How to Stop a Biological Clock

An ugly face won't do, but there are ways

Galileo is supposed to have discovered the law of motion of the simple harmonic pendulum by timing swings of a pendulum in the Pisa cathedral against the beat of his heart. No physicist today would consider the human heartbeat an accurate enough timepiece for measuring physical phenomena, but a lot of natural processes are timed by biological clocks.

The animal and vegetable kingdoms are full of repetitive rhythms. Some of them coincide with the cycles of the physical (astronomical) world. There are circadian (daily) rhythms, monthly and yearly rhythms. There are shellfish that open and close their shells according to the cycle of tides. Biological clocks are thus a realm where physics and biology meet—and not only physics and biology, but the behavioral sciences as well. Many human activities are related to biological clocks. To come back to the heartbeat, some anthropologists see it as the source of music and dance: The heart was the world's first tom-tom. This may explain why Galileo was bored with the Gregorian chant (or did they use Ambrosian chant in the Pisa cathedral in those days?): From the oompah point of view the chant is virtually arhythmic.

The motion of a pendulum can be changed and even stopped by appropriate physical intervention. Is there some intervention that can change the phase of a biological clock or even stop it entirely? There is, says A. T. Winfree of Purdue University, and for biological mechanisms that are chemically and physiologically quite diverse the procedure follows the same mathematical law, a law that is based not on the internal physical and chemical workings that produce the rhythms, but on the outward mathematical shape, the topology of their behavior. It is, he says, "a mathematical generalization of biological processes that function periodically."

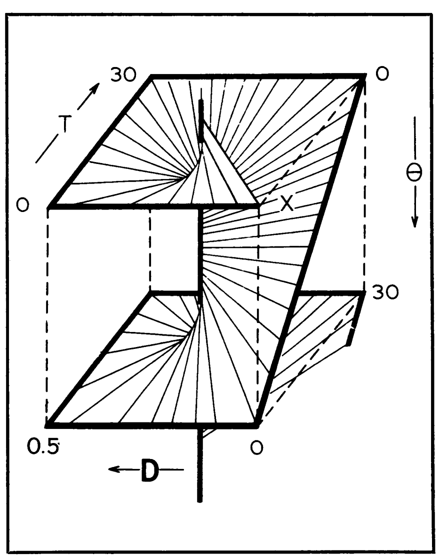
In describing his work at the recent meeting of the American Physical Society in Chicago, Winfree gave two experimental examples in detail: the emergence of fruit flies from the pupa and the production of ATP and alcohol by yeast cells.

Yeast cells use glucose and oxygen to make the energy-rich molecule ATP and alcohol. The amount of the coenzyme NADH that appears in this process reaches a maximum a moment after the oxygen originally in the cell is used up. From the maximum it oscillates with a 30-second period in a wave that gradually dies away to zero amplitude.

Giving the yeast cell a dosage of oxygen at some point in this cycle will reset the biological clock—change the phase of the oscillations. Winfree's ex-

periments studied the "rephasing as a function of when in the cycle you hit it and how hard you hit it."

There are three variables to consider: the amount of oxygen in the dosage, the time since the last NADH maximum at which the dose is administered, and the time until the next NADH maximum after the dose is administered. When a graph is made, the phase changes for different doses and times fall along a spiraling surface, a helicoid. The axis of this helicoid represents a singularity, a critical dose and



Winfree/Arch. Biochem. Biophys.

The helicoid surface generated by changes in the phase of biological clocks. The axis of the screw is the singularity at which the clock is stopped. This particular case is for the yeast-cell experiment. D is the dose; T is the time past NADH maximum; theta is the time until next maximum.

time combination, which does not reset the clock but stops it altogether. In other words the amplitude becomes zero and the phase becomes indeterminate. This singularity is "a necessary topological consequence of having a helicoid," says Winfree. He points out that the experimental result could have been deduced by "numerical analysis of the complex reaction kinetics involved; the fact that it *wasn't* underscores the utility of topological methods in analyzing very complex systems."

In fact the yeast helicoid is similar to the phase resetting pattern of a pendulum when one changes its momentum. The pendulum too has a critical time and dosage: The right impulse at the bottom of the swing can stop it cold. It was in fact this characteristic of the pendulum that led Winfree to seek critical time and dosage properties in biological rhythms, and he says: "A diversity of living organisms responds this way though they have no pendulum."

Another is the fruit fly, *Drosophila.* It starts its life as a worm in garbage. Then it forms a pupa inside which it metamorphoses to an adult. The adults emerge from the pupae in daily pulses, not in a continuous stream. In this case the daily cycle can be destroyed by shining a pulse of light at the appropriate strength on the pupae at the appropriate time in the cycle. Similarly, the 24-hour sleep and waking cycle of adult fruit flies can be suppressed, giving them chronic insomnia, by an appropriate light pulse at the right time. It happens to be about the equivalent of a few minutes of full moonlight at about midnight.

The case of the fruit fly and the light is not peculiar, says Winfree. There are many examples from many laboratories. The phenomena are not predicted by knowledge of their internal behavior as are the motions of the planets in the sky, but rather from considerations of the topology of oscillating systems. It seems that the helicoid surfaces are the key: Systems that have the proper mathematical characteristics for producing them will be susceptible. Winfree calls it "a crude sketch of an argument that has to be made with care. It depends only on abstract and general system qualities."

Nevertheless, it has been shown, he says, that a daily pulse of light can determine when crop plants set seed and whether field insects survive the winter. "Some of the topological peculiarities of these cycles may repay study." Such knowledge may also be useful in medical situations that involve biochemical intervention in rhythmic functions such as cell division and proliferation, the daily cycle of sleep and waking and the menstrual cycles of women. □