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Abstract

Timing machinery is a model of concurrent timed computation, in which a machine state may spontaneously time out and emit a signal that may trigger activity elsewhere within the machine. We derive a master ordinary differential equation for the machine state by imposing Poisson- and Markov-like restrictions on the behavior of a stochastic timing machine. This equation and the machine it describes generalize the chemical master equation and Gillespie stochastic exact simulation algorithm, used widely in studies of chemical systems with many species, prokaryotic genetic circuits, genetic regulatory networks, and gene expression in single cells.

Keywords: timing machine, computation, concurrency, master equation, stochastic simulation

Introduction

"Timing machinery" is a model of concurrent computation best left loosely specified, but characterized by explicit addition of time-related structure to conventional state machinery (not necessarily finite state machinery). The type of timing machine introduced here is a *timeout machine*, wherein the time-related structure is based on the metaphor of a "timer", i.e., a gadget that can be preset to an amount of time and counts down to 0, leading to a state transition. With additional structure a timeout machine may be a triggered timeout machine, wherein arrivals of signals emitted upon timeouts cause state transitions. An intermediate variation between timeout machine and triggered timeout machine is the *interruptible timeout machine*, wherein signals are emitted upon timeout and accumulate, but are not considered to cause state transitions.

We derive a master ordinary differential equation for the state of an interruptible timing machine by imposing Poisson- and Markov-like restrictions on its behavior. The master equation we derive is a strict generalization of the chemical master equation [Gil92, SFH89, Chapter 14]. Justification for exact simulation of our generalized master equation is a strict generalization of that for Gillespie's simulation algorithm [Gil77, SFH89, Section 2.7, Appendix 2.3].

Timing machine formalisms appearing in the literature include the *timed automaton* [DA90], and the *stochastic timed automaton* [MMN+03]. The timed automaton is based on the metaphor of a "stopwatch", i.e., a gadget which can be reset to 0, which can be read at any time, and when halted reads out an amount of time elapsed. Such gadgets can be reset by state transitions, and read to qualify state transitions. The theory of *timed automata* was introduced because, "[a]lthough the decision to abstract away from quantitative time has had many advantages, it is ultimately counterproductive when reasoning about systems that must interact with physical processes." The crucial element of that theory is the addition of "stopwatches" to finite state machinery. Another related model is the theory of *process algebra with timing* [BM02], useful for describing concurrent systems in which several components interact and communicate with each other. Master equations and associated simulation algorithms for these formalisms have not appeared in the literature, to the best of our knowledge.

This paper is organized as follows. In the first section we state our results. In the second section, a timing machine for the exact simulation of solutions to a master equation is represented using a graphical syntax. The proofs are given in the third section. Our conclusions are given in the fourth section.

1 A Generalized Stochastic Master Equation

Let $\mathbf{N}$ denote the totally ordered set of natural numbers $0, 1, 2, \dots$ and let $\mathbf{T}$ denote the set $[0, \infty)$ of non-negative real numbers with the usual topology. Members of $\mathbf{T}$ play two roles: $t \in \mathbf{T}$ may be regarded as a "point in time" or, if $0 < t$, as a "duration." For $a \leq b \in \mathbf{T}$ the closed interval from a to b is denoted by $[a, b]$ and has the usual subspace topology. The Kronecker delta symbol $\boldsymbol{\delta}$ is a $\{0, 1\}$-valued function of two variables defined by $\boldsymbol{\delta}(x, y) = 1$ if and only if $x = y$. The characteristic function $\chi_A : \mathbf{T} \to \{0, 1\}$ for $A \subseteq \mathbf{T}$ is defined by $\chi_A(t) = 1$ if and only if $t \in A$. Note the relationship $\chi_{[0,t]}(\tau) = \sum_{0 \leq t' \leq t} \boldsymbol{\delta}(\tau, t')$.

For any set X let $X^* = 1 \ \dot\cup \ X \ \dot\cup \ X^2 \ \dot\cup \ X^3 \ \dot\cup \ \cdots$ denote the set of all finite sequences of elements of X, including the empty sequence ϵ of length 0. Concatenation of two sequences x, y is denoted by $x \cdot y$.

Definition 1.1. An **interruptible timeout machine** (ITM) G is a system of **parts** G_α where $\alpha \in \mathcal{A}$. Each part G_α has a set E_α of **activations** and a function $h_\alpha : E_\alpha \to \mathbf{T}$ whose value $h_\alpha(e) > 0$ is the **timeout duration** of e. Communication between the parts of the machine is via signals emitted when they timeout. That is, for each part of the machine there is a module $\mathbf{V}_\alpha$ (over a ring, e.g., a vector space) and there is a function $\sigma_\alpha^\beta : E_\beta \to \mathbf{V}_\alpha$. The value $\sigma_\alpha^\beta(e)$ is the **signal** to part G_α upon timeout of activation e in part G_β. Let

$$\mathrm{Tot}_e^\beta = \bigoplus_{\alpha \in \mathcal{A}} \sigma_\alpha^\beta(e)$$

denote the total signal emitted by part G_β upon timeout of $e \in E_\beta$.

Consider a function $\omega : \mathbf{N} \to \prod_{\beta \in \mathcal{A}} (\mathbf{T} \times \mathrm{E}_\beta)$. For $N \geq 0$, if $\omega_\beta(N) = (d, e)$ let $d_N^\beta(\omega) = d$, $e_N^\beta(\omega) = e$, so $d_N^\beta : \Omega_G \to \mathbf{T}$ and $e_N^\beta : \Omega_G \to E_\beta$. Define $\Delta_N^\beta : \Omega_G \to \mathbf{T}$ by

$$\Delta_N^\beta = h_\beta(e_N^\beta)\boldsymbol{\delta}(d_N^\beta, 0) + d_N^\beta(1 - \boldsymbol{\delta}(d_N^\beta, 0)), N \geq 0.$$

Thus, Δ_N^β is the full timeout duration of e_N^β if $d_N^\beta = 0$ and is $d_N^\beta > 0$ if e_N^β is interrupted at time d_N^β during activation. Also define $t_N^\beta : \Omega_G \to \mathbf{T}$ by $t_0^\beta = 0$ and for $N > 0$

$$t_N^\beta = \sum_{n=0}^{N-1} \Delta_n^\beta.$$

A **run** of G is a function $\omega : \mathbf{N} \to \prod_{\beta \in \mathcal{A}} (\mathbf{T} \times \mathrm{E}_\beta)$ such that $\omega_\beta(N) = (d, e)$ implies $0 \leq d \leq h_\beta(e)$ for $N \in \mathbf{N}$, and moreover the sum

$$N_e^\beta(t) = \sum_{N \geq 0} \chi_{[0,t]}(t_N^\beta)\boldsymbol{\delta}(e_N^\beta, e)\boldsymbol{\delta}(d_N^\beta, 0)(1 - \boldsymbol{\delta}(\mathrm{Tot}_e^\beta, 0))$$

is *finite*. We explain this as follows. The condition that $N_e^\beta(t)(\omega)$ be finite for a run ω is equivalent to $t_N^\beta(\omega) \to \infty$ as $N \to \infty$. Let Ω_G denote the set of all runs, so $N_e^\beta(t) : \Omega_G \to \mathbf{N}$. If $\omega_\beta(N) = (d, e)$ and $d = 0$, we say that activation e "times out"; if $d > 0$ we say that e is "prevented from timeout," or "interrupted." An interrupted activation fails to send a signal because it never reaches its timeout duration. Thus, $N_e^\beta(t)(\omega)$ is the total count of non-zero signal ($\mathrm{Tot}_e^\beta \neq 0$) timeout ($d_N^\beta = 0$) events in component ω_β up to and including time t.

Let $E_{\mathcal{A}} = \{\, (\beta, e) \,|\, \beta \in \mathcal{A} \,\wedge\, e \in E_\beta\}$ and abbreviate $\sum_{(\beta,e)\in E_{\mathcal{A}}}$ to $\sum_{(\beta,e)}$. (Likewise for $\prod, \bigcup, \bigwedge$.) Hence, $N(t) : \Omega_G \to \mathbf{N}$ defined by $N(t) = \sum_{(\beta,e)} N_e^\beta(t)$ gives the total number of non-zero signal timeout events up to and including time t.

Now, assume that $(\Omega_G, \mathcal{F}_G, P_G)$ is a probability space. Thus, each of the functions

$$\begin{aligned} N_e^\beta, N(t) &: \Omega_G \to \mathbf{N} \\ d_N^\beta, \Delta_N^\beta, t_N^\beta &: \Omega_G \to \mathbf{T} \\ e_N^\beta &: \Omega_G \to E_\beta \end{aligned}$$

is a random variable. Let $\mathbf{V} = \bigoplus_{\alpha\in\mathcal{A}} \mathbf{V}_\alpha$ and assume there is given an initial signal $v_0 \in \mathbf{V}$. We are interested in the **total signal** random variable

$$X(t) : \Omega_G \to \mathbf{V}$$

defined by $X(0) = v_0$ and

$$X(t) = v_0 + \sum\nolimits_{(\beta,e)} N_e^\beta(t)\mathrm{Tot}_e^\beta.$$

This formula says that the total (or "integrated") signal to machine part G_α at time t is the (α component of the) initial signal plus non-zero signals emitted to G_α by timeouts of all activations of other parts G_β that occur up to and including time t. The N^{th} timeout of a particular part G_β may emit signals to multiple other parts G_α. The **instantaneous signal to G_α at time t** is defined by the equations $\mathrm{Sig}_\alpha(0) = (v_0)_\alpha$ and

$$\mathrm{Sig}_\alpha(t) = \sum\nolimits_{(\beta,e)} \sum\nolimits_{N\geq 0} \boldsymbol{\delta}(t_N^\beta, t)\boldsymbol{\delta}(e_N^\beta, e)\boldsymbol{\delta}(d_N^\beta, 0)\sigma_\alpha^\beta(e).$$

Proposition 1.1. $X_\alpha(t) = \sum_{0\leq t'\leq t} \mathrm{Sig}_\alpha(t')$.

For $t \leq t' \in \mathbf{T}$ let $N(t,t') = N(t') - N(t)$, and for a "small" duration $\Delta t > 0$ increments of $N_e^\beta(t), N(t), X(t)$ are defined by

$$\begin{aligned}
\Delta N_e^\beta(t) &= N_E^\beta(t+\Delta t) - N_e^\beta(t),\\
\Delta N(t) &= N(t+\Delta t) - N(t), \text{ and}\\
\Delta X(t) &= X(t+\Delta t) - X(t) = \sum\nolimits_{(\beta,e)} \Delta N_e^\beta(t)\mathrm{Tot}_e^\beta.
\end{aligned}$$

Note that $\Delta N(t) = N(t, t+\Delta t)$.

Definition 1.2. A **Poisson structure** for an interruptible timeout machine G is given by a set of functions $\lambda_e^\beta : \mathbf{V} \to (0,\infty)$ for $\beta \in \mathcal{A}, e \in E_\beta$ such that

(PS1) $P_G\left[\Delta N(t) \geq 2 \,|X(t) = v\right] = o(\Delta t)$;

(PS2) $P_G\left[\Delta N_e^\beta(t) = 1 \wedge \Delta X(t) = \mathrm{Tot}_e^\beta \,|X(t) = v\right] = \lambda_e^\beta(v)\Delta t + o(\Delta t)$;

(PS3) $P_G\left[\Delta N_e^\beta(t_2) = 1 \wedge \Delta X(t_2) = \mathrm{Tot}_e^\beta \,|X(t_2) = v_2 \wedge X(t_1) = v_1\right]$
$= P_G\left[\Delta N_e^\beta(t_2) = 1 \wedge \Delta X(t_2) = \mathrm{Tot}_e^\beta \,|X(t_2) = v_2\right]$ if $0 \leq t_1 \leq t_2$,

where $o(\Delta t)$ is a function such that $\lim\limits_{\Delta t\to 0} o(\Delta t)/\Delta t = 0$. Henceforth, $x \cong y$ stands for $x = y + o(\Delta t)$. Define $\lambda(v) = \sum_{(\beta,e)} \lambda_e^\beta$.

Conditions (PS1)-(PS2) are close to standard for the Poisson process [Bil86]. Condition (PS3) is a limited Markov process requirement. The following proposition is stated for completeness.

Proposition 1.2. The following statements hold.

(i) $P_G\left[\Delta N(t)=1\,|X(t)=v\right] \cong \sum_{(\beta,e)} P_G\left[\Delta N_e^\beta(t)=1 \wedge \Delta X(t)=\mathrm{Tot}_e^\beta\,|X(t)=v\right]$.

(ii) $P_G\left[\Delta N(t)=0\,|X(t)=v\right] \cong 1-\lambda(v)\Delta t$.

(iii) $P_G\left[\Delta N_e^\beta(t+t')=1 \wedge \Delta X(t+t')=\mathrm{Tot}_e^\beta\,|\Delta N(t+t')=1 \wedge N(t,t+t')=0 \wedge X(t)=v\right]$ $=\dfrac{\lambda_e^\beta(v)}{\lambda(v)}$.

(iv) $P_G\left[N(t,t+t')=0\,|X(t)=v\right]=e^{-\lambda(v)t'}$.

(v) $P_G\left[\Delta X(t)\neq 0 \wedge X(t)=v\,|X(0)=v_0\right] \cong$ $\sum_{(\beta,e)} P_G\left[\Delta N_e^\beta(t)=1 \wedge \Delta X(t)=\mathrm{Tot}_e^\beta \wedge X(t)=v\,|X(0)=v_0\right]$.

Theorem 1.1 (Master Equation)**.**

$$\frac{d}{dt}P_G\left[X(t)=v\,|X(0)=v_0\right]=$$
$$\sum_{(\beta,e)}\left(\lambda_e^\beta(v-\mathrm{Tot}_e^\beta)P_G\left[X(t)=v-\mathrm{Tot}_e^\beta\,|X(0)=v_0\right]-\lambda_e^\beta(v)P_G\left[X(t)=v\,|X(0)=v_0\right]\right).$$

Comment 1. For the reaction system

$$B_1+X \underset{c_2}{\overset{c_1}{\rightleftharpoons}} X+X \qquad\qquad X+X \underset{c_4}{\overset{c_3}{\rightleftharpoons}} B_2+B_3$$

Daniel T. Gillespie gives the following chemical master equation (using his notation):

$$\frac{d}{dt}P\left(n,t\,|n_0,t_0\right)=$$
$$\sum_{v=-2}^{Min(2,n)}\left[W(v\,|n-v)P\left(n-v,t\,|n_0,t_0\right)-W(-v\,|n)P\left(n,t\,|n_0,t_0\right)\right],$$

where $W(v|n)$ is defined in terms of the "specific probability rates" c_1,c_2,c_3,c_4. The index v is over the change in the number of X molecules given that the numbers of B_1,B_2,B_3 molecules are constant (they are "buffered reagents")

[Gil92]. Our index β corresponds to his v if v is taken to represent a specific chemical reaction.

Theorem 1.1 generalizes the chemical master equation in two ways. First, by summing over e for each β, it allows for the possibility that at different times the state $X_\alpha(t)$ may change in different ways according to activity of the reaction that causes the change. Second, another level of causality arises from changes in activity in G_β triggered by the crossing of thresholds by $X_\alpha(t)$.

In the Gillespie stochastic simulation algorithm [Gil92, Gil77], one iterates the process of choosing two (pseudo-)random numbers in the unit interval, and by the method of inversion [BFS83], produces from them two numbers distributed according to the two independent probability density functions. Thus, one factor says what reaction is to occur, and the other factor says when it should occur. Then the state is updated according to the reaction chosen. The Gillespie algorithm has found widespread use in the simulation of genetic regulatory systems, see [Jon02] for a review; stochastic gene expression in a single cell [ELSS02]; and prokaryotic gene circuits [MA98, MA97]. Efficient implementations of the Gillespie algorithm have been developed [GB00] for chemical systems with many species and many channels.

Theorem 1.2 (Stochastic Simulation)**.**

$$P_G\left[\left(\Delta N_e^\beta(t) = 1 \wedge \Delta X(t) = \mathrm{Tot}_e^\beta\right) \wedge \left(N(t, t+t') = 0 \wedge \Delta N(t, t+t') = 1\right) | X(t) = v\right]$$
$$\cong \left(\frac{\lambda_e^\beta(v)}{\lambda(v)}\right)\left(\lambda(v) e^{-\lambda(v)t'}\right)\Delta t.$$

Comment 2. This formula exhibits the joint probability density function of the "what and when" of a signal emission as a product of density functions. Therefore, it generalizes the justification for Gillespie's exact stochastic simulation algorithm to stochastic interruptible timeout machines.

2 Generalized Stochastic Simulation Timing Machine

2.1 Timing Machine Diagram Syntax

The syntax of timing machine diagrams summarized in Figure 1 is as simple as possible. In the left column are the diagram and corresponding formula elements

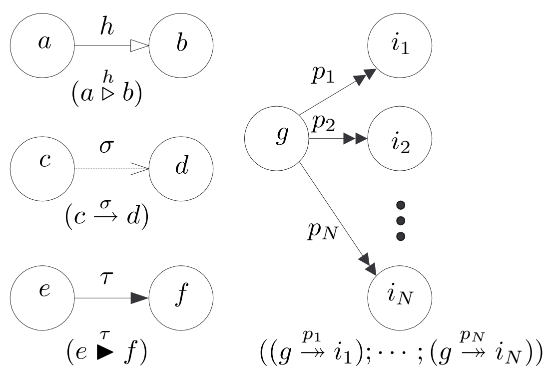

Figure 1: The syntax for timing machine diagrams.

for timeout, signal, and trigger. On the right is an element for probabilistic timing machines. The semantics of this is that if state g is active then there is an immediate transition to i_n with probability p_n, it being understood, of course, that $p_1 + \cdots + p_N = 1$.

Example 1. Principal aspects of timing machinery converge in Figure 2.
The concise formula corresponding to Figure 2

$$A \triangleq (\forall k \in \{1, \ldots, K\})((a \overset{J_k(X)}{\twoheadrightarrow} b_k \overset{\tilde{W}_k(X)/2}{\triangleright} b_k \overset{\tilde{W}_k(X)/2}{\triangleright} c_k \overset{\Delta X_k}{\triangleright} a) \wedge (c_k \rightarrow B))$$

models a chemical reaction whose vector of concentrations $X = X(t)$ is at the

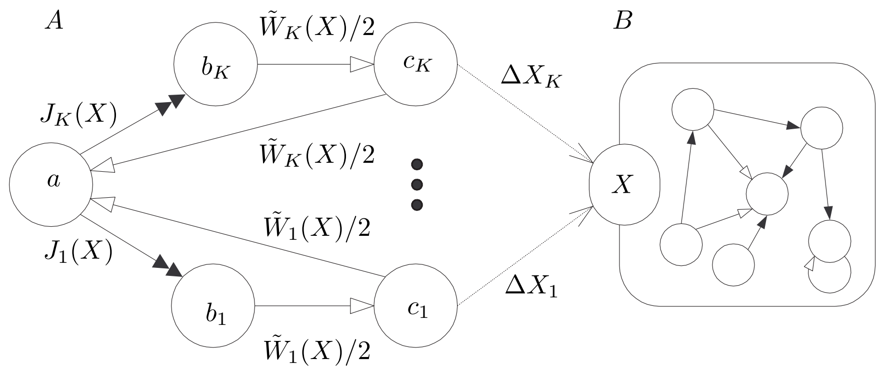

Figure 2: Stochastic interruptible timeout machine diagram for simulation of a chemical reaction.

enclosure of part B. That is to say, signals arriving from part A are integrated in X. The signals $\Delta X_k, k = 1, \ldots, K$ arise from timeout of chemical reactions represented by nodes $c_k, k = 1, \ldots, K$. When a is activated it undergoes a transition automatically to b_k with concentration-dependent probability $J_k(X)$, where $J_1(X) + \cdots + J_K(X) = 1$. Then b_k times out to c_k after waiting time given by the random variable $\tilde{W}_k(X)/2$ with assumed exponential distribution; c_k times out back to a with the same waiting time. Thus, on average the reaction c_k repeats with waiting time $\tilde{W}_k(X)$. Therefore, part A together with X expresses the Gillespie exact stochastic simulation algorithm. Beyond that, the new element of structure provided by timing machinery is that X may undergo threshold crossings and thereby trigger transitions of part B. The implication is that the states of B are “macroscopic” states driven by the “microscopic” chemical reactions reflected in the concentrations X, and timeout of these macroscopic states may emit signals that influence the states of other machines. In this way timing machinery offers an expanded repertoire of models for biological phenomena, including the promise of a mechanism for modeling “feedback between levels.” [Ree04]

3 Proofs

Proof of Proposition 1.1. *A straightforward calculation from the definitions and the identity* $(1-\boldsymbol{\delta}(\mathrm{Tot}_e^\beta,0))\mathrm{Tot}_e^\beta = \mathrm{Tot}_e^\beta$. $\square$

Proof of Proposition 1.2.

(i) By definition,

$$[\Delta N_e^\beta(t)=1 \,\wedge\, \Delta X(t)=\mathrm{Tot}_e^\beta] = [\Delta N_e^\beta(t)=1 \,\wedge\, \sum\nolimits_{(\beta',e')\neq(\beta,e)} \Delta N_{e'}^{\beta'}(t)\mathrm{Tot}_{e'}^{\beta'}=0].$$

Therefore, $[\Delta N(t)=1] = \bigcup_{(\beta,e)} [\Delta N_e^\beta(t)=1 \,\wedge\, \Delta X(t)=\mathrm{Tot}_e^\beta]$. *Take the intersection of both sides with* $[X(t)=v]$, *compute the probability of each side and divide both sides by* $P_G[X(t)=v]$ *to obtain the result.*

(ii) From (PS1) it follows that

$$P_G\left[\Delta N(t)=0\,|X(t)=v\right] \cong 1 - P_G\left[\Delta N(t)=1\,|X(t)=v\right],$$

and by (PS2),

$$\begin{aligned} P_G\left[\Delta N(t)=1\,|X(t)=v\right] &= \sum\nolimits_{(\beta,e)} P_G\left[\Delta N_e^\beta(t)=1 \,\wedge\, \Delta X(t)=\mathrm{Tot}_e^\beta\,|X(t)=v\right] \\ &\cong \sum\nolimits_{(\beta,e)} \lambda_e^\beta(v)\Delta t = \lambda(v)\Delta t. \end{aligned}$$

(iii)

$$P_G\left[\Delta N_e^\beta(t+t')=1 \wedge \Delta X(t+t')=\mathrm{Tot}_e^\beta\,|\Delta N(t+t')=1 \wedge N(t,t+t')=0 \wedge X(t)=v\right]$$
$$=P_G\left[\Delta N_e^\beta(t+t')=1 \wedge \Delta X(t+t')=\mathrm{Tot}_e^\beta\,|\Delta N(t+t')=1 \wedge X(t+t')=v\right]$$
$$=\frac{P_G\left[\Delta N_e^\beta(t+t')=1 \wedge \Delta X(t+t')=\mathrm{Tot}_e^\beta \wedge \Delta N(t+t')=1\,|X(t+t')=v\right]}{P_G\left[\Delta N(t+t')=1\,|X(t+t')=v\right]}$$
$$=\frac{P_G\left[\Delta N_e^\beta(t+t')=1 \wedge \Delta X(t+t')=\mathrm{Tot}_e^\beta\,|X(t+t')=v\right]}{P_G\left[\Delta N(t+t')=1\,|X(t+t')=v\right]}=\frac{\lambda_e^\beta(v)}{\lambda(v)}.$$

The first equality follows from $X(t)=v \wedge N(t,t+t')=0 \Rightarrow X(t+t')=v$ and the Markov property (PS3). The second equality is by definition of conditional probability, and the third equality follows from (PS1).

(iv) Calculate

$$P_G\left[N(t,t+t'+\Delta t)=0\,|X(t)=v\right]$$
$$=P_G\left[N(t,t+t')=0 \wedge \Delta N(t+t')=0\,|X(t)=v\right]$$
$$=P_G\left[\Delta N(t,t+t')=0\,|N(t,t+t')=0 \wedge X(t)=v\right]P_G\left[N(t,t+t')=0\,|X(t)=v\right]$$
$$=P_G\left[\Delta N(t,t+t')=0\,|X(t+t')=v\right]P_G\left[N(t,t+t')=0\,|X(t)=v\right]$$
$$=(1-P_G\left[\Delta N(t,t+t')=1\,|X(t+t')=v\right])P_G\left[N(t,t+t')=0\,|X(t)=v\right]$$

by (PS3). Therefore,

$$P_G\left[N(t,t+t'+\Delta t)=0\,|X(t)=v\right]-P_G\left[N(t,t+t')=0\,|X(t)=v\right]$$
$$=-P_G\left[\Delta N(t+t')=1\,|X(t)=v\right]$$
$$=-P_G\left[\bigvee\nolimits_{(\beta,e)}(\Delta N_e^\beta(t+t')=1 \wedge \Delta X(t+t')=\mathrm{Tot}_e^\beta)\,|X(t+t')=v\right]$$
$$\cong -\sum\nolimits_{(\beta,e)}\lambda_e^\beta(v)\Delta t=-\lambda(v)\Delta t.$$

by (PS1). Dividing through by Δt and taking the limit as $\Delta t \to 0$ together with the initial condition $P_G\left[N(t,t) = 0\,|X(t) = v\right] = 1$ yields an elementary ordinary differential equation initial value problem whose solution is the stated result.

(v) Calculate

$$\begin{aligned}
&P_G[\Delta X(t) \neq 0 \,\wedge\, X(t) = v \,\wedge\, X(0) = v_0] \\
&= P_G[\Delta X(t) \neq 0 \,\wedge\, X(t) = v \,\wedge\, X(0) = v_0 \,\wedge\, \Delta N(t) \in \mathbf{N}] \\
&= \sum\nolimits_{K \geq 0} P_G[\Delta X(t) \neq 0 \,\wedge\, X(t) = v \,\wedge\, X(0) = v_0 \,\wedge\, \Delta N(t) = K] \\
&= P_G[\Delta X(t) \neq 0 \,\wedge\, X(t) = v \,\wedge\, X(0) = v_0 \,\wedge\, \Delta N(t) = 0] \\
&+ P_G[\Delta X(t) \neq 0 \,\wedge\, X(t) = v \,\wedge\, X(0) = v_0 \,\wedge\, \Delta N(t) = 1] \\
&+ \sum\nolimits_{K \geq 2} P_G[\Delta X(t) \neq 0 \,\wedge\, X(t) = v \,\wedge\, X(0) = v_0 \,\wedge\, \Delta N(t) = K].
\end{aligned}$$

The first term of this sum is 0 since $\Delta N(t) = 0 \Rightarrow \Delta X(t) = 0$. The third term summing for $K \geq 2$ is $o(\Delta t)$ by (PS1). Calculate the second term:

$$\begin{aligned}
&P_G[\Delta X(t) \neq 0 \,\wedge\, X(t) = v \,\wedge\, X(0) = v_0 \,\wedge\, \Delta N(t) = 1] \\
&= P_G[\Delta X(t) \neq 0 \,\wedge\, X(t) = v \,\wedge\, X(0) = v_0 \,\wedge\, \sum\nolimits_{(\beta,e)} \Delta_e^\beta(t) = 1] \\
&= \sum\nolimits_{(\beta,e)} P_G[\Delta X(t) \neq 0 \,\wedge\, X(t) = v \,\wedge\, X(0) = v_0 \,\wedge\, \Delta_e^\beta(t) = 1 \,\wedge\, \bigwedge\nolimits_{(\beta',e') \neq (\beta,e)} \Delta_e^\beta(t) = 0] \\
&= \sum\nolimits_{(\beta,e)} P_G[\Delta_e^\beta(t) = 1 \,\wedge\, \Delta X(t) = \mathrm{Tot}_e^\beta \,\wedge\, X(t) = v \,\wedge\, X(0) = v_0]
\end{aligned}$$

.

Combining these calculations and dividing through by $P_G[X(0) = v_0]$ yields the stated equality. □

Proof of Theorem 1.1. The event

$$
\begin{aligned}
[X(t+\Delta t)=v] &= [X(t)=v \wedge \Delta X(t)=0] \cup [X(t)=v-\Delta X(t) \wedge \Delta X(t)\neq 0] \\
&= ([X(t)=v] \setminus [X(t)=v \wedge \Delta X(t)\neq 0]) \cup [X(t)=v-\Delta X(t) \wedge \Delta X(t)\neq 0]
\end{aligned}
$$

by the identity $A\cap B = A\setminus(A\cap(S\setminus B))$ *for any sets* $A, B \subseteq S$. *Therefore, intersecting throughout with* $[X(0)=v_0]$ *and applying laws of probability, calculate*

$$
\begin{aligned}
&P_G\left[X(t+\Delta X)=v\,|X(0)=v_0\right] - P_G\left[X(t)=v\,|X(0)=v_0\right] \\
&= P_G\left[\Delta X(t)\neq 0 \wedge X(t)=v-\Delta X(t)\,|X(0)=v_0\right] \\
&- P_G\left[\Delta X(t)\neq 0 \wedge X(t)=v\,|X(0)=v_0\right] \\
&\cong \sum\nolimits_{(\beta,e)} P_G\left[\Delta N_e^\beta(t)=1 \wedge \Delta X(t)=\mathrm{Tot}_e^\beta \wedge X(t)=v-\mathrm{Tot}_e^\beta\,|X(0)=v_0\right] \\
&- \sum\nolimits_{(\beta,e)} P_G\left[\Delta N_e^\beta(t)=1 \wedge \Delta X(t)=\mathrm{Tot}_e^\beta \wedge X(t)=v\,|X(0)=v_0\right] \\
&= \sum\nolimits_{(\beta,e)} \Big(P_G\left[\Delta N_e^\beta(t)=1 \wedge \Delta X(t)=\mathrm{Tot}_e^\beta \,\middle|\, X(t)=v-\mathrm{Tot}_e^\beta \wedge X(0)=v_0\right] \\
&\qquad \times P_G\left[X(t)=v-\mathrm{Tot}_e^\beta\,|X(0)=v_0\right] \\
&\qquad - P_G\left[\Delta N_e^\beta(t)=1 \wedge \Delta X(t)=\mathrm{Tot}_e^\beta\,|X(t)=v \wedge X(0)=v_0\right] \\
&\qquad \times P_G\left[X(t)=v\,|X(0)=v_0\right]\Big) \\
&= \sum\nolimits_{(\beta,e)} \Big(P_G\left[\Delta N_e^\beta(t)=1 \wedge \Delta X(t)=\mathrm{Tot}_e^\beta \,\middle|\, X(t)=v-\mathrm{Tot}_e^\beta\right] \\
&\qquad \times P_G\left[X(t)=v-\mathrm{Tot}_e^\beta\,|X(0)=v_0\right] \\
&\qquad - P_G\left[\Delta N_e^\beta(t)=1 \wedge \Delta X(t)=\mathrm{Tot}_e^\beta\,|X(t)=v\right] \\
&\qquad \times P_G\left[X(t)=v\,|X(0)=v_0\right]\Big)
\end{aligned}
$$

$$\cong \sum_{(\beta,e)} \Big(\lambda_e^\beta(v - \mathrm{Tot}_e^\beta)\Delta t P_G \Big[X(t) = v - \mathrm{Tot}_e^\beta \,|X(0) = v_0\Big] - \lambda_e^\beta(v)\Delta t P_G \left[X(t) = v \,|X(0) = v_0\right]\Big).$$

Dividing through by Δt and taking the limit as $\Delta t \to 0$ yields the stated ordinary differential equation. □

Proof of Theorem 1.2. Calculate

$$P_G \Big[\Delta N_e^\beta(t) = 1 \wedge \Delta X(t) = \mathrm{Tot}_e^\beta \wedge \Delta N(t+t') = 1 \wedge N(t, t+t') = 0 \,|X(t) = v\Big]$$
$$= P_G \Big[\Delta N_e^\beta(t) = 1 \wedge \Delta X(t) = \mathrm{Tot}_e^\beta \wedge \Delta N(t+t') = 1 \,|N(t, t+t') = 0 \wedge X(t) = v\Big]$$
$$\times P_G \left[N(t, t+t') = 0 \,|X(t) = v\right]$$
$$= P_G \Big[\Delta N_e^\beta(t) = 1 \wedge \Delta X(t) = \mathrm{Tot}_e^\beta \,|N(t, t+t') = 0 \wedge X(t) = v\Big] P_G \left[N(t, t+t') = 0 \,|X(t) = v\right]$$
$$= P_G \Big[\Delta N_e^\beta(t) = 1 \wedge \Delta X(t) = \mathrm{Tot}_e^\beta \,|X(t+t') = v\Big] P_G \left[N(t, t+t') = 0 \,|X(t) = v\right]$$
$$\cong \lambda_e^\beta(v)\Delta t \, e^{-\lambda(v)t'}.$$

The result follows by multiplying and dividing by $\lambda(v)\Delta t$. □

2 Conclusion

Timeout machinery is a model of real-time concurrency, which instead of "stopwatch", adds the notion of "timeout" to state machinery. We have generalized the master equation and its associated exact stochastic simulation algorithm (originally due to Gillespie) to stochastic interruptible timeout machinery. We ask whether other varieties of timing machinery, such as timed automata [DA90] (or theories such as process algebra with timing [BM02]) admit a master equation and an associated exact stochastic simulation algorithm.

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