Universal Diffusion–Dynamics Laws in Stochastic Reaction Networks

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Many biological activities are induced by cellular chemical reactions of diffusing reactants. The dynamics of such systems can be captured by stochastic reaction networks. A recent numerical study has shown that diffusion can significantly enhance the fluctuations in gene regulatory networks. However, the general relation between diffusion and stochastic system dynamics remains unveiled. Here we examine the general relation and find the universal law under which the steady-state distribution in complex balanced networks is diffusion-independent. Here, complex balance is the non-equilibrium generalization of detailed balance. We also find that for a diffusion-included network with a Poisson-like steady-state distribution, the diffusion can be ignored at steady-state. We then derive a necessary and sufficient condition for such steady-state network distributions. Moreover, we exactly prove that the stochastic dynamics of linear reaction networks are unaffected by diffusion at any arbitrary time. Our findings shed light on the fundamental question of when diffusion can be neglected, or (if non-negligible) its effects on the stochastic dynamics of the reaction network.

Introduction.—Diverse biological phenomena, such as cellular signal transduction and gene expression systems, are commonly studied by stochastic reaction network modeling [1–3]. These systems involve a set of reactant species which react through several channels. In most of the existing studies, such systems are often assumed to be well mixed, meaning that the diffusion coefficients of the reactants are infinitely large [4–10]. However, experiments have shown that reactants in cells diffuse at considerably low rates [11], and that the smallest timescale of the system is little larger than the timescale of molecular diffusion. In such cases, the well-mixed assumption cannot accurately obtain the stochastic dynamics of the system. For example, living cells continuously receive signals at their receptors, which are subsequently transmitted to the nucleus through biochemical reaction networks [12–15]. This process is strongly influenced by extrinsic and intrinsic noise arising from fluctuations in the input and reactions. These effects induce unavoidable fluctuations in the biomolecule concentrations, which deteriorate the fidelity of information transfer [16, 17]. By accurately evaluating the fluctuations, we would better understand the mechanism underlying signal transmission in cells. In a numerical study of gene regulatory networks, Ref. [18] showed that the fluctuations are larger in the model with diffusion than in its well-mixed counterpart. Thus, how diffusion relates to the stochastic dynamics of reaction networks is a pertinent question. Recently, Ref. [19] has numerically studied the effects of diffusion on single-cell variability in multicellular organisms, and the limits of slow and fast diffusion have been investigated.

The Langevin equation, which can be derived from an equivalent Fokker–Planck equation or the Poisson representation, can handle continuum-limit diffusion in reaction networks [20–23]. However, the Langevin equation is applicable to biochemical reactions occurring in infinite space with no physical boundary, which is unrealistic in biological cells. This Letter investigates the relation between diffusion and the stochastic dynamics of reaction networks within a physical reflecting boundary. In this system, the reactants diffuse without escaping within the closed 3-dimensional space. Intriguingly, we find a universal law: that diffusion does not affect the steady-state distribution of complex balanced networks, which have a Poisson-like distribution. Our proof reveals that if the network presents a steady-state distribution of that form, diffusion can be neglected. We then calculate the necessary and sufficient condition for such steady-state network distributions. We also find another law in which steady-state is not a mandatory requirement. Specifically, we exactly prove that at any arbitrary time, the stochastic dynamics of the system are diffusion-independent in linear reaction networks.

Models.—Consider a general reaction network consisting of $N$ reactant species $X_1, \ldots, X_N$ and $R$ reactions $\mathcal{R}_1, \ldots, \mathcal{R}_R$. Assume that all reactions occur inside a cell with fixed volume $\Omega$, and that reaction $\mathcal{R}_j$ ($1 \leq j \leq R$) is of the form

$$s_{1j}X_1 + \cdots + s_{Nj}X_N \xrightarrow{k_j} r_{1j}X_1 + \cdots + r_{Nj}X_N,$$

where $s_{ij}, r_{ij} \in \mathbb{N}_{\geq 0}$ are the stoichiometric coefficients and $k_j \in \mathbb{R}_{>0}$ is the macroscopic reaction rate. Here $\mathbb{N}_{\geq 0}$ denotes the set of non-negative integers. $\mathbb{R}_{>0}$ and $\mathbb{R}_{\geq 0}$ are defined analogously. If $\sum_{i=1}^{N} s_{ij} \leq 1$ for all $j = 1, \ldots, R$, then the reaction network is linear; otherwise, it is nonlinear. The state of the system is fully determined by the molecule-number vector of all reactant species in the system, $n = [n_1, \ldots, n_N]^T$, where $n_i \in \mathbb{N}_{\geq 0}$ is the number of molecules of species $X_i$. Assuming mass-action kinetics, the time evolution of a well-mixed system can be described by the following chemical master equ-
tion (CME) [22]:
\[
\partial_t P(n, t) = \sum_{j=1}^{R} (E^j - V_j - 1) f_j(n, \Omega) P(n, t),
\]
where \( V = [r_{ij} - s_{ij}] \in \mathbb{Z}^{N \times R} \) is a stoichiometric matrix, \( V_j \) denotes the \( j \)th column of matrix \( V \), and \( E^z \) is an operator that replaces \( n \) with \( n + x \). \( P(n, t) \) is the probability of the system being in state \( n \) at time \( t \), and the propensity function \( f_j(n, \Omega) \) of reaction \( R_j \) is given by
\[
f_j(n, \Omega) = k_j \Omega^{1 - \sum_{i=1}^{N} s_{ij}} \prod_{i=1}^{N} \frac{n_i!}{(n_i - s_{ij})!}.
\]
To include diffusion in stochastic spatial dynamics, many researchers apply the reaction–diffusion master equation (RDME) [22, 24–28], in which space is partitioned discretely into many voxels. It is known that the RDME is accurate if an appropriate combination of the time- and length-scale is chosen [25, 26, 29–31]. We assume from now on that the volume of the system is optimally divided into small voxels and as such, the RDME yields a good description of the time evolution of the probability distribution. Diffusion then occurs among the voxels, and the reaction can occur within the same voxel considered to be a well-mixed system. Assume that the volume \( \Omega \) is divided into a set \( \mathcal{V} \) of voxels labeled by integers \( v = 1, 2, \ldots, |\mathcal{V}| \). Each voxel \( v \) occupies a constant volume \( \omega \) and contains \( n_v \) molecules of reactant species \( X_i \). The state vector of voxel \( v \) is denoted as \( n_v = [n_{v1}, \ldots, n_{vN}]^T \). The state of the whole system is then described as the molecule-number vector \( n \) of each species in each voxel, namely, \( n = [n_1^T, \ldots, n_{|\mathcal{V}|}^T] \). We also define a vector \( 1_{vi} \in \mathbb{Z}^{1/|\mathcal{V}|} \), in which the number of molecules of all species in all voxels is zero except for species \( X_i \) in voxel \( v \) (which is one), and a vector \( \tilde{V}_{vj} \in \mathbb{Z}^{V/|\mathcal{V}|} \), in which all elements are zero except in voxel \( v \) (which holds \( V_j \)). As the diffusion of each species into neighboring voxels can be considered as a first-order reaction, the diffusion-included reaction network can be described in the following form:
\[
s_{1j}X_1^v + \cdots + s_{Nj}X_N^v \xrightarrow{k_j} r_{1j}X_1^{v'} + \cdots + r_{Nj}X_N^{v'},
\]
where \( X_i^v \) refers to species \( X_i \) in voxel \( v \), \( d_i \) is the diffusion rate of species \( X_i \), and \( V_v \) is the set of voxels neighboring \( v \). The stochastic dynamics of the system can then be described by the following RDME:
\[
\partial_t P(n, t) = \sum_{v \in \mathcal{V}} \sum_{v' \in V_v} \sum_{i=1}^{N} (E^{v_{vi}} - 1) d_i n_{vi} P(n, t) + \sum_{v \in \mathcal{V}} \sum_{j=1}^{R} \left( E^{-V_j - 1} \right) f_{vj}(n, \omega) P(n, t),
\]
where \( f_{vj}(n, \omega) \) is the propensity function, given by
\[
f_{vj}(n, \omega) = k_j \omega^{1 - \sum_{i=1}^{N} s_{ij}} \prod_{i=1}^{N} \frac{n_i!}{(n_i - s_{ij})!}.
\]
In the large-diffusion limit, the RDME converges to the CME [32].
Before stating the first result, we describe several existing concepts and results of deterministic reaction networks. For each reaction \( R_j \) \( (1 \leq j \leq R) \), the linear combinations \( \sum_{i=1}^{N} s_{ij} X_i \) and \( \sum_{i=1}^{N} r_{ij} X_i \) of the species in Eq. (1) are called the complexes of the reaction. Defining \( C = \{C_1, C_2, \ldots, C_M\} \) as the set of complexes, with \( M = |C| \), each reaction can be expressed as \( C_i \xrightarrow{a_{ii}} C_i' \), where \( a_{ii} \) denotes the reaction rate. For each \( 1 \leq i, i' \leq N \), \( a_{ii'} = 0 \) if \( C_i \rightarrow C_i' \) is not present in the reaction network; otherwise, \( a_{ii'} = k_j \) for some \( 1 \leq j \leq R \).

The matrix \( A \in \mathbb{R}^{M \times M} \), called the Kirchhoff matrix of the reaction network, is defined as follows:
\[
[A]_{ii'} = \begin{cases} -\sum_{j=1}^{M} a_{ij} & \text{if } i = i' \\ a_{ij} & \text{if } i \neq i' \end{cases}.
\]

In a deterministic system, the vector of species concentrations \( c = [c_1, c_2, \ldots, c_N]^T \in \mathbb{R}^N \) temporally evolves as described by the following differential equations, which express the different form of rate equations:
\[
\partial_t c = Y \cdot A \cdot \Psi(c),
\]
where \( Y = [y_{ij}] \in \mathbb{N}^{N \times M} \) is the matrix of stoichiometric compositions of the complexes, i.e., \( y_{ij} \) is the stoichiometric coefficient of \( C_j \) corresponding to species \( X_i \), and \( \Psi : \mathbb{R}^N \rightarrow \mathbb{R}^M \) is a mapping given by
\[
\Psi(c) = \prod_{i=1}^{N} c_i^{y_{ii}}, \quad j = 1, \ldots, M.
\]

A reaction network is called complex balanced at \( c \in \mathbb{R}^N \) if \( A \cdot \Psi(c) = 0 \). This condition means that for each complex \( C_i \in C, \sum_{C_i \rightarrow C_i'} a_{ii'} \Psi(c) = \sum_{C_i' \rightarrow C_i} a_{ii'} \Psi(c) \). In this case, \( c \) is a positive equilibrium of the network.

The following states our first main result.

**Theorem 1.** If a reaction network is complex balanced, its steady-state distribution is unaffected by diffusion.

**Proof.** As the network is complex balanced, there exists a positive equilibrium \( c = [c_1, \ldots, c_N]^T \in \mathbb{R}^N \) such that \( A \cdot \Psi(c) = 0 \). We note that the only requirement in our proof is the existence of some \( c \) such that \( A \cdot \Psi(c) = 0 \). Here, \( c \) is not the steady-state concentration in the presence of diffusion. Let \( \Gamma \subseteq \mathbb{R}^N \) be the state space of the network, which may depend on the initialization. First, we prove the following ansatz: that the steady-state distribution of the RDME is given by a product.
$P_Γ(n,t)$ of Poisson distributions:

$$P_Γ(n,t) = \begin{cases} \mathcal{N}_Γ \prod_{v \in V} \prod_{i=1}^N \frac{(ω_{ci})^{n_{vi}}}{n_{vi}!}, & \text{if } \sum_{v \in V} n_{vi} \in Γ \\ 0, & \text{if } \sum_{v \in V} n_{vi} \notin Γ \end{cases}$$

(9)

where $\mathcal{N}_Γ$ is the normalizing constant. For each $n_{vi} \in \mathbb{N}_{\geq 0}$, we define $P_Γ^* (n_{vi}) = \prod_{i=1}^N \frac{(ω_{ci})^{n_{vi}}}{n_{vi}!}$. $P_Γ(n)$ can then be expressed as $P_Γ(n) = \mathcal{N}_Γ \prod_{v \in V} P_Γ^* (n_{vi})$. Now, we need to show that $\partial_t P_Γ(n,t) = 0$. Substituting $P_Γ(n,t)$ in Eq. (9) into Eq. (4), the first term of the right-hand side becomes [33]

$$\sum_{v \in V} \sum_{v' \notin V \in N_v(v)}^{N} \left( E^{1,v} - 1_{v'} - 1 \right) d_i n_{vi} P_Γ(n,t) = 0. \quad (10)$$

The second term on the right-hand side becomes the sum of the following values over all voxels $v \in V$

$$\sum_{j=1}^{R} \left( E^{−V_j} - 1 \right) f_{j}(n_{vi}, ω) P_Γ(n_{vi}, t)$$

$$= \mathcal{N}_Γ \prod_{v \neq v'} P_Γ^*(n_{vj}, t) \sum_{j=1}^{R} \left( E^{−V_j} - 1 \right) f_{j}(n_{vj}, ω) P_Γ^*(n_{vj}, t).$$

Exploiting the condition $A \cdot Ψ(\omega) = 0$, one can prove that [33–35]

$$\sum_{j=1}^{R} \left( E^{−V_j} - 1 \right) f_{j}(n_{vj}, ω) P_Γ^*(n_{vj}, t) = 0. \quad (11)$$

Therefore, the second term also disappears and we obtain the desired result $\partial_t P_Γ(n,t) = 0$. Let $\nbar{Γ} = \sum_{v \in V} n_{vi}$ represent the number of molecules of all species, i.e., $\nbar{Γ}$ is the total number of molecules of species $X_i$ in the system. To complete our theorem, we compute the steady-state distribution $P_Γ(\nbar{Γ})$, and show its diffusion-independence. The explicit form of $P_Γ(\nbar{Γ})$ is obtained as follows [33]:

$$P_Γ(\nbar{Γ}) = \sum_{n: \sum_{v \in V} n_{vi} = \nbar{Γ}} P_Γ(n) = \mathcal{N}_Γ \prod_{i=1}^N \frac{(ω_{ci})^{\nbar{Γ}_{i}}}{\nbar{Γ}_i!}. \quad (12)$$

As $\mathcal{N}_Γ = \left( \sum_{n \in Γ} \prod_{i=1}^N \frac{(ω_{ci})^{n_{vi}}}{n_{vi}!} \right)^{-1}$ does not depend on diffusion, the distribution $P_Γ(\nbar{Γ})$ is also independent of diffusion.

Our theoretical result was verified in simulations of the following complex balanced network:

$$0 \xrightarrow{k_1} X_1 + 2 X_2 \xrightarrow{k_2} X_2 \xrightarrow{k_3} 0 \xrightarrow{0}. \quad (13)$$

We considered three cases with different numbers of voxels in the system volume: 1 voxel (a well-mixed system), 100 voxels, and 225 voxels. In the 100- and 225-voxel systems, the diffusion coefficients differed among the species.

The steady-state distributions of species $X_1$ and $X_2$ are plotted in Fig. 1. The distributions of both species are consistent in all three cases. From these result, it is pertinent to ask which conditions define a complex balanced network. Ref. [36] proved that a weakly reversible reaction network with zero deficiency is a complex balanced network. This implies that in some cases, a complex balanced network can be identified by its network topology. In [37], complex balanced realizations of a given kinetic polynomial system were computed by a linear programming algorithm.

Thus far, we have shown that the steady-state distribution of a complex balanced network is a product of Poisson distributions. A network with such a distribution implies that the system is diffusion-independent at steady-state. Therefore, we desire to know the condition under which the system establishes a Poisson-like steady-state distribution. This condition is embodied in the following theorem.

**Theorem 2.** The network possesses the steady-state distribution defined in Eq. (9) in all state spaces $Γ \subseteq \mathbb{N}_{\geq 0}$ if and only if it is complex balanced.

**Proof.** We use the Fock space representation [38] to describe the molecule-number changes of each species inside each voxel. A state vector $|n \rangle$ with configuration $n$ means that $n_{vi}$ molecules of species $X_i$ exist in voxel $v$. Using the annihilation and creation operators $a_{vi}, a_{vi}^\dagger$, i.e., $a_{vi}|n_{vi}\rangle = n_{vi}|n_{vi}-1\rangle, a_{vi}^\dagger|n_{vi}\rangle = |n_{vi}+1\rangle$, we can map the probability distribution $P_Γ(n,t)$ to a state vector $|ψ(t)\rangle_Γ$, defined by

$$|ψ(t)\rangle_Γ = \sum_{n \in Γ} P_Γ(n,t)|n\rangle = \sum_{n \in Γ} P_Γ(n,t)(a_{vi}^\dagger)^n|0\rangle. \quad (14)$$

This expression sums over all possible configurations $n$ weighted by their occurrence probabilities at time $t$. To establish the time evolution of this state vector, we apply
the master equation to obtain the following Schrödinger equation:
\[
\partial_t |\psi(t)\rangle_\Gamma = -\mathcal{H}(a^\dagger, a)|\psi(t)\rangle_\Gamma, \tag{15}
\]
where \(\mathcal{H}(a^\dagger, a)\) represents the Hamiltonian action on the Fock space, expressed as shown in [33]. In general, \(\mathcal{H}(a^\dagger, a)\) is the sum of several sub-actions created by each reaction of the system, e.g., a reaction of the form \(\sum_{i=1}^N s_{ij} X_i^\dagger \xrightarrow{k_j} \sum_{i=1}^N r_{ij} X_i\) yields a sub-action \(k_j \omega^\dagger \cdots \sum_{i=1}^N \prod_{j=1}^N (a^\dagger_{v_i} - \prod_{j=1}^N (a^\dagger_{v_i})(\sum_{i=1}^N (a_{v_i})^n_{v_i}) \prod_{i=1}^N (a_{v_i})^n_{v_i}.\) The action \(\mathcal{H}(a^\dagger, a)\) is considered to be normally ordered, i.e., \(a^\dagger\) is always to the left of \(a_{v_i}\). In a steady-state system, \(\mathcal{H}(a^\dagger, a)|\psi(t)\rangle_\Gamma = 0\). Consequently, \(\mathcal{H}(a^\dagger, a)|\psi(t)\rangle\) is also 0, where the state \(|\psi(t)\rangle\) is defined as follows:
\[
|\psi(t)\rangle = \sum_{\Gamma} \frac{|\psi(t)\rangle_\Gamma}{N_\Gamma} = \prod_{i=1}^N \prod_{v=1}^N \sum_{n_{v_i} \geq 0} \frac{(\omega c_{v_i} a_{v_i}^\dagger)^{n_{v_i}}}{n_{v_i}!} |0\rangle = c^{\sum_{v,i} \omega c_i a_{v_i}^\dagger} |0\rangle.
\]
In other words, the following condition
\[
\mathcal{H}(a^\dagger, a)e^{\sum_{v,i} \omega c_i a_{v_i}^\dagger} |0\rangle = 0 \tag{16}
\]
must hold. To derive a further condition with no involvement of \(a^\dagger\) and \(a\), we consider the coherent states \(|\phi_{v_i}\rangle\) and \(|\phi_{v_i}\rangle\), denoting the right and left eigenstates of \(a_{v_i}\) and \(a_{v_i}^\dagger\), respectively. Specifically, \(a_{v_i} |\phi_{v_i}\rangle = \phi_{v_i} |\phi_{v_i}\rangle\) and \(a_{v_i}^\dagger |\phi_{v_i}\rangle = \phi_{v_i} |\phi_{v_i}\rangle\), with complex eigenvalue \(\phi_{v_i} \in \mathbb{C}\). Multiplying both sides of Eq. (16) by the left coherent state \(|\phi\rangle\), we obtain [33]
\[
0 = \langle \phi | \mathcal{H}(a^\dagger, a)e^{\sum_{v,i} \omega c_i a_{v_i}^\dagger} |0\rangle \Leftrightarrow 0 = \mathcal{H}(\phi^*, \omega \overline{c}), \tag{17}
\]
where \(\overline{c} \in \mathbb{R}^{\lvert V \rvert N}\) is defined as \(\overline{c}_{v_i} = c_{v_i}\). As \(\mathcal{H}(\phi^*, \omega \overline{c})\) is a polynomial of \(\phi^*\), this result is possible only when the coefficients of all monomials are zero. Each reaction of the form \(C_i \xrightarrow{k_i} C_i\) in voxel \(v\) contributes to \(\mathcal{H}(\phi^*, \omega \overline{c})\) a quantum \(\omega_{c_i} \Psi(\phi_{v_i}^*) \Psi(\overline{c})\). Therefore, by collecting the coefficients of \(\Psi(\phi_{v_i}^*)\) for each \(i = 1, \ldots, M\) and \(v \in V\), we obtain the following relation [33]:
\[
\mathcal{H}(\phi^*, \omega \overline{c}) = 0, \quad \forall \phi \in \mathbb{C}^{\lvert V \rvert N} \Leftrightarrow A \cdot \Psi(\overline{c}) = 0, \tag{18}
\]
meaning that the network is complex balanced at \(\overline{c}\). From these results, we conclude that the necessary and sufficient condition for a steady-state distribution (Eq. (9)) is that the network is complex balanced. □

Above we investigated the relation between diffusion and the distributions of the reactant species in steady-state. We now present another result that holds under non-steady-state conditions.

**Theorem 3.** In linear reaction networks, the stochastic dynamics of the system are unaffected by diffusion at any arbitrary time.

**Proof.** The system volume \(\Omega\) is related to the voxel volume \(\omega\) as \(\Omega = |V| \omega\). Now, for each state vector \(\tilde{n} = [\tilde{n}_1, \tilde{n}_2, \ldots, \tilde{n}_N]\) \(N \in \mathbb{N}\) representing the number of molecules of the reactant species, i.e., \(\tilde{n}_i\) is the total number of molecules of species \(X_i\) in the system, we define the set \(S(\tilde{n}) = \{ n \in \mathbb{N}_0^N | \sum_{v \in V} n_v = \tilde{n} \}\). Let \(P(\tilde{n}, t)\) be the probability of the system being in state \(\tilde{n}\) at time \(t\). In terms of \(P(n, t)\), this probability becomes \(P(\tilde{n}, t) = \sum_{n \in S(\tilde{n})} P(n, t)\). As \(\sum_{\tilde{n}} P(\tilde{n}, t) = 1\), \(P(\tilde{n}, t)\) is a probability distribution. To show that this probability distribution satisfies the CME given by Eq. (2), we calculate the time derivative of \(P(\tilde{n}, t)\) as follows:
\[
\partial_t P(\tilde{n}, t) = \sum_{n \in S(\tilde{n})} \partial_t P(n, t). \tag{19}
\]
Substituting Eq. (4) into the right-hand side of Eq. (19), we obtain an equation with both diffusion and reaction terms on the right. After some algebraic transformations, the diffusion term disappears and only the reaction term remains [33]. As the reaction network is linear, i.e., \(\sum_{i=1}^N s_{ij} \leq 1 \forall j = 1, \ldots, R\), the propensity function \(f_{ij}(n, \omega)\) must be one of two forms:
\[
f_{ij}(n, \omega) = k_j n_{v_i} \quad \text{or} \quad k_j \omega.
\]
Substituting the exact form of each propensity function into Eq. (19), we finally obtain the following master equation for \(P(\tilde{n}, t)\) [33]:
\[
\partial_t P(\tilde{n}, t) = \sum_{j=1}^R \left( e^{-V_j} - 1 \right) f_j(\tilde{n}, \Omega) P(\tilde{n}, t). \tag{20}
\]
Obviously, this differential equation is identical to the CME stated in Eq. (2), and contains no diffusion factors. Therefore, we conclude that diffusion does not affect the stochastic dynamics of the network at any arbitrary time. □

The result was verified on a simple linear reaction network, namely, a coarse-grained model of enzymatic reactions and gene expressions. The network consists of two reactant species \(X_1\) and \(X_2\) and four reactions [6, 39]:
\[
\emptyset \xrightarrow{k_1} X_1, X_1 \xrightarrow{k_2} X_2, X_2 \xrightarrow{k_3} \emptyset. \tag{21}
\]
Again, we divided the cell volume into 1, 100, and 225 voxels with different diffusion coefficients of \(X_1\) and \(X_2\). The result is displayed in Fig. 2. As before, the distributions of each species at times \(t = 1\) and \(t = 10\) are identical in all three cases.

**Conclusions.**—We proved that diffusion in complex-balanced networks does not affect the steady-state distribution of the system. We also showed that a diffusion-included reaction network has a Poisson-like steady-state distribution if and only if it is complex balanced, analogously to the well-mixed case described in [40]. Moreover, we demonstrated that in linear reaction networks, the
stochastic system dynamics are diffusion-independent at any arbitrary time. These results help to clarify the conditions under which diffusion is negligible. Under such conditions, the system can be described by the CME instead of the intractable RDME. In nonlinear networks that are not complex-balanced, how diffusion affects the stochastic system dynamics, or whether it can be ignored, requires further investigation.

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This supplementary material details the calculations in the main text. The equation and figure numbers in this section are prefixed with S (e.g., Eq. (S1) or Fig. S1). The non-prefixed numbers (e.g., Eq. (1) or Fig. 1) refer to items in the main text.

1 Detailed calculations of Theorem 1

1.1 Details of Equation (10)

Equation (9) describes the following distribution:

\[ P_T(n, t) = \left\{ \begin{array}{ll} N_T \prod e \in V \prod i=1^N \frac{(\omega c_i)^{n_{v_i}}}{n_{v_i}!}, & \text{if } \sum_{e \in V} n_v \in \Gamma \\
0, & \text{if } \sum_{e \in V} n_v \notin \Gamma. \end{array} \right. \]

\( P_T(n, t) \) can be expressed as \( P_T(n) = N_T \prod e \in V P^*_T(n_v) \), where \( P^*_T(n_v) = \prod_{i=1}^N (\omega c_i)^{n_{v_i}}/n_{v_i}! \) for each \( n_v \).

The detailed calculation of Eq. (10) is given below:

\[
\sum_{v \in V} \sum_{v' \in N_v(v)} \sum_{i=1}^N \left( E^{I_{v_i}-1} - 1 \right) d_i n_{v_i} P_T(n, t) = \sum_{v \in V} \sum_{v' \in N_v(v)} \sum_{i=1}^N \left( d_i (n_{v_i} + 1) P_T(n + 1_{v_i} - 1_{v'_i}, t) - d_i n_{v_i} P_T(n, t) \right)
\]

\[
= \sum_{i=1}^N \sum_{v \in V} \sum_{v' \in N_v(v)} \left( N_T (n_{v_i} + 1) \frac{(\omega c_i)^{n_{v_i}+1}}{(n_{v_i}+1)!} \frac{(\omega c_i)^{n_{v'_i}-1}}{(n_{v'_i}-1)!} \prod_{\forall \neq i} \frac{\omega c_i^{n_{v_i}} \omega c_{v'_i}^{n_{v'_i}}}{n_{v_i}! n_{v'_i}!} \prod_{\forall \neq v, v'} P^*_T(n_v, t) - n_{v_i} P_T(n, t) \right)
\]

\[
= \sum_{i=1}^N \sum_{v \in V} \sum_{v' \in N_v(v)} \left( N_T (\omega c_i)^{n_{v_i}} \frac{1}{n_{v_i}!} \frac{1}{(n_{v'_i}-1)!} \prod_{\forall \neq i} \frac{(\omega c_i)^{n_{v_i}} \omega c_{v'_i}^{n_{v'_i}}}{n_{v_i}! n_{v'_i}!} \prod_{\forall \neq v, v'} P^*_T(n_v, t) - n_{v_i} P_T(n, t) \right)
\]

\[
= \sum_{i=1}^N \sum_{v \in V} \sum_{v' \in N_v(v)} \left( n_{v_i} P_T(n, t) - n_{v_i} P_T(n, t) \right)
\]

\[ = 0. \]

1.2 Detailed calculations of Equation (11)

We now reveal the details of Eq. (11). Specifically, we show that if \( A \cdot \Psi(c) = 0 \), then

\[
\sum_{j=1}^R \left( E^{-V_j} - 1 \right) f_j(n_v, \omega) P^*_T(n_v, t) = 0.
\]  

(S1)

The equation \( A \cdot \Psi(c) = 0 \) means that \( \sum_{C_i \rightarrow C_{v_i}} a_{v_i} \Psi_i(c) - \sum_{C_{v_i} \rightarrow C_i} a_{v_i} \Psi_i(c) = 0 \) for each complex \( C_v \in C \). The left side of Eq. (S1) can be transformed as

\[
\sum_{j=1}^R \left( E^{-V_j} - 1 \right) f_j(n_v, \omega) P^*_T(n_v, t)
\]
\[
R \sum_{j=1}^N (f_j(n_v - V_j, \omega) P^*_v(n_v - V_j, t) - f_j(n_v, \omega) P^*_v(n_v, t))
\]

\[
= \sum_{C_i \rightarrow C_{i'}} a_{ii'} \omega^{1 - \sum_{k=1}^N y_{ki}} \left( \prod_{k=1}^N \frac{(n_{vk} + y_{ki} - y_{ki'})!}{(n_{vk} - y_{ki}!)!} \frac{(\omega c_k)^{n_{vk} + y_{ki} - y_{ki'}}!}{(n_{vk} + y_{ki} - y_{ki'})!} - \prod_{k=1}^N \frac{(\omega c_k)^{n_{vk}!}}{(n_{vk} - y_{ki}!)!} \right)
\]

\[
= \omega \sum_{C_i \rightarrow C_{i'}} \left( \sum_{C_{i'} \in C} \frac{\Psi_i(c) \prod_{k=1}^N (\omega^{n_{vk} - y_{ki'}} e_k^{n_{vk}})^{(\omega c_k)^{n_{vk} - y_{ki'}}!}}{(\omega c_k)^{n_{vk}}!} - \sum_{C_{i'} \in C} a_{ii'} \prod_{k=1}^N (\omega^{n_{vk} - y_{ki'}} e_k^{n_{vk}})! \right)
\]

\[
= \omega \sum_{C_{i'} \in C} \frac{1}{\prod_{k=1}^N (\omega^{n_{vk} - y_{ki'}} e_k^{n_{vk}})!} \left( \sum_{C_i \rightarrow C_{i'}} a_{ii'} \frac{\Psi_i(c)}{\Psi_i'(c)} - \sum_{C_{i'} \rightarrow C_i} a_{ii'} \frac{\Psi_i'(c)}{\Psi_i(c)} \right)
\]

\[
= 0.
\]

The same result (but omitting the details) is given in [1].

### 1.3 Detailed calculations of Equation (12)

Finally, we compute the explicit form of the distribution \(P^*_v(\hat{n})\) in Eq. (12). We have

\[
P^*_v(\hat{n}) = \sum_{n_v} \frac{P_v(n_v)}{\sum_{n_v} P_v(n_v)} \prod_{v \in V} \frac{(\omega c_v)^{n_v!}}{n_v!} \tag{S2}
\]

\[
= \mathcal{N}_v \prod_{i=1}^N \left( \sum_{n_{vi} = \bar{n}_i} \prod_{i \in \bar{V}} \frac{(\omega c_i)^{n_{vi}}}{n_{vi}!} \right) \tag{S3}
\]

\[
= \mathcal{N}_v \prod_{i=1}^N \left( \frac{(\omega c_i)^{\bar{n}_i}}{\bar{n}_i!} \sum_{n_{vi} \geq 0 \forall v \in \bar{V}} \frac{(\sum_{v \in \bar{V}} n_{vi})!}{\prod_{v \in \bar{V}} n_{vi}!} \right) \tag{S4}
\]

\[
= \mathcal{N}_v \prod_{i=1}^N \frac{(\omega c_i)^{\bar{n}_i}}{\bar{n}_i!} \left| \bar{V} \right|^{\bar{n}_i} \tag{S5}
\]

\[
= \mathcal{N}_v \prod_{i=1}^N \frac{(\Omega c_i)^{\bar{n}_i}}{\bar{n}_i!} \tag{S6}
\]

In transforming Eq. (S4) to Eq. (S5), we exploited the following equality:

\[
\sum_{x_1, \ldots, x_m \geq 0, \sum_{i=1}^m x_i = n} \frac{(x_1 + \cdots + x_m)!}{x_1! \cdots x_m!} = m^n, \quad \forall m \in \mathbb{N}_{>0}, n \in \mathbb{N}_{\geq 0}. \tag{S7}
\]

### 2 Detailed calculations of Theorem 2

Before presenting the calculations, we state several properties of the bosonic operators \(a_{v,i}^\dagger\) and \(a_{v,i}\).

\[
|n_{vi}\rangle = (a_{v,i}^\dagger)^{n_{vi}} |0\rangle,
\]

\[
\sum_{x_1, \ldots, x_m \geq 0, \sum_{i=1}^m x_i = n} \frac{(x_1 + \cdots + x_m)!}{x_1! \cdots x_m!} = m^n, \quad \forall m \in \mathbb{N}_{>0}, n \in \mathbb{N}_{\geq 0}.
\]
\[(a_{vi})^l(a_{vi}^\dagger)^k|n_{vi}\rangle = \left[ \prod_{j=0}^{l-1} (n_{vi} + k - j) \right] |n_{vi} + k - l\rangle,\]
\[(a_{vi}^\dagger)^k(a_{vi})^l|n_{vi}\rangle = \left[ \prod_{j=0}^{l-1} (n_{vi} - j) \right] |n_{vi} + k - l\rangle\]

\[|a_{vi}, a_{vi'}\rangle = a_{vi}a_{vi'}^\dagger - a_{vi'}a_{vi} = \delta_{vi'vi},\]
\[|a_{vi}, a_{vi'}\rangle = [a_{vi}, a_{vi'}] = 0.\]

For a general configuration \( n \), we define the corresponding state vector |n\rangle as

\[|n\rangle = (a_{vi}^\dagger)^n|0\rangle = \prod_{v \in V} \prod_{i=1}^{N} (a_{vi}^\dagger)^{n_{vi}}|0\rangle. \quad (S8)\]

For convenience, we note that

\[e^{ca_{vi}}f(a_{vi}) = f(a_{vi} + c)e^{ca_{vi}}, \quad (S9)\]
\[e^{ca_{vi}^\dagger}f(a_{vi}) = f(a_{vi} - c)e^{ca_{vi}^\dagger}, \quad (S10)\]

where \( c \in \mathbb{C} \) is a complex number and \( f \) is an arbitrary function.

### 2.1 Detailed calculations of Equation (15)

We first derive the explicit form of the Hamiltonian action \( \mathcal{H}(a^\dagger, a) \) in Eq. (15). Suppose that the network contains a set \( R \) of reactions \( R_j \) of the general form \( \sum_{v \in V} \sum_{i=1}^{N} p_{vi}^j X_i^v \rightarrow \sum_{v \in V} \sum_{i=1}^{N} q_{vi}^j X_i^v \), where \( p_{vi}^j \) and \( q_{vi}^j \) are the stoichiometric coefficients. For each reaction \( R_j \), we define a stoichiometric vector \( V_j^v \in \mathbb{Z}^{|V|^N} \) as \( V_j^v = q_{vi}^j - p_{vi}^j \). Starting from the master equation, we have

\[\frac{\partial_t |\psi(t)\rangle_G}{\partial \Gamma} = \sum_{n \in \Gamma} \sum_{R_j \in \mathcal{R}} k_{ji} \omega^{1 - \sum_{v,i} p_{vi}^j} \left[ \prod_{v,i} \left( \frac{(n_{vi} + p_{vi}^j - q_{vi}^j)^!}{(n_{vi} - q_{vi}^j)^!} P_T(n - V_j^v, t)(a^\dagger)^n - V_j^v|0\rangle \right) \prod_{v,i} \left( \frac{n_{vi}^!}{(n_{vi} - p_{vi}^j)^!} P_T(n, t)(a^\dagger)^n|0\rangle \right) \right].\]

Note that the two terms inside the bracket can be obtained using operators as follows:

\[\prod_{v,i} \frac{(n_{vi} + p_{vi}^j - q_{vi}^j)^!}{(n_{vi} - q_{vi}^j)^!} P_T(n - V_j^v, t)(a^\dagger)^n|0\rangle = \prod_{v,i} (a_{vi}^\dagger)^{p_{vi}^j} (a_{vi})^{q_{vi}^j} P_T(n - V_j^v, t)(a^\dagger)^n - V_j^v|0\rangle,\]
\[\prod_{v,i} \frac{n_{vi}^!}{(n_{vi} - p_{vi}^j)^!} P_T(n, t)(a^\dagger)^n|0\rangle = \prod_{v,i} (a_{vi}^\dagger)^{p_{vi}^j} (a_{vi})^{q_{vi}^j} P_T(n, t)(a^\dagger)^n|0\rangle.\]

Using these equalities, \( \frac{\partial_t |\psi(t)\rangle_G}{\partial \Gamma} \) is calculated as follows:

\[\frac{\partial_t |\psi(t)\rangle_G}{\partial \Gamma} = \sum_{n \in \Gamma} \sum_{R_j \in \mathcal{R}} k_{ji} \omega^{1 - \sum_{v,i} p_{vi}^j} \left[ \prod_{v,i} (a_{vi}^\dagger)^{q_{vi}^j} (a_{vi})^{p_{vi}^j} P_T(n - V_j^v, t)(a^\dagger)^n - V_j^v|0\rangle \right] \]
\[\prod_{v,i} (a_{vi}^\dagger)^{p_{vi}^j} (a_{vi})^{q_{vi}^j} \sum_{n \in \Gamma} P_T(n, t)(a^\dagger)^n|0\rangle\]
\[\prod_{v,i} (a_{vi}^\dagger)^{p_{vi}^j} (a_{vi})^{q_{vi}^j} \sum_{n \in \Gamma} P_T(n, t)(a^\dagger)^n|0\rangle \]
= \sum_{R_j \in R} k_j \omega^{1-\Sigma_{v,i} s_{ij}} \left[ \prod_{v,i} (a_{vi})^r_{ij} - \prod_{v,i} (a_{vi})^{s_{ij}} \right] \prod_{v,i} (a_{vi})^{p_{ij}} v(t) \Gamma.

Thus, the general form of $H$ is obtained as

$$H(a^\dagger, a) = \sum_{R_j \in R} k_j \omega^{1-\Sigma_{v,i} s_{ij}} \left[ \prod_{v,i} (a_{vi})^r_{ij} - \prod_{v,i} (a_{vi})^{s_{ij}} \right] \prod_{v,i} (a_{vi})^{p_{ij}}.$$  \hspace{1cm} (S11)

For a diffusion-included reaction network involving the following reactions

$$s_1 X^v_1 + \cdots + s_N X^v_N \rightarrow r_1 X^v_1 + \cdots + r_N X^v_N,$$

the Hamiltonian action $H(a^\dagger, a)$ in Eq. (15) takes the following form

$$H(a^\dagger, a) = \sum_{j=1}^{R} \sum_{v \in V} k_j \omega^{1-\Sigma_{v,i} s_{ij}} \left[ \prod_{i=1}^{N} (a_{vi})^{r_{ij}} - \prod_{i=1}^{N} (a_{vi})^{s_{ij}} \right] \prod_{i=1}^{N} (a_{vi})^{p_{ij}} + \sum_{i=1}^{N} \sum_{v \in V} \sum_{v' \in N_e(v)} d_i (a_{vi}^r - a_{vi}^s)a_{vi}.$$  \hspace{1cm} (S12)

Note that this form of $H$ is already normal-ordered.

### 2.2 Detailed calculations of Equation (17)

Equation (17) is derived through the following steps:

$$0 = \langle \phi | H(a^\dagger, a) e^{\Sigma_{v,i} \omega c_{vi} a_{vi}^r} | 0 \rangle$$  \hspace{1cm} (S13)

$$\Rightarrow 0 = \langle \phi | e^{\Sigma_{v,i} \omega c_{vi} a_{vi}^r} | H(a^\dagger, a + \omega \bar{c}) | 0 \rangle$$  \hspace{1cm} (S14)

$$\Rightarrow 0 = e^{\Sigma_{v,i} \omega c_{vi} a_{vi}^r} \langle \phi | H(a^\dagger, a + \omega \bar{c}) | 0 \rangle$$  \hspace{1cm} (S15)

$$\Rightarrow 0 = e^{\Sigma_{v,i} \omega c_{vi} a_{vi}^r} \langle \phi | H(\phi^*, \omega \bar{c}) | 0 \rangle$$  \hspace{1cm} (S16)

$$\Rightarrow 0 = e^{\Sigma_{v,i} \omega c_{vi} a_{vi}^r} H(\phi^*, \omega \bar{c}) \langle \phi | 0 \rangle$$  \hspace{1cm} (S17)

$$\Rightarrow 0 = H(\phi^*, \omega \bar{c}).$$  \hspace{1cm} (S18)

In Eq. (S14), we have used the property stated in Eq. (S10). In Eq. (S16), the operators $a_{vi}^r (v \in V, i = 1, \ldots, N)$ are absorbed into $|0\rangle$ ($\cdot \cdot \cdot a_{vi}^r |0\rangle = 0$), and the operators $a_{vi}^r$ are replaced by $\phi_{vi}^r$ ($\cdot \cdot \cdot \langle \phi_{vi}^r |0\rangle = \langle \phi_{vi}^r |\phi_{vi}^r\rangle$). The result Eq. (S18) is obtained by noting that

$$e^{\Sigma_{v,i} \omega c_{vi} a_{vi}^r} \neq 0,$$

$$\langle \phi | 0 \rangle = \prod_{v,i} \langle \phi_{vi}^r |0\rangle = \prod_{v,i} e^{-\frac{1}{2} \langle \phi_{vi}^r |\phi_{vi}^r\rangle} \neq 0.$$

### 2.3 Detailed calculations of Equation (18)

Equation (18) is given by

$$H(\phi^*, \omega \bar{c}) = 0, \forall \phi \in C^{|V||N|} \Rightarrow A \cdot \Psi(c) = 0.$$

The Hamiltonian action $H(a^\dagger, a)$ is described by

$$H(a^\dagger, a) = \sum_{j=1}^{R} \sum_{v \in V} k_j \omega^{1-\Sigma_{v,i} s_{ij}} \left[ \prod_{i=1}^{N} (\phi_{vi}^r)^{r_{ij}} - \prod_{i=1}^{N} (\phi_{vi}^r)^{s_{ij}} \right] \prod_{i=1}^{N} (\omega \bar{c}_{vi})^{p_{ij}} + \sum_{i=1}^{N} \sum_{v \in V} \sum_{v' \in N_e(v)} d_i (\phi_{vi}^r - \phi_{vi}^s) \omega \bar{c}_{vi} = 0$$

The case $H(\phi^*, \omega \bar{c}) = 0$ is equivalent to

$$\sum_{j=1}^{R} \sum_{v \in V} k_j \omega^{1-\Sigma_{v,i} s_{ij}} \left[ \prod_{i=1}^{N} (\phi_{vi}^r)^{r_{ij}} - \prod_{i=1}^{N} (\phi_{vi}^r)^{s_{ij}} \right] \prod_{i=1}^{N} (\omega \bar{c}_{vi})^{p_{ij}} + \sum_{i=1}^{N} \sum_{v \in V} \sum_{v' \in N_e(v)} d_i (\phi_{vi}^r - \phi_{vi}^s) \omega \bar{c}_{vi} = 0$$
\[ \sum_{C_j \rightarrow C_j'} \sum_{v \in V} \omega a_{jj'} [\Psi_j'(\phi^*) - \Psi_j(\phi^*)] \Psi_j'(c) + \sum_{i=1}^{N} d_i \sum_{v, v' \in \mathcal{V}} \left[ (\phi^*_{v_i'} - \phi^*_{v_i}) \omega \tilde{c}_{v_i} + (\phi^*_{v_i} - \phi^*_{v_i'}) \omega \tilde{c}_{v_i'} \right] = 0 \]

\[ \sum_{\phi \in \mathcal{C} \setminus [\mathcal{V} \setminus N]} \omega \sum_{v, v' \in \mathcal{C}} \Psi_j'(\phi^*) \left[ \sum_{C_j \rightarrow C_j'} a_{jj'} \Psi_j'(c) - \sum_{C_j \rightarrow C_j'} a_{jj'} \Psi_j(c) \right] = 0, \quad \forall \phi \in \mathcal{C} \setminus [\mathcal{V} \setminus N] \]

\[ \sum_{C_j \rightarrow C_j} a_{jj'} \Psi_j'(c) - \sum_{C_j \rightarrow C_j} a_{jj'} \Psi_j(c) = 0, \quad \forall C_j \in \mathcal{C} \]

\[ A \cdot \Psi(c) = 0. \]

### 3 Detail calculations of Theorem 3

The master equation of \( P(\hat{n}, t) \) is derived as follows:

\[
\frac{\partial}{\partial t} P(\hat{n}, t) = \sum_{n \in S(\hat{n})} \partial_n P(n, t)
= \sum_{n \in S(\hat{n})} \left( \sum_{v \in \mathcal{V}} \sum_{v' \in N_v(v)} \sum_{i=1}^{N} \left( d_i(n_{vi} + 1)P(n + 1_{vi} - 1_{v'i}, t) - d_i n_{vi} P(n, t) \right) \right)
+ \sum_{v \in \mathcal{V}} \sum_{j=1}^{R} \left( f_{v_j}(n - \hat{V}_v, \omega)P(n - \hat{V}_v, t) - f_{v_j}(n, \omega)P(n, t) \right).
\]

As \( n \in S(\hat{n}) \rightarrow n + 1_{vi} - 1_{v'i} = \hat{n} \in S(\hat{n}) \), the first term of the right-hand side in Eq. (S19) becomes

\[
\sum_{n \in S(\hat{n})} \sum_{v \in \mathcal{V}} \sum_{v' \in N_v(v)} \sum_{i=1}^{N} \left( d_i(n_{vi} + 1)P(n + 1_{vi} - 1_{v'i}, t) - d_i n_{vi} P(n, t) \right)
= \sum_{\hat{n} \in S(\hat{n})} \sum_{v \in \mathcal{V}} \sum_{v' \in N_v(v)} \sum_{i=1}^{N} \left( d_i(n_{vi} + 1)P(\hat{n} + 1_{vi} - 1_{v'i}, t) - d_i n_{vi} P(n, t) \right)
= \sum_{\hat{n} \in S(\hat{n})} \sum_{v \in \mathcal{V}} \sum_{v' \in N_v(v)} \sum_{i=1}^{N} \left( d_i n_{vi} P(\hat{n}, t) \right)
= 0.
\]

As the reaction network is linear, the propensity function \( f_{v_j}(n, \omega) \) takes one of two forms: \( f_{v_j}(n, \omega) = k_j n_{vi} \) or \( f_{v_j}(n, \omega) = k_j \omega \), where \( k_j \) is the reaction rate and \( i \) is the index of some species.

(i) When \( f_{v_j}(n, \omega) = k_j n_{vi} \), the second term can be transformed as follows:

\[
\sum_{\hat{n} \in S(\hat{n})} \sum_{v \in \mathcal{V}} \left( f_{v_j}(n - \hat{V}_v, \omega)P(n - \hat{V}_v, t) - f_{v_j}(n, \omega)P(n, t) \right)
= k_j \sum_{n \in S(\hat{n})} \sum_{v \in \mathcal{V}} \left( (n_{vi} - V_{jv})P(n - \hat{V}_v, t) - n_{vi} P(n, t) \right)
= k_j \left( \sum_{n \in S(\hat{n})} \sum_{v \in \mathcal{V}} (n_{vi} - V_{jv})P(n - \hat{V}_v, t) - \sum_{n \in S(\hat{n})} n_{vi} P(n, t) \right)
= k_j \left( \sum_{n \in S(\hat{n})} \sum_{v \in \mathcal{V}} n_{vi} P(n - \hat{V}_v, t) - \sum_{n \in S(\hat{n})} V_{jv} P(n - \hat{V}_v, t) - \sum_{n \in S(\hat{n})} \hat{n}_{i} P(n, t) \right)
= k_j \left( \sum_{\hat{n} \in S(\hat{n} - V_{jv})} \sum_{v \in \mathcal{V}} (\hat{n}_{vi} + V_{jv})P(\hat{n}, t) - V_{jv} \sum_{v \in \mathcal{V}} \sum_{n \in S(\hat{n})} P(n - \hat{V}_v, t) - \hat{n}_{i} P(\hat{n}, t) \right)
= k_j \left( (\hat{n}_i - V_{jv})P(\hat{n} - V_j, t) + V_{jv} |\hat{V}| P(\hat{n} - V_j, t) - V_{jv} |\hat{V}| P(\hat{n} - V_j, t) - \hat{n}_{i} P(\hat{n}, t) \right)
\]
\[
= k_j(\hat{n}_i - V_{ji}) P(\hat{n} - V_j, t) - k_j \hat{n}_i P(\hat{n}, t).
\]

(ii) When \( f_{vj}(n, \omega) = k_j \omega \), we similarly have
\[
\sum_{n \in S(\hat{n})} \sum_{v \in V} \left( f_{vj}(n - \tilde{V}_{vj}, \omega) P(n - \tilde{V}_{vj}, t) - f_{vj}(n, \omega) P(n, t) \right)
= k_j \sum_{n \in S(\hat{n})} \sum_{v \in V} \left( \omega P(n - \tilde{V}_{vj}, t) - \omega P(n, t) \right)
= k_j \left( \sum_{n \in S(\hat{n})} \sum_{v \in V} \omega P(n - \tilde{V}_{vj}, t) - \sum_{n \in S(\hat{n})} \sum_{v \in V} \omega P(n, t) \right)
= k_j \Omega P(\hat{n} - V_j, t) - k_j \Omega P(\hat{n}, t).
\]

The master equation of \( P(\hat{n}, t) \) is then obtained as
\[
\partial_t P(\hat{n}, t) = \sum_{j=1}^{R} (f_j(\hat{n} - V_j, \Omega) P(\hat{n} - V_j, t) - f_j(\hat{n}, \Omega) P(\hat{n}, t)). \tag{S21}
\]

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