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MINIREVIEW

The Constrained Hoop: an Explanation of the Overshoot in Cell Length during a Shift-Up of *Escherichia coli*†

STEPHEN COOPER

Department of Microbiology and Immunology, University of Michigan Medical School, Ann Arbor, Michigan 48109-0620

INTRODUCTION

When *Escherichia coli* or *Salmonella typhimurium* growing in minimal medium are shifted to a richer medium, the rate of mass synthesis increases almost immediately to the new growth rate. There is a delay (rate maintenance) before the rate of increase in cell number changes to the new and faster rate (3, 17). This eventually leads to cells growing in a steady state at the higher growth rate with a larger mass per cell (28). Woldringh et al. (34) reported the unexpected result that the cell length overshoots the final cell length during a shift-up. The average cell length increases after a shift-up to a value greater than the final cell length and then slowly decreases to the final cell length.

This review presents an explanation of length overshoot in light of a recent explanation of cell wall synthesis during the division cycle (4, 6). First, our current understanding of murein structure and synthesis in gram-negative bacteria will be described. This forms the basis of the explanation of how the cell wall increases in area during the division cycle. This will be followed by a discussion of the steady-state shapes of bacteria at different growth rates. Once the shapes and sizes of bacteria at different growth rates and how these shapes are produced during steady-state growth are understood, the length overshoot during a shift-up can be explained.

GROWTH OF THE PEPTIDOGLYCAN SACCULUS

The bacterial peptidoglycan is a covalently linked enclosure that holds the cell together against high internal pressures. How does a cell grow, and the peptidoglycan surface enlarge, in the face of such pressures? Figure 1 is a schematic diagram of the murein of a cell. The stretched linkers are at the outside of the cell. New cross-links, which connect the glycan strands that are destined to separate, are in place before the stretched cross-links are broken. The glycan strands go around the circumference of the cell, perpendicular to the long axis of the cell. The peptide cross-links are parallel to the long axis of the cell. Koch (18) proposed that the stretching of the peptidoglycan leads to bends in the bond angles, lowering the energy of activation for the cutting reaction. As the sacculus is stretched by increasing mass, there is a steady decrease in the energy of activation for cutting the cross-links. When a cross-link is cut and new material rises to a load-bearing position, there is an infinitesimal increase in cell volume, relaxing the stretch on all the other stressed cross-links in the peptidoglycan. With continued growth and cuttings, the cell wall creates a volume that accommodates the cytoplasm of the cell.

A simple way to understand the cell wall is to imagine a balloon made of a special material. As more air is blown into the balloon, the volume and area increase and new material enters the surface of the balloon. Unlike a rubber balloon, in which the stress on the wall increases as the internal pressure increases, with this new type of cell wall new material is continuously added so that the stress on the wall remains constant. The stress on the cell surface remains constant, the pressure inside the cell remains constant, and as the volume expands to just enclose the cell mass, the cell density remains constant. This model of cell growth is consistent with (i) the observation of a constant cell density at different growth rates and at different times during the division cycle (21, 22); (ii) the observation of a constant turgor pressure during the division cycle (20); (iii) the observed decrease in side wall synthesis during invagination (35); (iv) the diffuse, nonzonal incorporation of peptidoglycan in the side wall (35); and (v) the direct determination of the ratio of the rate of peptidoglycan synthesis to protein synthesis during the division cycle in *S. typhimurium* (4) and *E. coli* (6). The rate of peptidoglycan synthesis during the division cycle is approximately exponential. A formula describing the rate of synthesis of peptidoglycan during the division cycle has been derived (4).

CELL SHAPE DURING THE DIVISION CYCLE

During steady-state growth, the cell grows in length while maintaining a constant diameter (1, 23, 35). The data on this point is convincing. Nevertheless, variations in the diameter of the cell during the division cycle have been proposed. Trueba and Woldringh (30) observed a negative correlation between the cell radius and cell length; the cell diameter decreased as the length increased. An alternative explanation of this observation (pointed out by David Appleby) is that wider cells divide at lower cell lengths. If cell mass or volume were correlated with the initiation of DNA synthesis, then one would expect wider cells to divide at shorter cell lengths. This occurs because the wider cells (in the distribution of cell widths around some mean width) would initiate DNA synthesis at shorter lengths; they can achieve the requisite inititaion volume or initiation mass at these shorter lengths when the cell is wider. Therefore, one would not expect to find many long and wide cells. This analysis predicts a negative correlation between length and width, while the cell diameter, on average, remains constant during the division cycle. For this reason, as well as the experimen-

† This paper is dedicated to the memory of Ole Maaløe (1915–1988), in whose laboratory the concepts of balanced growth and precise transitions between steady states of growth became of fundamental importance for bacterial physiology.

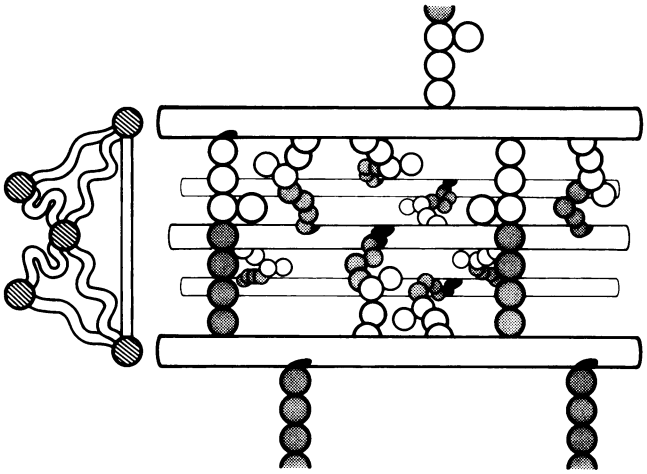

FIG. 1. Schematic illustration of the murein structure of a gram-negative bacterium. Circles are amino acids connecting two glycan chains (rods). The straight connections indicate stressed peptidoglycan at the surface of the cell. Below the stressed peptidoglycan are strands that are pulled into the plane of the peptidoglycan when the existing load-bearing cross-links are severed. At the left is an end view of the peptidoglycan structure, showing the taut connection between the outermost strands and the looser connections between the unstressed inner strands.

tal problems in determining cell widths and lengths, one cannot conclude that the diameter changes during the division cycle. We can assume that the cell grows with a constant diameter during the division cycle. Cell growth during the division cycle is due solely to changes in cell length. A similar argument about correlated variables will explain some unusual results regarding the rate of peptidoglycan synthesis in constricting and nonconstricting cells.

Structural considerations also suggest that cells grow only in length. The glycan chains are arranged primarily in the hoop direction around the gram-negative cell, i.e., perpendicular to the long axis of the cell (31). These chains are relatively short, and any one chain does not completely encircle the cell (13). As new chains are inserted between the resident hoop-like glycan chains (2, 7) the cell grows in length. It is difficult to imagine how the cell circumference could vary during the division cycle with the glycan chains arranged in a hoop-like manner around the circumference of the cell.

CELL SHAPE AT DIFFERENT GROWTH RATES

There have been a number of electron and light microscopic measurements of the lengths and widths of cells growing at different rates. Some of these measurements are collected in Table 1. The lengths and widths at different growth rates are summarized in terms of a shape factor, f, which is the ratio of length to width. If the shape factor is constant, then the cells are the same shape. The data in Table 1 indicate that while there is some variability in shape, the shape is less variable than cell size. Woldringh et al. (33) determined the shape factor for *E. coli* B/rA growing at 17 different rates; the shape factor was constant. The evidence indicates that cell shape is constant but that cell size varies when cells are grown at different rates.

There are some results that do not support the hypothesis that a constant cell shape is maintained at different growth rates (24, 30); nevertheless, the shape varies much less than

TABLE 1. Dimensions of *E. coli* B/r growing at different rates[a]

Method of analysis and growth temp (reference)	Doubling time	2R	L	L/2R (f)
Electron microscopy, 37°C (30)	22.5	0.96	2.64	2.75
	60	0.73	2.00	2.74
	109	0.57	1.51	2.65
	125	0.61	1.66	2.72
	194	0.53	1.68	3.17
Electron microscopy, 37°C (29)	19	1.1	3.81	3.46
	48	0.7	3.06	4.37
	78	0.51	2.84	5.57
	80	0.57	2.94	5.16
	119	0.52	2.66	5.12
Light microscopy, 37°C (29)	19	0.9	4.26	4.73
	48	0.74	3.37	4.55
	119	0.57	2.58	4.53
Light microscopy, 22°C (29)	63	0.86	3.69	4.29
	164	0.83	3.08	3.71
	551	0.66	2.32	3.52

[a] R, Radius; L, length.

the size. The agreement of light microscopic determinations (Table 1) with the electron microscopic results supports the concept of a constant shape at different growth rates. In the original description of different physiological states at different growth rates (28), the diameters of cells varied (e.g., at 2.73, 1.85, 1.0, and 0.61 doublings per h, the diameters of the cells were 1.43, 1.22, 0.93, and 0.87 μm, respectively), while the volume was proportional to the change in cell mass. This means that the cell length increases in proportion to the cell radius; therefore, cell shape is constant.

A physiological argument in support of the constant shape of bacteria growing at different growth rates comes from studies of the segregation patterns of chromosomes and minichromosomes. Helmstetter and Leonard (15) explained the observed nonrandom segregation pattern of DNA in terms of the fraction of the cell surface that is pole area. The observed degree of nonrandom segregation in cells growing at different rates is constant, consistent with a constant cell shape at different growth rates (C. E. Helmstetter, personal communication). Theoretical considerations also led Zaritsky (36) to propose that bacteria retained a constant shape factor at different growth rates.

It is possible to calculate cell surface area at different growth rates from the assumption that cell shape is constant. Theoretically, one can say that the cell mass or volume increases proportional to $2^{(C + D)/\tau}$, with τ equal to the doubling time (9), and with C equal to the time for a round of DNA replication and D equal to the time between termination and cell division. Therefore, surface area increases proportional to $2^{2(C + D)/3\tau}$, and the radius and length increase proportional to $2^{(C + D)/3\tau}$. Measurements of cell length over a range of 0.6 to 3.0 doublings per h fit this prediction (11). This is additional support for the proposal that the cell maintains a constant shape at different growth rates. For each growth rate and for a given volume and constant shape, one can derive the length, radius, and area of a cell. If cell shape remains constant throughout the shift-up and volume expands to accommodate the new mass made after the shift-up, one can calculate the length and area of the cell during this transition. There is an exponential increase in the mass and volume, with corresponding exponential increases in the length, radius, and area of the cell.

After approximately 60 min (3, 17), a new steady state for average cell volume and mass is reached. Thus, if cell shape were constant during a shift-up, for each of these parameters there would be an immediate increase, culminating in the final values 60 min after the shift-up.

CELL SHAPE AFTER A SHIFT-UP

When measurements are made on cell size and cell shape during a shift-up, a constant shape is not observed (34). The final steady-state length is reached after an initial overshoot. From observations of cell size during a shift-up, it is clear that the cell radius does not increase at the same rate as the cell length. A previous explanation by Grover et al. (14) of this overshoot was based on linear surface growth at a rate proportional to the growth rate of the culture, with a doubling in rate at a particular time during the division cycle. I will explain the observed overshoot by proposing that it is more difficult for a rod-shaped cell to change its circumference than to change its length; this is the constrained-hoop model. Before the constrained-hoop model is presented, the pattern of cell wall synthesis during the division cycle of cells growing at a steady state with no change in average cell size will be described. After that an analysis of the changes in cell wall synthesis when there is a change in the average size of the cells in a culture will be presented.

RATE AND TOPOGRAPHY OF CELL SURFACE SYNTHESIS DURING THE DIVISION CYCLE

There have been many proposals describing the growth pattern of gram-negative rods such as *E. coli*. Grover et al. (12, 14, 26, 36) analyzed a model in which circular growth zones are produced at particular times during the cell cycle. These zones grow at rates proportional to the growth rate. Pierucci (24) proposed that new growth zones, with a finite life span, are activated at the initiation of new rounds of chromosome replication. Pritchard (25) proposed that cell wall synthesis was determined by an unregulated gene located near the terminus of the chromosome. A doubling in the rate of surface synthesis was predicted to occur when this gene replicated. The rate of envelope synthesis at each of these zones was assumed to be constant. Another model was proposed by Donachie et al. (10, 11) wherein cells abruptly increased their rate of elongation at a critical length; this length was proposed to be twice the minimal cell length. All these models relied heavily on evidence that the rate of peptidoglycan synthesis was constant in the first part of the division cycle and doubled at mid-cycle (16). These models were also consistent with zonal growth of the cell surface (27). One characteristic shared by these models is that a rule is proposed describing how the cell wall grows. The growth of the surface follows this rule irrespective of other syntheses occurring in the cell. Recently, Woldringh et al. (35) proposed that at the start of invagination there is an abrupt change in cell wall synthetic activities from wall synthesis to pole synthesis. They observed that the rate of incorporation of peptidoglycan precursors into the side wall decreased in cells undergoing constriction. None of these models yield an exponential increase in cell volume. As cell mass increases exponentially (5), one would expect cell cycle variation in cell density.

I have proposed that cell wall is extended in response to the increase in cell mass. The cell can be visualized as a pressure vessel. For each increase in cell mass, the wall growth accommodates the increase by increasing the cell volume (4, 6). The osmotic pressure in the cell, the turgor pressure on the cell wall, and the cell density overall are constant during the division cycle. A formula has been derived for the ratio of the rate of surface synthesis to the rate of mass synthesis (4). Experimental determinations of this ratio using the membrane elution technique supported the proposed model (4, 6). Furthermore, this model explained the finding (35) that the rate of side wall growth decreased in constricting cells. The explanation of this unusual result is that the pole grows, and the mass that is not accommodated by pole growth is accommodated by side wall synthesis. When constriction occurs, there is a relief of the stress on the side wall and a decrease in the rate of side wall synthesis. This analysis is consistent with the diffuse, nonzonal incorporation of material into the side wall (35). The general applicability of this analysis is supported by the report that the rate of side wall synthesis in *Bacillus megaterium* decreases when cells undergo constriction (8). This description is an application of the surface stress model of Koch (18).

Most recently, an alternative proposal by Wientjes and Nanninga (32) suggested that the peptidoglycan of the cell "increased more or less exponentially during the division cycle". They also reported a difference in the rate of peptidoglycan synthesis, as measured by diaminopimelic acid incorporation, in constricting cells compared with in unconstricted cells of the same size. They concluded that there was a sudden change in peptidoglycan synthesis at the start of invagination. While the exponential synthesis is completely in accord with the pressure model of cell wall regulation described above, the observed difference between constricting and nonconstricting cells contradicts the pressure model (4, 6). This contradictory result can be explained by noting that cells in a population have a diameter that varies around some mean. For a given length, a cell with a larger width will have a larger volume than a cell with a smaller width. This larger cell volume means more mass and more surface area. The rate of peptidoglycan synthesis would be expected to be greater in the larger cells (4). If cells that are larger form constrictions at the same observed length as cells that do not form constrictions, one would expect to find constricted cells with a greater rate of peptidoglycan synthesis, even though the length of the cells is the same. We see here the same problem of correlated variables that we noted above when analyzing the reported decrease in cell width during the division cycle. Not only would we expect the wider cells to initiate DNA synthesis earlier, but we would also expect the wider cells to exhibit a larger rate of diaminopimelic acid incorporation. Thus, the autoradiographic data on the rates of peptidoglycan synthesis (32) are consistent with the pressure model of wall synthesis (4).

The cell is a pressure vessel in which growth of the surface occurs as a response to the hydrostatic pressure inside the cell. During steady-state growth, there is no variation in cell diameter. When we consider that the cell diameter increases with increasing growth rate, we can apply this pressure regulation of cell surface synthesis to the growth of the cell during a shift-up.

THE CONSTRAINED-HOOP MODEL

As seen above, the cell grows during steady-state growth by increasing in length with a constant average width or diameter. The mechanism for length extension is easy the visualize because of the insertion of new strands between hoops of glycan chains encircling the cell perpendicular to

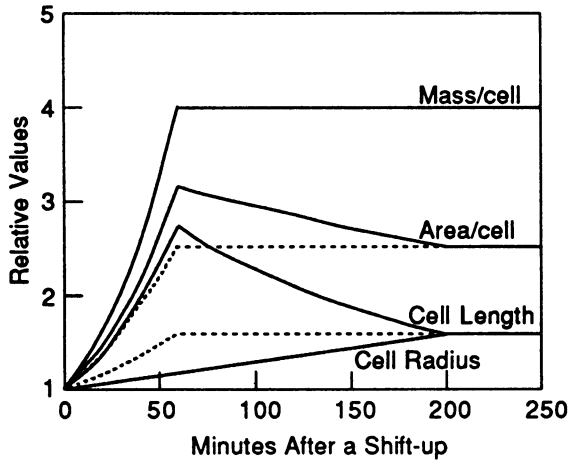

FIG. 2. Relative values for the mass, area, radius, and length of a cell during a shift-up. The initial cell is assumed to have a radius of 0.5 and a side wall length of 2.0; the total cell length is therefore 3.0. All values are normalized to 1.0 at the start of the shift-up. The cell mass increases by a factor of 4 for a shift-up from a 60-min doubling time to a 20-min doubling time. Dashed lines for length and area are for a constant shape during a shift-up. Dashed line for radius, assuming constant shape, is the same as for cell length. The increase in cell mass is the same for both the constant shape and the constrained-hoop model. Solid lines represent the predicted cell area and cell length during a shift-up assuming a constrained hoop. The radius of the cell increases linearly between zero time and 200 min. The calculations were performed as follows. At each time point, the new mass was calculated. The radius and length of the cell were then calculated, assuming either a constant shape or a linearly increasing radius (constrained hoop). Finally, the area of the cell was calculated from the length and the radius. As noted in the text, this is an exaggerated example, and any particular set of data could be fit by varying the time and the pattern of radius increase.

the long axis of the cell (2). Changes in diameter are more difficult to envision. Koch (19) outlined the problems involved in this change. A steady-state, constant-diameter, growing cell can be maintained by having the newly inserted strands inserted in a one-to-one correspondence with the preexisting material encircling the cell perpendicular to the long axis. As more hoops of peptidoglycan made up of relatively short lengths of glycan chain (13) are inserted into the cell wall between the resident hoops, the cell grows in length. When the diameter increases during the increase in the growth rate of a culture, there must be a greater circumferential length of new peptidoglycan in the hoop direction compared with the circumferential length of old peptidoglycan made before the shift-up. It is proposed here that the cell slowly accommodates its diameter to the new cell size. During a shift-up, the rate of mass synthesis changes immediately and requires a concomitant immediate increase in the cell volume to maintain a constant density (22) and turgor pressure (20). The only way for a cell to grow is for it to increase in length. The cell is like a balloon that is constrained in a tube of constant diameter. If air is inserted while the balloon is prevented from expanding in circumference, the balloon must extend its length; so it is with bacteria. The relatively slow increase in the radius of the cell leads to an overshoot in the length of the cell.

The increase in length and area of a cell during a shift-up with a linear increase in the radius over a period longer than 60 min have been calculated. The results shown in Fig. 2 assume that the time required for the radius to increase to its

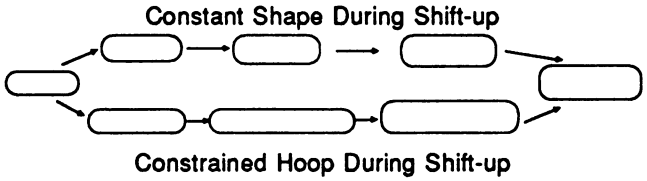

FIG. 3. Comparison of cell growth with either a constant shape or a constrained hoop during shift-up.

final value is 200 min. The linear increase in radius is accompanied by an overshoot in cell length to a value greater than the final steady-state value. For different patterns of radius increase (exponential, linear, hyperbolic, etc.) and for different times at which the final radius is achieved, one can obtain any particular length pattern. The more quickly the radius reaches the final value, the lower the overshoot in length. The pattern predicted is consistent with the observations of Woldringh et al. (34) on the overshoot in cell length during a shift-up. The increase shown in Fig. 2 is an exaggerated example. The experimentally observed overshoot is only 11% (34). By choosing a shorter time over which the radius increases (e.g., 80 rather than 200 min) or by choosing a different pattern of increase (e.g., not linear), we may fit any length overshoot. The constrained-hoop model predicts that the length overshoot is greatest when cells at slow growth rates are shifted up to fast growth rates. A schematic illustration of the constrained-hoop model and a comparison of it with a constant shape model are presented in Fig. 3.

Pritchard suggested earlier (25) that "the resistance of the cell to expansion in girth" is assumed to be "greater than its resistance to expansion in length". This suggestion was accompanied by a proposal that there is a doubling in the rate of cell wall synthesis at some time during the division cycle. Systematic changes in the hydrostatic pressure inside the cell were postulated. No relationship between the cell growth pattern and the increase in cell volume was proposed.

WHY CONSTANT SHAPE?

The question of how the bacterial cell determines its shape may best be answered by understanding why, once a particular shape is chosen, the cell maintains that shape at all growth rates and not by understanding why a particular shape is chosen. Why does the cell, upon increasing its growth rate, change its radius to accommodate a larger volume? It could be that the radius, which the cell has such difficulty in changing, remains constant at all growth rates. Only the cell length would then change to accommodate the increased mass per cell at higher growth rates. There may be an optimal relationship between the length and the width (or, more likely, between the areas of poles and side walls) that is best for a cell at all growth rates.

To summarize, the shape of the cell during steady-state growth and during a shift-up may be explained in terms of the arrangement of peptidoglycan chains around the surface of the cell. The cell surface expands to just enclose the mass of the cell with a constant density and a constant turgor pressure. During steady-state growth, the cell grows with constant diameter. During a shift-up, the slow accommodation of the cell to a new radius leads to an overshoot in cell length. The decrease in cell length after the overshoot is not due to a contraction of the individual cells. Rather, it is due

to a rapid rate of cell division with a slight decrease in the rate of cell elongation. This decrease in the rate of cell elongation occurs because the increasing diameter of the cell allows the cell mass to be accommodated without a concomitant increase in cell length. Furthermore, no proposal is made here as to how the cell chooses a particular length or diameter at a given growth rate. What is conjectured here is that the cell chooses its final cell shape, and that cell shape—the width-to-length ratio—is the same at all growth rates.

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