Continuous time random walks in closed and open single-molecule systems with microscopic reversibility

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Abstract. – Continuous time random walk (CTRW) is studied with a new dynamic equation based on the age-structure of states. For a CTRW in a closed molecular system, two necessary conditions for microscopic reversibility are introduced: 1) independence of transition direction and waiting time for every state and 2) detailed balance among the transition probabilities. Together they are also sufficient condition. For a CTRW in an open system with explicit chemical energy input 1) still holds while 2) breaks down. Hence, CTRW models not satisfying 1) are either inconsistent with thermodynamics or cannot attain equilibrium due to hidden dissipation in non-Markovian states. Each CTRW defines a unique *corresponding Markov process* (cMP). The steady-state distribution of a CTRW equals that of the corresponding Markov process, and the two systems have the same steady-state flux, the same exit probabilities and the same mean trapping times. Mechanicity is discussed; a paradox observed by Kolomeisky and Fisher (*J. Chem. Phys.*, **113** (2000) 10867) is resolved.

Stochastic models are the theoretical basis for describing dynamics of biological, chemical and physical processes at the single-molecule level [1, 2]. Recent studies in single-molecule spectroscopy and enzymology have invigorated a classic subject, the continuous time random walks (CTRW), which was developed and extensively studied many years ago by Montroll and coworkers [3, 4]. See [5–7] for the recent work that motivated CTRW in connection to single motor proteins and single-enzyme kinetics.

Applying stochastic models to molecular procsses requires serious considerations of the microscopic reversibility. When a closed molecular system with fluctuations reaches its stationary state, it is necessarily a chemical equilibrium with zero flux in any part of the system. This realization led to the introduction of detailed balance (DB) as a necessary condition for Markov kinetic models of closed system [8]. The celebrated fluctuation-dissipation relation [9] is in fact an explicit expression of detailed balance in the Langevin dynamics [10]. When a molecular system is in an open environment with sustained chemical input and dissipation, detailed balance breaks down [2, 11], which gives rise to free energy transduction, such as in

motor proteins [7,12]. For both discrete and continuous Markov processes, detailed balance is sufficient and necessary for the time reversibility in the stationary fluctuations, and for zero flux in steady state [13].

The microscopic reversibility discussed in this paper is the time reversibility of stationary stochastic processes [13]. For a molecular system in equilibrium, the time reversibility means its thermal fluctuation as a function of time is statistically invariant under time reversal [14]. This is a constraint to be satisfied by every stochastic model of a molecular system. The focus of this paper is to introduce the microscopic reversibility to CTRW models. Interestingly it turns out that detailed balance is no longer sufficient for the reversibility of a closed CTRW model. It can be shown that, even though there is no net flux between any two states, a stationary CTRW with detailed balance still might not obey time reversibility [15], as required in a fluctuating chemical equilibrium [14]. Several recent work have observed a separability, *i.e.*, statistical independence, between the transition direction and the waiting time of the kinetic state [16]. Mathematically, we have been able to show that the independence together with detailed balance is in fact equivalent to time reversibility for Markov renewal processes (MRP) [15]. The present work introduces the *direction-time independence* (DTI) into the theory of CTRW and explores its consequences.

Molecular systems can, and should be described at different levels. Stocahstic models are powerful in describing complex systems, such as biological macromolecules (enzymes) and amorphous solids [17], for which a first-principle approach is neither practical nor informative. Because these stochastic models are not completely based on first principles, fundamental thermodynamics are applied to put constraints on these models. Microscopic reversibility and detailed balance are precisely such constraints. The direction-time independence (DTI) was assumed in the early CTRW models of transport in disordered solids [4]. But CTRW with coupled space-time memory kernels appeared in many later works as a more general model for anomalous transport.

The CTRW models usually start with the kinetic parameters $\psi_{ij}(t)$, the waiting time probability density of jumping from state i to state j at time t for the first time since arriving in state i exactly at time zero. Let T be the time elapsed until the first jump out of state i and let J be the destination of the jump. T is called the waiting time at state i. Both T and J are random variables. The direction-time independence (DTI) means T and J are independent of each other. Mathematically, $\psi_{ij}(t)$ is defined as

$$\psi_{ij}(t) \equiv \lim_{\Delta t \to 0} \frac{P[T \leq t + \Delta t, J = j] - P[T \leq t, J = j]}{\Delta t}. \tag{1}$$

This is a generalization of the standard Markov transition with exponential waiting time [18], also known as semi-Markov processes [19]. An alternative starting point is a generalized master equation (GME) which replaces the rate constants in the standard master equation with time-dependent memory kernels $K_{ij}(t)$ [6,18]. $K_{ij}(t)$ will be defined and discussed later. Below, we first introduce the dynamic equation with age-structure originated from our work on Markov renewal processes. By showing an equivalence between the dynamic equation of age-structure and the generalized master equation, the direction-time independence is rigorously established as a condition for reversibility in CTRW.

Age-structure and memory kernel of CTRWs. There are two distinct, complementary mathematical approaches to a CTRW. One is in terms of a generalized master equation with a memory kernel and the other is in terms of the age-structure of each state. The former is widely known in physics and chemistry [3,5,6,18]. The latter, is known in the mathematical literature [15,19].

In the age-structure formalism, a system is characterized by $r_{im}(\tau, t)$, which is the probability density that the system is in state i with age τ at time t, given that the system arrives at state m at time $= 0$. Here the age of the system in state i is the time elapsed until the latest arrival at state i. The dynamic equation for the probability density is [15]

$$\frac{\partial r_{im}(\tau, t)}{\partial t} = -\frac{\partial r_{im}(\tau, t)}{\partial \tau} - \sum_j \beta_{ij}(\tau) r_{im}(\tau, t), \tag{2}$$

$$\beta_{ij}(\tau) \equiv \frac{\psi_{ij}(\tau)}{\Phi_i(\tau)}, \quad \Phi_i(\tau) \equiv \sum_j \int_\tau^\infty \psi_{ij}(\tau') \mathrm{d}\tau', \tag{3}$$

with combined initial and boundary conditions: $r_{im}(0, t) = \delta(t)\delta_{im} + \sum_j \int_0^\infty \beta_{ji}(\tau) r_{jm}(\tau, t) \mathrm{d}\tau$. Here $\beta_{ij}(\tau)$ is called a hazard function, and is the conditional transition probability density from i to j at age τ, given that no transition occurs in age $[0, \tau)$. $\Phi_i(\tau)$ is the probability that no transition occurs at state i in age $[0, \tau)$. Equation (2) is the starting point of a mathematical study on detailed balance and reversibiltiy of Markov renewal processes. Equation (2) can be integrated to obtain an integral relation

$$r_{im}(\tau, t) = \Phi_i(\tau) r_{im}(0, t - \tau),$$
$$r_{im}(0, t) = \delta(t)\delta_{im} + \sum_j \int_0^t \psi_{ji}(s) r_{jm}(0, t - s) \mathrm{d}s. \tag{4}$$

In the generalized master equation formalism, the same system is characterized by the probability of state i at time t: $G_{im}(t) = \int_0^t r_{im}(\tau, t) \mathrm{d}\tau$. We then can show that [20]

$$\frac{\mathrm{d}G_{im}(t)}{\mathrm{d}t} = \sum_j \int_0^t \left(K_{ji}(t - \tau) G_{jm}(\tau) - K_{ij}(t - \tau) G_{im}(\tau) \right) \mathrm{d}\tau, \tag{5}$$

where the memory kernel $K_{ij}(t)$ is defined through its Laplace transform [18]:

$$\overline{K}_{ij}(\nu) \equiv \frac{\overline{\psi}_{ij}(\nu)}{\overline{\Phi}_i(\nu)}. \tag{6}$$

Equation (5) is the generalized master equation with memory. It reduces to the standard master equation in the Laplace domain if $\overline{K}_{ij}(\nu)$ are constant; while eq. (2) reduces to the standard master equation in the time domain if $\beta_{ij}(\tau)$ are constant. It can be shown that $\overline{K}_{ij}(\nu)$ are constant if and only if $\beta_{ij}(\tau)$ are constant. Equation (5) is the starting point of several recent studies on single-molecule kinetics [5,6], replacing the standard master equation for Markov processes.

Detailed balance. If G_i^* is the statinary solution to the GME (5), then

$$\int_0^\infty \left(K_{ji}(t) G_j^* - K_{ij}(t) G_i^* \right) \mathrm{d}t = G_j^* \left(\frac{p_{ji}}{\theta_j} \right) - G_i^* \left(\frac{p_{ij}}{\theta_i} \right) = 0$$

is detailed balance, which indicates no net flux between states i and j. Note that $\int_0^\infty K_{ij}(t)\mathrm{d}t = \overline{K}_{ij}(0) = \overline{\psi}_{ij}(0)/\overline{\Phi}_i(0) = p_{ij}/\theta_i$, where $p_{ij} = \int_0^\infty \psi_{ij}(t)\mathrm{d}t$ is the transition probability from state i to state j, irrespective of the waiting time and $\theta_i = \int_0^\infty \Phi_i(t)\mathrm{d}t = \int_0^\infty t \sum_j \psi_{ij}(t)\mathrm{d}t$ is the mean waiting time in the state i, irrespective of the transition destiny. Detailed balance means that for every connected loop path $(i_0, i_1, i_2, ..., i_n, i_0)$ the loop condition is satisfied [13]:

$$\frac{p_{i_0,i_1} p_{i_1,i_2} \cdots p_{i_{n-1},i_n} p_{i_n,i_0}}{p_{i_1,i_0} p_{i_2,i_1} \cdots p_{i_n i_{n-1}}, p_{i_0,i_n}} = 1. \tag{7}$$

Microscopic reversibility. Detailed balance is known to be an equivalent condition for reversibility in Markov kinetic models [8]. This is no longer the case for the generalized master equation. Several recent works have suggested that an additional condition is required [15,16]. The condition is that for each state, the transition direction and the waiting time are statistically independent (DTI). Mathematically, this is, $\psi_{ij}(t) = p_{ij}\psi_i(t)$, where $\sum_j p_{ij} = 1$ and $\int_0^\infty \psi_i(t)\mathrm{d}t = 1$ [21]. This splitting [16] immediately leads to the direction-time independence in $\beta_{ij}(\tau) = p_{ij}\left[\psi_i(\tau)/\Phi_i(\tau)\right]$ [15], as well as the direction-time independence in the memory kernel: $\overline{K}_{ij} = p_{ij}\overline{K}_i(\nu)$, where $\overline{K}_i(\nu) = \left[\overline{\psi}_i(\nu)/\overline{\Phi}_i(\nu)\right]$ is independent of j, and contains the waiting time distribution. In particular, $\overline{K}_i(\nu)$ satisfies $\overline{K}_i(0) = 1/\theta_i$ and $\overline{K}'_i(0) = -\mathcal{M}_i/2$ where $\mathcal{M}_i \equiv (1 - \sigma_i^2/\theta_i^2)$ is called the mechanicity parameter [5] and σ_i^2 is the variance of the waiting time. Thus, $\overline{K}_i(\nu)$ has the expansion [5] $\overline{K}_i(\nu) = 1/\theta_i - \mathcal{M}_i\nu/2 + O(\nu^2)$.

The breakdown of detailed balance in a Markov model is the hallmark of an open system with sustained chemical energy input and dissipation [2,12]. For CTRW models of open systems, we suggest that the direction-time independence is still to be respected. This assmption implies that there is no "hidden" futile chemical reaction cycles within the individual non-Markovian states of a CTRW.

Corresponding Markov process and Stationary solution of a CTRW. For each generalized master equation, there is a corresponding Markov process (cMP), with transition rate $k_{ij} \equiv \overline{K}_{ij}(0) = p_{ij}/\theta_i$. Note that the corresponding Markov process of a CTRW can be viewed as another CTRW with memory kernel $\overline{K}_{ij}(\nu) = p_{ij}/\theta_i$, independent of ν. The stationary probability of (5), G_i^*, can be obtained by taking the limit of (5) as $t \to \infty$: $\sum_j(G_j^* p_{ji}/\theta_j) - G_i^*/\theta_i = 0$, which is the same as the master equation for the cMP of (5). With the stationary distribution G_i^*, the net flux from state i to state j in the steady state, if they are directly connected, is $J_{ij} = G_i^* p_{ij}/\theta_i - G_j^* p_{ji}/\theta_j$. Notice that the CTRW and its cMP have the same stationary distribution and the same steady-state flux.

Trapping probabilities and mean trapping times. If a CTRW has M absorbing states, *i.e.*, traps $\ell_1, \ell_2, \cdots, \ell_M$, with $K_{\ell_i,j}(t) = 0$ for all i and j, then the system eventually reaches the M absorbing states with total probability 1. Suppose the system starts in state m. Laplace transformation leads (5) to

$$\nu\overline{G}_{im}(\nu) = \delta_{im} + \sum_j \left(\overline{K}_{ji}(\nu)\overline{G}_{jm}(\nu) - \overline{K}_{ij}(\nu)\overline{G}_{im}(\nu)\right). \tag{8}$$

The trapping probabilities are easily obtained from (8) by expansion in the power of ν. They are exactly the same as those for the cMP (see derivations in the appendix).

In the calculations of trapping probabilities, the direction-time independence (DTI) has not been evoked. With the DTI $\psi_{ij}(t) = p_{ij}\psi_i(t)$, or equivalently $\overline{K}_{ij}(\nu) = p_{ij}\overline{K}_i(\nu)$, one can further obtain closed-form solutions for the mean trapping time [6] as well as the steady-state flux when there is no trap [5]. Again, they are in fact all equal to those of the cMP (see derivations in the appendix).

Direction-time independence (DTI) arises in enzyme kinetic models. Consider the sequential enzyme kinetic model shown in fig. 1A. We are interested in comparing the cycle time for the forward cycle and the backward cycle. For mathematical convenience, we number the states in two cycles from left to right as $(0, 1, \ldots, N+1, \ldots, 2N+1, 2N+2)$. We let the enzyme start at state $N+1$ at time 0 and make states 0 and $2N+2$ absorbing. Let $p_i(t)$ be the probability of state i at time t. Let $\boldsymbol{p}(t) = (p_1(t), \ldots, p_{2N+1}(t))^T$. Let $\boldsymbol{A}$ be the $N \times N$ tridiagonal matrix with $A_{i-1,i} = w_i$, $A_{i+1,i} = u_i$ and $A_{i,i} = -(w_i + u_i)$. Let $\boldsymbol{B}$ be the $(2N+1) \times (2N+1)$ tridiagonal matrix with $B_{i-1,i} = w_{i_2}$, $B_{i+1,i} = u_{i_2}$ and $B_{i,i} = -(w_{i_2} + u_{i_2})$, where $i_2 = \mathrm{mod}(i, N+1)$. The governing equation for $\boldsymbol{p}(t)$ is $\boldsymbol{p}'(t) = \boldsymbol{B}\boldsymbol{p}(t)$. Taking Laplace
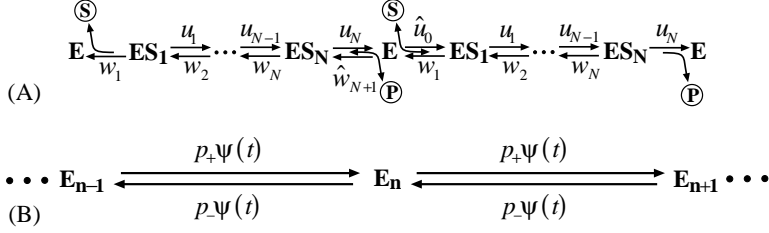
Fig. 1 – A first-passage model and a CTRW stepping model based on the first-passage model for single-molecule enzyme reactions. (A) A first-passage model. Two cycles are shown where the two ends are made absorbing, representing respectively the forward and the backward enzyme cycles. In the substrate binding step $E \to ES_1$, the transition rate is $u_0 = c_S \hat{u}_0$, where $\hat{u}_0$ is the second-order substrate binding rate and c_S is the substrate concentration. Similarly, in the product binding step (reversal of product release) $E \to ES_N$, the transition rate is $w_{N+1} = c_P w_{\hat{N}+1}$, where $\hat{w}_{N+1}$ is the second-order product binding rate and c_P is the product concentration. As we will show, starting at state E in the middle, the trapping time distribution is the same for forward cycles and backward cycles. (B) A CTRW model based on (A) describes the number of cycles finished. The CTRW based on (A) satisfies the direction-time independence.

transform yields $(\boldsymbol{B} - \nu \boldsymbol{I})\overline{\boldsymbol{p}}(\nu) = -\boldsymbol{p}(0)$. The Laplace transforms of forward and backward cycle time probability densities are, respectively, $\overline{\psi}_+(\nu) = u_N \overline{p}_{2N+1}(\nu)$ and $\overline{\psi}_-(\nu) = w_1 \overline{p}_1(\nu)$. Using Cramer's rule to solve the linear system $(\boldsymbol{B} - \nu \boldsymbol{I})\overline{\boldsymbol{p}}(\nu) = -\boldsymbol{p}(0)$, we get $\overline{p}_{2N+1}(\nu) = B(\nu)_{2N+1}/B(\nu)$ and $\overline{p}_1(\nu) = B(\nu)_1/B(\nu)$ where $B(\nu) = \det(\boldsymbol{B} - \nu \boldsymbol{I})$ and $B(\nu)_j$ is the determinant of $(\boldsymbol{B} - \nu \boldsymbol{I})$ with the j-th column replaced by $-\boldsymbol{p}(0)$. Using the properties of determinants, we derive $B(\nu)_{2N+1} = -\det(\boldsymbol{A})u_0 u_1 \cdots u_{N-1}$ and $B(\nu)_1 = -\det(\boldsymbol{A})w_1 w_2 \cdots w_N$. So we have

$$\frac{\overline{\psi}_+(\nu)}{\overline{\psi}_-(\nu)} = \frac{u_0 u_1 \cdots u_{N-1} u_N}{w_0 w_1 w_2 \cdots w_N} = \frac{p_+}{p_-}, \tag{9}$$

where p_+ and p_- are the probabilities of forward and backward cycles respectively [15, 16]. Equation (9) shows the transition direction and the waiting time are independent (DTI). In the cycle perspective, the enzyme is described by a CTRW model with memory kernel: $p_+ \overline{\psi}(\nu)$ and $p_- \overline{\psi}(\nu)$ as shown in fig. 1B. Expanding $\overline{\psi}(\nu) = \overline{\psi}_+(\nu)/p_+$ at $\nu = 0$, we can show that

$$\begin{aligned} \theta &= (u_N/p_+)(B^{-2})_{2N+1,N+1}, \\ \sigma^2 &= -2(u_N/p_+)(B^{-3})_{2N+1,N+1} - \theta^2, \end{aligned}$$

where θ and σ^2 are the mean and variance of the enzyme cycle time. Equation (9) is a generalization of what obtained in [16], which showed equal mean trapping time.

1-dimensional CTRW with direction-time independence. We now focus on the 1-dimensional CTRW shown in fig. 1B and study the steady-state flux and dispersion. Kolomeisky *et al.* [5] have shown that many aspects of the system can be analytically solved. As we showed earlier, the steady-state flux J is equal to that of the cMP, which is given by $J = (p_+ - p_-)/\theta$. The dispersions of cMP and CTRW are not the same, however. For the cMP, the dispersion is simply $1/(2\theta)$. But for the CTRW, the dispersion is $1/(2\theta) - (p_+ - p_-)^2 \mathcal{M}/(2\theta)$ [22], which agrees with [5]. More interestingly, we are able to show that eq. (9) is also valid for single-enzyme reactions governed by a sequence of heterogeneous CTRW steps with direction-time independence. That is, eq. (9) is still valid if in fig. 1A all Markov transitions are replaced by CTRW steps with waiting time probability densities $u_i(t) = u_i f_i(t)$ and $w_i(t) = w_i f_i(t)$.

This result suggests that enzyme kinetics can always be analyzed by breaking down to a first-passage problem, which yields direction-time independence, and a stepping problem in terms of CTRW with direction-time independence, as illustrated in fig. 1.

Resolution of a paradox. Kolomeiskey and Fisher discussed a paradoxical feature of the kinetics of non-exponential waiting time [5]. They introduced the concept of *mechanicity*: $\mathcal{M} = 1 - \frac{\sigma^2}{\theta^2}$ for a waiting time distribution. $\mathcal{M} = 0$ for an exponential distribution, *i.e.*, purely chemical transition, and $\mathcal{M} = 1$ for a mechanical transition with no variance in time. $\mathcal{M} < 0$ means a timer *with variance greater* than exponential [23]. In [5] a paradoxical feature was discovered (see on p. 10872, between eqs. (56) and (57)): even if $\mathcal{M}_j^+$ and $\mathcal{M}_j^-$ both vanish for a state, $\frac{\mathrm{d}}{\mathrm{d}\nu}\overline{K}_j^+(0)$ and $\frac{\mathrm{d}}{\mathrm{d}\nu}\overline{K}_j^-(0)$ do not! This paradox is due to the violation of direction-time independence (DTI). If DTI holds, then the paradox is resolved.

In summary, we have introduced the microscopic reversibility to CTRW models. For CTRW models, the time-reversibility is equivalent to detailed balance plus transition direction–waiting time independence (DTI). Therefore, CTRW models with DTI, such as the CTRW models of transport in disordered solids in [4], are consistent with thermodynamics. A CTRW state without DTI contains a hiddeen "driving force" implicitly. The hidden driving force comes from a hidden reaction that is connected to an open system. As a result, a CRTW model without DTI cannot attain equilibrium due to the dissipation in the hidden reaction. If a CRTW model without DTI is used to describe an equilibrium, then it is inconsistent with thermodynamics.

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APPENDIX

For conciseness, we use g_i to denote G_{im}. For $i, j, m \notin \{\ell_k\}$ and $\ell \in \{\ell_k\}$, we notice that $\pi_\ell(\nu) = \nu \overline{g}_\ell(\nu)$ is the Laplace transform of the probability density of trapping time and $\pi_\ell(0)$ is the trapping probability of state ℓ. In an absorbing state ℓ, we have $\overline{K}_{\ell j}(\nu) = 0$ and eq. (8) leads to $\pi_\ell(\nu) = \nu \overline{g}_\ell(\nu) = \sum_j \overline{K}_{j\ell}(\nu)\overline{g}_j(\nu)$. These are valid for both the CTRW and its cMP. The CTRW and its cMP are related by $\overline{K}_{ij}^{cMP}(\nu) = \overline{K}_{ij}^{CTRW}(0)$. Setting $\nu = 0$ in (8) yields $\pi_\ell(0) = \sum_j \overline{K}_{j\ell}(0)\overline{g}_j(0)$ where $\{\overline{g}_i(0), i \notin \{\ell_k\}\}$ is determined by the linear system

$$0 = \delta_{im} + \sum_j \left(\overline{K}_{ji}(0)\overline{g}_j(0) - \overline{K}_{ij}(0)\overline{g}_i(0) \right).$$

Since the CTRW and its cMP have the same $\overline{K}_{ij}(0) = \frac{p_{ij}}{\theta_i}$, it follows that both the CTRW and its cMP have the same $\{\overline{g}_i(0), i \notin \{\ell_k\}\}$ and the same trapping probabilities. Note that the derivation of trapping probabilities does not require the direction time independence (DTI).

The mean trapping time of state ℓ is $\frac{-\pi_\ell'(0)}{\pi_\ell(0)}$. With the DTI $\overline{K}_{ij}(\nu) = p_{ij}\overline{K}_i(\nu)$, expanding eq. (8) to the linear term and letting $h_i \equiv \left(\overline{K}_i(\nu)\overline{g}_i(\nu) \right)'_{\nu=0}$, we obtain $\pi_\ell'(0) = \sum_j p_{j\ell}h_j$ where $\{h_i, i \notin \{\ell_k\}\}$ is determined by the linear system $\overline{g}_i(0) = \sum_j \{p_{ji}h_j - p_{ij}h_i\}$. It follows that both the CTRW and its cMP have the same mean trapping times.

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[20] Let $\Theta_i(t) = r_{im}(0, t)$; eq. (4) yields $G_i = \Phi_i * \Theta_i$ and $\Theta_i = \delta(t)\delta_{im} + \sum_j \psi_{ji} * \Theta_j$. Laplace transforms leads to $\overline{G}_i(\nu) = \overline{\Phi}_i(\nu)\overline{\Theta}_i(\nu)$ and $\overline{\Theta}_i(\nu) = \delta_{im} + \sum_j \overline{\psi}_{ji}(\nu)\overline{\Theta}_j(\nu)$. Using $\overline{\Phi}_i(\nu) = \frac{1}{\nu}\left(1 - \sum_j \overline{\psi}_{ij}(\nu)\right)$ and eliminating Θ, we have $\nu\overline{G}_i(\nu) - \delta_{im} = \sum_j \left(\frac{\overline{\psi}_{ji}(\nu)}{\overline{\Phi}_j(\nu)}\overline{G}_j(\nu) - \frac{\overline{\psi}_{ij}(\nu)}{\overline{\Phi}_i(\nu)}\overline{G}_i(\nu)\right)$, which is the Laplace transform of eq. (5).

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