The smallest clock

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Abstract. If one considers bacteria as clocks they may be the smallest clocks allowed by quantum mechanical considerations. Diffusion explains why such a small clock is calibrated in minutes. Similar considerations may also limit human nanotechnology.

Résumé. Si on considère les bactéries comme des horloges minuscules, on les reconnaîtra comme les plus petites horloges permises par la théorie des quanta. La diffusion explique pourquoi ces horloges se calibrent en minutes. Des considérations semblables peuvent aussi limiter la nanotechnologie humaine.

How small can a clock be? Here by a *clock* is meant not only a precisely periodic phenomenon, but also a recording mechanism which registers the elapsed time. Einstein realized the importance of this additional requirement in his definition of time (Einstein 1905a) as 'the position of the small hand of my watch'. Without such a mechanism the periodic phenomenon is only an oscillator not yet connected to 'hands' which can record the passage of time. There are extremely small structures which embody periodic processes, such as the very stable atomic transitions which are used in macroscopic 'atomic clocks' or the flagella of *Spirillum* (which rotate at 40 Hz) but none of these also contain within themselves 'hands' in the form of a self-recording mechanism.

Wigner (1957, 1960) and Salecker and Wigner (1958) have considered the question of the relation between the size of a microscopic clock and its running time. They argue that the fundamental limitation of the size of such a clock is greater than that indicated by the uncertainty principle if one requires that the clock must still show the proper time after being read once and also that the spread in the position of the clock not introduce statistical inaccuracies in the measurement of time. Let T be the 'running time' of the clock (the maximum time interval it can measure), τ its accuracy (the minimum interval significant in its operation), and λ the linear spread in its position. Assuming that the clock has only one spatial dimension, they estimate that the clock's size is limited by

$$\lambda > \left(\frac{\hbar T}{M}\right)^{1/2}. \quad (1)$$

The mass of the clock is then limited by

$$M > (\hbar/c^2\tau)(T/\tau) \quad (2)$$

whereas the uncertainty principle alone would only have required the lower limit $M > (\hbar/c^2\tau)$. In their calculations Salecker and Wigner explicitly include the 'hands' of the clock by postulating that the clock includes what they call a 'pointer' which can indicate one of n possible eigenstates ψ_k of the clock, where $T = n\tau$. They also show schematically how such a clock might be constructed and so the lower limit given seems realistic. From such considerations Wigner (1957) concluded that 'a clock is an essentially nonmicroscopic object'. For instance, Zimmerman (1962) points out that a clock of accuracy 10^{-17} s and running time 10^{-13} s would have to weigh 10^7 daltons.

The question naturally follows: how closely can one approach these fundamental limitations in practice? I would like to suggest that such a minimally small clock is already available in the form of bacteria. Consider the well known species *Escherischia coli*, so often used in molecular biology. *E. coli* has a very well defined asexual reproduction time of 20 minutes at blood heat (37 °C). There is also a well defined time for its sexual conjugation; the passage of the single DNA strand from male (Hfr) to female (F^-) cell takes 89 minutes. During this passage the traits encoded in the DNA can be quite accurately located along the DNA, as in the well known 'blender' experiment of Wollman *et al* (1956), in which the mating is interrupted at given times by putting the bacteria in a blender. For example, the loci *Y*, *z*, *o*, *i* controlling lactose metabolism pass at 10 minutes after the beginning of mating, as can be observed by growing the bacteria in suitable cultures. Thus the bacteria act as clocks not only by virtue of containing a periodic process within them (the periodic replication of the DNA) but because they have 'hands' which record the time governed by that process. As Schrödinger (1956) noted, the genetic molecule cannot be reduced further in size without subjecting it to random fluctuations which would impair its function of transmitting certain traits intact to future generations;

he compared these activities of the organism to clockwork in that a clock also needs to be sufficiently solid to withstand disorderly heat motion. Our argument aims to extend Schrödinger's general considerations concerning limitations of space to limitations of time.

The clocklike genetic action of organisms has a certain universality in the sense that the rate of replication of DNA appears to be quite similar in all cells and even seems to be independent of the rate of growth of the cell mass, which in general varies with the temperature (Kornberg 1980, Chandler *et al* 1975). Throughout our discussion *E. coli* has simply been a convenient and familar example of a procaryotic bacterium; there are many other suitable organisms of similar size, all of which lack a nucleus and are about five hundred times smaller than the smallest eucaryotic (nucleated) cells, of which yeast or the cells of higher organisms are examples. There are also still smaller organisms, such as rickettsias and mycoplasmas, which seem to be true bacteria having their own protein-synthesizing systems (unlike viruses) as well as their own DNA and RNA. Rickettsias and chlamydias (diameter 0.2–0.3 μm) seem to be obligate intracellular parasites whose reproductive cycle is closely linked to the energy provided by a host cell; their 'clock' appears essentially dependent on the clock of the larger host cell. The very smallest bacteria seem to be mycoplasmas (diameter 0.3 μm) whose mass is 8×10^{-14} g, about twenty times smaller than that of *E. coli* (Morowitz and Wallace 1973, Razin 1978). It is also true that the rate of replication is similar in even smaller organisms such as viruses. Viruses do act as clocks in the exact ordering and timing of the steps by which they methodically destroy their bacterial hosts, but since they cannot replicate without these hosts they are not autonomous clocks as bacteria are.

If one substitutes for the running time T the genome reproduction time of a typical mycoplasma (roughly 50–100 min in the cases studied by Furness (1975)) and its mass (8×10^{-14} g) into equation (1) one obtains as the minimum size of such a clock $\lambda \approx 0.07$–$0.09\,\mu$m, which is in fact close to the observed diameter of the very smallest observed mycoplasmas (0.3 μm). For the case of *E. coli* we obtain $\lambda \approx 0.01\,\mu$m, so that *E. coli* are about a hundred times bigger than the Wigner–Salecker limit would allow. Let us take this as an indication that such a mycoplasma is about as small a clock as the limits of Salecker and Wigner would require. If this is correct, then mycoplasmas are not only the smallest known clocks but also are close to achieving the limit of smallness indicated by quantum theory.

This limit is also consistent with estimates of the minimum size of the genome of a bacterium (Watson *et al* 1987) and of the minimum size into which that genome can be packed (Morowitz and Wallace 1973). Such results would make sense on evolutionary grounds since organisms of minimal size might well have a selective advantage over larger and less efficient competitors. However, our arguments are very crude approximations to what is an extremely complex biochemical system; a much more profound analysis would be required to understand fully how such cells act as clocks. In particular, it is not at all clear what the accuracy of such a bacterial clock means in terms of the Wigner–Salecker model, which suggests $\tau = \lambda/c \approx 10^{-16}$ s for mycoplasmas, vastly less than the observed variation in time of bacterial reproduction (not much less than a minute). However, such extremely small times may be those needed for the bacterium to 'scan' the macromolecules involved with sufficient accuracy to ensure that accurate replication and timekeeping is maintained. Perhaps our results will help raise the questions that such a deeper analysis can address properly. Even if our present analysis finally proves too crude it does bring to light the interesting coincidence between the minimum size of a clock deduced from first principles and the observed limit on the size of bacteria. Such considerations might also illuminate the workings of circadian rhythms, especially the extent to which those rhythms are guided by external sources of influence or by purely internal biochemical processes (Brown *et al* 1970). The measurement of biological time on the cellular level is also crucial to the development of organisms (Watson *et al* 1987).

Although the rate of reproduction of *E. coli* can go down if the ambient temperature is lowered, the smallest time interval that can be recorded by observing the transfer of genetic information does not seem to go below about a minute. That is, though this 'clock' can run about ten times slower in the cold it seems to have an upper limit of speed given by the ordinary conditions of growth. For instance, at 20 °C (the lowest temperature observed for regular growth) the generation time is 120 minutes, which is only six times longer than that at blood heat (20 minutes), the optimal temperature for growth. Even at optimal conditions the loci that are observed passing in the 'blender experiment' seem not to come closer than about a minute apart. In this sense one can roughly say that this clock is 'calibrated' in minutes, which seem to be the smallest significant time span that it can register under the best circumstances.

If indeed this is the smallest clock, one wonders why its time scale is given in minutes rather than in much smaller time intervals, for one minute is about the time required to make an MRNA chain which can direct the synthesis of an average *E. coli* protein containing 300 to 400 amino acids; the average half-life of MRNA in the cell is also about 1.5 minutes. H J Morowitz has pointed out to me that the fundamental processes involved, including the replication rate of DNA, all ultimately are limited by the rate at which diffusion can bring precursors to the site where they are assembled. This is the realm of low Reynolds number, $\mathscr{R} = av\rho/\eta \ll 1$, in which inertial effects are negligible compared to diffusion, since for the macromolecules of size 10–1000 Å that are found in the cell the Reynolds number is no bigger than about 10^{-5} (Purcell 1977). It is a classic result of mathematical biophysics (Rashevsky 1948) that such diffusive processes in a cell should have characteristic times of about 10^3 s since the corresponding diffusion constants are in the range of roughly 10^{-7}–10^{-6} cm^2 s^{-1}. Although such values for the diffusion constant are empirically derived it is interesting that one can also estimate them from first principles. The Sutherland–Einstein relation for the diffusion constant of spheres of radius a immersed in a liquid of viscosity η is $D = kT/6\pi\eta a$ (Einstein 1905b). Since the viscosity of water at blood heat is 8×10^{-3} Poise, if one considers the diffusion of organic molecules of radius 30 Å one then estimates diffusion constants roughly of order 10^{-6} cm^2 s^{-1}. The time scale derived from such diffusion considerations is consistent with the time scale of loci on the DNA and both suggest that in general the biological time scale is naturally set in the range of not much less than a minute.

These same considerations might well *apply to the* new realm of nanotechnology where machines are contemplated whose size is about 10^9 atoms (Feynman 1961, Drexler 1987). For such machines rough estimates lead to self-reproduction times of about 10^3 s, comparable in order of magnitude to the diffusion-limited times for bacteria noted above. Although such machines do not seem to be affected by the uncertainty principle since they are composed of so many atoms, by the same considerations adduced for bacteria they may well face the same limit of size given by equation (1) since they would need to be clocks as well as automata if they are to execute a series of tasks in prescribed times. Thus it may be of importance that such machines are essentially self-regulating clocks which may be operating at the lower limit allowed by Wigner's considerations. Indeed, these considerations may set the lower limit of the size of any such microscopic machinery, whether natural or man-made.

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