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Authors' reply

Length growth in fission yeast: is growth exponential? – No

Despite the assertion by Cooper (2) that length growth is exponential, his Fig. 1 shows this to be untrue. It has been known for many years (4) that growth in length in fission yeast ceases for about the last 20 % of the cell cycle and it is usually assumed that this is because the capacity for wall synthesis is concentrated on forming the septum. It is not, however, a period when bulk growth stops since increases continue in dry mass, protein and RNA (4). However, there is a marked change in the rate of wall extension at the beginning of this period.

There is another more subtle change in the rate of extension which Cooper (2) has also ignored in his advocacy of a simple exponential growth pattern. It is clear from his Comment and his earlier book (1) that what he has in mind is an exponential pattern in which the rate doubles over the cycle. In this case, there are no sharp rate change points (RCPs) either during the cell cycle or at division when one cell becomes two daughter cells. However, in wild-type fission yeast, the rate only increases by an average of about 30 % through the growing period of interphase (6). To maintain balanced growth, the rate of the system as a whole must increase by another 70 % at division. Only then will each daughter cell have the same growth pattern as its mother cell. The existence of the rate change at division has been shown in the following way (unpublished measurements). The sum of the initial growth rates of two daughter cells after a division was compared to the growth rate of their mother cell just before its constant length period. There was a rate increase in four cases out of five of the wild-type cells examined. After a block and release experiment with *cdc2*, the population is not in balanced growth and a rate change during the growth period cannot be observed in these oversized cells (6). However, using the method above showed a rate change at division in six out of eight cases examined. So length growth is not exponential and there are two marked rate changes. Nor is it simply a matter of switching growth off and on since the rate change at division involves a marked acceleration of the system.

There remains the problem of the third rate change during the interphase growth

period. It is not easy, considering the scatter in length measurements, to be certain of two linear segments with a rate change which averages only 30 % and can be less (4, 6). The linear regression on a semi-logarithmic plot used by Cooper (2) is not sufficiently sensitive, so we have used the much more sensitive measure of the rates of length growth. The difference between successive length measurements was taken from the unsmoothed data and these differences were then smoothed by the 'rsmooth' command of the Minitab program. One result is given in Fig. 1 with the length measurements and the smoothed rates. The rate pattern is clearly one that would be given by two linear segments with a rate change of about 30 %, though the sharpness of the step rise will be somewhat diminished by the smoothing process. It is quite different from exponential growth where the rate should increase steadily throughout the growth period. So here is a cell which certainly does not grow exponentially. In other cells which we have examined, the pattern is less clear. There is a step at the RCP but there may also be other rate changes before and after this point which vary with the exact points at which the growth period starts and stops. These are not regular in their appearance and pattern, and occur because of the high sensitivity of the analysis on data that are limited by slight changes in focus and by limited resolution of the optics and of the measurements on projected photographic images.

This degree of variation makes it impossible to use a formal statistical test between two simple models of linear versus exponential growth. However, we have seen no cell showing simple exponential growth. Estimation of the RCP by eye is surprisingly effective since the eye carries on a smoothing process over minor changes. It is worth mentioning that the growth curves for *wee1* mutants have a much more conspicuous interphase rate change of 100 % and no rate

Fig. 1. Length extension in the growing period of a single wild-type cell of *Schizosaccharomyces pombe*. Lower curve, cell length; upper curve, smoothed rate of extension (see text).

change at division (6). The existence of this large rate change was demonstrated clearly by our new method of generating difference patterns. It seems most unlikely that the elimination of the *wee1* gene product causes a change from exponential interphase growth to two linear segments.

It is all very well to trot out old Father William (of Occam), but few people will believe that his famous 'Razor' is a suitable tool to shape all cell growth to the same simple exponential. It may be that the various bulk parameters of growth have the same exponential pattern in *Escherichia coli*, but this is not so in some other eukaryotic cells. In fission yeast, the growth patterns for volume, dry mass and total protein are all different from each other (4) and the same is true in budding yeast. None of these patterns in fission yeast is a simple exponential. Moving to different cells, growth curves with falling rates through the cycle (the opposite of an exponential) have been found in reduced weight (= dry mass) in *Amoeba proteus* (5) and in dry mass and volume in *Streptococcus faecalis* (3).

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Further correspondence

The central question asked here is “Do the data that were used to show two linear segments during the first 80 % of the division cycle also support exponential growth?” I can only reiterate, despite the assertion by J. M. Mitchison, A. Sveiczer & B. Novak (above) that my Fig. 1 definitely shows that length growth is exponential and not bilinear. *Res ipsa loquitur*. The data in Fig. 1 of J. M. Mitchison, A. Sveiczer & B. Novak (above) are difficult to analyse as the smoothing function (‘rsmooth’) seems to

have obliterated any observed variations such as those at 70–75 min and 90–95 min in the rate graph. In any case, the raw data of their Fig. 1 appear compatible with an exponential function and would show this if plotted using semi-logarithmic coordinates. The variability of the data (although no error bars are shown) blurs the distinction between bilinear or exponential growth.

Stephen Cooper

The ‘central question’ for Cooper must surely be whether there is a simple exponential growth law without RCPs for the whole cell cycle. This is clearly not so, since there are RCPs at the beginning and end of the constant length period. The third RCP during the growth period is conspicuous in *wee1* mutants (ignored by Cooper, though he has had the data), but less so in wild-type cells because the change in rate is smaller. In his supplementary correspondence, Cooper says that his Fig. 1 “definitely shows that length growth is exponential and not bilinear”. This is highly misleading, since Fig. 1 only shows

the exponential model and not the bilinear model, which would be extremely similar to an exponential on this semi-logarithmic plot. Indeed he finds that the numerical distinctions (r^2 values) between the different models are negligible. He has therefore to rely on the very weak argument that an exponential is preferable because it has fewer parameters and is simpler. This pre-judges the issue between simplistic models and the real life of cells. He ignores the fact that we have used a much more sensitive method which is equivalent to sequential differentiation in our Fig. 1, which shows a cell with a clear bilinear pattern. Smoothing processes have to be used with care since they obviously reduce variations but they are needed with ‘noisy’ data such as raw cell lengths. What Cooper does not mention is that our data used in his Fig. 1 had been smoothed by the same process used in our Fig. 1. Error bars, incidentally, are not appropriate in this work since individual cells grow at different rates and have different RCPs.

J. M. Mitchison, A. Sveiczer and B. Novak