta])$ as the total extrinsic noise in the system. In summary we have the following definition of intrinsic and extrinsic noise

$$\text{Total Extrinsic Noise} = \text{Var}(\mathbb{E}[X_\theta^* | \theta])$$

$$\text{Total Intrinsic Noise} = \mathbb{E}[\text{Var}(X_\theta^* | \theta)]$$

Of course both these terms add up to the full cell-to-cell variability $\text{Var}(X_\theta^*)$ due to (37).

The straightforward computation of intrinsic and extrinsic noise is challenging because the experimental data cannot provide a cell population with the same parameters θ for estimating $\mathbb{E}[X_\theta^* | \theta]$ and $\text{Var}(X_\theta^* | \theta)$. Fortunately, ergodicity provides us a solution for computing these conditional mean and variance from single-cell time-course data. Specifically, (35) and (36) suggest that these conditional mean and variance can be approximated by

$$\mathbb{E}[X_\theta^* | \theta] \approx \frac{1}{T} \int_0^T X_\theta(t) dt \quad \text{and} \quad \text{Var}(X_\theta^* | \theta) \approx \frac{1}{T} \int_0^T (X_\theta(t))^2 dt - \left(\frac{1}{T} \int_0^T X_\theta(t) dt \right)^2$$

for large time T . Recall that the dynamics of $X_\theta(t)$ is measured in a microscope platform. Therefore, when the measurement noise is negligible, the time integrals above can be straightforwardly computed by the measured single-cell time-course data of $X_\theta(t)$. Finally, the intrinsic noise and extrinsic noise can be evaluated by

$$\text{Total Intrinsic Noise} \approx \mathbb{E} \left(\frac{1}{T} \int_0^T (X_\theta(t))^2 dt - \left(\frac{1}{T} \int_0^T X_\theta(t) dt \right)^2 \right)$$

$$\text{Total Extrinsic Noise} \approx \text{Var} \left[\frac{1}{T} \int_0^T X_\theta(t) dt \right]$$

for large time T .

To further validate this noise decomposition method, let us outline a couple of edge cases where one of the two noise components is zero. First, let us consider the scenario that the dynamics $\{X_\theta(t)\}_{t \geq 0}$ is deterministic, and described by a system of ordinary differential equations (ODEs) that depend on the cell-specific parameter θ . In this case, ergodicity is tantamount to this ODE system having a globally attracting θ -dependent fixed point $\bar{X}_\theta$. One can easily check that in this scenario

$$\lim_{T \rightarrow \infty} \frac{1}{T} \int_0^T X_\theta(t) dt = \bar{X}_\theta \quad \text{and} \quad \lim_{T \rightarrow \infty} \frac{1}{T} \int_0^T (X_\theta(t))^2 dt = \bar{X}_\theta^2$$

868 which shows that the intrinsic noise component would be close to zero (for large T). This is what we would expect as the
869 dynamics is deterministic and hence there is no noise due to the random firing of reactions. Now consider another scenario
870 where the parameter is not random, but a deterministic constant $\theta = \theta_c$ which is the same for each cell. In this case the
871 conditional expectation in (35) becomes an unconditional expectation which computes to a deterministic constant (rather than
872 a random variable). Hence its variance is zero which shows that the extrinsic noise component would be close to zero (for large
873 T). Again this is consistent with our expectation because there is no variability in θ .

S9. An idea of applying the RB-CME solver for computing the stationary distribution

In this paper, our RB-CME solver is designed to solve the CME in a finite time interval. Here, we present an idea of applying our method to compute the stationary distribution of the CME based on the ergodicity assumption.

When a system is ergodic, the stationary distribution ($\mathbb{P}_{st}(x)$) can be approximated by

$$\mathbb{P}_{st}(x) \approx \underbrace{\frac{1}{T} \int_0^T \mathbb{1}(X(t) = x) dt}_{\widehat{\mathbb{P}}_{er}(x)}$$

for a large T . Following this formula, one can estimate the stationary distribution by the time occupation measure of a sufficiently long simulated trajectory [29]. Moreover, when the bias is negligible, the performance of this method can be evaluated by the variance of the random variable $\widehat{\mathbb{P}}_{er}(x)$.

Similarly, we can also approximate the stationary distribution by

$$\mathbb{P}_{st}(x) \approx \underbrace{\frac{1}{T} \int_0^T \mathbb{E} \left[\mathbb{1}(X(t) = x) \middle| \widetilde{X}(s), 0 \leq s \leq t \right] dt}_{\widehat{\mathbb{P}}_{RB}(x)},$$

where $\widetilde{X}(t)$ is the leader system. Then, we can also estimate the stationary distribution by generating a sufficiently long trajectory and applying the RB-CME solver to the conditional expectation in the above formula. Again, when the bias is negligible, the performance of this method can be evaluated by the variance of $\widehat{\mathbb{P}}_{RB}(x)$.

Both methods are developed based on the ergodicity assumption. We next show that the one using the RB-CME solver is no less accurate. The key is to compare the variance of $\widehat{\mathbb{P}}_{er}(x)$ and $\widehat{\mathbb{P}}_{RB}(x)$. First, it can be easily shown that

$$\begin{aligned} \text{Var} \left(\widehat{\mathbb{P}}_{er}(x) \right) &= \mathbb{E} \left[\left(\widehat{\mathbb{P}}_{er}(x) - \widehat{\mathbb{P}}_{RB}(x) \right)^2 \right] + \mathbb{E} \left[\left(\widehat{\mathbb{P}}_{RB}(x) - \frac{1}{T} \int_0^T \mathbb{P}(X(t) = x) dt \right)^2 \right] \\ &\quad + 2\mathbb{E} \left[\left(\widehat{\mathbb{P}}_{er}(x) - \widehat{\mathbb{P}}_{RB}(x) \right) \left(\widehat{\mathbb{P}}_{RB}(x) - \frac{1}{T} \int_0^T \mathbb{P}(X(t) = x) dt \right) \right] \end{aligned}$$

Note that $\mathbb{E} \left[\left(\widehat{\mathbb{P}}_{RB}(x) - \frac{1}{T} \int_0^T \mathbb{P}(X(t) = x) dt \right)^2 \right]$ is the variance of $\widehat{\mathbb{P}}_{RB}(x)$, and the last term satisfies

$$\begin{aligned} &\mathbb{E} \left[\left(\widehat{\mathbb{P}}_{er}(x) - \widehat{\mathbb{P}}_{RB}(x) \right) \left(\widehat{\mathbb{P}}_{RB}(x) - \frac{1}{T} \int_0^T \mathbb{P}(X(t) = x) dt \right) \right] \\ &= \mathbb{E} \left[\mathbb{E} \left[\left(\widehat{\mathbb{P}}_{er}(x) - \widehat{\mathbb{P}}_{RB}(x) \right) \left(\widehat{\mathbb{P}}_{RB}(x) - \frac{1}{T} \int_0^T \mathbb{P}(X(t) = x) dt \right) \middle| \widetilde{X}(s), 0 \leq s \leq T \right] \right] \\ &= \mathbb{E} \left[\mathbb{E} \left[\widehat{\mathbb{P}}_{er}(x) - \widehat{\mathbb{P}}_{RB}(x) \middle| \widetilde{X}(s), 0 \leq s \leq T \right] \left(\widehat{\mathbb{P}}_{RB}(x) - \frac{1}{T} \int_0^T \mathbb{P}(X(t) = x) dt \right) \right] \\ &= \mathbb{E} \left[0 \times \left(\widehat{\mathbb{P}}_{RB}(x) - \frac{1}{T} \int_0^T \mathbb{P}(X(t) = x) dt \right) \right] \\ &= 0. \end{aligned}$$

Therefore, we can conclude that

$$\text{Var} \left(\widehat{\mathbb{P}}_{er}(x) \right) \geq \text{Var} \left(\widehat{\mathbb{P}}_{RB}(x) \right)$$

which means that the method using RB-CME solver is no less accurate than the other one.

We leave a systematic exploration of this idea for future work.

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