Cancer Chemother Pharmacol (1981) 6: 11–18

Cancer Chemotherapy and Pharmacology

The Random Transition Model of the Cell Cycle

A Critical Review

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Summary. *The random transition model of the cell cycle has received much attention in recent years in attempts to describe and explain variations in cell cycle times.*

In this review we suggest statistical procedures for fitting the model to experimental data in place of the invalid techniques currently used. However, we also argue that there have been misconceptions about criteria for quality of fit of the model, and consequent biological interpretations. Other models fit just as well, and the analyses we describe do not provide evidence for any particular biological mechanism.

1. Introduction

The concept of a random transition in the cell cycle was suggested [54] to explain variations in cell cycle lengths. It has been used to make inferences about cell cycle length distributions [54] and sibling cell cycle length correlations [33, 47] and to explain the mechanism by which cells alter the lengths of their cycles under different conditions [46, 49]. Such inferences are based upon a mathematical model, the random transition model (RTM). This paper is a critical review of the use of this model.

By way of introduction it is pertinent to examine briefly the philosophy and purpose of mathematical modelling of biological processes. Four levels of sophistication and complexity can be distinguished, in increasing order of formality:

1) A model may be used for purely *descriptive* purposes. For example, it is a convenient summary of a set of data if one can say that it is approximately normally distributed with a certain mean and variance. No further use of the model will be made beyond this summary description.

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2) At a slightly more complex level, a model may have *explanatory* uses: statements about the shape of a distribution or the value of a parameter may be interpretable in a biological context.

3) More formally, a model may be used in an *inferential* manner. To evaluate an unknown constant on the basis of observed measurements, an estimate of the corresponding parameters of a suitable model is constructed. The choice of the model will in general change the estimate. Hence this choice is an important preliminary to the analysis and its assumption is part of any conclusion.

4) Finally a model may arise naturally from hypotheses concerning underlying biological mechanisms. Properties of the model, estimation of parameters, and statistical testing of hypotheses are now directly interpretable in a biological sense.

The first three categories are basically concerned with statistical analysis and representation of data. As such they contribute to making the transition from numerical results to scientific hypotheses. Category 4) models allow predictions concerning the properties of biological processes to be made and suggest where experiments can help to distinguish between different hypotheses. Hence they can make direct contributions to biological theory.

When discussing the success of a given model, it is important to keep in mind the level of formality which is to be understood. Most authors use the RTM in the sense of category 4), and make corresponding biological interpretations. They fail to realise that successful fitting of the RTM to empirical data in the descriptive sense does not guarantee that the original concept of a random transition is accurate.

Use of the RTM in this most formal sense depends upon the validity of the original biological hypotheses. Although some authors have reported controlling events which may correspond to a random transition [39, 6, 2, 51], it has not yet been firmly

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correlated with an identifiable process. Indeed some authors have suggested that a series of events rather than a single event controls progression through the G1 phase [40]. Experimental evidence concerning the nature of the G1 phase has been discussed at length elsewhere [3, 4, 42].

We shall concentrate here on the testing of the RTM against data and the means by which valid and invalid conclusions (Section 3) have been drawn and biological interpretations (Section 4) made. Finally we give our conclusions concerning the value of the RTM and discuss other possible models.

2. *Description of the Random Transition Concept and the RTM*

The concept of a random transition in the cell cycle was first suggested by Burns and Tannock [10], and subsequently developed by Smith and Martin [54]. Following their terminology, a cell can exist in two states A and B. In the A state a cell is not progressing towards division, being 'in limbo'. When a cell is in the B state the normal proliferative events, such as DNA synthesis and mitosis, occur. Transition from the A to the B state involves the operation of a random switch, which has a constant probability per unit time of being activated, independently of the time a cell has already spent in the A state. The length of the B state is approximately constant, having a relatively small variance.

The possible positioning of the A and B states with respect to the conventional G1, S, G2, and M cycle phases are shown in Fig. 1. In all cases the A state is placed in G1 to account for the relatively large variability reported in the length of this phase [54]. This large variability has recently been challenged [22] in a report that the lengths of S, G2, and M can be as variable as the length of G1. Figure 1 also shows three possible positions for the 'non-random' part of G1 (or $G1_B$). These possibilities were discussed by Smith and Martin [55], who concluded that it was most probably before the A state [case (i)].

From these hypotheses concerning the cell cycle we can derive the RTM in a mathematical form. The length of the cell cycle T_C comprises the sum of two random variables T_A and T_B. T_A has an exponential distribution with parameter K. T_B has a distribution with mean μ and variance σ^2, where σ^2 is 'small compared with' $1/K^2$. The transition probability P, which is quoted by most authors, is then the probability of a transition from A to B in unit time, given that a cell is initially in the A state,

$$P = 1 - e^{-K}.$$

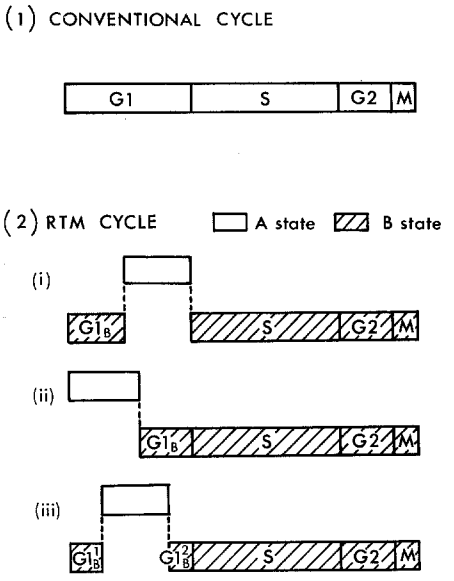

Fig. 1. Possible schemes for the location of the A and B states within the conventional cell cycle [54]

The following observations concerning the RTM should be noted.

1) The distribution of T_B and the size of the variance σ^2 are not fully defined. Testing the model with empirical data requires further assumptions.

2) Observed variations in the length of G1 between cell populations may be due to variations in the length of $G1_B$ as well as in T_A. This illustrates the important distinction between variations in T_C between cells in a homogeneous population under given growth conditions and between cells in different populations or subject to different growth conditions. An explanation of the latter does not require a 'random' event or switch, but merely an event with a mean length sensitive to conditions in the cell.

3) The position of the A state and measurement of T_A can only be made indirectly from the analysis of T_C. This makes identification and analysis of the A state difficult.

4) Other models can predict the same type of distribution for T_C. Obvious examples are the multi-type Markov models [57, 44]. In these the cell cycle is assumed to consist of a sequence of events (or subphases), whose lengths each have an exponential distribution. One only needs to assume that one event has a much lower exponential parameter than the others to imply a T_C distribution similar to that obtained in the RTM. Here the exponential distribution is chosen for mathematical convenience rather than for mechanistic reasons and the biological interpretation of such models is very different from the idea of an 'in limbo' state which controls the population growth and is situated in G1.

Together these four points imply that great care is required when conclusions are drawn from the analyses of empirical distributions of cell cycle lengths.

3. *Testing of the RTM*

The experimental data used to test the model are cell cycle times obtained by time-lapse microcinematography of cells growing in vitro. The theoretical distribution of T_C applies to the idealised situation of a homogeneous population of cells with independent cell cycle times under constant growth conditions. To make mechanistic interpretations of the RTM it is therefore important that the data have been obtained from cells in stable log-phase growth and with a cell line which has a low spontaneous mutation rate (i.e., with a population as homogeneous as possible).

Two different types of observations have been used to test the RTM. These are firstly the empirical cycle times of the whole population and secondly the differences in cycle times of sibling (sister) cells.

3.1. Fitting the RTM to Cycle Time Distribution. The usual starting point in fitting the RTM to data has been the so-called α-curve, a plot of the logarithm of the proportion of cycle times in the sample exceeding t against time t. This accords with the standard practice of graphing results so that the null hypothesis predicts a particularly simple form of curve: if T_B is constant and T_A exponentially distributed with rate K, the theoretical α-curve is horizontal until $t = T_B$ and thereafter decreases linearly with slope $-K$.

Among several drawbacks is one of definition: how *precisely* is the α-curve to be defined for a finite set of observed cycle times, possibly grouped or ungrouped, bearing in mind of course that zero cannot be plotted on a logarithmic scale? Use of α-curves may also be positively misleading, in suggesting that fitting a distribution is analogous to fitting a curve – a regression problem. Misinterpretation of the question in this way can have grave consequences when the plotted points are intrinsically highly correlated and have differing importances in conclusions for or against the model.

Fitting a straight line to the α-curve by eye to estimate parameters is indeed certainly incorrect and without foundation. Further, of course, any attempt to read off values of T_B by extrapolating back along lines of slope $-K$ from the data points is wrong.

Use of such ad hoc methods is quite unnecessary when standard statistical procedures are available. Here we would advocate parameter estimation by application of the established principle of maximum likelihood. Fitting a model to data is vacuous unless the quality of the resulting fit is assessed: for example the χ^2 goodness of fit test may be used. These procedures are quite standard [16] but we cannot find any mention of their use, or of any other reliable technique, in the literature on the RTM.

Any inference about the RTM is impossible until that model is fully specified. We need to know the form of the distribution of T_B, and even then can only proceed on some assumption, such as that T_A and T_B are independent random variables. We will make this assumption as it cannot be refuted on the basis of complete cell cycle time data alone.

The philosophy of the RTM is clearly most strongly supported if T_B is a constant. It is acknowledged [54], however, that empirical α-curves, with their rounded 'shoulders' differ sufficiently from the ideal 'dog-leg' shape for this assumption to be untenable. Perhaps the natural second candidate for T_B is a normally distributed random variable with mean μ and small variance σ^2.

We have fitted the resulting three-parameter (K, μ, σ) RTM to several data sets, including three used by Smith and Martin. The method of maximum likelihood does not provide explicit formulae for estimates except in certain simple situations. Generally, the maximisation must be performed numerically, either by a short special-purpose program or by means of a package.We used the package MLP [45], applied to the data grouped as published in the sources cited in Table 1. Further details of the computations may be obtained from the authors. The estimates obtained by Smith and Martin differ markedly from ours: part of their discrepancy is due to a transcription error concerning the labelling of the intervals into which the data are grouped, part to use of an invalid inferential method. Note also (see Table 1) that our resulting fitted mean ($\mu + 1/K$) and standard deviation $[(\sigma^2 + 1/K^2)^{1/2}]$ are close to the sample mean and standard deviation.

The χ^2 goodness of fit tests carried out on these data sets, with results summarised in Table 1, show that generally the data are consistent with this version of the RTM. (It is important to recall that in all statistical tests of significance, there is asymmetry between 'accepting' and 'rejecting' the null hypothesis: a set of data may be consistent with several contradictory hypotheses, so that 'a good fit' does not imply the model is correct.) Other authors have demonstrated comparable quality of fit to other models [17, 27, 37, 11]. In one respect, however, our estimates do challenge the RTM: they show that there is comparable variability in the two phases of the cell cycle. We should perhaps question whether

Table 1. Parameter estimates and goodness of fit for RTM with normally distributed T_B

Data[b]	Sample			Fitted		Estimates[a]				Goodness of fit		
	Size	Mean	SD	Mean	SD	K	μ	σ	$1/K$	χ^2	d.f.	P
Dawson et al. [13]	166	13.21	2.04	13.22	2.04	0.652	11.69	1.35	1.53	11.16	11	0.43
				11.17*	1.95*	0.60*	9.5*	1.0*	1.67*			
	190[c]	14.23[c]	3.58[c]	14.24[c]	3.31[c]	0.323[c]	11.15[c]	1.19[c]	3.09[c]	23.37[c]	17[c]	0.14[c]
Marin et al. [31]	94	17.61	3.33	17.63	3.21	0.322	14.52	0.83	3.11	7.50	6	0.28
				16.59*	2.71*	0.39*	14.0*	0.8*	2.59*			
Killander et al. [26]	218	19.33	2.78	19.35	2.83	0.469	17.22	1.86	2.13	7.76	3	0.051
				17.80*	3.05*	0.36*	15.0*	1.2*	2.80*			
	239[d]	–	–	20.46[d]	4.35[d]	0.245[d]	16.37[d]	1.49[d]	4.08[d]	16.79[d]	4[d]	0.002[d]
Froese data set 3 [17]	83	17.18	6.49	17.22	6.67	0.224	12.75	4.96	4.47	17.31	11	0.099
Hurwitz et al. [24]												
2nd gen.	320	18.38	2.62	18.37	2.37	0.437	16.08	0.59	2.29	13.33	3	0.004
3rd gen.	132	17.64	1.59	17.63	1.50	1.111	16.73	1.20	0.90	0.02	1	0.89
Drewinko et al. [14]	328	34.51	11.44	34.57	11.41	0.107	25.25	6.57	9.33	15.52	10	0.11
Nelson [38]	122[e]	–	–	10.60[e]	2.60[e]	0.437[e]	8.31[e]	1.23[e]	2.29[e]	15.56[e]	5[e]	0.008[e]

[a] All estimates are by maximum likelihood, except those marked *, from Smith and Martin [54]
[b] Where data values are not tabulated in references, they have been read off as accurately as possible from histograms, etc.
[c] Including film G, believed to be affected by spontaneous mutations
[d] Including 21 non-dividing cells (i.e. those not dividing during the period of observation)
[e] Including 4 non-dividing cells

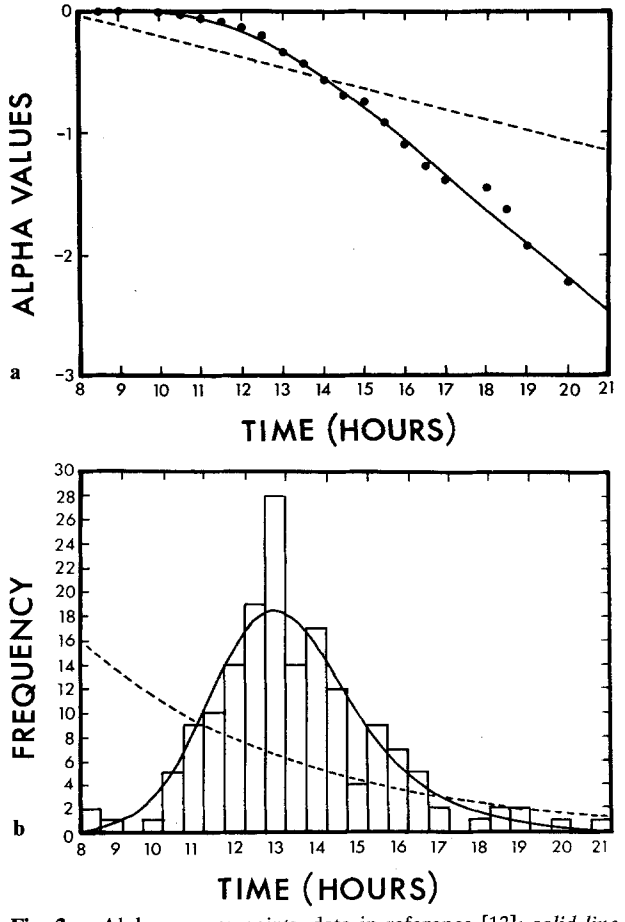

Fig. 2. a Alpha curves: *points*, data in reference [13]; *solid line*, fitted curve for the RTM with normally distributed T_B; *broken line*, fitted curve for the RTM with constant T_B; **b** a more informative display of the same data and fitted models

$\sigma^2 = \text{var}(T_B)$ is too large compared with $K^{-2} = \text{var}(T_A)$ to support the RTM.

It is useful to compare the empirical and fitted theoretical distributions graphically. The usual method, that used by Smith and Martin [54], is to superimpose the fitted α-curve onto a plot of the data (some of the data points are omitted in [54]). Because of the correlations we mentioned earlier, cumulative distributions always 'look' quite smooth: a more objective and standard basis for graphical comparison is a plot of the probability density function of the fitted distribution superimposed on a histogram of the data. These two types of graphs are illustrated for the same data sets in Fig. 2. The second plot displays the discrepancies between model and data and also demonstrates that, contrary to some claims, the distributions are only slightly skewed in some cases. The idealised RTM of a constant T_B and exponential T_A would of course produce a distribution with no left-hand tail at all.

3.2. Sibling Cell Cycle Times. We have so far only considered cell cycle times singly – that is in terms of univariate distributions – and have implicitly assumed cycle times of different cells to be independent. In fact, however, there is strong evidence for positive correlation between cycle times for sibling cells [41, 13, 26, 5, 23]. This requires us to postulate dependence between sibling cell cycle times, either between the T_B's or between the random transition switches, or both. However this is done, it constitutes an assumption additional to the original model.

The popular view of this dependency is the extreme one that the T_B's are so strongly correlated that they are identical, while the random transitions remain independent [33]. We then obtain the following representation for sibling times T_1, T_2:

$$T_1 = T_{A1} + T_B$$
$$T_2 = T_{A2} + T_B$$

where T_{A1}, T_{A2}, T_B are independent random variables and T_{A1} and T_{A2} each have an exponential distribution with rate K. If $\mathrm{var}(T_B) = \sigma^2$, we obtain quite simply

$$\text{Correlation } (T_1, T_2) = \frac{\sigma^2}{\sigma^2 + K^{-2}}$$

which is positive provided that σ^2 is non-zero. We note that this expression is equal to the proportion of the variance in cell cycle times attributable to the B phase of the cycle, so that, perhaps ironically, evidence for strong correlation is evidence denying that the A phase accounts for most of the variability in cell cycle times.

If the RTM augmented in this way is correct, analysis of the A phase is greatly facilitated, for of course

$$T_1 - T_2 = T_{A1} - T_{A2}\,,$$

whose distribution involves only the transition rate K and not the troublesome B phase. As shown by Shields [47], the absolute difference $|T_1 - T_2|$ in sibling cell cycle times is also exponentially distributed with the same parameter K. Thus, given the extra assumptions above, analysis of these differences is indeed an effective way to estimate K. What proponents of this practice do not apparently realise, however, is that the differences in sibling cycle times themselves offer no means of checking that the extra assumptions are reasonable. In particular, it has been shown [20, 43] that large classes of models for cell cycle times other than the RTM give an exponential distribution for $|T_1 - T_2|$.

It is usual to deal with empirical sibling cell cycle time differences with the aid of the so-called β-curve, i.e., the tail of the distribution on a logarithmic scale, exactly analogous to the α-curve [47]. This procedure suffers from the same drawbacks as does the use of α-curves (see Section 3.1). It is argued [47] that β-curves are more sensitive than α-curves at discriminating between models and for estimating K. As remarked above, the first claim is false but the second is probably true, *given* the additional assumptions. It has, however, been demonstrated [56, 11] that approximately exponential β-curves may be obtained from models other than the RTM, indicating once more that a good fit does not imply a model is correct.

Methods of analysis involving the full bivariate distribution of (T_1, T_2) seem to be needed: a likelihood approach may still be used and the data offer the opportunity of examining the extra assumptions made above. Some of the arguments of Shields [47] are correct, as his use of the *conditional* distribution of $|T_1 - T_2|$ given $\min(T_1, T_2)$ is essentially equivalent to use of the joint distribution of (T_1, T_2).

Other forms of dependence between T_1 and T_2 could be postulated – the T_B's may be highly correlated rather than identical, or the random switches may be 'linked'. The exact model that is relevant depends on the origin of measurement of T_1 and T_2 in the cell cycle.

4. *Biological Interpretations of the RTM*

Based on the analyses of α- and β-curves, the random transition concept of the cell cycle has been used to explain the existence of quiescent phases [49] and the effect of ageing on cell cycle times [53]. Even if we supported the methods of analysis used, there are several objections to these interpretations of the RTM.

4.1. Quiescence and Control of Growth Rate. Since the term 'G0 phase' was introduced to describe the status of cells which were apparently blocked in what would otherwise be considered the G1 phase of their cycle [28], there has been much controversy over its real nature. Some authors claim that it is just a very long G1 and others that it is a different type of phase (for review see [3, 19]).

It has been claimed [49] that the G0 phase was really an A state which had a low exponential parameter. Thus all cells in the population were able to cycle and there were no distinct proliferating and non-proliferating subpopulations. The value of K would determine, and it is claimed control, the rate of growth of the population. While it is clear that when cell populations grow slowly the value of K obtained from the α-curve may well be reduced, this is not proof that the value of K is the factor which actually causes the slow growth, rather than an indirect effect.

Another problem with the interpretation of G0 as a long A state is in the behaviour of cells which are stimulated out of quiescence. It has been shown [6–8] that such cells enter the S phase with first-order kinetics, but only after a lag period, and that the

length of this lag is independent of serum concentration but dependent on protein synthesis. It has also been demonstrated [50] that the length of the lag is dependent on cell size at the time of stimulation.

The only interpretation of this lag period consistent with the G0 phase being an A state is that some time is required for change in the value of K, at the end of which the change occurs abruptly. This seems unlikely and also tends to contradict the idea of the A state being a limbo in which nothing occurs. It was to overcome this problem that the two-random-transition concept of the cell cycle was suggested [9]: this will be discussed later.

4.2. Ageing of Cells. Grove and Cristofalo [21] analysed cell cycle times of ageing WI-38 cell cultures with reference to the RTM. They concluded that the α-curve showed a lengthening of T_B and did not possess the conventional asymptotic straight line portion. Smith [53] reanalysed the data in a different way and claimed it was consistent with the RTM. Since then other contradictory papers have been published [32, 48, 52].

There are severe problems in making inferences concerning the mechanism of ageing from such data. Skehan and Friedman [52] discussed problems of pooling data from generations with changing growth behaviour. Basically, the assumption of a homogeneous population under constant growth conditions is no longer valid [15]. It is therefore not meaningful to make interpretations concerning the mechanisms of ageing in individual cells using a model such as the RTM.

5. *Conclusions and Other Possible Models*

The use of the RTM has been based upon incorrect statistical analysis and an incompletely defined model. When we performed a statistical analysis properly with specific well-defined models we found that:

(1) a model in which T_B = constant did not fit the empirical data;

(2) a model in which T_B was normally distributed fitted the data adequately but the variance of T_B was of a similar order to the variance of T_A;

(3) several other distributions also fitted the data.

Hence the RTM with a suitable distribution for T_B can provide an adequate description of the empirical data. The observation that the variance of T_B may be of a similar size to that of T_A is not a direct contradiction of the model, as no precise assumption is made. It is against the spirit of the model, however, and care must be taken in making interpretations which are based upon the assumed invariability of T_B.

The only inferences which can be made from the RTM concern the lengths of the A and B states. Other models (e.g., [1, 57]) allow estimation of the lengths of individual G1, S, G2, and M cycle phases. Hence, until an A state is actually identified other models may provide better tools for inferential purposes.

The use of the RTM in making biological interpretations is also subject to uncertainties. It does not seem to be adequate to explain the behaviour of cells stimulated out of quiescence and cannot be applied with confidence to interpret the changes in cycle parameters during ageing. It is therefore necessary to consider other concepts of the cell cycle and models which might be more appropriate for such purposes.

Most other concepts of the cell cycle have defined a sequence of states or phases which constitute the observed cycle. Depending on the assumptions concerning the distributions of the lengths of such phases and the correlations between individual phases, several different mathematical models have been suggested [57, 1, 25, 30]. Most of them are based on the definition of the four conventional phases G1, S, G2, and M. Quiescence and the behaviour of slowly proliferating cells have been considered by introducing additional phases which the cell may enter (or leave) in a manner depending on the population size or environmental conditions (e.g., [44]).

In recent years an alternative concept of the cell cycle has been proposed. This involves two parallel sequences of events: the DNA-division or chromosome cycle (CC) and the growth cycle (GC) [34–36, 29, 12]. Events in the CC include DNA replication and mitosis. These are under strict genetic control. Events in the GC are related to cytoplasmic growth and protein synthesis. Hence the length of the CC is determined mainly by genetic factors and the length of the GC by growth conditions. Normally the entry to the S phase is identified as the point where the two cycles must synchronise and restart together. Other interactions between the cycles are assumed to be less rigid.

This suggests that a more natural origin for the cell cycle is the beginning of the S phase (Fig. 3) and that the inter-S time is the maximum of the lengths of the CC and the GC. A G1 phase would then only be observed if the GC was longer than the CC [29]. This concept explains the relative variability in the length of G1 under different growth conditions, the similarity in size of cells entering the S period, and the correlation in sibling cycle lengths.

The extension of the RTM as suggested by Brooks et al. [9] can be formulated within this concept (Fig. 3). The CC is the original B state and is assumed constant. The GC is made up of three subphases: the original A state plus a constant lag phase L, plus another state Q, which has an exponential distribution. The length of the lag phase T_L is assumed in general to be greater than that of T_B and hence the GC is longer than the CC.

The intermitotic time in a cell is equal to the length of its CC plus the difference between the lengths of the GC and CC which started in its mother (see Fig. 3). Under suitable conditions on the exponential parameters K_A, K_Q and the lag parameter T_L, α- and β-curves corresponding to the original RTM can be predicted. In this case, however, we also have a possible mechanism for sibling cell correlations and for the existence of a lag after stimulation out of quiescence. All three parameters, K_A, K_Q, and T_L, can affect the length of the cell cycle, suggesting three possible control mechanisms.

This model has not yet been applied as widely as the RTM. However, it does seem to provide more possibilities for biological interpretation and, as a special case of the more general CC/GC concept, a convergence of opinion concerning the nature of the cell cycle. It is to be hoped that the statistical analysis of data by means of this and other new models will be based upon the standard methods which we have discussed here.

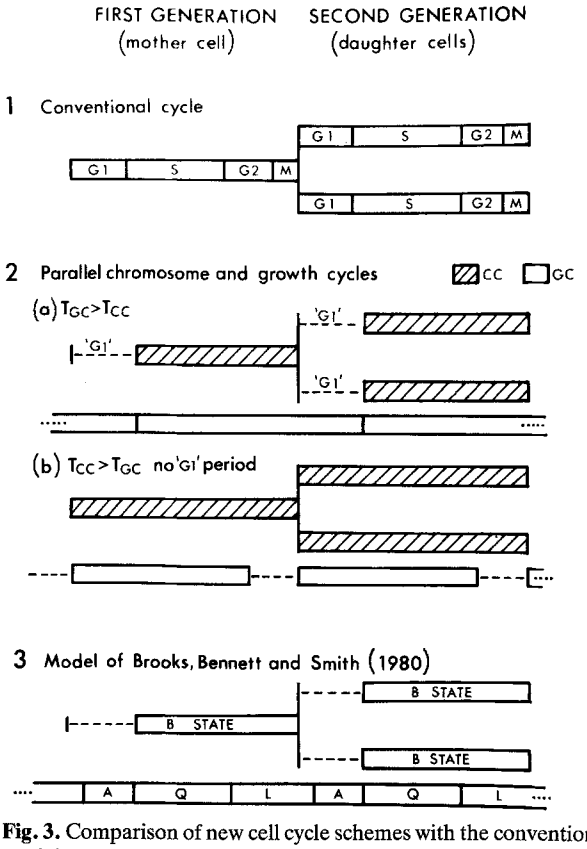

Fig. 3. Comparison of new cell cycle schemes with the conventional model

Acknowledgements. This work was performed while the second author was visiting Heidelberg. He is grateful for the hospitality he received there, and the financial support of Sonderforschungsbereich 123.

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Received March 2/Accepted March 23, 1981