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Random dynamics of gene transcription activation in single cells

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ABSTRACT

The recent measurements of gene transcription activity at single cell resolution revealed that genes are often transcribed randomly and discontinuously. In order to elucidate how the environmental signals contribute to the stochasticity of gene transcription, a random transition model was recently proposed [M. Tang, The mean and noise of stochastic gene transcription, *J. Theor. Biol.* 253 (2008) 271–280; M. Tang, The mean frequency of transcriptional bursting and its variation in single cells, *J. Math. Biol.* (2009) doi:10.1007/s00285-009-0258-7, in press; published online: March 10, 2009]. In this model it is assumed that the transcription system transits randomly between three different functional states, quantifying the timing and strength of gene transcription by a sequence of probability functions $P_{nx}(t)$, coupled in an infinite differential system of master equations. Here $n \geq 1$ are integers and x specifies each of the three functional states.

In this work we further study this model aiming to understand the stochastic dynamics of gene transcription. When $n \leq 3$, the exact form of $P_{nx}(t)$ is found analytically by solving the system of master equations. For larger n however, it is unfeasible to find $P_{nx}(t)$ explicitly, so we explore the properties of probability functions by analyzing the master operator L that transforms $P_{(n-1)x}(t)$ to $P_{nx}(t)$. We prove that L “mollifies” the behavior of $P_{(n-1)x}(t)$ by increasing its order of differentiability and by flattening its growth globally. We also show that the n -th cycle of transcription activity condenses at distinct peak instants, with a decreasing peak strength with respect to n . The timings of these peak instants

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are estimated and several further open questions toward a general theory are discussed.

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1. Introduction

Gene transcription is central to life: it transfers the information stored in DNA to instructions for the synthesis of RNAs and proteins, and its products in turn execute virtually all important cellular functions to accomplish life’s feats of surviving, growing, moving and reproducing.

Induced gene transcription is itself the final outcome of a cascade of cellular signaling processes: In response to an environmental change, a signal transduction network could be turned on to induce binding of sequence specific transcription factors (TF) to their cognate sites in gene promoters. The induced binding activity could then facilitate (or impede) assembling of basal transcription machinery to activate (or repress) gene transcription [11,24]. There could be a large number of proteins in the excited signal transduction and gene regulation network, and even a more astounding number of interactions between these proteins. The likelihood of a gene being transcribed depends on the succession of the protein interactions, which are typically random events due to the diffusion of proteins in the cell [7,12,16,20].

It was widely accepted in biology that genes are transcribed in a deterministic and continuous manner. This notion has been reversed by recent measurements at single cell resolution, which have created revealing evidence that, often, individual genes are transcribed randomly and discontinuously [3,13,14,18,19,23]. The precise counting of nascent transcripts or proteins in single cells is now possible due to the recent development of RNA and protein detection techniques [1,2,4,17,25]. The counting revealed that transcripts and proteins are made in a bursting fashion that short periods of quick production of multiple molecules are followed by relatively long periods of no production. It has been proposed that bursting arises from random switching between “gene on” and “gene off” states [8,10,15,17]. However, this proposition does not address what mechanisms are responsible for the random toggle between the gene on state and the gene off state.

In order to elucidate how the environmental signals contribute to the stochasticity of gene transcription, a random transition model was recently proposed and studied [21,22]. In the model, it is assumed that the transcription system transits randomly between the ground state Q , the excited state Y , and the engaged state E , along the Markov chain $Q \xrightarrow{\kappa} Y \xrightarrow{\lambda} E \xrightarrow{\gamma} Q \xrightarrow{\kappa} \dots$, where each arrow denotes a Poisson process. The three parameters κ , λ , and γ are called the *induction strength*, *activation strength*, and *promoter fragility*, respectively. It is unusual that the transition from Q to Y is treated as an irreversible stochastic process; see [21,22] for detailed discussion for supporting experimental evidence. As λ and γ are determined by the biochemical properties of the TF and the genetic properties of the gene, they remain essentially constants in the transcription system. In contrast, when the induction agents are not stably applied, the parameter κ can inherit their temporal variation and spatial heterogeneity. In this case, κ becomes a function of time and the spatial variables, and further transfers the heterogeneities to the gene expression profiles.

In this work we study the stochastic dynamics of gene transcription for the three state model discussed above. As in the original work [21,22], we assume that the induction agents are applied stably so that κ is kept as a constant. We aim to generate illuminating insights for the development of a general theory on the stochastic dynamics of gene transcription for which cellular signals vary in time and space. Let $X = X(t)$ denote the discrete variable specifying the transcription system state, with $X(t) = q, y$, and e if the system is at states Q, Y and E at time $t \geq 0$, respectively. Let $N(t)$ be the variable counting the number of the state transition events. We say that

$$(N(t), X(t)) = (n, x), \quad n \in \{1, 2, 3, \dots\} \text{ and } x \in \{q, y, e\},$$

if the transcription system is at state X with time t , and has visited X exactly n times (including the current visiting) since time zero. As in most experimental assays, we assume $(N(0), X(0)) = (1, q)$

in order to examine how gene transcription responds to the induction signals. As time goes on, the system could shift to the excited state, and then transfer to the engaged state. Sequentially, the transition of the variables $(N(t), X(t))$ is described by the infinite Markov chain

$$(1, q) \xrightarrow{\kappa} (1, y) \xrightarrow{\lambda} (1, e) \xrightarrow{\gamma} (2, q) \xrightarrow{\kappa} \dots (n, y) \xrightarrow{\lambda} (n, e) \xrightarrow{\gamma} (n+1, q) \xrightarrow{\kappa} \dots \tag{1.1}$$

Define $P_{nx}(t) = \text{Prob}\{(N(t), X(t)) = (n, x)\}$ to be the probability that the system is at state X the n -th time at time t . The related mathematical question is to find the exact form of the three functions and to determine their analytical properties under the initial condition

$$P_{1q}(0) = 1 \quad \text{and} \quad P_{nx}(0) = 0 \quad \text{if } x \neq q. \tag{1.2}$$

Clearly $P_{1q}(t) = \exp(-\kappa t)$, hence it decays exponentially. The rest of $P_{nx}(t)$ are governed by the system of master equations

$$\frac{dP_{ny}(t)}{dt} = \kappa P_{nq}(t) - \lambda P_{ny}(t), \tag{1.3}$$

$$\frac{dP_{ne}(t)}{dt} = \lambda P_{ny}(t) - \gamma P_{ne}(t), \tag{1.4}$$

$$\frac{dP_{(n+1)q}(t)}{dt} = -\kappa P_{(n+1)q}(t) + \gamma P_{ne}(t). \tag{1.5}$$

The simplicity of these linear equations has persuaded us to compute $P_{nx}(t)$ directly through iterative integrations [5,22]. However, our computation in Section 3 clearly shows that it is an unfeasible task to obtain the exact form of $P_{nx}(t)$ for all $n \geq 4$. We have to rely on indirect methods to investigate the analytical properties of $P_{nx}(t)$. For this purpose, we may treat the cyclic transition of the three system states as a delayed renewal process, and apply the standard renewal theory of stochastic processes [9] and the Laplace–Stieltjes transform [6]. However, this method does not permit a simple extension to the general case when κ changes in time and space, for which the transition within the three states is no longer a delayed renewal process. Therefore, we utilize a different and self-contained approach, whose extension to the general theory could be less demanding technically.

Our approach relies on the analysis of the master operator L defined as follows: For any given continuous function $f(t)$, $t \geq 0$, we define

$$L(f(t)) = \kappa\lambda\gamma \int_0^t E_{11}(t-s)f(s) ds, \tag{1.6}$$

where the kernel function $E_{11}(t) = P_{1e}(t)/(\kappa\lambda)$. For simplicity, we assume throughout all this paper that the three parameters κ , λ and γ are distinct to each other. In this case

$$E_{11}(t) = \frac{e^{-\kappa t}}{(\kappa - \lambda)(\kappa - \gamma)} + \frac{e^{-\lambda t}}{(\lambda - \gamma)(\lambda - \kappa)} + \frac{e^{-\gamma t}}{(\gamma - \kappa)(\gamma - \lambda)}.$$

The prominent importance of the operator L in our study lies on the following property first established in [22]:

$$P_{nx}(t) = L(P_{(n-1)x}(t)) = \dots = L^{n-1}(P_{1x}(t)), \quad n > 1, \quad x = q, y, e. \tag{1.7}$$

By studying how the properties of $f(t)$ is retained or transformed by L , (1.7) allows us to obtain analytical properties of $P_{nx}(t)$ in a systematic way.

Let $f(t)$ be a function of class $C^l([0, t_0])$, $l \geq 0$, and $0 < t_0 \leq \infty$. In [22] it was shown that $F(t) = L(f(t))$ is of class $C^{l+3}([0, t_0])$, $F(0) = F'(0) = F''(0) = 0$, and $F'''(0) = \kappa\lambda\gamma f(0)$. Hence L “mollifies” the behavior of $f(t)$ by increasing its order of differentiability globally and flattening its growth locally. In Section 2 we investigate the mollification property further and show that L indeed flattens the growth of $f(t)$ globally.

Theorem 1.1. *Let $f(t)$ be a function of class $C^l([0, t_0])$, $l \geq 0$, and $0 < t_0 < \infty$. Let $F(t) = L(f(t))$. Then there exists a constant $C_0 = C_0(t_0; \kappa, \lambda, \gamma) < 1$ such that the L^1 norm and the L^∞ norm of the image is reduced according to*

$$\int_0^{t_0} |F(t)| dt \leq C_0 \int_0^{t_0} |f(t)| dt, \quad \text{and} \quad \max_{[0, t_0]} |F(t)| \leq C_0 \max_{[0, t_0]} |f(t)|. \tag{1.8}$$

Consequently, in any compact subset of $[0, \infty)$, $\lim_{n \rightarrow \infty} L^n(f(t)) = 0$. Furthermore, zero is the only fixed point of L in the linear space $C^0([0, \infty))$.

For a finite number $t_0 > 0$, this theorem shows that L defines a contraction map in the space $C^0([0, t_0])$ equipped with either L^1 or L^∞ norm; here the condition $t_0 < \infty$ is essential, because the L^1 norm of $F(t)$ in $C^0([0, \infty))$ is not reduced but maintained when $f(t) \geq 0$ for $t \in (0, \infty)$.

In Section 2 we also describe several qualitative properties that are preserved under the operation of L , including in particular a P-type property. A differentiable function $f(t)$ defined in $(0, \infty)$ is of P-type if it is positive in $(0, \infty)$, it vanishes at both zero and infinity, and has a finite L^1 norm and a unique critical point over $(0, \infty)$, see Definition 2.1.

Theorem 1.2. (1) *The image $L(f(t))$ is a P-type function as long as $f(t)$ is of P-type.*

(2) *Each of $P_{nx}(t)$, except $P_{1q}(t)$, is a P-type function.*

(3) *Denote the unique positive critical point of $P_{ne}(t)$ by T_{ne} , then $T_{(n-1)e} < T_{ne}$ and the sequence of maximum values $\{P_{ne}(T_{ne})\}$ is decreasing.*

(4) *For each $n > 1$ and $t > T_{(n-1)e}$, denote by t_{nf} the unique number in the interval $(0, T_{(n-1)e})$ such that $P_{(n-1)e}(t_{nf}) = P_{(n-1)e}(t)$. Define T_{ng} to be the largest number t such that $E_{11}(t - t_{nf}) \geq E_{11}(t - T_{(n-1)e})$. Then $T_{ne} > T_{ng} > T_{(n-1)e}$.*

T_{ne} defines the exact time at which the n -th cycle of mRNA synthesizing process is most likely to be seen and we called it the peak instant. The value $P_{ne}(T_{ne})$ determines the largest portion of the cells in the isogenic cell population that can undergo the n -th cycle of mRNA production concurrently. A quantitative description of T_{ne} and $P_{ne}(T_{ne})$ would help to determine the timing and strength of transcriptional bursts. Theorem 1.2(4) estimates the relocation of T_{ne} with respect to $T_{(n-1)e}$. It remains an open question to describe more precisely the time sequence $\{T_{ne}\}$ in terms of κ , λ and γ .

There are more open questions left for future studies: Theorem 1.2(3) only indicates that the sequence $\{P_{ne}(T_{ne})\}$ is decreasing, but provides no further information on their corresponding values. It would be interesting and useful to characterize $\{P_{ne}(T_{ne})\}$ in a more quantitative way, but since $P_{ne}(T_{ne})$ cannot be found explicitly, this may require innovative ideas. It would also be very important to describe how each of κ , λ and γ contributes individually to the timing and strength of gene transcription activation. The corresponding mathematical question leads naturally to a system of partial differential equations.

We devote Section 3 to the computation of $P_{nx}(t)$, $n \leq 3$. Despite the fact that Eqs. (1.3)–(1.5) are linear and simple, the computation needs various sophisticated analytical strategies to manipulate multiple terms as computer softwares provide little help. To write down $P_{nx}(t)$ in compact forms, we use the simplification symbols first introduced in [22]. For a pair of real numbers i and j , define

$$\kappa_{ij} = \frac{1}{(\kappa - \lambda)^i (\kappa - \gamma)^j}, \quad \lambda_{ij} = \frac{1}{(\lambda - \gamma)^i (\lambda - \kappa)^j}, \quad \gamma_{ij} = \frac{1}{(\gamma - \kappa)^i (\gamma - \lambda)^j}. \tag{1.9}$$

Notice that the order $\kappa \rightarrow \lambda \rightarrow \gamma \rightarrow \kappa \rightarrow \lambda \rightarrow \dots$ in the Markov chain (1.1) is used in these symbols, which are not symmetric on i and j . Let

$$E_{ij}(t) = \kappa_{ij}e^{-\kappa t} + \lambda_{ij}e^{-\lambda t} + \gamma_{ij}e^{-\gamma t}. \tag{1.10}$$

Then we have

$$P_{1e}(t) = \kappa\lambda E_{11}(t), \tag{1.11}$$

and as presented in Proposition 3.2,

$$P_{2e}(t) = \kappa^2\lambda^2\gamma(tE_{22}(t) + 2E_{23}(t) + 2E_{32}(t)).$$

The explicit formula for $P_{3e}(t)$ is also derived and clearly shows that the complexity of $P_{ne}(t)$ increases dramatically as n becomes large. Due to the symmetry of $E_{11}(t)$ on the system parameters κ , λ and γ , $\gamma P_{ne}(t)$ inherits the same symmetry, which makes $P_{ne}(t)$ significantly simpler than $P_{nq}(t)$ or $P_{ny}(t)$, which have more fragile expressions. However, even in the analytical expression of $P_{3e}(t)$, there are a large number of terms that cannot be absorbed by E_{**} functions. This makes its exact form still complex, although it is the most compact form we can manage to derive. Our goal in the computation of these functions is to exhibit the nature and the complexity of $P_{nx}(t)$, and demonstrates why we cannot solve master equations (1.3)–(1.5) subject to the initial condition (1.2) completely, even though these equations appear simple. We also provide a technical hint for the calculation of $P_{nx}(t)$ for $n \geq 4$, or the analogs of $P_{nx}(t)$ when more functional states are incorporated in the transcription system.

2. Properties of the master operator L and $P_{nx}(t)$

As in the earlier study [22], our interest in the master operator L is originated by its basic property (1.7). We are particularly interested in identifying the mathematical properties that are preserved under the mapping of L to help us deduce properties of $P_{nx}(t)$ from those of $P_{(n-1)x}(t)$. This is of primary importance for understanding the dynamical behavior of $P_{nx}(t)$ as their exact forms are typically unavailable.

In addition, we point out that the significance of L could be assessed in some more general setting: First, it can be applied to a much broader class of functions than $P_{nx}(t)$, since $L(f(t))$ is well defined as long as f is integrable. This establishes its mathematical interest independent of the study of master equations. Second, L can be extended in an obvious fashion to the case when more functional states, and an equal number of transition parameters, are integrated into the transcription system. Most of the properties of L proved in this section can be generalized by using similar arguments, which could provide a feasible approach for studying more complex models in signal transduction or gene expression networks.

2.1. Mollification property of L

Our first result shows that the master operator L “mollifies” the behavior of $f(t)$ by increasing its order of differentiability and flattening its growth globally.

Theorem 2.1 (Mollification property). *Let $f(t)$ be a function of class $C^l([0, t_0])$, $l \geq 0$, and $0 < t_0 \leq \infty$. Let $F(t) = L(f(t))$. Then*

(1) [22] $F(t)$ is of class $C^{l+3}([0, t_0])$, and

$$F(0) = F'(0) = F''(0) = 0, \quad F'''(0) = \kappa\lambda\gamma f(0). \tag{2.1}$$

(2) For a finite $t_0 > 0$, define the positive constant

$$C_0 = C_0(t_0; \kappa, \lambda, \gamma) = (1 - e^{-\kappa t_0})(1 - e^{-\lambda t_0})(1 - e^{-\gamma t_0}) < 1.$$

Then the L^1 norm of the image is reduced according to

$$\int_0^{t_0} |F(t)| dt \leq C_0 \int_0^{t_0} |f(t)| dt. \tag{2.2}$$

Consequently, in any compact subset A of $[0, \infty)$, $\lim_{n \rightarrow \infty} \int_A |L^n(f(t))| dt = 0$.

(3) For a finite $t_0 > 0$, the L^∞ norm of the image is reduced according to

$$\max_{[0, t_0]} |F(t)| \leq C_0 \max_{[0, t_0]} |f(t)|. \tag{2.3}$$

Consequently, in any compact subset of $[0, \infty)$, $\lim_{n \rightarrow \infty} L^n(f(t)) = 0$. Furthermore, zero is the only fixed point of L in the linear space $C^0([0, \infty))$.

Proof. (1) To make our discussion self-contained, we outline the proof here, although the technical detail has been given in [22]. For a given function $f(t) \in C^1([0, t_0])$, consider the system of equations

$$x'_1 = \kappa f(t) - \lambda x_1, \quad x'_2 = \lambda x_1 - \gamma x_2, \quad x'_3 = \gamma x_2 - \kappa x_3, \tag{2.4}$$

deduced by a modification of (1.3)–(1.5). Then the unique solution of (2.4) subject to

$$x_1(0) = x_2(0) = x_3(0) = 0 \tag{2.5}$$

satisfies

$$x_3(t) = F(t) = L(f(t)). \tag{2.6}$$

The conclusion can be obtained by studying the initial value problem (2.4)–(2.5).

(2) Let $(x_1(t), x_2(t), x_3(t))$ be the unique solution of (2.4) subject to (2.5). Then

$$\begin{aligned} \int_0^{t_0} |x_1(t)| dt &\leq \kappa \int_0^{t_0} \int_0^t e^{-\lambda(t-s)} |f(s)| ds dt \\ &= \kappa \int_0^{t_0} e^{\lambda s} |f(s)| \int_s^{t_0} e^{-\lambda t} dt ds \\ &= \frac{\kappa}{\lambda} \int_0^{t_0} |f(s)| (1 - e^{-\lambda(t_0-s)}) ds \\ &\leq \frac{\kappa}{\lambda} (1 - e^{-\lambda t_0}) \int_0^{t_0} |f(t)| dt. \end{aligned} \tag{2.7}$$

Similar calculation yields

$$\int_0^{t_0} |x_2(t)| dt \leq \frac{\lambda}{\gamma} (1 - e^{-\gamma t_0}) \int_0^{t_0} |x_1(t)| dt$$

and

$$\int_0^{t_0} |x_3(t)| dt \leq \frac{\gamma}{\kappa} (1 - e^{-\kappa t_0}) \int_0^{t_0} |x_2(t)| dt.$$

As $x_3(t) = F(t)$ by (2.6), applying these three inequalities iteratively yields (2.2). Denote by t_0 an upper bound of the compact set A so that $A \subset [0, t_0]$. Then (2.2) gives

$$\left| \int_A L^n(f(t)) dt \right| \leq \int_0^{t_0} |L^n(f(t))| dt \leq C_0^n \int_0^{t_0} |f(t)| dt,$$

which implies the remaining part of the conclusion immediately.

(3) Similar to the proof of (2.7), we have, for any $t \leq t_0$,

$$\begin{aligned} |x_1(t)| &\leq \kappa \int_0^t e^{-\lambda(t-s)} |f(s)| ds \leq \kappa \max_{[0,t_0]} |f(t)| \int_0^t e^{-\lambda(t-s)} ds \\ &= \frac{\kappa}{\lambda} \max_{[0,t_0]} |f(t)| (1 - e^{-\lambda t}) \leq \frac{\kappa}{\lambda} (1 - e^{-\lambda t_0}) \max_{[0,t_0]} |f(t)|. \end{aligned}$$

This gives

$$\max_{[0,t_0]} |x_1(t)| \leq \frac{\kappa}{\lambda} (1 - e^{-\lambda t_0}) \max_{[0,t_0]} |f(t)|.$$

Similar estimates hold when x_1, x_2, x_3 , and the parameters κ, λ , and γ are interchanged appropriately. Applying these estimates iteratively we get (2.3). The rest of the conclusion is easily obtained so we omit its proof. \square

For a finite number $t_0 > 0$, Theorem 2.1 shows that L defines a contraction map in the space $C^0([0, t_0])$ equipped with either L^1 or L^∞ norm. Here t_0 being finite is essential since under some mild condition on f , a slight modification of the proof of (2.2) yields

$$\int_0^\infty F(t) dt = \int_0^\infty f(t) dt. \tag{2.8}$$

See the proof of (2.7) for detail. In particular, if $f(t) \geq 0$ in $(0, \infty)$ and $\int_0^\infty f(t) dt < \infty$, then the L^1 norm of the image function in $C^0([0, \infty))$ is not reduced but preserved.

Applying (2.8) to the probability functions $P_{nx}(t)$, $x = q, y, e$, we derive

$$\int_0^\infty \kappa P_{nq}(t) dt = \int_0^\infty \lambda P_{ny}(t) dt = \int_0^\infty \gamma P_{ne}(t) dt = 1, \quad n \geq 1. \tag{2.9}$$

These simple identities can be proved by other means: Since $P_{nx}(t)$ (except $P_{1q}(t)$) vanishes at both zero and infinity, integration of Eqs. (1.3)–(1.5) over $(0, \infty)$ directly reveals that the three integrals in (2.9) are equal. They must equal 1 since $\int_0^\infty \kappa P_{1q}(t) dt = 1$. Alternatively, we can interpret the integral $\int_0^t \kappa P_{nq}(t) dt$ as the probability that the transcription system has left the state (n, q) during the time interval $(0, t)$, a definite event that occurs sooner or later. It implies immediately that $\int_0^\infty \kappa P_{nq}(t) dt = 1$, and the same interpretation of the other two integrals establishes (2.9).

The reduction of the L^1 norm in the finite interval under the mapping of L , and the retaining of the norm over $(0, \infty)$, demonstrate that the constant C_0 characterizes the reduction quite well. However, at least for a large class of functions that we discuss later, the L^∞ norm over $(0, \infty)$ is not maintained but *reduced*. Thus (2.3) does not provide a sharp estimate of the maximum of the image function $F(t)$, leaving open the delicate issue of obtaining one.

Next, we discuss the asymptotic behavior of $F(t) = L(f(t))$. Assuming that f is continuous and bounded in $[0, \infty)$ we would like to ask does L mollify the function at infinity as well, in the sense that $F(\infty) = \lim_{t \rightarrow \infty} F(t) = 0$? To answer this question, we use definitions (1.10) and (1.6) to compute, for $f(t) \equiv 1$,

$$\begin{aligned} F(t) &= \kappa \lambda \gamma \int_0^t (\kappa_{11} e^{-\kappa(t-s)} + \lambda_{11} e^{-\lambda(t-s)} + \gamma_{11} e^{-\gamma(t-s)}) ds \\ &= \kappa \lambda \gamma \left(\frac{\kappa_{11}}{\kappa} (1 - e^{-\kappa t}) + \frac{\lambda_{11}}{\lambda} (1 - e^{-\lambda t}) + \frac{\gamma_{11}}{\gamma} (1 - e^{-\lambda t}) \right) \\ &= 1 - \kappa \lambda \gamma \left(\frac{\kappa_{11}}{\kappa} e^{-\kappa t} + \frac{\lambda_{11}}{\lambda} e^{-\lambda t} + \frac{\gamma_{11}}{\gamma} e^{-\lambda t} \right), \end{aligned} \tag{2.10}$$

where in the last step we applied the third equality proved in Lemma 3.1. Apparently, $F(\infty) = 1$, but $\neq 0$, which furnishes a negative answer to the question.

Therefore, to ensure that $F(\infty) = 0$, some additional condition is needed. We provide one of such conditions in

Theorem 2.2. *Let $f(t) \in C^0([0, \infty))$ and $\int_0^\infty |f(t)| dt < \infty$. Then $\lim_{t \rightarrow \infty} L(f(t)) = 0$.*

Proof. For any given $\epsilon > 0$, it suffices to show that there exists a number $T = T(\epsilon) > 0$ such that if $t \geq 2T$, then

$$\int_0^t E_{11}(t-s) |f(s)| ds < \epsilon. \tag{2.11}$$

Let $0 < a < \min\{\kappa, \lambda, \gamma\}$. Then there exists a constant $e_0 > 0$ such that

$$E_{11}(t) < e_0 e^{-at} \quad \text{for all } t > 0. \tag{2.12}$$

Since $\int_0^\infty |f(t)| dt < \infty$, we have, for $t \geq T$,

$$\int_T^t E_{11}(t-s)|f(s)| ds \leq e_0 \int_T^t |f(s)| ds \leq e_0 \int_T^\infty |f(s)| ds < \epsilon/2$$

provided that T is sufficiently large. On the other hand, if $t \geq 2T$ and T is sufficiently large, then by (2.12) we derive

$$\begin{aligned} \int_0^T E_{11}(t-s)|f(s)| ds &\leq \max\{E_{11}(t); t \geq T\} \int_0^T |f(s)| ds \\ &< e_0 e^{-aT} \int_0^\infty |f(s)| ds < \epsilon/2. \end{aligned}$$

Hence (2.11) follows and the proof is completed. \square

We note that under the conditions of Theorem 2.2, it could happen that $f(t)$ itself does not tend to zero as $t \rightarrow \infty$. In this case, the operator L does mollify the asymptotic behavior of f , although this mollifying impact is much weaker than the one near $t = 0$.

2.2. Inherited property of $L(f(t))$

For a given function $f(t)$ with some known analytical properties, it is useful to know if $F(t) = L(f(t))$ inherits these properties. For instance, we like to know if the sign or monotonicity of $f(t)$ is preserved under the mapping of L . This question turns out to be a nontrivial one as we can construct increasing function $f(t)$ in a finite interval in which its image $F(t)$ is decreasing.

To provide a technical tool for answering this question, we prove a simple lemma asserting that L and the differentiation operator D commute if and only if $f(0) = 0$.

Lemma 2.1. *Let $f(t) \in C_0^1([0, t_0])$ with $0 < t_0 \leq \infty$, then*

$$\frac{d}{dt}L(f(t)) = L(f'(t)) + \kappa\lambda\gamma f(0)E_{11}(t). \tag{2.13}$$

Consequently $LD = DL$ if and only if $f(0) = 0$, where D denotes the derivative with respect to t .

Proof. The proof uses $E_{11}(0) = \kappa_{11} + \lambda_{11} + \gamma_{11} = 0$ and follows a straightforward calculation; an integration by parts gives

$$\begin{aligned} L(f'(t)) &= \kappa\lambda\gamma \int_0^t E_{11}(t-s)f'(s) ds \\ &= -\kappa\lambda\gamma f(0)E_{11}(t) - \kappa\lambda\gamma \int_0^t f(s) dE_{11}(t-s). \end{aligned} \tag{2.14}$$

On the other hand, by definition (1.6) we find

$$\begin{aligned}
 \frac{d}{dt}L(f(t)) &= \kappa\lambda\gamma \frac{d}{dt} \int_0^t E_{11}(t-s)f(s) ds \\
 &= \kappa\lambda\gamma E_{11}(0)f(t) + \kappa\lambda\gamma \int_0^t \frac{d}{dt} E_{11}(t-s)f(s) ds \\
 &= -\kappa\lambda\gamma \int_0^t f(s) dE_{11}(t-s).
 \end{aligned} \tag{2.15}$$

Clearly, (2.14) and (2.15) imply (2.13) and that $LD = DL$ if and only if $f(0) = 0$. \square

Definition 2.1. A differentiable function $f(t)$ defined in $(0, \infty)$ is of P-type if

- (1) it is positive in $(0, \infty)$ and it vanishes at both zero and infinity;
- (2) it has a unique critical point within $(0, \infty)$; and
- (3) it has a finite L^1 norm, i.e., $\int_0^\infty f(t) dt < \infty$.

It is clear that a P-type function $f(t)$ takes its absolute maximum value at the unique critical point in $(0, \infty)$, and a positive scalar multiple of a P-type function is again a P-type function. By Theorem 2.3(3), it is easily seen that all probability functions $P_{nx}(t)$ (except the first one $P_{1q}(t)$) are P-type functions, which motivates us to give the name “P-type”. By (2.9), the P-type functions $\kappa P_{nq}(t)$ ($n > 1$), $\lambda P_{ny}(t)$ and $\gamma P_{ne}(t)$ are probability density functions for some random variables.

Theorem 2.3. Each of the following properties of $f(t)$ is inherited by $F(t) = L(f(t))$:

- (1) $f(t)$ is continuous and nonnegative (or positive) in $(0, t_0)$;
- (2) $f(t)$ is differentiable and increasing in $(0, t_0)$, provided additionally that $f(0) \geq 0$;
- (3) $f(t)$ is a P-type function.

In the third case, denote by τ_f the unique critical point of f in $(0, \infty)$, and τ_F the unique critical point of F . Then

$$\tau_f < \tau_F \quad \text{and} \quad \max_{(0,\infty)} f(t) = f(\tau_f) > \max_{(0,\infty)} F(t) = F(\tau_F). \tag{2.16}$$

Proof. (1) It is a consequence of definition (1.6) and the fact that $P_{1e}(t) > 0$ and $E_{11}(t)$ for all $t > 0$, which is easy to prove. See (1.11).

(2) If $f'(t) > 0$ in $(0, t_0)$, then so does $L(f'(t)) > 0$ by the first part. Hence (2.13) implies that $F'(t) > 0$ in this interval since $f(0) \geq 0$.

(3) Let $f(t)$ be a P-type function. Then $F(t) > 0$ in $(0, \infty)$ by part (1) of this theorem; $F(t) \in C^4((0, \infty))$, and it vanishes at zero by part (1) of Theorem 2.1; and $F(t)$ vanishes at infinity by Theorem 2.2. Furthermore, by part (2) of Theorem 2.1, $\int_0^\infty |F(t)| dt < \infty$. Hence conditions (1) and (3) of Definition 2.1 are satisfied.

As $F(t)$ is positive and vanishes at both zero and infinity, it must have critical points within $(0, \infty)$. Let $\tau > 0$ be an arbitrary critical point of F . Since f increases in $(0, \tau_f]$, by definition (1.6) it is easy to see that $L(f'(t)) > 0$ for all $t \in (0, \tau_f]$. As $f(0) = 0$ and $LD = DL$, $F'(t) = L(f'(t)) > 0$ in $(0, \tau_f]$. This proves $\tau > \tau_f$. By part (3) of Theorem 2.1, it holds that $F(\tau) < f(\tau_f)$. Therefore, if τ is the unique critical point of F (so that $\tau = \tau_F$), then (2.16) necessarily follows.

It remains to prove the uniqueness of τ . For this purpose we see that it is enough to show that $F''(\tau) < 0$, so that F assumes local maximum value at τ and then τ must be unique. We first derive

an interesting identity on $E_{11}(t)$. For $z = \kappa, \lambda$ or γ , define its conjugate to be $\tilde{z} = \kappa + \lambda + \gamma - z$, that is,

$$\tilde{\kappa} = \lambda + \gamma, \quad \tilde{\lambda} = \kappa + \gamma, \quad \tilde{\gamma} = \kappa + \lambda.$$

These conjugates induce symbols $\tilde{\kappa}_{11}, \tilde{\lambda}_{11}$ and $\tilde{\gamma}_{11}$ as defined in (1.9). These symbols are invariant under conjugate transformation, as shown, for instance, by

$$\tilde{\kappa}_{11} = \frac{1}{(\tilde{\kappa} - \tilde{\lambda})(\tilde{\kappa} - \tilde{\gamma})} = \frac{1}{(\lambda - \kappa)(\gamma - \kappa)} = \kappa_{11}.$$

Similar to (1.10), define $\tilde{E}_{11}(t) = \tilde{\kappa}_{11}e^{-\tilde{\kappa}t} + \tilde{\lambda}_{11}e^{-\tilde{\lambda}t} + \tilde{\gamma}_{11}e^{-\tilde{\gamma}t}$. Then we have

$$E''_{11}(t)E_{11}(t) - E'^2_{11}(t) = -\tilde{E}_{11}(t), \tag{2.17}$$

which can be verified by a straightforward calculation as follows:

$$\begin{aligned} & E''_{11}(t)E_{11}(t) - E'^2_{11}(t) \\ &= (\kappa^2\kappa_{11}e^{-\kappa t} + \lambda^2\lambda_{11}e^{-\lambda t} + \gamma^2\gamma_{11}e^{-\gamma t})(\kappa_{11}e^{-\kappa t} + \lambda_{11}e^{-\lambda t} + \gamma_{11}e^{-\gamma t}) \\ &\quad - (\kappa\kappa_{11}e^{-\kappa t} + \lambda\lambda_{11}e^{-\lambda t} + \gamma\gamma_{11}e^{-\gamma t})^2 \\ &= (\kappa^2 + \lambda^2)\kappa_{11}\lambda_{11}e^{-(\kappa+\lambda)t} + (\kappa^2 + \gamma^2)\kappa_{11}\gamma_{11}e^{-(\kappa+\gamma)t} + (\lambda^2 + \gamma^2)\lambda_{11}\gamma_{11}e^{-(\lambda+\gamma)t} \\ &\quad - 2\kappa\lambda\kappa_{11}\lambda_{11}e^{-(\kappa+\lambda)t} - 2\kappa\gamma\kappa_{11}\gamma_{11}e^{-(\kappa+\gamma)t} - 2\lambda\gamma\lambda_{11}\gamma_{11}e^{-(\lambda+\gamma)t} \\ &= (\kappa - \lambda)^2\kappa_{11}\lambda_{11}e^{-(\kappa+\lambda)t} + (\kappa - \gamma)^2\kappa_{11}\gamma_{11}e^{-(\kappa+\gamma)t} + (\lambda - \gamma)^2\lambda_{11}\gamma_{11}e^{-(\lambda+\gamma)t} \\ &= -\gamma_{11}e^{-(\kappa+\lambda)t} - \lambda_{11}e^{-(\kappa+\gamma)t} - \kappa_{11}e^{-(\lambda+\gamma)t} \\ &= -\tilde{\gamma}_{11}e^{-\tilde{\gamma}t} - \tilde{\lambda}_{11}e^{-\tilde{\lambda}t} - \tilde{\kappa}_{11}e^{-\tilde{\kappa}t} = -\tilde{E}_{11}(t). \end{aligned}$$

It follows from (2.17) that $E_{11}(t)$ is a log concave function for all $t > 0$, as the second order derivative of $\log E_{11}(t)$ is negative. In other words, the ratio $E'_{11}(t)/E_{11}(t)$ is decreasing for all $t > 0$. Associated with $\tau > \tau_f$ we define

$$C_f = E'_{11}(t)/E_{11}(t)|_{t=\tau-\tau_f}.$$

Because $E_{11}(t)$ is positive for all positive t , this implies that $E'_{11}(t) > C_f E_{11}(t)$ for $0 < t < \tau - \tau_f$ and $E'_{11}(t) < C_f E_{11}(t)$ for $\tau - \tau_f < t < \tau$. Setting $t = \tau - s$ then gives

$$-\frac{dE_{11}(\tau - s)}{ds} - C_f E_{11}(\tau - s) = \begin{cases} < 0, & \text{for } 0 < s < \tau_f, \\ > 0, & \text{for } \tau_f < s < \tau. \end{cases} \tag{2.18}$$

Continuing the computation of (2.15), and noticing that $E_{11}(0) = E'_{11}(0) = 0$ and $f(0) = 0$, we find

$$\begin{aligned} F''(t) &= \kappa\lambda\gamma \frac{d}{dt} \int_0^t \frac{d}{dt} E_{11}(t - s) f(s) ds = \kappa\lambda\gamma \int_0^t \frac{d^2}{dt^2} E_{11}(t - s) f(s) ds \\ &= \kappa\lambda\gamma \int_0^t f(s) d\left(\frac{d}{ds} E_{11}(t - s)\right) = -\kappa\lambda\gamma \int_0^t f'(s) \frac{d}{ds} E_{11}(t - s) ds. \end{aligned} \tag{2.19}$$

Since $F'(\tau) = 0$, it holds that

$$\begin{aligned}
 - \int_0^\tau f'(s) \frac{d}{ds} E_{11}(\tau - s) ds &= - \int_0^\tau f'(s) \frac{d}{ds} E_{11}(\tau - s) ds - C_f \int_0^\tau f'(s) E_{11}(\tau - s) ds \\
 &= \int_0^\tau f'(s) \left(-\frac{d}{ds} E_{11}(\tau - s) - C_f E_{11}(\tau - s) \right) ds < 0
 \end{aligned}$$

by (2.18) and the fact that $f'(s) > 0$ for $0 < s < \tau_f$, and $f'(s) < 0$ for $s > \tau_f$. Combining this with (2.19), we see that $F''(\tau) < 0$ and the proof is completed. \square

We remark that the uniqueness of positive critical points of $F(t)$ can also be proved by investigating the localization of critical points of $x_1(t)$, $x_2(t)$ and $x_3(t) = F(t)$ defined by the initial value problem (2.4)–(2.5). Our proof given above is preferred because technically it only requires $E_{11}(t)$ to be log concave.

We also notice that the additional assumption $f(0) \geq 0$ is essential for the assertion of part (2) in Theorem 2.3. Indeed, for any given number $\epsilon > 0$, we can construct a function $f(t)$ such that $f(0) = -\epsilon$, $f(t)$ is strictly increasing in $(0, 1)$, and yet $F(t)$ is strictly decreasing in $(0, 1)$. The construction of such a function f is simple, in principle, following from (2.13) and having $f'(t)$ small compared to ϵ . However the actual construction is omitted for brevity.

2.3. Reallocation of the peak instant

By Theorem 2.3 and (1.7) we see that all functions $P_{ne}(t)$ are of P-type. Consequently, each of $P_{ne}(t)$ admits a unique positive critical point where it attains its absolute maximum value. Denote this unique critical point by T_{ne} , then

$$0 < T_{1e} < T_{2e} < \dots < T_{ne} < \dots, \tag{2.20}$$

and the maximum values $\{P_{ne}(T_{ne})\}$ constitutes a decreasing sequence by (2.16). For its biological significance, we call T_{ne} the *peak instant* as it defines the exact time at which the n -th cycle of mRNA synthesizing process is *most likely* to be seen, and $P_{ne}(T_{ne})$ predicts the *largest* portion of the cells in the isogenic cell population that undergo the n -th cycle of mRNA production concurrently.

In applications, it is therefore a very important question to estimate accurately the peak instant T_{ne} and to determine how it relates to the timing of cell division. As the exact form of $P_{ne}(t)$ is not known when $n > 3$, this cannot be done by working with the function $P_{ne}(t)$ directly. Indeed, even for the cases $n = 1, 2$ and 3 , for which $P_{ne}(t)$ have been found analytically, finding the critical point exactly is very complicated, if not impossible. We turn to the study of the operation of L on a P-type function $f(t)$, and discuss how the critical point of the image $F(t) = L(f(t))$ is reallocated.

Let $f(t)$ be a P-type function, and $F(t) = L(f(t))$. Denote by τ_f and τ_F their unique positive critical points, respectively, and denote by $\tau_e > 0$ the unique critical point of $E_{11}(t)$ as it is also a P-type function. Notice that by (1.11), $\tau_e = T_{1e}$. If $\tau_f < \tau_e$, then by the symmetry of F on f and E_{11} and Theorem 2.3, it is clear that $\tau_F > \tau_e$. For this reason and the fact that $T_{ne} > \tau_e$ for $n > 1$, we shall only consider the case $\tau_f \geq \tau_e$ further.

Lemma 2.2. *Let $f(t)$ be a P-type function whose unique positive critical point $\tau_f \geq \tau_e$. For any $t \geq \tau_f$, let t_f be the unique number in $(0, \tau_f)$ such that $f(t) = f(t_f)$. Then there exists a unique number $T > \tau_f$ such that*

$$E_{11}(T - t_f) = E_{11}(T - \tau_f). \tag{2.21}$$

Proof. Since $f(t)$ is a P-type function that increases in $(0, \tau_f)$ and decreases in (τ_f, ∞) , for each $t > \tau_f$ there corresponds a unique number $t_f \in (0, \tau_f)$ such that $f(t) = f(t_f)$. We first consider the case that $t > \tau_f$ is sufficiently close to τ_f , then it is clear that t_f is also close to τ_f since f takes its unique maximum value at τ_f . Therefore, both $t - \tau_f > 0$ and $t - t_f > 0$ are within the range where E_{11} is an increasing function. Because $t - \tau_f < t - t_f$, we obtain $E_{11}(t - \tau_f) > E_{11}(t - t_f)$. Next, we consider the case when $t > \tau_f$ is sufficiently large. In this case, t_f becomes sufficiently small because $\lim_{t \rightarrow \infty} t_f = 0$ as f vanishes at both zero and infinity. Therefore, both $t - \tau_f > 0$ and $t - t_f > 0$ become very large, and must lie within the range where E_{11} is a decreasing function, implying that $E_{11}(t - \tau_f) < E_{11}(t - t_f)$. Taken together, the continuity of f and E_{11} we see that there must be some T satisfying Eq. (2.21).

Now we prove that there is only one $T > 0$ satisfying (2.21). We do this by showing that (2.21) is not valid if T is replaced with any $t > T$. Because $T - \tau_f < T - T_f$ and $E_{11}(t)$ is increasing in $(0, \tau_e)$ and decreasing in (τ_e, ∞) , we see that

$$T - \tau_f < \tau_e < T - T_f. \tag{2.22}$$

Now, if (2.21) were valid for some $t > T$, then (2.22) should hold when T is replaced by t . It follows that $T - \tau_f < t - \tau_f < \tau_e$, and therefore $E_{11}(t - \tau_f) > E_{11}(T - \tau_f)$. On the other hand, from $t_f < T_f$ it follows that $t - t_f > T - T_f > \tau_e$ and $E_{11}(t - t_f) < E_{11}(T - T_f)$ as E_{11} is decreasing in (τ_e, ∞) . Hence by (2.21) one sees clearly that $E_{11}(t - t_f) < E_{11}(t - \tau_f)$. Thus there is no numbers larger than T satisfying (2.21), and the uniqueness of T is proved. \square

From the proof of this lemma it is seen that T defined by (2.21) is indeed the largest number t such that $E_{11}(t - t_f) \geq E_{11}(t - \tau_f)$.

Theorem 2.4. Let $f(t)$ be a P-type function and let τ_e, τ_f and τ_F be the respective unique positive critical points of $E_{11}(t), f(t)$ and $F(t) = L(f(t))$. Assume $\tau_f \geq \tau_e$. If T is the unique value determined by (2.21), then $\tau_F > T$ and consequently $\tau_F > t$ whenever $E_{11}(t - t_f) \geq E_{11}(t - \tau_f)$.

Proof. We need to show that $F'(t) > 0$ for all $0 < t \leq T$. From the discussion in the proof of Theorem 2.3 it is clear that $F'(t) < 0$ as long as $t > \tau_f$. Hence we only have to prove $F'(T) > 0$ which, in view of $f(0) = 0$, and Lemma 2.1 is equivalent to

$$\int_0^T E_{11}(T - s) f'(s) ds > 0. \tag{2.23}$$

Decomposing $(0, T)$ into three subintervals $(0, T_f), (T_f, \tau_f)$ and (τ_f, T) , and noticing that $f'(s) > 0$ for $0 < s < \tau_f$ and $f'(s) < 0$ for $s > \tau_f$, we find

$$\begin{aligned} \int_0^T E_{11}(T - s) f'(s) ds &> \int_{T_f}^{\tau_f} E_{11}(T - s) f'(s) ds + \int_{\tau_f}^T E_{11}(T - s) f'(s) ds \\ &= \int_{f(T_f)}^{f(\tau_f)} E_{11}(T - s) dx + \int_{f(\tau_f)}^{f(T)} E_{11}(T - s) dx. \end{aligned}$$

For the first integral of the last expression, both $T - s$ and τ_e belong to the interval $(T - \tau_f, T - t_f)$ by (2.22). Hence E_{11} increases first and then decreases, and $E_{11}(t - s) > E_{11}(T - t_f) = E_{11}(T - \tau_f)$. It follows that

$$\int_{f(T_f)}^{f(\tau_f)} E_{11}(T - s) dx > E_{11}(T - \tau_f)(f(\tau_f) - f(T_f)).$$

Similarly, when $s \in (\tau_f, T)$, $E_{11}(T - s) < E_{11}(T - \tau_f)$ and

$$\begin{aligned} \int_{f(\tau_f)}^{f(T)} E_{11}(T - s) dx &> -E_{11}(T - \tau_f)(f(\tau_f) - f(T)) \\ &= -E_{11}(T - \tau_f)(f(\tau_f) - f(T_f)) \end{aligned}$$

since $f(T) = f(T_f)$. Thus (2.23) follows at once, and the proof is completed. \square

2.4. Properties of $P_{nx}(t)$

The analytical results we have obtained on the operator L can be readily applied to the study of the probability functions $P_{nx}(t)$. We present here some of the properties of $P_{ne}(t)$ to characterize the random dynamics of gene on state E. In a parallel fashion, we can derive similar results on $P_{nq}(t)$ and $P_{ny}(t)$ to characterize the random dynamics of gene induction and gene excitation governed by the three state model. For simplicity, we only discuss $P_{ne}(t)$ in detail.

Theorem 2.5. (1) Each of $P_{ne}(t)$ is a P-type function. Denote its unique positive critical point by T_{ne} , then $\{T_{ne}\}$ is an increasing sequence, and the sequence of maximum values $\{P_{ne}(T_{ne})\}$ is decreasing.

(2) In addition to the fact that all $P_{ne}(t)$ vanish at $t = 0$, their initial dynamics is further quantified by

$$P_{ne}(0) = P'_{ne}(0) = \dots = P^{(3n-2)}_{ne}(0) = 0, \quad P^{(3n-1)}_{ne}(0) = (\kappa\lambda)^n \gamma^{n-1}, \quad n \geq 1. \tag{2.24}$$

(3) For each $n > 1$ and $t > T_{(n-1)e}$, denote by t_{nf} the unique number in the interval $(0, T_{(n-1)e})$ such that $P_{(n-1)e}(t_{nf}) = P_{(n-1)e}(t)$. Define T_{ng} to be the largest number t such that $E_{11}(t - t_{nf}) \geq E_{11}(t - T_{(n-1)e})$. Then $T_{ne} > T_{ng} > T_{(n-1)e}$.

Proof. (1) As we have already mentioned, $P_{1e}(t) = \kappa\lambda E_{11}(t)$ is a P-type function. By Theorem 2.3(3) all functions $P_{ne}(t)$, $n \geq 1$, are of P-type. The remaining assertion of this part follows from (2.16) at once.

(2) By direct calculation it is easy to find that $P_{1e}(0) = P'_{1e}(0) = 0$ and $P''_{1e}(0) = \kappa\lambda$. Applying the mollification property of L repeatedly we establish (2.24) in general.

(3) Note that T_{1e} , the unique positive critical point of $P_{1e}(t)$ is equal to τ_e , the unique positive critical point of $E_{11}(t)$. Therefore, the critical points T_{ne} , $n > 1$, appear behind τ_e so that the assertion follows from Theorem 2.4 immediately. \square

3. Calculation of $P_{nx}(t)$, $n = 1, 2, 3$

Even though $E_{ij}(t)$ and the operator L are well-defined when two or three of κ , λ and γ are identical, our calculation will be presented only for distinct parameters. By taking limits appropriately, the results can be extended to the degenerate cases when two or more of them are the same.

The functions $P_{1x}(t)$ are simple:

$$P_{1q}(t) = e^{-\kappa t}, \quad P_{1y}(t) = \frac{\kappa}{\lambda - \kappa} (e^{-\kappa t} - e^{-\lambda t}), \tag{3.1}$$

and $P_{1e}(t)$ is given by (1.11). In what follows, we compute $P_{2x}(t)$ and $P_{3e}(t)$, using the fundamental property (1.7) of the master operator L . The calculation demonstrates clearly that the analytical expressions of $P_{nx}(t)$ are very complicated, complexity dramatically increases with n , $n \geq 3$. Finding $P_{3x}(t)$ is already a highly nontrivial and tedious process. It requires various sophisticated analytical strategies to manipulate multiple terms, since computer softwares provide little help. We will not continue our calculation for $n \geq 4$ for its enormous technical complexity. As the calculation is inevitably complex, we try to make the exposition as less tedious, and sometimes even joyful, as possible.

We begin with some interesting identities of the symbols defined in (1.9).

Lemma 3.1. *Let κ_{ij} , λ_{ij} and γ_{ij} be defined in (1.9). Then*

$$\kappa_{11} + \lambda_{11} + \gamma_{11} = 0, \quad \kappa\kappa_{11} + \lambda\lambda_{11} + \gamma\gamma_{11} = 0, \quad \text{and} \quad \frac{\kappa_{11}}{\kappa} + \frac{\lambda_{11}}{\lambda} + \frac{\gamma_{11}}{\gamma} = \frac{1}{\kappa\lambda\gamma}. \quad (3.2)$$

Proof. These identities can be verified by working with definition (1.9) directly. We prove the third identity which is slightly harder than the others. By the first equality, we change γ_{11} to $-\kappa_{11} - \lambda_{11}$ and convert the left side of the third equality to

$$\begin{aligned} \kappa_{11} \left(\frac{1}{\kappa} - \frac{1}{\gamma} \right) + \lambda_{11} \left(\frac{1}{\lambda} - \frac{1}{\gamma} \right) &= \frac{\gamma - \kappa}{(\kappa - \lambda)(\kappa - \gamma)\kappa\gamma} + \frac{\gamma - \lambda}{(\lambda - \gamma)(\lambda - \kappa)\lambda\gamma} \\ &= \frac{1}{\kappa\gamma(\lambda - \kappa)} + \frac{1}{\lambda\gamma(\kappa - \lambda)} \end{aligned}$$

which is evidently $1/(\kappa\lambda\gamma)$. The proof is completed. \square

Lemma 3.2. *Let κ_{ij} , λ_{ij} and γ_{ij} be defined in (1.9). We also have*

$$\lambda_{12} + \gamma_{21} = \kappa_{12} + \kappa_{21}, \quad \kappa_{12} + \lambda_{21} = \gamma_{12} + \gamma_{21}, \quad \gamma_{12} + \kappa_{21} = \lambda_{12} + \lambda_{21}, \quad (3.3)$$

$$-\kappa_{(i+1)j}\lambda_{11} - \kappa_{i(j+1)}\gamma_{11} = \kappa_{(i+1)(j+2)} + \kappa_{(i+2)(j+1)}, \quad (3.4)$$

and

$$-\kappa_{(i+2)j}\lambda_{11} - \kappa_{i(j+2)}\gamma_{11} = \kappa_{(i+3)(j+1)} + \kappa_{(i+2)(j+2)} + \kappa_{(i+1)(j+3)}. \quad (3.5)$$

The proof of (3.3)–(3.5) is omitted since all equalities can be verified directly. By permutation symmetry, each of (3.4) and (3.5) has two analogous identities which we do not write out explicitly. These identities will be needed in simplifying various terms in our calculation of $P_{nx}(t)$.

Lemma 3.3. *The images of $\exp(-\kappa t)$, $\exp(-\lambda t)$, and $\exp(-\gamma t)$ under the mapping of the master operator L are*

$$L(e^{-\kappa t}) = \kappa\lambda\gamma(\kappa_{11}te^{-\kappa t} + (\kappa_{12} + \kappa_{21})e^{-\kappa t} - \lambda_{12}e^{-\lambda t} - \gamma_{21}e^{-\gamma t}), \quad (3.6)$$

$$L(e^{-\lambda t}) = \kappa\lambda\gamma(\lambda_{11}te^{-\lambda t} + (\lambda_{12} + \lambda_{21})e^{-\lambda t} - \gamma_{12}e^{-\gamma t} - \kappa_{21}e^{-\kappa t}), \quad (3.7)$$

$$L(e^{-\gamma t}) = \kappa\lambda\gamma(\gamma_{11}te^{-\gamma t} + (\gamma_{12} + \gamma_{21})e^{-\gamma t} - \kappa_{12}e^{-\kappa t} - \lambda_{21}e^{-\lambda t}). \quad (3.8)$$

Proof. Applying L to $\exp(-\kappa t)$ we find

$$\begin{aligned} L(e^{-\kappa t}) &= \kappa \lambda \gamma \int_0^t (\kappa_{11} e^{-\kappa t} + \lambda_{11} e^{(\lambda-\kappa)s-\lambda t} + \gamma_{11} e^{(\gamma-\kappa)s-\gamma t}) ds \\ &= \kappa \lambda \gamma (\kappa_{11} t e^{-\kappa t} + \lambda_{12} e^{-\kappa t} - \lambda_{12} e^{-\lambda t} + \gamma_{21} e^{-\kappa t} - \gamma_{21} e^{-\gamma t}). \end{aligned}$$

By the first identity of the three parallel relations (3.3) we can rewrite this as (3.6). By permutation symmetry we obtain (3.7)–(3.8) from (3.6). \square

Proposition 3.1. *The probability functions $P_{2q}(t)$ and $P_{2y}(t)$ are provided by*

$$P_{2q}(t) = \kappa \lambda \gamma (\kappa_{11} t e^{-\kappa t} + (\kappa_{12} + \kappa_{21}) e^{-\kappa t} - \lambda_{12} e^{-\lambda t} - \gamma_{21} e^{-\gamma t}), \tag{3.9}$$

and

$$-\frac{P_{2y}(t)}{\kappa^2 \lambda \gamma} = \kappa_{21} t e^{-\kappa t} + (\kappa_{22} + 2\kappa_{31}) e^{-\kappa t} + \lambda_{12} t e^{-\lambda t} + (\lambda_{22} + 2\lambda_{13}) e^{-\lambda t} - \gamma_{22} e^{-\gamma t}. \tag{3.10}$$

Proof. From (1.7) and (3.1) it is seen that $P_{2q}(t)$ is simply the image of $e^{-\kappa t}$; hence (3.9) follows from (3.6) immediately. By (1.7) and (3.1) again we find

$$P_{2y}(t) = \frac{\kappa}{\lambda - \kappa} L(e^{-\kappa t} - e^{-\lambda t}) = -\kappa (\kappa_{10} L(e^{-\kappa t}) + \lambda_{01} L(e^{-\lambda t})).$$

Substituting (3.6) and (3.7) gives

$$\begin{aligned} P_{2y}(t) &= -\kappa^2 \lambda \gamma (\kappa_{21} t e^{-\kappa t} + (\kappa_{22} + \kappa_{31}) e^{-\kappa t} + \lambda_{13} e^{-\lambda t} - \kappa_{10} \gamma_{21} e^{-\gamma t} \\ &\quad + \lambda_{12} t e^{-\lambda t} + (\lambda_{13} + \lambda_{22}) e^{-\lambda t} - \lambda_{01} \gamma_{12} e^{-\gamma t} + \kappa_{31} e^{-\kappa t}), \end{aligned}$$

here we have used the simple relations $\kappa_{10} \kappa_{ij} = \kappa_{(i+1)j}$ and $\lambda_{10} \lambda_{ij} = \lambda_{(i+1)j}$. To move on, we note that

$$\kappa_{10} \gamma_{10} + \lambda_{01} \gamma_{01} = \frac{1}{(\kappa - \lambda)(\gamma - \kappa)} + \frac{1}{(\lambda - \kappa)(\gamma - \lambda)} = \frac{1}{(\gamma - \kappa)(\gamma - \lambda)} = \gamma_{11}$$

and therefore $\kappa_{10} \gamma_{21} + \lambda_{01} \gamma_{12} = \gamma_{22}$. This helps derive (3.10) finally. \square

In order to analyze $P_{ne}(t)$ and the power L^n in a more systematic way, we first calculate the convolution of $E_{11}(t)$ and $t^i E_{ij}(t)$, $i = 0, 1$.

Lemma 3.4. *The convolution of $E_{ij}(t)$ and $E_{11}(t)$ is*

$$\begin{aligned} \int_0^t E_{ij}(t-s) E_{11}(s) ds &= t E_{(i+1)(j+1)}(t) + E_{(i+1)(j+2)}(t) + E_{(i+2)(j+1)}(t) \\ &\quad + \kappa_{11} (\lambda_{i(j+1)} + \gamma_{(i+1)j}) e^{-\kappa t} + \lambda_{11} (\gamma_{i(j+1)} + \kappa_{(i+1)j}) e^{-\lambda t} \\ &\quad + \gamma_{11} (\kappa_{i(j+1)} + \lambda_{(i+1)j}) e^{-\gamma t}. \end{aligned}$$

When $i = j = 1$ we have in particular

$$\int_0^t E_{11}(t - s)E_{11}(s) ds = tE_{22}(t) + 2E_{23}(t) + 2E_{32}(t). \tag{3.11}$$

The convolution of $tE_{ij}(t)$ and $E_{11}(t)$ is

$$\begin{aligned} \int_0^t (t - s)E_{ij}(t - s)E_{11}(s) ds &= \int_0^t sE_{ij}(s)E_{11}(t - s) ds \\ &= \frac{t^2}{2}E_{(i+1)(j+1)}(t) + t(E_{(i+1)(j+2)}(t) + E_{(i+2)(j+1)}(t)) \\ &\quad + E_{(i+1)(j+3)}(t) + E_{(i+2)(j+2)}(t) + E_{(i+3)(j+1)}(t) \\ &\quad + (\lambda_{ij}\kappa_{31} + \gamma_{ij}\kappa_{13})e^{-\kappa t} + (\kappa_{ij}\lambda_{13} + \gamma_{ij}\lambda_{31})e^{-\lambda t} \\ &\quad + (\kappa_{ij}\gamma_{31} + \lambda_{ij}\gamma_{13})e^{-\gamma t}. \end{aligned}$$

Proof. Using definition (1.10), we expand the product of $E_{ij}(t - s)$ and $E_{11}(s)$ as

$$\begin{aligned} E_{ij}(t - s)E_{11}(s) &= E_{(i+1)(j+1)}(t) + \kappa_{ij}\lambda_{11}e^{(\kappa-\lambda)s-\kappa t} + \kappa_{11}\lambda_{ij}e^{(\lambda-\kappa)s-\lambda t} \\ &\quad + \kappa_{ij}\gamma_{11}e^{(\kappa-\gamma)s-\kappa t} + \kappa_{11}\gamma_{ij}e^{(\gamma-\kappa)s-\gamma t} + \gamma_{ij}\lambda_{11}e^{(\gamma-\lambda)s-\gamma t} + \gamma_{11}\lambda_{ij}e^{(\lambda-\gamma)s-\lambda t}. \end{aligned}$$

Integrating both sides gives

$$\begin{aligned} \int_0^t E_{ij}(t - s)E_{11}(s) ds &= tE_{(i+1)(j+1)}(t) + \kappa_{(i+1)j}\lambda_{11}(e^{-\lambda t} - e^{-\kappa t}) + \kappa_{11}\lambda_{i(j+1)}(e^{-\kappa t} - e^{-\lambda t}) \\ &\quad + \kappa_{i(j+1)}\gamma_{11}(e^{-\gamma t} - e^{-\kappa t}) + \kappa_{11}\gamma_{(i+1)j}(e^{-\kappa t} - e^{-\gamma t}) \\ &\quad + \gamma_{i(j+1)}\lambda_{11}(e^{-\lambda t} - e^{-\gamma t}) + \gamma_{11}\lambda_{(i+1)j}(e^{-\gamma t} - e^{-\lambda t}) \\ &= tE_{(i+1)(j+1)}(t) + (\kappa_{(i+1)j}\lambda_{11} - \kappa_{11}\lambda_{i(j+1)})(e^{-\lambda t} - e^{-\kappa t}) \\ &\quad + (\kappa_{i(j+1)}\gamma_{11} - \kappa_{11}\gamma_{(i+1)j})(e^{-\gamma t} - e^{-\kappa t}) \\ &\quad + (\gamma_{i(j+1)}\lambda_{11} - \gamma_{11}\lambda_{(i+1)j})(e^{-\lambda t} - e^{-\gamma t}). \end{aligned}$$

After multiplication and reorganization of terms this is changed to

$$\begin{aligned} &tE_{(i+1)(j+1)}(t) - (\kappa_{(i+1)j}\lambda_{11} + \kappa_{i(j+1)}\gamma_{11})e^{-\kappa t} - (\lambda_{(i+1)j}\gamma_{11} + \lambda_{i(j+1)}\kappa_{11})e^{-\lambda t} \\ &\quad - (\gamma_{(i+1)j}\kappa_{11} + \gamma_{i(j+1)}\lambda_{11})e^{-\gamma t} + \kappa_{11}(\lambda_{i(j+1)} + \gamma_{(i+1)j})e^{-\kappa t} \\ &\quad + \lambda_{11}(\kappa_{(i+1)j} + \gamma_{i(j+1)})e^{-\lambda t} + \gamma_{11}(\kappa_{i(j+1)} + \lambda_{(i+1)j})e^{-\gamma t}. \end{aligned}$$

Applying (3.4) we replace $-\kappa_{(i+1)j}\lambda_{11} - \kappa_{i(j+1)}\gamma_{11}$ by $\kappa_{(i+1)(j+2)} + \kappa_{(i+2)(j+1)}$; similarly, by permutation symmetry, we also replace the coefficients of the other two negative terms by $\lambda_{(i+1)(j+2)} + \lambda_{(i+2)(j+1)}$ and $\gamma_{(i+1)(j+2)} + \gamma_{(i+2)(j+1)}$, respectively. It is easy to see that the final result is identical with the one given in the lemma.

In the special case when $i = j = 1$, we have

$$\lambda_{i(j+1)} + \gamma_{(i+1)j} = \lambda_{12} + \gamma_{21} = \kappa_{12} + \kappa_{21},$$

by (3.3). Hence

$$\kappa_{11}(\lambda_{i(j+1)} + \gamma_{(i+1)j}) = \kappa_{(i+1)(j+2)} + \kappa_{(i+2)(j+1)} \quad \text{for } i = j = 1, \tag{3.12}$$

and similar identities hold when κ , λ and γ are permuted properly. After replacing several terms appropriately using (3.12) and its analogous identities, the first formula of this lemma is then reduced to (3.11).

The expansion of $sE_{ij}(s)$ and $E_{11}(t - s)$ follows from the one given at the beginning of the proof of this lemma. Integrating the expansion yields

$$\begin{aligned} & \int_0^t sE_{ij}(s)E_{11}(t - s) ds \\ &= \frac{t^2}{2} E_{(i+1)(j+1)}(t) - (\kappa_{(i+1)j}\lambda_{11} + \kappa_{i(j+1)}\gamma_{11})te^{-\kappa t} - (\lambda_{i(j+1)}\kappa_{11} + \lambda_{(i+1)j}\gamma_{11})te^{-\lambda t} \\ & \quad - (\gamma_{i(j+1)}\lambda_{11} + \gamma_{(i+1)j}\kappa_{11})te^{-\gamma t} + (\lambda_{ij}\kappa_{31} + \gamma_{ij}\kappa_{13} - \kappa_{(i+2)j}\lambda_{11} - \kappa_{i(j+2)}\gamma_{11})e^{-\kappa t} \\ & \quad + (\kappa_{ij}\lambda_{13} + \gamma_{ij}\lambda_{31} - \lambda_{i(j+2)}\kappa_{11} - \lambda_{(i+2)j}\gamma_{11})e^{-\lambda t} \\ & \quad + (\kappa_{ij}\gamma_{31} + \lambda_{ij}\gamma_{13} - \gamma_{(i+2)j}\kappa_{11} - \gamma_{i(j+2)}\lambda_{11})e^{-\gamma t}. \end{aligned}$$

It is seen that the coefficients of $t \exp(-\kappa t)$, $t \exp(-\lambda t)$ and $t \exp(-\gamma t)$ have already appeared during the computation of the convolution of $E_{ij}(t)$ and $E_{11}(t)$, so they can be replaced in the same way. By (3.5), we also replace $-\kappa_{(i+2)j}\lambda_{11} - \kappa_{i(j+2)}\gamma_{11}$ by $\kappa_{(i+3)(j+1)} + \kappa_{(i+2)(j+2)} + \kappa_{(i+1)(j+3)}$; similar replacements of the rest of the negative coefficients using the permutation symmetry then yield the final result. \square

We remark that the simple relation (3.12) is valid only when $i = j = 1$, and there is no analogous relation in other cases, even when $i = j = 2$. Therefore, except for $i = j = 1$, the convolution of $E_{ij}(t)$ and $E_{11}(t)$ always contain several residual terms that cannot be absorbed into the E_{**} functions as in (3.11).

By (1.11) and definition (1.6) we find that

$$L(f(t)) = \gamma \int_0^t P_{1e}(t - s)f(s) ds.$$

This similarity between $P_{1e}(t)$ and L is indeed inherited by $P_{ne}(t)$ and the power L^n for all $n > 1$.

Proposition 3.2. For any $n \geq 1$, it holds that

$$L^n(f(t)) = \gamma \int_0^t P_{ne}(t - s)f(s) ds. \tag{3.13}$$

For $n = 2, 3$, $P_{ne}(t)$ are expressed explicitly by

$$P_{2e}(t) = \kappa^2 \lambda^2 \gamma (tE_{22}(t) + 2E_{23}(t) + 2E_{32}(t)), \tag{3.14}$$

and

$$\begin{aligned} P_{3e}(t) &= \kappa^3 \lambda^3 \gamma^2 \int_0^t ((t-s)E_{22}(t-s) + 2E_{23}(t-s) + 2E_{32}(t-s))E_{11}(s) ds \\ &= \kappa^3 \lambda^3 \gamma^2 (t^2 E_{33}(t)/2 + 3t(E_{34}(t) + E_{43}(t)) + 3E_{35}(t) + 5E_{44}(t) + 3E_{53}(t) \\ &\quad + (\lambda_{22}\kappa_{31} + \gamma_{22}\kappa_{13})e^{-\kappa t} + (\kappa_{22}\lambda_{13} + \gamma_{22}\lambda_{31})e^{-\lambda t} + (\kappa_{22}\gamma_{31} + \lambda_{22}\gamma_{13})e^{-\gamma t} \\ &\quad + 2\kappa_{11}(\lambda_{24} + \gamma_{33})e^{-\kappa t} + 2\lambda_{11}(\gamma_{24} + \kappa_{33})e^{-\lambda t} + 2\gamma_{11}(\kappa_{24} + \lambda_{33})e^{-\gamma t} \\ &\quad + 2\kappa_{11}(\lambda_{33} + \gamma_{42})e^{-\kappa t} + 2\lambda_{11}(\gamma_{33} + \kappa_{42})e^{-\lambda t} + 2\gamma_{11}(\kappa_{33} + \lambda_{42})e^{-\gamma t}). \end{aligned}$$

Proof. First, (3.13) holds for $n = 1$ as we mentioned right before the statement of this proposition. We next prove it for $n = 2$. By definition (1.6), we have

$$\begin{aligned} L^2(f(t)) &= \kappa \lambda \gamma \int_0^t E_{11}(t-s)L(f(s)) ds \\ &= (\kappa \lambda \gamma)^2 \int_0^t E_{11}(t-s) \int_0^s E_{11}(s-r)f(r) dr ds \\ &= (\kappa \lambda \gamma)^2 \int_0^t f(r) \int_r^t E_{11}(t-s)E_{11}(s-r) ds dr \\ &= (\kappa \lambda \gamma)^2 \int_0^t f(s) \int_s^t E_{11}(t-r)E_{11}(r-s) dr ds. \end{aligned}$$

On the other hand, by (1.6) and (1.7) we find

$$P_{2e}(t) = L(P_{1e}(t)) = \kappa \lambda L(E_{11}(t)) = \kappa^2 \lambda^2 \gamma \int_0^t E_{11}(t-s)E_{11}(s) ds. \tag{3.15}$$

Substituting this into the right hand side of (3.13) we obtain

$$\gamma \int_0^t P_{2e}(t-s)f(s) ds = (\kappa \lambda \gamma)^2 \int_0^t f(s) \int_0^{t-s} E_{11}(t-s-x)E_{11}(x) dx ds.$$

The substitution $r = x + s$ changes this double integral into the form exactly the same as the one right above (3.15). This proves (3.13) for $n = 2$. In general, assume that (3.13) holds for $n = N$, $N \geq 2$, then

$$\begin{aligned} L^{N+1}(f(t)) &= \kappa\lambda\gamma \int_0^t E_{11}(t-s)L^N(f(s))ds \\ &= \kappa\lambda\gamma^2 \int_0^t E_{11}(t-s) \int_0^s P_{Ne}(s-r)f(r)dr ds. \end{aligned}$$

Continuing in a similar way as above, with one of E_{11} replaced by P_{Ne} , we can show that (3.13) still holds for $n = N + 1$. By induction, (3.13) is proved for all $n \geq 1$.

The exact form (3.14) follows from (3.11) and (3.15) directly. The exact form of $P_{3e}(t)$ is obtained by applying Lemma 3.4. The computation is straightforward, and the detail is omitted for simplicity. □

It is interesting to observe that, because the linear operator L is a symmetric form of κ , λ and γ , $P_{ne}(t)$ (more precisely, $\gamma P_{ne}(t)$) is also a symmetry form of these parameters for each $n \geq 1$. This symmetry is not shared by either $P_{nq}(t)$ or $P_{ny}(t)$, which have more fragile expressions than $P_{ne}(t)$. In the analytical expression of $P_{3e}(t)$, there are a large number of terms that cannot be absorbed by E_{**} functions. This makes its exact form complex, although it is the most compact form we can manage to derive. Apparently, it is not encouraging to continue the calculation for $n > 3$. Basically, it is impractical to find the exact forms of $P_{nx}(t)$ in general, so their properties need to be explored by indirect methods.

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