J. Math. Biol. (1992) 30: 775–800

Journal of
Mathematical
Biology

The statistical dynamics of recurrent biological events

Andrzej Lasota[1], Michael C. Mackey[2]*, and Joanna Tyrcha[3]

[1] Institute of Mathematics, Silesian University, ul. Bankowa 14, 40-007 Katowice, Poland

[2] Departments of Physiology and Physics and Center for Nonlinear Dynamics, McGill University, 3655 Drummond Street, Montreal, H3G 1Y6 Canada

[3] Institute of Computer Science, Polish Academy of Sciences, PKiN, PO Box 22, 00-901 Warsaw, Poland

Received November 28, 1990; received in revised form August 27, 1991

Abstract. In this paper we develop a general modeling framework within which many models for systems which produce events at irregular times through a combination of probabilistic and deterministic dynamics can be comprehended. We state and prove new sufficient conditions for the global asymptotic behaviour of the density evolution in these systems, and apply our results to many previously published models for the cell division cycle. In addition, we develop a new interpretation for the statistics of action potential production in excitable cells.

Key words: Statistical dynamics – Asymptotic periodicity – Asymptotic stability – Cell cycle models – Neuron interspike interval statistics

Introduction

In the biological sciences we are accustomed to dealing with data that often appear to be produced by systems that have a mixture of deterministic and probabilistic dynamics. Classical physiological examples are the release of transmitter at the synapse or neuromuscular junction, the onset of mitosis and cytokinesis in cells, and the generation of action potentials in neurons and other excitable cells. Many other examples may be found in Glass and Mackey (1988).

It is interesting that although the underlying dynamics that give rise to these discrete and observable events are continuous in time, more often than not we either do not have complete knowledge of these and/or are unable to precisely monitor these changes continuously. Rather, we only have the timing of the discrete events themselves and perhaps measured values of a few variables at these times. Thus, in a very real sense our experimental data gives something approximating a Poincaré section through a continuous time attractor in a higher order phase space. However, this apparent limitation has been quite successfully turned around in a variety of biological situations to construct

* To whom correspondence should be sent

discrete time models relating successive values of the accessible state variables (Glass and Mackey 1988).

In this paper we develop a general modeling framework for the treatment of the statistical dynamics of systems in which easily identifiable events occur at irregular times. Though we clearly have biological systems in mind, the development here is applicable to non-biological systems as well.

The outline of the paper is as follows. In the first section, we formulate our model in terms of a discrete time dynamical system with stochastic perturbations. From this formulation, in Sect. 2 we derive an integral recurrence relation for densities describing the statistical behaviour of trajectories. (For continuous time systems an analogous situation occurs when passing from a stochastic differential equation to the corresponding Fokker–Planck equation.) Section 3 develops the concept of the Markov operator, a linear integral operator that describes the evolution of densities in stochastically perturbed systems, as well as two types of stability behaviour that sequences of densities derived from Markov operators may have. In Sect. 4 we state and prove two new sufficient conditions for these types of stability of densities. Section 5 presents a minor digression in that we examine the corresponding stability properties of measures that may be of use when densities do not exist.

In our theory, a concept that we call the internal or physiological time of the system plays an important role. With respect to this time our model behaves the same way in each period between consecutive events, but not with respect to the physical time. The use of the internal time significantly simplifies the theory. In Sect. 6 we explicitly consider the nature of this internal time, since in many examples (in particular in all models of the cell cycle) the physiological time is hidden in the description of the system. In Sect. 7, we show how many existing models for the cell division process may be encompassed within the general framework of the theory developed in earlier sections. Finally, in Sect. 8 we develop a new model for the stochastic production of action potentials by excitable cells, and examine the correlation between successive interspike intervals as predicted by the model.

1 The basic system

The description of our system is the following. We consider a (biological) system which produces events. In addition to the usual laboratory time the system is also assumed to have an internal or physiological time. We denote this internal time by τ to distinguish it from the laboratory (or clock) time t. When an event appears the physiological time resets from the value $\tau = \tau_{\max}$ to $\tau = 0$. We assume that the rate of maturation $d\tau/dt$ depends on the amount of an activator (or maturation factor) which we denote by a. Thus we have

$$\frac{d\tau}{dt} = \varphi(a), \quad \varphi \geqslant 0. \tag{1.1}$$

We further assume that the activator is produced by a dynamics described by the solution to the differential equation

$$\frac{da}{dt} = g(a), \quad g \geqslant 0. \tag{1.2}$$

The solution of (1.2) satisfying the initial condition $a(0) = r$ will be denoted by

$$a(t) = \Pi(t, r),$$

and we assume it is defined for all $t \geqslant 0$. When an event is produced at a time $\tau = \tau_{\max}$ and activator level $a_{\max}$, then a portion $\varrho = \varrho(a_{\max})$ of $a_{\max}$ is consumed in the production of the event. Thus after the event the activator resets to the level

$$a = a_{\max} - \varrho(a_{\max}). \tag{1.3}$$

We call the function $y - \varrho(y)$ the *reset function*, and assume it is invertible. The inverse of $y - \varrho(y)$ is denoted by λ.

Our main assumption is related to the physiological time. Namely we assume that the survival function of $\tau_{\max}$ is independent of the initial value of the activator. We denote this survival function by H. Thus, using the notion of conditional probability we may write

$$\text{prob}(\tau_{\max} \geqslant x \mid a(\tau = 0) = r) = H(x) \tag{1.4}$$

for every $r > 0$. We feel that this assumption corresponds to the intuitive meaning of the physiological time, and offer a mathematical argument for it in Sect. 6. In the terminology of population dynamics we could say that the lifespan of an organism will be shorter when its rate of maturation is increased.

With these assumptions, we will derive a recurrence relation for the values of activator at the times when events occur. Assume that the events appear at the times

$$t_0 < t_1 < t_2 < \cdots.$$

Let a_n be the amount of the activator at the beginning of the time interval (t_n, t_{n+1}). According to Eq. (1.2), this amount at time $t \in (t_n, t_{n+1})$ is given by

$$a = \Pi(t - t_n, a_n).$$

Now using (1.1) we may calculate the physiological time τ corresponding to t. Namely

$$\tau = \int_{t_n}^{t} \varphi(\Pi(s - t_n, a_n))\, ds. \tag{1.5}$$

Substitute $z = \Pi(s - t_n, a_n)$, $dz = g(\Pi(s - t_n, a_n))\, ds$ and observe that $z = a_n$ for $s = t_n$ and $z = a$ for $s = t$. Then (1.5) becomes

$$\tau = \int_{a_n}^{a} q(z)\, dz = Q(a) - Q(a_n), \tag{1.6}$$

where

$$q(z) = \frac{\varphi(z)}{g(z)} \quad \text{and} \quad Q(z) = \int_0^z q(y)\, dy. \tag{1.7}$$

The function q has a simple biological interpretation, since it gives the rate of change of the physiological time relative to the activator.

When t approaches t_{n+1}, the physiological time τ and the amount of the activator a take their maximal values which we denote by τ_n and $a_{\max,n}$ respectively. In this case Eq. (1.6) gives

$$\tau_n = Q(a_{\max,n}) - Q(a_n). \tag{1.8}$$

Further, from the definition of the reset function we have $a_{n+1} = \lambda^{-1}(a_{\max,n})$, and consequently

$$a_{n+1} = \lambda^{-1}(Q^{-1}(Q(a_n) + \tau_n)) \quad \text{for } n = 0, 1, \ldots. \tag{1.9}$$

This is the desired recurrence relation between successive activator levels at event occurrence. By assumption, the variables a_n and τ_n are independent, see Eq. (1.4), and thus we may consider (1.9) as a discrete time dynamical system with stochastic perturbations by the τ_n.

The behaviour of this sytem from a statistical point of view may be described by the sequence of distributions

$$F_n(x) = \text{prob}(a_n < x) \quad \text{for } n = 0, 1, \ldots.$$

In Sect. 5 we derive some sufficient conditions for the convergence of F_n. Before this we derive a recurrence formula for the densities $f_n = dF_n/dx$ in the next section, and then examine the convergence properties of the densities f_n in Sects. 3 and 4.

2 The evolution of densities

Set $H_1 = 1 - H$ and denote by $h = H_1'$ the density function of the distribution of τ_n (assuming that this density exists). If a_n has a distribution F_n then $Q(a_n)$ has the distribution function $G_n(x) = F_n(Q^{-1}(x))$. Further, since a_n and τ_n are independent, the variable $u_n = Q(a_n) + \tau_n$ has a distribution function given by the convolution

$$\int_0^x h(x-y)\, dG_n(y) = \int_0^{Q^{-1}(x)} h(x - Q(y))\, dF_n(y). \tag{2.1}$$

Finally, $\lambda^{-1}(Q^{-1}(a_n))$ has the distribution function

$$\int_0^{\lambda(x)} H(Q(\lambda(x)) - Q(y))\, dF_n(y).$$

From this and the definition of the density, it follows that $a_{n+1} = \lambda^{-1}(Q^{-1}(u_n))$ has a density

$$f_{n+1}(x) = \lambda'(x) q(\lambda(x)) \int_0^{\lambda(x)} h(Q(\lambda(x)) - Q(y)) f_n(y)\, dy. \tag{2.2}$$

Introducing the operator P defined by

$$Pf(x) = \int_0^{\lambda(x)} \left[-\frac{\partial}{\partial x} H(Q(\lambda(x)) - Q(y)) \right] f(y)\, dy, \tag{2.3}$$

we may write these relations in the more abbreviated forms $f_{n+1} = Pf_n$ and $f_n = P^n f_0$. Under some simple regularity conditions concerning λ, Q and H, Eq. (2.3) defines a Markov operator on the space $L^1(R_+)$ of all integrable functions defined on the half line $R_+ = [0, \infty)$. These assumptions will be formulated in the next section where some concepts from the theory of Markov operators are presented.

At this point it is worth noting the explicit use of the inverse function $Q^{-1}(x)$ in the derivation of Eqs. (1.9) and (2.2). In some applications it may happen that the functions $\varphi(x)$ and $q(x)$ vanish on an interval $0 \leqslant x \leqslant x_0$ and are only

positive for $x > x_0$. In this case it is clear that $Q(x)$ as given by (1.7) also vanishes for $0 \leqslant x \leqslant x_0$ and is thus not invertible. However, as we show in the Appendix Eqs. (1.9) and (2.2) are still valid.

If the densities f_n are given then it is easy to find the density of the distribution of the interevent intervals, i.e., the time intervals $\Delta t_n = t_{n+1} - t_n$ between the n^{th} and $(n+1)^{\text{st}}$ events. In fact Eq. (1.5) with $t = t_{n+1}$ gives

$$\tau_n = \int_{t_n}^{t_{n+1}} \varphi(\Pi(s - t_n, a_n))\, ds = \int_0^{\Delta t_n} \varphi(\Pi(s, a_n))\, ds.$$

Therefore

$$\begin{aligned} \text{prob}(\Delta t_n \geqslant x) &= \text{prob}\left(\tau_n \geqslant \int_0^x \varphi(\Pi(s, a_n))\, ds\right) \\ &= \int_0^\infty \text{prob}\left(\tau_n \geqslant \int_0^x \varphi(\Pi(s, t))\, ds \,\middle|\, a_n = r\right) f_n(r)\, dr. \end{aligned}$$

From this and (1.4) it follows immediately that

$$\text{prob}(\Delta t_n \geqslant x) = \int_0^\infty H\left(\int_0^x \varphi(\Pi(s, r))\, ds\right) f_n(r)\, dr.$$

By differentiation we can find the density distribution function of Δt_n which we denote by $\alpha_n(x)$. Namely, the density of the interevent intervals is

$$\alpha_n(x) = \int_0^\infty h\left(\int_0^x \varphi(\Pi(s, r))\, ds\right) \varphi(\Pi(x, r)) f_n(r)\, dr. \tag{2.4}$$

In the particular case when $f_n = f_*$, $(n = 0, 1, \ldots)$ is a time independent stationary sequence, α_n has the same property.

3 Markov operators

In this section we commence our study of the asymptotic properties of the operator

$$Pf(x) = \int_0^{\lambda(x)} K(x, y) f(y)\, dy, \tag{3.1}$$

where

$$K(x, y) = -\frac{\partial}{\partial x} H(Q(\lambda(x)) - Q(y)). \tag{3.2}$$

We will assume that Q, λ and H satisfy the following conditions:

1. The functions $Q : R_+ \to R_+$ and $\lambda : R_+ \to R_+$ are non-decreasing and absolutely continuous on each subinterval $[0, c]$ of the half-line R_+. Moreover

$$Q(0) = \lambda(0) = 0 \quad \text{and} \quad \lim_{x \to \infty} Q(x) = \lim_{x \to \infty} \lambda(x) = \infty. \tag{3.3}$$

2. The function $H : R_+ \to R_+$ is non-increasing, absolutely continuous on each interval $[0, c]$, and

$$H(0) = 1, \qquad \lim_{x \to \infty} H(x) = 0. \tag{3.4}$$

We use these assumptions in both Sects. 3 and 4 and we will not repeat them in the statements of the theorems.

Next, we introduce the concept of a Markov operator (see Lasota and Mackey 1985), and then show that Eqs. (3.1) and (3.2) define a Markov operator. Let D be the set of all densities on R_+, i.e.,

$$D = \{f \in L^1 : f \geqslant 0 \text{ and } \|f\| = 1\},$$

where $L^1 = L^1(R_+)$ and $\|\cdot\|$ is the norm in L^1. A linear operator $P : L^1 \to L^1$ is called a *Markov operator* if $P(D) \subset D$. It is clear that if P is a Markov operator and $f \in L^1$, then $\|Pf\| \leqslant \|f\|$.

To show that (3.1)–(3.2) is a Markov operator follows quite easily as a corollary from the relation

$$\int_0^\infty V(Q(\lambda(x)))Pf(x)\,dx = \int_0^\infty f(y)\,dy \int_0^\infty V(x + Q(y))h(x)\,dx, \tag{3.5}$$

where $f \in L^1$ is non-negative and $V : R_+ \to R_+$ is an arbitrary Borel measurable function. To verify (3.5), note that from (2.3)

$$I = \int_0^\infty V(Q(\lambda(x)))Pf(x)\,dx$$

$$= \int_0^\infty \lambda'(x)q(\lambda(x))V(Q(\lambda(x)))\,dx \int_0^{\lambda(x)} h(Q(\lambda(x)) - Q(y))f(y)\,dy.$$

Setting $z = \lambda(x)$ we have

$$I = \int_0^\infty V(Q(z))q(z)\,dz \int_0^z h(Q(z) - Q(y))f(y)\,dy$$

$$= \int_0^\infty f(y)\,dy \int_y^\infty V(Q(z))h(Q(z) - Q(y))q(z)\,dz.$$

Now substituting $Q(z) - Q(y) = x$, we immediately obtain

$$I = \int_0^\infty f(y)\,dy \int_0^\infty V(x + Q(y))h(x)\,dx$$

which completes the derivation of Eq. (3.5).

Observe that both sides of (3.5) can be infinite. However, if we take $V \equiv 1$, then (3.5) becomes

$$\int_0^\infty Pf(x)\,dx = \int_0^\infty f(y)\,dy \int_0^\infty h(y)\,dy = \int_0^\infty f(y)\,dy,$$

thus demonstrating that $Pf \in D$ for $f \in D$, and thus the operator defined by Eqs. (3.1) and (3.2) is a Markov operator.

In studying the asymptotic properties of the sequence of iterates $\{P^n\}$ it is convenient to introduce the definitions of asymptotic stability and asymptotic periodicity.

The iterates $\{P^n\}$ of a Markov operator P are called *asymptotically stable* if there exists $f_* \in D$ such that $Pf_* = f_*$ and

$$\lim_{x \to \infty} \|P^n f - f_*\| = 0 \quad \text{for } f \in D. \tag{3.6}$$

It is evident that any f_* satisfying (3.6) is unique.

The sequence $\{P^n\}$ is called *asymptotically periodic* if there exists a finite sequence of densities $g_1, \ldots, g_r$, a sequence of linear functionals $\lambda_1, \ldots, \lambda_r$, and a permutation ω of the integers $1, \ldots, r$ such that

$$Pg_i = g_{\omega(i)}, \qquad g_i g_j = 0 \quad \text{for } i \neq j$$

and

$$\lim_{n \to \infty} \left\| P^n f - \sum_{i=1}^{r} \lambda_i(f) g_{\omega^n(i)} \right\| = 0 \quad \text{for } f \in L^1. \tag{3.7}$$

Clearly, an asymptotically periodic operator P with $r = 1$ is asymptotically stable. Using this observation it is easy to prove (Lasota and Mackey 1985) the following

Lemma 1 *If $\{P^n\}$ is an asymptotically periodic sequence of the iterates of a Markov operator P, and there exists a set $B \subset R_+$ of positive measure such that for every $f \in D$ the inequality*

$$P^n f(x) > 0 \quad \textit{for } x \in B \text{ a.e.} \tag{3.8}$$

holds for sufficiently large $n \geqslant n_0(f)$, then $\{P^n\}$ is asymptotically stable.

General sufficient conditions for asymptotic stability and asymptotic periodicity have been summarized by Lasota and Mackey (1985) and extended by Komornik and Lasota (1987). The essence of these results is contained in the following theorem in which the standard Lebesgue measure on R_+ is denoted by m.

Theorem 1 *Let $P : L^1 \to L^1$ be a Markov operator. If there exist constants $\delta > 0$ and $\theta < 1$ and a measurable set $B \subset R_+$ of finite measure such that for every $f \in D$ there is an integer $n_0(f)$ for which*

$$\int_{(R_+ \setminus B) \cup G} P^n f(x)\, dx \leqslant \theta \quad \textit{for } n \geqslant n_0(f) \textit{ and } m(G) \leqslant \delta, \tag{3.9}$$

then the sequence $\{P^n\}$ is asymptotically periodic.

Theorem 1 will be our main tool in studying the asymptotic properties of the operator P defined by Eqs. (3.1) and (3.2). Consequently, the following remarks are important to understand the role of inequality (3.9) even though they are not used in later proofs.

Condition (3.9) can be reformulated as follows. There exists a weakly compact set $\mathscr{F} \subset L^1$ and a constant $\theta < 1$ such that

$$\limsup_{n \to \infty} d(P^n f, \mathscr{F}) \leqslant \theta \quad \text{for } f \in D,$$

where $d(f, \mathscr{F})$ denotes the distance (in L^1 norm) between the function f and the set $\mathscr{F}$. From this interpretation it is clear that (3.9) is a rather mild condition. It should also be noted that the space L^1 plays an important role. Results analogous to those of Theorem 1 in other Banach spaces require, in general, much more restrictive assumptions (Miklavčič 1988, Sine 1989). For example, $\mathscr{F}$ must be strongly compact and $\theta = 0$.

Theorem 1 also has some relation to the theory of Harris operators (Foguel 1969). Namely, in the important special case when P is an integral operator, Theorem 1 implies that the operator

$$\bar{P}f = \frac{1}{f_*} P(f f_*)$$

acting on the space $L^1(C, m_*)$, where $C = \bigcup_i \operatorname{supp} g_i$ and $dm_* = f_* dm$, is a Harris operator. This observation easily explains the orthogonality condition $g_i g_j = 0$ for $i \neq j$ which appears in the definition of asymptotic periodicity. Namely the sets $W_i = \operatorname{supp} g_i$ play the role of atoms of the field Σ_1 on which the Harris operator $\bar{P}$ acts like a point transformation ($\bar{P} 1_{W_i} = 1_{W_j}$). Lemma 1 gives a simple condition which implies that, in fact, there is only one atom in Σ_1.

4 Asymptotic behaviour of densities

We start with a criterion for asymptotic periodicity. Throughout, we use the standard notation for the scalar product of two functions f and g:

$$\langle f, g \rangle = \int_0^\infty f(x) g(x)\, dx.$$

Theorem 2 *Assume that*

$$m_\epsilon \equiv \int_0^\infty x^\epsilon h(x)\, dx < \infty \tag{4.1}$$

for some $\epsilon > 0$, *and that*

$$\liminf_{x \to \infty} \frac{Q(\lambda(x))}{Q(x)} > 1. \tag{4.2}$$

Then the sequence $\{P^n\}$ *with* P *given by Eqs.* (3.1) *and* (3.2) *is asymptotically periodic.*

Proof. Suppose $0 \leqslant \epsilon_1 \leqslant \epsilon_2$ so $x^{\epsilon_1} \leqslant 1 + x^{\epsilon_2}$ for $x \geqslant 0$. As a consequence we have $m_{\epsilon_1} \leqslant 1 + m_{\epsilon_2}$. If m_{ϵ_2} is bounded, thus satisfying (4.1), then it is clear that m_{ϵ_1} also satisfies (4.1). Thus, it may be assumed that $\epsilon \leqslant 1$ in (4.1) without any loss of generality.

Let $U(x) = [Q(\lambda(x))]^\epsilon$, so from (3.5) it follows that

$$\langle U, Pf \rangle = \int_0^\infty f(y)\, dy \int_0^\infty [x + Q(y)]^\epsilon h(x)\, dx \quad \text{for } f \in D.$$

For $\epsilon \leqslant 1$, we have $[x + Q(y)]^\epsilon \leqslant x^\epsilon + [Q(y)]^\epsilon$. Furthermore, by using (4.2) we may choose $\alpha < 1$ and $x_0 \geqslant 0$ such that $[Q(x)]^\epsilon \leqslant \alpha [Q(\lambda(x))]^\epsilon$ for $x \geqslant x_0$. Therefore

$$\langle U, Pf \rangle \leqslant \int_0^\infty f(y)\, dy \int_0^\infty x^\epsilon h(x)\, dx + \int_0^{x_0} f(y) [Q(y)]^\epsilon\, dy \int_0^\infty h(x)\, dx$$

$$+ \int_{x_0}^\infty f(y) [Q(y)]^\epsilon\, dy \int_0^\infty h(x)\, dx.$$

Replacing $[Q(y)]^\epsilon$ in the last integral by $\alpha [Q(\lambda(y))]^\epsilon$, and remembering that both f and h are densities and that $Q(z)$ is not a decreasing function of z, we obtain

$$\langle U, Pf \rangle \leqslant \alpha \langle U, f \rangle + \beta \quad \text{for } f \in D, \tag{4.3}$$

wherein

$$\beta = [Q(x_0)]^\epsilon + \int_0^\infty x^\epsilon h(x)\,dx.$$

Denote by D_0 the set of all $f \in D$ such that $\langle U, f\rangle < \infty$, and choose a $\gamma > \beta/(1-\alpha)$. From Eq. (4.3) it follows that $\langle U, P^n f\rangle < \gamma$ for $f \in D_0$ and sufficiently large n, say $n \geqslant n_0(f)$. As a consequence of the Chebyshev inequality (Lasota and Mackey 1985, Proposition 5.7.1), we have

$$\int_c^\infty P^n f(x)\,dx \leqslant \frac{\gamma}{L} \quad \text{for } n \geqslant n_0(f),\ c \geqslant 0, \tag{4.4}$$

where $L = \inf\{U(x) : x \geqslant c\} = U(c)$. Since $U(x) \to \infty$ as $x \to \infty$, we may choose c such that $\gamma/L < 1$. Observe that if in the left hand side of (4.4) we replace $f \in D_0$ by $\bar{f} \in D$ then the integral changes its value by at most

$$\|P^n f - P^n \bar{f}\| \leqslant \|f - \bar{f}\|.$$

Since the set D_0 is dense in D, this implies that (4.4) holds for all $f \in D$ (changing γ if necessary). Next, let $G \subset [0, c]$ be an arbitrary measurable set and define

$$w(x) = 1_{Q(\lambda(G))}(x),$$

where 1_C denotes the characteristic (indicator) function of the set C. It is evident that $1_G(x) \leqslant w(Q(\lambda(x)))$, and by Eq. (3.5)

$$\int_G Pf(x)\,dx \leqslant \int_0^\infty f(y)\,dy \int_h^\infty h(x)w(x + Q(y))\,dx.$$

Let $2\sigma = 1 - \gamma/L$. Since h is integrable on R_+ there is an $\eta > 0$ such that

$$\int_F h(x)\,dx \leqslant \sigma \quad \text{for } F \subset R_+,\ m(F) \leqslant \eta,$$

where again $m(F)$ is the standard Lebesgue measure of the set F on the real line.

Because of the absolute continuity of $Q \circ \lambda$, we can always find a $\delta > 0$ such that $m(Q(\lambda(G))) \leqslant \eta$ for $G \subset [0, c]$ with $m(G) \leqslant \delta$. Consequently,

$$\int_0^\infty h(x)w(x + Q(y))\,dx = \int_{Q(\lambda(G)) - Q(y)} h(x)\,dx \leqslant \sigma$$

whenever $G \subset [0, c]$ and $m(G) \leqslant \delta$. In particular, for $n \geqslant 1$

$$\int_G P^n f(x)\,dx = \int_0^\infty P^{n-1} f(y)\,dy \int_0^\infty h(x)w(x + Q(y))\,dx \leqslant \sigma$$

if $G \subset [0, c]$ and $m(G) \leqslant \delta$. This last inequality, in conjunction with Eq. (4.4), implies that

$$\int_{G \cup [c,\infty]} P^n f(x)\,dx \leqslant \frac{\gamma}{L} + \sigma = 1 - \sigma$$

for $f \in D$, $n \geqslant n_0(f)$, and arbitrary $G \subset [0, c]$ satisfying $m(G) \leqslant \delta$. This shows that the sufficient condition (3.9) for asymptotic periodicity is satisfied with $B = [0, c)$ and $\theta = 1 - \sigma$, so the proof is complete. □

Lemma 1 and Theorem 2 allow us to formulate a sufficient condition for asymptotic stability, given in the following

Theorem 3 *Assume that P is defined by Eqs.* (3.1) *and* (3.2), *and that conditions* (4.1) *and* (4.2) *are satisfied. If there is a number $x_0 \geqslant 0$ such that*

$$h(x) > 0 \quad \text{for } x > x_0, \tag{4.5}$$

then the sequence $\{P^n f\}$ is asymptotically stable

Proof. From our assumptions, it follows that P satisfies (4.3) and thus, by the Chebyshev inequality, there is a $c > 0$ such that

$$\int_0^c P^n f(x)\, dx > 0 \tag{4.6}$$

for every $f \in D$ and sufficiently large $n \geqslant n_0(f)$. Since $\lambda(x) \to \infty$ and $Q(x) \to \infty$ as $x \to \infty$, there is also an $x_1 \geqslant 0$ such

$$\lambda(x) > c \quad \text{and} \quad Q(\lambda(x)) - Q(y) > x_0 \quad \text{for } x \geqslant x_1,\ y \leqslant c. \tag{4.7}$$

Define $B = \{x \geqslant x_1 : (Q(\lambda(x)))' > 0\}$. It is evident that the set B has positive measure since $Q(\lambda(x))$ is absolutely continuous and is not constant on $[x_1, \infty)$. Now let $f \in D$ be fixed and take $n \geqslant n_0(f) + 1$. Then from (3.1) and (3.2)

$$P^n f(x) \geqslant (Q(\lambda(x)))' \int_0^c h(Q(\lambda(x)) - Q(y)) P^{n-1} f(y)\, dy \quad \text{for } x \geqslant x_1. \tag{4.8}$$

According to (4.5) and (4.7) we have $h(Q(\lambda(x)) - Q(y)) > 0$ for $x \geqslant x_1$, $y \leqslant c$. From this and (4.6) it follows that the integral in (4.8) is different from zero. Thus $P^n f(x) > 0$ for $x \in B$ and $n \geqslant n_0(f) + 1$. According to Lemma 1, the proof is complete. □

5 Asymptotic stability of measures

Theorem 3 gives a sufficient condition for asymptotic stability in terms of the evolution of densities under the action of the Markov operator defined by Eqs. (3.1) and (3.2). This condition is completely dependent on the absolute continuity of H, as set forward in condition 2.

However, by considering the recurrence relation of Eq. (1.9) we may also derive another sufficient condition for the asymptotic behaviour of the model system framed in terms of the convergence properties of measures. Specifically, we consider the recurrence relation (1.9) as a special case of the more general discrete time dynamical system

$$a_{n+1} = S(a_n, \tau_n) \quad n = 0, 1, \ldots. \tag{5.1}$$

In considering (5.1), we will introduce the concept of the asymptotic stability of measures, and prove a sufficient stability criterion analogous to that of Theorem 3.

In considering (5.1), assume that the function $S : R_+ \times R_+ \to R_+$ is continuous and that the random variables

$$a_0, \tau_0, \tau_1, \ldots \tag{5.2}$$

are independent and non-negative with probability one. Also assume that $\tau_0, \tau_1, \ldots$ are equally distributed with a common cumulative distribution function given by

$$H_1(x) = 1 - H(x) = \text{prob}(\tau_n < x).$$

In this section we are interested in the asymptotic behaviour of the distributions

$$F_n(x) = \text{prob}(a_n < x) \quad \text{for } n = 0, 1, \ldots.$$

We will say that the sequence $\{F_n\}$ of distribution functions is *weakly convergent* to a distribution function F_* if

$$\lim_{n \to \infty} F_n(x) = F_*(x)$$

for every point x at which F_* is continuous. The dynamical system (5.1) is called *weakly asymptotically stable* if there is a unique distribution function F_* such that $\{F_n\}$ converges weakly to F_* for every initial distribution function F_0.

The following theorem is a special (one dimensional) case of a more general result proved in Lasota and Mackey (1989).

Theorem 4 *Assume that S and τ_n satisfy the inequalities*

$$E(|S(x, \tau_n) - S(z, \tau_n)|) < |x - z| \quad \textit{for } x \neq z, \tag{5.3}$$

and

$$E(|S(x, \tau_n)|^\gamma) \leqslant \alpha |x|^\gamma + \beta, \tag{5.4}$$

where E denotes the mathematical expectation and α, β, and γ are non-negative constants with $\alpha < 1$ and $\gamma > 1$. Then the dynamical system (5.1) is weakly asymptotically stable.

Using the cumulative distribution function $H_1 = 1 - H$, we may rewrite (5.3) and (5.4) in the forms

$$\int_0^\infty |S(x, y) - S(z, y)| \, dH_1(y) < |x - z| \quad \text{for } x \neq z \tag{5.5}$$

and

$$\int_0^\infty |S(x, y)|^\gamma \, dH_1(y) \leqslant \alpha |x|^\gamma + \beta \tag{5.6}$$

respectively.

Remark 1 Note that in the special case that $S(x, y) = T(x) + y$, with $T: R_+ \to R_+$, so the dynamical system (5.1) has the form

$$a_{n+1} = T(a_n) + \tau_n,$$

then Lasota and Tyrcha (1991) have shown that the conditions (5.5) and (5.6) may be replaced by

$$|T(x) - T(z)| < |x - z| \quad \text{for } x \neq z$$

and

$$\int_0^\infty x \, dH_1(x) < \infty, \quad T(x) \leqslant \alpha x + \beta$$

respectively.

In considering the applicability of Theorem 4, the following observations are important. From Eq. (5.1) it immediately follows that

$$F_{n+1}(x) = \int_0^\infty \text{prob}(S(z, \tau_n) < x \,|\, a_n = z)\, dF_n(z) \quad \text{for } n = 0, 1, \ldots. \tag{5.7}$$

Since both a_n and τ_n are independent, we also may write

$$\text{prob}(S(z, \tau_n) < x \,|\, a_n = z) = \text{prob}(S(z, \tau_n) < x) = \int_0^\infty 1_{B(x,z)}(y)\, dH_1(y), \tag{5.8}$$

where $B(x, z) = \{y : S(z, y) < x\}$. Equations (5.7) and (5.8) illustrate that the sequence $\{F_n\}$ is completely determined by F_0 under the assumption that a_n and τ_n are independent for every value of n. The more restrictive assumption that the entire sequence (5.2) consists of independent random variables does not change the calculation of F_n, and thus we may also apply Theorem 4 in the case where we have pairwise independent (a_n, τ_n). In particular, Theorem 4 applies to the dynamical system (1.9).

It is interesting to note that Eqs. (5.7) and (5.8) offer a new way to derive the recurrence relation (2.2) for the densities. Namely, for the dynamical system (1.9) we have

$$S(z, y) = \lambda^{-1}(Q^{-1}(Q(z) + y)),$$

and as a consequence

$$\begin{aligned} B(x, z) &= \{y : S(z, y) < x\} \\ &= \{y \in R_+ : y < Q(\lambda(x)) - Q(z)\}. \end{aligned}$$

Thus, in this circumstance condition (5.8) now yields

$$\text{prob}(S(z, \tau_n) < x) = \begin{cases} H_1(Q(\lambda(x)) - Q(z)) & \text{for } \lambda(x) \geqslant z \\ 0 & \text{for } \lambda(x) < z \end{cases}.$$

Substituting this into (5.7), we obtain

$$F_{n+1}(x) = \int_0^{\lambda(x)} H_1(Q(\lambda(x)) - Q(z))\, dF_n(z),$$

and differentiating with respect to x yields (2.2).

6 A criterion for independence

The assumed independence of a_n and τ_n plays a crucial role in the theory as developed to this point. It is obvious that this assumption is not easily justified even if one accepts the intuitive interpretation of biological time which has been used to support our independence assumption. In this section we present a mathematical argument to strengthen the plausibility of the independence assumption concerning a_n and τ_n.

Lemma 2 *Assume that X and Y are random variables such that $Y \geqslant X \geqslant 0$ with probability 1, and that the conditional probability of Y with respect to X satisfies*

$$\text{prob}(Y \geqslant y \,|\, X = r) = H(Q(y) - Q(r)) \quad \textit{for } y \geqslant r \geqslant 0, \tag{6.1}$$

where $Q: R_+ \to R_+$ is strictly increasing and onto, and $H: R_+ \to [0, 1]$ is a decreasing function. Then H is the survival function for the random variable $Q(Y) - Q(X)$ and the variables $Q(Y) - Q(X)$ and X are independent.

Proof. Denote by F_X the cumulative distribution function for X. Then it follows that

$$\begin{aligned}\text{prob}(Q(Y) - Q(X) \geqslant u, X \geqslant v) &= \int_v^\infty \text{prob}(Q(Y) - Q(X) \geqslant u \,|\, X = r) F_X(dr) \\ &= \int_v^\infty \text{prob}(Y \geqslant Q^{-1}(u + Q(r)) \,|\, X = r) F_X(dr) \\ &\quad \text{for } u \geqslant 0, v \geqslant 0.\end{aligned}$$

From this and Eq. (6.1) we have

$$\begin{aligned}\text{prob}(Q(Y) - Q(X) \geqslant u, X \geqslant v) &= \int_v^\infty H(Q(Q^{-1}(u + Q(r)) - Q(r))) F_X(dr) \\ &= \int_v^\infty H(u) F_X(dr) \\ &= H(u)(1 - F_X(v))\end{aligned}$$

which completes the proof. □

We will want to be able to use Lemma 2 in situations where $Q(x)$ vanishes for $x \leqslant x_0$ (see the remarks following our derivation of Eq. (2.2) and the Appendix). It is straightforward to show that Lemma 2 also holds in the case that $Q(x)$ is invertible for $x \geqslant x_0$ and if $Y \geqslant x_0$ with probability one.

To illustrate the usefulness of Lemma 2 in understanding the independence assumption, return to the considerations of Sect. 1. However, now we assume neither the existence of an internal (biological) time nor do we make the assumption embodied in Eq. (1.4). Rather, we assume that the activator substance is produced according to Eq. (1.2) as before, and the following condition:

The probability that an event occurs in the time interval $[t, t + \Delta t]$, given that it has not occurred up to time t, is equal to

$$\varphi(a(t))\, \Delta t + o(\Delta t), \tag{6.2}$$

where $a(t)$ is the activator level at time t. As before, we assume that after the event occurs, the activator level is reset to the level $\lambda^{-1}(a_{\max})$.

Now consider the situation in which the system starts at time $t = 0$, when the previous event occurred, with an activator level $a(0) = r$. By (1.2), the activator level at time t is simply

$$a(t) = \Pi(t, r).$$

Furthermore, using (6.2) it is easy to calculate the probability that the next event appears at a time $t_1 > t$. Namely,

$$\text{prob}(t_1 \geqslant t \,|\, a(0) = r) = \exp\left\{-\int_0^t \varphi(\Pi(s, r))\, ds\right\}.$$

Making, as before, the change of variables $z = \Pi(s, r)$ we have

$$\text{prob}(t_1 \geqslant t \mid a(0) = r) = \exp\left\{-\int_r^{a(t)} q(z)\, dz\right\}$$
$$= \exp\{-Q(a(t)) + Q(r)\}.$$

Clearly, the condition $t_1 \geqslant t$ is equivalent to $a_{\max} \geqslant y$ where $y = a(t)$. Thus,

$$\text{prob}(a_{\max} \geqslant y \mid a(0) = r) = \exp\{-Q(y) + Q(r)\}.$$

By Lemma 2, this shows that the variables $Q(a_{\max}) - Q(a(0))$ and $a(0)$ are independent, and furthermore that $Q(a_{\max}) - Q(a(0))$ has an exponential survival function e^{-x}.

Now define

$$\tau = Q(a(t)) - Q(a(0)) \tag{6.3}$$

so, in particular,

$$\tau_{\max} = Q(a_{\max}) - Q(a(0)).$$

Then, since

$$\frac{d\tau}{dt} = q(a(t))a'(t) = q(a(t))g(a(t)) = \varphi(a(t))$$

we know that the function τ satisfies Eq. (1.1). Furthermore, $\tau_{\max}$ is independent of $a(0)$ and has the exponential survival function $H(x) = e^{-x}$.

Thus, through the use of Lemma 2 we have been able to demonstrate the existence of a function having all of the characteristics that we originally postulated for the internal (biological) time. As a consequence, the activator levels a_n satisfy the recurrence relation (1.9) with exponentially distributed τ_n and the density distribution functions f_n of a_n satisfy the operator equation $f_{n+1} = Pf_n$ with P defined by

$$Pf(x) = \lambda'(x)q(\lambda(x)) \int_0^{\lambda(x)} \exp\left\{-\int_y^{\lambda(x)} q(z)\, dz\right\} f(y)\, dy. \tag{6.4}$$

It is important to mention that Eq. (1.9), when $H(x) = e^{-x}$, was first derived by Loskot (personal communication) during the analysis of the operator (6.4) introduced by Tyrcha (1988).

In subsequent sections, we will refer to the system (6.4) as an *exponential model* with transition probability given by (6.2).

7 Cell cycle models

In this section we offer the first of two concrete examples of the application of the general formulation of the previous sections by considering several mathematical models of the cell division cycle.

In interpreting the cell division cycle within the context of the general model presented here, we associate the occurrence of an event with a triggering of the process which ultimately leads to mitosis and cytokinesis, and the activator is associated with an (as yet) hypothetical substance called *mitogen* that is necessary but not sufficient for cell division to occur.

We first consider the class of models proposed by Lasota and Mackey (1984), Tyson and Hannsgen (1986), and Tyrcha (1988). Within the framework of this paper, these models may be described as follows.

During the lifetime of the cell it must traverse two phases of the cell cycle denoted by A and B. The end of phase B coincides with cell division. The duration of phase B is constant, and denoted by t_B, while the length t_A of phase A is considered to be a random variable. The transition from phase A to phase B is taken to be coincident with the occurrence of an event, and the probability that this event occurs during the interval $[t, t + \Delta t]$ is given by (6.2) where $a(t)$ is the mitogen level. The production of mitogen is governed by Eq. (1.2) with $g(x) > 0$ for $x > 0$. Within the context of the general framework developed earlier, the transition between phases A and B, i.e., when the event occurs, corresponds to the moment when the activator has a level $a_{\max,n}$. Since the production of mitogen during B is still governed by Eq. (1.2), at cell division (the end of B) the activator has a level of $\Pi(t_B, a_{\max,n})$. Finally, in these models the mitogen is assumed to be divided equally between both daughter cells at cell division, so

$$\tfrac{1}{2}\Pi(t_B, a_{\max,n}) = \lambda^{-1}(a_{\max,n}) = a_{n+1}, \tag{7.1}$$

or

$$\lambda(x) = \Pi(-t_B, 2x).$$

This class of cell cycle models satisfies all of the conditions of the exponential model described in Sect. 6, and have an internal time defined by (6.3). Furthermore, the quantities of mitogen in consecutive generations of newly born cells satisfy the recurrence relation (1.9), with τ_n having a survival function e^{-x}. Lastly, the transition operator for the evolution of mitogen density is given by Eq. (6.4).

There are two specific features of these cell cycle models that deserve mention. First, the reset function is not arbitrary but is explicitly defined by Eq. (7.1). Secondly, Eq. (2.4) gives the distribution of the lengths of the phase A of the cell cycle, with the density of the duration of the entire cell cycle given by

$$\bar{\alpha}_n(t) = \begin{cases} \alpha_n(t - t_B) & \text{for } t \geqslant t_B \\ 0 & \text{for } t < t_B \end{cases}. \tag{7.2}$$

The description of the cell cycle that we have given here was first proposed by Tyrcha (1988). It reduces to the Lasota and Mackey (1984) model if $t_B = 0$, and to the Tyson and Hannsgen (1986) model if $g(x) = kx$ and

$$\varphi(x) = \begin{cases} p & \text{for } x \geqslant 1 \\ 0 & \text{for } x < 1 \end{cases},$$

where k and p are positive constants.

It is interesting to examine these models in the light of our stability results of Theorems 3 and 4. First, note that conditions (4.1) and (4.5) are automatically satisfied with $h(x) = e^{-x}$. Thus, to apply Theorem 3 it is sufficient to verify (4.2).

For the Lasota–Mackey model, $\lambda(x) = \Pi(0, 2x) = 2x$ and condition (4.2) reduces to

$$\liminf_{x \to \infty} \frac{Q(2x)}{Q(x)} = \liminf_{x \to \infty} \frac{\int_0^{2x} q(z)\, dz}{\int_0^x q(z)\, dz} > 1. \tag{7.3}$$

For $q(y)$ bounded, (7.3) is more general than the original asymptotic stability condition of $\liminf_{x\to\infty} q(x) > 0$ stated in Lasota and Mackey (1984) since $\liminf_{x\to\infty} q(x) > 0$ then implies (7.3).

In the case of the Tyson and Hannsgen (1986) cell cycle model, a simple application of Eq. (7.1) gives $\lambda(x) = x/\sigma$ where $\sigma = \frac{1}{2}e^{kt_B}$. Moreover, $Q(x) = (p/k)\ln^+ x$ where $\ln^+ x = \max(0, \ln x)$. Therefore,

$$\lim_{x\to\infty} \frac{Q(\lambda(x))}{Q(x)} = \lim_{x\to\infty} \frac{\ln\left(\frac{x}{\sigma}\right)}{\ln x} = 1,$$

and condition (4.2) is never satisfied. However, in this case we may use Theorem 4 to examine the stability. Equation (1.9), with $\lambda^{-1}(x) = \sigma x$, $Q(x) = (p/k)\ln^+ x$, and $Q^{-1}(x) = e^{kx/p}$ reduces to

$$a_{n+1} = \sigma \max(1, a_n)\, e^{k\tau_n/p}.$$

An elementary calculation shows that inequalities (5.5) and (5.6), with

$$S(x, y) = \sigma \max(1, x)\, e^{ky/p}$$

and $H_1(y) = 1 - e^{-y}$ are satisfied whenever $k/p < 1 - \sigma$. This inequality for weak asymptotic stability was derived by Tyson and Hannsgen (1986).

As another example, extensions proposed by Tyson and Hannsgen (1985) and Hannsgen et al. (1985) of the well known cell cycle models of Smith and Martin (1973) and Shields (1977) also fall within the general framework of this paper.

In these situations, we also assume that the cell goes through phases A and B, and that the length t_B of phase B is constant. Once again the end of the B phase marks cell division. The length t_A of the phase A is considered to be a random variable with a density distribution function ψ, so

$$\text{prob}(t_A \geqslant x) = \int_x^\infty \psi(z)\, dz.$$

The activator (mitogen) is once again produced with dynamics described by Eq. (1.2), is assumed to not affect t_A, and divides equally between mother and daughter cells at division. Thus, by assumption, t_A and $a(0)$ are independent.

To show how this model may be incorporated into our general framework, assume as before that the event corresponds to the transition point between the phases A and B. Furthermore, set

$$\varphi(x) \equiv 1, \quad H(x) = \int_x^\infty \psi(z)\, dz,$$

and define λ by Eq. (7.1). The condition $\varphi \equiv 1$ simply means that the internal (biological) time τ and laboratory times t are either identical during any given cell cycle, or differ by a constant amount.

Using the special form of the function $q = 1/g$, the recurrence relation (1.9) may be considerably simplified. Thus, solving (1.2) with $a(0) = r$ we have

$$\int_r^{a(t)} \frac{dx}{g(x)} = t \quad \text{or} \quad Q(a(t)) - Q(r) = t.$$

This, in turn, implies

$$a(t) = \Pi(t, r) = Q^{-1}(Q(r) + t),$$

and in particular

$$\lambda(x) = \Pi(-t_B, 2x) = Q^{-1}(Q(2x) - t_B).$$

Finally,

$$S(x, y) = \lambda^{-1}(Q^{-1}(Q(x) + y)) = \tfrac{1}{2}Q^{-1}(Q(x) + y + t_B),$$

and the dynamical system (1.7) reduces to

$$a_{n+1} = \tfrac{1}{2}Q^{-1}(Q(a_n) + \tau_n + t_B), \tag{7.4}$$

where $\tau_n = t_{A_n}$ denotes the length of the A phase during the nth cellular generation.

A comparison of Eqs. (1.9) and (7.4) suggests the following correspondence. Introduce a new variable $\bar{\tau}_n = t_B + \tau_n$ with the density distribution function

$$h(x) = \begin{cases} \psi(x - t_B) & \text{for } x \geqslant t_B \\ 0 & \text{for } x < t_B \end{cases},$$

and a new reset function $\bar{\lambda}(x) = \frac{1}{2}x$. This corresponds to shifting events to the division points $t_{A_n} + t_B$. With these new functions, (7.4) is once again a special case of (1.9), and the corresponding recurrence relation for densities has the form $f_{n+1} = Pf_n$ with P given by

$$Pf(x) = 2q(2x) \int_0^{2x} h(Q(2x) - Q(y))f(y)\, dy. \tag{7.5}$$

The operator P defined by (7.5) is easily studied using Theorems 2 and 3. Thus, if P satisfies conditions (4.1) and (4.2), then the sequence $\{P^n\}$ is asymptotically periodic. If, in addition, P satisfies (4.5), then $\{P^n\}$ is asymptotically stable. Condition (4.1) is quite mild, and rather easily satisfied. For example, it holds (with $\epsilon = 1$) when t_A has a finite mean value. However, the inequalities (4.2) and (4.5) are much more difficult to apply.

To illustrate this, consider the specific case in which $g(x) = kx^{\alpha}$. Then

$$Q(x) = \frac{x^{1-\alpha}}{k(1-\alpha)}, \quad \alpha \neq 1, \tag{7.6}$$

and $Q(2x)/Q(x) = 2^{1-\alpha}$. Thus according to Theorem 2 for $\alpha < 1$ and

$$E(\bar{\tau}_n) = \int_0^{\infty} xh(x)\, dx < \infty, \tag{7.7}$$

where $E(\cdot)$ denotes the mathematical expectation, the system is asymptotically periodic. Using Theorem 4 we will show that it is, in fact, asymptotically stable without any additional assumptions concerning h. In particular, we will not require (4.5).

To demonstrate asymptotic stability, consider the recurrence relation (7.4) with Q defined by (7.6). An elementary calculation gives

$$a_{n+1} = \tfrac{1}{2}[a_n^{1-\alpha} + k(1-\alpha)\bar{\tau}_n]^{1/(1-\alpha)}. \tag{7.8}$$

Set $b_n = a_n^{1-\alpha}$ to obtain

$$b_{n+1} = (\tfrac{1}{2})^{1-\alpha}[b_n + k(1-\alpha)\bar{\tau}_n]. \tag{7.9}$$

Theorem 4 in conjunction with Remark 1 shows that for $\alpha < 1$ the dynamical system (7.9) is weakly asymptotically stable. Thus the sequence of cumulative distribution functions

$$G_n(x) = \text{prob}(b_n < x)$$

is weakly convergent to a distribution function G_*. Since the distribution functions F_n of a_n satisfy $F_n(x) = G_n(x^{1-\alpha})$, they converge weakly to $F_*(x) = G_*(x^{1-\alpha})$. However, by Theorem 2 we know that for $\alpha < 1$ the system (7.8) is asymptotically periodic which implies that the sequences of densities $f_n = dF_n/dx$ are compact in L^1 norm. This demonstrates that (7.8) is strongly asymptotically stable, i.e. for every density $f \in D$ the sequence $\{P^n f\}$ converges in L^1 norm to the stationary density $f_* = dF_*/dx$.

Note that for $\alpha > 1$ every solution $a(t)$ of Eq. (1.2) with $g(x) = kx^\alpha$ ($k > 0$, $\alpha > 1$), and $a(0) > 0$ escapes to infinity in a finite time. Consequently, the system is not well defined.

However, the intermediate case of $\alpha = 1$ is interesting in the following sense. When $\alpha = 1$, Eq. (7.4) reduces to

$$a_{n+1} = \tfrac{1}{2} a_n e^{k\bar{\tau}_n}. \tag{7.10}$$

Clearly, $a_n = 0$ ($n = 0, 1, \ldots$) is a stationary solution corresponding to the distribution

$$F_*(x) = \begin{cases} 1 & \text{for } x > 0 \\ 0 & \text{for } x \leqslant 0 \end{cases}. \tag{7.11}$$

Using the method of characteristic functions, it is easy to verify that (7.11) is the unique stationary distribution of the dynamical system defined by Eq. (7.10), and that for $E(k\bar{\tau}) < \ln 2$ this system is weakly asymptotically stable.

Hannsgen et al. (1985) studied the case when $\alpha = 1$ using Mellin transformation techniques, and the case of $\alpha = 0$ using lower bound function techniques. In the latter case, they also assumed that h is positive on a sufficiently large interval. Here we have carried through the complete analysis for arbitrary α satisfying $0 \leqslant \alpha \leqslant 1$ without imposing other conditions on the function h. We have been able to do this through the simultaneous use of the asymptotic properties of the dynamical system defining the trajectories of $\{a_n\}$ and the Markov operator generating the sequence $\{f_n\}$ of densities.

8 Integrate and fire models for biological processes

Integrate and fire models for the generation of action potentials by excitable cells (neurons) have formed the basis for a number of treatments of stochastic single cell activity (Tuckwell 1989). Furthermore, they have enjoyed great popularity in the modeling of many other types of biological processes (Glass and Mackey 1979, 1988; Glass et al. 1980; Lasota and Mackey 1985) in which there is evidence that some state variable must reach a threshold before an event is initiated, for example in models of respiratory rhythmogenesis.

However, in showing how the general formulation of the previous sections may be used to treat integrate and fire models, we will phrase the presentation in terms of the genesis of action potentials. Our model is based on standard and commonly accepted properties of excitable membranes. The novelty is that under

quite natural assumptions the generation of action porentials can be described as a special case of Eq. (1.9), and this formulation gives a simple explanation of known experimental observations related to the distribution of action potential occurrence times.

We consider a single cell subject to a time invariant depolarizing current I, derived either from an external source (experimentally imposed or due to the presynaptic activity of another neuron) or internally if the cell is a pacemaker cell. In the absence of any depolarizing input, the membrane potential V will spontaneously return to the resting potential if perturbed from that point. In the presence of the current I, the membrane potential is assumed to have dynamics described by

$$\frac{dV}{dt} = \bar{V} - G(V), \tag{8.1}$$

where $\bar{V}$ is the constant depolarizing potential induced by the current I, and $G(V)$ is directly related to the nonlinear voltage dependent ionic currents through the membrane (Mackey 1975). In this formulation, all potentials V are measured relative to the resting potential, and time is measured in units of the membrane time constant. Further, we have $G(V)V > 0$ for $V \neq 0$. The activator of our general formulation is identified with the membrane potential

$$a(t) = V(t).$$

Thus, Eq. (8.1) can be written in the form

$$\frac{dV}{dt} = g(V), \quad \text{with } g(V) = \bar{V} - G(V). \tag{8.2}$$

If we wish to use a linear approximation in place of (8.2), we write $G(V) \simeq kV$ so

$$\frac{dV}{dt} = \bar{V} - kV. \tag{8.3}$$

Because of the nature of $G(V)$, there is a unique positive value of V, say $V = V_M$, such that $g(V_M) = 0$. (In the linear case, $V_M = \bar{V}/k$.) Note that the qualitative behaviour of the solutions of Eqs. (8.2) and (8.3) is similar for

$$V < V_M, \qquad t \geqslant 0,$$

since every solution starting with the initial value $V(0) < V_M$ is strictly increasing and asymptotically approaches V_M as $t \to \infty$.

We assume that during an action potential there is a stereotyped sequence of channel openings and closings so the membrane potential resets by a constant amount V_R and

$$\lambda^{-1}(x) = x - V_R \tag{8.4}$$

where V_R is a positive constant.

However, the form of the function φ is somewhat more difficult to determine. Note that in order to produce an action potential at time t, the value of the activator $V(t)$ must be larger than V_R. Therefore, we take $\varphi(x) = 0$ for $x \leqslant V_T$ where V_T is a constant threshold and $V_T > V_R$. For $x > V_T$ we assume that $\varphi(x)$ is positive.

Making these connections, we now show that the general method we have developed is able to explain:

1. The existence of a minimum period of time between action potentials, known as the refractory period.

2. The correlation coefficient κ between successive interspike intervals (Δt_n) is negative.

3. κ becomes small when the mean of Δt_n becomes large.

By Eq. (8.2), the time Δt_n between the nth and $(n+1)$st action potentials is given by

$$\int_{V_n}^{V_{\max,n}} \frac{dx}{g(x)} = \Delta t_n, \tag{8.5}$$

Since the $V_{\max,n}$ are always smaller than V_M we have

$$V_{n+1} = V_{\max,n} - V_R < V_M - V_R. \tag{8.6}$$

Furthermore, the $V_{\max,n}$ are always larger than V_T, so the integral (8.5) is bounded from below by

$$\int_{V_M - V_R}^{V_T} \frac{dx}{g(x)} = t_a. \tag{8.7}$$

We can thus associate t_a with the existence of a positive refractory time by simply assuming that

$$V_T > V_M - V_R. \tag{8.8}$$

The assumption embodied in Eq. (8.8) also considerably simplifies the corresponding recurrence relation (1.9) for V_n, giving

$$Q(x) = \begin{cases} 0 & \text{for } 0 \leqslant x < V_T \\ \int_{V_T}^{x} q(y)\, dy & \text{for } V_T \leqslant x \leqslant V_M \end{cases}, \tag{8.9}$$

where, as usual, $q = \varphi/g$. Furthermore, from Eqs. (8.6) and (8.8) we have that $V_n < V_T$ so $Q(V_n) = 0$ for all n, and the recurrence relation (1.9) (with $\lambda^{-1}(x) = x - V_R$) becomes

$$V_{n+1} = Q^{-1}(\tau_n) - V_R \quad \text{for } n = 0, 1, \ldots, \tag{8.10}$$

where the internal times τ_n are all distributed with the same exponential density e^{-x}.

Initially, the recurrence relation (8.10) does not appear especially interesting. For example, the question of asymptotic stability is now trivial since all of the variables V_n are distributed with the same density. However, (8.10) in combination with (8.5) gives us a tool to examine the correlation between successive interspike intervals Δt_n and Δt_{n+1}. Define

$$G(x) = \left| \int_{V_T}^{x} \frac{dy}{g(y)} \right|.$$

Then, since $V_{\max,n} > V_T > V_n$, Eq. (8.5) may be rewritten in the form

$$\Delta t_n = G(V_n) + G(V_{\max,n}) = G(V_n) + G(V_{n+1} + V_R).$$

Using this and (8.10) we obtain

$$\Delta t_n = G(Q^{-1}(\tau_{n-1}) - V_R) + G(Q^{-1}(\tau_n)). \tag{8.11}$$

Observe that in this expression the Δt_n are given in terms of τ_n's only, and these in turn depend on the external excitation of the neuron. We assume here that the variables $\tau_0, \tau_1, \ldots$ are independent, which is a weaker condition than used in many other studies, e.g. see Gerstein and Mandelbrot (1964). As we show below, the assumed independence of the $\tau_0, \tau_1, \ldots$ only implies that the external inputs to the neuron are not correlated with the state of the neuron, and does not imply that the interspike intervals Δt_n are uncorrelated.

With this independence assumption, we now turn to a calculation of the correlation coefficient

$$\kappa = \frac{\mu(\Delta t_n, \Delta t_{n+1})}{\sigma(\Delta t_n)\sigma(\Delta t_{n+1})}, \tag{8.12}$$

where μ denotes the covariance

$$\mu(\Delta t_n, \Delta t_{n+1}) = E(\Delta t_n \, \Delta t_{n+1}) - E(\Delta t_n)E(\Delta t_{n+1}),$$

E is the mathematical expectation, and $\sigma(\Delta t_n)$ is the standard deviation of Δt_n.

Define

$$\xi_n = G(Q^{-1}(\tau_n) - V_R), \qquad \eta_n = G(Q^{-1}(\tau_n)). \tag{8.13}$$

Then $\Delta t_n = \xi_{n-1} + \eta_n$ and

$$\mu = E((\xi_n + \eta_{n+1})(\xi_{n-1} + \eta_n)) - E(\xi_n + \eta_{n+1})E(\xi_{n-1} + \eta_n).$$

Since the only variables that may not be independent are those with the same subscript n, this latter expression simplifies to

$$\mu = E(\xi_n \eta_n) - E(\xi_n)E(\eta_n). \tag{8.14}$$

As we noted above, the variables τ_n are distributed with an exponential density e^{-x}, so the variables $Q^{-1}(\tau_n)$ are distributed with the density

$$s(x) = \frac{dQ(x)}{dx} e^{Q(x)} = \begin{cases} 0 & \text{for } 0 \leqslant x < V_T \\ q(x)\, e^{-Q(x)} & \text{for } V_T \leqslant x < V_M \end{cases}.$$

Using this in conjunction with the definition of ξ_n and η_n we have

$$E(\xi_n) = \int_{V_T}^{V_M} G(x - V_R)s(x)\, dx, \qquad E(\eta_n) = \int_{V_T}^{V_M} G(x)s(x)\, dx,$$

and

$$E(\xi_n \eta_n) = \int_{V_T}^{V_M} G(x)G(x - V_R)s(x)\, dx.$$

These relations give

$$\mu = \int_{V_T}^{V_M} \left\{ G(x - V_R) - \int_{V_T}^{V_M} G(y - V_R)s(y)\, dy \right\} G(x)s(x)\, dx. \tag{8.15}$$

We are going to prove that the correlation coefficient κ is negative. Due to the nonnegativity of the standard deviations, this reduces to a proof that $\mu < 0$.

We first consider the function

$$r(x) = G(x - V_R) - \bar{G} \quad \text{where } \bar{G} = \int_{V_T}^{V_M} G(y - V_R)s(y)\,dy.$$

For $x \in [V_T, V_M]$ we have $x - V_R < V_T$ and

$$r(x) = \int_{x - V_R}^{V_T} \frac{dy}{g(y)} - \bar{G}$$

is a strictly decreasing function in this interval. Moreover, from the definition of r it follows that its average value calculated with the weighting function $s(x)$ vanishes, i.e.,

$$\int_{V_T}^{V_M} r(x)s(x)\,dx = 0. \tag{8.16}$$

Since $s(x) > 0$ for $V_T < x < V_M$, this implies the existence of a unique point $x_0 \in (V_T, V_M)$ such that

$$r(x) > 0 \quad \text{for } V_T \leqslant x < x_0 \quad \text{and} \quad r(x) < 0 \quad \text{for } x_0 < x \leqslant V_M.$$

We can rewrite Eq. (8.16) in the form

$$\int_{V_T}^{x_0} r(x)s(x)\,dx = \int_{x_0}^{V_M} [-r(x)]s(x)\,dx, \tag{8.17}$$

in which the integrands $r(x)s(x)$ and $[-r(x)]s(x)$ are strictly positive. Furthermore, $G(x)$ is positive and strictly increasing in the interval (V_T, V_M). From (8.17) and this observation it follows directly that

$$\int_{V_T}^{x_0} r(x)G(x)s(x)\,dx < \int_{x_0}^{V_M} [-r(x)]G(x)s(x)\,dx.$$

By Eq. (8.15) the last inequality is equivalent to $\mu < 0$ and thus we have proved that the correlation coefficient κ between successive interspike intervals is negative.

Note in particular that our proof of the negativity of the correlation coefficient κ between successive interspike intervals is independent of any further assumptions concerning the functions g and φ.

Now we turn to a consideration of the dependence of κ on the parameters describing the system, and we pick some specific forms for g and φ. We assume that g is linear, $g(x) = \bar{V} - kx$ as in Eq. (8.3), and that $\varphi(x)$ is constant for $x \geqslant V_T$ so

$$\varphi(x) = \begin{cases} 0 & \text{for } x < V_T \\ p & \text{for } x \geqslant V_T \end{cases}.$$

These assumptions are similar to those of the Tyson–Hannsgen (1986) model of the cell cycle considered in the previous section.

Now we have $V_M = \bar{V}/k$ and

$$Q(x) = \frac{p}{k} \ln^+ \left(\frac{V_M - x}{V_M - V_T} \right), \qquad G(x) = \frac{1}{k} \left| \ln \left(\frac{V_M - x}{V_M - V_T} \right) \right|.$$

Consequently, according to (8.13) we have

$$\xi_n = \frac{1}{k} \ln\left(\frac{V_R}{V_M - V_T} + e^{-k\tau_n/p}\right), \qquad \eta_n = \frac{\tau_n}{p}.$$

Since the τ_n are distributed with the density e^{-x}, this finally gives

$$E(\xi_n \eta_n) = \frac{1}{pk} \int_0^\infty x\, e^{-x} \ln\left(\frac{V_R}{V_M - V_T} + e^{-kx/p}\right) dx$$

and

$$E(\xi_n) = \frac{1}{k} \int_0^\infty e^{-x} \ln\left(\frac{V_R}{V_M - V_T} + e^{-kx/p}\right) dx, \qquad E(\eta_n) = \frac{1}{p}.$$

Substituting these expressions into (8.15) we obtain

$$\mu = \frac{1}{pk} \int_0^\infty (x-1)\, e^{-x} \ln\left(\frac{V_R}{V_M - V_T} + e^{-kx/p}\right) dx.$$

The integral on the right hand side is easy to evaluate, and we obtain

$$\begin{aligned} |\mu| &\leqslant \frac{1}{pk} \int_0^\infty (x+1)\, e^{-x} \ln\left(\frac{V_R}{V_M - V_T} + 1\right) dx \\ &\leqslant \frac{2}{pk} \ln\left(\frac{V_R}{V_M - V_T} + 1\right). \end{aligned} \tag{8.18}$$

Furthermore, since the process is stationary we have $\sigma(\Delta t_n) = \sigma(\Delta t_{n+1})$ and the denominator in (8.12) has the form

$$\sigma(\Delta t_n)\sigma(\Delta t_{n+1}) = \sigma^2(\Delta t_n) = \sigma^2(\xi_n) + \sigma^2(\eta_n).$$

Evidently $\sigma(\eta_n) = (1/p)\sigma(\tau_n) = 1/p$ and $\sigma^2(\Delta t_n) \geqslant 1/p^2$. From this and (8.18) it follows that

$$|\kappa| = \frac{|\mu|}{\sigma^2(\Delta t_n)} \leqslant p^2 |\mu| \leqslant \frac{2p}{k} \ln\left(\frac{V_R}{V_M - V_T} + 1\right). \tag{8.19}$$

Finally, note that

$$E(\Delta t_n) = E(\xi_n) + E(\eta_n) = \frac{1}{k} \int_0^\infty e^{-x} \ln\left(\frac{V_R}{V_M - V_T} + e^{-kx/p}\right) dx + \frac{1}{p}. \tag{8.20}$$

We know that $\mu < 0$ for $p > 0$, and from inequality (8.19) it follows that $\kappa \to 0$ as $p \to 0$. On the other hand, (8.20) implies that $E(\Delta t_n) \to \infty$ as $p \to 0$. Alternately, if we look at the effects of changing the depolarizing input $\bar{V}$ (equivalent to changing V_M), then it is easy to show that $(\partial E(\Delta t_n)/\partial V_M) < 0$ so increasing $\bar{V}$ causes a decrease in $E(\Delta t_n)$ and the neuron firing frequency increases as expected. Furthermore, we may also easily show that $(\partial \mu/\partial V_M) < 0$. Thus, if the average length of the interval spike intervals is large (low firing frequency), then the correlation coefficient κ of successive interspike intervals is small and negative. These behaviours, along with the negativity of κ, are well documented experimentally (Mannard et al. 1977).

Appendix

Here we show that Eqs. (1.9) and (2.2) are still valid in the case that $Q(x)$, as given by (1.7), vanishes for $0 \leqslant x \leqslant x_0$ and is thus not invertible.

Define $Q^{-1}(x)$ as the inverse of $Q(x)$ restricted to $x \geqslant x_0$. Then we have

$$Q(Q^{-1}(x)) = x \quad \text{for } x \geqslant 0,$$

while

$$Q^{-1}(Q(x)) = x \quad \text{for } x \geqslant x_0.$$

With Q^{-1} defined in this way, we can proceed to repeat the derivation of Eqs. (1.9) and (2.2).

With respect to (1.9), first note that $a_{\max,n} \geqslant x_0$ with probability one since $\varphi(x) = 0$ for $x < x_0$. Further, from (1.8) we have

$$Q(a_{\max,n}) = Q(a_n) + \tau_n. \tag{A.1}$$

Applying Q^{-1} to (A.1) we have

$$a_{\max,n} = Q^{-1}(Q(a_n) + \tau_n).$$

Finally, using the definition of the reset function $[a_{n+1} = \lambda^{-1}(a_{\max,n})]$ we once again obtain (1.9).

To show that (2.2) is also valid with Q^{-1} as defined, we first find the distribution function for a_{n+1} given by (1.9). We start by considering the variable $u_n = Q(a_n) + \tau_n$.

Let F_n denote the distribution function of a_n. Then it follows that

$$\text{prob}(Q(a_n) < x) = 0 \quad \text{if } x \leqslant 0$$

while

$$\text{prob}(Q(a_n) < x) = \text{prob}(a_n < Q^{-1}(x)) = F_n(Q^{-1}(x)) \quad \text{if } x > 0.$$

Thus

$$G_n(x) = \begin{cases} 0 & \text{for } x \leqslant 0 \\ F_n(Q^{-1}(x)) & \text{for } x > 0 \end{cases},$$

is the distribution function of $Q(a_n)$.

It is clear that the variable u_n has a distribution function given by the convolution

$$\begin{aligned} S_n(x) &= \int_{-\infty}^{+\infty} H_1(x-y)\, dG_n(y) = \int_{[0,x]} H_1(x-y)\, dG_n(y) \\ &= H_1(x)F_n(x_0) + \int_{(0,x]} H_1(x-y)\, dF_n(Q^{-1}(y)). \end{aligned}$$

Defining a new variable $z = Q^{-1}(y)$ we may rewrite this as

$$\begin{aligned} S_n(x) &= H_1(x)F_n(x_0) + \int_{x_0}^{Q^{-1}(x)} H_1(x - Q(z))\, dF_n(z) \\ &= H_1(x) \int_0^{x_0} dF_n(z) + \int_{x_0}^{Q^{-1}(x)} H_1(x - Q(z))\, dF_n(z). \end{aligned}$$

Since $Q(z) = 0$ for $z \leqslant x_0$ we also have

$$S_n(x) = \int_0^{x_0} H_1(x - Q(z))\, dF_n(z) + \int_{x_0}^{Q^{-1}(x)} H_1(x - Q(z))\, dF_n(z)$$

$$= \int_0^{Q^{-1}(x)} H_1(x - Q(z))\, dF_n(z). \tag{A.2}$$

Let the distribution function of $Q^{-1}(u_n)$ be T_n. Then we have

$$T_n(x) = 0 \quad \text{for } x \leqslant x_0,$$

while

$$T_n(x) = \text{prob}(Q^{-1}(u_n) < x) = \text{prob}(u_n < Q(x)) = S_n(Q(x)) \quad \text{for } x > x_0.$$

Using Eq. (A.2) we can rewrite the last expression as

$$T_n(x) = \int_0^{Q^{-1}(Q(x))} H_1(Q(x) - Q(z))\, dF_n(z)$$

$$= \int_0^{x} H_1(Q(x) - Q(z))\, dF_n(z) \quad \text{for } x > x_0,$$

so finally

$$T_n(x) = \int_0^{x} H_1(Q(x) - Q(z))\, dF_n(z) \quad \text{for } x > 0.$$

From this we immediately obtain (2.2).

References

1. Foguel, S. R.: The Ergodic Theory of Markov Processes. New York: Van Nostrand Reinhold 1969
2. Gerstein, G. L., Mandelbrot, B.: Random walk model for the spike activity of a single neuron. Biophys. J. **4**, 41–68 (1964)
3. Glass, L., Mackey, M. C.: A simple model for phase locking of biological oscillators. J. Math. Biol. **7**, 339–352 (1979)
4. Glass, L., Mackey, M. C.: From Clocks to Chaos: The Rhythms of Life. Princeton: Princeton University Press 1988
5. Glass, L., Graves, C., Petrillo, G. Mackey, M. C.: Unstable dynamics of a periodically driven oscillator in the presence of noise. J. Theor. Biol. **86**, 455–475 (1980)
6. Hannsgen, K. B., Tyson, J. J., Watson, L. T.: Steady state size distribution in probabilistic models of the cell division cycle. SIAM J. Appl. Math. **45**, 523–540 (1985)
7. Komornik, J., Lasota, A.: Asymptotic decomposition of Markov operators. Bull. Pol. Acad. Sci., Math. **35**, 321–327 (1987)
8. Lasota, A., Mackey, M. C.: Globally asymptotic properties of proliferating cell populations. J. Math. Biol. **19**, 43–62 (1984)
9. Lasota, A., Mackey, M. C.: Probabilistic Properties of Deterministic Systems. Cambridge: Cambridge University Press 1985
10. Lasota, A., Mackey, M. C.: Stochastic perturbation of dynamical systems: The weak convergence of measures. J. Math. Anal. Appl. **138**, 232–248 (1989)
11. Lasota, A., Tyrcha, J.: On the strong convergence to equilibrium for randomly perturbed dynamical systems. Ann. Pol. Math. **53**, 79–89 (1991)
12. Mackey, M. C.: Ion Transport Through Biological Membranes. Berlin Heidelberg New York: Springer 1975

13. Mannard, A., Rajchgot, P., Polosa, C.: Effect of post-impulse depression on background firing of sympathetic preganglionic neurons. Brain Res. **126**, 243–261 (1977)
14. Miklavčič, M.: Asymptotic periodicity of the iterates of positivity preserving operators. Trans. Am. Math. Soc. **307**, 469–480 (1988)
15. Shields, R.: Transition probability and the origin of variation in the cell cycle. Nature **267**, 704–707 (1977)
16. Sine, R.: Weakly constricted operators and Jamison convergence theorem. Proc. Am. Math. Soc. **106**, 751–755 (1989)
17. Smith, J. A., Martin, L.: Do cells cycle? Proc. Natl. Acad. Sci., USA **70**, 1263–1267 (1973)
18. Tuckwell, H. C.: Stochastic Processes in the Neurosciences. Philadelphia: Society for Industrial and Applied Mathematics 1989
19. Tyrcha, J.: Asymptotic stability in a generalized probabilistic deterministic model of the cell cycle. J. Math. Biol. **26**, 465–475 (1988)
20. Tyson, J. J., Hannsgen, K. B.: Global asymptotic stability of the size distribution in probabilistic model of the cell cycle. J. Math. Biol. **22**, 61–68 (1985)
21. Tyson, J. J., Hannsgen, K. B.: Cell growth and division: A deterministic probabilistic model of the cell cycle. J. Math. Biol. **23**, 231–246 (1986)