J. Math. Biology (1984) 19: 43–62

Journal of
Mathematical
Biology

Globally asymptotic properties of proliferating cell populations

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Abstract. This paper presents a general model for the cell division cycle in a population of cells. Three hypotheses are used: (1) There is a substance (mitogen) produced by cells which is necessary for mitosis; (2) The probability of mitosis is a function of mitogen levels; and (3) At mitosis each daughter cell receives exactly one-half of the mitogen present in the mother cell. With these hypotheses we derive expressions for the α and β curves, the distributions of mitogen and cell cycle times, and the correlation coefficients between mother–daughter (ρ_{md}) and sister–sister (ρ_{ss}) cell cycle times.

The distribution of mitogen levels is shown to be given by the solution to an integral equation, and under very mild assumptions we prove that this distribution is globally asymptotically stable. We further show that the limiting logarithmic slopes of $\alpha(t)$ and $\beta(t)$ are equal and constant, and that $\rho_{md} \leqslant 0$ while $\rho_{ss} \geqslant 0$. These results are in accord with the experimental results in many different cell lines. Further, the transition probability model of the cell cycle is shown to be a simple special case of the model presented here.

Key words: Cellular proliferation — cell cycle time — linear operators — distribution of mitogen level

I. Introduction

The elapsed time between cell birth and cellular division is known as the cell cycle, or generation, time T. In a steady state population of cells that appear to be identical at birth, it is a curious but universal phenomenon that the distribution of generation times, $\psi(t)$, is broad and often closely approximated by a log-normal distribution. Further, if a population of cells is synchronized by mitotic blockade and subsequently released, then the distribution of cell cycle times in successive generations rapidly approaches the same distribution $\psi(t)$ observed in the steady state population.

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The correlation coefficient, ρ_{md}, between the cell cycle times of a mother cell and her daughter cells, in a variety of cellular populations, consistently falls between 0 and $-\frac{1}{2}$. This observation has been widely interpreted by many investigators to indicate an influence of one generation of cells on the cell cycle times of their progeny. Conversely, the correlation coefficient between the cell cycle times of daughter cell pairs with the same mother cell, ρ_{ss}, is positive. This is in sharp contrast to the total lack of correlation between the cell cycle times of unrelated cells.

As an outgrowth of the work of Smith and Martin [14], in which the "transition-probability" model for the cell cycle was introduced, it has become popular among experimentalists to characterize populations of cells by the fraction of cells undivided at a time t after their birth. This index is denoted by $\alpha(t)$ and is clearly related to $\psi(t)$ by

$$\alpha(t) = 1 - \int_0^t \psi(x)\, dx.$$

Further clues concerning cell population dynamics may be obtained by examining the fraction of sibling cell pairs whose intermitotic times differ by at least a time t. This statistic, first introduced in [7], is denoted by $\beta(t)$. It has been a common observation [1, 9–14] that the limiting (large t) logarithmic slopes of $\alpha(t)$ and $\beta(t)$ are constant and equal.

This paper shows that the qualitative characteristics of $\alpha(t)$ and $\beta(t)$ are predicted by a very simple and general model for the cell cycle. Further, the model predicts a rapid approach of the distribution of cell cycle times to a stable distribution, the asymptotic properties of $\alpha(t)$ and $\beta(t)$, and that ρ_{md} is negative and ρ_{ss} is positive.

The next section presents the model and derivations of $\alpha(t)$ and $\beta(t)$. The model rests on three hypotheses: (1) There is some substance produced by the cell (which we call mitogen for convenience) necessary for mitosis; (2) The probability of mitosis in a given cell is a function of cellular mitogen levels; and (3) At mistosis each daughter cell receives exactly one-half of its mothers mitogen content.

In the third section we prove that the distribution of mitogen, and thus the distribution of cell cycle times, is globally asymptotically stable. Finally, in Sect. IV we show that the asymptotic properties of $\alpha(t)$ and $\beta(t)$ are consistent with experimental observations, as are ρ_{md} and ρ_{ss}. We also show that the "transition-probability" model for the cell cycle is a special case of the model presented here.

II. Model for the cell cycle

The concept that there exists some substance(s) (mitogen) necessary for mitosis is not a new one, and indeed there exists abundant experimental evidence supporting the concept [see [8] for an excellent review of this literature]. Other workers have argued that, in addition, cell mass may play a critical role in the initiation of mitosis and cytokinesis.

Whatever the identity of the variables necessary to initiate the cell division process is ultimately shown to be, here we assume that the process is governed

by the production and magnitude of a single variable which, for convenience, we refer to as mitogen.

Consider a given cell in a large population that was born at a time $t=0$, and let m be the mitogen level for this cell. Our first hypothesis is that the evolution of mitogen with time following cellular birth is governed by

$$m'(t)=g(m), \qquad m(0)=r. \tag{1}$$

We always denote the solution to equation (1) by $m(r, t)$.

We consider two possible cases for mitogen production.

Case I. The mitogen level is *a priori* bounded.

In this case we assume that g is a C^1 function on the finite closed interval $[0, 2l]$, and that

$$g(x)>0 \quad \text{for } 0<x<2l \tag{2}$$

and

$$g(2l)=0.$$

Generally, the value $g(0)$ is unimportant for our considerations. However, if $g(0)=0$ then we assume $g'(0)>0$.

Case II. The mitogen level is *a priori* unbounded.

Under this circumstance we assume that g is a C^1 function on the half line $[0, \infty)$, and that

$$g(x)>0 \quad \text{for } x>0. \tag{4}$$

As in Case I we require that $g'(0)>0$ when $g(0)=0$. We further assume that for every $r\geqslant 0$ the solution $m(r, t)$ of (1) is defined for all $t\geqslant 0$. This is equivalent to

$$\int_{\varepsilon}^{\infty}\frac{du}{g(u)}=\infty, \qquad 0<\varepsilon<2l,$$

which is automatically satisfied in Case I since g is a C^1 function and satisfies (3).

On occasion, we will treat Cases I and II together, so $l=\infty$ in some equations is not excluded.

Our second hypothesis is that a cell containing an amount m of mitogen at time t has the probability

$$\phi(m)\Delta t+o(\Delta t)$$

of dividing in the time interval $[t, t+\Delta t]$. [At this point we wish to note out that, although throughout this paper we talk of probabilities, the model can equally well be formulated in terms of "fractions of cells". The model thus admits both deterministic and stochastic interpretations. The advantage of using the probabilistic approach is that some elements of the derivations are made easier.]

The function ϕ is assumed to be non-negative and C^1 on $[0, 2l]$, and such that:

$$\phi(0)=0, \qquad \liminf_{x\to 2l}\phi(x)>0, \qquad l<\infty; \tag{5a}$$

$$\phi(0)=0, \qquad \liminf_{x\to\infty}\frac{\phi(x)}{g(x)}>0, \qquad l=\infty. \tag{5b}$$

Conditions (5a) and (5b) simply state that mitogen is necessary for mitosis, and that mitosis is likely when mitogen levels are near their maximum values.

A. *Derivation of* $\alpha(t)$.

These two hypotheses are sufficient to determine $\alpha(t)$. Denote, as before, the generation or cell cycle time of a given cell by T. We consider T to be a random variable (all random variables will be denoted by capital letters). If $\alpha(r, t)$ is the probability that $T \geq t$ given that the initial mitogen level was r, or

$$\alpha(r, t) \doteq \text{Prob}(T \geq t | m(0) = r), \tag{6}$$

then from our two hypotheses we have

$$\alpha(r, t) = \exp\left[-\int_0^t \phi(m(r, s))\, ds \right]. \tag{7}$$

Thus $\alpha(r, t)$ is the expression for α in a population of cells having the same mitogen level r at birth. The derivative

$$-\frac{\partial \alpha(r, t)}{\partial t} = \phi(m(r, t))\alpha(r, t),$$

which we denote by $\alpha_t(r, t)$, is the density function for the distribution of generation times in these cells.

In general the initial amount of mitogen, r, is presumably not fixed in a population, but rather is distributed on the interval $[0, l)$ with a density $f(r)$. Thus, the fraction of cells in a population having initial mitogen levels r between r_1 and r_2 is given by

$$\int_{r_1}^{r_2} f(r)\, dr,$$

and the α curve for the entire cellular population is given by

$$\alpha(t) = \text{Prob}(T \geq t) = \int_0^l \alpha(r, t) f(r)\, dr. \tag{8}$$

Finally we note that the density function for the distribution of generation times in the entire population of cells is given by

$$\psi(t) = -\int_0^l \alpha_t(r, t) f(r)\, dr.$$

B. *Derivation of* $\beta(t)$

To derive an expression for $\beta(t)$, we require our third and final hypothesis: Each newly born sister cell receives exactly one-half of the mitogen present in the mother cell at mitosis.

We consider two sister cells with the same initial mitogen level r, and let T_1 and T_2 denote their respective generation times. Defining

$$\beta(r, t) \doteq \text{Prob}(|T_1 - T_2| \geq t | m(0) = r) \tag{9}$$

we have

$$\beta(r, t) = \iint_{|y-x| \geq t} \alpha_t(r, x)\alpha_t(r, y)\, dx\, dy = 2 \iint_{y-x \geq t} \alpha_t(r, x)\alpha_t(r, y)\, dx\, dy.$$

If we set $z = y - x$ then this last expression becomes

$$\beta(r, t) = 2 \int_0^\infty \left[\int_t^\infty \alpha_t(r, x)\alpha_t(r, x+z)\, dz \right] dx$$

$$= 2 \int_0^\infty \alpha_t(r, x)[\alpha(r, \infty) - \alpha(r, x+t)]\, dx.$$

From Eqs. (2) through (4), for all l we have

$$\lim_{t \to \infty} m(r, t) = 2l \tag{10}$$

and so from (5) and (7)

$$\lim_{x \to \infty} \alpha(r, x) = 0, \qquad r > 0. \tag{11}$$

Thus

$$\beta(r, t) = -2 \int_0^\infty \alpha_t(r, x)\alpha(r, x+t)\, dx. \tag{12}$$

As for $\alpha(t)$, we must account for the initial distribution of mitogen in order to calculate the total population β curve:

$$\beta(t) = \text{Prob}(|T_1 - T_2| \geq t) = \int_0^l \beta(r, t) f(r)\, dr. \tag{13}$$

Thus, using (12) we finally have

$$\beta(t) = -2 \int_0^\infty \int_0^l \alpha_t(r, x)\alpha(r, x+t) f(r)\, dx\, dr. \tag{14}$$

C. The distribution of mitogen

Our final task in the formulation of this model is to derive an equation connecting the initial mitogen distributions in successive generations of cells. Let f_1 be the initial distribution in one generation, and f_2 be the distribution in the progeny of this generation.

To start we assume that in the first generation of cells the initial mitogen level was fixed at r, and we denote by R the initial amount of mitogen in the next generation. By our third hypothesis,

$$R - \tfrac{1}{2} m(r, T) \tag{15}$$

where T is the generation time of cells in the first generation, so

$$\text{Prob}(R \geq x | m(0) = r) = \text{Prob}(m(r, T) \geq 2x). \tag{16}$$

The function $t \to m(r, t)$, at fixed r, increases from $m(r, 0) = r$ to $m(r, \infty) = 2l$. Hence, for each $x \in [\frac{1}{2}r, l)$ there is exactly one time $\tau(r, t)$ such that

$$m(r, \tau(r, x)) = 2x.$$

Further, for each $x \in [\frac{1}{2}r, l)$ the condition $R \geq x$ is equivalent to $T \geq \tau(r, x)$ so Eq. (16) may be rewritten as

$$\text{Prob}(R \geq x | m(0) = r) = \begin{cases} 1, & 0 \leq x < \frac{1}{2}r \\ \alpha(r, \tau(r, x)), & \frac{1}{2}r \leq x < l. \end{cases} \tag{17}$$

If we set $y = m(r, s)$ in Eq. (7), then $dy = dm(r, s) = g(m(r, s)\, ds = g(y)\, ds$ and as a consequence

$$\alpha(r, \tau(r, x)) = \exp\left\{ -\int_r^{2x} \frac{\phi(y)}{g(y)}\, dy \right\}.$$

Let

$$q(x) = \phi(x)/g(x) \tag{18}$$

so Eq. (17) becomes

$$\text{Prob}(R \geq x | m(0) = r) = \exp\left\{ -\int_r^{\max(2x, r)} q(y)\, dy \right\}. \tag{19}$$

In the first generation of cells mitogen is distributed with a density f_1, so

$$\text{Prob}(R \geq x) = \int_0^l \text{Prob}(R \geq x | m(0) = r) f_1(r)\, dr.$$

However, since f_2 is the density for the distribution of R we must also have

$$\text{Prob}(R \geq x) = \int_x^l f_2(r)\, dr,$$

so

$$\int_x^l f_2(r)\, dr = \int_0^l \text{Prob}(R \geq x | m(0) = r) f_1(r)\, dr.$$

Differentiating this last expression with respect to x and using equation (19) we obtain

$$f_2(x) = \int_0^l k(x, r) f_1(r)\, dr$$

where

$$k(x, r) = \begin{cases} 0, & 0 \leq x < \frac{1}{2}r \\ 2q(2x) \exp\left\{ -\int_r^{2x} q(y)\, dy \right\}, & \frac{1}{2}r \leq x < l. \end{cases} \tag{20}$$

By induction, the density for the initial mitogen distribution in the n the generation, f_n, must satisfy

$$f_n(x) = \int_0^l k(x, r) f_{n-1}(r)\, dr. \tag{21}$$

Substitution of (20) into (21) gives the more explicit representation for $f_n(x)$

$$f_n(x) = 2q(2x) \exp\left\{ -\int_0^{2x} q(y)\, dy \right\} \int_0^{\min(2x,l)} f_{n-1}(r) \exp\left[\int_0^r q(y)\, dy \right] dr. \tag{22}$$

Should it happen that $q(y) = 0$ for $y < l$, then (22) takes the simple form

$$f_n(x) = 2q(2x) \exp\left\{ -\int_l^{2x} q(y)\, dy \right\}, \quad \text{for } 0 \leqslant x < l,$$

Thus, in this very special case the sequence $\{f_n\}$ for $n > 2$ is stationary regardless of the initial density f_1.

III. Stability of the mitogen distribution

In the previous section we derived a curious and interesting integral equation (21) connecting the initial mitogen distributions in successive generations of cells. In this section we shall prove, subject to some mild conditions on $k(x, y)$, that the $f_n(x)$ approach a unique limit as $n \to \infty$, i.e. there is a unique solution to

$$f(x) = \int_0^l k(x, r) f(r)\, dr. \tag{23}$$

This will require some other results which we develop below.

However, before presenting this material note that a closer consideration of (23) raises the question of the existence of a solution, much less its convergence. To be specific, pick $g(x) = c > 0$, c a constant, and $\phi(x) = x$. Now $q(x) = x/c$,

$$k(x, r) = \begin{cases} 0 & \text{if } x \leqslant \frac{1}{2}r \\ (4x/c) \exp\left[-\dfrac{2x^2}{c} + \dfrac{r^2}{2c} \right] & \text{if } x > \frac{1}{2}r, \end{cases}$$

and (23) takes the specific form

$$f(x) = (4x/c) \exp(-2x^2/c) \int_0^{2x} \exp(r^2/2c) f(r)\, dr. \tag{24}$$

This integral equation is equivalent to the first order differential equation

$$cxf'(x) + (4x^2 - c) f(x) - 4x^2 f(2x) = 0$$

with an advanced argument. [This may be easily shown by dividing both sides of (24) by $(4x/c) \exp(-2x^2/c)$ and differentiating].

That Eq. (24) even has a solution is interesting because of the curious analytic properties $f(x)$ must have. First, since the right-hand side of (24) is continuous, the solution must be continuous. Secondly, since any solution is continuous it

must be C^1 since, for continuous f, the right-hand side of (24) is C^1. By induction, we therefore conclude that every integrable solution of Eq. (24) must be C^∞ on the half line $[0, \infty)$. On the other hand, any solution f of (24) must satisfy $f(0) = 0$. Differentiating, we also find that $f'(0) = 0$, and by induction it is easy to show that any solution of (24) must satisfy $f^{(n)}(0) = 0$ for all n. Thus we conclude that any solution f of Eq. (24) is C^∞ on $[0, \infty)$ but is not analytic at $x = 0$!

Before stating and proving our main result, we require some other background material from the theory of integral equations with positive kernels. However, since we are interested not only in the existence of solutions but also their stability, and the kernel $k(x, y)$ is generally unbounded (as in the previous example), some recent results from ergodic theory [5] will prove more useful than classical results related to the Krein–Rutman theorem.

Denote by D the set of all real valued functions on $[0, 1)$ which satisfy

$$f(x) \geq 0 \quad \text{and} \quad \int_0^l f(x)\, dx = 1. \tag{25}$$

Such functions $f \in D$ will be called *densities*, and no distinction will be made between two elements of D which differ only on a set of measure zero.

For the purposes of this section let $k(x, y)$ be a measurable function defined for $x, y \in [0, l)$, l finite or not, satisfying

$$k(x, y) \geq 0 \quad \text{and} \quad \int_0^l k(x, y)\, dx = 1 \quad \text{for all } y. \tag{26}$$

Such functions k will be called *stochastic kernels*. Further, let an operator $P: L^1 \to L^1$ be defined by

$$Pf(x) = \int_0^l k(x, y) f(y)\, dy. \tag{27}$$

A function h will be called a *lower bound function* for the operator (27) if, for every $f \in D$, there exists an integer $n_0(f)$ such that

$$P^n f(x) \geq h(x), \qquad n \geq n_0(f). \tag{28}$$

A lower bound function will be called *non-trivial* if

$$h(x) \geq 0 \quad \text{and} \quad \int_0^l h(x)\, dx > 0. \tag{29}$$

With these definitions and notation, we may state the following:

Theorem 1 [5]. *If, for a given stochastic kernel k, there is a nontrivial lower bound function for the operator* (27), *then the equation*

$$f(x) = \int_0^l k(x, y) f(y)\, dy$$

has a unique solution $f_* \in D$. Moreover, for any other density $f \in D$

$$\lim_{n \to \infty} \int_0^l |P^n f(x) - f_*(x)|\, dx = 0.$$

For bounded intervals $[0, l)$, $l<\infty$, it is sometimes easy to demonstrate the existence of a lower bound function. It is sufficient to find any nontrivial h satisfying (29) and

$$k(x, y) \geq h(x) \quad \text{for } x, y \in [0, l). \tag{30}$$

In this case we have

$$P^n f(x) = \int_0^l k(x, y) P^{n-1} f(y)\, dy \geq h(x) \int_0^l P^{n-1} f(y)\, dy = h(x).$$

Therefore, condition (28) is satisfied for $n \geq 1$.

For $l = \infty$ there is little hope of finding a lower bound function satisfying (30) since, for most stochastic kernels, $\inf_{y \in [0,\infty)} k(x, y) = 0$. However, we may prove the following useful result.

Theorem 2. *If $k(x, y)$, $x, y \in [0, \infty)$, is a stochastic kernel such that*

$$\int_0^\infty x k(x, y)\, dx \leq \gamma y + \delta, \qquad y \geq 0, \tag{31}$$

for some constants γ and δ, $\gamma \leq 1$, and if

$$\inf_{y \in [0,a]} k(x, y) > 0 \tag{32}$$

for every finite a, then there exists a non-trivial lower bound function for the operator (27).

Proof. Consider the sequence

$$E_n(f) = \int_0^\infty x P^n f(x)\, dx = \int_0^\infty \int_0^\infty x k(x, y) P^{n-1} f(y)\, dy\, dx$$

$$\leq \int_0^\infty P^{n-1} f(y)(\gamma y + \delta)\, dy \leq \gamma E_{n-1}(f) + \delta,$$

which shows that

$$E_n(f) \leq \frac{\delta}{1-\gamma} + 1$$

for sufficiently large n, say $n \geq n_0(f)$. The function $E_n(f)$ is the mathematical expectation corresponding to the density $P^n(f)$. Since

$$E_n(f) \geq \int_a^\infty x P^n f(x)\, dx \geq a \int_a^\infty P^n f(x)\, dx = a \left\{1 - \int_0^a P^n f(x)\, dx\right\}$$

we have

$$\int_0^a P^n f(x)\, dx \geq 1 - \frac{E_n(f)}{a}.$$

Choosing $a > \delta/(1-\gamma) + 1$ we have

$$\int_0^a P^n f(x)\, dx \geq 1 - \frac{1}{a}\left[\frac{\delta}{1-\gamma} + 1\right] \doteq \varepsilon > 0$$

for $n \geq n_0(f)$, and finally

$$P^n f(x) = \int_0^\infty k(x, y) P^{n-1} f(y)\, dy$$

$$\geq \inf_{y \in [0,a]} k(x, y) \int_0^a P^{n-1} f(y)\, dy$$

$$\geq \varepsilon \inf_{y \in [0,a]} k(x, y)$$

for $n \geq n_0(f) + 1$.

Hence, setting

$$h(x) = \varepsilon \inf_{y \in [0,a]} k(x, y)$$

condition (28) is satisfied which completes the proof.

Our next task is to point out some properties of the function $q(x)$ defined by Eq. (18). From our assumptions concerning g and ϕ it easily follows that q satisfies:

(i) $q(x) \geq 0$ and $q(x)$ is continuous for $x \in [0, 2l)$;
(ii) $\int_0^{2l} q(x)\, dx = \infty$, l finite or not; and
(iii) $\lim_{x \to \infty} \inf q(x) > 0$ when $l = \infty$.

With properties (i), (ii), and Eq. (20) it is easy to show that $k(x, r)$ is a stochastic kernel. Thus from (i),

$$k(x, r) \geq 0 \quad \text{for } 0 \leq x, r < l. \tag{33}$$

Furthermore,

$$\int_0^l k(x, r)\, dx = -\exp\left\{ -\int_r^{2x} q(s)\, ds \right\} \Bigg|_{x=r/2}^{x=l}$$

so by (ii)

$$\int_0^l k(x, r)\, dx = 1. \tag{34}$$

From (33) and (34) it follows that for every initial density $f_1 \in D$, all successive densities obtained from (21) are also in D.

We are now ready to state and prove our main result concerning the density of the mitogen distribution.

Theorem 3. *Assume that the function q is defined on $[0, 2l)$, l finite or infinite, and satisfies conditions* (i) *through* (iii) *above. Then there exists a unique density f_* which satisfies the integral equation*

$$f_*(x) = \int_0^l k(x, y) f_*(y)\, dy \tag{35}$$

with $k(x, r)$ defined by (20). *Further, for every $f_1 \in D$ the sequence* (21) *converges to f_* strongly in L^1, i.e.*

$$\lim_{n \to \infty} \int_0^l |f_n(x) - f_*(x)|\, dx = 0.$$

Thus, this theorem ensures that there is a unique stationary density for the mitogen distribution, and that this density is globally asymptotically stable. Furthermore, there is a unique density function $\psi(t)$ for the distribution of cell cycle times in the entire population of cells.

Proof. We consider the cases l finite and infinite separately.

Case I. l finite. Consider $k(x, r)$ for $x \in [\frac{1}{2}l, l)$. Then $\frac{1}{2}r < x$ for every $r \in [0, l)$ and as a consequence

$$k(x, r) = 2q(2x) \exp\left\{ -\int_r^{2x} q(y)\, dy \right\} \geqslant 2q(2x) \exp\left\{ -\int_0^{2x} q(y)\, dy \right\}$$

for $x \in [\frac{1}{2}l, l)$. Setting

$$h(x) = \begin{cases} 0 & \text{for } 0 \leqslant x < \frac{1}{2}l \\ 2q(2x) \exp\left\{ -\int_0^{2x} q(y)\, dy \right\} & \text{for } \frac{1}{2}l \leqslant x < l \end{cases}$$

we have

$$k(x, r) \geqslant h(x) \quad \text{for all } 0 \leqslant r < l, 0 \leqslant x < l.$$

Also

$$\int_0^l h(x)\, dx = -\exp\left\{ -\int_0^{2x} q(y)\, dy \right\} \Bigg|_{x=l/2}^{x=l}$$

Using (ii) we finally obtain

$$\int_0^l h(x)\, dx = \exp\left\{ -\int_0^l q(y)\, dy \right\} > 0.$$

Thus in this case the theorem follows from Theorem 1.

Case II. l infinite. First we examine the integral

$$\int_0^\infty xk(x, r)\, dx = \int_{r/2}^\infty 2xq(2x) \exp\left[-\int_r^{2x} q(y)\, dy \right] dx.$$

Integrating by parts we have

$$\int_0^\infty xk(x, r)\, dx = -x \exp\left\{ -\int_r^{2x} q(y)\, dy \right\} \Bigg|_{x=r/2}^{x=\infty} + \int_{r/2}^\infty \exp\left[-\int_r^{2x} q(y)\, dy \right] dx. \tag{36}$$

From property (iii) of q it follows that there is an $\varepsilon > 0$ and $d \geqslant 0$ such that

$$q(x) \geqslant \varepsilon \quad \text{for } x \geqslant d,$$

and, as a consequence

$$\lim_{x \to \infty} x \exp\left\{ -\int_r^{2x} q(y)\, dy \right\} = 0. \tag{37}$$

Furthermore,

$$\int_{r/2}^{\infty} \exp\left[-\int_{r}^{2x} q(y)\,dy\right] dx \leq \int_{r/2}^{\infty} \exp\{-\varepsilon[2x-\max(r,d)]\}\,dx$$
$$= \frac{1}{2\varepsilon}\exp\{-\varepsilon[r-\max(r,d)]\} \leq \frac{1}{2\varepsilon}\exp(\varepsilon d). \tag{38}$$

Consequently from (36) through (38) we obtain

$$\int_0^{\infty} xk(x,r)\,dx \leq \frac{r}{2} + \frac{1}{2\varepsilon}\exp(\varepsilon d)$$

so the kernel satisfies Eq. (31) of our Theorem 2 with $\gamma = \frac{1}{2}$. It only remains to show that k satisfies (32).

Let $r_0 \geq 0$ be an arbitrary finite real number. Consider $k(x, r)$ for $0 \leq r \leq r_0$ and $x \geq \frac{1}{2}r_0$. Then

$$k(x,r) = 2q(2x)\exp\left\{-\int_r^{2x} q(y)\,dy\right\}$$
$$\geq 2q(2x)\exp\left\{-\int_0^{2x} q(y)\,dy\right\} \quad \text{for } 0 \leq r \leq r_0,\ x \geq \tfrac{1}{2}r_0,$$

and, as a consequence,

$$\inf_{0\leq r\leq r_0} k(x,r) \geq h(x) = \begin{cases} 0 & \text{for } x < \frac{1}{2}r_0 \\ 2q(2x)\exp\left\{-\int_0^{2x} q(y)\,dy\right\} & \text{for } x \geq \frac{1}{2}r_0 \end{cases}$$

Further,

$$\int_0^{\infty} h(x)\,dx = \int_{r_0/2}^{\infty} 2q(2x)\exp\left[-\int_0^{2x} q(y)\,dy\right] dx$$
$$= \exp\left\{-\int_0^{r_0} q(y)\,dy\right\} > 0,$$

thus completing the proof of the theorem.

IV. Consequences of the model

There are several interesting direct consequences of our theorems of the previous section demonstrating the existence of a globally asymptotically stable density f_*. These results are of importance experimentally for they relate to the asymptotic, large t, behaviour of $\alpha(t)$ and $\beta(t)$, and the correlation coefficients between sister–sister and mother–daughter cell cycle times. Even more importantly they are valid for a large class of functions ϕ and g.

First, under the mild assumption that $\phi(x)=0$ for $0\leq x\leq \varepsilon$ for ε small and that $\lim_{x\to 2l}\phi(x)=\phi(2l)$ exists, then as we have shown in Appendix A

$$\lim_{t\to\infty}\frac{d}{dt}[\log\alpha(t)]=\lim_{t\to\infty}\frac{d}{dt}[\log\beta(t)]=-\phi(2l).$$

Secondly, as shown in Appendices B and C respectively, $\rho_{ss}\geq 0$ and $\rho_{md}\leq 0$. These findings are in accord with the commonly observed features of cell cycle data as mentioned in the Introduction.

It was over 30 years ago when it was first observed that the cell cycle could be viewed as containing four discrete phases: the DNA synthesis period (S), the mitotic period (M), the phase between the completion of M and the initiation of S (known as $G1$), and the period between the completion of S and the beginning of M (called $G2$) [3]. Cells were thought to progress through these stages in a sequential and orderly fashion. This model was later expanded by including a resting ($G0$) phase into which all cells entered after mitosis, and from which cells were recruited randomly into $G1$ [4]. This "$G0$ cell cycle model" has been analyzed several times [2, 6].

Smith and Martin [14] reformulated the $G0$ cell cycle model into what has since become popularly known as the transition probability model for the cell cycle. They postulated that the cell cycle consists of a completely deterministic B phase encompassing a portion of $G1$, S, $G2$, and M, and an indeterminate or stochastic A state following mitosis. The A state contains $G0$ and the remainder of $G1$ from the $G0$ model of the cell cycle. They postulated that while a cell is resident in the A state it is not progressing toward mitosis, and that its probability per unit time of entering the B state (the transition probability) is modifiable by environmental factors.

The transition probability model is a special case of the model presented here. If we set

$$\phi(m)=\begin{cases}0 & 0\leq m<\bar{m}\\ \lambda & \bar{m}\leq m\end{cases} \tag{39}$$

and

$$g(m)=\begin{cases}c>0 & 0\leq m<\bar{m}\\ 0 & \bar{m}\leq m,\end{cases} \tag{40}$$

then it is an immediate consequence of equations (7) and (8) that

$$\alpha(t)=\begin{cases}1 & 0\leq t\leq \bar{t}\\ \exp[-\lambda(t-\bar{t})] & \bar{t}<t\end{cases} \tag{41}$$

where $\bar{t}$ is such that $m(r,\bar{t})=\bar{m}$, so $\bar{t}=\bar{m}/2c$. Furthermore from (14), it is straightforward to show that $\beta(t)=\exp(-\lambda t)$. These expressions for $\alpha(t)$ and $\beta(t)$ are identical with those originally derived [7, 14]. The functions $\phi(m)$ and $g(m)$, given by (39) and (40) respectively, do not satisfy the regularity conditions we have specified. However if we pick sufficiently smooth functions that are "close" to (39) and (40) then they will satisfy our criteria and the discontinuous change in the slope of $\alpha(t)$ which occurs at $t=\bar{t}$ will become smooth.

Acknowledgements. This work was supported by a grant (A-0091) from the Natural Sciences and Engineering Research Council of Canada and by an exchange fellowship (to M.C.M.) from the National Academy of Sciences (USA) and P.A.N. (Poland).

Appendix A. Asymptotic behaviour of $\alpha(t)$ and $\beta(t)$

In data sets, it is commonly observed that the limiting (large t) logarithmic slopes of $\alpha(t)$ and $\beta(t)$ are equal. Here we show that this is expected from the model presented here.

For the α and β curves we have, according to (8) and (14) respectively,

$$\frac{d}{dt}[\log \alpha(t)] = \frac{\alpha'(t)}{\alpha(t)} = \int_0^l \alpha_t(r, t) f_*(r)\, dr \Big/ \int_0^l \alpha(r, t) f_*(r)\, dr$$

and

$$\frac{d}{dt}[\log \beta(t)] = \frac{\beta'(t)}{\beta(t)}$$
$$= \int_0^\infty \int_0^l \alpha_t(r, x)\alpha_t(r, x+t) f_*(r)\, dx\, dr \Big/ \int_0^\infty \int_0^l \alpha_t(r, x)\alpha(r, x+t) f_*(r)\, dx\, dr$$

Using Eq. (7) we may rewrite these formulae in the forms

$$\frac{d}{dt}[\log \alpha(t)] = -\int_0^l \phi(m(r, t)) p_0(r, t)\, dr \tag{A1}$$

and

$$\frac{d}{dt}[\log \beta(t)] = -\int_0^\infty \int_0^l \phi(m(r, x+t)) p_1(r, x, t)\, dx\, dr \tag{A2}$$

respectively, where

$$p_0(r, t) = \alpha(r, t) f_*(r) \Big/ \int_0^l \alpha(y, t) f_*(y)\, dy \tag{A3}$$

and

$$p_1(r, x, t) = \alpha_t(r, x)\alpha(r, x+t) f_*(r) \Big/ \int_0^\infty \int_0^l \alpha_t(y, z)\alpha(y, z+t) f_*(y)\, dz\, dy \tag{A4}$$

Assume that $\phi(x) = 0$ for very small x, say $0 \leq x \leq \varepsilon$, which simply means that mitosis cannot occur until the mitogen level exceeds ε. Then by Eqs. (20) and (35), $f_*(x) = 0$ for $0 \leq x \leq \frac{1}{2}\varepsilon$, and from (A3) and (A4)

$$p_0(r, t) = 0, \qquad p_1(r, x, t) = 0 \tag{A5}$$

for $0 \leq r \leq \frac{1}{2}\varepsilon$. From our assumptions concerning g (namely that $g(x) > 0$ for $0 < x < 2l$) it follows that

$$\lim_{t \to \infty} m(r, t) = 2l$$

uniformly for $\frac{1}{2}\varepsilon \leq r \leq 2l$. Thus, assuming that $\phi(x)$ has the limit $\phi(2l)$ as $x \to 2l$, we have

$$\lim_{t \to \infty} \phi(m(r, t)) = \phi(2l) \tag{A6}$$

uniformly for $\varepsilon \leq r \leq 2l$.

It is easy to verify that the kernels p_0, p_1 are nonnegative and satisfy

$$\int_0^l p_0(r, t)\, dr = 1 \quad \text{and} \quad \int_0^\infty \int_0^l p_1(r, x, t)\, dx\, dr = 1. \tag{A7}$$

From these and Eqs. (A1) and (A2) it follows that

$$\left|\frac{d}{dt}[\log \alpha(t)]+\phi(2l)\right| \leqslant \int_{\varepsilon}^{l} |\phi(2l)-\phi(m(r,t))| p_0(r,t)\, dr$$

and

$$\left|\frac{d}{dt}[\log \beta(t)]+\phi(2l)\right| \leqslant \int_0^{\infty}\int_{\varepsilon}^{l} |\phi(2l)-\phi(m(r,x+t))| p_1(r,x,t)\, dx\, dr.$$

Thus from (A6) and (A7) we have

$$\lim_{t\to\infty}\frac{d}{dt}[\log \alpha(t)] = \lim_{t\to\infty}\frac{d}{dt}[\log \beta(t)] = -\phi(2l),$$

and the limiting logarithmic slopes of $\alpha(t)$ and $\beta(t)$ are indeed equal.

Appendix B. Sister–sister cell cycle time correlations

Let T_1 and T_2 denote the cell cycle times of two sister cells. Note that

$$\text{Prob}(T_1 \geqslant t_1,\ T_2 \geqslant t_2) = \int_0^{l} \text{Prob}(T_1 \geqslant t_1,\ T_2 \geqslant t_2 | m(0)=r) f_*(r)\, dr$$

where

$$\text{Prob}(T_1 \geqslant t_1,\ T_2 \geqslant t_2 | m(0)=r) = \alpha(r,t_1)\alpha(r,t_2).$$

Thus the joint density distribution function $f(t_1, t_2)$ is given by

$$f(t_1,t_2) = \int_0^{l} \alpha_t(r,t_1)\alpha_t(r,t_2) f_*(r)\, dr.$$

Note that $f(t_1, t_2) = f(t_2, t_1)$.

The correlation coefficient between sister cell generation times T_1, T_2 is given by

$$\rho_{ss} = \frac{E(T_1T_2)-E(T_1)E(T_2)}{[E(T_1^2)E(T_2^2)]^{1/2}} \tag{B1}$$

To evaluate the various terms in (B1), we need

$$\begin{aligned} E(T_1^n T_2^m) &= \int_0^{\infty}\int_0^{\infty} t_1^n t_2^m f(t_1,t_2)\, dt_1\, dt_2 \\ &= \int_0^{\infty}\int_0^{\infty}\int_0^{l} t_1^n t_2^m \alpha_t(r,t_1)\alpha_t(r,t_2) f_*(r)\, dt_1\, dt_2\, dr \\ &= \int_0^{l} f_*(r)\left[\int_0^{\infty} t^n \alpha_t(r,t)\, dt\right]\cdot\left[\int_0^{\infty} t^m \alpha_t(r,t)\, dt\right] dr. \end{aligned}$$

Since

$$-\int_0^{\infty} \alpha_t(r,t)\, dt = 1$$

and

$$-\int_0^{\infty} t^n \alpha_t(r,t)\, dt = n\int_0^{\infty} t^{n-1}\alpha(r,t)\, dt$$

we have immediately that

$$E(T_1) = E(T_2) = \int_0^\infty \int_0^l \alpha(r, t) f_*(r)\, dt\, dr = \int_0^\infty \alpha(t)\, dt,$$

$$E(T_1^2) = E(T_2^2) = 2 \int_0^\infty \int_0^\infty t\alpha(r, f) f_*(r)\, dt\, dr = 2 \int_0^\infty t\alpha(t)\, dt,$$

and

$$E(T_1 T_2) = \int_0^l \left\{ \int_0^\infty \alpha(r, t)\, dt \right\}^2 f_*(r)\, dr.$$

The numerator of (B1), given by the above formulae as

$$N = \int_0^l \left[\int_0^\infty \alpha(r, t)\, dt \right]^2 f_*(r)\, dr - \left\{ \int_0^l \left[\int_0^\infty \alpha(r, t)\, dt \right] f_*(r)\, dr \right\}^2$$

will determine the sign of ρ_{ss}. If we set

$$\int_0^\infty \alpha(r, t)\, dt = \eta(r) \quad \text{and} \quad F(r) = \int_0^r f_*(y)\, dy$$

then N may be written more compactly as

$$N = \int_0^l [\eta(r)]^2\, dF(r) - \left\{ \int_0^l \eta(r)\, dF(r) \right\}^2.$$

and positivity of N results from the Cauchy inequality. Thus $\rho_{ss} \geqslant 0$.

Appendix C. Mother–daughter cell cycle time correlations

Let T_1 and T_2 denote the life time of a mother and its daughter cell respectively. To calculate the point density function $f(t_1, t_2)$ for (T_1, T_2) we start from the obvious equality

$$\int_{\Delta_1} \int_{\Delta_2} f(t, s)\, dt\, ds = \text{Prob}(T_1 \in \Delta_1,\ T_2 \in \Delta_2)$$

$$= \int_0^l \text{Prob}(T_1 \in \Delta_1,\ T_2 \in \Delta_2 | m_1(0) = r) f_*(r)\, dr, \tag{C1}$$

where $\Delta_1 = [t_1, t_1 + \varepsilon_1]$, $\Delta_2 = [t_2, t_2 + \varepsilon_2]$ and the condition $m_1(0) = r$ means that the mother cell has an initial amount r of mitogen. We have

$$\text{Prob}(T_1 \in \Delta_1,\ T_2 \in \Delta_2 | m_1(0) = r)$$

$$= \text{Prob}(T_1 \in \Delta_1 | m_1(0) = r)[\text{Prob}(t_2 \in \Delta_2 | m_1(0) = r,\ T_1 = t_1) + o(\varepsilon_1 \varepsilon_2)]. \tag{C2}$$

The conditions $m_1(0) = r$ and $T_1 = t_1$ are equivalent to the assumption that the daughter cell starts with an initial amount of mitogen equal to $\frac{1}{2}m(r, t_1)$. Thus

$$\text{Prob}(T_1 \in \Delta_1 | m_1(0) = r) = -\int_{\Delta_1} \alpha_t(r, t)\, dt$$

and

$$\text{Prob}(T_2 \in \Delta_2 | m_1(0) = r,\ T_1 = t_1) = -\int_{\Delta_2} \alpha_t(\tfrac{1}{2}m(r, t_1), t)\, dt$$

Substituting this into (C2) and using (C1) we immediately obtain an expression for the joint density distribution function $f(t_1, t_2)$:

$$f(t_1, t_2) = \int_0^l \alpha_t(r, t_1)\alpha_t(\tfrac{1}{2}m(r, t_1), t_2) f_*(r)\, dr.$$

Now let us calculate

$$E(T_1^n) = \int_0^\infty \int_0^\infty t_1^n f(t_1, t_2)\, dt_1\, dt_2 = \int_0^\infty \int_0^l \left\{ \int_0^\infty \alpha_t(\tfrac{1}{2}m(r, t_1), t_2)\, dt_2 \right\} t_1^n \alpha_t(r, t_1) f_*(r)\, dt_1\, dr.$$

Since

$$-\int_0^\infty \alpha_t(\tfrac{1}{2}m(r, t_1), t_2)\, dt_2 = 1$$

we have

$$E(T_1^n) = -\int_0^\infty \int_0^l t^n \alpha_t(r, t) f_*(r)\, dt\, dr = n \int_0^\infty \int_0^l t^{n-1} \alpha(r, t) f_*(r)\, dt\, dr$$

$$= n \int_0^\infty t^{n-1} \alpha(t)\, dt \tag{C3}$$

In an analogous fashion,

$$E(T_2^n) = \int_0^\infty \int_0^\infty t_2^n f(t_1, t_2)\, dt_1\, dt_2$$

$$= \int_0^\infty \int_0^\infty \int_0^l t_2^n \alpha_t(r, t_1)\alpha_t(\tfrac{1}{2}m(r, t_1), t_2) f_*(r)\, dt_1\, dt_2\, dr,$$

and substituting $\frac{1}{2}m(r, t_1) = x$ or $t_1 = \tau(r, x)$ we obtain

$$E(T_2^n) = \int_0^\infty \int_0^l \int_0^l t^n \alpha_t(r, \tau(r, x))\alpha_t(x, t) f_*(r)\tau_x(r, x)\, dt\, dr\, dx.$$

To simplify this expression for $E(T_2^n)$ further, note that if we set $t = \tau(r, \frac{1}{2}y)$ in (20), then $y = m(r, t)$ and $dy = dm(r, t) = g(m(r, t))\, dt$ so

$$k(x, r) = -\frac{\partial}{\partial x}\left\{ \exp\left[-\int_0^{\tau(r,x)} \frac{\phi(m(r, t))}{g(m(r, t))} g(m(r, t))\, dt \right] \right\}$$

$$= -\frac{\partial}{\partial x}\left\{ \exp\left[-\int_0^{\tau(r,x)} \phi(m(r, t))\, dt \right] \right\}$$

or using (7),

$$k(x, r) = -\alpha_t(r, \tau(r, x))\tau_x(r, x). \tag{C4}$$

Hence

$$-\int_0^l \alpha_t(r, \tau(r, x))\tau_x(r, x) f_*(r)\, dr = \int_0^l k(x, r) f_*(r)\, dr = f_*(x)$$

and

$$E(T_2^n) = -\int_0^\infty \int_0^l t^n \alpha_t(x, t) f_*(x)\, dt\, dx = n \int_0^\infty \int_0^l t^{n-1} \alpha(x, t) f_*(x)\, dt\, dx$$

$$= n \int_0^\infty t^{n-1} \alpha(t)\, dt. \tag{C5}$$

Finally

$$E(T_1T_2)=\int_0^\infty\int_0^\infty t_1t_2f(t_1,t_2)\,dt_1\,dt_2$$
$$=\int_0^\infty\int_0^\infty\int_0^l t_1t_2\alpha_t(r,t_1)\alpha_t(\tfrac{1}{2}m(r,t_1),t_2)f_*(r)\,dt_1\,dt_2\,dr$$
$$=-\int_0^\infty\int_0^\infty\int_0^l t_1\alpha_t(r,t_1)\alpha(\tfrac{1}{2}m(r,t_1),t_2)f_*(r)\,dt_1\,dt_2\,dr.$$

Using the substitution $\frac{1}{2}m(r_1,t_1)=x$ we obtain

$$E(T_1T_2)=-\int_0^\infty\int_0^l\int_0^l \tau(r,x)\tau_x(r,x)\alpha_t(r,\tau(r,x))\alpha(x,t)f_*(r)\,dt\,dr\,dx. \tag{C6}$$

In comparison with the case for sister cells, the numerator

$$N=E(T_1T_2)-E(T_1)E(T_2) \tag{C7}$$

in the mother–daughter correlation coefficient is much more complicated. To better understand the structure of N we rewrite $E(T_1T_2)$, $E(T_1)$ and $E(T_2)$ in a special way. Multiplying (C6) by the equality

$$\int_0^l f_*(z)\,dz=1$$

we obtain

$$E(T_1T_2)=-\int_0^\infty\int_0^l\int_0^l\int_0^l \tau(r,x)\tau_x(r,x)\alpha_t(r,\tau(r,x))\alpha(x,t)f_*(r)f_*(z)\,dt\,dr\,dx\,dz \tag{C8}$$

Further multiplying

$$E(T_1)=-\int_0^\infty\int_0^l t\alpha_t(r,t)f_*(r)\,dt\,dr=-\int_0^l\int_0^l \tau(r,x)\tau_x(r,x)\alpha_t(r,\tau(r,x))f_*(r)\,dr\,dx$$

by

$$E(T_2)=\int_0^\infty\int_0^l \alpha(z,t)f_*(z)\,dt\,dz$$

[see (C3) and (C5)] we have

$$E(T_1)E(T_2)=-\int_0^\infty\int_0^l\int_0^l\int_0^l \tau(r,x)\tau_x(r,x)\alpha_t(r,\tau(r,x))\alpha(z,t)f_*(r)f_*(z)\,dt\,dr\,dx\,dz. \tag{C9}$$

Setting

$$\omega(x,z)=-f_*(z)\int_0^l \tau(r,x)\tau_x(r,x)\alpha_t(r,\tau(r,x))f_*(r)\,dr \tag{C10}$$

and using (C8) and (C9) we may rewrite the numerator N in (C7)

$$N=\int_0^l\int_0^l \omega(x,z)[a(x)-a(z)]\,dx\,dz=\int_S[\omega(x,z)-\omega(z,x)][a(x)-a(z)]\,dx\,dz, \tag{C11}$$

where

$$a(x)=\int_0^\infty \alpha(x,t)\,dt$$

and $S=\{(x,z)\colon 0\leqslant x\leqslant z\leqslant l\}$. Observe that $a(x)$ is a decreasing function of x since $\alpha(x,t)$ is a decreasing function of x for each fixed t. Thus in order to prove that N is not positive it is enough to verify that

$$\omega(x,z)\leqslant\omega(z,z)\quad\text{for } x\leqslant z. \tag{C12}$$

Using (C4) we may rewrite (C10) in the form

$$\omega(x, z) = f_*(z)u(x)$$

where

$$u(x) = \int_0^l k(x, r)\tau(r, x)f_*(r)\, dr.$$

Thus inequality (C12) is equivalent to

$$\frac{u(x)}{f_*(x)} \leqslant \frac{u(z)}{f_*(z)} \quad \text{for } x \leqslant z.$$

which simply means that the function

$$\frac{u(x)}{f_*(x)} = \frac{1}{f_*(x)} \int_0^l k(x, r)\tau(r, x)f_*(r)\, dr = \frac{\int_0^l k(x, r)\tau(r, x)f_*(r)\, dr}{\int_0^l k(x, r)f_*(r)\, dr} \tag{C13}$$

must be increasing.

Since $\tau(r, x)$ is increasing in x this is easily demonstrated when $\phi(x) = 0$ for $0 \leqslant x \leqslant l$ (which means that the minimal amount of mitogen necessary for mitosis is at least one half of its maximum). In fact in this case $k(x, r)$ is a product of two functions which depend only upon x and r respectively [see (20)] and (C13) may be rewritten as

$$\frac{u(x)}{f_*(x)} = \int_0^l \tau(r, x)\delta(r)f_*(r)\, dr \Big/ \int_0^l \delta(r)f_*(r)\, dr$$

where

$$\delta(r) = \exp\left\{\int_0^r q(y)\, dy\right\}.$$

Since $\tau(r, x)$ is strictly increasing in x the quotient $u(x)/f_*(x)$ is also increasing, which in turn implies that the correlation coefficient ρ_{md} is negative.

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Received June 30/Revised October 17, 1983