Journal of Theoretical Biology 380 (2015) 585–589

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Letter to Editor

Chromosome replication status and DNA content at any cell age in a bacterial cell cycle

HIGHLIGHTS

- An algorithm to determine DNA content at any bacterial cell cycle age is presented.
- If C, D and τ are known, G per cell and per chromosome at any cell age is obtained.
- If C, D and τ are known, the rate of DNA synthesis per fork at any age is obtained.
- A description of the overlapping of the replication rounds can be obtained.
- This algorithm provides a tool for analysing *in vivo* DNA content at any cell age.

ARTICLE INFO

Keywords:
G per cell
G per age
DNA content
Bacteria
Cell cycle
Replication rate
Rate of fork movement

ABSTRACT

An algorithm is presented to determine the chromosome replication status, the rate of DNA synthesis per fork, and the amount of DNA in chromosome equivalents (G) per chromosome, per cell and per age throughout a bacterial cell cycle. This algorithm is the only attempt to study replication and the G value at any cell age since the general model of the bacterial cell cycle by Cooper and Helmstetter (1968, *J. Mol. Biol.* 31, 619–644). To help using it, two implementations are provided.

1. Introduction

Chromosome replication is not necessarily limited to a single cell division cycle in bacteria. Under slow-growth conditions in poor media, the bacterial cell cycle resembles the eukaryotic cell cycle but, under fast-growth conditions, initiation of replication may occur in the previous cycle, or even two cycles before termination of replication. Consequently, the initiation event can occur in a cell despite the corresponding initiation event might have occurred in its mother or grandmother cell.

In their seminal work, Cooper and Helmstetter (1968) divided the bacterial cell cycle into three discrete periods delimited by the four singular events, cell birth, initiation and termination of chromosome replication and cell division. In a steady state of exponentially growing cultures, the time between consecutive events of initiation, or termination, is equal to the inter-division time τ and to the time required to double cell mass and cell number in the population. The model, which has passed the test of time, enables calculation of the average number of chromosome equivalents per cell, to be

$$G_{cell} = (2^{(C+D)/t} - 2^{D/t})/(\ln 2\ C/t),$$

where C is the time required for chromosome replication, from initiation to termination, and D is the time between the end of replication and consequent cell division. A detailed analysis of the changes of G with cell age has not been published previously. Here, I describe an algorithm to determine the values of G per cell, as well as the replication rate, at any age throughout the cell cycle.

2. Theory

During a cell cycle in steady state growth, one initiation and one termination of chromosome replication, and only one, must take place. The time between two consecutive initiation events, or between two consecutive termination events, is equal to the time from cell birth to cell division, and equal to the time required to double cell mass, and to double cell number, and is called τ. The cell age at which initiation of chromosome replication takes place, in contrast to the eukaryotic cell cycle, does not need to occur in the same cycle as termination. Initiation of replication and cell division occur in the same cell cycle only in slow-growing bacteria (Fig. 1A). Fast-growing cells may initiate replication in the previous division cycle (Fig. 1B and C), or even two cycles before it terminates (Fig. 1D). Consequently, the initiation event in a cycle might correspond to the replication of a chromosome that terminates in daughter or even granddaughter cells.

The presence of the two replication events, initiation and termination, in every cell cycle, defines three periods along the

http://dx.doi.org/10.1016/j.jtbi.2015.06.008
0022-5193/

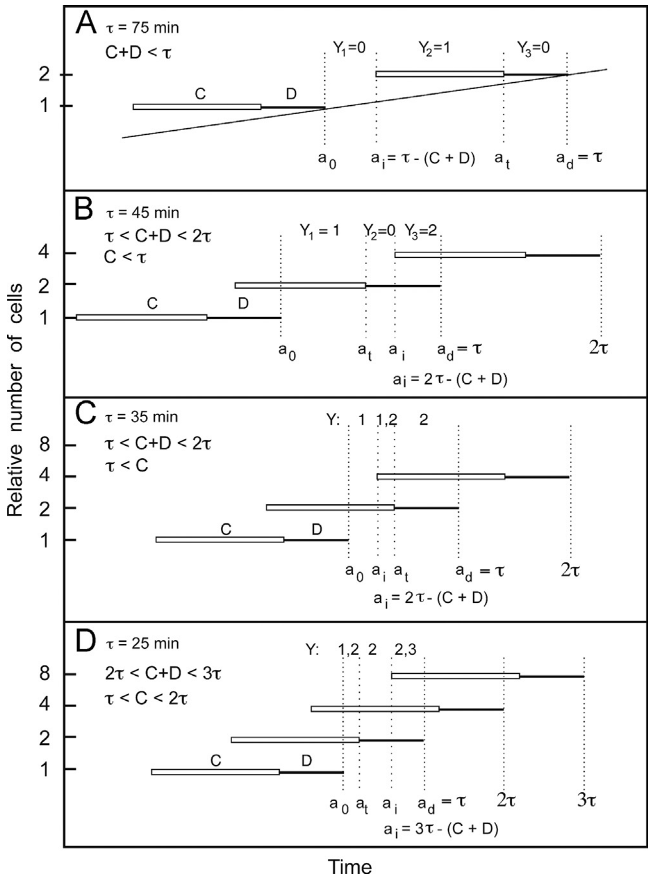

Fig. 1. Layout of the shape of the cell cycle of four bacterial cultures having the same *C*, 40 min, and *D*, 20 min, periods and growing at four different growth rates. *C* is the time for replicating the whole chromosome; *D* is the time from replication termination and cell division; τ is the time required for mass or the number of cells to double; *Y* is the state of chromosome replication with periods: 0 meaning no replication, 1 when the only ongoing replication is the one that will terminate in that cell cycle and will activate division of that cell, 2 when the only ongoing replication is the one that will terminate in the daughter's cell cycle; hence, 1, 2 means that the two replication periods are overlapped, and so on; *a* represents the cell age and is subscripted with *0* at birth, with *i* at initiation of replication, with *t* at the termination of replication, and with *d* at cell division.

cycle. Depending on whether the age of initiation of replication, a_i, occurs before or after termination, a_t, the first period spans from cell birth, $a=0$, to the first replication event (*i.e.*, to either a_i or a_t); the second period is from the first to the second replication event; and the third period is from the second replication event and cell division, $a=\tau$. Consequently, during any of these three periods, 0, 1, 2, or 3 replication rounds, or *C* periods, might overlap.

Thus, I can define *Y* as the argument that shows what chromosome, or *C* periods, is replicating together during a particular period. Consequently, *Y* has a qualitative value. It acquires a value 0 during a period devoid of replication (Fig. 1A and B), a value of 1 when the only active replication cycle is the one that will terminate during that same cell cycle and will determine the next cell division (A, B and C), and $Y=2$ when the only active replication is the one that will terminate during the following cell cycle and will determine the daughter's cell division (Fig. 1B, C and D). *Y* has a value of 1,2 when the two replication rounds are active during a period. In the same way, *Y* equals 1,2,3 when the three replication rounds overlap, one that will terminate in the present cell cycle, one in the daughters' cell cycle, and one in the grand-daughters' cell cycle. Other values for *Y* can be 1,2,3,4, or 2,3, or 2,3,4, or 3, or 3,4 (Table 1).

Table 1
Y and *ter/cell* values in each of the three periods of the cell cycle for twelve bacterial cultures with different cell cycle parameters.

Cell cycle parameters			1st period		2nd period		3rd period	
			Y	*ter*	*Y*	*ter*	*Y*	*ter*
$C+D<\tau$			0	1	1	1	0	2
$\tau<C+D<2\tau$	$C<\tau$	$D<\tau$	1	1	0	2	2	2
	"	$\tau<D$	0	2	2	2	0	4
	$\tau<C$	$D<\tau$	1	1	1,2	1	2	2
$2\tau<C+D<3\tau$	$C<\tau$	$\tau<D$	2	2	0	4	3	4
	$\tau<C<2\tau$	$D<\tau$	1,2	1	2	2	2,3	2
	"	$\tau<D$	2	2	2,3	2	3	4
	$2\tau<C$	$D<\tau$	1,2	1	1,2,3	1	2,3	2
$3\tau<C+D<4\tau$	$\tau<C<2\tau$	$\tau<D$	2,3	2	3	4	3,4	4
	$2\tau<C<3\tau$	$D<\tau$	1,2,3	1	2,3	2	2,3,4	2
	"	$\tau<D$	2,3	2	2,3,4	2	3,4	4
	$3\tau<C<4\tau$	$D<\tau$	1,2,3	1	1,2,3,4	1	2,3,4	2

The age for initiation and for termination of replication, normalized to τ, can be calculated from Fig. 1 to be:

$$a_i = 1 + \text{int}((C+D)/\tau) - (C+D)/\tau \tag{1}$$

$$a_t = 1 + \text{int}(D/\tau) - D/\tau \tag{2}$$

Therefore, a bacterial cell cycle can be defined by the extent and the replication status of its three periods, the first period being the time from a_0 to a_i, if $a_i < a_t$, the second period being from a_i to a_t, and the third period being from a_t to a_d.

Determining the amount of DNA, in genome equivalents, per cell, G_{cell}, at any cell age, a_n, requires finding out the *ter/cell* ratio and *Y* value for each cell cycle period. These values are obtained from the following C language lines:

```
ter/cell=tc=1
if ((C+D)<T) {'a'}
else if ((C+D)>T and (C+D)<2T) {'b'}
     else if ((C+D)>2T and (C+D)<3T) {'c'}
          else if ((C+D)>3T and (C+D)<4T) {'d'}
'a'
if (an<T-(C+D)) {Y[1]=0}
else if (an<T-D) {Y[2]=1}
     else {Y[3]=0; tc=2}
'b'
if (C<T and D<T)
     {
     if (an<T-D) {Y[1]=1}
     else {tc=2}
     if (an<2T-(C+D)) {Y[2]=0}
     else {Y[3]=2}
     }
if (C<T and D>T)
     {
          if (an<2T-(C+D)) {Y[1]=0; tc=2}
          if (an<T-D) {Y[2]=2; tc=2}
          else {tc=4; Y[3]=0}
          }
if (C>T)
     {
     if (an<2T-(C+D)) {Y[1]=1}
     else if (an<T-D) {Y[2]=1,2}
          else {tc=2; Y[3]=2}
     }
'c'
if (C<T and D>T)
     {
```