MATTERS ARISING

A 'random transition' in the cell cycle?

EVIDENCE is presented by Shields[1], partly mathematical and partly from real and simulated experiments, that the cell cycle contains an exponentially distributed phase. Unfortunately, there are flaws in his probabilistic argument at two points. His conclusions are probably not invalidated, but it seems appropriate to point out the errors in the hope that they will not be repeated elsewhere.

We are concerned with the probability distribution of cell cycle times, and with the distribution of the difference in cycle time of sister cells. It seems that sister cycle times T_1, T_2, say, may be well represented in terms of three independent random variables T_B, U_1, U_2 as

$$\begin{aligned} T_1 &= T_B + U_1 \\ T_2 &= T_B + U_2 \end{aligned} \qquad (1)$$

Here, U_1 and U_2 are identically distributed, whereas T_B is common to the two sisters and must be a non-constant random variable for T_1 and T_2 to be correlated. Shields himself mentions that the T_i values are correlated, quoting a typical value for the correlation coefficient of 0.78; according to representation (1) above, the correlation is in general

$$\rho(T_1, T_2) = \frac{\mathrm{Var}(T_B)}{\mathrm{Var}(T_B) + \mathrm{Var}(U_i)} \qquad (2)$$

In contradiction to this, Shields then assumes that T_1 and T_2 are independent, in order to derive an expression for $\beta(t)$, the survivor function of $|T_1 - T_2|$, in terms of $Q(t)$, that of T_i. In fact, this argument may be rescued: in view of representation (1), $|T_1 - T_2| = |U_1 - U_2|$. On the basis of empirical α curves, we might assume the model

$$\begin{aligned} Q^*(t) &= Pr\{T_i > t + T_B\} \\ &= Pr\{U_i > t\} \\ &= \exp(-kt), \qquad t \geq 0, i = 1, 2 \end{aligned} \qquad (3)$$

from which it is true that

$$\begin{aligned} \beta(t) &= Pr\{|T_1 - T_2| > t\} \\ &= Pr\{|U_1 - U_2| > t\} \\ &= \exp(-kt), \qquad t \geq 0 \end{aligned} \qquad (4)$$

This approach is tantamount to redefining Shields' function $Q(t)$ as a conditional survivor function.

The second flaw concerns Shields' claim at the end of paragraph 5 that representation (4) implies representation (3). This is not the case, and many other forms of $Q^*(t)$ give the same expression for $\beta(t)$: for example, the whole family

$$Q^*(t) = \left(1 + 2d^2 \sin^2\left(\frac{kt}{d}\right)\right) \times \exp(-kt), \qquad t \geq 0 \qquad (5)$$

as d varies from 0 (corresponding to representation (3)) to $1/2^{1/2}$. These solutions are illustrated in Fig. 1; presumably, however, they are rather unlikely to represent correctly the biological reality. Further, Shields' observation that exponential β curves are obtainable irrespective of the age of the younger of a sister pair is, of course, conclusive evidence that representation (3) is the correct solution, as such curves completely determine the joint distribution of (T_1, T_2).

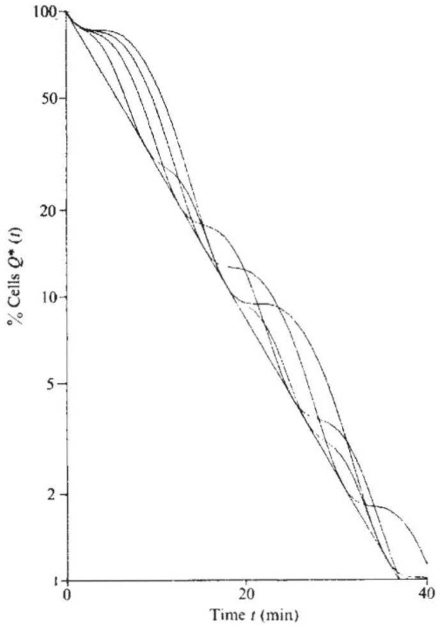

Fig. 1 Semi-logarithmic plot of $Q^*(t) = \left(1 + 2d^2 \sin^2\left(\frac{kt}{d}\right)\right) e^{-kt}$ against t for $k = \frac{1}{8}$ and $d^2 = 0, \frac{1}{8}, \frac{1}{4}, \frac{3}{8}$ and $\frac{1}{2}$.

I thank Russell Smith for finding the counter-example (5) above.

PETER J. GREEN

Department of Mathematics, Science Laboratories, South Road, Durham DH1 3LE, UK

1. Shields, R. *Nature* **273**, 755–758 (1978).

SHIELDS REPLIES—Green is quite right to point out that the cell cycle times of sister cells are frequently correlated and that my equation for the distribution of differences of sister cell cycle times is not valid without qualification. We have argued that correlations in the cycle times of sister cells arise because the cell cycle consists of two parts, one of which (the B phase) is common to the sisters, whereas the other (A state) is independently and identically distributed. According to this model, the correlation of cell cycle times of sister cells arises from the identity of the B phase, the differences from the A state. If these assumptions are correct, what does an exponential distribution of differences in cell cycle time (the β curve) tell us? Green points out that many A state distributions will give exponential curves (an example is given in his paper); this is why I added the condition that exponential β curves were obtained irrespective of the cell cycle times of the younger cell in the cell pair when curves are calculated from cohorted data.

If this condition is met, then, as Green pointed out, the A state must be exponentially distributed. However, if A states are not independently and identically distributed, other cell cycle models can be devised which give exponential β curves (D. Rigney, personal communication). What I had intended to do was to focus attention on the statistic $|T_1 - T_2|$, which has been largely ignored in cell cycle analysis. It should not be forgotten that any proposed cell cycle model should explain the exponential nature of $|T_1 - T_2|$ as well as give a description of the overall distribution of cell cycle times in a cell population. A modified version of the original transition probability hypothesis seems to do this successfully[1].

ROBERT SHIELDS

Unilever Research, Colworth House, Sharnbrook, Bedford MK44 1LQ, UK

1. Brooks, R. F., Bennett, D. C. & Smith, J. A. *Cell* **19** (in the press).

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