



# Solving the chemical master equation for monomolecular reaction systems and beyond: a Doi-Peliti path integral view

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## Abstract

The chemical master equation (CME) is a fundamental description of interacting molecules commonly used to model chemical kinetics and noisy gene regulatory networks. Exact time-dependent solutions of the CME—which typically consists of infinitely many coupled differential equations—are rare, and are valuable for numerical benchmarking and getting intuition for the behavior of more complicated systems. Jahnke and Huisinga’s landmark calculation of the exact time-dependent solution of the CME for monomolecular reaction systems is one of the most general analytic results known; however, it is hard to generalize, because it relies crucially on special properties of monomolecular reactions. In this paper, we rederive Jahnke and Huisinga’s result on the time-dependent probability distribution and moments of monomolecular reaction systems using the Doi-Peliti path integral approach, which reduces solving the CME to evaluating many integrals. While the Doi-Peliti approach is less intuitive, it is also more mechanical, and hence easier to generalize. To illustrate how the Doi-Peliti approach can go beyond the method of Jahnke and Huisinga, we also find an explicit and exact time-dependent solution to a problem involving an autocatalytic reaction that Jahnke and Huisinga identified as not solvable using their method. Most interestingly, we are able to find a formal exact time-dependent solution for any CME whose list of reactions involves only zero and first order reactions, which may be the most general result currently known. This formal solution also yields a useful algorithm for efficiently computing numerical solutions to CMEs of this type.

**Keywords** Chemical master equation · Explicit solution formula · Continuous-time Markov process · Path integral · Doi-Peliti

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## 1 Introduction

The chemical master equation (CME) provides a fundamental description of well-mixed molecules interacting with each other via a set of chemical reactions (McQuarrie 1967; Gillespie 1992, 2000, 2007; Gillespie et al. 2013; Fox and Munsky 2017; Munsky et al. 2018). It models dynamics that are discrete (the state of the system is a set of nonnegative integers) and stochastic (chemical reactions occur with some probability). The CME has recently enjoyed tremendous success as a framework for understanding noisy single cell data (Neuert et al. 2013; Munsky et al. 2015; Fox et al. 2016; Munsky et al. 2018; Weber et al. 2018; Fox and Munsky 2019; Fox et al. 2019), particularly in simple model organisms like yeast where techniques like single-molecule Fluorescence *in situ* Hybridization (smFISH) allow RNA molecule numbers to be counted accurately (Raj et al. 2008; Femino et al. 1998; Rahman 2013). Outside of cell and molecular biology, master equations have been successfully used to model population dynamics (Ovaskainen and Meerson 2010; Melbinger et al. 2010; Assaf and Meerson 2017), traffic (Nagel and Schreckenberg 1992; Mahnke and Pieret 1997; Mahnke et al. 2005), and gas phase chemical kinetics (Miller and Klippenstein 2006; Glowacki et al. 2012; Jasper et al. 2014), among other things.

Although it is very useful for defining discrete stochastic models, the CME generally cannot be solved directly. One typically resorts to an approximate approach, like using Gillespie's algorithm (Gillespie 1976, 1977) to extract information from many brute force simulations, or using finite state projection (Munsky and Khammash 2006; Pele et al. 2006; Fox et al. 2016; Fox and Munsky 2019), or partitioning the system (e.g. low versus high copy number, slow versus fast time scale) (Harris and Clancy 2006; Harris et al. 2009; Iyengar et al. 2010; Bokes et al. 2012; Hasenauer et al. 2014; Kan et al. 2016), or solving a continuous approximation to the CME like the chemical Langevin equation (Gillespie 2000, 2002; Grima et al. 2011; Vastola and Holmes 2020).

Unsurprisingly, exact time-dependent solutions of the CME are particularly rare, and have only been computed for a small number of specific cases. This is because they involve dealing with additional complexity on top of what is required to compute steady state solutions, which are themselves extremely difficult to compute and only known in a small number of cases (see e.g. Schnoerr et al. (2017) for some discussion). McQuarrie (1967) describes some of the early attempts: in 1940, Max Delbrück evaluated the CME for the autocatalytic reaction  $S \rightarrow S + S$  (Delbrück 1940); in 1954, Renyi solved the binding reaction  $A + B \rightarrow C$  (Rényi 1954); in 1960, Ishida solved the death reaction  $S \rightarrow \emptyset$  and presented the first CME solution with time-dependent rates (Ishida 1960); in 1963 and 1964, McQuarrie et al. solved many simple systems (including  $A + A \rightarrow B$  and  $A + B \rightarrow C$ ) using the method of generating functions (McQuarrie 1963; McQuarrie et al. 1964).

The situation did not change appreciably until Jahnke and Huisinga's landmark paper (Jahnke and Huisinga 2007), more than forty years later. Their 2007 paper constituted a major advance in our collective understanding of the CME; they were able to solve the CME for a system with an *arbitrary* number of species experiencing an

*arbitrary* number of reactions whose rates have *arbitrary* time-dependence, *provided that* the reactions consisted of some combination of birth ( $\emptyset \rightarrow S_k$ ), death ( $S_j \rightarrow \emptyset$ ), and conversion ( $S_j \rightarrow S_k$ ).<sup>1</sup> The shocking generality of their result, as well as the explicitness of the solution they wrote down (in Theorem 1 of that paper), was powerful.

Since 2007, there have been few new results of the same generality. Reis et al. (2018) extend Jahnke and Huisinga's result by considering hierarchical first-order reaction networks (which allow a certain subset of first-order reactions that is strictly larger than the set of monomolecular reactions). However, there has not been (for example) any result on the solution to general first-order reactions, or general bimolecular reactions. At present, even finding the exact solutions of simple systems that involve bimolecular reactions is nontrivial: the work of Laurenzi ( $A + B \leftrightarrow C$ ) (Laurenzi 2000), as well as Arslan and Laurenzi ( $A + B \leftrightarrow A + A$ ) (Arslan and Laurenzi 2008) are two examples.

One drawback of Jahnke and Huisinga's paper is that it essentially relied on guessing the solution. It was well-known that Poisson and multinomial distributions solved the CME in special cases, and that these distributions had certain desirable properties (e.g. a Poisson distribution stays a Poisson distribution, and a multinomial distribution stays a multinomial distribution; see Sect. 3 of their paper). To derive their Theorem 1, these properties were exploited, along with the fact that only monomolecular reactions were considered. Of course, their method completely breaks down for a system that is only slightly more complicated; as they point out in Sect. 6 of Jahnke and Huisinga (2007), adding an autocatalytic reaction  $S \rightarrow S + S$  to a system they can easily solve manages to make it beyond the scope of their results.

Hence, it would be nice if there was a method to obtain their classic result that did not rely on systematic guessing. In this paper, we offer the Doi-Peliti path integral approach to solving the CME as one such method. The Doi-Peliti approach allows one to 'turn the crank', so to speak, and generate a time-dependent solution of the CME through a straightforward but difficult calculation. Importantly, it is system-agnostic: one does not need to know properties like 'Poisson distributions stay Poisson', or assume the solution takes a certain form.

Doi-Peliti field theory—which emerged from the pioneering papers of researchers like (Doi 1976a, b), Peliti (1985, 1986), Peliti and Zhang (1985), and Grassberger and Scheunert (1980), Grassberger (1982, 1989), Cardy and Grassberger (1985)—reframes solving the CME as a field theory problem. This enables the use of powerful approximation schemes, like the renormalization group and diagrammatic perturbation theory (Mattis and Glasser 1998; Lee 1994; Lee and Cardy 1994, 1995; van Wijland et al. 1998; Canet et al. 2004; Canet 2006; Tuber et al. 2005). While Doi-Peliti field theory is still somewhat obscure in mathematical biology, it has seen the occasional application: e.g. to understand population dynamics given colored noise (Fung et al. 2017), age dependent branching processes (Greenman and Chou 2016; Greenman 2017), and large deviations in gene regulatory networks (Bressloff 2014; Assaf and Meerson 2017). Although not Doi-Peliti, a qualitatively similar path integral has been

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<sup>1</sup> These systems are called "monomolecular" because all allowed reactions have at most one molecule as input, and at most one molecule as output.

used to solve the CME for a multistep transcription and translation process (Albert 2019).

We will use Doi-Peliti field theory to rederive Jahnke and Huisinga's Theorem 1. Moreover, in order to show that the Doi-Peliti path integral approach is strictly *more* powerful than the one used by Jahnke and Huisinga, we use it to exactly solve a problem they said their method could not, as well as a far more general problem (the CME whose list of reactions consists of any combination of zero and first order reactions). We solve these additional problems in complete generality, and obtain exact time-dependent solutions assuming rates with arbitrary time-dependence.

The paper is organized as follows. In Sect. 2, we state the problems we will solve—involving (i) monomolecular systems, (ii) one species birth-death-autocatalysis, and (iii) arbitrary combinations of zero and first order reactions—as well as our main results on their solutions. We also discuss a few interesting theoretical and numerical applications of our main results. In Sect. 3, we present the main result of Doi-Peliti theory, which we use to derive the aforementioned results. The associated technical machinery is developed in Appendix B. Sections 4 and 5 contain technical calculations that derive our results for monomolecular systems and one species birth-death-autocatalysis, with our most general results (for systems involving arbitrary combinations of zero and first order reactions) derived and discussed in the somewhat technical Appendices D and E. Finally, in Sect. 6, we discuss the merits and drawbacks of the Doi-Peliti approach to solving the CME, and speculate on how it could be further utilized.

## 2 Problem statements and main results

In this section, we introduce in detail the specific problems we will solve, and we present our main results regarding their solutions. Although the Doi-Peliti method is not completely rigorous, the solutions we obtain using it can be rigorously checked by direct substitution into the CME—a tedious but usually straightforward process.

We present results for several systems, in order of increasing complexity: the chemical birth-death process, monomolecular reactions, single species birth-death-autocatalysis, and arbitrary combinations of zero and first order reactions with arbitrarily many species. While the chemical birth-death process is a kind of monomolecular reaction system, we include it here to give mathematicians new to the CME a toy example (that can be stated with minimal notational baggage) of the kind of results we are seeking.

### 2.1 The chemical birth-death process as a prototype

The chemical birth-death process is simple enough to be biologically relevant [it can be used to model how the number of a single type of mRNA or protein in a single cell changes stochastically with time in the absence of significant regulation, Fox and Munsky 2017; Munsky et al. 2018; Bressloff 2017], but complicated enough to have nontrivial dynamics (the number of molecules does not increase without bound or shrink to zero in the long time limit, allowing there to exist a Poisson-like steady

state probability distribution). It is linear (in several distinct but related senses of the word), allowing its associated CME to be exactly solved via a variety of methods [(e.g. separation of variables and ladder operators (Vastola 2019a), and via a path integral different from the one we will discuss here (Vastola and Holmes 2020)].

It is characterized by the chemical reactions



where  $k(t)$  and  $\gamma(t)$  parameterize the small time birth and death rates, respectively.<sup>2</sup> The time-dependence of these parameters is allowed to be arbitrary as long as they both remain nonnegative and finite for all times. The corresponding CME reads

$$\begin{aligned} \frac{\partial P(x, t)}{\partial t} &= k(t) [P(x - 1, t) - P(x, t)] \\ &+ \gamma(t) [(x + 1)P(x + 1, t) - xP(x, t)] \end{aligned} \quad (2)$$

where  $P(x, t)$  is the probability that the state of the system is  $x \in \mathbb{N} := \{0, 1, 2, \dots\}$  at time  $t \geq t_0$ . We are particularly interested in the transition probability  $P(x, t; \xi, t_0)$ , i.e. the solution of Eq. 2 whose probability distribution is initially certain. This corresponds to choosing the specific initial condition  $P(x, t_0) = \delta(x - \xi)$  for some  $\xi \in \mathbb{N}$ , where  $\delta(z)$  denotes the Kronecker delta function (which equals one if  $z = 0$  and zero otherwise). If the transition probability is known, the solution to Eq. 2 for an arbitrary initial distribution  $P_0(x)$  can be written

$$P(x, t) = \sum_{y=0}^{\infty} P(x, t; y, t_0) P_0(y). \quad (3)$$

In practice, we are also interested in several other properties of the solution. In particular, we are interested in the long time behavior described by the steady state probability distribution

$$P_{ss}(x) := \lim_{t \rightarrow \infty} P(x, t; \xi, t_0), \quad (4)$$

moments like

$$\langle x(t) \rangle := \sum_{x=0}^{\infty} x P(x, t)$$

<sup>2</sup> In particular, if the system has  $x$  molecules of species  $S$  at time  $t$ , the probability that the birth reaction happens in a window of time  $[t, t + \Delta t)$  is approximately  $k(t)\Delta t$ , and the probability that the death reaction happens is approximately  $\gamma(t)x\Delta t$ . See Gillespie (2000) for more details on the interpretation of and formalism underlying the CME.

$$\langle x(t)[x(t) - 1] \rangle := \sum_{x=0}^{\infty} x(x - 1)P(x, t), \tag{5}$$

and the complex-valued (i.e.  $g \in \mathbb{C}$ ) probability generating function

$$\psi(g, t) := \sum_{x=0}^{\infty} P(x, t) g^x, \tag{6}$$

whose derivatives correspond to various moments of interest. In fact, knowing the generating function is equivalent to knowing  $P(x, t)$ , and its time evolution is described by a PDE analogous to the CME:

$$\frac{\partial \psi(g, t)}{\partial t} = k(t)[g - 1]\psi(g, t) - \gamma(t)[g - 1]\frac{\partial \psi(g, t)}{\partial g}. \tag{7}$$

The initial condition corresponding to  $P(x, t_0) = \delta(x - \xi)$  is  $\psi(g, t_0) = g^\xi$ , as can be verified using the definition of  $\psi$ . We can also take its long time limit, which we will denote by  $\psi_{ss}(g)$ .

The main result for the chemical birth-death process is the following.

**Theorem 1** (Chemical birth-death process) *Consider the system described by Eq. 2 (and Eq. 7). Let  $\lambda(t)$  and  $w(t)$  be the solutions of*

$$\begin{aligned} \dot{\lambda} &= k - \gamma\lambda, \quad \lambda(t_0) = 0 \\ \dot{w} &= -\gamma w, \quad w(t_0) = 1. \end{aligned} \tag{8}$$

Then if  $P(x, t_0) = \delta(x - \xi)$  for some  $\xi \in \mathbb{N}$ , we have:

(i)

$$P(x, t; \xi, t_0) = \sum_{k=0}^{\min(x, \xi)} \frac{\lambda(t)^{x-k} e^{-\lambda(t)}}{(x - k)!} \binom{\xi}{k} w(t)^k [1 - w(t)]^{\xi - k} \tag{9}$$

(ii)

$$\langle x(t) \rangle = \xi w(t) + \lambda(t) \tag{10}$$

(iii)

$$\langle x(t)[x(t) - 1] \rangle = w(t)^2 \xi (\xi - 1) + 2\lambda(t)w(t)\xi + \lambda(t)^2 \tag{11}$$

(iv)

$$\psi(g, t) = [1 + (g - 1)w(t)]^\xi e^{(g-1)\lambda(t)} \tag{12}$$

All results can be obtained independently of one another using the Doi-Peliti approach described in the following sections. Alternatively, one can verify directly that  $P(x, t; \xi, t_0)$  satisfies Eq. 2 or that  $\psi(g, t)$  satisfies Eq. 7, and then obtain the rest of the results by brute force calculation.

These results simplify tremendously in the long time limit if  $k$  and  $\gamma$  are time-independent, essentially because  $P(x, t)$  reduces to a Poisson distribution regardless of one's choice of initial distribution  $P(x, t_0)$ .

**Corollary 1** (Long time behavior of chemical birth-death process) *Let  $k$  and  $\gamma$  be time-independent, and define  $\mu := k/\gamma$ . In the long time limit, we have:*

$$(i) \quad P_{ss}(x) = \frac{\mu^x e^{-\mu}}{x!} \quad (13)$$

$$(ii) \quad \langle x \rangle = \mu \quad (14)$$

$$(iii) \quad \langle x[x-1] \rangle = \mu^2 \quad (15)$$

$$(iv) \quad \psi_{ss}(g) = e^{(g-1)\mu} \quad (16)$$

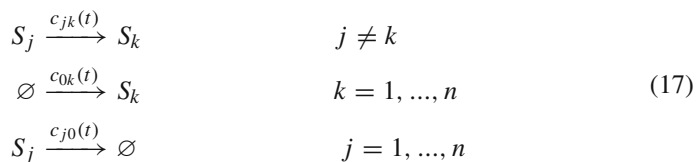
This follows from taking the  $t \rightarrow \infty$  limit of the previous results, since  $w(t) \rightarrow 0$  and  $\lambda(t) \rightarrow \mu$ .

Results on the chemical birth-death process are far from new. Still, we ask the reader to keep these results in the back of their mind as we go on to discuss the analogous results for more complicated systems. Because the chemical birth-death process is so fundamental, more complicated results often reduce to these in the appropriate limit.

## 2.2 Monomolecular results

Heuristically, monomolecular reaction systems are the minimal multi-species generalization of the chemical birth-death process. Like the chemical birth-death process, they exhibit a certain kind of linearity; we will see that their solutions are completely determined by a system of linear ordinary differential equations (ODEs).

Let us define them. Consider a system with  $n$  chemical species  $S_1, \dots, S_n$ , whose reaction list reads



i.e. all possible monomolecular reactions (birth, death, and conversion) are allowed<sup>3</sup>. Note that the rates are allowed to have arbitrary time-dependence as long as  $0 \leq$

<sup>3</sup> The one exception is the trivial conversion reaction  $S_k \rightarrow S_k$ , which is disallowed because including it would be pointless. To ease notation (i.e. to avoid writing  $j \neq k$  many times), we follow Jahnke and Huisinga and define  $c_{kk} := 0$  for all  $k = 1, \dots, n$ .

$c_{jk}(t) < \infty$  for all  $j, k$  and all times  $t \geq t_0$ . The corresponding CME reads

$$\begin{aligned} \frac{\partial P(\mathbf{x}, t)}{\partial t} &= \sum_{k=1}^n c_{0k}(t) [P(\mathbf{x} - \boldsymbol{\epsilon}_k, t) - P(\mathbf{x}, t)] \\ &+ \sum_{k=1}^n c_{k0}(t) [(x_k + 1)P(\mathbf{x} + \boldsymbol{\epsilon}_k, t) - x_k P(\mathbf{x}, t)] \\ &+ \sum_{j=1}^n \sum_{k=1}^n c_{jk}(t) [(x_j + 1)P(\mathbf{x} + \boldsymbol{\epsilon}_j - \boldsymbol{\epsilon}_k, t) - x_j P(\mathbf{x}, t)] \end{aligned} \tag{18}$$

where  $P(\mathbf{x}, t)$  is the probability that the state of the system is  $\mathbf{x} := (x_1, \dots, x_n)^T \in \mathbb{N}^n$  at time  $t \geq t_0$ , and where  $\boldsymbol{\epsilon}_k$  is the  $n$ -dimensional vector with a 1 in the  $k$ th place and zeros everywhere else.

The exact solution to Eq. 18, given the initial condition  $P(\mathbf{x}, t_0) = \delta(\mathbf{x} - \boldsymbol{\xi})$  for some vector  $\boldsymbol{\xi} := (\xi_1, \dots, \xi_n)^T \in \mathbb{N}^n$  (where  $\delta(\mathbf{z})$  is the multivariate generalization of the Kronecker delta function, which equals one if  $\mathbf{z} = \mathbf{0}$  and zero otherwise), is reported in Theorem 1 of Jahnke and Huisinga (2007). In order to state their solution, we will need some notation.

Define the matrix  $\mathbf{A}(t)$  and vector  $\mathbf{b}(t)$  by

$$\begin{aligned} A_{jk}(t) &:= c_{kj}(t) \text{ for } j \neq k \geq 1 \\ A_{kk}(t) &:= -\sum_{j=0}^n c_{kj}(t) \text{ for } 1 \leq k \leq n \\ \mathbf{b}(t) &:= (c_{01}(t) \ c_{02}(t) \ \dots \ c_{0n}(t))^T . \end{aligned} \tag{19}$$

The deterministic reaction rate equations corresponding to our reaction list can be written in terms of  $\mathbf{A}(t)$  and  $\mathbf{b}(t)$  as

$$\dot{\mathbf{x}} = \mathbf{A}(t)\mathbf{x} + \mathbf{b}(t) . \tag{20}$$

Because Eq. 20 is linear, the solution with initial condition  $\boldsymbol{\xi} = (\xi_1, \dots, \xi_n)$  can be written as

$$\mathbf{x}(t) = \sum_{k=1}^n \xi_k \mathbf{w}^{(k)}(t) + \boldsymbol{\lambda}(t) \tag{21}$$

where the vectors  $\mathbf{w}^{(1)}(t), \dots, \mathbf{w}^{(n)}(t)$  and  $\boldsymbol{\lambda}(t)$  are defined as

$$\begin{aligned} \dot{\mathbf{w}}^{(k)} &= \mathbf{A}(t)\mathbf{w}^{(k)} , \quad \mathbf{w}^{(k)}(t_0) = \boldsymbol{\epsilon}_k \\ \dot{\boldsymbol{\lambda}} &= \mathbf{A}(t)\boldsymbol{\lambda} + \mathbf{b}(t) , \quad \boldsymbol{\lambda}(t_0) = \mathbf{0} . \end{aligned} \tag{22}$$



As we will shortly observe, the solution to the deterministic reaction rate equations is intimately related to the solution of the CME (at least for monomolecular reactions).

Now define the 1-norm of a vector  $\mathbf{x}$  as

$$|\mathbf{x}| := \sum_{k=1}^n |x_k|. \tag{23}$$

Define, because they will appear throughout this paper, multi-dimensional generalizations of powers, factorials, sums, integrals, and derivatives:

$$\begin{aligned} \mathbf{v}^{\mathbf{x}} &:= v_1^{x_1} \cdots v_n^{x_n} \\ \mathbf{x}! &:= x_1! \cdots x_n! \\ \sum_{\mathbf{x}} &:= \sum_{x_1=0}^{\infty} \cdots \sum_{x_n=0}^{\infty} \\ \int d\mathbf{x} &:= \int dx_1 \cdots \int dx_n \\ \left(\frac{d}{d\mathbf{z}}\right)^{\mathbf{x}} &:= \left(\frac{d}{dz_1}\right)^{x_1} \cdots \left(\frac{d}{dz_n}\right)^{x_n}. \end{aligned} \tag{24}$$

Using the above shorthand, we can define the product Poisson distribution as

$$\mathcal{P}(\mathbf{x}, \boldsymbol{\lambda}) := \frac{\lambda_1^{x_1}}{x_1!} \cdots \frac{\lambda_n^{x_n}}{x_n!} e^{-|\boldsymbol{\lambda}|} = \frac{\boldsymbol{\lambda}^{\mathbf{x}}}{\mathbf{x}!} e^{-|\boldsymbol{\lambda}|}, \tag{25}$$

the multinomial distribution as

$$\begin{aligned} \mathcal{M}(\mathbf{x}, N, \mathbf{w}) &:= \frac{N! [1 - |\mathbf{w}|]^{N-|\mathbf{x}|}}{(N - |\mathbf{x}|)!} \frac{w_1^{x_1}}{x_1!} \cdots \frac{w_n^{x_n}}{x_n!} \text{ if } |\mathbf{x}| \leq N \text{ and } x \in \mathbb{N}^N \\ &= \frac{N! [1 - |\mathbf{w}|]^{N-|\mathbf{x}|}}{(N - |\mathbf{x}|)!} \frac{\mathbf{w}^{\mathbf{x}}}{\mathbf{x}!} \text{ if } |\mathbf{x}| \leq N \text{ and } x \in \mathbb{N}^N, \end{aligned} \tag{26}$$

and the convolution of two probability distributions as

$$P_1(\mathbf{x}) \star P_2(\mathbf{x}) := \sum_{\mathbf{z}} P_1(\mathbf{z}) P_2(\mathbf{x} - \mathbf{z}) = \sum_{\mathbf{z}} P_1(\mathbf{x} - \mathbf{z}) P_2(\mathbf{z}) \tag{27}$$

where the sum is over all  $\mathbf{z} \in \mathbb{N}^n$  such that  $\mathbf{x} - \mathbf{z} \in \mathbb{N}^n$ . As in the one-dimensional case, we can also define the probability generating function

$$\psi(\mathbf{g}, t) := \sum_{\mathbf{x}} P(\mathbf{x}, t) \mathbf{g}^{\mathbf{x}} \tag{28}$$

where  $\mathbf{g} \in \mathbb{C}^n$ , which satisfies the PDE

$$\begin{aligned} \frac{\partial \psi(\mathbf{g}, t)}{\partial t} &= \sum_{k=1}^n c_{0k}(t) [g_k - 1] \psi(\mathbf{g}, t) \\ &\quad - \sum_{k=1}^n c_{k0}(t) [g_k - 1] \frac{\partial \psi(\mathbf{g}, t)}{\partial g_k} \\ &\quad + \sum_{j=1}^n \sum_{k=1}^n c_{jk}(t) [g_k - g_j] \frac{\partial \psi(\mathbf{g}, t)}{\partial g_j}. \end{aligned} \tag{29}$$

With all of that notation defined, we are ready to state the main result for monomolecular reaction systems, which was originally proved by Jahnke and Huisinga<sup>4</sup>.

**Theorem 2 (Jahnke-Huisinga monomolecular)** Consider the system described by Eq. 18 (and Eq. 29). Let  $\lambda(t)$  and  $\mathbf{w}(t)$  be the solutions of

$$\begin{aligned} \dot{\lambda} &= \mathbf{A}(t)\lambda + \mathbf{b}(t), \quad \lambda(t_0) = \mathbf{0} \\ \dot{\mathbf{w}}^{(k)} &= \mathbf{A}(t)\mathbf{w}^{(k)}, \quad \mathbf{w}^{(k)}(t_0) = \boldsymbol{\epsilon}_k. \end{aligned} \tag{30}$$

Then if  $P(\mathbf{x}, t_0) = \delta(\mathbf{x} - \boldsymbol{\xi})$  for some  $\boldsymbol{\xi} \in \mathbb{N}^n$ , we have:

(i)  $P(\mathbf{x}, t; \boldsymbol{\xi}, t_0) = \mathcal{P}(\mathbf{x}, \lambda(t)) \star \mathcal{M}(\mathbf{x}, \xi_1, \mathbf{w}^{(1)}(t)) \star \dots \star \mathcal{M}(\mathbf{x}, \xi_n, \mathbf{w}^{(n)}(t))$  (31)

(ii)  $\langle x_j(t) \rangle = \sum_{k=1}^n \xi_k w_j^{(k)}(t) + \lambda_j(t)$  (32)

(iii)  $\text{Cov}(x_j, x_\ell) = \begin{cases} \sum_{k=1}^n \xi_k w_j^{(k)} [1 - w_j^{(k)}] + \lambda_j & j = \ell \\ - \sum_{k=1}^n \xi_k w_j^{(k)} w_\ell^{(k)} & j \neq \ell \end{cases}$  (33)

(iv)  $\psi(\mathbf{g}, t) = \prod_{k=1}^n [1 + (\mathbf{g} - \mathbf{1}) \cdot \mathbf{w}^{(k)}(t)]^{\xi_k} e^{(\mathbf{g}-\mathbf{1}) \cdot \lambda(t)}$  (34)

All results can be obtained independently of one another using the Doi-Peliti approach described in the following sections. Alternatively, one can verify directly that  $P(\mathbf{x}, t; \boldsymbol{\xi}, t_0)$  satisfies Eq. 18 or that  $\psi(\mathbf{g}, t)$  satisfies Eq. 29 with the correct initial condition, and then obtain the rest of the results by brute force calculation.

### 2.3 Birth-death-autocatalysis results

In Sect. 6 of their classic paper (Jahnke and Huisinga 2007), Jahnke and Huisinga solve the CME corresponding to the autocatalytic reaction  $S \rightarrow S + S$  exactly; however,

<sup>4</sup> The generating function was not directly computed by them, but is essentially trivial to compute given their results.

they note that adding birth and death reactions yields a system not amenable to their approach. In this section, we present the exact time-dependent solution to this problem, whose reactions read



where the parameters controlling the rates of birth, death, and autocatalysis are all allowed to have arbitrary time-dependence as long as they are nonnegative and finite for all times. The CME reads

$$\begin{aligned}
 \frac{\partial P(x, t)}{\partial t} &= k(t) [P(x - 1, t) - P(x, t)] \\
 &\quad + \gamma(t) [(x + 1)P(x + 1, t) - xP(x, t)] \\
 &\quad + c(t) [(x - 1)P(x - 1, t) - xP(x, t)]
 \end{aligned}
 \tag{36}$$

where  $P(x, t)$  is the probability that the state of the system is  $x \in \mathbb{N}$  at time  $t \geq t_0$ . Meanwhile, the PDE satisfied by the probability generating function  $\psi$  reads

$$\begin{aligned}
 \frac{\partial \psi(g, t)}{\partial t} &= k(t)[g - 1]\psi(g, t) - \gamma(t)[g - 1] \frac{\partial \psi(g, t)}{\partial g} \\
 &\quad + c(t)[g - 1]g \frac{\partial \psi(g, t)}{\partial g}.
 \end{aligned}
 \tag{37}$$

Our main result on the solution of this system is the following.

**Theorem 3** (Birth-death-autocatalysis) *Consider the system described by Eq. 36 (and Eq. 37). Let  $q(s)$  and  $w(s)$  be the solutions of*

$$\begin{aligned}
 \frac{dq(s)}{ds} &= [c(t - s + t_0) - \gamma(t - s + t_0)]q(s) + ic(t - s + t_0)q(s)^2, \quad q(t_0) = p_f \\
 \frac{dw(s)}{ds} &= [c(t - s + t_0) - \gamma(t - s + t_0)]w(s), \quad w(t_0) = 1
 \end{aligned}
 \tag{38}$$

for arbitrary  $p_f \in \mathbb{R}$  and  $s \in [t_0, t]$ , where  $i$  denotes the imaginary unit.  $q(s)$  and  $w(s)$  can be explicitly written as

$$\begin{aligned}
 q(s) &= \frac{w(s)}{\frac{1}{p_f} - i \int_{t_0}^s c(t - t' + t_0)w(t') dt'} \\
 w(s) &= e^{\int_{t_0}^s c(t - t' + t_0) - \gamma(t - t' + t_0) dt'}.
 \end{aligned}
 \tag{39}$$

Then if  $P(x, t_0) = \delta(x - \xi)$  for some  $\xi \in \mathbb{N}$ , we have:

$$\begin{aligned}
 P(x, t; \xi, t_0) &= \frac{1}{2\pi} \int_{-\infty}^{\infty} dp_f \frac{[1 + iq(t)]^\xi e^{i \int_{t_0}^t k(t-s+t_0)q(s)ds}}{(1 + ip_f)^{x+1}} \\
 \psi(g, t) &= \left[ 1 + \frac{w(t)}{\frac{1}{g-1} - \int_{t_0}^t c(t-t'+t_0)w(t') dt'} \right]^\xi \times \\
 &\quad \times \exp \left\{ \int_{t_0}^t \frac{k(t-s+t_0)w(s)}{\frac{1}{g-1} - \int_{t_0}^s c(t-t'+t_0)w(t') dt'} ds \right\}.
 \end{aligned} \tag{40}$$

Moreover, if the parameters  $k$ ,  $\gamma$ , and  $c$  are all time-independent and non-zero, the function  $w(s)$  is explicitly

$$w(s) = e^{(c-\gamma)(s-t_0)} \tag{41}$$

and the transition probability can be rewritten as

$$\begin{aligned}
 P(x, t; \xi, t_0) &= \left[ \frac{\frac{\gamma}{c} - 1}{\frac{\gamma}{c} - w(t)} \right]^{k/c} \frac{[1 - w(t)]^{x-\xi}}{\left[ \frac{\gamma}{c} - w(t) \right]^x} \times \\
 &\quad \times \sum_{j=0}^{\xi} \binom{\xi}{j} \frac{(j + k/c)_x}{x!} \left[ 1 - \frac{\gamma}{c} w(t) \right]^{\xi-j} \left[ \frac{w(t) \left( \frac{\gamma}{c} - 1 \right)^2}{\frac{\gamma}{c} - w(t)} \right]^j
 \end{aligned} \tag{42}$$

where  $(y)_x := (y)(y + 1) \cdots (y + x - 1)$  is the Pochhammer symbol/rising factorial. The generating function in this case reduces to

$$\psi(g, t) = \left[ \frac{1 + (g - 1) \frac{c-\gamma w(t)}{c-\gamma}}{1 - (g - 1) \frac{c(w(t)-1)}{c-\gamma}} \right]^\xi \frac{1}{\left[ 1 - (g - 1) \frac{c(w(t)-1)}{c-\gamma} \right]^{k/c}}. \tag{43}$$

Note that the ODEs that appear here are more complicated than the ODEs that appear in the solution of the monomolecular problem (c.f. Eqs. 8 and 30) in at least two ways: the time-dependence of the coefficients is in the opposite direction of the time-dependence of the ODE solution (e.g.  $c(t - s + t_0)$  versus  $q(s)$ ), and one of the ODEs here is nonlinear. This indicates that adding the autocatalytic reaction to the birth-death system greatly increases the complexity of the dynamics.

The transition probability and probability generating function can be obtained independently of one another using the Doi-Peliti approach described in the following sections. Alternatively, one can verify directly that the probability generating function solves Eq. 37, and use the definition of the generating function to find the transition probability. Because the expression for the transition probability is somewhat complicated, verifying it directly is not recommended.

Interestingly, when  $\xi = 0$  the time-dependent result above reduces to a negative binomial distribution

$$P(x, t; 0, t_0) = \frac{(k/c)_x}{x!} (1-p)^r p^x \quad (44)$$

with

$$p := \frac{1-w(t)}{\frac{\gamma}{c}-w(t)} \quad r := \frac{k}{c}, \quad (45)$$

which mirrors the well-known result that the time-dependent solution of the birth-death process reduces to a Poisson distribution with a time-dependent mean when  $\xi = 0$ .

It is expected that this solution reduces to familiar distributions in certain limits; in particular, as Jahnke and Huisinga originally point out, it should interpolate between a binomial distribution, a Poisson distribution, and a negative binomial distribution. Indeed it does, with these special cases corresponding to the  $k = c = 0$  (pure death),  $\gamma = c = 0$  (pure birth), and  $k = \gamma = 0$  (pure autocatalysis) limits, respectively. We formalize this in the following corollary.

**Corollary 2** (*Limiting behavior of the birth-death-autocatalysis transition probability*)  
The transition probability  $P(x, t; x_0, t_0)$  becomes (i) binomial in the limit that  $k \rightarrow 0$  and  $c \rightarrow 0$ , (ii) Poisson in the limit that  $\gamma \rightarrow 0$  and  $c \rightarrow 0$ , and (iii) negative binomial in the limit that  $k \rightarrow 0$  and  $\gamma \rightarrow 0$ . That is,

$$\lim_{k,c \rightarrow 0} P(x, t; x_0, t_0) = \binom{\xi}{x} [w(t)]^x [1-w(t)]^{\xi-x} \quad (46)$$

for  $x \leq \xi$  and 0 otherwise, i.e. a binomial distribution;

$$\lim_{\gamma,c \rightarrow 0} P(x, t; x_0, t_0) = \frac{\lambda(t)^{x-\xi} e^{-\lambda(t)}}{(x-\xi)!} \quad (47)$$

for  $x \geq \xi$  and 0 otherwise, i.e. a (shifted) Poisson distribution; and

$$\lim_{k,\gamma \rightarrow 0} P(x, t; x_0, t_0) = \binom{x-1}{\xi-1} [w(t)]^\xi [1-w(t)]^{x-\xi} \quad (48)$$

which is nonzero only for  $x \geq \xi$ , i.e. a (shifted) negative binomial distribution.

These limits can be taken directly, and are relatively straightforward; see Sect. 5 for the calculations.

It is also true that the solution of this problem reduces to a birth-death process in the  $c \rightarrow 0$  limit (i.e. the limit in which autocatalysis no longer happens). This is easiest

to show using the generating function (Eq. 43), along with the identities

$$\begin{aligned} \lim_{c \rightarrow 0} \frac{1 + (g - 1) \frac{c - \gamma w(t)}{c - \gamma}}{1 - (g - 1) \frac{c(w(t) - 1)}{c - \gamma}} &= 1 + (g - 1)e^{-\gamma(t-t_0)} \\ \lim_{c \rightarrow 0} \left[ 1 - (g - 1) \frac{c(w(t) - 1)}{c - \gamma} \right]^{-k/c} &= e^{\frac{k}{\gamma}(g-1)[1-e^{-\gamma(t-t_0)}]}. \end{aligned} \tag{49}$$

If the autocatalytic reaction tends to occur more frequently than the degradation reaction (i.e. if  $c > \gamma$ ), the number of molecules almost surely blows up to infinity in the long time limit. However, if degradation tends to overtake autocatalysis (i.e. if  $\gamma > c$ ), then the steady state distribution exists and is nontrivial.

**Corollary 3** (Long time behavior of birth-death-autocatalysis) *Let  $k$ ,  $\gamma$ , and  $c$  be time-independent, and suppose that  $\gamma > c$ . In the long time limit, we have:*

$$\begin{aligned} P_{ss}(x) &= \left(\frac{\gamma - c}{\gamma}\right)^{k/c} \frac{\left(\frac{c}{\gamma}\right)^x}{x!} \left(\frac{k}{c}\right)_x \\ &= \left(\frac{\gamma - c}{\gamma}\right)^{k/c} \frac{\left(\frac{c}{\gamma}\right) \cdots \left(\frac{c}{\gamma}\right)}{x!} \left(\frac{k}{c}\right) \cdots \left(\frac{k}{c} + x - 1\right) \\ \psi_{ss}(g) &= \left(\frac{\gamma - c}{\gamma}\right)^{k/c} \frac{1}{\left[1 - \frac{cg}{\gamma}\right]^{k/c}} \\ \langle x \rangle &= \frac{k}{\gamma - c} \\ \text{var}(x) &= \frac{k}{\gamma} \frac{1}{(1 - c/\gamma)^2}. \end{aligned} \tag{50}$$

Moreover, these reduce to the  $P_{ss}$  and  $\psi_{ss}$  for the chemical birth-death process in the  $c \rightarrow 0$  limit, i.e.

$$\begin{aligned} \left(\frac{\gamma - c}{\gamma}\right)^{k/c} \frac{\left(\frac{c}{\gamma}\right)^x}{x!} \left(\frac{k}{c}\right)_x &\rightarrow \frac{\mu^x}{x!} e^{-\mu} \\ \left(\frac{\gamma - c}{\gamma}\right)^{k/c} \frac{1}{\left[1 - \frac{cg}{\gamma}\right]^{k/c}} &\rightarrow e^{(g-1)\mu} \\ \frac{k}{\gamma - c} &\rightarrow \frac{k}{\gamma} \\ \frac{k}{\gamma} \frac{1}{(1 - c/\gamma)^2} &\rightarrow \frac{k}{\gamma}. \end{aligned} \tag{51}$$

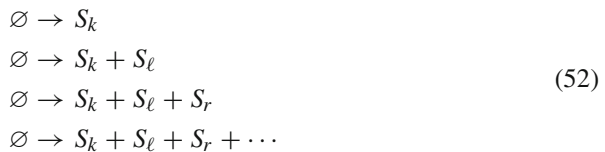
The simplest way to find  $P_{ss}$  is to solve the steady state CME directly (i.e. set  $\partial P/\partial t = 0$  and solve the resulting recurrence relation). Alternatively, noting that  $w \rightarrow 0$ , one

can straightforwardly take the  $t \rightarrow \infty$  limit of our result from Theorem 3. The  $c \rightarrow 0$  is also easy to take. Computing moments is most easily done by taking derivatives of  $\psi_{ss}(g)$ .

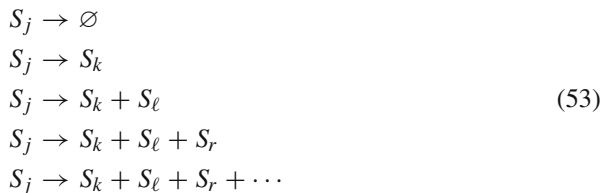
## 2.4 Zero and first order reactions

While obtaining the solution to the birth-death-autocatalysis system is certainly interesting, the problem itself is quite special: it is one-dimensional, and involves only three chemical reactions. What else can the Doi-Peliti approach be used to solve? What kind of sets of chemical reactions are tractable?

The full potential of the Doi-Peliti approach is not clear. As a partial answer to this question, however, we offer a result of somewhat shocking generality: a formal solution to the CME of any system whose reaction list only contains zero and first order reactions. By zero order reactions, we mean reactions like



and so on, i.e. reactions requiring no molecules as input. By first order reactions, we mean reactions like



and so on, i.e. reactions requiring exactly one molecule as input. The time-dependence of each rate is assumed to be arbitrary as long as rates are nonnegative and finite for all times. The birth reactions described in the previous sections are examples of zero order reactions, while the death and conversion reactions are examples of first order reactions. Other biologically relevant examples of first order reactions include catalytic production ( $S_j \rightarrow S_j + S_k$ ,  $j \neq k$ ) and splitting ( $S_j \rightarrow S_k + S_\ell$ ,  $j \neq k$ ,  $j \neq \ell$ ).

The list of all possible zero and first order reactions also includes many reactions that are almost certainly *not* biologically relevant—at least for mechanistic models of interacting molecules whose reactions can all be directly justified via an appeal to the physics of molecular collisions<sup>5</sup>. For example, the reaction where one molecule splits into *exactly* one hundred molecules with no intermediate splitting is first order. Of course, reactions more complicated than bimolecular may nonetheless be useful

<sup>5</sup> As notes (Gillespie 2000), such systems involve reactions that are at most bimolecular (at most two input molecules, and at most two output molecules).

and important for constructing effective models of various biological and chemical systems.

The CME of this system is somewhat tedious to write down, so we will instead note that the PDE satisfied by the generating function can be written in the form

$$\begin{aligned} \frac{\partial \psi(\mathbf{g}, t)}{\partial t} = & \sum_{\kappa_1, \dots, \kappa_n} \alpha_{\kappa_1, \dots, \kappa_n}(t) (g_1 - 1)^{\kappa_1} \dots (g_n - 1)^{\kappa_n} \psi(\mathbf{g}, t) \\ & + \sum_{k=1}^n \sum_{\kappa_1, \dots, \kappa_n} \beta_{\kappa_1, \dots, \kappa_n}^k(t) (g_1 - 1)^{\kappa_1} \dots (g_n - 1)^{\kappa_n} \frac{\partial \psi(\mathbf{g}, t)}{\partial g_k} \end{aligned} \tag{54}$$

where the precise form of the coefficients  $\alpha_{\kappa_1, \dots, \kappa_n}(t)$  and  $\beta_{\kappa_1, \dots, \kappa_n}^k(t)$  are determined by the details of one's list of reactions. The  $\kappa_1$  through  $\kappa_n$  should be thought of as indexing the various powers of  $(g_j - 1)$  that appear. Our main result for this class of systems is the following.

**Theorem 4** (*Arbitrary combinations of zero and first order reactions*) Consider the system described by Eq. 54. Let  $\mathbf{q}(s) = (q_1(s), \dots, q_n(s)) \in \mathbb{C}^n$  be the solution of the 'auxiliary ODEs'

$$\frac{dq_j(s)}{ds} = -i \sum_{\kappa_1, \dots, \kappa_n} \beta_{\kappa_1, \dots, \kappa_n}^j(t - s + t_0) [iq_1(s)]^{\kappa_1} \dots [iq_n(s)]^{\kappa_n}, \quad q_j(t_0) = p_j^f \tag{55}$$

for some  $\mathbf{p}^f \in \mathbb{C}^n$ , with  $s \in [t_0, t]$ . Then if  $P(\mathbf{x}, t_0) = \delta(\mathbf{x} - \boldsymbol{\xi})$  for some  $\boldsymbol{\xi} \in \mathbb{N}^n$ , we have

$$P = \int_{\mathbb{R}^n} \frac{d\mathbf{p}^f}{(2\pi)^n} \frac{[\mathbf{1} + i\mathbf{q}(t)]^{\boldsymbol{\xi}} e^{i\int_{t_0}^t \sum \alpha_{\kappa_1, \dots, \kappa_n}(t-s+t_0) [iq_1(s)]^{\kappa_1} \dots [iq_n(s)]^{\kappa_n} ds}}{(\mathbf{1} + i\mathbf{p}^f)^{\mathbf{x}+1}} \tag{56}$$

for the transition probability, and

$$\begin{aligned} \psi(\mathbf{g}, t) = & [\mathbf{1} + i\mathbf{q}(t)]^{\boldsymbol{\xi}} \times \\ & \times \left. e^{i\int_{t_0}^t \sum \alpha_{\kappa_1, \dots, \kappa_n}(t-s+t_0) [iq_1(s)]^{\kappa_1} \dots [iq_n(s)]^{\kappa_n} ds} \right|_{\mathbf{p}^f = -i(\mathbf{g}-1)} \end{aligned} \tag{57}$$

for the probability generating function.

Computing the generating function involves computing a contour integral whose integrand has a simple pole at  $-i(\mathbf{g} - \mathbf{1})$ . This is why we set  $\mathbf{p}^f$  (as an argument of the integrand) equal to complex values in Eq. 57, even though (as an integration variable) we have  $\mathbf{p}^f \in \mathbb{R}^n$  in Eq. 56.

In principle, Theorem 4 could be justified by directly substituting  $P$  or  $\psi$  into the relevant equations. A less cumbersome way to justify it, which is not reliant on Doi-Peliti theory, is discussed in Appendix E. In some sense, all other results in this paper



are corollaries of this result. But it is helpful to study the simpler cases in their own right, both to double-check the correctness of this more general result, and to develop a sense for how to derive these solutions.

While this result is shockingly general, it also appears to be incredibly formal. Is reducing the problem of solving the CME (an infinite number of coupled linear ODEs) to the problem of solving  $n$  (where  $n$  is the number of chemical species) coupled nonlinear ODEs much of an improvement? Perhaps surprisingly, the answer often seems to be yes. In the next two subsections, we will show why by considering a few example systems.

Interestingly, the degree of nonlinearity that appears in the auxiliary ODEs above depends upon a product of output molecule stoichiometries (for example:  $S \rightarrow S + S$  yields a  $q^2$  nonlinearity because there are two output molecules). Nonlinearities in the corresponding reaction rate equations depend instead on a product of input stoichiometries—and hence the reaction rate equations are linear for this class of systems.

## 2.5 Some theoretical consequences of the general result

### 2.5.1 Solution to a nonlinear problem involving a single species

Consider the one species system whose reaction list consists of



for some integer  $n > 0$  and  $m \neq 1$ . We have seen a few special cases already: the case  $n = 1$  and  $m = 0$  corresponds to the birth-death process; the case  $n = 1$  and  $m = 2$  corresponds to the birth-autocatalysis process (which can be obtained from our birth-death-autocatalysis result by taking the death rate to zero); and other previously seen special cases (e.g. pure birth, pure death, and pure autocatalysis) follow from taking either  $k \rightarrow 0$  or  $\gamma \rightarrow 0$ . The CME for this system reads

$$\begin{aligned} \frac{\partial P(x, t)}{\partial t} &= k [P(x - n, t) - P(x, t)] \\ &+ \gamma [(x + 1 - m)P(x + 1 - m, t) - xP(x, t)] . \end{aligned} \quad (59)$$

This is one of the simplest nontrivial examples of a system where one expects to run into difficulties with applying Theorem 4; using it, we obtain a solution in terms of highly nonlinear ODEs. In particular (taking  $w(s) := iq(s) + 1$  for convenience), we have to solve the auxiliary ODE

$$\frac{dw(s)}{ds} = \gamma [w(s)^m - w(s)] . \quad (60)$$

Suppose we are interesting in computing the generating function  $\psi(g, t)$ . For simplicity, we will take  $\xi = 0$  and  $t_0 = 0$  and assume time-independent  $k$  and  $\gamma$  (this does not affect our ability to get results, but does slightly affect the compactness of the answer). Then our initial condition is  $w(0) = g$ . In terms of  $w(s)$ , the full solution is

$$\log \psi(g, t) = k \int_0^t [w(s)^n - 1] ds . \tag{61}$$

Can a highly nonlinear problem like this be solved using Theorem 4? It turns out that the answer is yes.

**Corollary 4** (*Nonlinear one species system solution*) Consider the system described by Eq. 59, and assume  $P(x, 0) = \delta(x)$  (i.e. there are initially no molecules in the system). Define

$$r := \frac{n}{1 - m}$$

$$f(g, t) := \left(\frac{e^{\gamma t}}{g}\right)^{m-1} + 1 - e^{\gamma(m-1)t} . \tag{62}$$

Then the probability generating function is given by

$$\log \psi(g, t) = k \int_0^t \{ [f(g, s)]^r - 1 \} ds . \tag{63}$$

Moreover, this integral can be evaluated explicitly. If  $g = 1$ ,  $\log \psi = 0$ . If  $n = m - 1$  and  $g \neq 1$ , the probability generating function is

$$\psi(g, t) = \left[ e^{\gamma(m-1)t} + g^{m-1} \left( 1 - e^{\gamma(m-1)t} \right) \right]^{-\frac{k}{\gamma(m-1)}} . \tag{64}$$

Otherwise, for  $n \neq m - 1$  and  $g \neq 1$ , the probability generating function is

$$\log \psi(g, t) = -k t + \frac{k}{\gamma} \frac{f(g, t)^{r+1}}{n - m + 1} {}_2F_1(1, r + 1; r + 2; f(g, t))$$

$$- \frac{k}{\gamma} \frac{g^{n-m+1}}{n - m + 1} {}_2F_1(1, r + 1; r + 2; g^{1-m}) \tag{65}$$

where  ${}_2F_1$  denotes the ordinary hypergeometric function. We can also derive the time-dependent mean

$$\langle x(t) \rangle = \frac{kn}{\gamma(1 - m)} \left[ 1 - e^{(m-1)\gamma t} \right] \tag{66}$$

and time-dependent variance, which equals

$$\text{var}(x(t)) = \langle x(t)^2 \rangle - \langle x(t) \rangle^2 = \frac{k}{\gamma} \left[ 1 - e^{-\gamma t} \right] \tag{67}$$

if  $r = 1$ , and

$$\text{var}(x(t)) = \frac{kn(1-r)}{2\gamma} \left[ \left( e^{(m-1)\gamma t} - \frac{1}{1-r} \right)^2 - \left( 1 - \frac{1}{1-r} \right)^2 \right] \tag{68}$$

otherwise.

**Proof** The relevant ODE (Eq. 60) is separable; solving in the standard way, we obtain

$$w(s) = f(g, s)^{1/(1-m)}. \tag{69}$$

Now we have

$$\log \psi(g, t) = k \int_0^t \{ [f(g, s)]^r - 1 \} ds. \tag{70}$$

The nontrivial part of this integral (for  $g \neq 1$ ) is of the form

$$\int_0^t [1 + Ae^{Bs}]^r ds \tag{71}$$

for appropriate  $A$  and  $B$ ; this integral is equal to

$$t - \frac{1}{B} \log \left( \frac{1 + Ae^{Bt}}{1 + A} \right) \tag{72}$$

if  $r = -1$ , and

$$\begin{aligned} & -\frac{(1 + Ae^{Bt})^{r+1}}{B(r+1)} {}_2F_1(1, r+1; r+2; 1 + Ae^{Bt}) \\ & + \frac{(1 + A)^{r+1}}{B(r+1)} {}_2F_1(1, r+1; r+2; 1 + A) \end{aligned} \tag{73}$$

otherwise. Carrying out these integrals yields the generating function answers above. Moments are most easily computed by taking derivatives of Eq. 63 directly. For example,

$$\begin{aligned} \langle x(t) \rangle &= \left. \frac{\partial [\log \psi]}{\partial g} \right|_{g=1} \\ &= kn \int_0^t e^{\gamma(m-1)s} ds \\ &= \frac{kn}{\gamma(1-m)} [1 - e^{(m-1)\gamma t}]. \end{aligned} \tag{74}$$

□

On the other hand, it should be noted that the system described by Eq. 59 is very special, and that although Eq. 60 is indeed nonlinear, it is an unusually tractable nonlinear ODE. Modifying the reaction list (Eq. 58) by doing something as simple as adding a degradation reaction ( $S \rightarrow \emptyset$ ) yields a problem that may not have a ‘nice’ closed form solution at all.

In other words, being able to obtain explicit generating function results (especially time-dependent results rather than stationary results) is the exception rather than the norm. For ‘most’ CMEs, even with only one chemical species, this appears to be extremely challenging or impossible. This seems to be true whether or not one is using the Doi-Peliti approach to derive solutions.

### 2.5.2 Stationary solution of the two-stage model of protein synthesis

One nontrivial and biologically important class of systems covered by this result is all systems involving gene switching and/or protein dynamics. The most well-studied CME involving proteins is the so-called two-stage model, involving two species (one kind of mRNA and one kind of protein) and four reactions (transcription, translation, mRNA degradation, and protein degradation). The reaction list is given by



and the corresponding CME is

$$\begin{aligned}
 \frac{\partial P(m, p, t)}{\partial t} &= \alpha_m [P(m - 1, p, t) - P(m, p, t)] \\
 &\quad + \alpha_p m [P(m, p - 1, t) - P(m, p, t)] \\
 &\quad + \gamma_m [(m + 1)P(m + 1, p, t) - mP(m, p, t)] \\
 &\quad + \gamma_p [(p + 1)P(m, p + 1, t) - pP(m, p, t)] .
 \end{aligned}
 \tag{76}$$

Note that we are using the symbol  $m$  here to denote mRNA counts, whereas we used  $m$  to denote a stoichiometric coefficient in the previous example.

Although a problem like this looks innocuous, it is known to be somewhat difficult to solve. The steady state solution was first computed by Bokes et al. (2012), and the time-dependent solution was first given by Pendar et al. (2013). To showcase the ability of Theorem 4 to deal with problems like this, we will show how it can be used to straightforwardly obtain the steady state solution  $P_{ss}(m, p)$  of Eq. 76.

**Corollary 5** (*Two-stage model steady state solution*) Consider the system described by Eq. 76. Define  $G_m := g_m - 1$  and  $G_p := g_p - 1$  to ease notation. The steady state

probability generating function, which is defined to be

$$\psi_{ss}(g_m, g_p) = \sum_{m=0}^{\infty} \sum_{p=0}^{\infty} P_{ss}(m, p) (g_m)^m (g_p)^p, \quad (77)$$

is given by

$$\log \psi_{ss}(g_m, g_p) = \frac{\alpha_m}{\gamma_m} \sum_{n=0}^{\infty} \sum_{r=0}^{\infty} \frac{(-1)^n \left(\frac{\alpha_p}{\gamma_p} G_p\right)^{n+r}}{n!r! [1 + n(\gamma_p/\gamma_m)]} \left[ \frac{\frac{\alpha_p}{\gamma_p} G_p}{n+r+1} + G_m \right]. \quad (78)$$

Using it, we can compute moments like

$$\begin{aligned} \langle m \rangle &= \frac{\alpha_m}{\gamma_m} \\ \langle p \rangle &= \frac{\alpha_m \alpha_p}{\gamma_m \gamma_p} \\ \text{var}(m) - \langle m \rangle &= 0 \\ \text{var}(p) - \langle p \rangle &= \frac{\alpha_m}{\gamma_m} \left(\frac{\alpha_p}{\gamma_p}\right)^2 \frac{\gamma_p}{\gamma_m + \gamma_p} \\ \text{Cov}(m, p) &= \frac{\alpha_m \alpha_p}{\gamma_m \gamma_p} \frac{\gamma_p}{\gamma_m + \gamma_p}. \end{aligned} \quad (79)$$

**Proof** The relevant auxiliary ODEs are given by (where we have relabeled  $i q_1$  and  $i q_2$  to  $m$  and  $p$  for better intuition)

$$\begin{aligned} \frac{dm(s)}{ds} &= -\gamma_m m(s) + \alpha_p p(s) [1 + m(s)] \\ \frac{dp(s)}{ds} &= -\gamma_p p(s) \end{aligned} \quad (80)$$

where in this case (since we are interested in the steady state generating function) we have  $m(0) = G_m$  and  $p(0) = G_p$ . Trivially, we have

$$p(s) = G_p e^{-\gamma_p s} \quad (81)$$

which means  $m(s)$  satisfies

$$\frac{dm(s)}{ds} = -\gamma_m m(s) + \alpha_p G_p e^{-\gamma_p s} [1 + m(s)] \quad (82)$$

i.e. a linear first order ODE with time-dependent coefficients. Using the usual integrating factor method, we obtain

$$m(s) = G_m e^{-f(s)} + \alpha_p e^{-f(s)} \int_0^s p(u) e^{f(u)} du \quad (83)$$

where we define

$$f(s) := \gamma_m s - \frac{\alpha_p}{\gamma_p} G_p [1 - e^{-\gamma_p s}]. \tag{84}$$

This integral can be written more explicitly by Taylor expanding  $\exp(f(u))$ , and swapping the sum and integral. That is:

$$\begin{aligned} \int_0^s p(u)e^{f(u)} du &= G_p \int_0^s e^{-\gamma_p u} e^{\gamma_m u - \frac{\alpha_p}{\gamma_p} G_p [1 - e^{-\gamma_p u}]} du \\ &= G_p e^{-\frac{\alpha_p}{\gamma_p} G_p} \int_0^s e^{(\gamma_m - \gamma_p)u} e^{\frac{\alpha_p}{\gamma_p} G_p e^{-\gamma_p u}} du \\ &= G_p e^{-\frac{\alpha_p}{\gamma_p} G_p} \sum_{r=0}^{\infty} \frac{\left(\frac{\alpha_p}{\gamma_p} G_p\right)^r}{r!} \int_0^s e^{[\gamma_m - (r+1)\gamma_p]u} du \\ &= G_p e^{-\frac{\alpha_p}{\gamma_p} G_p} \sum_{r=0}^{\infty} \frac{\left(\frac{\alpha_p}{\gamma_p} G_p\right)^r}{r!} \frac{(e^{[\gamma_m - (r+1)\gamma_p]s} - 1)}{\gamma_m - (r+1)\gamma_p}. \end{aligned} \tag{85}$$

To make doing this expansion slightly more straightforward, we have assumed  $\gamma_m \neq \gamma_p$ ; this assumption does not affect the final result, where the  $\gamma_m \rightarrow \gamma_p$  limit can be harmlessly taken. We can also expand  $\exp(-f(s))$  outside of the integral:

$$e^{-f(s)} = \sum_{n=0}^{\infty} \sum_{r=0}^{\infty} \frac{(-1)^n \left(\frac{\alpha_p}{\gamma_p} G_p\right)^{n+r}}{n!r!} e^{-(\gamma_m + n\gamma_p)s}. \tag{86}$$

All together, we can write  $m(s)$  as

$$\begin{aligned} m(s) &= G_m \sum_{n=0}^{\infty} \sum_{r=0}^{\infty} \frac{(-1)^n \left(\frac{\alpha_p}{\gamma_p} G_p\right)^{n+r}}{n!r!} e^{-(\gamma_m + n\gamma_p)s} \\ &+ \alpha_p G_p \sum_{n=0}^{\infty} \sum_{r=0}^{\infty} \frac{(-1)^n \left(\frac{\alpha_p}{\gamma_p} G_p\right)^{n+r}}{n!r!} \frac{[e^{-(n+r+1)\gamma_p s} - e^{-(\gamma_m + n\gamma_p)s}]}{\gamma_m - (r+1)\gamma_p}. \end{aligned} \tag{87}$$

In terms of  $m(s)$ , the steady state generating function can be written

$$\log \psi_{ss}(g_m, g_p) = \alpha_m \int_0^{\infty} m(s) ds \tag{88}$$

where we have intentionally omitted the  $\xi$ -dependent factor. It does not contribute—and in fact, the steady state solution does not depend on the system’s initial condition (i.e.  $\delta(m - \xi_m)\delta(p - \xi_p)$  for some  $\xi_m, \xi_p \in \mathbb{N}$ ). This is because

$$[1 + m(\infty)]^{\xi_m} \cdot [1 + p(\infty)]^{\xi_p} = 1 \tag{89}$$

since  $m(\infty) = p(\infty) = 0$ . Evaluating the integral, we have

$$\begin{aligned} \log \psi_{ss} &= \alpha_m G_m \sum_{n=0}^{\infty} \sum_{r=0}^{\infty} \frac{(-1)^n \left(\frac{\alpha_p}{\gamma_p} G_p\right)^{n+r}}{n!r!} \frac{1}{\gamma_m + n\gamma_p} \\ &+ \alpha_m \alpha_p G_p \sum_{n=0}^{\infty} \sum_{r=0}^{\infty} \frac{(-1)^n \left(\frac{\alpha_p}{\gamma_p} G_p\right)^{n+r}}{n!r!} \frac{\left[\frac{1}{\gamma_p(n+r+1)} - \frac{1}{\gamma_m + n\gamma_p}\right]}{\gamma_m - (r+1)\gamma_p}. \end{aligned} \tag{90}$$

Noting that

$$\frac{1}{\gamma_p(n+r+1)} - \frac{1}{\gamma_m + n\gamma_p} = \frac{\gamma_m - (r+1)\gamma_p}{[\gamma_m + n\gamma_p]\gamma_p(n+r+1)}, \tag{91}$$

we can rearrange the above to obtain Eq. 78, the desired result. Moments can be obtained by noting that the first few terms of Eq. 78 are

$$\begin{aligned} \log \psi_{ss}(g_m, g_p) &= \frac{\alpha_m \alpha_p}{\gamma_m \gamma_p} \left[ G_p + \frac{\gamma_p}{\gamma_m + \gamma_p} \frac{G_p^2}{2} + \dots \right] \\ &+ \frac{\alpha_m}{\gamma_m} G_m \left[ 1 + \frac{\gamma_p}{\gamma_m + \gamma_p} \frac{\alpha_p}{\gamma_p} G_p + \dots \right] \end{aligned} \tag{92}$$

and taking the appropriate derivatives:

$$\begin{aligned} \left. \frac{\partial \log \psi_{ss}}{\partial G_m} \right|_{G_m=G_p=0} &= \langle m \rangle \\ \left. \frac{\partial \log \psi_{ss}}{\partial G_p} \right|_{G_m=G_p=0} &= \langle p \rangle \\ \left. \frac{\partial^2 \log \psi_{ss}}{\partial G_m^2} \right|_{G_m=G_p=0} &= \text{var}(m) - \langle m \rangle \\ \left. \frac{\partial^2 \log \psi_{ss}}{\partial G_p^2} \right|_{G_m=G_p=0} &= \text{var}(p) - \langle p \rangle \\ \left. \frac{\partial^2 \log \psi_{ss}}{\partial G_m \partial G_p} \right|_{G_m=G_p=0} &= \text{Cov}(m, p). \end{aligned} \tag{93}$$

□

A quick bit of technical minutiae: naively, our expression for  $\log \psi_{ss}(g_m, g_p)$  appears different from the one in Bokes et al. (2012). In our notation, their solution (their Eq.

22) reads

$$\log \psi_{ss}(g_m, g_p) = \frac{\alpha_m}{\gamma_p} \sum_{n=1}^{\infty} \frac{\left(\frac{\alpha_p}{\gamma_p} G_p\right)^n}{n (\gamma_m/\gamma_p)_n} + \frac{\alpha_m}{\gamma_m} G_m \sum_{n=0}^{\infty} \frac{\left(\frac{\alpha_p}{\gamma_p} G_p\right)^n}{(1 + \gamma_m/\gamma_p)_n} \tag{94}$$

where  $(a)_n$  denotes the Pochhammer symbol/rising factorial. One can show, either using computer algebra software or by resumming one or the other series, that this is precisely equal to Eq. 78. Also, as Bokes et al. note, this solution can be rewritten as

$$\begin{aligned} \log \psi_{ss}(g_m, g_p) &= \frac{\alpha_m \alpha_p}{\gamma_m \gamma_p} G_p \int_0^1 {}_1F_1\left(1; 1 + \frac{\gamma_m}{\gamma_p}; \frac{\alpha_p}{\gamma_p} s G_p\right) ds \\ &+ \frac{\alpha_m}{\gamma_m} G_m {}_1F_1\left(1; 1 + \frac{\gamma_m}{\gamma_p}; \frac{\alpha_p}{\gamma_p} G_p\right), \end{aligned} \tag{95}$$

a form that is somewhat more useful for numerical implementations.

In general, because the class of all systems involving birth reactions and first order reactions with at most two outputs yields Ricatti-like ODEs, an exact solution for systems with arbitrary mRNA dynamics (e.g. transcription, splicing, and degradation reactions) and protein dynamics (translation reactions) may be possible. But we will not pursue this idea here.

See (Vastola et al. 2021a) for a recent treatment of the problem of a switching gene coupled to mRNA dynamics, and (Vastola et al. 2021b) for what is essentially an application of Theorem 4 to that system.

### 2.6 Some numerical consequences of the general result

While the theoretical results described in the previous subsection are interesting, they may be far less practically relevant than the potential numerical applications of Theorem 4. Numerically solving the CME is known to be a difficult problem, especially when the number of species or typical molecule numbers in one’s system (i.e. the effective dimensionality of the state space) get large.

Theorem 4 offers a new way to numerically compute CME solutions (for systems involving only zero and first order reactions) that potentially has nontrivial speed and parallelization advantages. Consider Eq. 57, the general expression we derived for the probability generating function. The probability generating function is related to the probability distribution via an inverse Fourier transform; in particular (using  $e^{i\theta}$  instead of  $g$  for additional clarity), we have

$$\begin{aligned} \psi(\theta, t) &= \sum_{x=0}^{\infty} P(x, t) e^{i\theta x} \\ P(x, t) &= \int_{-\pi}^{\pi} \frac{d\theta}{2\pi} e^{-i\theta x} \psi(\theta, t) \end{aligned} \tag{96}$$



for one species models, and similar expressions for many species models. Theorem 4 says that we can compute CME solutions (for systems involving only zero and first order reactions) using the following algorithm:

1. Numerically compute the solution of Eq. 55, a system of (possibly nonlinear) ODEs, for various different initial conditions.
2. Numerically integrate those ODE solutions (to evaluate the integral in Eq. 57) to obtain the probability generating function.
3. Use fast Fourier transform software packages to compute the inverse Fourier transform, and hence obtain the desired solution.

To understand this idea more clearly, take the example of the birth-death-autocatalysis system whose results are described in Sect. 2.3. Suppose we wanted to compute the steady state probability distribution  $P_{ss}(x)$ . According to the above prescription, we begin by writing down the nonlinear ODE

$$\frac{dx(s)}{ds} = (c - \gamma)x(s) + cx(s)^2 \quad (97)$$

where  $x(s) := iq(s)$  and  $x(0) = g - 1 = e^{i\theta} - 1$ . In order to compute  $P_{ss}(x)$ , we must solve this ODE for sufficiently many  $g$  on the complex unit circle (or equivalently, for sufficiently many  $\theta \in [-\pi, \pi]$ ). The computation for one value of  $\theta$  does not affect the computation for another value of  $\theta$ , so these computations can be done in parallel.

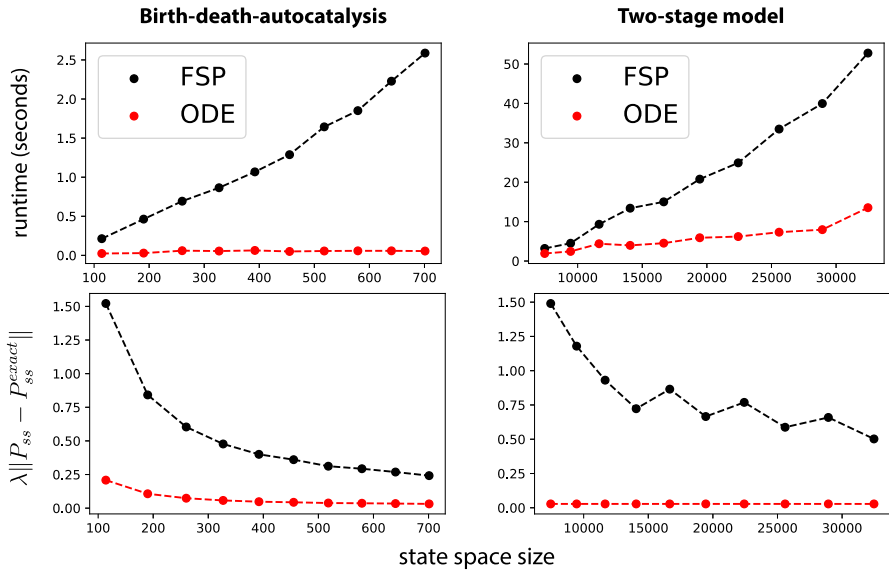
After numerically solving this ODE for many different initial conditions in parallel, the steady state probability generating function can be obtained from

$$\log \psi_{ss}(\theta, t) = k \int_0^\infty x(s) ds \quad (98)$$

using standard numerical integration methods like the trapezoidal rule. Then  $P_{ss}(x)$  can be recovered from exponentiating and inverse fast Fourier transforming this result.

Interestingly, this kind of approach may be preferable in many situations to explicitly solving for the probability generating function, even if a closed form analytic solution is available. This is because analytic solutions may have numerical stability problems (i.e. taking some problem parameters very large or small may yield numerical overflow). See (Vastola et al. 2021a) for some discussion of this in the context of an analytic solution for a CME involving gene switching, transcription, and splicing.

This approach is also fast, comparing favorably with competing state of the art methods like finite state projection (Munsky and Khammash 2006; Pele et al. 2006; Fox et al. 2016; Fox and Munsky 2019). Modifying sparse-matrix-based optimized finite state projection code from Fox and Munsky (2019) to solve the birth-death-autocatalysis system and two-stage model, and varying state space size, we can see that this ODE-based approach scales somewhat better as the state space size increases (Fig. 1). Furthermore, accuracy (as measured against the known exact results) is actually found to be better using the ODE approach. This comparison is not meant to be exhaustive or conclusive; however, what it does show is that the numerical approach suggested by Theorem 4 is promising.



**Fig. 1** Timing and accuracy of novel ODE approach versus finite state projection. Black dots: finite state projection (FSP). Red dots: the ODE approach described in this section. For two models (the birth-death-autocatalysis model and the two-stage model) and different parameter sets, steady state probability distributions were computed on a truncated state space using both finite state projection and the ODE method. Because the state space has been truncated, both distributions correspond to vectors with nonnegative entries in a finite-dimensional space. Runtime was measured in seconds, and accuracy was measured by computing the usual  $L_2$  distance (for finite-dimensional vectors) between the obtained distributions and the known exact results (Eq. 50 for birth-death-autocatalysis; Eq. 95 for the two-stage model). Distances were scaled by a factor  $\lambda := 1/0.001$  to make typical values around 1 for plotting. State space size—a measure of how many values of the probability distribution must be computed, and a factor known to be important in FSP runtime—was defined in an ad-hoc way in terms of steady state moments to be  $\langle x \rangle + 4\sqrt{\text{var}(x)}$  in the birth-death-autocatalysis case (c.f. Eq. 50), and  $[(m) + 4\sqrt{\text{var}(m)}] \times [(p) + 4\sqrt{\text{var}(p)}]$  in the two-stage case (c.f. Eq. 79). For both models, FSP tended to take longer and be less accurate, especially as the state space size increased. Birth-death autocatalysis parameters:  $\gamma = 1$ ,  $c = 0.8$ , and  $k$  was varied between 10 – 100. Two-stage model parameters:  $\alpha_p = 10$ ,  $\gamma_m = 20$ ,  $\gamma_p = 1$ , and  $\alpha_m$  was varied between 330 – 800

We will not pursue the numerical applications of Theorem 4 further here, as the focus of this paper is on its derivation. But we hope to study this novel numerical approach to solving the CME in future work—for example, see (Vastola et al. 2021b) for the application of Theorem 4 to efficient parameter inference for many-species models of bursty transcription and splicing, and for a detailed discussion of how to implement this numerical approach efficiently.

One should keep in mind that this numerical approach exclusively applies to systems involving only zero and first order reactions, which means that many biologically significant reaction types (especially binding reactions like  $A + B \rightarrow C$ ) are excluded. It is unclear whether the strategy of reducing the problem of solving the CME to the problem of numerically solving a system of  $n$  nonlinear ODEs, suitably modified, might also apply to a broader class of systems.

### 3 Reframing the problem and basic Doi-Peliti formalism

In this section, we describe the basic elements of the Doi-Peliti approach to solving the CME. From here on out, we will make extensive use of Dirac's bra-ket notation instead of notation more familiar to linear algebra and stochastic processes; this nonstandard choice is justified, and the details of how this notation relates to standard notation are briefly reviewed, in Appendix A.

Consider an arbitrary CME involving  $n \geq 1$  chemical species and  $M \geq 1$  chemical reactions, which can be written (Gillespie 2000)

$$\frac{\partial P(\mathbf{x}, t)}{\partial t} = \sum_{j=1}^M a_j(\mathbf{x} - \mathbf{v}_j, t) P(\mathbf{x} - \mathbf{v}_j, t) - a_j(\mathbf{x}, t) P(\mathbf{x}, t) \quad (99)$$

where the propensity function of the  $j$ th reaction is  $a_j(\mathbf{x}, t)$ , and the stoichiometry change associated with the  $j$ th reaction firing is  $\mathbf{v}_j$ .

In order to apply the Doi-Peliti technique, we first need to rewrite the CME in terms of states and operators in a certain Hilbert space. Consider an infinite-dimensional Hilbert space spanned by the  $|\mathbf{x}\rangle$  states/basis vectors (where  $\mathbf{x} = (x_1, \dots, x_n)^T \in \mathbb{N}^n$ ), in which an arbitrary state  $|\phi\rangle$  is written

$$|\phi\rangle = \sum_{x_1=0}^{\infty} \cdots \sum_{x_n=0}^{\infty} c(\mathbf{x}) |\mathbf{x}\rangle \quad (100)$$

for some generally complex-valued coefficients  $c(\mathbf{x})$ . These states can be added and multiplied by (complex) scalars in the usual way.

There is one basis vector for every possible state  $\mathbf{x} \in \mathbb{N}^n$  of the system, which we can write as either  $|x_1 x_2 \cdots x_n\rangle$  or  $|(x_1, x_2, \dots, x_n)\rangle$ . For example, we have basis vectors  $|00 \cdots 0\rangle$ ,  $|01 \cdots 0\rangle$ ,  $|20, 45, 1, \cdots 10\rangle$ , and so on; one interpretation of these objects is that they encode a certain generalization of probability distributions on the state space, given that they assign every  $\mathbf{x} \in \mathbb{N}^n$  a complex number<sup>6</sup>.

It should be noted that the basis vectors cannot be combined since they represent distinct directions in the Hilbert space, i.e.  $|\mathbf{x}\rangle + |\mathbf{y}\rangle \neq |\mathbf{x} + \mathbf{y}\rangle$ . We will denote the zero vector by  $0$ , which we emphasize for clarity's sake is distinct from the basis vector  $|\mathbf{0}\rangle$  (e.g.  $|\mathbf{0}\rangle + 0 = |\mathbf{0}\rangle$ ). Two relevant inner products we can endow this space with (without which we would just have a vector space) are described in Appendix B.4.

To ease notation, we remind the reader that we will write

$$\sum_{\mathbf{x}} := \sum_{x_1=0}^{\infty} \cdots \sum_{x_n=0}^{\infty} . \quad (101)$$

<sup>6</sup> We are essentially working in suitable  $\ell^2$  spaces. But we will not worry too much about this, since our methods have other more serious rigor-related issues (related to the delta function, swapping infinite integrals, taking limits, etc.).

The state we are principally interested in is the generating function, which is essentially the function  $\psi(\mathbf{g}, t)$  described earlier, but using different notation. See Appendix A.3 for some discussion of how this notion of the generating function relates to the analytic function construction usually used (i.e. the one that appears throughout Sect. 2).

**Definition 1** The *generating function* is defined to be the state

$$|\psi(t)\rangle := \sum_{\mathbf{x}} P(\mathbf{x}, t) |\mathbf{x}\rangle \quad (102)$$

where  $P(\mathbf{x}, t)$  is some solution to the CME (i.e. its precise form depends on the chosen initial condition  $P(x, t_0)$ ).

For the rest of this paper, we will only be concerned with the case where  $P(\mathbf{x}, t_0) = \delta(\mathbf{x} - \boldsymbol{\xi})$  for some  $\boldsymbol{\xi} \in \mathbb{N}^n$  (we remind the reader that  $\delta$  here denotes the multivariate generalization of the Kronecker delta function), so we will always assume that  $|\psi(t_0)\rangle = |\boldsymbol{\xi}\rangle$ .

Because the generating function  $|\psi(t)\rangle$  depends on  $P(\mathbf{x}, t)$ , whose dynamics are controlled by the CME,  $|\psi(t)\rangle$  also has dynamics; we can write the equation controlling them (its ‘equation of motion’) in the form

$$\frac{\partial |\psi\rangle}{\partial t} = \hat{H} |\psi\rangle \quad (103)$$

where the Hamiltonian operator  $\hat{H}$  is a linear operator whose precise form depends on the CME. For the reader familiar with quantum mechanics, this is analogous to the equation of motion for a quantum mechanical state. For the reader familiar with stochastic processes,  $\hat{H}$  is equivalent to the forward operator of the corresponding Markov process, or the adjoint of its infinitesimal generator. In any case, it is this equation that we will solve instead of the CME.

It may or may not be helpful for the reader to think of  $\hat{H}$  as a (possibly infinite-dimensional) matrix, and of Eq. 103 as a vector representation of the CME. Although it is infinite-dimensional in essentially every case we care about in this paper, it would literally be a matrix if we were solving a CME with a finite state space. One example of a problem with a finite state space is the pure conversion process ( $A \leftrightarrow B$ ), which involves  $A$  molecules and  $B$  molecules randomly converting between each other; it has a finite state space because the total number of molecules remains constant.

The core result of applying Doi-Peliti field theory to solving the CME is the following.

**Theorem 5** (*Doi-Peliti path integral solution*) Consider an arbitrary CME (Eq. 99) with initial condition  $P(\mathbf{x}, t_0) = \delta(\mathbf{x} - \boldsymbol{\xi})$  for some  $\boldsymbol{\xi} \in \mathbb{N}^n$ . The corresponding generating function satisfies Eq. 103 for some linear operator  $\hat{H}$ . The Doi-Peliti approach involves formally solving Eq. 103 via

$$|\psi(t)\rangle = \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} |\mathbf{z}^f\rangle U(i\mathbf{p}^f, t; \mathbf{z}^0, t_0) (\mathbf{1} + i\mathbf{p}^0)^\xi e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0 - i\mathbf{p}^f \cdot \mathbf{z}^f} \tag{104}$$

where  $\mathbf{z}^0$  and  $\mathbf{z}^f$  are both integrated over  $(0, \infty)^n$ , and  $\mathbf{p}^0$  and  $\mathbf{p}^f$  are both integrated over  $\mathbb{R}^n$ . The ‘coherent state’  $|\mathbf{z}^f\rangle$  (for, in this case, some  $\mathbf{z}^f \in (0, \infty)^n$ ) can be written

$$|\mathbf{z}^f\rangle = \sum_{\mathbf{y}} \frac{z_1^{y_1} \cdots z_n^{y_n}}{y_1! \cdots y_n!} e^{-(z_1 + \cdots + z_n)} |\mathbf{y}\rangle = \sum_{\mathbf{y}} \frac{\mathbf{z}^{\mathbf{y}}}{\mathbf{y}!} e^{-\mathbf{z} \cdot \mathbf{1}} |\mathbf{y}\rangle . \tag{105}$$

The function  $U(i\mathbf{p}^f, t; \mathbf{z}^0, t_0)$  is the ‘propagator’, and equals the path integral

$$U = \lim_{N \rightarrow \infty} \int \prod_{\ell=1}^{N-1} \frac{d\mathbf{z}^\ell d\mathbf{p}^\ell}{(2\pi)^n} \exp \left\{ \sum_{\ell=1}^{N-1} -i\mathbf{p}^\ell \cdot (\mathbf{z}^\ell - \mathbf{z}^{\ell-1}) + \Delta t \mathcal{H}(i\mathbf{p}^\ell, \mathbf{z}^{\ell-1}, t_{\ell-1}) + \Delta t \mathcal{H}(i\mathbf{p}^f, \mathbf{z}^{N-1}, t_{N-1}) + i\mathbf{p}^f \cdot \mathbf{z}^{N-1} \right\} \tag{106}$$

where  $\Delta t := (t - t_0)/N$ . The ‘Hamiltonian kernel’  $\mathcal{H}$  that appears in the above path integral expression is equal to

$$\mathcal{H}(i\mathbf{p}, \mathbf{z}, t) = \sum_{j=1}^M [(1 + i\mathbf{p})^{p_j} - 1] \sum_{\mathbf{y}} \frac{\mathbf{z}^{\mathbf{y}} (1 + i\mathbf{p})^{\mathbf{y}}}{\mathbf{y}!} e^{-\mathbf{z} \cdot (1 + i\mathbf{p})} a_j(\mathbf{y}, t) . \tag{107}$$

The generating function solution (Eq. 104) can be directly converted into solutions for the transition probability and moments. Using the shorthand  $P := P(\mathbf{x}, t; \xi, t_0)$  and  $U := U(i\mathbf{p}^f, t; \mathbf{z}^0, t_0)$ , the transition probability equals

$$P = \frac{1}{\mathbf{x}!} \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} (\mathbf{z}^f)^{\mathbf{x}} e^{-\mathbf{z}^f \cdot \mathbf{1}} U (\mathbf{1} + i\mathbf{p}^0)^\xi e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0 - i\mathbf{p}^f \cdot \mathbf{z}^f} . \tag{108}$$

First order moments  $\langle x_k(t) \rangle$  (for some  $k = 1, \dots, n$ ) are equal to

$$\langle x_k(t) \rangle = \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} z_k^f U (\mathbf{1} + i\mathbf{p}^0)^\xi e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0 - i\mathbf{p}^f \cdot \mathbf{z}^f} . \tag{109}$$

Obtaining higher order (factorial) moments involves replacing  $z_k^f$  with the appropriate product. For example:

$$\begin{aligned} \langle x_j(t)x_k(t) \rangle &= \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} [z_j^f z_k^f] U (\mathbf{1} + i\mathbf{p}^0)^\xi e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0 - i\mathbf{p}^f \cdot \mathbf{z}^f} \\ \langle x_j(t)[x_j(t) - 1] \rangle &= \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} [z_j^f]^2 U (\mathbf{1} + i\mathbf{p}^0)^\xi e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0 - i\mathbf{p}^f \cdot \mathbf{z}^f} . \end{aligned} \tag{110}$$

We develop the Doi-Peliti machinery needed to establish the above result in Appendix B. Knowing the associated technical details is not crucial for understanding the calculations in the following two sections.

### 4 Monomolecular calculations

In this section, we present the calculations relevant to proving the formulas from Theorems 1 and 2 using the Doi-Peliti approach. First, we evaluate the path integral expression for the propagator  $U$ . Then we use the explicit form of the propagator to derive the transition probability and several moments. We do not explicitly show how to compute the generating function directly from the propagator, because it is very similar to the other calculations.

#### 4.1 Evaluating the propagator path integral

In this section, we will evaluate the path integral expression for the propagator  $U$  (Eq. 106) given our specific dynamics, which are captured by the Hamiltonian kernel  $\mathcal{H}$ . We make free use of a formal integral representation of the Dirac delta function. According to Appendix C, for monomolecular systems

$$\begin{aligned}
 -i\mathcal{H}(i\mathbf{p}^\ell, \mathbf{z}^{\ell-1}, t_{\ell-1}) &= \sum_{k=1}^n c_{0k}(t_{\ell-1})p_k^\ell - \sum_{k=1}^n c_{k0}(t_{\ell-1})p_k^\ell z_k^{\ell-1} \\
 &+ \sum_{j=1}^n \sum_{k=1}^n c_{jk}(t_{\ell-1}) \left[ p_k^\ell - p_j^\ell \right] z_j^{\ell-1}.
 \end{aligned}
 \tag{111}$$

**Lemma 1** (*Monomolecular propagator*) *The propagator for the monomolecular system is*

$$U(i\mathbf{p}^f, t; \mathbf{z}^0, t_0) = e^{i\mathbf{p}^f \cdot \mathbf{z}(t)}
 \tag{112}$$

where

$$\mathbf{z}(t) := \sum_{k=1}^n z_k^0 \mathbf{w}^{(k)}(t) + \boldsymbol{\lambda}(t)
 \tag{113}$$

with  $\mathbf{w}^{(k)}(t)$  and  $\boldsymbol{\lambda}(t)$  as defined in Theorem 2.

**Proof** Begin with the path integral expression for  $U$  (Eq. 106). Let us first integrate over the  $p_k^\ell$  (where  $\ell \in \{1, \dots, N - 1\}$  and  $k \in \{1, \dots, n\}$ ). For fixed  $\ell$  and  $k$ , these integrals look like

$$\int_{-\infty}^{\infty} \frac{dp_k^\ell}{2\pi} \exp \left\{ -ip_k^\ell \left[ (z_k^\ell - z_k^{\ell-1}) - \Delta t \left( c_{0k}^{\ell-1} - c_{k0}^{\ell-1} z_k^{\ell-1} + \sum_{j=1}^n c_{jk}^{\ell-1} z_j^{\ell-1} - c_{kj}^{\ell-1} z_k^{\ell-1} \right) \right] \right\}
 \tag{114}$$

where  $c_{jk}^{\ell-1}$  is shorthand for  $c_{jk}(t_{\ell-1})$ . Using the usual integral representation of the Dirac delta function, these integrals are easily done to obtain  $n \cdot (N - 1)$  delta function constraints:

$$\delta \left[ (z_k^\ell - z_k^{\ell-1}) - \Delta t \left( c_{0k}^{\ell-1} - c_{k0}^{\ell-1} z_k^{\ell-1} + \sum_{j=1}^n c_{jk}^{\ell-1} z_j^{\ell-1} - c_{kj}^{\ell-1} z_k^{\ell-1} \right) \right]. \tag{115}$$

Fortunately, that is *exactly* how many integrals we have left to do. Notice that the constraints force

$$z_k^\ell = z_k^{\ell-1} + \Delta t \left( c_{0k}^{\ell-1} - c_{k0}^{\ell-1} z_k^{\ell-1} + \sum_{j=1}^n c_{jk}^{\ell-1} z_j^{\ell-1} - c_{kj}^{\ell-1} z_k^{\ell-1} \right) \tag{116}$$

which exactly corresponds to taking an Euler time step given the deterministic dynamics described by the reaction rate equations, Eq. 20. What remains of our calculation is to evaluate

$$U = \lim_{N \rightarrow \infty} \exp \left\{ \Delta t \mathcal{H}(i\mathbf{p}^f, \mathbf{z}^{N-1}, t_{N-1}) + i\mathbf{p}^f \cdot \mathbf{z}^{N-1} \right\} \tag{117}$$

given Eq. 116, the constraint on  $\mathbf{z}^{N-1}$  relating it (via  $(N - 1)$  Euler time steps) to  $\mathbf{z}^0$ . We have

$$\begin{aligned} & i\mathbf{p}^f \cdot \mathbf{z}^{N-1} + \Delta t \mathcal{H}(i\mathbf{p}^f, \mathbf{z}^{N-1}, t_{N-1}) \\ &= i \sum_{k=1}^n p_k^f \left\{ z_k^{N-1} + \Delta t \left[ c_{0k}^{N-1} - c_{k0}^{N-1} z_k^{N-1} + \sum_{j=1}^n c_{jk}^{N-1} z_j^{N-1} - c_{kj}^{N-1} z_k^{N-1} \right] \right\} \\ &= i \sum_{k=1}^n p_k^f z_k^N \end{aligned} \tag{118}$$

where we define  $z_k^N$  as the result of taking  $N$  time steps of length  $\Delta t$  according to Eq. 116 given the initial condition  $z_k^0$ . In the  $N \rightarrow \infty$  limit,  $z_k^N \rightarrow z_k(t)$ , where  $z_k(t)$  is defined as the  $k$ th component of the solution to Eq. 20. As described in Sect. 2,  $\mathbf{z}(t)$  can be decomposed in terms of  $\lambda(t)$  and the  $\mathbf{w}^{(k)}(t)$ .  $\square$

While it may seem like this path integral calculation was completely trivial, it is simple mostly because we put in the legwork to define and characterize the Grassberger-Scheunert product (in Appendix B.4) beforehand. Had we constructed a path integral based on the exclusive product instead of the Grassberger-Scheunert product, this calculation would have involved extra steps. These extra steps would either involve dealing with extra terms after enforcing the delta function constraints,

or shifting integration variables in a mathematically dubious way (i.e. making the so-called Doi shift).

Now that we have computed the propagator  $U$ , Theorem 5 tells us how to derive the transition probability and moments. Because the transition probability and moment calculations are somewhat involved, we first present them for the one species system (i.e. the chemical birth-death process).

### 4.2 One species transition probability derivation

**Lemma 2** (*One species monomolecular transition probability*) *For the single species monomolecular system (i.e. the chemical birth-death process), the transition probability  $P(x, t; \xi, t_0)$  is*

$$\begin{aligned}
 P &= \sum_{k=0}^{\min(x, \xi)} \left[ \frac{\lambda(t)^{x-k} e^{-\lambda(t)}}{(x-k)!} \right] \left[ \binom{\xi}{k} w(t)^k [1-w(t)]^{\xi-k} \right] \\
 &= \mathcal{P}(x, \lambda(t)) \star \mathcal{M}(x, \xi, w(t))
 \end{aligned}
 \tag{119}$$

where  $w(t)$  and  $\lambda(t)$  are as defined in Theorem 1.

**Proof** Using Eq. 108, we have

$$P(x, t; \xi, t_0) = \frac{1}{x!} \int \frac{dz^f dp^f}{2\pi} \frac{dz^0 dp^0}{2\pi} (z^f)^x e^{-z^f} e^{ip^f z(t)} (1+ip^0)^\xi e^{-ip^0 z^0 - ip^f z^f} \tag{120}$$

The integral over  $p^f$  is easily done:

$$\int_{-\infty}^{\infty} \frac{dp^f}{2\pi} e^{ip^f [z(t) - z^f]} = \delta(z(t) - z^f). \tag{121}$$

Enforcing the delta function constraint removes the integral over  $z^f$ . Since  $z(t) = z^0 w(t) + \lambda(t)$ ,

$$\begin{aligned}
 P &= \frac{1}{x!} \int \frac{dz^0 dp^0}{2\pi} [z^0 w(t) + \lambda(t)]^x e^{-[z^0 w(t) + \lambda(t)]} (1+ip^0)^\xi e^{-ip^0 z^0} \\
 &= \frac{e^{-\lambda(t)}}{x!} \int \frac{dz^0 dp^0}{2\pi} [z^0 w(t) + \lambda(t)]^x e^{z^0 [1-w(t)]} (1+ip^0)^\xi e^{-z^0 [1+ip^0]}.
 \end{aligned}
 \tag{122}$$

This can be rewritten as

$$\begin{aligned}
 P &= \frac{e^{-\lambda(t)}}{x!} \int \frac{dz^0 dp^0}{2\pi} [z^0 w(t) + \lambda(t)]^x e^{z^0 [1-w(t)]} \left( -\frac{d}{dz^0} \right)^\xi e^{-z^0 [1+ip^0]} \\
 &= \frac{e^{-\lambda(t)}}{x!} \int \frac{dz^0 dp^0}{2\pi} \left( \frac{d}{dz^0} \right)^\xi \left\{ [z^0 w(t) + \lambda(t)]^x e^{z^0 [1-w(t)]} \right\} e^{-z^0 [1+ip^0]}
 \end{aligned}
 \tag{123}$$



where we integrated by parts in the second step. The  $p^0$  integral can now be done:

$$\int_{-\infty}^{\infty} \frac{dp^0}{2\pi} e^{-ip^0 z^0} = \delta(z^0). \tag{124}$$

We now have

$$P = \frac{e^{-\lambda(t)}}{x!} \int_0^\infty dz^0 \left(\frac{d}{dz^0}\right)^\xi \left\{ \left[ z^0 w(t) + \lambda(t) \right]^x e^{z^0 [1-w(t)]} \right\} e^{-z^0} \delta(z^0). \tag{125}$$

If we can evaluate the derivative, then we can easily evaluate the integral using the delta function. Using the binomial theorem,

$$\left[ z^0 w(t) + \lambda(t) \right]^x = \sum_{k=0}^x \binom{x}{k} w(t)^k \lambda(t)^{x-k} (z^0)^k. \tag{126}$$

Since

$$(z^0)^k e^{z^0 [1-w(t)]} = \sum_{j=0}^\infty \frac{(z^0)^{j+k} [1-w(t)]^j}{j!}, \tag{127}$$

the derivative of a specific term is

$$\begin{aligned} & \left(\frac{d}{dz^0}\right)^\xi \left\{ (z^0)^k e^{z^0 [1-w(t)]} \right\} \\ &= \sum_{j=0}^\infty \frac{(j+k)(j+k-1)\cdots(j+k-\xi+1) (z^0)^{j+k-\xi} [1-w(t)]^j}{j!}. \end{aligned} \tag{128}$$

When enforcing the delta function constraint that  $z^0 = 0$ , all terms will disappear from this series except for the constant term. The constant term is the term with  $j+k = \xi$ , which reads

$$\frac{\xi!}{(\xi-k)!} [1-w(t)]^{\xi-k} \theta(\xi-k) \tag{129}$$

where the step function  $\theta$ , defined as

$$\theta(\xi-k) := \begin{cases} 1 & k \leq \xi \\ 0 & k > \xi \end{cases} \tag{130}$$

must be there since the result will be zero if  $k > \xi$ . Hence,

$$\begin{aligned}
 P &= \frac{e^{-\lambda(t)}}{x!} \sum_{k=0}^x \binom{x}{k} w(t)^k \lambda(t)^{x-k} \frac{\xi!}{(\xi-k)!} [1-w(t)]^{\xi-k} \theta(\xi-k) \\
 &= e^{-\lambda(t)} \sum_{k=0}^{\min(x,\xi)} \binom{\xi}{k} w(t)^k \lambda(t)^{x-k} \frac{1}{(x-k)!} [1-w(t)]^{\xi-k} \\
 &= \sum_{k=0}^{\min(x,\xi)} \left[ \frac{\lambda(t)^{x-k} e^{-\lambda(t)}}{(x-k)!} \right] \left[ \binom{\xi}{k} w(t)^k [1-w(t)]^{\xi-k} \right] \\
 &= \mathcal{P}(x, \lambda(t)) \star \mathcal{M}(x, \xi, w(t))
 \end{aligned}
 \tag{131}$$

as desired. □

### 4.3 General transition probability derivation

**Lemma 3** (*Monomolecular transition probability*) *For the general monomolecular system, the transition probability  $P(\mathbf{x}, t; \xi, t_0)$  is*

$$P = \mathcal{P}(\mathbf{x}, \lambda(t)) \star \mathcal{M}(\mathbf{x}, \xi_1, \mathbf{w}^{(1)}(t)) \star \dots \star \mathcal{M}(\mathbf{x}, \xi_n, \mathbf{w}^{(n)}(t))
 \tag{132}$$

where  $\lambda(t)$  and the  $\mathbf{w}^{(j)}(t)$  are as defined in Theorem 2.

**Proof** The general case proceeds analogously to the one species case. The main difference is that we must do the appropriate multivariable generalization of each of the steps in the previous subsection (e.g. use the multinomial theorem instead of the binomial theorem). Using Eq. 108,

$$P(\mathbf{x}, t; \xi, t_0) = \frac{1}{\mathbf{x}!} \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} (\mathbf{z}^f)^{\mathbf{x}} e^{-\mathbf{z}^f \cdot \mathbf{1}} e^{i\mathbf{p}^f \cdot \mathbf{z}(t)} (\mathbf{1} + i\mathbf{p}^0)^\xi e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0 - i\mathbf{p}^f \cdot \mathbf{z}^f}.
 \tag{133}$$

The integrals over  $p_1^f, \dots, p_n^f$  yield delta functions:

$$\int \frac{d\mathbf{p}^f}{(2\pi)^n} e^{i\mathbf{p}^f \cdot [\mathbf{z}(t) - \mathbf{z}^f]} = \delta(z_1(t) - z_1^f) \dots \delta(z_n(t) - z_n^f) = \delta(\mathbf{z}(t) - \mathbf{z}^f).
 \tag{134}$$

Enforcing the delta function constraints removes the integrals over  $z_1^f, \dots, z_n^f$ . Using Eq. 113,

$$\begin{aligned}
 P &= \frac{1}{\mathbf{x}!} \int \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} \left[ \sum_{k=1}^n z_k^0 \mathbf{w}^{(k)} + \lambda \right]^{\mathbf{x}} e^{-[\sum_{k=1}^n z_k^0 \mathbf{w}^{(k)} + \lambda] \cdot \mathbf{1}} (\mathbf{1} + i\mathbf{p}^0)^\xi e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0} \\
 &= \frac{e^{-|\lambda(t)|}}{\mathbf{x}!} \int \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} \left[ \sum_{k=1}^n z_k^0 \mathbf{w}^{(k)} + \lambda \right]^{\mathbf{x}} e^{\sum_{k=1}^n z_k^0 (1 - |\mathbf{w}^{(k)}|)} (\mathbf{1} + i\mathbf{p}^0)^\xi e^{-\mathbf{z}^0 \cdot [\mathbf{1} + i\mathbf{p}^0]}.
 \end{aligned}
 \tag{135}$$

Reusing the notation we used earlier to denote many derivatives with respect to each variable (Eq. 263), we can rewrite this result as

$$\begin{aligned}
 P &= \frac{e^{-|\lambda(t)|}}{\mathbf{x}!} \int \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} \left[ \sum_{k=1}^n z_k^0 \mathbf{w}^{(k)} + \lambda \right]^{\mathbf{x}} e^{\sum_{k=1}^n z_k^0 (1-|\mathbf{w}^{(k)}|)} \left( -\frac{d}{d\mathbf{z}^0} \right)^{\xi} e^{-\mathbf{z}^0 \cdot [\mathbf{1} + i\mathbf{p}^0]} \\
 &= \frac{e^{-|\lambda(t)|}}{\mathbf{x}!} \int \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} \left( \frac{d}{d\mathbf{z}^0} \right)^{\xi} \left\{ \left[ \sum_{k=1}^n z_k^0 \mathbf{w}^{(k)} + \lambda \right]^{\mathbf{x}} e^{\sum_{k=1}^n z_k^0 (1-|\mathbf{w}^{(k)}|)} \right\} e^{-\mathbf{z}^0 \cdot [\mathbf{1} + i\mathbf{p}^0]}
 \end{aligned} \tag{136}$$

where we integrated by parts many times in the second step. The  $p_1^0, \dots, p_n^0$  integrals can now be done:

$$\int \frac{d\mathbf{p}^0}{(2\pi)^n} e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0} = \delta(z_1^0) \cdots \delta(z_n^0) = \delta(\mathbf{z}^0). \tag{137}$$

We now have

$$P = \frac{e^{-|\lambda(t)|}}{\mathbf{x}!} \int d\mathbf{z}^0 \left( \frac{d}{d\mathbf{z}^0} \right)^{\xi} \left\{ \left[ \sum_{k=1}^n z_k^0 \mathbf{w}^{(k)} + \lambda \right]^{\mathbf{x}} e^{\sum_{k=1}^n z_k^0 (1-|\mathbf{w}^{(k)}|)} \right\} e^{-\mathbf{z}^0 \cdot \mathbf{1}} \delta(\mathbf{z}^0). \tag{138}$$

If we can evaluate the derivative, then we can easily evaluate the integral using the delta function. Recall that

$$\left[ \sum_{k=1}^n z_k^0 \mathbf{w}^{(k)} + \lambda \right]^{\mathbf{x}} = \left[ \sum_{k=1}^n z_k^0 w_1^{(k)} + \lambda_1 \right]^{x_1} \cdots \left[ \sum_{k=1}^n z_k^0 w_n^{(k)} + \lambda_n \right]^{x_n}. \tag{139}$$

Using the multinomial theorem,

$$\left[ \sum_{k=1}^n z_k^0 w_j^{(k)} + \lambda_j \right]^{x_j} = \sum_{v_1^j + \dots + v_{n+1}^j = x_j} \binom{x_j}{v_1^j \cdots v_{n+1}^j} [z_1^0 w_j^{(1)}]^{v_1^j} \cdots [z_n^0 w_j^{(n)}]^{v_n^j} [\lambda_j]^{v_{n+1}^j} \tag{140}$$

for each  $j = 1, \dots, n$ . Write  $|\mathbf{v}_\ell| := v_1^\ell + \dots + v_n^\ell$ . Putting these multinomial expansions together, our integral now involves computing  $n$  expressions of the form

$$\left( \frac{d}{dz_\ell^0} \right)^{\xi_\ell} \left\{ [z_\ell^0]^{|\mathbf{v}_\ell|} e^{z_\ell^0 (1-|\mathbf{w}^{(\ell)}|)} \right\} \Bigg|_{z_\ell^0=0} = \frac{\xi_\ell!}{(\xi_\ell - |\mathbf{v}_\ell|)!} (1 - |\mathbf{w}^{(\ell)}|)^{\xi_\ell - |\mathbf{v}_\ell|} \theta(\xi_\ell - |\mathbf{v}_\ell|) \tag{141}$$

where we have used the result from earlier (Eq. 129) to evaluate it. When enforcing the delta function constraint that  $z_\ell^0 = 0$  for all  $\ell = 1, \dots, n$ , we get

$$\frac{e^{-|\lambda(t)|}}{\mathbf{x}!} \sum_{v_k^j} \left\{ \prod_{j=1}^n \binom{x_j}{v_1^j \dots v_{n+1}^j} [w_j^{(1)}]^{v_1^j} \dots [w_j^{(n)}]^{v_n^j} [\lambda_j]^{v_{n+1}^j} \frac{\xi_j!}{(\xi_j - |\mathbf{v}_j|)!} (1 - |\mathbf{w}^{(j)}|)^{\xi_j - |\mathbf{v}_j|} \theta(\xi_j - |\mathbf{v}_j|) \right\} \tag{142}$$

for  $P$ . This is the final result, but let us rewrite it so that we recover the result from Theorem 1 (Eq. 31) of Jahnke and Huisinga’s paper. Note that

$$e^{-|\lambda(t)|} \prod_{j=1}^n \frac{[\lambda_j]^{v_{n+1}^j}}{v_{n+1}^j!} = \frac{\lambda(t)^{\mathbf{v}_{n+1}}}{\mathbf{v}_{n+1}!} e^{-|\lambda(t)|} = \mathcal{P}(\mathbf{v}_{n+1}, \lambda(t)). \tag{143}$$

Also,

$$\begin{aligned} & \frac{\xi_k! (1 - |\mathbf{w}^{(k)}|)^{\xi_k - |\mathbf{v}_k|}}{(\xi_k - |\mathbf{v}_k|)!} \theta(\xi_k - |\mathbf{v}_k|) \prod_{j=1}^n \frac{[w_j^{(k)}]^{v_k^j}}{v_k^j!} \\ &= \frac{\xi_k! (1 - |\mathbf{w}^{(k)}|)^{\xi_k - |\mathbf{v}_k|}}{(\xi_k - |\mathbf{v}_k|)!} \theta(\xi_k - |\mathbf{v}_k|) \frac{[\mathbf{w}^{(k)}]^{\mathbf{v}_k}}{\mathbf{v}_k!} \\ &= \mathcal{M}(\mathbf{v}_k, \xi_k, \mathbf{w}^{(k)}). \end{aligned} \tag{144}$$

We are left with

$$\begin{aligned} P &= \sum_{v_k^j} \mathcal{P}(\mathbf{v}_{n+1}, \lambda(t)) \mathcal{M}(\mathbf{v}_1, \xi_1, \mathbf{w}^{(1)}) \dots \mathcal{M}(\mathbf{v}_n, \xi_n, \mathbf{w}^{(n)}) \\ &= \sum_{v_k^j} \mathcal{P}(\mathbf{x} - \mathbf{v}_1 - \dots - \mathbf{v}_n, \lambda(t)) \mathcal{M}(\mathbf{v}_1, \xi_1, \mathbf{w}^{(1)}) \dots \mathcal{M}(\mathbf{v}_n, \xi_n, \mathbf{w}^{(n)}) \tag{145} \\ &= \mathcal{P}(\mathbf{x}, \lambda(t)) \star \mathcal{M}(\mathbf{x}, \xi_1, \mathbf{w}^{(1)}(t)) \star \dots \star \mathcal{M}(\mathbf{x}, \xi_n, \mathbf{w}^{(n)}(t)) \end{aligned}$$

which matches Eq. 31. □

If we wanted to compute the moments of  $P(\mathbf{x}, t)$ , we could just use Eq. 31 and carry out the calculation directly; however, the Doi-Peliti approach offers a way to compute moments which bypasses  $P(\mathbf{x}, t)$  completely. In other words, if we are *only* interested in moments, the work from the previous section is unnecessary. Instead, we can use Eq. 109 and Eq. 110 from Theorem 5. As with the previous calculation, we will warm up with the one species case before treating the multi-species case.

### 4.4 One species moments derivation

**Lemma 4** (*One species monomolecular moments*) For the single species monomolecular system (i.e. the chemical birth-death process), the first and second factorial moments are

$$\begin{aligned} \langle x(t) \rangle &= \xi w(t) + \lambda(t) \\ \langle x(t)[x(t) - 1] \rangle &= w(t)^2 \xi (\xi - 1) + 2\lambda(t)w(t)\xi + \lambda(t)^2 \end{aligned} \tag{146}$$

where  $w(t)$  and  $\lambda(t)$  are as defined in Theorem 1.

**Proof** Using Eq. 109,

$$\langle x(t) \rangle = \int \frac{dz^f dp^f}{2\pi} \frac{dz^0 dp^0}{2\pi} z^f e^{ip^f z(t)} (1 + ip^0)^\xi e^{-ip^0 z^0 - ip^f z^f}. \tag{147}$$

The  $p^f$ ,  $z^f$ , and  $p^0$  integrals can be done as in Sect. 4.2, leaving

$$\langle x(t) \rangle = \int_0^\infty dz^0 \left( \frac{d}{dz^0} \right)^\xi \left\{ \left[ z^0 w(t) + \lambda(t) \right] e^{z^0} \right\} e^{-z^0} \delta(z^0). \tag{148}$$

The derivative is easily evaluated, and we obtain

$$\langle x(t) \rangle = \int_0^\infty dz^0 \left[ \xi w(t) e^{z^0} + z(t) e^{z^0} \right] e^{-z^0} \delta(z^0) = \xi w(t) + \lambda(t), \tag{149}$$

which is just the solution to the one species reaction rate equation with  $x(t_0) = \xi$ , just as expected. The second factorial moment can be computed in similar fashion:

$$\begin{aligned} \langle x(t)[x(t) - 1] \rangle &= \int \frac{dz^f dp^f}{2\pi} \frac{dz^0 dp^0}{2\pi} (z^f)^2 e^{ip^f z(t)} (1 + ip^0)^\xi e^{-ip^0 z^0 - ip^f z^f} \\ &= \int_0^\infty dz^0 \left( \frac{d}{dz^0} \right)^\xi \left\{ \left[ z^0 w(t) + \lambda(t) \right]^2 e^{z^0} \right\} e^{-z^0} \delta(z^0) \\ &= w(t)^2 \xi (\xi - 1) + 2\lambda(t)w(t)\xi + \lambda(t)^2. \end{aligned} \tag{150}$$

□

Higher factorial moments can be computed in exactly the same way.

### 4.5 General moments derivation

Unlike in the one species case, there are many first moments:  $\langle x_1(t) \rangle, \dots, \langle x_n(t) \rangle$ . There are also many second moments. To summarize them usefully, we compute the covariance matrix elements (i.e.  $\text{Cov}(x_j, x_\ell) := \langle x_j(t)x_\ell(t) \rangle - \langle x_j(t) \rangle \langle x_\ell(t) \rangle$  for all pairs of  $j$  and  $\ell$ ).

**Lemma 5** (*Monomolecular moments*) *For the general monomolecular system, the first moments, second factorial moments, and covariance matrix elements are given by*

$$\begin{aligned}
 \langle x_j(t) \rangle &= \sum_{k=1}^n \xi_k w_j^{(k)}(t) + \lambda_j(t) & j = 1, \dots, n \\
 \langle x_j x_\ell \rangle &= \sum_{k=1}^n \sum_{k'=1}^n \xi_k \xi_{k'} w_j^{(k)} w_\ell^{(k')} \\
 &\quad + \sum_{k=1}^n \xi_k \left[ w_j^{(k)} \lambda_\ell + w_\ell^{(k)} \lambda_j - w_j^{(k)} w_\ell^{(k)} \right] + \lambda_j \lambda_\ell & j \neq \ell \\
 \langle x_j(t) [x_j(t) - 1] \rangle &= \sum_{k=1}^n \sum_{k'=1}^n \xi_k \xi_{k'} w_j^{(k)} w_j^{(k')} \\
 &\quad + \sum_{k=1}^n \xi_k \left[ 2w_j^{(k)} \lambda_j - \left( w_j^{(k)} \right)^2 \right] + \lambda_j^2 & j = 1, \dots, n \\
 \text{Cov}(x_j, x_\ell) &= \begin{cases} \sum_{k=1}^n \xi_k w_j^{(k)} \left[ 1 - w_j^{(k)} \right] + \lambda_j & j = \ell \\ -\sum_{k=1}^n \xi_k w_j^{(k)} w_\ell^{(k)} & j \neq \ell \end{cases} & (151)
 \end{aligned}$$

where  $\lambda(t)$  and the  $\mathbf{w}^{(j)}(t)$  are as defined in Theorem 2.

**Proof** Picking a specific  $x_j$  and using Eq. 109, we have

$$\langle x_j(t) \rangle = \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} z_j^f e^{i\mathbf{p}^f \cdot \mathbf{z}(t)} (\mathbf{1} + i\mathbf{p}^0)^\xi e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0 - i\mathbf{p}^f \cdot \mathbf{z}^f}. \quad (152)$$

The  $\mathbf{p}^f$ ,  $\mathbf{z}^f$ , and  $\mathbf{p}^0$  integrals can be done as in Sect. 4.3, yielding

$$\begin{aligned}
 \langle x_j(t) \rangle &= \int d\mathbf{z}^0 \left( \frac{d}{d\mathbf{z}^0} \right)^\xi \left\{ \left[ \sum_{k=1}^n z_k^0 w_j^{(k)} + \lambda_j \right] e^{\mathbf{z}^0 \cdot \mathbf{1}} \right\} e^{-\mathbf{z}^0 \cdot \mathbf{1}} \delta(\mathbf{z}^0) \\
 &= \sum_{k=1}^n \xi_k w_j^{(k)}(t) + \lambda_j(t)
 \end{aligned} \quad (153)$$

which is the  $j$ th component of the solution to Eq. 20 with  $\mathbf{x}(t_0) = \xi$ .

Let us compute  $\langle x_j(t)x_\ell(t) \rangle$  for  $j \neq \ell$ . To start off,

$$\langle x_j(t)x_\ell(t) \rangle = \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} z_j^f z_\ell^f e^{i\mathbf{p}^f \cdot \mathbf{z}(t)} (\mathbf{1} + i\mathbf{p}^0)^\xi e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0 - i\mathbf{p}^f \cdot \mathbf{z}^f}. \quad (154)$$

Proceeding as we just did, we obtain

$$\begin{aligned} \langle x_j x_\ell \rangle &= \int d\mathbf{z}^0 \left( \frac{d}{d\mathbf{z}^0} \right)^\xi \left\{ \left[ \sum_{k=1}^n z_k^0 w_j^{(k)} + \lambda_j \right] \left[ \sum_{k'=1}^n z_{k'}^0 w_\ell^{(k')} + \lambda_\ell \right] e^{\mathbf{z}^0 \cdot \mathbf{1}} \right\} e^{-\mathbf{z}^0 \cdot \mathbf{1}} \delta(\mathbf{z}^0) \\ &= \sum_{k=1}^n \sum_{k'=1}^n \xi_k \xi_{k'} w_j^{(k)} w_\ell^{(k')} + \sum_{k=1}^n \xi_k \left[ w_j^{(k)} \lambda_\ell + w_\ell^{(k)} \lambda_j - w_j^{(k)} w_\ell^{(k)} \right] + \lambda_j \lambda_\ell. \end{aligned} \quad (155)$$

For the similar case  $j = \ell$ , we obtain

$$\begin{aligned} \langle x_j(t) [x_j(t) - 1] \rangle &= \int d\mathbf{z}^0 \left( \frac{d}{d\mathbf{z}^0} \right)^\xi \left\{ \left[ \sum_{k=1}^n z_k^0 w_j^{(k)} + \lambda_j \right]^2 e^{\mathbf{z}^0 \cdot \mathbf{1}} \right\} e^{-\mathbf{z}^0 \cdot \mathbf{1}} \delta(\mathbf{z}^0) \\ &= \sum_{k=1}^n \sum_{k'=1}^n \xi_k \xi_{k'} w_j^{(k)} w_j^{(k')} + \sum_{k=1}^n \xi_k \left[ 2w_j^{(k)} \lambda_j - \left( w_j^{(k)} \right)^2 \right] + \lambda_j^2. \end{aligned} \quad (156)$$

Putting these results together, we find that the covariance of  $x_j$  and  $x_\ell$  is

$$\text{Cov}(x_j, x_\ell) = \begin{cases} \sum_{k=1}^n \xi_k w_j^{(k)} \left[ 1 - w_j^{(k)} \right] + \lambda_j & j = \ell \\ - \sum_{k=1}^n \xi_k w_j^{(k)} w_\ell^{(k)} & j \neq \ell \end{cases}. \quad (157)$$

Hence, we have recovered the moment results from Sect. 4.2 of Jahnke and Huisinga.  $\square$

## 5 Birth-death-autocatalysis calculations

In this section, we present the calculations relevant to proving the formulas from Theorem 3 on the birth-death-autocatalysis system. First, we evaluate the path integral expression for the propagator  $U$ . Then we use the explicit form of the propagator to derive the transition probability, and several interesting limiting forms of it. We do not explicitly show how to compute the generating function directly from the propagator, because it is very similar to the other calculations.

### 5.1 Evaluating the propagator

According to Appendix C, for the birth-death-autocatalysis system we have

$$\mathcal{H}(ip, z, t) = ip \left[ k + (c - \gamma)z \right] - c p^2 z. \quad (158)$$

This propagator calculation is somewhat more involved than the one for the monomolecular system.

**Lemma 6** (*Birth-death-autocatalysis propagator*) *The propagator for the birth-death-autocatalysis system is*

$$U(ip_f, t; z_0, t_0) = \exp \left\{ iz_0 q(t) + i \int_{t_0}^t k(s) q(t - s + t_0) ds \right\} \tag{159}$$

where  $q(s)$  is as in Theorem 3.

**Proof** The path integral expression for the propagator  $U(ip_f, z_0)$  is

$$U = \lim_{N \rightarrow \infty} \int \prod_{\ell=1}^{N-1} \frac{dz_\ell dp_\ell}{2\pi} \exp \left\{ \sum_{\ell=1}^{N-1} -ip_\ell(z_\ell - z_{\ell-1}) + \Delta t \mathcal{H}(ip_\ell, z_{\ell-1}, t_{\ell-1}) + \Delta t \mathcal{H}(ip_f, z_{N-1}, t_{N-1}) + ip_f z_{N-1} \right\} \tag{160}$$

where we have used slightly different notation than before since there is only one chemical species. In order to evaluate this path integral, first integrate over each  $z_\ell$ , and then integrate over each  $p_\ell$ . Collecting terms containing  $z_\ell$ , the integral over each  $z_\ell$  looks like

$$\int_0^\infty \frac{dz_\ell}{2\pi} \exp \left\{ z_\ell \left[ -c_\ell \Delta t p_{\ell+1}^2 + i(c_\ell - \gamma_\ell) \Delta t p_{\ell+1} - i(p_\ell - p_{\ell+1}) \right] \right\} = \frac{1}{2\pi i} \frac{1}{(p_\ell - p_{\ell+1}) - \Delta t [(c_\ell - \gamma_\ell) p_{\ell+1} + ic_\ell p_{\ell+1}^2]} \tag{161}$$

The integrals over  $p_\ell$  can now be done—but they must be done in a specific order. Do the integral over  $p_{N-1}$ , then  $p_{N-2}$ , and so on, until the integral over  $p_1$  has been done. Each of these integrals is schematically

$$\frac{1}{2\pi i} \int_{-\infty}^\infty dp_\ell \frac{f(p_\ell)}{(p_\ell - p_{\ell+1}) - \Delta t [(c_\ell - \gamma_\ell) p_{\ell+1} + ic_\ell p_{\ell+1}^2]} \tag{162}$$

where the function  $f(p_\ell)$  has no poles. This means that each integral can be evaluated using Cauchy’s integral formula, so that the net effect of doing them is to enforce the  $(N - 1)$  constraints

$$p_\ell = p_{\ell+1} + \Delta t [(c_\ell - \gamma_\ell) p_{\ell+1} + ic_\ell p_{\ell+1}^2] \tag{163}$$

on the  $p_\ell$  for  $\ell = 1, \dots, N - 1$ . There are no more integrals to do, so all that remains is to evaluate what’s left of the propagator using these constraints. Eq. 163 looks like an Euler time step, although it is ‘backwards’—we go from  $p_{\ell+1}$  to  $p_\ell$  instead of the other way around. Define  $q_{N-\ell} := p_\ell$  so that it reads

$$q_{N-\ell} = q_{N-\ell-1} + \Delta t [(c_\ell - \gamma_\ell) q_{N-\ell-1} + ic_\ell q_{N-\ell-1}^2] \tag{164}$$



Choosing  $\ell = N - n$ , we find

$$q_n = q_{n-1} + \Delta t \left[ (c_{N-n} - \gamma_{N-n}) q_{n-1} + i c_{N-n} q_{n-1}^2 \right]. \tag{165}$$

This corresponds to dynamics

$$\frac{dq(s)}{ds} = [c(t - s + t_0) - \gamma(t - s + t_0)] q(s) + i c(t - s + t_0) q(s)^2 \tag{166}$$

where  $s \in [t_0, t]$  and  $q(t_0) = p_f$ . As can be verified by substitution, Eq. 166 is solved by

$$q(s) = \frac{w(s)}{\frac{1}{p_f} - i \int_{t_0}^s c(t - t' + t_0) w(t') dt'} \tag{167}$$

where  $w(t)$  is the solution to

$$\frac{dw(s)}{ds} = [c(t - s + t_0) - \gamma(t - s + t_0)] w(s) \tag{168}$$

with  $w(t_0) = 1$  (c.f. Eq. 30), i.e.

$$w(s) = e^{\int_{t_0}^s c(t-t'+t_0) - \gamma(t-t'+t_0) dt'}. \tag{169}$$

The continuous limit of Eq. 163 is then  $p(s) := q(t - s + t_0)$ . With that done, the propagator with most terms integrated out reads

$$U = \lim_{N \rightarrow \infty} \exp \left\{ i \sum_{\ell=1}^{N-1} k_{\ell-1} p_{\ell} \Delta t + i p_1 z_0 + \Delta t \left[ i p_1 (c_0 - \gamma_0) z_0 - c_0 p_1^2 z_0 \right] \right\}. \tag{170}$$

The term on the right is just another Euler time step, so we can write it as

$$i z_0 \left\{ p_1 + \Delta t \left[ p_1 (c_0 - \gamma_0) - c_0 p_1^2 \right] \right\} = i z_0 p_0 \tag{171}$$

where we define

$$p_0 := p_1 + \Delta t \left[ p_1 (c_0 - \gamma_0) - c_0 p_1^2 \right]. \tag{172}$$

In the limit as  $N \rightarrow \infty$ ,  $p_0 \rightarrow p(t_0) = q(t)$ . The term on the left is just a Riemann sum:

$$\sum_{\ell=1}^{N-1} k_{\ell-1} p_{\ell} \Delta t \approx \int_{t_0}^t k(s) p(s) ds = \int_{t_0}^t k(s) q(t - s + t_0) ds. \tag{173}$$

Hence, our final answer for the propagator  $U$  is

$$U(ip_f, t; z_0, t_0) = \exp \left\{ iz_0q(t) + i \int_{t_0}^t k(t-s+t_0)q(s) ds \right\} \tag{174}$$

where we have reparameterized the integral on the right to swap  $s$  and  $(t-s+t_0)$ .  $\square$

The above calculation strategy, which involved converting the evaluation of many contour integrals into the problem of solving a nonlinear ODE, is somewhat dubious; we did not properly verify that the conditions of Cauchy’s integral formula were satisfied. Nonetheless, this strategy turns out to be very powerful, as it enables us to find a much more general result for systems involving only zero and first order reactions (see Appendix D).

As an aside, we note that this calculation closely resembles the Martin-Siggia-Rose-Janssen-De Dominicis path integral computation from our earlier paper (Vastola 2019b): in particular, many applications of Cauchy’s integral formula and another ‘backwards’ Euler time step constraint are both involved.

### 5.2 Deriving the transition probability

As in Sect. 4.2 and 4.3, we will use the propagator derived in the previous section to derive an expression for the transition probability  $P(x, t; \xi, t_0)$ .

**Lemma 7** (*Birth-death-autocatalysis transition probability*) *For the birth-death-autocatalysis system, the transition probability  $P(x, t; \xi, t_0)$  is*

$$P(x, t; \xi, t_0) = \frac{1}{2\pi} \int_{-\infty}^{\infty} dp_f \frac{[1 + iq(t)]^\xi e^{i \int_{t_0}^t k(t-s+t_0)q(s) ds}}{(1 + ip_f)^{x+1}} \tag{175}$$

where  $q(s)$  is as in Theorem 3.

**Proof** Using Eq. 108, we have

$$P(x, t; \xi, t_0) = \frac{1}{x!} \int \frac{dz_f dp_f}{2\pi} \frac{dz_0 dp_0}{2\pi} (z_f)^x e^{-z_f} \times \tag{176}$$

$$\times e^{iz_0q(t) + i \int_{t_0}^t k(t-s+t_0)q(s) ds} (1 + ip_0)^\xi e^{-ip_0z_0 - ip_fz_f} .$$

The integral over  $z_0$  is

$$\int_0^\infty \frac{dz_0}{2\pi} e^{-iz_0[p_0 - q(t)]} = \frac{1}{2\pi i} \frac{1}{p_0 - q(t)} . \tag{177}$$

The integral over  $p_0$  can be performed using Cauchy’s integral formula:

$$\frac{1}{2\pi i} \int_{-\infty}^{\infty} dp_0 \frac{(1 + ip_0)^\xi}{p_0 - q(t)} = [1 + iq(t)]^\xi . \tag{178}$$

The integral over  $z_f$  can be recognized as a Laplace transform:

$$\int_0^\infty dz_f (z_f)^x e^{-z_f[1+ip_f]} = \frac{x!}{(1 + ip_f)^{x+1}} . \tag{179}$$

Putting these together, we obtain the desired result. □

We will leave our solution in this form, since it is difficult to evaluate the contour integral without knowing the explicit time-dependence of the rates. In the next few sections, we will examine a few special cases.

### 5.3 Time-independent rates

**Lemma 8** (*Birth-death-autocatalysis transition probability for time-independent rates*)  
 Suppose the parameters  $k$ ,  $\gamma$ , and  $c$  are all time-independent and non-zero. Then the transition probability can be rewritten as

$$P = \left(\frac{\gamma/c - 1}{\gamma/c - w}\right)^{k/c} \frac{(1-w)^{x-\xi}}{(\gamma/c - w)^x} \times \sum_{j=0}^{\xi} \binom{\xi}{j} \frac{(j+k/c)_x}{x!} \left[1 - \frac{\gamma}{c} w\right]^{\xi-j} \left[\frac{w(\gamma/c - 1)^2}{\gamma/c - w}\right]^j \tag{180}$$

where  $(y)_x := (y)(y+1)\cdots(y+x-1)$  is the Pochhammer symbol/rising factorial, and where  $w(t) = e^{-(\gamma-c)(t-t_0)}$ .

**Proof** In this case,  $q(t)$  reads

$$\begin{aligned} \dot{q} &= [c - \gamma] q + ic q^2 \\ q(t) &= \frac{e^{(c-\gamma)T}}{\frac{1}{p_f} - i\frac{c}{c-\gamma} [e^{(c-\gamma)T} - 1]} = \frac{w(t)}{\frac{1}{p_f} - i\frac{c}{c-\gamma} [w(t) - 1]} \end{aligned} \tag{181}$$

where  $T := t - t_0$ . We have

$$\int_{t_0}^t q(s) ds = \frac{i}{c} \log \left\{ 1 - \frac{ic}{c - \gamma} [e^{(c-\gamma)T} - 1] p_f \right\} \tag{182}$$

so that the convolution term from the propagator reads

$$e^{ik \int_{t_0}^t q(s) ds} = \frac{1}{\left[1 - \frac{ic}{c-\gamma} [e^{(c-\gamma)T} - 1] p_f\right]^{k/c}} = \frac{1}{\left[1 - iB(t)p_f\right]^{k/c}} \tag{183}$$

where we define

$$B(t) := \frac{c}{c - \gamma} [w(t) - 1] . \tag{184}$$

It is important to note that Eq. 183 has no poles in the upper half-plane (the region around which we are integrating), regardless of whether  $c - \gamma > 0$ ,  $c - \gamma < 0$ , or  $c = \gamma$ . Next,

$$1 + iq(t) = 1 + \frac{iw(t)p_f}{1 - iB(t)p_f} = \left[ 1 - \frac{w(t)}{B(t)} \right] + \frac{w(t)}{B(t)} \frac{1}{[1 - iB(t)p_f]} \tag{185}$$

so that

$$[1 + iq(t)]^\xi = \sum_{j=0}^{\xi} \binom{\xi}{j} \left[ 1 - \frac{w(t)}{B(t)} \right]^{\xi-j} \left( \frac{w(t)}{B(t)} \right)^j \frac{1}{[1 - iB(t)p_f]^j}. \tag{186}$$

Putting all these results together, our expression for the transition probability is

$$P = \sum_{j=0}^{\xi} \binom{\xi}{j} \left[ 1 - \frac{w(t)}{B(t)} \right]^{\xi-j} \left( \frac{w(t)}{B(t)} \right)^j \frac{1}{x! i^x} \times \left\{ \frac{x!}{2\pi i} \int_{-\infty}^{\infty} dp_f \frac{1}{[1 - iB(t)p_f]^{j+k/c}} \frac{1}{(p_f - i)^{x+1}} \right\}. \tag{187}$$

Since

$$\begin{aligned} & \frac{d^x}{dp_f^x} \left[ \frac{1}{[1 - iB(t)p_f]^{j+k/c}} \right]_{p=i} \\ &= \frac{i^x B(t)^x}{[1 + B(t)]^{j+k/c+x}} \left( j + \frac{k}{c} \right) \left( j + \frac{k}{c} + 1 \right) \cdots \left( j + \frac{k}{c} + x - 1 \right) \end{aligned} \tag{188}$$

we have

$$\begin{aligned} P &= \sum_{j=0}^{\xi} \binom{\xi}{j} \left[ 1 - \frac{w(t)}{B(t)} \right]^{\xi-j} \left( \frac{w(t)}{B(t)} \right)^j \frac{(j + k/c)_x}{x!} \frac{B(t)^x}{[1 + B(t)]^{j+k/c+x}} \\ &= \left( \frac{1 - \frac{\gamma}{c}}{w - \frac{\gamma}{c}} \right)^{k/c} \left( \frac{w - 1}{w - \frac{\gamma}{c}} \right)^x \sum_{j=0}^{\xi} \binom{\xi}{j} \frac{(j + k/c)_x}{x!} \\ &\quad \times \left[ 1 - \left( 1 - \frac{\gamma}{c} \right) \frac{w}{w - 1} \right]^{\xi-j} \left[ \frac{w \left( 1 - \frac{\gamma}{c} \right)^2}{(w - 1) \left( w - \frac{\gamma}{c} \right)} \right]^j \\ &= \left( \frac{\frac{\gamma}{c} - 1}{\frac{\gamma}{c} - w} \right)^{k/c} \frac{(1 - w)^{x-\xi}}{\left( \frac{\gamma}{c} - w \right)^x} \times \\ &\quad \times \sum_{j=0}^{\xi} \binom{\xi}{j} \frac{(j + k/c)_x}{x!} \left[ 1 - \frac{\gamma}{c} w \right]^{\xi-j} \left[ \frac{w \left( \frac{\gamma}{c} - 1 \right)^2}{\frac{\gamma}{c} - w} \right]^j \end{aligned} \tag{189}$$

where  $(y)_x := (y)(y + 1) \cdots (y + x - 1)$  is the Pochhammer symbol/rising factorial. This can also be written in terms of the hypergeometric function  ${}_2F_1(a, b; c; x)$ .  $\square$

### 5.4 Binomial, Poisson, and negative binomial special cases

**Proof** (Corollary 2) Return to the original contour integral for time-dependent rates (Eq. 40), and set  $k = c = 0$ , but leave the time-dependence of  $\gamma(t)$  arbitrary. We have

$$w(t) := \exp \left[ - \int_{t_0}^t \gamma(t') dt' \right] \tag{190}$$

$$q(t) = w(t) p_f \tag{191}$$

$$P(x, t; \xi, t_0) = \frac{1}{2\pi} \int_{-\infty}^{\infty} dp_f \frac{[1 + iw(t)p_f]^\xi}{(1 + ip_f)^{x+1}}. \tag{192}$$

The function in the numerator has no poles, so the contour integral can easily be evaluated using Cauchy’s integral formula. The result is

$$P(x, t; \xi, t_0) = \binom{\xi}{x} [w(t)]^x [1 - w(t)]^{\xi-x} \tag{193}$$

for  $x \leq \xi$  and 0 otherwise, i.e. a binomial distribution.

Return to the original contour integral for time-dependent rates (Eq. 40), and set  $\gamma = c = 0$ , but leave the time-dependence of  $k(t)$  arbitrary. We have

$$\lambda(t) := \int_{t_0}^t k(t') dt' \tag{194}$$

$$q(t) = p_f \tag{195}$$

$$P(x, t; \xi, t_0) = \frac{1}{2\pi} \int_{-\infty}^{\infty} dp_f \frac{e^{i\lambda(t)p_f}}{(1 + ip_f)^{x+1-\xi}}. \tag{196}$$

This contour integral can be evaluated using either Cauchy’s integral formula or a table of integrals (c.f. Gradshteyn and Ryzhik (2014) ET I 118(3), in section 3.382, on pg. 365). The result is

$$P(x, t; \xi, t_0) = \frac{\lambda(t)^{x-\xi} e^{-\lambda(t)}}{(x - \xi)!} \tag{197}$$

for  $x \geq \xi$  and 0 otherwise, i.e. a (shifted) Poisson distribution.

Return to the original contour integral for time-dependent rates (Eq. 40), and set  $k = \gamma = 0$ , but leave the time-dependence of  $c(t)$  arbitrary. In this case, we will define  $w(t)$  differently from before as

$$w(t) := \exp \left[ - \int_{t_0}^t c(t') dt' \right] \tag{198}$$

i.e. as the reciprocal of what we previously called  $w(t)$ . This is to match the result from Jahnke and Huisinga. Now we have

$$q(t) = \frac{w(t)^{-1}}{\frac{1}{p_f} - i[w(t)^{-1} - 1]} \quad (199)$$

$$P(x, t; \xi, t_0) = \frac{1}{2\pi} \int_{-\infty}^{\infty} dp_f \frac{1}{(1 + ip_f)^{x-\xi+1}} \frac{1}{[1 - i(w(t)^{-1} - 1)p_f]^\xi}. \quad (200)$$

The term on the right has no poles in the upper half-plane, so we can evaluate it using Cauchy's formula to find

$$P(x, t; \xi, t_0) = \binom{x-1}{\xi-1} [w(t)]^\xi [1 - w(t)]^{x-\xi} \quad (201)$$

which is nonzero only for  $x \geq \xi$ , i.e. we have a shifted negative binomial distribution.  $\square$

## 6 Discussion and conclusion

We rederived Jahnke and Huisinga's classic result on monomolecular reaction systems (c.f. Theorem 2 and Eq. 31) using the Doi-Peliti coherent state path integral approach, which reduces solving the CME to the computation of many integrals. In addition, we also derived an explicit exact time-dependent solution to a problem involving an autocatalytic reaction that was beyond the scope of Jahnke and Huisinga's method (c.f. Theorem 3 and Eq. 40), and a formal exact solution for systems involving arbitrary combinations of zero and first order reactions (c.f. Theorem 4 and Eq. 57; see Appendix D and Appendix E for the proof). We hope that our calculations, as well as our detailed description of the Doi-Peliti formalism, help make the Doi-Peliti method more accessible to mathematical biologists studying the CME.

The strength of the Doi-Peliti approach—that calculations require nothing more clever than evaluating many integrals—is probably also its primary weakness. In Jahnke and Huisinga's original paper (Jahnke and Huisinga 2007), they began with proofs of partial results that offered intuition for why their main result is true: in short, Poisson remains Poisson, and multinomial remains multinomial. In contrast, our calculation does not seem to offer such insight en route to the full solution. This may make it easier to generalize to other kinds of systems (as we did in Sect. 5 and Appendix D), but it is a little unsatisfying.

Still, the Doi-Peliti approach *was* able to generate a solution in a nontrivial case where Jahnke and Huisinga's approach broke down, and we showed that it can offer solutions in far more general and nontrivial cases in Appendix D. While the calculation is likely to be tedious, it seems possible that the Doi-Peliti approach could also be used to find explicit generating functions and transition probabilities (i.e. involving the explicit solution for  $\mathbf{q}(t)$ ) for suitable generalizations of (for example) the birth-death-autocatalysis system, like one that involves many birth reactions, death reactions, and

reactions of the form  $S_j \rightarrow S_k + S_\ell$ . It is not clear what new insights are necessary to solve explicitly for  $\mathbf{q}(t)$  in cases like this.

Another obvious objection to the Doi-Peliti approach is that it is not entirely mathematically rigorous: in rederiving Jahnke and Huisinga's result, we freely swapped many improper integrals, frequently utilized the integral representation of the Dirac delta function, and so on. But we did get answers, and the method is likely to yield answers for problems that other methods cannot currently solve. If nothing else, the Doi-Peliti approach can be used as a tool to generate answers, which can be justified as rigorously correct using some other method (e.g. by showing that they solve the CME directly).

How far can one push the Doi-Peliti approach to obtaining exact solutions? One important class of systems whose CME solutions would be extremely useful to know are bimolecular systems, whose reactions involve at most two input molecules and two output molecules (e.g. binding reactions  $A + B \rightarrow C$ ). Because binding reactions are ubiquitous in biology, and because there is a sense in which *all* chemical reaction systems (as notes in Gillespie (2000)) can be reduced to a list of at most bimolecular reactions<sup>7</sup>, this solution or some suitably approximated version of it would include nearly all systems of practical interest. As we noted earlier in the introduction, solutions are only known for this class of systems in extremely special cases (e.g. Laurenzi (2000), Arslan and Laurenzi (2008)). Can the Doi-Peliti technique solve bimolecular reaction networks, or some nontrivial subclass of them?

The answer is currently unclear. As we point out in Appendix E, the success of the Doi-Peliti approach in solving zero and first order reaction networks is essentially equivalent to the fact that these systems can be treated using the method of characteristics. From the path integral point of view, this means that the evaluation of many integrals can be reduced to solving some (possibly nonlinear) system of ODEs. This idea, at least in its current form, appears to no longer work when reactions with two input molecules are permitted.

To see why, consider the one species system whose reaction list consists only of  $X + X \xrightarrow{c} \emptyset$ ; this is in some sense the simplest nontrivial example of a system in which complications arise. The Hamiltonian kernel of this system is

$$\mathcal{H}(ip, z, t) = -\frac{c}{2} (ip) (ip + 2) z^2. \quad (202)$$

This gives rise to terms like  $p_\ell^2 z_{\ell-1}^2$  inside the path integral, which yield Gaussian integrals with respect to either the  $p_\ell$  or  $z_\ell$ . Even in this simple case, it is unclear how to evaluate all of these Gaussian integrals, or to convert the problem of evaluating them into something simpler (e.g. solving an ODE or recurrence relation of some kind). Furthermore, the Hamiltonian kernel above actually yields integrals that appear not to be well-defined (since integrals whose integrands go like  $\exp\{p_\ell^2 z_{\ell-1}^2\}$  diverge for  $z_{\ell-1} \in (0, \infty)$  and  $p_\ell \in (-\infty, \infty)$ ), although this can in principle be circumvented

<sup>7</sup> A related fact is that systems involving reactions with more than two input molecules can be well-approximated by systems involving reactions with *at most* two input molecules; this is a recent result due to Tomislav (2021).

by choosing a different resolution of the identity (c.f. Appendix B.5) as the foundation of the path integral for these problems.

More broadly, it is not clear to what extent the difficulties the Doi-Peliti approach seems to have with higher-order reactions are particular to it, or shared by essentially every approach for solving the CME. Although this is difficult to determine, we can note for now that since the Doi-Peliti approach appears to be able to reproduce every kind of exact result currently known (or at least currently known to the author; this includes time-dependent, stationary, single species, multi-species, etc. results), the challenges it faces in generalizing to more complicated systems are probably shared by other known methods.

While we did not resort to approximations in this paper, it is worth noting that utilizing Doi-Peliti path integrals enables the use of powerful perturbative and asymptotic expansions. For most systems of interest in mathematical biology (e.g. gene networks with many species and interactions), this is the way in which the Doi-Peliti approach can be practically applied. See Weber and Frey (2017), and Assaf and Meerson (2017), for recent reviews discussing approximation techniques related to path integral descriptions of the CME.

The Doi-Peliti path integral is just one example of a stochastic path integral (Weber and Frey 2017; Vastola and Holmes 2019). The Onsager-Machlup (Onsager and Machlup 1953; Machlup and Onsager 1953; Graham 1977; Hertz et al. 2016) and Martin-Siggia-Rose-Janssen-De Dominicis (Martin et al. 1973; Janssen 1976; DE Dominicis 1976; De Dominicis and Peliti 1978; Hertz et al. 2016) path integrals are two other examples, which offer an alternative to the Fokker-Planck equation in the same way the Doi-Peliti path integral is an alternative to the CME. While exact computations of these path integrals are also tedious, they are just as mechanical—one can ‘turn the crank’ and generate answer, without relying on (for example) *a priori* knowledge of special functions to solve differential equations (Vastola 2019a, b).

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## A Quantum vs standard notation

In this paper, we make abundant use of Dirac’s bra-ket notation for vectors and inner products. While this notation is standard in quantum mechanics, it is less often used in areas with a more strictly mathematical bent. In this appendix, we briefly explain our justification for this nonstandard choice, and review its relationship with notation more commonly used in linear algebra and stochastic processes, so that this paper can be more easily read by mathematicians unfamiliar with quantum mechanical notation.

### A.1 Brief justification for quantum notation

Although it is not normally used in the study of stochastic processes, it is the author’s strong belief that the bra-ket notation originally developed for quantum mechanics is



most appropriate here. Because this notation makes it harder for most mathematicians to read this paper, here we briefly argue why this is necessary.

Given that the problems we are attempting to solve are quite complicated, carefully choosing notation is important; a bad choice of notation would clutter our already complicated arguments, making them nearly impossible to understand. We would like notation that (i) *generalizes* cleanly to complicated systems in arbitrarily many dimensions; (ii) *simplifies* the construction of the Doi-Peliti path integral; and (iii) is *suggestive* of the operations we want to take, and not suggestive of operations that are not valid.

Let us say more about each heuristic requirement:

1. **Generalizes:** We are studying systems for which there are  $n$  distinct chemical species, where  $n \geq 1$  is some positive integer. We have seen that this forces us to work in a Hilbert space where each basis vector can be identified with an element of  $\mathbb{N}^n$ . We need notation for each basis vector, as well as for sums over  $\mathbb{N}^n$ , integrals over  $\mathbb{R}^n$ , and eigenvectors with eigenvalues  $\mathbf{z} \in \mathbb{C}^n$ . Denoting basis vectors, eigenvectors, and things like sums and integrals cleanly in arbitrarily many dimensions is easy using bra-ket notation.
2. **Simplifies:** Constructing the Doi-Peliti path integral involves using many identity operators/resolutions of the identity (see Appendix B.5). This is cleanest with bra-ket notation, and using alternative notation obfuscates these steps.
3. **Suggestive/not confusing:** We have to compute many inner products, as well as different kinds of inner products. Bra-ket notation allows them to be denoted simply, e.g. the inner product of  $|x\rangle$  and  $|y\rangle$  is  $\langle x|y\rangle$ . If we used generating function notation, where we have  $g^x$  instead of  $|x\rangle$  and  $g^y$  instead of  $|y\rangle$ , we would have to define strange operations like  $g^x \cdot g^y = x! \delta(x-y)$ . Moreover, this notation suggests operations like  $g^x g^y = g^{x+y}$  are valid, although they are not. Vector notation (using e.g.  $e_x$  and  $e_y$  to denote basis vectors) would be somewhat confusing, because we are already considering vectors like  $\mathbf{x} \in \mathbb{N}^n$  to denote particular states of our system.

Aside from issues of notation, there is a ‘deeper’ reason this path integral requires special notation, whereas for others (see e.g. Bressloff (2014)) standard notation and a Chapman-Kolmogorov-based argument suffices. Most of the time, when path integrals are applied to stochastic processes or mathematical biology, what one is *really* doing is applying the Chapman-Kolmogorov equation many times. This has the interpretation that one is imagining all possible paths from one state to another state and appropriately discretizing them.

This kind of path integral is qualitatively different. It involves expanding an abstract object (rather than the transition probability itself) in terms of coherent states (which we will define later), which are themselves kind of abstract Poisson-like distributions. There does not seem to be the same obvious interpretation linking this path integral to the Chapman-Kolmogorov equation, or to all possible paths through state space (the space of all possible configurations of the system, i.e.  $\mathbb{N}^n$  for a system with  $n$  distinct chemical species). For a state space path integral representation of the CME with such an interpretation, see Vastola and Holmes (2020).

### A.2 Mathematical details of notation correspondence

For now, we will work in one dimension for simplicity. Consider a complex vector space  $V$  with a countable basis  $\mathbf{e}_0, \mathbf{e}_1, \mathbf{e}_2, \dots$ , so that an arbitrary state in this space reads

$$\phi = \sum_{x=0}^{\infty} c(x) \mathbf{e}_x \tag{203}$$

for some complex coefficients  $c(x)$ . In terms of bra-ket notation, we would denote the basis vectors (also called ‘kets’ or ‘states’) by  $|0\rangle, |1\rangle, |2\rangle, \dots$  and an arbitrary state by

$$|\phi\rangle = \sum_{x=0}^{\infty} c(x) |x\rangle, \tag{204}$$

which essentially amounts to the identifications  $\mathbf{e}_x \rightarrow |x\rangle$  and  $\phi \rightarrow |\phi\rangle$ .

Define the inner product  $\langle \mathbf{e}_x, \mathbf{e}_y \rangle := \delta(x - y)$  for all  $x, y \in \mathbb{N}$ , and extend it to arbitrary states by linearity. Using bra-ket notation, we would write

$$\langle x|y\rangle = \delta(x - y). \tag{205}$$

At this point, there are not yet any significant differences between the two choices of notation. The significant differences begin when we consider linear functionals like the functional  $L_y : V \rightarrow \mathbb{C}$  defined by its action on a basis vector  $\mathbf{e}_x$ :

$$L_y(\mathbf{e}_x) := \langle \mathbf{e}_y, \mathbf{e}_x \rangle. \tag{206}$$

Using bra-ket notation, we would denote  $L_y$  by  $\langle y|$  (this is called a ‘bra’), and  $L_y$  acting on  $\mathbf{e}_x$  by  $\langle y|x\rangle$  (the inner product is sometimes called a ‘bra-ket’). This allows us to represent Fourier-like identities like

$$\phi = \sum_{y=0}^{\infty} \langle \mathbf{e}_y, \phi \rangle \mathbf{e}_y \tag{207}$$

via

$$|\phi\rangle = \sum_{y=0}^{\infty} \langle y|\phi\rangle |y\rangle, \tag{208}$$

or more succinctly by defining the operator

$$1 = \sum_{y=0}^{\infty} |y\rangle \langle y| \tag{209}$$

which by definition is equal to the identity operator. Equations like these are often called ‘resolutions of the identity’, because they recast the identity operator in some convenient form. The notation above is meant to be highly suggestive; one can imagine it ‘bumping into’ a vector/state  $|\phi\rangle$  from the left to recover Eq. 208.

This notation also makes it easy to repeatedly apply resolutions of the identity, and to see what the result will be. Compare

$$\phi = \sum_{y_1, y_2, y_3} \langle \mathbf{e}_{y_3}, \mathbf{e}_{y_2} \rangle \langle \mathbf{e}_{y_2}, \mathbf{e}_{y_1} \rangle \langle \mathbf{e}_{y_1}, \phi \rangle \mathbf{e}_{y_3} \quad (210)$$

to

$$|\phi\rangle = \sum_{y_1, y_2, y_3} |y_3\rangle \langle y_3|y_2\rangle \langle y_2|y_1\rangle \langle y_1|\phi\rangle . \quad (211)$$

The above can be obtained simply by inserting Eq. 209 next to  $|\phi\rangle$  many times.

One helpful feature of bra-ket notation is that eigenvectors are traditionally labeled by their eigenvalues. For example, if  $\hat{A}\phi = \lambda\phi$ , it is traditional to write  $\phi$  as

$$\phi \rightarrow |\lambda\rangle , \quad (212)$$

so that  $\hat{A}|\lambda\rangle = \lambda|\lambda\rangle$ . We used this throughout the paper to denote coherent states, which we defined to be eigenstates of the annihilation operators.

Matrix elements—expressions of the form  $\langle \phi_2, \hat{A}\phi_1 \rangle$  for two vectors  $\phi_1$  and  $\phi_2$  and some operator  $\hat{A}$ —are denoted by

$$\langle \phi_2 | \hat{A} | \phi_1 \rangle . \quad (213)$$

This notation is convenient when we are computing matrix elements involving operators and their eigenstates. For example, let  $\hat{a}$  be an operator,  $\hat{a}^\dagger$  be its Hermitian conjugate, and  $\phi_1 \rightarrow |\lambda_1\rangle$  and  $\phi_2 \rightarrow |\lambda_2\rangle$  be eigenstates with eigenvalues  $\lambda_1$  and  $\lambda_2$ , respectively. Then on the one hand, we have

$$\langle \phi_2, \hat{a}^\dagger \hat{a} \phi_1 \rangle = \langle \hat{a} \phi_2, \hat{a} \phi_1 \rangle = \lambda_2^* \lambda_1 \langle \phi_2, \phi_1 \rangle \quad (214)$$

in standard notation. On the other hand, we have

$$\langle \lambda_2 | \hat{a}^\dagger \hat{a} | \lambda_1 \rangle = \lambda_2^* \lambda_1 \langle \lambda_2 | \lambda_1 \rangle \quad (215)$$

using bra-ket notation, where we imagine  $\hat{a}^\dagger$  ‘acting to the left’ and  $\hat{a}$  ‘acting to the right’.

That is about all there is to say about the correspondence between bra-ket notation and typical vector space notation. One should keep in mind that the strength of bra-ket notation is in repeatedly applying the identity operator/resolutions of the identity, which is required to construct the Doi-Peliti path integral. The correspondence is summarized (for arbitrary dimensions, using the notation introduced in Sect. 2) in Table 1.

**Table 1** Let  $\mathbf{x} \in \mathbb{R}^n$ , and let the notation be as in Sect. 2.2 (e.g.  $\mathbf{x}! := x_1! \cdots x_n!$ ). This table summarizes the correspondence between quantum and standard notation for several objects discussed in this appendix, as well as objects discussed elsewhere in this paper (e.g. coherent states)

Object	Bra-ket notation	Standard notation
basis vector/ket	$ \mathbf{x}\rangle$	$\mathbf{e}_x$
linear functional/bra	$\langle \mathbf{x} $	$L_x : \mathbf{e}_y \mapsto \langle \mathbf{e}_x, \mathbf{e}_y \rangle$
zero vector	0	0
arbitrary state	$ \phi\rangle = \sum_{\mathbf{x}} c(\mathbf{x})  \mathbf{x}\rangle$	$\phi = \sum_{\mathbf{x}} c(\mathbf{x}) \mathbf{e}_x$
inner product	$\langle \mathbf{x} \mathbf{y}\rangle$	$\langle \mathbf{e}_x, \mathbf{e}_y \rangle$
operator matrix element	$\langle \mathbf{x} \mathcal{A} \mathbf{y}\rangle = \langle \mathbf{x} \mathcal{A}^\dagger \mathbf{y}\rangle$	$\langle \mathbf{e}_x, \mathcal{A} \mathbf{e}_y \rangle = \langle \mathcal{A}^\dagger \mathbf{e}_x, \mathbf{e}_y \rangle$
generating function	$ \psi(t)\rangle = \sum_{\mathbf{x}} P(\mathbf{x}, t)  \mathbf{x}\rangle$	$\psi(t) = \sum_{\mathbf{x}} P(\mathbf{x}, t) \mathbf{e}_x$
coherent state (c.s.)	$ \mathbf{z}\rangle = \sum_{\mathbf{y}} \frac{\mathbf{z}^{\mathbf{y}}}{\mathbf{y}!} e^{-\mathbf{z} \cdot \mathbf{1}}  \mathbf{y}\rangle$	$\text{cs}(\mathbf{z}) = \sum_{\mathbf{y}} \frac{\mathbf{z}^{\mathbf{y}}}{\mathbf{y}!} e^{-\mathbf{z} \cdot \mathbf{1}} \mathbf{e}_y$
c.s. identity operator	$ \mathbf{x}\rangle = \int_{(0,\infty)^n} dz \int_{\mathbb{R}^n} \frac{d\mathbf{p}}{(2\pi)^n}  \mathbf{z}\rangle \langle -i\mathbf{p} \mathbf{x}\rangle e^{-i\mathbf{z} \cdot \mathbf{p}}$	$\mathbf{e}_x = \int_{(0,\infty)^n} dz \int_{\mathbb{R}^n} \frac{d\mathbf{p}}{(2\pi)^n} \text{cs}(\mathbf{z}) \langle \text{cs}(-i\mathbf{p}), \mathbf{e}_x \rangle e^{-i\mathbf{z} \cdot \mathbf{p}}$

### A.3 Three ways to write the generating function

A few words should also be said about the relationship between various ways to write the generating function. We remind the reader that it is defined (in one dimension again, for simplicity) in terms of standard/Euclidean notation and bra-ket notation via

$$\psi = \sum_{x=0}^{\infty} P(x, t) \mathbf{e}_x \qquad |\psi\rangle = \sum_{x=0}^{\infty} P(x, t) |x\rangle \tag{216}$$

where  $P(x, t)$  is a solution to the CME. These objects live in a Hilbert space, and so we can add them, take inner products, and so on. But what we usually mean by the label ‘generating function’ is the analytic function

$$\psi(g, t) = \sum_{x=0}^{\infty} P(x, t) g^x \tag{217}$$

with  $g \in \mathbb{C}$ , which is not a vector at all. How do these different notions of the generating function relate, and why do we choose to primarily work with the former instead of the latter?

It turns out that the Hilbert space objects and analytic function form are completely equivalent, up to the identification  $g^x \rightarrow |x\rangle$ , and that working with one instead of the other is mostly a matter of taste or convenience. As we note in Appendix E, the analytic function form can be recovered from the vector form by taking the appropriate

Grassberger-Scheunert inner product:

$$\langle g^* - 1 | \psi(t) \rangle = \sum_{x=0}^{\infty} P(x, t) \langle g^* - 1 | x \rangle = \sum_{x=0}^{\infty} P(x, t) (1 + g - 1)^x = \psi(g, t). \quad (218)$$

More interestingly, the equations of motion they satisfy exactly correspond. For example, in the case of the chemical birth-death process, we remind the reader that  $\psi(g, t)$  satisfies the PDE

$$\frac{\partial \psi(g, t)}{\partial t} = k(t)[g - 1]\psi(g, t) - \gamma(t)[g - 1] \frac{\partial \psi(g, t)}{\partial g} \quad (219)$$

whereas  $|\psi\rangle$  satisfies the equation

$$\frac{\partial |\psi\rangle}{\partial t} = \hat{H} |\psi\rangle \quad (220)$$

where in this case the Hamiltonian operator  $\hat{H}$  is given (in terms of our original creation and annihilation operators) by

$$\hat{H} = k(\hat{\pi} - 1) - \gamma(\hat{\pi} - 1)\hat{a}. \quad (221)$$

This is the same as the above PDE, provided one makes the identifications

$$\begin{aligned} \hat{\pi} &\rightarrow g \\ \hat{a} &\rightarrow \frac{\partial}{\partial g}. \end{aligned} \quad (222)$$

These identifications work more generally (for arbitrary numbers of dimensions, and an arbitrary list of reactions). Although they are equivalent, one form of the generating function is often more convenient to use than the other. In our case, we use the Hilbert space form for almost the entirety of this paper, because it allows us to exploit bra-ket notation to denote applying many resolutions of the identity (c.f. Appendix B.5), and to work straightforwardly in terms of matrix elements of the Hamiltonian.

Finally, we should say that the coherent state resolution of the identity we used many times to construct the Doi-Peliti path integral (c.f. Sect. B.5) can be written in terms of ordinary functions as

$$g^x = \int_0^{\infty} dz \int_{-\infty}^{\infty} \frac{dp}{2\pi} e^{z(g-1)} (1 + ip)^x e^{-izp} \quad (223)$$

in one dimension, and

$$\mathbf{g}^{\mathbf{x}} = \int_{(0, \infty)^n} d\mathbf{z} \int_{\mathbb{R}^n} \frac{d\mathbf{p}}{(2\pi)^n} e^{\mathbf{z} \cdot (\mathbf{g} - \mathbf{1})} (\mathbf{1} + i\mathbf{p})^{\mathbf{x}} e^{-i\mathbf{z} \cdot \mathbf{p}} \quad (224)$$

in arbitrarily many dimensions. However, attempting to construct the path integral using this notation instead of bra-ket notation is significantly messier, so we have avoided it.

## B Constructing the Doi-Peliti path integral

In this appendix, we develop the technical machinery of Doi-Peliti theory in order to prove Theorem 5.

### B.1 Time evolution of the generating function

Pressing the analogy between  $\hat{H}$  and matrices, we have the usual formal solution for the generating function  $|\psi(t)\rangle$  in terms of the (time-ordered) exponential of  $\hat{H}$ .

**Proposition 1** (*Formal solution for the generating function*) *The equation of motion for the generating function  $|\psi(t)\rangle$  (Eq. 103) has the formal solution*

$$\begin{aligned} |\psi(t)\rangle &= \hat{T} e^{\int_{t_0}^t \hat{H}(t') dt'} |\psi(t_0)\rangle \\ &= \sum_{j=0}^{\infty} \frac{1}{j!} \int_{t_0}^t \cdots \int_{t_0}^t \hat{T} \left[ \hat{H}(t_1) \cdots \hat{H}(t_n) \right] dt_1 \cdots dt_n \\ &= 1 + \int_{t_0}^t \hat{H}(t_1) dt_1 + \frac{1}{2} \int_{t_0}^t \int_{t_0}^t \hat{T} \left[ \hat{H}(t_1) \hat{H}(t_2) \right] dt_1 dt_2 + \cdots \end{aligned} \tag{225}$$

where  $\hat{T}$  is the time-ordering symbol, whose action on a product of operators is defined to be

$$\hat{T} \left[ \hat{A}_1(t) \hat{A}_2(t') \right] := \begin{cases} \hat{A}_1(t) \hat{A}_2(t') & t \geq t' \\ \hat{A}_2(t') \hat{A}_1(t) & t < t' \end{cases} . \tag{226}$$

To show this, substitute this expression for the generating function directly into Eq. 103. The presence of the time-ordering symbol makes this more subtle than it would be in the case of a time-independent Hamiltonian (i.e. in the case where the reaction parameters were all time-independent), but this is essentially a standard exercise (Schwartz 2014).

One should be careful, both in this proposition and throughout the remainder of this paper, to note that the exponential of  $\hat{H}$  is not even well-defined if  $\hat{H}$  is an unbounded operator. Although we will not attempt to take care of issues like this, one possible approach to making this line of argument more rigorous would be to use a truncated state space, as one does in numerical approaches like finite state projection (Munsky and Khammash 2006; Pele et al. 2006; Fox et al. 2016; Fox and Munsky 2019)—in that case, because  $|\psi(t)\rangle$  would be a finite-dimensional vector and  $\hat{H}$  would be equivalent to a (finite-dimensional) matrix, no problems would arise.

**Corollary 6** For time-independent  $\hat{H}$ , the above formal solution reduces to

$$|\psi(t)\rangle = e^{\hat{H}(t-t_0)} |\psi(t_0)\rangle . \quad (227)$$

**Proof** One can either show that this solves the equation of motion directly, or simplify the result above.  $\square$

Fortunately, we will never have to work with a time-ordered exponential of operators directly. The first salient consequence of the formal solution for us is that

$$|\psi(t + \Delta t)\rangle \approx \left[ 1 + \hat{H}(t)\Delta t \right] |\psi(t)\rangle \quad (228)$$

for sufficiently small  $\Delta t$ , with the approximation becoming exact in the  $\Delta t \rightarrow 0$  limit. Notice that this also matches what we would find by naively approximating the time derivative with a finite difference in Eq. 103.

This formal solution motivates defining the time evolution operator, which carries the solution at time  $t_1$  (the state  $|\psi(t_1)\rangle$ ) to the solution at time  $t_2$  (the state  $|\psi(t_2)\rangle$ ).

**Definition 2** The *time evolution operator*  $\hat{U}(t_2, t_1)$  is defined as

$$\begin{aligned} \hat{U}(t_2, t_1) &:= \hat{T} e^{\int_{t_1}^{t_2} \hat{H}(t') dt'} \\ &= 1 + \int_{t_1}^{t_2} \hat{H}(s_1) ds_1 + \frac{1}{2} \int_{t_1}^{t_2} \int_{t_1}^{t_2} \hat{T} \left[ \hat{H}(s_1) \hat{H}(s_2) \right] ds_1 ds_2 + \dots \end{aligned} \quad (229)$$

for any two times  $t_1 \leq t_2$ . In terms of the time evolution operator, the formal solution for  $|\psi(t)\rangle$  can be written

$$|\psi(t)\rangle = \hat{U}(t, t_0) |\psi(t_0)\rangle . \quad (230)$$

The second salient consequence of Proposition 1 is that this operator has an important composition property.

**Proposition 2** (*Composition property of the time evolution operator*) The time evolution operator  $\hat{U}$  has the property that

$$\hat{U}(t_2, t_1) = \hat{U}(t_2, t') \hat{U}(t', t_1) \quad (231)$$

for any time  $t'$  with  $t_1 \leq t' \leq t_2$ .

**Proof** This is most easily seen using the infinite series form of the time evolution operator  $\hat{U}$ , by expanding both sides and showing that they match at each order.  $\square$

## B.2 Basic operators

Because we are interested in the dynamics of the generating function  $|\psi(t)\rangle$ , we need to introduce operators to act on it. In particular, we need to introduce operators that will allow us to write down the Hamiltonian operator  $\hat{H}$ .

For an arbitrary CME (Eq. 99), the Hamiltonian operator  $\hat{H}$  can be written in terms of certain linear operators. In particular, define the operators  $\hat{x}_k$  (for all  $k = 1, \dots, n$ ) and  $\hat{r}_j(t)$  (for all  $j = 1, \dots, M$ ), which act on an arbitrary basis ket  $|\mathbf{x}\rangle$  according to

$$\begin{aligned}\hat{x}_k |\mathbf{x}\rangle &= x_k |\mathbf{x}\rangle \\ \hat{r}_j(t) |\mathbf{x}\rangle &= a_j(\mathbf{x}, t) |\mathbf{x} + \mathbf{v}_j\rangle.\end{aligned}\quad (232)$$

In terms of them, the Hamiltonian operator  $\hat{H}$  can be written

$$\hat{H} = \sum_{j=1}^M \hat{r}_j(t) - a_j(\hat{\mathbf{x}}, t) \quad (233)$$

where  $a_j(\hat{\mathbf{x}}, t) |\mathbf{x}\rangle = a_j(\mathbf{x}, t) |\mathbf{x}\rangle$ . But perhaps more usefully, all of the Hamiltonian operators we consider in this paper can *also* be written in terms of so-called annihilation operators  $\hat{a}_k$  and creation operators  $\hat{\pi}_k$ .

**Definition 3** Define the *annihilation* and *creation operators*  $\hat{a}_j$  and  $\hat{\pi}_j$  for all  $j = 1, \dots, n$  as the operators whose action on a basis vector  $|\mathbf{x}\rangle$  is

$$\begin{aligned}\hat{a}_j |\mathbf{x}\rangle &= x_j |\mathbf{x} - \boldsymbol{\epsilon}_j\rangle \\ \hat{\pi}_j |\mathbf{x}\rangle &= |\mathbf{x} + \boldsymbol{\epsilon}_j\rangle\end{aligned}\quad (234)$$

where we remind the reader that  $\boldsymbol{\epsilon}_j$  is the  $n$ -dimensional vector with a 1 in the  $j$ th place and zeros everywhere else.

It is easy to show that these operators satisfy the commutation relations analogous to those seen in quantum mechanics [(for example, in the ladder operator treatment of the harmonic oscillator, Griffiths and Schroeter 2018, or in the canonical quantization approach to quantum field theory, Schwartz 2014]. These properties will be used in calculations a few times throughout this paper.

**Proposition 3** Recall that, for two operators  $\hat{A}_1$  and  $\hat{A}_2$ , their commutator is defined to be  $[\hat{A}_1, \hat{A}_2] := \hat{A}_1\hat{A}_2 - \hat{A}_2\hat{A}_1$ . The creation and annihilation operators satisfy the commutation relations

$$[\hat{a}_j, \hat{\pi}_k] = \delta(j - k), \quad [\hat{a}_j, \hat{a}_k] = [\hat{\pi}_j, \hat{\pi}_k] = 0. \quad (235)$$

**Proof** Use their definitions to straightforwardly show this. □



In essence, the Doi-Peliti approach to solving Eq. 103 involves using many coherent state ‘resolutions of the identity’ (a phrase we will define shortly) to rewrite Eq. 225 as a coherent state path integral. Once that path integral is evaluated, quantities like moments and  $P(\mathbf{x}, t)$  can be recovered by manipulating the path integral solution in specific ways. In order to follow this prescription, we will need to define coherent states, define inner products, and construct associated resolutions of the identity; that is our next task.

### B.3 Coherent states

Because we will be expressing the Hamiltonian operator in terms of creation and annihilation operators, it is convenient to work in terms of states that behave simply when acted upon by these operators. These are the so-called coherent states, which are often used to study the semiclassical limit of quantum mechanics. Here, we will only care about them for their algebraic properties; while their biological meaning is not completely obscure (they are essentially states that correspond to Poisson distributions), thinking about it is not necessary in what follows.

**Definition 4** Let  $\mathbf{z} = (z_1, \dots, z_n)^T \in \mathbb{C}^n$ . A *coherent state* is a state

$$|\mathbf{z}\rangle := \sum_{\mathbf{y}} c(\mathbf{y}) |\mathbf{y}\rangle \quad (236)$$

satisfying

$$\begin{aligned} \hat{a}_j |\mathbf{z}\rangle &= z_j |\mathbf{z}\rangle && \text{for all } j = 1, \dots, n \\ \sum_{\mathbf{y}} c(\mathbf{y}) &= 1 \end{aligned} \quad (237)$$

i.e. it is an eigenstate of all annihilation operators  $\hat{a}_j$ , and it has a specific normalization.

By imposing the eigenstate constraint on an arbitrary state, it is straightforward to determine the coefficients  $c(\mathbf{y})$  explicitly. Coherent states can also be written in terms of a specific combination of creation operators acting on the ‘vacuum’ state  $|\mathbf{0}\rangle$ . We make these statements more precise in the following proposition.

**Proposition 4** *The coherent state  $|\mathbf{z}\rangle$  can explicitly be written in the following two equivalent forms:*

(i)

$$|\mathbf{z}\rangle = \sum_{\mathbf{y}} \frac{z_1^{y_1} \cdots z_n^{y_n}}{y_1! \cdots y_n!} e^{-(z_1 + \cdots + z_n)} |\mathbf{y}\rangle = \sum_{\mathbf{y}} \frac{\mathbf{z}^{\mathbf{y}}}{\mathbf{y}!} e^{-\mathbf{z} \cdot \mathbf{1}} |\mathbf{y}\rangle \quad (238)$$

(ii)

$$|\mathbf{z}\rangle = \sum_{\mathbf{y}} \frac{[z_1(\hat{\pi}_1 - 1)]^{y_1} \cdots [z_n(\hat{\pi}_n - 1)]^{y_n}}{y_1! \cdots y_n!} |\mathbf{0}\rangle = e^{\mathbf{z} \cdot (\hat{\pi} - \mathbf{1})} |\mathbf{0}\rangle \quad (239)$$

where  $\hat{\boldsymbol{\pi}} := (\hat{\pi}_1, \dots, \hat{\pi}_n)^T$ .

**Proof** Showing (i) is straightforward. To show (ii), first note that  $[\hat{a}_j, (\hat{\pi}_j - 1)^y] = y(\hat{\pi}_j - 1)^{y-1}$  for all  $y \in \mathbb{N}$ , a useful commutator result that can be proved by induction. Using this, along with the facts that  $\hat{a}_j$  commutes with  $\hat{\pi}_k$  for  $k \neq j$  and the  $\hat{\pi}_k$  all commute with each other, we have

$$\begin{aligned} \hat{a}_j |z\rangle &= e^{\mathbf{z} \cdot (\hat{\boldsymbol{\pi}} - \mathbf{1}) - z_j (\hat{\pi}_j - 1)} \sum_{y_j=0}^{\infty} \frac{z_j^{y_j}}{y_j!} \hat{a}_j (\hat{\pi}_j - 1)^{y_j} |\mathbf{0}\rangle \\ &= e^{\mathbf{z} \cdot (\hat{\boldsymbol{\pi}} - \mathbf{1}) - z_j (\hat{\pi}_j - 1)} \sum_{y_j=0}^{\infty} \frac{z_j^{y_j}}{y_j!} \left\{ (\hat{\pi}_j - 1)^{y_j} \hat{a}_j + y_j (\hat{\pi}_j - 1)^{y_j-1} \right\} |\mathbf{0}\rangle \tag{240} \\ &= z_j e^{\mathbf{z} \cdot (\hat{\boldsymbol{\pi}} - \mathbf{1}) - z_j (\hat{\pi}_j - 1)} \sum_{y_j=1}^{\infty} \frac{z_j^{y_j-1} (\hat{\pi}_j - 1)^{y_j-1}}{(y_j - 1)!} |\mathbf{0}\rangle \\ &= z_j |z\rangle . \end{aligned}$$

Hence, this expression satisfies the eigenstate constraint. Noting that eigenstates are unique up to a proportionality constant, to show that it satisfies the normalization constraint (and hence is the same as the expression given by (i)), observe that

$$\begin{aligned} e^{\mathbf{z} \cdot (\hat{\boldsymbol{\pi}} - \mathbf{1})} |\mathbf{0}\rangle &= \sum_{\mathbf{y}} \frac{z_1^{y_1} \dots z_n^{y_n} [(-1)^{y_1 + \dots + y_n} + \dots]}{y_1! \dots y_n!} |\mathbf{0}\rangle \tag{241} \\ &= e^{-\mathbf{z} \cdot \mathbf{1}} |\mathbf{0}\rangle + \dots \end{aligned}$$

i.e. the coefficient of  $|\mathbf{0}\rangle$  is  $e^{-\mathbf{z} \cdot \mathbf{1}}$ , because every other term in the above expansion contains a creation operator. Because this is the same as the coefficient of  $|\mathbf{0}\rangle$  in (i), we have equivalence.  $\square$

In what follows, we will generally reserve the letters  $\mathbf{z}$  and  $\mathbf{p}$  for coherent states.

### B.4 Inner products

Now we will define two inner products on our space, each of which individually turns it into a Hilbert space: the exclusive product, and the Grassberger-Scheunert product. Both were introduced by Grassberger and Scheunert in a 1980 paper that clearly describes their motivation and properties (Grassberger and Scheunert 1980); we are calling their “inclusive” inner product the Grassberger-Scheunert product to recognize their contribution.

Briefly, the exclusive product is useful for computing  $P(\mathbf{x}, t)$ , while the Grassberger-Scheunert product is useful for simplifying path integral calculations (specifically, we avoid having to perform a “Doi shift” (Cardy et al. 2008; Weber and Frey 2017); see Eq. 3.4 of Peliti (1985) for an example of the Doi shift) and computing moments. We will use both inner products in solving the CME.

In this section and the following sections, the reader should keep in mind that  $\langle \mathbf{x} | \hat{A}(t) | \mathbf{y} \rangle$ , where  $\hat{A}(t)$  is some possibly time-dependent operator, means the same as  $\langle \mathbf{e}_x, \hat{A}(t) \mathbf{e}_y \rangle$  in more standard notation. See Appendix A for more details.

**Definition 5** Let  $|\mathbf{x}\rangle$  and  $|\mathbf{y}\rangle$  be basis vectors. Their *exclusive product* is defined to be

$$\langle \mathbf{x} | \mathbf{y} \rangle_{ex} := \mathbf{x}! \delta(\mathbf{x} - \mathbf{y}) . \quad (242)$$

Extending this by linearity, define the exclusive product of two arbitrary states  $|\phi_1\rangle$  and  $|\phi_2\rangle$  as (c.f. Eq. 100)

$$\langle \phi_2 | \phi_1 \rangle_{ex} = \sum_{\mathbf{x}} \mathbf{x}! c_2^*(\mathbf{x}) c_1(\mathbf{x}) . \quad (243)$$

**Definition 6** Let  $|\mathbf{x}\rangle$  and  $|\mathbf{y}\rangle$  be basis vectors, and define  $\hat{\mathbf{a}} := (\hat{a}_1, \dots, \hat{a}_n)^T$ . Their *Grassberger-Scheunert product* is defined to be

$$\langle \mathbf{x} | \mathbf{y} \rangle := \langle \mathbf{x} | e^{\hat{\pi} \cdot \mathbf{1}} e^{\hat{\mathbf{a}} \cdot \mathbf{1}} | \mathbf{y} \rangle_{ex} = \sum_{\mathbf{k}} \frac{\mathbf{x}! \mathbf{y}!}{(\mathbf{x} - \mathbf{k})! (\mathbf{y} - \mathbf{k})! \mathbf{k}!} \quad (244)$$

where the sum on the right is over all values of  $\mathbf{k} \in \mathbb{N}^n$  with  $k_j \leq \min(x_j, y_j)$  for all  $j = 1, \dots, n$ . Extending this by linearity, define the Grassberger-Scheunert product of two arbitrary states  $|\phi_1\rangle$  and  $|\phi_2\rangle$  as

$$\langle \phi_2 | \phi_1 \rangle = \langle \phi_2 | e^{\hat{\pi} \cdot \mathbf{1}} e^{\hat{\mathbf{a}} \cdot \mathbf{1}} | \phi_1 \rangle_{ex} . \quad (245)$$

While it is not obvious just from looking at them, it is straightforward to show that the operator-based and sum-based definitions are equivalent (see Grassberger and Scheunert (1980) and the appendix to Peliti (1985)).

The primary reason these inner products are useful to define is that the creation and annihilation operators behave well under Hermitian conjugation with respect to them.

**Proposition 5** (*Hermitian conjugates of creation and annihilation operators*) Let  $|\mathbf{x}\rangle$  and  $|\mathbf{y}\rangle$  be basis vectors. With respect to the exclusive product,  $\hat{a}_j$  and  $\hat{\pi}_j$  are Hermitian conjugates of each other for all  $j = 1, \dots, n$ , i.e.

$$\begin{aligned} (\hat{a}_j)^\dagger &= \hat{\pi}_j \\ \langle \mathbf{x} | \hat{a}_j | \mathbf{y} \rangle_{ex} &= \langle \mathbf{y} | \hat{\pi}_j | \mathbf{x} \rangle_{ex} . \end{aligned} \quad (246)$$

With respect to the Grassberger-Scheunert product, the Hermitian conjugate of  $\hat{a}_j$  is

$$(\hat{a}_j)^\dagger = \hat{\pi}_j - 1 \quad (247)$$

for all  $j = 1, \dots, n$ , i.e.

$$\langle \mathbf{x} | \hat{a}_j | \mathbf{y} \rangle = \langle \mathbf{y} | \hat{\pi}_j - 1 | \mathbf{x} \rangle . \quad (248)$$

**Proof** Showing that  $\hat{\pi}_j$  and  $\hat{a}_j$  are Hermitian conjugates with respect to the exclusive product is straightforward given their definitions, so we will show that  $(\hat{a}_j)^\dagger = \hat{\pi}_j - 1$  with respect to the Grassberger-Scheunert product.

Recall the result mentioned in the proof of Proposition 4 that  $[\hat{a}_j, (\hat{\pi}_j - 1)^y] = y(\hat{\pi}_j - 1)^{y-1}$  for all  $y \in \mathbb{N}$ . Using just the same argument, one can show  $[\hat{a}_j, \hat{\pi}_j^y] = y(\hat{\pi}_j)^{y-1}$  for all  $y \in \mathbb{N}$ . This, in turn, can be used to prove that

$$e^{\hat{\pi}_j} \hat{a}_j = (\hat{a}_j - 1) e^{\hat{\pi}_j}. \tag{249}$$

Let  $|\mathbf{x}\rangle$  and  $|\mathbf{y}\rangle$  be arbitrary basis vectors. Now we can say that

$$\begin{aligned} \langle \mathbf{x} | \hat{a}_j | \mathbf{y} \rangle &= \langle \mathbf{x} | e^{\hat{\pi} \cdot \mathbf{1}} e^{\hat{\mathbf{a}} \cdot \mathbf{1}} \hat{a}_j | \mathbf{y} \rangle_{ex} \\ &= \langle \mathbf{x} | e^{\hat{\pi}_j} \hat{a}_j e^{\hat{\pi} \cdot \mathbf{1} - \hat{\pi}_j} e^{\hat{\mathbf{a}} \cdot \mathbf{1}} | \mathbf{y} \rangle_{ex} \\ &= \langle \mathbf{x} | (\hat{a}_j - 1) e^{\hat{\pi}_j} e^{\hat{\pi} \cdot \mathbf{1} - \hat{\pi}_j} e^{\hat{\mathbf{a}} \cdot \mathbf{1}} | \mathbf{y} \rangle_{ex} \\ &= \langle \mathbf{x} + \epsilon_j | e^{\hat{\pi} \cdot \mathbf{1}} e^{\hat{\mathbf{a}} \cdot \mathbf{1}} | \mathbf{y} \rangle_{ex} - \langle \mathbf{x} | e^{\hat{\pi} \cdot \mathbf{1}} e^{\hat{\mathbf{a}} \cdot \mathbf{1}} | \mathbf{y} \rangle_{ex} \\ &= \langle \mathbf{x} + \epsilon_j | \mathbf{y} \rangle - \langle \mathbf{x} | \mathbf{y} \rangle \end{aligned} \tag{250}$$

where we have used the fact that  $\hat{\pi}_j$  and  $\hat{a}_j$  are Hermitian conjugates with respect to the exclusive product in the next to last step. But this is the same as

$$\langle \mathbf{y} | \hat{\pi}_j - 1 | \mathbf{x} \rangle = \langle \mathbf{y} | \mathbf{x} + \epsilon_j \rangle - \langle \mathbf{y} | \mathbf{x} \rangle \tag{251}$$

because the Grassberger-Scheunert product of two basis vectors is symmetric. Hence,  $\hat{a}_j$  and  $\hat{\pi}_j - 1$  are Hermitian conjugates with respect to the Grassberger-Scheunert product.  $\square$

Now let us compute some inner products that we will use later.

**Proposition 6** (*Useful inner products*) *Let  $|\mathbf{x}\rangle$  be a basis vector, and let  $|\mathbf{z}\rangle$  and  $|\mathbf{p}\rangle$  be coherent states. Then*

(i)

$$\langle \mathbf{x} | \mathbf{z} \rangle_{ex} = \mathbf{z}^{\mathbf{x}} e^{-\mathbf{z} \cdot \mathbf{1}} \tag{252}$$

(ii)

$$\langle \mathbf{x} | \mathbf{z} \rangle = (\mathbf{1} + \mathbf{z})^{\mathbf{x}} \tag{253}$$

(iii)

$$\langle \mathbf{p} | \mathbf{z} \rangle_{ex} = e^{\mathbf{p}^* \cdot \mathbf{z} - (\mathbf{p}^* + \mathbf{z}) \cdot \mathbf{1}} \tag{254}$$

(iv)

$$\langle \mathbf{p} | \mathbf{z} \rangle = e^{\mathbf{p}^* \cdot \mathbf{z}}. \quad (255)$$

Moreover, we remind the reader that other results (e.g.  $\langle \mathbf{z} | \mathbf{x} \rangle = (\mathbf{1} + \mathbf{z}^*)^{\mathbf{x}}$ ) can be obtained from the above ones by taking a complex conjugate.

**Proof** First, the exclusive product of a basis state  $|\mathbf{x}\rangle$  with a coherent state  $|\mathbf{z}\rangle$  is

$$\langle \mathbf{x} | \mathbf{z} \rangle_{ex} = \sum_{\mathbf{y}} \frac{\mathbf{z}^{\mathbf{y}}}{\mathbf{y}!} e^{-\mathbf{z} \cdot \mathbf{1}} \langle \mathbf{x} | \mathbf{y} \rangle_{ex} = \sum_{\mathbf{y}} \frac{\mathbf{z}^{\mathbf{y}}}{\mathbf{y}!} e^{-\mathbf{z} \cdot \mathbf{1}} \mathbf{x}! \delta_{\mathbf{x}\mathbf{y}} = \mathbf{z}^{\mathbf{x}} e^{-\mathbf{z} \cdot \mathbf{1}}. \quad (256)$$

Next, the Grassberger-Scheunert product of a basis state  $|\mathbf{x}\rangle$  with a coherent state  $|\mathbf{z}\rangle$  is

$$\begin{aligned} \langle \mathbf{x} | \mathbf{z} \rangle &= \left\langle \mathbf{x} \left| e^{\hat{\pi} \cdot \mathbf{1}} e^{\hat{\mathbf{a}} \cdot \mathbf{1}} \right| \mathbf{z} \right\rangle_{ex} \\ &= e^{\mathbf{z} \cdot \mathbf{1}} \left\langle \mathbf{x} \left| e^{\hat{\pi} \cdot \mathbf{1}} \right| \mathbf{z} \right\rangle_{ex} \\ &= e^{(\mathbf{z} + \mathbf{1}) \cdot \mathbf{1}} \left\langle \mathbf{x} \left| e^{(\mathbf{z} + \mathbf{1}) \cdot (\hat{\pi} - \mathbf{1})} \right| \mathbf{0} \right\rangle_{ex} \\ &= e^{(\mathbf{z} + \mathbf{1}) \cdot \mathbf{1}} \langle \mathbf{x} | \mathbf{z} + \mathbf{1} \rangle_{ex} \\ &= (\mathbf{1} + \mathbf{z})^{\mathbf{x}} \end{aligned} \quad (257)$$

where we have used that  $|\mathbf{z}\rangle$  is an eigenstate of the annihilation operators  $\hat{a}_j$ , the operator representation of  $|\mathbf{z}\rangle$  from Proposition 4, and Eq. 256. The exclusive product of two coherent states is

$$\langle \mathbf{p} | \mathbf{z} \rangle_{ex} = \sum_{\mathbf{y}} \frac{(\mathbf{p}^*)^{\mathbf{y}}}{\mathbf{y}!} e^{-\mathbf{p}^* \cdot \mathbf{1}} \langle \mathbf{y} | \mathbf{z} \rangle_{ex} = \sum_{\mathbf{y}} \frac{(\mathbf{p}^*)^{\mathbf{y}} \mathbf{z}^{\mathbf{y}}}{\mathbf{y}!} e^{-(\mathbf{p}^* + \mathbf{z}) \cdot \mathbf{1}} = e^{\mathbf{p}^* \cdot \mathbf{z} - (\mathbf{p}^* + \mathbf{z}) \cdot \mathbf{1}}. \quad (258)$$

Finally, the Grassberger-Scheunert product of two coherent states is

$$\langle \mathbf{p} | \mathbf{z} \rangle = \left\langle \mathbf{p} \left| e^{\hat{\pi} \cdot \mathbf{1}} e^{\hat{\mathbf{a}} \cdot \mathbf{1}} \right| \mathbf{z} \right\rangle_{ex} = e^{(\mathbf{p}^* + \mathbf{z}) \cdot \mathbf{1}} \langle \mathbf{p} | \mathbf{z} \rangle_{ex} = e^{\mathbf{p}^* \cdot \mathbf{z}} \quad (259)$$

where we have used Eq. 258.  $\square$

## B.5 Resolution of the identity

The phrase ‘resolution of the identity’ refers to a useful way to write the identity operator. In our case, we would like to write the identity operator in terms of coherent states, which will allow us to construct the Doi-Peliti path integral. The relevant proposition, using coherent states and the Grassberger-Scheunert product, is the following.

**Proposition 7** (*Identity operator in terms of coherent states*) Let  $|\mathbf{x}\rangle$  be a basis vector, and  $|\mathbf{z}\rangle$  and  $|-i\mathbf{p}\rangle$  be coherent states. Then

$$|\mathbf{x}\rangle = \int_{(0,\infty)^n} d\mathbf{z} \int_{\mathbb{R}^n} \frac{d\mathbf{p}}{(2\pi)^n} |\mathbf{z}\rangle \langle -i\mathbf{p}|\mathbf{x}\rangle e^{-i\mathbf{z}\cdot\mathbf{p}} \tag{260}$$

i.e.

$$1 = \int_{(0,\infty)^n} d\mathbf{z} \int_{\mathbb{R}^n} \frac{d\mathbf{p}}{(2\pi)^n} |\mathbf{z}\rangle \langle -i\mathbf{p}| e^{-i\mathbf{z}\cdot\mathbf{p}} \tag{261}$$

is the identity operator (because the relationship holds for basis vectors, it holds for all states by linearity).

**Proof** To establish Eq. 261, first observe that

$$\begin{aligned} & \int_{(0,\infty)^n} d\mathbf{z} \int_{\mathbb{R}^n} \frac{d\mathbf{p}}{(2\pi)^n} |\mathbf{z}\rangle \langle -i\mathbf{p}|\mathbf{x}\rangle e^{-i\mathbf{z}\cdot\mathbf{p}} \\ &= \int_{(0,\infty)^n} d\mathbf{z} \int_{\mathbb{R}^n} \frac{d\mathbf{p}}{(2\pi)^n} |\mathbf{z}\rangle (\mathbf{1} + i\mathbf{p})^{\mathbf{x}} e^{-i\mathbf{z}\cdot\mathbf{p}} \\ &= \sum_{\mathbf{y}} \frac{1}{\mathbf{y}!} |\mathbf{y}\rangle \int_{(0,\infty)^n} d\mathbf{z} \mathbf{z}^{\mathbf{y}} \int_{\mathbb{R}^n} \frac{d\mathbf{p}}{(2\pi)^n} (\mathbf{1} + i\mathbf{p})^{\mathbf{x}} e^{-\mathbf{z}\cdot(\mathbf{1}+i\mathbf{p})} \\ &= \sum_{\mathbf{y}} \frac{1}{\mathbf{y}!} |\mathbf{y}\rangle \int_{(0,\infty)^n} d\mathbf{z} \mathbf{z}^{\mathbf{y}} \left(-\frac{d}{d\mathbf{z}}\right)^{\mathbf{x}} \int_{\mathbb{R}^n} \frac{d\mathbf{p}}{(2\pi)^n} e^{-\mathbf{z}\cdot(\mathbf{1}+i\mathbf{p})} \end{aligned} \tag{262}$$

for all basis kets  $|\mathbf{x}\rangle$ , where we remind the reader of the shorthand

$$\left(\frac{d}{d\mathbf{z}}\right)^{\mathbf{x}} := \left(\frac{d}{dz_1}\right)^{x_1} \cdots \left(\frac{d}{dz_n}\right)^{x_n} \tag{263}$$

used to ease notation. Integrate the last line of Eq. 262 by parts to obtain

$$\begin{aligned} & \sum_{\mathbf{y}} \frac{1}{\mathbf{y}!} |\mathbf{y}\rangle \int_{(0,\infty)^n} d\mathbf{z} \left(\frac{d}{d\mathbf{z}}\right)^{\mathbf{x}} [\mathbf{z}^{\mathbf{y}}] e^{-\mathbf{z}\cdot\delta(\mathbf{z})} \\ &= \sum_{\mathbf{y}} \frac{1}{\mathbf{y}!} |\mathbf{y}\rangle \mathbf{x}! \delta(\mathbf{y} - \mathbf{x}) \\ &= |\mathbf{x}\rangle \end{aligned} \tag{264}$$

which confirms that Eq. 261 is a resolution of the identity. □

Because Eq. 261 is essentially due to the usual integral representation of the Dirac delta ‘function’, one should be careful to note that the above identity is not totally rigorous (without more carefully appealing to the machinery of distributions). Still, it

is hard to do without it in what follows; as we are about to see, it enables the entire path integral approach.

We can use the coherent state resolution of the identity (Eq. 261) we just constructed to rewrite our formal solution for  $|\psi(t)\rangle$  (Eq. 225). Applying it twice, we have the following result.

**Corollary 7** (*Generating function in terms of coherent states*) *The generating function can be written in the form*

$$|\psi(t)\rangle = \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} |\mathbf{z}^f\rangle \langle -i\mathbf{p}^f | \hat{U}(t, t_0) | \mathbf{z}^0 \rangle \langle -i\mathbf{p}^0 | \psi(t_0) \rangle e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0 - i\mathbf{p}^f \cdot \mathbf{z}^f}. \tag{265}$$

**Proof** Apply Proposition 7 to the formal solution for  $|\psi(t)\rangle$  (c.f. Eq. 230) twice.  $\square$

The object that appears in the middle of this expression is sufficiently important that it deserves its own name.

**Definition 7** The *propagator* is defined as the matrix element

$$U(i\mathbf{p}^f, t; \mathbf{z}^0, t_0) := \langle -i\mathbf{p}^f | \hat{U}(t, t_0) | \mathbf{z}^0 \rangle. \tag{266}$$

where  $|-i\mathbf{p}^f\rangle$  and  $|\mathbf{z}^0\rangle$  are coherent states, and  $\hat{U}(t, t_0)$  is the time evolution operator. Usually, we will refer to it using the abbreviated notation  $U(i\mathbf{p}^f, \mathbf{z}^0)$ .

Now we will construct a coherent state path integral expression for the propagator—this is one of the most important equations in this paper, as it forms the basis of Doi-Peliti path integral calculations.

**Proposition 8** (*Path integral expression for the propagator*) *The propagator  $U(i\mathbf{p}^f, t; \mathbf{z}^0, t_0)$  is equal to the path integral*

$$U = \lim_{N \rightarrow \infty} \int \prod_{\ell=1}^{N-1} \frac{d\mathbf{z}^\ell d\mathbf{p}^\ell}{(2\pi)^n} \exp \left\{ \sum_{\ell=1}^{N-1} -i\mathbf{p}^\ell \cdot (\mathbf{z}^\ell - \mathbf{z}^{\ell-1}) + \Delta t \mathcal{H}(i\mathbf{p}^\ell, \mathbf{z}^{\ell-1}, t_{\ell-1}) + \Delta t \mathcal{H}(i\mathbf{p}^f, \mathbf{z}^{N-1}, t_{N-1}) + i\mathbf{p}^f \cdot \mathbf{z}^{N-1} \right\} \tag{267}$$

where  $\Delta t := (t - t_0)/N$  and the Hamiltonian kernel  $\mathcal{H}$  is defined as

$$\mathcal{H}(i\mathbf{p}, \mathbf{z}, t) := \langle -i\mathbf{p} | \hat{H}(t) | \mathbf{z} \rangle e^{-i\mathbf{p} \cdot \mathbf{z}} \tag{268}$$

where  $|-i\mathbf{p}\rangle$  and  $|\mathbf{z}\rangle$  are coherent states with  $\mathbf{p}, \mathbf{z} \in \mathbb{R}^n$ .

**Proof** First write the time evolution operator  $U(t, t_0)$  as a product of many time evolution operators using the composition property (Eq. 231):

$$\hat{U}(t, t_0) = \hat{U}(t, t_{N-1}) \hat{U}(t_{N-1}, t_{N-2}) \cdots \hat{U}(t_1, t_0) \tag{269}$$

where  $t_\ell := t_0 + \ell \Delta t$  for  $\ell = 0, \dots, N$ , and  $\Delta t := (t - t_0)/N$ . Now insert  $(N - 1)$  resolutions of the identity to write

$$U = \int \prod_{\ell=1}^{N-1} \frac{d\mathbf{z}^\ell d\mathbf{p}^\ell}{(2\pi)^n} \langle -i\mathbf{p}^f \mid \hat{U}(t, t_{N-1}) \mid \mathbf{z}^{\ell-1} \rangle \cdots \langle -i\mathbf{p}^1 \mid \hat{U}(t_1, t_0) \mid \mathbf{z}^0 \rangle e^{-i \sum_{\ell=1}^{N-1} \mathbf{p}^\ell \cdot \mathbf{z}^\ell}. \tag{270}$$

To arrive at our desired path integral, all we must do is compute the matrix elements in the above equation. Assuming that  $N$  is large enough that  $\Delta t$  is very small, we have that

$$\hat{U}(t_\ell, t_{\ell-1}) \approx 1 + \hat{H}(t_{\ell-1}) \Delta t \tag{271}$$

i.e.  $\hat{U}$  is equal to its first order Taylor expansion. Moreover, this inequality becomes exact in the  $N \rightarrow \infty$  limit. Using this,

$$\langle -i\mathbf{p}^\ell \mid \hat{U}(t_\ell, t_{\ell-1}) \mid \mathbf{z}^{\ell-1} \rangle \approx e^{i\mathbf{p}^\ell \cdot \mathbf{z}^{\ell-1}} + \Delta t \langle -i\mathbf{p}^\ell \mid \hat{H}(t_{\ell-1}) \mid \mathbf{z}^{\ell-1} \rangle. \tag{272}$$

By the definition of the Hamiltonian kernel,

$$\begin{aligned} \langle -i\mathbf{p}^\ell \mid \hat{U}(t_\ell, t_{\ell-1}) \mid \mathbf{z}^{\ell-1} \rangle &\approx e^{i\mathbf{p}^\ell \cdot \mathbf{z}^{\ell-1}} \left[ 1 + \mathcal{H}(i\mathbf{p}^\ell, \mathbf{z}^{\ell-1}, t_{\ell-1}) \Delta t \right] \\ &\approx e^{i\mathbf{p}^\ell \cdot \mathbf{z}^{\ell-1} + \Delta t \mathcal{H}(i\mathbf{p}^\ell, \mathbf{z}^{\ell-1}, t_{\ell-1})} \end{aligned} \tag{273}$$

where we have again used the fact that  $\Delta t$  is small. Putting all of these matrix elements together, our final coherent state path integral expression for  $U(i\mathbf{p}^f, \mathbf{z}^0)$  reads

$$\begin{aligned} U = \lim_{N \rightarrow \infty} \int \prod_{\ell=1}^{N-1} \frac{d\mathbf{z}^\ell d\mathbf{p}^\ell}{(2\pi)^n} \exp \left\{ \sum_{\ell=1}^{N-1} -i\mathbf{p}^\ell \cdot (\mathbf{z}^\ell - \mathbf{z}^{\ell-1}) + \Delta t \mathcal{H}(i\mathbf{p}^\ell, \mathbf{z}^{\ell-1}, t_{\ell-1}) \right. \\ \left. + \Delta t \mathcal{H}(i\mathbf{p}^f, \mathbf{z}^{N-1}, t_{N-1}) + i\mathbf{p}^f \cdot \mathbf{z}^{N-1} \right\} \end{aligned} \tag{274}$$

where the  $N \rightarrow \infty$  limit must be taken so that the approximation we made in Eq. 271 becomes exact. □

Note that we have (i) free interchanged the  $N \rightarrow \infty$  limit with many integrals over  $\mathbb{R}^n$  and  $(0, \infty)^n$ ; (ii) repeatedly used Eq. 261, which is based on a formal integral representation of the Dirac delta function; and (iii) based this expansion on  $\hat{U}$  without even checking that the exponential of the Hamiltonian operator is well-defined. This is just to caution the reader that the Doi-Peliti approach requires extensive mathematical legwork to be made completely rigorous (as with all path integral approaches). For our present purpose, it is sufficient to use it to obtain answers that can be rigorously checked.



## B.6 Grassberger-Scheunert creation operators

As we noted in Appendix B.4, the Hermitian conjugate of the annihilation operator  $\hat{a}_j$  with respect to the Grassberger-Scheunert product is  $\hat{\pi}_j - 1$  for all  $j = 1, \dots, n$ . Motivated by this, we define the Grassberger-Scheunert creation operators.

**Definition 8** The *Grassberger-Scheunert* creation operators are defined to be

$$\hat{a}_j^+ := \hat{\pi}_j - 1 \quad (275)$$

for all  $j = 1, \dots, n$ .

In the rest of the appendices, we will take ‘creation operator’ without qualification to mean one of these operators.

All Hamiltonians we consider may be expressed in terms of creation operators and annihilation operators. For example, the Hamiltonian operator corresponding to the chemical birth-death process (c.f. Sect. 2.1 and Eq. 2) can be shown to read

$$\hat{H} = k(t)\hat{a}^+ - \gamma(t)\hat{a}^+\hat{a} \quad (276)$$

which is a specific case of a result we derive later (see Appendix C). Note that this expression is ‘normal ordered’—all creation operators are to the left of all annihilation operators. For all (possibly time-dependent) operators  $\hat{A}(t)$  in this form, i.e.

$$\hat{A}(t) := \sum_{\kappa_1, \dots, \kappa_n, \rho_1, \dots, \rho_n} d_{\rho_1, \dots, \rho_n}^{\kappa_1, \dots, \kappa_n}(t) (\hat{a}_1^+)^{\kappa_1} \dots (\hat{a}_n^+)^{\kappa_n} (\hat{a}_1)^{\rho_1} \dots (\hat{a}_n)^{\rho_n}, \quad (277)$$

coherent state matrix elements are easily evaluated by exploiting that  $(\hat{a}_j)^{\dagger} = \hat{a}_j^+$  and that the coherent states are eigenstates of the annihilation operators. The particular result is the following.

**Proposition 9** (*Coherent state matrix elements of normal ordered operators*) Let  $|\mathbf{z}\rangle$  and  $|\mathbf{p}\rangle$  be coherent states, and  $\hat{A}(t)$  be an arbitrary (possibly time-dependent) operator that is normal ordered (i.e. all creation operators are to the left of all annihilation operators). The coherent state matrix element  $\langle \mathbf{p} | \hat{A}(t) | \mathbf{z} \rangle$  can be evaluated to be

$$\langle \mathbf{p} | \hat{A}(t) | \mathbf{z} \rangle = e^{\mathbf{p}^* \cdot \mathbf{z}} \sum_{\kappa_1, \dots, \kappa_n, \rho_1, \dots, \rho_n} d_{\rho_1, \dots, \rho_n}^{\kappa_1, \dots, \kappa_n}(t) (p_1^*)^{\kappa_1} \dots (p_n^*)^{\kappa_n} (z_1)^{\rho_1} \dots (z_n)^{\rho_n} \quad (278)$$

**Proof** Use the linearity of the inner product to take the sum out, then use the facts that  $(\hat{a}_j)^{\dagger} = \hat{a}_j^+$ ,  $\hat{a}_k |\mathbf{z}\rangle = z_k |\mathbf{z}\rangle$ , and  $\langle \mathbf{p} | \hat{a}_k^+ = p_k^* \langle \mathbf{p} |$ . Finally, note that  $\langle \mathbf{p} | \mathbf{z} \rangle = e^{\mathbf{p}^* \cdot \mathbf{z}}$ .  $\square$

We will use this result in Appendix C to derive many Hamiltonian kernels.

### B.7 Probability distribution and moments

We need some way to extract information (like the transition probability  $P(\mathbf{x}, t)$  or factorial moments) from the generating function  $|\psi(t)\rangle$ . It turns out that we can achieve this using the exclusive product (Peliti 1985) and Grassberger-Scheunert product (Grassberger and Scheunert 1980).

**Proposition 10** (Extracting transition probabilities and moments from the generating function) *Transition probabilities can be obtained from the generating function using the exclusive product, and factorial moments can be obtained from the generating function using the Grassberger-Scheunert product and the annihilation operators. In particular,*

$$P(\mathbf{x}, t) = \frac{\langle \mathbf{x} | \psi(t) \rangle_{ex}}{\mathbf{x}!} \tag{279}$$

and

$$\begin{aligned} \langle x_j(t) \rangle &= \langle \mathbf{0} | \hat{a}_j | \psi(t) \rangle \\ \langle x_j(t)x_k(t) \rangle &= \langle \mathbf{0} | \hat{a}_j \hat{a}_k | \psi(t) \rangle \\ \langle x_j(t)[x_j(t) - 1] \rangle &= \langle \mathbf{0} | \hat{a}_j^2 | \psi(t) \rangle \\ \langle x_j(t)[x_j(t) - 1][x_j(t) - 2] \rangle &= \langle \mathbf{0} | \hat{a}_j^3 | \psi(t) \rangle . \end{aligned} \tag{280}$$

**Proof** By the definition of the exclusive product,

$$\frac{\langle \mathbf{x} | \psi(t) \rangle_{ex}}{\mathbf{x}!} = \sum_{\mathbf{y}} P(\mathbf{y}, t) \frac{\langle \mathbf{x} | \mathbf{y} \rangle_{ex}}{\mathbf{x}!} = \sum_{\mathbf{y}} P(\mathbf{y}, t) \delta(\mathbf{x} - \mathbf{y}) = P(\mathbf{x}, t) . \tag{281}$$

By the explicit definition of the Grassberger-Scheunert product of two basis vectors (c.f. Eq. 244), note that  $\langle \mathbf{0} | \mathbf{x} \rangle = 1$  for all  $\mathbf{x} \in \mathbb{N}^n$ . Then

$$\begin{aligned} \langle \mathbf{0} | \hat{a}_j | \psi(t) \rangle &= \langle \mathbf{0} | \sum_{\mathbf{x}} P(\mathbf{x}, t) \hat{a}_j | \mathbf{x} \rangle \\ &= \langle \mathbf{0} | \sum_{\mathbf{x}} P(\mathbf{x}, t) x_j | \mathbf{x} - \epsilon_j \rangle \\ &= \sum_{\mathbf{x}} P(\mathbf{x}, t) x_j \langle \mathbf{0} | \mathbf{x} - \epsilon_j \rangle \\ &= \sum_{\mathbf{x}} x_j P(\mathbf{x}, t) \\ &= \langle x_j(t) \rangle . \end{aligned} \tag{282}$$

The other expectation value formulas can be demonstrated in a similar fashion. □

With this done, we have all of the machinery necessary to prove Theorem 5, which allows us to solve all of the problems identified in Sect. 2.

### B.8 Proof of main Doi-Peliti result

**Proof** (Theorem 5) Since  $P(\mathbf{x}, t_0) = \delta(\mathbf{x} - \boldsymbol{\xi})$  for some  $\boldsymbol{\xi} \in \mathbb{N}^n$ , we have that  $|\psi(t_0)\rangle = |\boldsymbol{\xi}\rangle$ . By Proposition 6, if  $|-i\mathbf{p}^0\rangle$  is a coherent state with  $\mathbf{p}^0 \in \mathbb{R}^n$ , then

$$\langle -i\mathbf{p}^0 | \psi(t_0) \rangle = \langle -i\mathbf{p}^0 | \boldsymbol{\xi} \rangle = \langle \boldsymbol{\xi} | -i\mathbf{p}^0 \rangle^* = (\mathbf{1} + i\mathbf{p}^0)^\xi. \tag{283}$$

Applying Corollary 7, we have that

$$\begin{aligned} |\psi(t)\rangle &= \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} |\mathbf{z}^f\rangle \langle -i\mathbf{p}^f | \hat{U}(t, t_0) | \mathbf{z}^0 \rangle \langle -i\mathbf{p}^0 | \psi(t_0) \rangle e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0 - i\mathbf{p}^f \cdot \mathbf{z}^f} \\ &= \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} |\mathbf{z}^f\rangle U(i\mathbf{p}^f, t; \mathbf{z}^0, t_0) (\mathbf{1} + i\mathbf{p}^0)^\xi e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0 - i\mathbf{p}^f \cdot \mathbf{z}^f}, \end{aligned} \tag{284}$$

establishing Eq. 104.

We proved the path integral expression for the propagator (Eq. 106) in Proposition 8. Our expression for the Hamiltonian kernel (Eq. 107) can be derived using a formula for  $\hat{H}$  that we identified earlier (Eq. 233). Note,

$$\begin{aligned} \mathcal{H}(i\mathbf{p}, \mathbf{z}, t) &= \langle -i\mathbf{p} | \hat{H}(t) | \mathbf{z} \rangle e^{-i\mathbf{p} \cdot \mathbf{z}} \\ &= e^{-i\mathbf{p} \cdot \mathbf{z}} \sum_{j=1}^M \langle -i\mathbf{p} | \hat{r}_j(t) - a_j(\hat{\mathbf{x}}, t) | \mathbf{z} \rangle. \end{aligned} \tag{285}$$

Using the explicit formula for  $|\mathbf{z}\rangle$  from Proposition 4, we have that

$$\begin{aligned} \mathcal{H} &= e^{-i\mathbf{p} \cdot \mathbf{z}} \sum_{j=1}^M \sum_{\mathbf{y}} \frac{\mathbf{z}^{\mathbf{y}}}{\mathbf{y}!} e^{-\mathbf{z} \cdot \mathbf{1}} \langle -i\mathbf{p} | \hat{r}_j(t) - a_j(\hat{\mathbf{x}}, t) | \mathbf{y} \rangle \\ &= e^{-i\mathbf{p} \cdot \mathbf{z}} \sum_{j=1}^M \sum_{\mathbf{y}} \frac{\mathbf{z}^{\mathbf{y}}}{\mathbf{y}!} e^{-\mathbf{z} \cdot \mathbf{1}} \{ a_j(\mathbf{y}, t) \langle -i\mathbf{p} | \mathbf{y} + \mathbf{v}_j \rangle - a_j(\mathbf{y}, t) \langle -i\mathbf{p} | \mathbf{y} \rangle \}. \end{aligned} \tag{286}$$

Using Proposition 6 to evaluate the Grassberger-Scheunert products, we have

$$\begin{aligned} \mathcal{H} &= e^{-i\mathbf{p} \cdot \mathbf{z}} \sum_{j=1}^M \sum_{\mathbf{y}} \frac{\mathbf{z}^{\mathbf{y}}}{\mathbf{y}!} e^{-\mathbf{z} \cdot \mathbf{1}} a_j(\mathbf{y}, t) \{ (\mathbf{1} + i\mathbf{p})^{\mathbf{y} + \mathbf{v}_j} - (\mathbf{1} + i\mathbf{p})^{\mathbf{y}} \} \\ &= e^{-i\mathbf{p} \cdot \mathbf{z}} \sum_{j=1}^M [(\mathbf{1} + i\mathbf{p})^{\mathbf{v}_j} - 1] \sum_{\mathbf{y}} \frac{\mathbf{z}^{\mathbf{y}} (\mathbf{1} + i\mathbf{p})^{\mathbf{y}}}{\mathbf{y}!} e^{-\mathbf{z} \cdot \mathbf{1}} a_j(\mathbf{y}, t) \\ &= \sum_{j=1}^M [(\mathbf{1} + i\mathbf{p})^{\mathbf{v}_j} - 1] \sum_{\mathbf{y}} \frac{\mathbf{z}^{\mathbf{y}} (\mathbf{1} + i\mathbf{p})^{\mathbf{y}}}{\mathbf{y}!} e^{-\mathbf{z} \cdot (\mathbf{1} + i\mathbf{p})} a_j(\mathbf{y}, t) \end{aligned} \tag{287}$$

which is precisely Eq. 107. By Eq. 279 from Proposition 10,

$$\begin{aligned}
 P &= \frac{\langle \mathbf{x} | \psi(t) \rangle_{ex}}{\mathbf{x}!} \\
 &= \frac{1}{\mathbf{x}!} \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} \langle \mathbf{x} | \mathbf{z}^f \rangle_{ex} U \left( \mathbf{1} + i\mathbf{p}^0 \right)^\xi e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0 - i\mathbf{p}^f \cdot \mathbf{z}^f}. \tag{288}
 \end{aligned}$$

By Proposition 6, this equals

$$P = \frac{1}{\mathbf{x}!} \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} \left( \mathbf{z}^f \right)^{\mathbf{x}} e^{-\mathbf{z}^f \cdot \mathbf{1}} U \left( \mathbf{1} + i\mathbf{p}^0 \right)^\xi e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0 - i\mathbf{p}^f \cdot \mathbf{z}^f}, \tag{289}$$

establishing Eq. 108. By Eq. 280 from Proposition 10, we have

$$\begin{aligned}
 \langle x_k(t) \rangle &= \langle \mathbf{0} | \hat{a}_k | \psi(t) \rangle \\
 &= \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} \langle \mathbf{0} | \hat{a}_k | \mathbf{z}^f \rangle U \left( \mathbf{1} + i\mathbf{p}^0 \right)^\xi e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0 - i\mathbf{p}^f \cdot \mathbf{z}^f} \\
 &= \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} z_k^f \langle \mathbf{0} | \mathbf{z}^f \rangle U \left( \mathbf{1} + i\mathbf{p}^0 \right)^\xi e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0 - i\mathbf{p}^f \cdot \mathbf{z}^f}. \tag{290}
 \end{aligned}$$

By Proposition 6, this equals

$$\langle x_k(t) \rangle = \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} z_k^f U \left( \mathbf{1} + i\mathbf{p}^0 \right)^\xi e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0 - i\mathbf{p}^f \cdot \mathbf{z}^f}, \tag{291}$$

establishing Eq. 109. Similarly,

$$\begin{aligned}
 \langle x_j(t)x_k(t) \rangle &= \langle \mathbf{0} | \hat{a}_j \hat{a}_k | \psi(t) \rangle \\
 &= \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} \langle \mathbf{0} | \hat{a}_j \hat{a}_k | \mathbf{z}^f \rangle U \left( \mathbf{1} + i\mathbf{p}^0 \right)^\xi e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0 - i\mathbf{p}^f \cdot \mathbf{z}^f} \\
 &= \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} z_j^f z_k^f \langle \mathbf{0} | \mathbf{z}^f \rangle U \left( \mathbf{1} + i\mathbf{p}^0 \right)^\xi e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0 - i\mathbf{p}^f \cdot \mathbf{z}^f} \\
 &= \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} z_j^f z_k^f U \left( \mathbf{1} + i\mathbf{p}^0 \right)^\xi e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0 - i\mathbf{p}^f \cdot \mathbf{z}^f} \tag{292}
 \end{aligned}$$

and

$$\begin{aligned}
 \langle x_j(t)[x_j(t) - 1] \rangle &= \langle \mathbf{0} | \hat{a}_j^2 | \psi(t) \rangle \\
 &= \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} \langle \mathbf{0} | \hat{a}_j^2 | \mathbf{z}^f \rangle U \left( \mathbf{1} + i\mathbf{p}^0 \right)^\xi e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0 - i\mathbf{p}^f \cdot \mathbf{z}^f}
 \end{aligned}$$

$$\begin{aligned}
&= \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} \left[ z_j^f \right]^2 \langle \mathbf{0} | \mathbf{z}^f \rangle U (\mathbf{1} + i\mathbf{p}^0)^\xi e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0 - i\mathbf{p}^f \cdot \mathbf{z}^f} \\
&= \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} \left[ z_j^f \right]^2 U (\mathbf{1} + i\mathbf{p}^0)^\xi e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0 - i\mathbf{p}^f \cdot \mathbf{z}^f}, \quad (293)
\end{aligned}$$

establishing Eq. 110. Expressions for higher order (factorial) moments can be derived by an identical argument.  $\square$

## C Hamiltonian kernels

In this appendix, we derive the Hamiltonian kernels for the various models we consider. In principle, there are a few ways to do this. One way is to directly evaluate Eq. 107 for a given model. Another is to first write down the Hamiltonian operator  $\hat{H}$  in terms of annihilation operators and Grassberger-Scheunert creation operators (in normal ordered form), and then apply Proposition 9. In the spirit of Doi-Peliti theory, we use the latter approach here.

### C.1 Monomolecular

**Lemma 9** *The Hamiltonian operator corresponding to the monomolecular CME (Eq. 18) is*

$$\begin{aligned}
\hat{H} &= \sum_{k=1}^n c_{0k}(t) [\hat{\pi}_k - 1] - \sum_{k=1}^n c_{k0}(t) [\hat{\pi}_k - 1] \hat{a}_k \\
&\quad + \sum_{j=1}^n \sum_{k=1}^n c_{jk}(t) [\hat{\pi}_k - \hat{\pi}_j] \hat{a}_j. \quad (294)
\end{aligned}$$

**Proof** First, take the time derivative of  $|\psi(t)\rangle$ :

$$\begin{aligned}
\frac{\partial |\psi\rangle}{\partial t} &= \sum_{\mathbf{x}} \frac{\partial P(\mathbf{x}, t)}{\partial t} |\mathbf{x}\rangle \\
&= \sum_{\mathbf{x}} \left\{ \sum_{k=1}^n c_{0k}(t) [P(\mathbf{x} - \boldsymbol{\epsilon}_k, t) - P(\mathbf{x}, t)] \right. \\
&\quad + \sum_{k=1}^n c_{k0}(t) [(x_k + 1)P(\mathbf{x} + \boldsymbol{\epsilon}_k, t) - x_k P(\mathbf{x}, t)] \\
&\quad \left. + \sum_{j=1}^n \sum_{k=1}^n c_{jk}(t) [(x_j + 1)P(\mathbf{x} + \boldsymbol{\epsilon}_j - \boldsymbol{\epsilon}_k, t) - x_j P(\mathbf{x}, t)] \right\} |\mathbf{x}\rangle \quad (295)
\end{aligned}$$

where we have used Eq. 18. Reindex the sums over  $\mathbf{x}$  so that this expression reads

$$\begin{aligned} \frac{\partial |\psi\rangle}{\partial t} = & \sum_{\mathbf{x}} \left\{ \sum_{k=1}^n c_{0k}(t) [ |\mathbf{x} + \boldsymbol{\epsilon}_k\rangle - |\mathbf{x}\rangle ] \right. \\ & + \sum_{k=1}^n c_{k0}(t) [ x_k |\mathbf{x} - \boldsymbol{\epsilon}_k\rangle - x_k |\mathbf{x}\rangle ] \\ & \left. + \sum_{j=1}^n \sum_{k=1}^n c_{jk}(t) [ x_j |\mathbf{x} - \boldsymbol{\epsilon}_j + \boldsymbol{\epsilon}_k\rangle - x_j |\mathbf{x}\rangle ] \right\} P(\mathbf{x}, t). \end{aligned} \quad (296)$$

Using the creation and annihilation operators we defined earlier, the right-hand side can be written as

$$\begin{aligned} & \sum_{\mathbf{x}} \left\{ \sum_{k=1}^n c_{0k}(t) [ \hat{\pi}_k - 1 ] + \sum_{k=1}^n c_{k0}(t) [ \hat{a}_k - \hat{\pi}_k \hat{a}_k ] \right. \\ & \quad \left. + \sum_{j=1}^n \sum_{k=1}^n c_{jk}(t) [ \hat{a}_j \hat{\pi}_k - \hat{\pi}_j \hat{a}_j ] \right\} P(\mathbf{x}, t) |\mathbf{x}\rangle \\ = & \left\{ \sum_{k=1}^n c_{0k}(t) [ \hat{\pi}_k - 1 ] + \sum_{k=1}^n c_{k0}(t) [ \hat{a}_k - \hat{\pi}_k \hat{a}_k ] \right. \\ & \quad \left. + \sum_{j=1}^n \sum_{k=1}^n c_{jk}(t) [ \hat{a}_j \hat{\pi}_k - \hat{\pi}_j \hat{a}_j ] \right\} |\psi(t)\rangle. \end{aligned} \quad (297)$$

Comparing this with the definition of the Hamiltonian operator (c.f. Eq. 103), we have our result. □

The Hamiltonian can be written more compactly in terms of the Grassberger-Scheunert creation operators:

**Corollary 8** *In terms of the Grassberger-Scheunert creation operator, the Hamiltonian is*

$$\hat{H} = \sum_{k=1}^n c_{0k}(t) \hat{a}_k^+ - \sum_{k=1}^n c_{k0}(t) \hat{a}_k^+ \hat{a}_k + \sum_{j=1}^n \sum_{k=1}^n c_{jk}(t) [ \hat{a}_k^+ - \hat{a}_j^+ ] \hat{a}_j. \quad (298)$$

**Proof** Start with the result above and make the identification  $\hat{a}_j^+ = \hat{\pi}_j - 1$ . □

Note that this expression is ‘normal ordered’—all creation operators are to the left of all annihilation operators. This allows us to use Proposition 9 to compute the Hamiltonian kernel.

**Corollary 9** *The Hamiltonian kernel for the monomolecular CME is*

$$\begin{aligned}
 -i\mathcal{H}(i\mathbf{p}^\ell, \mathbf{z}^{\ell-1}, t_{\ell-1}) &= \sum_{k=1}^n c_{0k}(t_{\ell-1}) p_k^\ell - \sum_{k=1}^n c_{k0}(t_{\ell-1}) p_k^\ell z_k^{\ell-1} \\
 &+ \sum_{j=1}^n \sum_{k=1}^n c_{jk}(t_{\ell-1}) [p_k^\ell - p_j^\ell] z_j^{\ell-1}.
 \end{aligned} \tag{299}$$

**Proof** Make the identifications  $\hat{a}_j^+ \rightarrow ip_j^\ell$  and  $\hat{a}_j \rightarrow z_j^{\ell-1}$  in the Hamiltonian above.  $\square$

### C.2 Birth-death-autocatalysis

**Lemma 10** *The Hamiltonian operator corresponding to the birth-death-autocatalysis CME (Eq. 36) is*

$$\hat{H} = \hat{a}^+ [k + (c - \gamma)\hat{a} + c \hat{a}^+ \hat{a}]. \tag{300}$$

**Proof** Starting with Eq. 36, follow the argument from Lemma 9, and then substitute in the Grassberger-Scheunert creation operator.  $\square$

**Corollary 10** *The Hamiltonian kernel for the birth-death-autocatalysis CME is*

$$\mathcal{H}(ip, z, t) = ip [k + (c - \gamma)z] - c p^2 z. \tag{301}$$

**Proof** Make the identifications  $\hat{a}^+ \rightarrow ip$  and  $\hat{a} \rightarrow z$  in the Hamiltonian above.  $\square$

### C.3 Zero and first order reactions

Writing down the CME directly for this very general system is difficult; however, we *do* know that the Hamiltonian operator of a CME involving only zero and first order reactions only contains terms proportional to products of Grassberger-Scheunert creation operators. We also know that each of its terms involves at most one annihilation operator. Without loss of generality, we can assume the corresponding Hamiltonian operator can be written (c.f. Eq. 54)

$$\begin{aligned}
 \hat{H}(t) &= \sum_{\kappa_1, \dots, \kappa_n} \alpha_{\kappa_1, \dots, \kappa_n}(t) (\hat{a}_1^+)^{\kappa_1} \dots (\hat{a}_n^+)^{\kappa_n} \\
 &+ \sum_{k=1}^n \sum_{\kappa_1, \dots, \kappa_n} \beta_{\kappa_1, \dots, \kappa_n}^k(t) (\hat{a}_1^+)^{\kappa_1} \dots (\hat{a}_n^+)^{\kappa_n} \hat{a}_k
 \end{aligned} \tag{302}$$

for some coefficients  $\alpha_{\kappa_1, \dots, \kappa_n}(t)$  and  $\beta_{\kappa_1, \dots, \kappa_n}^j(t)$  that are determined by the details of one's list of reactions. The corresponding Hamiltonian kernel is

$$\begin{aligned} \mathcal{H}(i\mathbf{p}, \mathbf{z}, t) &= \left\langle -i\mathbf{p} \left| \hat{H}(t) \right| \mathbf{z} \right\rangle e^{-i\mathbf{p} \cdot \mathbf{z}} \\ &= \sum_{\kappa_1, \dots, \kappa_n} \alpha_{\kappa_1, \dots, \kappa_n}(t) (ip_1)^{\kappa_1} \dots (ip_n)^{\kappa_n} \\ &\quad + \sum_{k=1}^n \sum_{\kappa_1, \dots, \kappa_n} \beta_{\kappa_1, \dots, \kappa_n}^k(t) (ip_1)^{\kappa_1} \dots (ip_n)^{\kappa_n} z_k. \end{aligned} \tag{303}$$

### D Zero and first order calculations

In this section, we sketch the calculations necessary for proving the formulas from Theorem 4 on a system with arbitrary combinations of zero and first order reactions. We sketch how the path integral expression for the propagator  $U$  may be evaluated. We also use the explicit form of the propagator to derive the transition probability and generating function.

**Lemma 11** (*Zero and first order reactions propagator*) *The propagator for the system with arbitrary combinations of zero and first order reactions is*

$$U = \exp \left\{ i \mathbf{z}^0 \cdot \mathbf{q}(t) + \int_{t_0}^t \sum_{\kappa_1, \dots, \kappa_n} \alpha_{\kappa_1, \dots, \kappa_n}(t - s + t_0) [iq_1(s)]^{\kappa_1} \dots [iq_n(s)]^{\kappa_n} ds \right\} \tag{304}$$

where  $q(s)$  is as defined in Theorem 4.

**Proof** We will only sketch this proof, because the argument is exactly the same as the one presented in Lemma 6—the notation is just more cluttered, because we are now dealing with a multi-species system and an arbitrarily large list of reactions. One may notice, from a careful look at that prior argument, that its success did not depend on the detailed features of the birth-death-autocatalysis system at all; it only depended on the Hamiltonian containing terms at most first order in annihilation operators (i.e. no terms like  $\hat{a}_j \hat{a}_k$  or  $(\hat{a}_j)^6$  appear). Since this is also true in the current case, we can rerun that argument to find that the propagator can be written in terms of the solution  $\mathbf{q}(t)$  to

$$\frac{dq_j(s)}{ds} = -i \sum_{\kappa_1, \dots, \kappa_n} \beta_{\kappa_1, \dots, \kappa_n}^j(t - s + t_0) [iq_1(s)]^{\kappa_1} \dots [iq_n(s)]^{\kappa_n} \tag{305}$$

satisfying the initial condition  $q_j(t_0) = p_j^f$ . As before, the final propagator has two terms. There is one term that comes from  $\mathbf{p}^0 = \mathbf{q}(t)$  coupling to  $\mathbf{z}^0$ , and another term (due to the terms in the Hamiltonian involving no annihilation operators) that becomes a convolution integral. □



Next, we will derive the transition probability.

**Lemma 12** (Zero and first order reactions transition probability) *The transition probability for the system with arbitrary combinations of zero and first order reactions is*

$$P = \int_{\mathbb{R}^n} \frac{d\mathbf{p}^f}{(2\pi)^n} \frac{[\mathbf{1} + i\mathbf{q}(t)]^\xi e^{i\int_{t_0}^t \sum \alpha_{\kappa_1, \dots, \kappa_n} (t-s+t_0) [iq_1(s)]^{\kappa_1} \dots [iq_n(s)]^{\kappa_n} ds}}{(\mathbf{1} + i\mathbf{p}^f)^{\mathbf{x}+1}} \tag{306}$$

where  $q(s)$  is as in Theorem 4.

**Proof** Begin by using Eq. 108 to write

$$\begin{aligned} P &= \frac{1}{\mathbf{x}!} \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} (\mathbf{z}^f)^{\mathbf{x}} e^{-\mathbf{z}^f \cdot \mathbf{1}} U (\mathbf{1} + i\mathbf{p}^0)^\xi e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0 - i\mathbf{p}^f \cdot \mathbf{z}^f} \\ &= \frac{1}{\mathbf{x}!} \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} (\mathbf{z}^f)^{\mathbf{x}} e^{-\mathbf{z}^f \cdot \mathbf{1}} e^{i\mathbf{z}^0 \cdot \mathbf{q}(t)} (\mathbf{1} + i\mathbf{p}^0)^\xi \\ &\quad \times e^{-i\mathbf{p}^0 \cdot \mathbf{z}^0 - i\mathbf{p}^f \cdot \mathbf{z}^f} e^{i\int_{t_0}^t \sum_{\kappa_1, \dots, \kappa_n} \alpha_{\kappa_1, \dots, \kappa_n} (t-s+t_0) [iq_1(s)]^{\kappa_1} \dots [iq_n(s)]^{\kappa_n} ds} \end{aligned} \tag{307}$$

The integral over  $\mathbf{z}^0$  is

$$\int d\mathbf{z}^0 e^{-i\mathbf{z}^0 \cdot (\mathbf{p}^0 - \mathbf{q}(t))} = \frac{1}{i^n (\mathbf{p}^0 - \mathbf{q}(t))^{\mathbf{1}}} \tag{308}$$

the integral over  $\mathbf{p}^0$  is

$$\int \frac{d\mathbf{p}^0}{(2\pi i)^n} \frac{(\mathbf{1} + i\mathbf{p}^0)^\xi}{(\mathbf{p}^0 - \mathbf{q}(t))^{\mathbf{1}}} = (\mathbf{1} + i\mathbf{q}(t))^\xi \tag{309}$$

and the integral over  $\mathbf{z}^f$  is

$$\int d\mathbf{z}^f \frac{(\mathbf{z}^f)^{\mathbf{x}}}{\mathbf{x}!} e^{-\mathbf{z}^f \cdot (\mathbf{1} + i\mathbf{p}^f)} = \frac{1}{(\mathbf{1} + i\mathbf{p}^f)^{\mathbf{x}+1}} \tag{310}$$

leaving only the desired integral. □

Finally, we will derive the generating function.

**Lemma 13** (Zero and first order reactions generating function) *The generating function for the system with arbitrary combinations of zero and first order reactions is*

$$\begin{aligned} \psi(\mathbf{g}, t) &= [\mathbf{1} + i\mathbf{q}(t)]^\xi \times \\ &\quad \times e^{i\int_{t_0}^t \sum \alpha_{\kappa_1, \dots, \kappa_n} (t-s+t_0) [iq_1(s)]^{\kappa_1} \dots [iq_n(s)]^{\kappa_n} ds} \Big|_{\mathbf{p}^f = -i(\mathbf{g}-1)} \end{aligned} \tag{311}$$

where  $q(s)$  is as in Theorem 4.

**Proof** Begin with Eq. 104, the Doi-Peliti solution for the generating function. For proving this result, it is convenient to switch over to analytic notation, in which

$$\begin{aligned} |\psi(t)\rangle &\rightarrow \psi(\mathbf{g}, t) \\ |\mathbf{x}\rangle &\rightarrow \mathbf{g}^{\mathbf{x}} \\ |\mathbf{z}\rangle &\rightarrow e^{\mathbf{z}\cdot(\mathbf{g}-\mathbf{1})} . \end{aligned} \tag{312}$$

In particular, we have

$$\begin{aligned} \psi &= \int \frac{d\mathbf{z}^f d\mathbf{p}^f}{(2\pi)^n} \frac{d\mathbf{z}^0 d\mathbf{p}^0}{(2\pi)^n} e^{\mathbf{z}^f\cdot(\mathbf{g}-\mathbf{1})} e^{i\mathbf{z}^0\cdot\mathbf{q}(t)} (\mathbf{1} + i\mathbf{p}^0)^\xi \\ &\times e^{-i\mathbf{p}^0\cdot\mathbf{z}^0 - i\mathbf{p}^f\cdot\mathbf{z}^f} e^{\int_{t_0}^t \sum_{\kappa_1, \dots, \kappa_n} \alpha_{\kappa_1, \dots, \kappa_n}(t-s+t_0) [iq_1(s)]^{\kappa_1} \dots [iq_n(s)]^{\kappa_n} ds} . \end{aligned} \tag{313}$$

The integral over  $\mathbf{z}^0$  is

$$\int d\mathbf{z}^0 e^{-i\mathbf{z}^0\cdot(\mathbf{p}^0-\mathbf{q}(t))} = \frac{1}{i^n (\mathbf{p}^0 - \mathbf{q}(t))^{\mathbf{1}}} , \tag{314}$$

the integral over  $\mathbf{p}^0$  is

$$\int \frac{d\mathbf{p}^0}{(2\pi i)^n} \frac{(\mathbf{1} + i\mathbf{p}^0)^\xi}{(\mathbf{p}^0 - \mathbf{q}(t))^{\mathbf{1}}} = (\mathbf{1} + i\mathbf{q}(t))^\xi , \tag{315}$$

and the integral over  $\mathbf{z}^f$  is

$$\int d\mathbf{z}^f e^{-\mathbf{z}^f\cdot[-(\mathbf{g}-\mathbf{1})+i\mathbf{p}^f]} = \frac{1}{[-(\mathbf{g} - \mathbf{1}) + i\mathbf{p}^f]^{\mathbf{1}}} , \tag{316}$$

leaving only the integral

$$\int \frac{d\mathbf{p}^f}{(2\pi i)^n} \frac{[\mathbf{1} + i\mathbf{q}(t)]^\xi e^{\int_{t_0}^t \sum_{\kappa_1, \dots, \kappa_n} \alpha_{\kappa_1, \dots, \kappa_n}(t-s+t_0) [iq_1(s)]^{\kappa_1} \dots [iq_n(s)]^{\kappa_n} ds}}{[\mathbf{p}^f + i(\mathbf{g} - \mathbf{1})]^{\mathbf{1}}} . \tag{317}$$

This integral is a simple contour integral (the numerator is the exponential of a function analytic in  $\mathbf{p}^f$ ), whose evaluation via Cauchy’s integral formula corresponds to the desired result. □

### E Another view of the propagator

The mess of formalism aside, a coarse view of what we have been doing is that we have been calculating the propagator  $U$ , which we remind the reader is defined via

$$U(i\mathbf{p}^f, t; \mathbf{z}^0, t_0) := \left\langle -i\mathbf{p}^f \left| \hat{U}(t, t_0) \right| \mathbf{z}^0 \right\rangle \tag{318}$$

where  $|z^0\rangle$  and  $|-i\mathbf{p}^f\rangle$  are coherent states. We computed  $U$  by evaluating many integrals, and then used the formula (c.f. Corollary 7)

$$|\psi(t)\rangle = \int \frac{dz^f d\mathbf{p}^f}{(2\pi)^n} \frac{dz^0 d\mathbf{p}^0}{(2\pi)^n} |z^f\rangle U \left\langle -i\mathbf{p}^0 | \psi(t_0) \right\rangle e^{-i\mathbf{p}^0 \cdot z^0 - i\mathbf{p}^f \cdot z^f} \quad (319)$$

to recover the generating function  $|\psi(t)\rangle$ . This expression for  $|\psi(t)\rangle$  is then suitably manipulated to directly recover other objects of interest, like moments or transition probabilities.

Given the relatively simple-looking results we have derived for  $U$  (c.f. Lemmas 1, 6, and 11), one may wonder whether there is another way to derive it—in particular, does  $U$  satisfy some PDE?

In the following, it will be more convenient to switch to a more standard notation for the probability generating function:

$$|\psi(t)\rangle = \sum_{\mathbf{x}} P(\mathbf{x}, t) |\mathbf{x}\rangle \rightarrow \psi(\mathbf{g}, t) := \sum_{\mathbf{x}} P(\mathbf{x}, t) \mathbf{g}^{\mathbf{x}}, \quad (320)$$

which really just amounts to the replacement  $|\mathbf{x}\rangle \rightarrow \mathbf{g}^{\mathbf{x}}$ . This is related to our notation by taking the Grassberger-Scheunert product of the generating function with a coherent state  $|\mathbf{g}^* - \mathbf{1}\rangle$  for some  $\mathbf{g} \in \mathbb{C}^n$ :

$$\langle \mathbf{g}^* - \mathbf{1} | \psi(t) \rangle = \sum_{\mathbf{x}} P(\mathbf{x}, t) \langle \mathbf{g}^* - \mathbf{1} | \mathbf{x} \rangle = \sum_{\mathbf{x}} P(\mathbf{x}, t) (\mathbf{1} + (\mathbf{g} - \mathbf{1}))^{\mathbf{x}} = \psi(\mathbf{g}, t). \quad (321)$$

In this notation, the relationship between the generating function and the propagator reads

$$\psi(\mathbf{g}, t) = \int \frac{dz^f d\mathbf{p}^f}{(2\pi)^n} \frac{dz^0 d\mathbf{p}^0}{(2\pi)^n} e^{z^f \cdot (\mathbf{g} - \mathbf{1})} U \left\langle -i\mathbf{p}^0 | \psi(t_0) \right\rangle e^{-i\mathbf{p}^0 \cdot z^0 - i\mathbf{p}^f \cdot z^f}. \quad (322)$$

Recall that the generating function  $\psi(\mathbf{g}, t)$  satisfies a partial differential equation. For simplicity, suppose we are dealing with the chemical birth-death process, for which the relevant PDE reads

$$\frac{\partial \psi}{\partial t} = k(t)[g - 1]\psi - \gamma(t)[g - 1] \frac{\partial \psi}{\partial g}. \quad (323)$$

Substituting this into (the one-dimensional version of) Eq. 322, the right-hand side reads

$$\int \frac{dz_f dp_f}{2\pi} \frac{dz_0 dp_0}{2\pi} U \{k[g - 1] - \gamma[g - 1]z_f\} e^{z_f(g-1)} e^{-ip_f z_f} \langle -ip_0 | \psi(t_0) \rangle e^{-ip_0 z_0}. \quad (324)$$

But note that

$$\begin{aligned}
 (g - 1)e^{z_f(g-1)} &= \frac{\partial}{\partial z_f} e^{z_f(g-1)} \\
 z_f e^{-ip_f z_f} &= i \frac{\partial}{\partial p_f} e^{-ip_f z_f} .
 \end{aligned}
 \tag{325}$$

Using these identities, integrating by parts, and freely removing boundary terms, the right-hand side now reads

$$\int \frac{dz_f dp_f}{2\pi} \frac{dz_0 dp_0}{2\pi} \left\{ ip_f \left[ kU + i\gamma \frac{\partial U}{\partial p_f} \right] \right\} e^{z_f(g-1)} e^{-ip_f z_f} \langle -ip_0 | \psi(t_0) \rangle e^{-ip_0 z_0} .
 \tag{326}$$

This suggests that the expression given by Eq. 322 will solve the equation of motion for  $|\psi(t)\rangle$  (Eq. 103) if

$$\frac{\partial U(ip_f, z_0)}{\partial t} = ip_f \left[ kU(ip_f, z_0) + i\gamma \frac{\partial U(ip_f, z_0)}{\partial p_f} \right] .
 \tag{327}$$

It is easy to verify that our expression for the propagator of the chemical birth-death process (c.f. Lemma 1) does solve this PDE.

We can generalize this enough for our purposes, although it should be clear that this correspondence holds for any CME (and not just ones involving only zero and first order reactions).

**Proposition 11 (Propagator PDE)** *If the generating function  $\psi(\mathbf{g}, t)$  satisfies the PDE given by Eq. 54, then the propagator  $U(i\mathbf{p}^f, t; \mathbf{z}^0, t_0)$  satisfies a PDE*

$$\begin{aligned}
 \frac{\partial U}{\partial t} &= \sum_{\kappa_1, \dots, \kappa_n} \alpha_{\kappa_1, \dots, \kappa_n}(t) \left[ ip_1^f \right]^{\kappa_1} \cdots \left[ ip_n^f \right]^{\kappa_n} U \\
 &\quad - i \sum_{k=1}^n \sum_{\kappa_1, \dots, \kappa_n} \beta_{\kappa_1, \dots, \kappa_n}^k(t) \left[ ip_1^f \right]^{\kappa_1} \cdots \left[ ip_n^f \right]^{\kappa_n} \frac{\partial U}{\partial p_k^f}
 \end{aligned}
 \tag{328}$$

with initial condition  $U(i\mathbf{p}^f, t_0; \mathbf{z}^0, t_0) = \exp(i\mathbf{z}^0 \cdot \mathbf{p}^f)$  for arbitrary  $\mathbf{p}^f, \mathbf{z}^0 \in \mathbb{R}^n$ .

**Proof** Integrate by parts as in the one-dimensional example. The initial condition comes from the definition of  $U$ :

$$U(i\mathbf{p}^f, t_0; \mathbf{z}^0, t_0) = \left\langle -i\mathbf{p}^f \left| \hat{U}(t_0, t_0) \right| \mathbf{z}^0 \right\rangle = \left\langle -i\mathbf{p}^f | \mathbf{z}^0 \right\rangle = e^{i\mathbf{z}^0 \cdot \mathbf{p}^f} .
 \tag{329}$$

□

At this point, we should note that the PDE satisfied by the propagator (Eq. 328) and the PDE satisfied by the generating function (Eq. 54) are equivalent up to a change

of variables (i.e.  $\mathbf{g} - \mathbf{1} \rightarrow i\mathbf{p}^f$ ). Does this mean that the propagator, along with the entire Doi-Peliti artifice we have constructed, is extraneous?

While this is a reasonable question to ask, the answer is probably no. It is easy to see that our expressions for the propagator and our expressions for the generating function have tended to look somewhat different, with the latter almost always being more complicated. The main reason for this difference seems to be that the propagator's initial condition is much simpler than the initial condition for the generating function PDE, which usually permits finding explicit solutions of the propagator PDE.

Now that we have this result, how can we connect it with the propagator solution we found in Lemma 11 (for arbitrary combinations of zero and first order reactions, which includes all other propagators considered in this paper as special cases)? It turns out that there is a straightforward way to do this using the method of characteristics, a standard approach for solving first order PDEs like the one above.

The method involves supposing that the relevant independent variables (in this case,  $\mathbf{p}^f$  and  $t$ ) lie along some parameterized curve. For a pedagogical example applying this method to solve a toy problem in chemical kinetics (the chemical birth-death process with additive noise), see (Vastola 2019a).

**Lemma 14** (*Method of characteristics solution*) *The propagator for the system with arbitrary combinations of zero and first order reactions matches the one given by Lemma 11.*

**Proof** Suppose (where we use slightly different notation here, because only the initial condition of the PDE depends on  $\mathbf{z}^0$  and  $t_0$ ) that  $\mathbf{p}^f$  and  $t$  lie along curves parameterized by some parameter  $s$ , so that

$$\begin{aligned} \frac{\partial}{\partial s} \left[ U(\mathbf{p}^f(s), t(s)) \right] &= \frac{\partial U}{\partial t} \frac{\partial t}{\partial s} + \sum_{k=1}^n \frac{\partial U}{\partial p_k^f} \frac{\partial p_k^f}{\partial s} \\ &= -\frac{\partial U}{\partial t} - i \sum_{k=1}^n \sum_{\kappa_1, \dots, \kappa_n} \beta_{\kappa_1, \dots, \kappa_n}^k(t) \left[ ip_1^f \right]^{\kappa_1} \cdots \left[ ip_n^f \right]^{\kappa_n} \frac{\partial U}{\partial p_k^f}. \end{aligned} \quad (330)$$

Choose the curve so that

$$\begin{aligned} \frac{\partial t}{\partial s} &= -1 \\ \frac{\partial p_k^f}{\partial s} &= -i \sum_{\kappa_1, \dots, \kappa_n} \beta_{\kappa_1, \dots, \kappa_n}^k(t(s)) \left[ ip_1^f(s) \right]^{\kappa_1} \cdots \left[ ip_n^f(s) \right]^{\kappa_n}. \end{aligned} \quad (331)$$

Suppose that we are interested in  $U(i\mathbf{p}^f, t_f; \mathbf{z}^0, t_0)$  for some particular final time  $t_f$ . Solving the equation for  $t(s)$ , we have

$$t(s) = t_f - s + t_0 \quad (332)$$

where the arbitrary constant was chosen so that  $s \in [t_0, t_f]$  with  $t(t_0) = t_f$  and  $t(t_f) = t_0$ . Then the equation determining  $\mathbf{p}^f(s)$  reads

$$\frac{\partial p_k^f}{\partial s} = -i \sum_{\kappa_1, \dots, \kappa_n} \beta_{\kappa_1, \dots, \kappa_n}^k (t_f - s + t_0) [ip_1^f(s)]^{\kappa_1} \cdots [ip_n^f(s)]^{\kappa_n} \quad (333)$$

Notice that this is exactly the same as the equation satisfied by  $\mathbf{q}(s)$  (see Theorem 4). Moreover, our  $\mathbf{p}^f(s)$  and  $\mathbf{q}(s)$  satisfy the same initial condition:  $\mathbf{p}^f(s = t_0) = \mathbf{p}^f(t(s) = t_f) = \mathbf{p}^f$ , since the symbol  $\mathbf{p}^f$  means the value corresponding to the evaluation of  $U(i\mathbf{p}^f, t_f; \mathbf{z}^0, t_0)$  at the final time  $t_f$ . This point is somewhat subtle, so convince yourself of it before going forward.

Hence, we can make the identification  $\mathbf{p}^f(s) \rightarrow \mathbf{q}(s)$ . This means our PDE for  $U$  now reads

$$\frac{\partial U}{\partial s} = \sum_{\kappa_1, \dots, \kappa_n} \alpha_{\kappa_1, \dots, \kappa_n}(t) [iq_1]^{k_1} \cdots [iq_n]^{k_n} U \quad (334)$$

Solving this as usual, we have the solution

$$U(s) = C \exp \left\{ \int_{t_0}^s \sum_{\kappa_1, \dots, \kappa_n} \alpha_{\kappa_1, \dots, \kappa_n}(t - s + t_0) [iq_1(s)]^{k_1} \cdots [iq_n(s)]^{k_n} ds \right\} \quad (335)$$

for some constant  $C$  that depends on the initial condition. Implement the initial condition for  $s = t_0$  (i.e.  $t(s) = t_f$ ), noting that  $\mathbf{p}^f(s = t_0) = \mathbf{q}(s = t_f)$ . Finally, evaluate  $U(s)$  at  $s = t_f$  to obtain

$$U(t_f) = \exp \left\{ i\mathbf{z}^0 \cdot \mathbf{q}(t_f) + \int_{t_0}^{t_f} \sum_{\kappa_1, \dots, \kappa_n} \alpha_{\kappa_1, \dots, \kappa_n}(t - s + t_0) [iq_1(s)]^{k_1} \cdots [iq_n(s)]^{k_n} ds \right\} \quad (336)$$

which is the desired answer. □

After all this, it is natural to ask whether the path integral calculations were necessary if the answer for the propagator can be determined by solving a relatively simple PDE. The author can only note that he was able to come up with this alternative approach only after carefully studying the path integral answer. It is likely that there are other cases where one can ‘turn the crank’ to determine the path integral answer, and then justify that answer using some more conventional method after one realizes why it takes its precise form.

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