at a similar efficiency. Nonetheless, he and Prasher hope to address the difference by reducing the membranes' resistance. The improvement in ion conductivity would increase the power density of their ionocaloric device.

They have yet to test the system's durability, but it appears to show little fatigue. "You can repeat the freeze–thaw cycle as many times as you'd like," Lilley says. The ion-exchange membranes themselves were standard, commercial models, and the researchers have yet to develop others better suited for the electrolytes.

Still, Lilley and Prasher remain optimistic that a practical version of the new refrigerator technology is within reach. They have filed a US patent application.

R. Mark Wilson

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The subtle math of a heartbeat gone wrong

For one type of cardiac arrhythmia, trouble comes in threes.

A healthy heart leads from the top. In the upper right chamber is an oval-shaped strip of tissue, called the sinoatrial node, that serves as the heart's natural pacemaker. The periodic electrical impulses it emits are what keep the organ beating at its steady cadence.

Sometimes, though, the bottom of the heart gets its own ideas. An ectopic (out-of-place) pacemaker can form in one of the lower chambers and send out a separate set of competing signals to try to control the heart's rhythm. The result is a type of cardiac arrhythmia called parasystole. As heart conditions go, parasystole is more annoying than it is dangerous, although if left untreated in the long term it can be linked to complications.

In 1986 Leon Glass (a physicist turned physiologist at McGill University in Montreal) and colleagues showed that the beat patterns of parasystole should be uncannily regular.[1] For any given values of the two pacemaker periods, the number of intervening normal beats between two successive ectopic beats could take only three possible values. What those values are depends on the beat periods and the refractory period. But there are always just three.

Glass and colleagues' paper was theoretical, and it invoked a simplified model of parasystole. The authors neglected the spatial separation of the two pacemaker sites, the time it takes a signal to travel from one to the other, and all the irregularities and complexities of the physical heart.

Now McGill's Gil Bub and colleagues (including Glass) have returned to the problem to fill in the gaps.[2] Through lab experiments and a more detailed mathematical analysis, they've found that the central result of the 1986 paper—the trios of numbers of intervening beats—is applicable in the real world. In addition to highlighting a surprising connection between math, physics, and biology, the

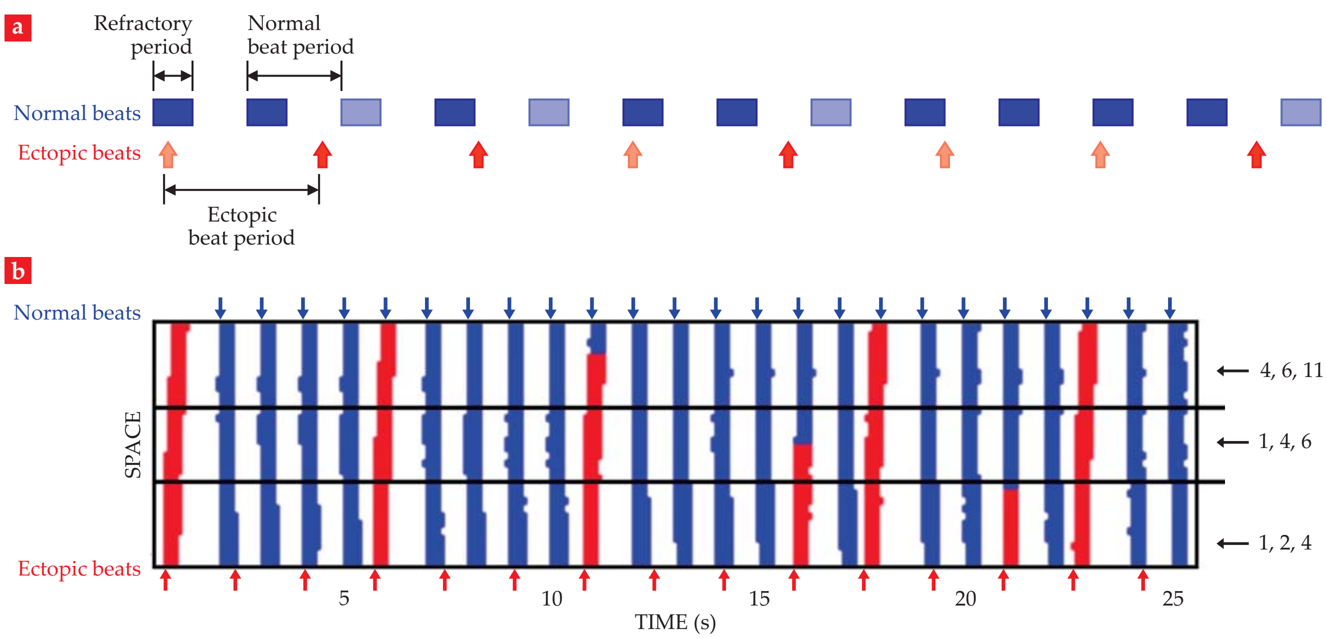

FIGURE 1. COMPETING PACEMAKERS. (a) In a simple model of a cardiac arrhythmia called parasystole, the heart's normal pacemaker and an ectopic, out-of-place pacemaker each generate periodic beat signals. If a signal falls within the previous beat's refractory period, it's blocked (light shaded symbols); otherwise, it goes through (dark solid symbols). No matter the ratio of beat periods, the number of normal beats between two successive ectopic beats can have only three possible values. Here, those values are 1, 2, and 4. (Adapted from ref. 1.) **(b)** Optogenetic *in vitro* experiments explore the role of the pacemakers' spatial separation. The same intervening-beat trios still shine through, but which trio is observed is now a function of position. (Adapted from ref. 2.)

work is a step toward diagnosing parasystole in patients and guiding them to the most important treatment.

Feel the beat

Parasystole is one of a class of heart-rhythm disorders that are characterized by premature ventricular contractions (PVCs): The ventricles, or lower heart chambers, contract before the signal from the upper chamber tells them to. If PVCs are happening to you, it can feel like your heart is skipping beats.

Why would the heart be skipping beats, if the problem is that it's getting too many signals to beat? Heart tissue is a nonlinear medium: Unlike linear waves such as sound and light, which can pass right through each other, electromechanical waves in the heart don't act independently of one another. Rather, after each excitation, the tissue has a refractory period of a few hundred milliseconds, during which it can't be excited again. If a PVC prompts the heart to beat before an expected normal beat, the normal beat is blocked—and its absence can sometimes be felt.

PVCs can arise in several ways. They can be caused by an ectopic pacemaker, as in parasystole. Or they can result from cardiac reentry—in which a wave that started out as a normal beat propagates around in a circle and excites the heart again—or other causes.

The treatment for PVCs depends on what's causing them. Most don't need intervention at all, and those that do can often be remedied with medication or lifestyle changes. But sometimes it's necessary to use RF radiation to remove the ectopic pacemaker. A question of clinical interest, therefore, is whether the cause of PVCs can be diagnosed on the basis of the sequence of normal and ectopic beats alone: What patterns of heartbeats could signal that an arrhythmia is parasystole, rather than something else?

Three of hearts

In their 1986 attempt to answer that question, Glass and colleagues developed a model that's schematically shown in figure 1a. The normal and ectopic pacemakers each produce signals with a regular period. If an ectopic beat signal falls inside the normal pacemaker's refractory period (dark-blue rectangles), it's blocked (light-red arrows); otherwise, it goes through (dark-red arrows). Because of the asymmetry of how the heart conducts signals, an ectopic beat that goes through always blocks the next normal beat (light-blue rectangles), regardless of the refractory time. The question becomes, What possible sequences of dark rectangles and dark arrows can the model generate?

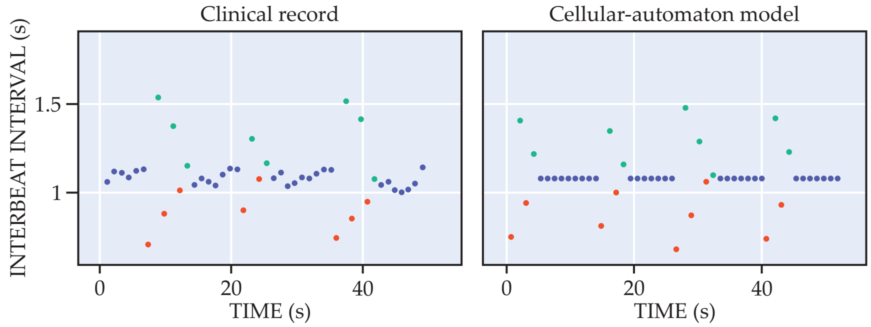

FIGURE 2. PARASYSTOLE IN PRACTICE. On the left is a plot of electrocardiogram data from a 71-year-old patient; the corresponding model simulation is shown on the right. Plotted on the vertical axis is the interbeat interval: the time from one heartbeat to the next. Shorter-than-usual intervals, shown in red, arise from normal beats followed by ectopic beats; longer-than-usual intervals, shown in green, are from ectopic beats followed by normal beats. Blue data points are the intervals between two normal beats. Between any pair of successive red points, the number of blue and green points is always 1, 8, or 10—one of the allowed trios the model predicts. (Adapted from ref. 2.)

Put that way, the problem is hardly limited to cardiac medicine. The same or similar dynamics can show up in many diverse contexts. (It's reminiscent, for example, of the question of how many steps you can take on a sidewalk before you step on a crack.) In fact, while Glass and colleagues were putting together their paper, they discovered that the problem had already been discussed in the mathematics literature.[3]

The main result—that there are only three possible values of the number of intervening normal beats between two successive ectopic beats—comes from looking closely at where each ectopic beat falls in the window between one refractory period and the next. If t is the position of one ectopic beat within the window and $f(t)$ is the position of the next, then f is a piecewise linear function that maps the window onto itself. As Glass and colleagues explained, there can be only two possible points of discontinuity: $f^{-1}(t_i)$, where t_i is the beginning of the window, and $f^{-1}(t_f)$, where t_f is the end of it. The function f therefore divides the window into three continuous segments, each with its own value for the number of intervening beats.

The space between

Glass and colleagues' model treated the normal and ectopic pacemakers as if they were right on top of each other. It gave no consideration to the time waves would take to travel from one pacemaker to the other, let alone the inhomogeneity of the tissue they would pass through along the way. "The behavior of the model with space has been an open problem since then," explains Bub. "But when Thomas Bury, who has a math background, joined my group as a postdoc, Leon saw the opportunity to revisit the question."

Bury and Glass turned back to the old proofs and extended them to the case of spatially separated pacemakers. They found a similar result: There are always three possible values for the number of intervening beats, except that now, which three values are allowed also depends on where in space the beats are measured.

Bury's augmented model took into account some of the effects of tissue heterogeneity. For example, the model still works if the wave speed is not uniform in space, or even if waves propagate at different speeds in each direction. But it's fundamentally one-dimensional and deterministic: It considers only one path that waves can take between the pacemakers, and the propagation is always perfectly predictable. Real hearts are more complicated than that, and cardiac waves can propagate in all kinds of messy ways. Would the tidy theoretical predictions survive the noise of a living system?

To find out, Khady Diagne—a PhD student in Bub's group—performed experiments on patches of heart tissue derived from mice. She used optogenetic technology to genetically engineer the tissue to be responsive to light, then created two artificial pacemakers by shining two spatially separated light pulses on the tissue patch. Figure 1b shows the results of one of her experiments; it agrees well with the theory, down to the different intervening-beat trios observed at different points in space.

Even in real hearts, the model has had some success. The left panel of figure 2 shows clinical data from a 71-year-old man with probable parasystole. The corresponding model simulation is shown at right.

Rhythm gone wrong, gone wrong

Looking for intervening-beat trios could be an appealing way for clinicians to distinguish parasystole from other conditions that cause PVCs so they can more confidently make decisions about treatment. But many complicating factors remain to be accounted for.

In Bury's model and Diagne's experiments, both pacemakers are perfectly steady over time. But real heart rates fluctuate in response to stress, activity, and other factors, and the normal and ectopic pacemakers don't have to move in tandem, so a patient might not exhibit any one intervening-beat trio for very long. To tease out the intervening-beat trios and diagnose parasystole, doctors may have to record a patient's heart rhythm for hours or days. Luckily, with today's wearable medical devices, such long records are easy to come by.

Moreover, and more importantly, the McGill group's research so far is limited to so-called pure parasystole, in which each pacemaker is unaffected by the other and the heart is healthy in every other respect. Clinically, pure parasystole is the exception, not the rule: Only one out of the 47 patients with frequent PVCs whose records the McGill group looked at seemed to have it. More commonly, patients might have modulated parasystole, in which signals from the normal pacemaker periodically reset the ectopic pacemaker's phase. Or their PVCs might arise from a combination of causes, such as an ectopic pacemaker and cardiac reentry working together in the same heart.

It's too early to tell just how valuable the intervening-beat math will be in understanding those more complicated arrhythmias, but it looks like Diagne's optogenetic experiments could be a useful platform for studying them. While some of the genetically engineered tissue patches showed the clean interactions of two light-induced pacemakers, as shown in figure 1a, others exhibited messier dynamics, including spontaneously formed natural pacemakers and forms of cardiac reentry. The researchers focused on the clean systems at first, but now they're keen to explore the messy ones. "I think the key is to have experiments that rival the clinical data in complexity and duration," says Bub. "That should allow us to tease out the mechanisms and provide a bridge between theoretical models and the clinical data."

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