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Authors
Xiong, Lingyun
Garfinkel, Alan

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TOPICAL REVIEW

Are physiological oscillations *physiological*?

Lingyun (Ivy) Xiong[1,2] and Alan Garfinkel[3]

[1]*Department of Stem Cell Biology and Regenerative Medicine, Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA*
[2]*Department of Quantitative and Computational Biology, University of Southern California, Los Angeles, CA, USA*
[3]*Departments of Medicine (Cardiology) and Integrative Biology and Physiology, University of California, Los Angeles, CA, USA*

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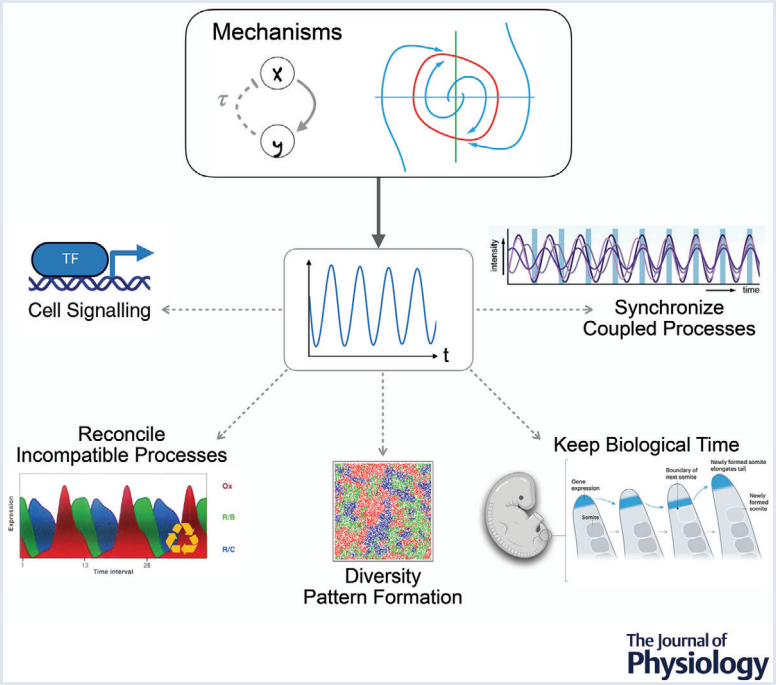
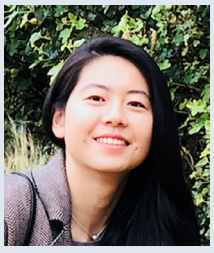


Abstract Despite widespread and striking examples of physiological oscillations, their functional role is often unclear. Even glycolysis, the paradigm example of oscillatory biochemistry, has seen

Lingyun (Ivy) Xiong is currently a postdoctoral fellow in the Department of Integrative Biology and Physiology, UCLA. Ivy's work focuses on dynamic processes in development, physiology, and cancer, with a special interest in the role of dynamic regulation in health and disease. By applying techniques from nonlinear dynamics, computational biology and quantitative imaging, her research aims to explain the spatiotemporal nature of diverse biological phenomena.



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questions about its oscillatory function. Here, we take a systems approach to argue that oscillations play critical physiological roles, such as enabling systems to avoid desensitization, to avoid chronically high and therefore toxic levels of chemicals, and to become more resistant to noise. Oscillation also enables complex physiological systems to reconcile incompatible conditions such as oxidation and reduction, by cycling between them, and to synchronize the oscillations of many small units into one large effect. In pancreatic β-cells, glycolytic oscillations synchronize with calcium and mitochondrial oscillations to drive pulsatile insulin release, critical for liver regulation of glucose. In addition, oscillation can keep biological time, essential for embryonic development in promoting cell diversity and pattern formation. The functional importance of oscillatory processes requires a re-thinking of the traditional doctrine of homeostasis, holding that physiological quantities are maintained at constant equilibrium values, a view that has largely failed in the clinic. A more dynamic approach will initiate a paradigm shift in our view of health and disease. A deeper look into the mechanisms that create, sustain and abolish oscillatory processes requires the language of nonlinear dynamics, well beyond the linearization techniques of equilibrium control theory. Nonlinear dynamics enables us to identify oscillatory ('pacemaking') mechanisms at the cellular, tissue and system levels.

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Corresponding author A. Garfinkel: Departments of Medicine (Cardiology) and Integrative Biology and Physiology, University of California, Los Angeles, CA 90095, USA. Email: agarfinkel@mednet.ucla.edu

Abstract figure legend Mechanisms and functions of physiological oscillations.

Homeostasis *vs.* oscillation in physiology

According to the doctrine of homeostasis, physiological regulation consists in maintaining key variables at constant equilibrium values, typically by using negative feedback loops. This view, influenced by control theory, leads to the widespread and widely taught belief that:

- 'normal body temperature is 37°C', maintained by a 'thermostat' in the hypothalamus;
- hormones are maintained at constant levels by negative feedback involving the hypothalamus and pituitary;
- blood glucose is held at constant levels by negative feedback involving insulin secretion by the pancreas;
- gene and protein expression, for example the tumour suppressor p53, when activated, is maintained at constant levels by negative feedback from inhibitors like Mdm2.

But, while physiological regulation is clearly present in these systems, it is simply not true that physiological quantities are regulated to equilibrium values (Fig. 1*A*–*D*). Instead:

- core body temperature oscillates with an amplitude ∼1°C in humans (Aschoff et al., 1971) and up to 3°C in mice (Griffis et al., 2022);
- sex hormone levels oscillate at a number of distinct time scales in humans (Licinio et al., 1998);
- glucose and insulin concentrations in the bloodstream oscillate over time scales of 2–10 min (high-frequency) and 100–120 min (ultradian) in humans, the latter of which is driven by negative feedback loops containing inherent time delays (Shapiro et al., 1988; Sturis, Polonsky, Blackman, et al., 1991; Sturis, Polonsky, Mosekilde, et al., 1991);
- upon DNA damage, p53 protein levels oscillate over a 5–6 h period, due to negative feedback with Mdm2 (Lahav et al., 2004).

Oscillation even marks the beginning of life: the first event after oocyte fertilization is the onset of intracellular calcium oscillations (Swann et al., 2006) (Fig. 1*E*).

Glycolysis

Oscillatory behaviour in glycolysis has been widely studied since the 1960s, demonstrated by sustained oscillations in the concentrations of glycolytic intermediates such as fructose 1,6-biphosphate, ATP and NADH (Goldbeter & Berridge, 2010; Merrins et al., 2016) with a period of ∼5 min. Glycolytic oscillations were first observed in yeast (Chance et al., 1964; Duysens & Amesz, 1957; Ghosh & Chance, 1964), but were also demonstrated in multiple mammalian systems (Frenkel, 1965; Smolen, 1995; Yang et al., 2008).

The mathematics of homeostasis and oscillation

Homeostasis. The mathematical expression of the doctrine of homeostasis is a stable equilibrium point

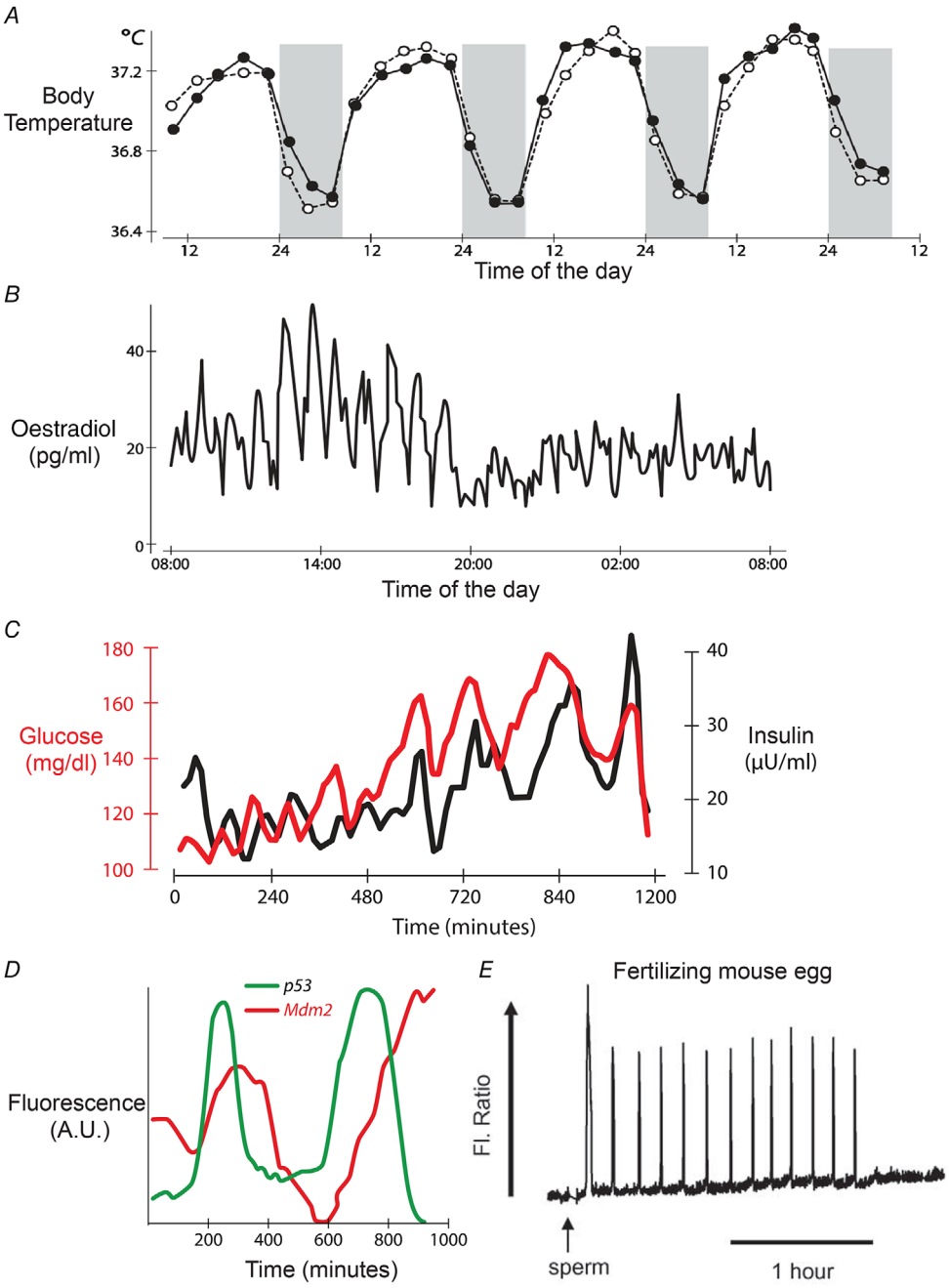

Figure 1. Oscillatory behaviours in physiology
A, average core body temperature (measured rectally) in six human subjects over 4 days (Aschoff et al., 1971). Filled circles represent the condition of an artificial light–dark cycle, while the open circles represent the same individuals in continuous darkness. Shaded areas are sleep times. *B*, multi-frequency oscillations in oestradiol in a 25-year-old healthy female, at mid-to-late follicular phase (Licinio et al., 1998). *C*, glucose and insulin oscillations in a human volunteer under constant glucose infusion (Sturis et al., 1991). *D*, the protein levels of the tumour suppressor p53 and its inhibitor Mdm2 show persistent oscillations in response to irradiation (Lahav et al., 2004). *A–D* were redrawn from the original publications and reprinted from 'Modelling Life' by Garfinkel et al. (2017), with permission of Springer. *E*, intracellular Ca^{2+} oscillations induced by fertilization in a mouse oocyte (Swann et al., 2006). Reprinted from 'PLCζ(zeta): a sperm protein that triggers Ca^{2+} oscillations and egg activation in mammals' by Swann et al. (2006), *Seminars in Cell & Developmental Biology* 17(2), 264–273, with permission of Elsevier.

(the 'set point') of a dynamical system. If the system deviates from the equilibrium point, negative feedback loops bring it back. In dynamical systems theory, this behaviour can be studied by linearizing the system around the equilibrium point (Hartman–Grobman theorem) and using eigenvalues to determine the system's stability, turning the problem into a linear differential equation with the set point as its stable equilibrium point.

Oscillation. Oscillatory systems, by contrast, are described not by stable equilibrium points but by stable oscillations, i.e. by limit cycle attractors (Garfinkel et al., 2017; Strogatz, 2015). Since there is no stable equilibrium point, and oscillation is the preferred behaviour of the system, the question of the system's regulation becomes mathematically more complex. Linearization is insufficient, and nonlinear dynamics is required. In particular, if the system's behaviour is described by a limit cycle attractor, then the regulatory mechanism has the job of not only creating the oscillation, but also maintaining its stability, i.e. the ability of the system to return to the limit cycle after perturbation.

While the remaining parts of this paper can be understood without the math, we highlight the theory behind oscillatory mechanisms in this section. Readers who are unfamiliar with the contents are encouraged to consult textbooks by Strogatz (2015) and by Garfinkel et al. (2017) for additional information.

Nonlinear dynamics also gives us insights into the mechanisms that can create and abolish oscillations, in the qualitative changes called *bifurcations*. There are four oscillatory bifurcations that can be produced by varying a single parameter. The best-known is Hopf bifurcation, but homoclinic bifurcation, saddle-node bifurcation of cycles (or 'periodics') and saddle-node on an invariant cycle (or 'infinite-period') bifurcation also have important examples (Strogatz, 2015, section 8.4).

Each of these bifurcations has a distinct phenomenology (Fig. 2), which can be used to identify it in a given system, physical or mathematical. Any one of the four bifurcations can govern the onset of an oscillation, and any one of the four can govern the offset of an oscillation, and it need not be the same bifurcation that created the oscillation. For example, one common scenario is for high-frequency oscillations to be created by Hopf bifurcation and to be extinguished by homoclinic bifurcation, a scenario that has been observed in neurons (Del Negro et al., 1998) and cardiac myocytes (Tran et al., 2009).

A *Hopf bifurcation*, whether supercritical (Fig. 2*A*) or subcritical (Fig. 2*B*), consists of a stable equilibrium point becoming unstable, and a new stable limit cycle appearing, surrounding that now-unstable equilibrium point. In a Hopf bifurcation we should therefore see an oscillation grow gradually from zero amplitude (if the bifurcation is supercritical) around the former equilibrium point, which remains roughly in the middle of the oscillatory maximum and minimum. If the bifurcation is subcritical, the oscillation may appear full-blown at a finite amplitude instead of growing from zero, but the oscillation still surrounds the former equilibrium point. In a Hopf bifurcation, as the oscillation develops, there is no significant change in frequency. These features describe a Hopf bifurcation in its forward mode. When a Hopf bifurcation governs the loss of an oscillation, the same scenario will be seen in reverse.

In a *saddle-node of cycles bifurcation* (Fig. 2*C*), a stable equilibrium point gains a pair of concentric surrounding periodic orbits. The inner periodic orbit is unstable, and the outer one is stable. Consequently, an initial condition inside the unstable periodic orbit will spiral into the stable equilibrium, while an initial condition outside the unstable periodic orbit will spiral out (or in) to the stable periodic orbit. Saddle-node of cycles bifurcations, when run in reverse, can terminate oscillations, as a stable oscillation collides with an unstable periodic orbit and is annihilated, leaving only the stable equilibrium point to govern the system.

In a saddle-node of cycles bifurcation, as opposed to the other types of oscillatory bifurcation, the initial stable equilibrium remains stable, and a new pair of periodic orbits is created. The fact that there is still a stable equilibrium point makes it possible to annihilate the oscillation with a single well-timed perturbation (Guevara, 2003; Guttman et al., 1980). Similarly, if the system is at the stable equilibrium, a single well-timed pulse can trigger sustained periodic oscillations. These phenomena cannot happen in the other oscillatory bifurcations.

The idea of 'well-timed' that is used here can only be understood by reference to nonlinear dynamics, in terms of trajectories in state space. The right-hand side of Fig. 2*C* illustrates this. For a single pulse to trigger an oscillation, it must push the state point sufficiently 'outward' as defined in state space (such as the perturbation to the point *c*), and for a pulse to annihilate an oscillation, the pulse must push the system sufficiently 'inward' to cross the unstable periodic orbit (such as the perturbation to the point *b*). Pushing the state point to the north (towards the point *d*), when the trajectory is at high values of the *y*-coordinate, will not work.

In a *saddle-node on an invariant cycle bifurcation* (Fig. 2*D*), in forward mode in the creation of an oscillation, the system state point, before bifurcation, is at rest at a stable equilibrium point on an invariant cycle. Post-bifurcation, the stable equilibrium collides with an unstable equilibrium point, also on the invariant cycle.

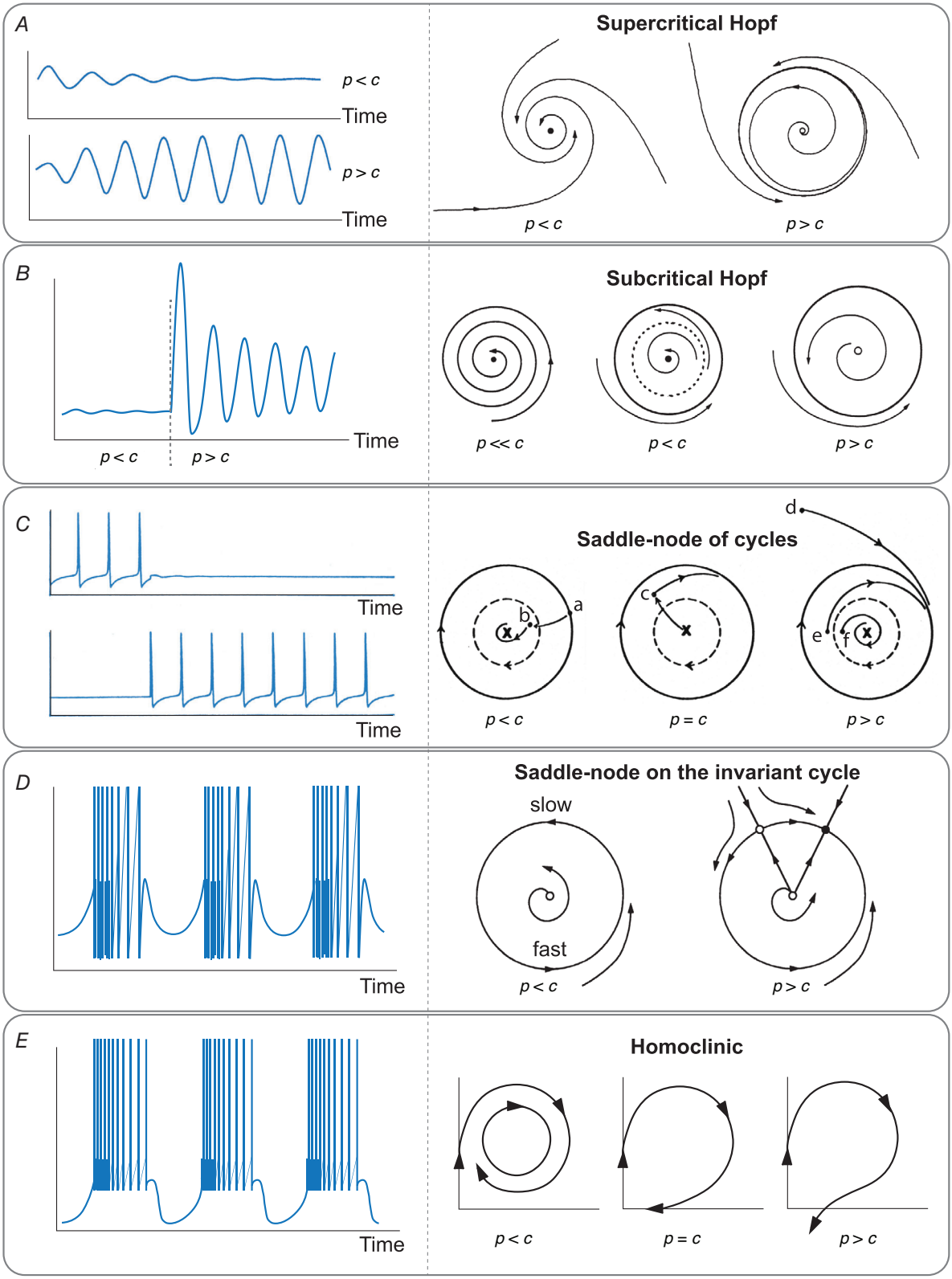

Figure 2. Bifurcations to create and abolish biological oscillations
Left: time series. Right: 2D phase portraits (state spaces with inscribed trajectories) pre- and post-bifurcation. *A*, supercritical Hopf bifurcation. *B*, subcritical Hopf bifurcation. *C*, saddle-node of cycles. *D*, saddle-node on an invariant cycle bifurcation. *E*, homoclinic bifurcation. See text for discussion.

The two annihilate each other, and a stable oscillation is born. In the reverse sequence, a pair of equilibria, one stable and one unstable, appear on an invariant cycle, and the oscillation is destroyed. The state point returns to the stable equilibrium as $t \to \infty$, thus giving this bifurcation the alternative name 'infinite-period bifurcation'. As the bifurcation is approached, the amplitude of the oscillations does not change, but their period increases (Strogatz, 2015; p 265)

In a *homoclinic bifurcation* (Fig. 2*E*), pre-bifurcation, a stable limit cycle, co-exists with a saddle point (an equilibrium point with one stable and one unstable direction) at the origin. As the bifurcation parameter is increased (or decreased), the stable limit cycle makes contact with the saddle point and becomes an infinite period homoclinic orbit. Post-bifurcation, the oscillation is destroyed.

The identification of distinct oscillatory bifurcations is an important source of insight into the oscillations that are called 'bursting'. Bursting oscillations are high-frequency oscillations, often superimposed on a more slowly oscillating baseline. Under normal conditions, bursting behaviour is seen in many types of neurons (Del Negro et al., 1998), and in pancreatic β-cells (Bertram et al., 1995), and, under pathological conditions (see below), in other types of neurons (Yang et al., 2018) and also pathologically in cardiac myocytes (where they are called 'early after-depolarizations') (Tran et al., 2009). Mathematically, the mechanisms of bursting onset and offset can be any one of the four bifurcations that can produce or abolish oscillation (Del Negro et al., 1998). Knowing which bifurcation underlies a given bursting behaviour enables us to devise mechanistic interventions to prevent unwanted oscillations (Madhvani et al., 2011; Tran et al., 2009).

Mechanisms of homeostasis and oscillation

The mechanism of homeostasis. The standard mechanism said to produce homeostasis is the action of *negative feedback loops*. The homeostatic paradigm, inspired by control theory, posits a 'set point' that is the target of the control mechanism (Fig. 3). The current state of the system is then compared to the set point, and the controller increases the state if the state is 'too low' (that is, below the set point) or decreases it if the state is 'too high' (that is, above the set point). But in many cases, the actual molecular and cellular basis for these mechanisms remains unknown.

The mechanisms of oscillation

Mechanism no. 1: steep negative feedback plus time delay. While negative feedback loops can produce a static equilibrium, the same loop can also produce oscillations. The conditions under which negative feedback produces one or the other response have been studied in many models (Fig. 4*A*). The pioneering work of Mackey and Glass studied a model of the negative feedback loop that controls CO_2 levels by adjusting the respiratory rate (Mackey & Glass, 1977).

Using bifurcation theory, Mackey and Glass were able to show that their system would undergo a qualitative change in its behaviour, a Hopf bifurcation, in which the formerly stable 'set point' of the controller becomes unstable and is replaced by a stable oscillation. Their model contained a parameter, n, that controlled the steepness of the negative feedback, and another parameter, τ, that reflected the time delay in the loop. They then showed that the system would undergo a Hopf bifurcation, and begin to oscillate, if the negative feedback is steep enough and there are sufficient

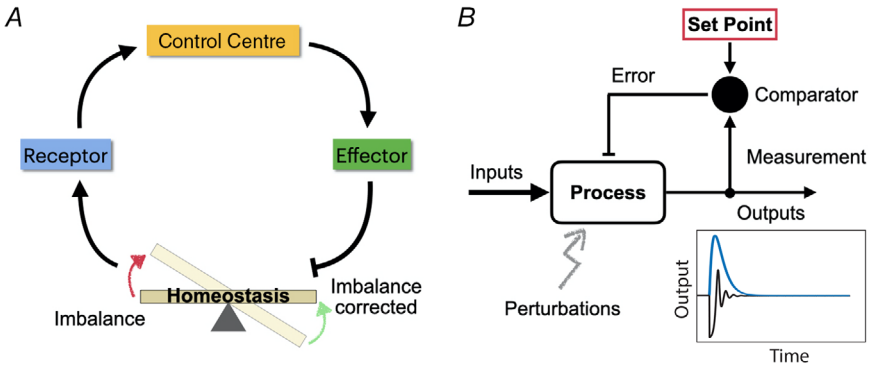

Figure 3. The mechanism of homeostasis
A, schematic representation of homeostasis: negative feedback counteracts imbalances to bring the system back to its original state. *B*, control theory provides an analogy for how the control centre reacts to perturbation, by 'comparing' it to a 'set point' and deriving an 'error signal' which is fed back to the system. Inset depicts responses under homeostatic control: (i) the optimal and most efficient response (blue), featuring a mono-exponential approach to equilibrium; and (ii) a typical but suboptimal response (black), with rapid approach but damped oscillations before returning to equilibrium.

time delays in the system. They derived a criterion for the Hopf bifurcation: the equilibrium point became unstable, and a stable oscillation appeared, when the product of n and τ exceeded a critical quantity (Fig. 4*B*).

Thus, nonlinear dynamics gives us a precise answer to the question: when does a negative feedback loop sustain equilibrium and when does it promote oscillation? The combination of sensitive negative feedback plus time delays is a frequent and common mechanism for biological oscillations, both good and bad. For example, the 2017 Nobel Prize for Physiology or Medicine was awarded to Hall, Rosbash and Young for the discovery of the mechanism of the circadian rhythm, in which 'several transcription factors operate in a genetic network incorporating autoregulatory [negative] feedback loops. Oscillations are achieved by delaying various steps in the network. For example, accumulation of one of the transcription factors – Period – is retarded in the cytoplasm by phosphorylation and degradation' (Young & Kay, 2001).

'Negative feedback with time delays' is also the driver of many functional rhythms in endocrine systems (Fig. 4*C*). For example, gonadal hormones exert negative feedback on hypothalamic secretion of hormone releasing factors. A hypothalamic–pituitary–gonadal (HPG) negative feedback loop will produce stable endocrine oscillations when the negative feedback becomes sufficiently steep (Garfinkel et al., 2017; Smith, 1980). In both males and females, puberty is marked by the onset of ultradian oscillations in multiple hormones on a time scale of hours: luteinizing hormone and oestrogen in females (Grumbach, 2002), and luteinizing hormone and testosterone in males (Katongole et al., 1971). In Smith's phrase, 'Puberty is a Hopf Bifurcation,' meaning that the HPG system will begin cycling when the hypothalamus becomes more sensitive to negative feedback from the gonads. Oscillations driven by negative feedback loops in the hypothalamic–pituitary–adrenal (HPA) axis produce oscillations in cortisol (Lightman et al., 2020; Walker et al., 2012).

When oscillation is produced by a 'negative feedback plus time delay' mechanism, the bifurcation underlying the onset of oscillation is typically a Hopf bifurcation, as Mackey and Glass found in their system and Smith found in the HPG system.

Mechanism no. 2: 'negative resistance'. There are other mechanisms of oscillation, some of which can be seen even in two-variable systems with no time delays. One simple model displaying this property is the Fitzhugh–Nagumo neuronal model (Keener & Sneyd, 2009: p 221) (see also Garfinkel et al., 2017: p 217). In this model, for all non-zero values of 'negative resistance', there is short-range destabilizing positive feedback, making the equilibrium point inherently unstable (Fig. 4*D*). The negative feedback at high voltage is stabilizing in this case and forces the state point to spiral inward. Trapped in the 2-D plane, between the spiralling-out at low voltages and the spiralling-in at high voltages, there is a single closed orbit, a (stable) limit cycle attractor (Fig. 4*D*) (Poincare–Bendixson theorem).

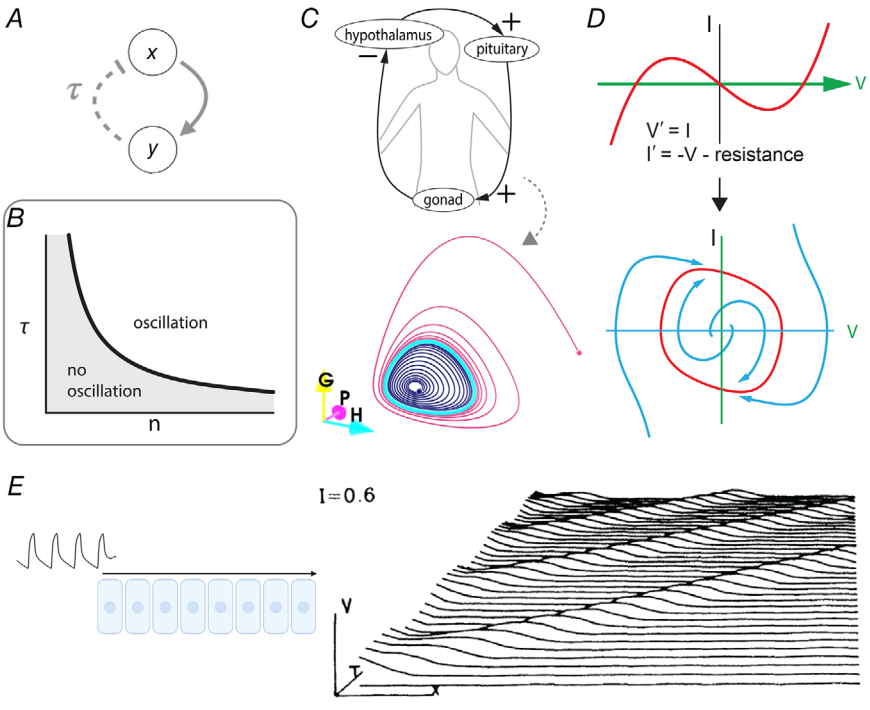

Figure 4. Mechanisms of oscillation
A, schematic representation of a 2-variable negative feedback loop with explicit time delay τ. *B*, Hopf bifurcation boundary for the negative feedback loop (n = slope of negative feedback). *C*, a 3-variable model of the HPG negative feedback loop, without explicit time delays (upper), can produce oscillation (lower) if the negative feedback is sufficiently steep. *D*, schematic representation of a 2-variable 'negative resistance' system (upper) can exhibit sustained oscillations, governed by a stable limit cycle attractor in 2D state space (lower). *E*, emergence of oscillatory behaviour in a reaction–diffusion PDE in 1 space dimension, x, whose local term was a simple Fitzhugh–Nagumo 2-variable model of an excitable cell, with a current source term I. Results from numerical simulations were reprinted from 'Hopf bifurcation to repetitive activity in nerve' by Rinzel & Keener (1983), *SIAM Journal on Applied Mathematics* 43(4), 907–922, with permission of the Society for Industrial and Applied Mathematics.

This mechanism can be thought of as 'fast self-activation and slow inhibition' or 'fast positive feedback and slow negative feedback'. This is akin to the spatial analogue of a 'short-range activation plus long-range inhibition' mechanism, taken from Gierer and Meinhardt's pioneering studies on *spatial* pattern formation (Gierer & Meinhardt, 1972), where the activation and inhibition are short-range and long-range in *physical* space. This was their generalization of the original mechanism for spatial oscillations proposed by Turing (1952).

Another example of a negative resistance oscillator is the membrane voltage oscillation driven by the negative resistance region of the NMDA receptor (Brodin et al., 1991), which has been found to be important in psychiatric depression (Yang et al., 2018) (see also Discussion). The negative resistance region is the part of the *I–V* curve that becomes more negative as voltage increases, i.e. it has a negative slope. The functional role of negative resistance regions can be understood by realizing that resistance in an electrical circuit plays the same role as friction in a mechanical system: it provides damping that turns the system behaviour into a stable equilibrium point. Negative resistance plays the opposite role, providing a positive feedback loop that turns the stable EP into an unstable one, surrounded by a stable limit cycle. For example, negative resistance regions of sodium and calcium channels act as the engines of cellular oscillations.

Recent work based on this observation has highlighted a mechanism, and a mechanistic approach to therapy, for the pathological oscillations that are seen in psychiatric depression. In rodent models of depression, including chronic restraint stress, neurons in the lateral habenula (LHb) have emergent high-frequency bursting oscillations in membrane potential (Yang et al., 2018). This bursting behaviour then facilitates synchronization to local field potentials, another hallmark of depression. Yang et al. showed that the bursting oscillation was itself caused by the activity of the NMDA receptor in LHb neurons, whose negative-resistance region turns the neuron into a negative-resistance oscillator. Their analysis provided a mechanism for therapy: the NMDA receptor blocker (and antidepressant) ketamine abolished bursting oscillations by reducing the negative resistance region, and ameliorated depression-like behaviour.

Mechanism no. 3: oscillatory emergence in tissue

Pacemaking in the cardiac sinoatrial node. In the cardiac sinoatrial node (SAN), the heart's natural pacemaker, there are at least two oscillatory mechanisms that operate within cells. One oscillation is the 'voltage clock'; its mechanism is a Hopf bifurcation. An ordinary myocyte is an excitable cell: its resting potential is a stable equilibrium point of the system. But in the SAN, there is an additional hyperpolarization-activated 'funny current' (I_f). I_f destabilizes the equilibrium point and turns the cell into a limit cycle oscillator. The other intracellular mechanism is the 'calcium clock': rhythmic local release of intracellular Ca^{2+} triggers a depolarizing current through the sodium–calcium exchange current, I_{ncx} (Donald & Lakatta, 2023). The mechanism of oscillation of the calcium clock in the cardiac SAN is also a Hopf bifurcation: an analytical bifurcation study by Kurata et al. (2012) of the 29-variable model by Maltsev & Lakatta (2009) found a Hopf bifurcation leading to voltage oscillations with increasing values of the sarcoplasmic reticulum Ca^{2+} uptake rate.

In addition to these cellular level oscillators, researchers have argued that a tissue-level rhythm need not arise from pre-existing cellular rhythms. Rather, they propose, the oscillatory activity *emerges* when cells, quiescent in isolation, are coupled together into tissue: 'the cardiac impulse is an emergent property of the SAN cellular network' (Bychkov et al., 2020; Maltsev & Stern, 2022). In their model, there are excitable (but not oscillatory) cells, coupled to other non-excitable cells. The non-excitable cells undergo subthreshold oscillations in intracellular Ca^{2+}, generating membrane potential oscillations 'via electrogenic Na/Ca exchange and further transferred and integrated (computed) by the excitable cells to reach its AP threshold, generating rhythmic pacemaking.'

Whether the origin of the cellular oscillation is sub-cellular or tissue-driven, it is still necessary to synchronize the action potentials of many thousands of cells into a coherent beat. Cellular activity must be synchronized into macroscopic patches of depolarizing cells if the impulse is to propagate through myocardial tissue. Plotnikov et al. estimated that the establishment of a pacemaker required the synchronization of at least 700,000 cells (Plotnikov et al., 2007), a figure that agrees with theoretical calculations by Weiss et al. (2010).

But *how* do they synchronize? While mechanisms of purely electrical synchronization certainly exist in the SAN (Guevara & Jongsma, 1990; Jalife & Antzelevitch, 1979), another synchronizing mechanism has been suggested to play a critical, if not *the* critical, role: mechanical stretch of the SAN cell, produced by tissue-level mechanical coupling, could both produce electrical depolarization and also synchronize it among many cells (MacDonald & Quinn, 2021).

It had been previously suggested theoretically that a coupled reaction-diffusion-mechanics partial differential equation (PDE) model of cardiac tissue can exhibit 'self-organized pacemakers' (Panfilov et al., 2005). And in real tissue, the ability of stretch to induce oscillations in otherwise quiescent SAN tissue has been known at least since (Lange et al., 1966) (Fig. 5) (see also Quinn & Kohl,

2021). More recently, MacDonald and Quinn suggested that 'SAN mechano-sensitivity has long been known to be a contributor to SAN pacemaking – both as a driver and regulator of automaticity – but its essential nature has been underappreciated' (MacDonald & Quinn, 2021). They demonstrate that mechanical stretch in SAN cells has the right phase resetting relationships that would be required for stretch to act as a synchronizer across cells. They propose that mechanics acts as the overall integrator and synchronizer of *all* the oscillatory mechanisms, both cellular and tissue-level, leading them to call tissue-level mechanics 'the grandfather clock of cardiac rhythm.'

The emergence of pathological oscillations in cardiac tissue. EADs and PVCs. Early After Depolarizations (EADs) are pathological oscillations that can be observed in isolated cardiac myocytes under a variety of conditions, including K^+ channel blockade, oxidative stress and hypokalaemia. These cellular level EADs are often cited as the cause of tissue-level premature ventricular complexes (PVCs), which can then propagate through ventricular tissue and become triggers of arrhythmias.

However, the idea that cellular level EADs cause tissue-level PVCs faces some major hurdles, especially the problem of synchronization: for a PVC to form, many neighbouring myocytes must simultaneously undergo EADs. If just a few cells were to develop EADs, the electrotonic load of neighbouring tissue would damp out the cellular misbehaviour. One estimate is that 700,000 cells would be required to generate a PVC, although this number would decrease in some pathological conditions (Weiss et al., 2010). This need for a macroscopic, tissue-level patch of activation similar to what has been found for pacemaking regions in the cardiac sinoatrial node: the theoretical estimate agreed 'with experimental data for the number of pacemaker cells required to generate a biological pacemaker' (Plotnikov et al., 2007).

Synchronized patches of EAD-generating cells have been observed in real hearts: in a study of arrhythmias induced in rabbit heart by oxidative stress, Sato et al. (2009), using optical mapping, showed that macroscopic patches of cells, each exhibiting synchronized EADs, appeared in the ventricles. These islands of EADs were observed as 'multiple shifting foci causing polymorphic tachycardia and fibrillation'. But it is something of a mystery how these cells synchronize into 'Islands of EADs'.

Tissue-level PVCs. More recently, an alternative scenario has been proposed, that PVCs can emerge at the tissue level as macroscopic patches of cells exhibiting EADs, created, not by a cellular instability, but by a tissue-level instability in cardiac wave propagation. The concept of a tissue-level instability was introduced by Huang et al. (2016). Using optical mapping of rabbit hearts, they noted that 'premature ventricular complexes (PVCs) were observed to originate from the steep spatial repolarization gradient (RG) regions'. They understood that this kind of tissue-level mechanism is 'different from the traditional thinking of PVCs', which is that they are a consequence of cellular phenomena, not a cause of them.

Other groups also called attention to the role of spatial, that is, tissue-level, mechanisms of EAD generation. Dutta et al. (2016) noted the 'facilitation of EADs in tissue' by tissue-level gradients, suggesting that 'electrotonic current flowing from the heterogeneous substrate of the Border Zone triggers EADs', which again points to a downwards causality in which tissue-level events cause cellular level events.

In cardiac electrophysiology, it has long been known that when a premature ectopic excitation (an 'R') occurs in the late recovery phase of the cardiac cycle (the 'T' wave on ECG), a re-entrant arrhythmia can be generated, which quickly degenerates into ventricular fibrillation, the leading cause of sudden cardiac death. This 'R on T' mechanism is well-understood. But the emergence of an ectopic R from the previous T-wave is a distinct phenomenon, dubbed 'R-from-T' (Liu et al., 2019; Qu et al., 2022). R-from-T can be a significant initiator of arrythmia, in which 'the PVC initiating re-entry is not a separate event from the T wave but rather is causally generated from the repolarization gradient that manifests as the T wave' (Qu et al., 2022).

Possibly the first recognition of the tissue-level emergence of oscillations was a mathematical study by Rinzel & Keener (1983). They studied a reaction-diffusion PDE in one space dimension, x, whose local term was a simple Fitzhugh–Nagumo two-variable model of an excitable cell, with a current source term I. They let $\phi(x)$ be

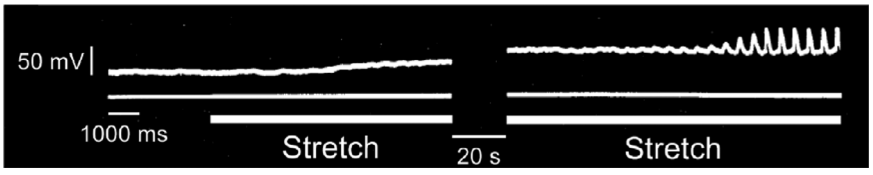

Figure 5. Tissue-level peacemaker oscillations induced by stretch in isolated SAN from feline heart
Adapted from Lange et al. (1966). Reprinted from 'Cardiac mechano-electric coupling: acute effects of mechanical stimulation on heart rate and rhythm' by Quinn & Kohl (2021), *Physiological Reviews* 101(1), 37–92, with permission of American Physiological Society.

the steady-state solution of the PDE and linearized around this steady-state to look for instability and bifurcation. They point out that the situation is essentially describable by a Schrodinger equation whose potential function is $f'(\phi(x))$, where f is the cubic activation function of the Fitzhugh–Nagumo local electrophysiology. Then they find that for sufficient values of the imposed current I, a Hopf bifurcation takes place, giving rise to an oscillatory instability that propagates across space (Fig. 4*E*).

Teplenin et al. (2018) continued the theme of using a spatial Schrodinger equation to find oscillatory bifurcations, specifically in application to the emergence of synchronized patches of oscillatory EADs. They found that ectopic excitations were generated by the PDE when the recovery from refractoriness was slowed, creating greater spatial gradients.

The bifurcation theory behind the tissue-level instability generating PVCs was worked out formally by Lin, Qu, and Wang (2023). By linear stability analysis, they showed that a Hopf bifurcation, depending on spatial repolarization gradients, led to local oscillations, which 'once their amplitudes are large enough, lead to spontaneous propagating excitations' manifesting as PVCs and sustained arrhythmias. Together, the work by a number of groups converges on the conclusion that PVCs can emerge as tissue-level instabilities, which cause cellular level EADs, and not the other way around.

Oscillation: physiological functions

Oscillations may be everywhere in physiological systems, but their physiological function is far from clear. Circadian rhythms clearly evolved to adapt to and take advantage of the external day–night cycle, but the role of other rhythms often remains elusive. It has even been argued that many finer-scale oscillations might not serve any biological functions at all; this has been suggested with regards to oscillations in glycolysis (Alberts, 2015; Chandra et al., 2011; El-Samad, 2021). Here, we summarize representative findings to provide evidence that oscillations are not an unwanted product of negative feedback regulation. Rather, they represent an essential design feature of nearly all physiological systems.

Oscillation as the preferred mode for communication

Avoiding adaptation and desensitization. In inter- and intra-cellular communication, oscillatory signalling is generally the preferred mode of behaviour. One reason for this is that, in many systems, constant high levels of signal lose their effect due to adaptation and saturation at the 'receiver'. For example, only periodic cAMP signals delivered with physiological frequency (every 5 min) could stimulate the aggregation and differentiation of starved social amoebae (Goldbeter, 1988), because cell-surface cAMP receptors become desensitized and degraded when stimulated with constant signals (Martiel & Goldbeter, 1987; Van Haastert et al., 1992). Such inhibition of surface receptors by chronic stimuli also applies to the receptors for insulin-like growth factor I (IGF-1) (Norstedt & Palmiter, 1984) and to the epidermal growth factor receptor (EGFR) (Klein et al., 2004).

Avoiding toxicity. Oscillatory signalling is also a solution to the dilemma that constant high levels of a protein can be toxic. In response to moderate DNA damage, p53 oscillates to trigger cell cycle arrest and DNA damage repair, a property that is essential for tumour suppression (Heltberg et al., 2022; Lahav et al., 2004; Xiong & Garfinkel, 2022). Cells with constant p53 of similar amplitude, on the other hand, readily undergo senescence or apoptosis within hours (Purvis et al., 2012). Moreover, constant high levels of p53 are known to be embryonic lethal (Marine et al., 2006) and can cause widespread tissue damage (Moyer et al., 2020). A similar phenomenon happens in the immune response: nuclear factor-κB activity in the nucleus oscillates when stimulated by endogenous or mild immunogenic signals, such as tumour necrosis factor-α and poly(I:C) (Adelaja et al., 2021), to selectively induce target gene expression (Heltberg et al., 2019; Hoffmann et al., 2002). Evidence also has suggested that this oscillatory behaviour could avoid extensive epigenome remodelling that is costly, as in extreme immune challenges, or deleterious, as in auto-immune diseases (Cheng et al., 2021).

Resistance to corruption by noise. Another desirable feature of oscillation is that oscillatory signalling is more resilient to noise and more resistant to corruption of its information. Information encoded in the frequency (i.e. frequency modulation, FM) is less sensitive to corruption by noise than information encoded in the amplitude (i.e. amplitude modulation, AM). This is why FM radio is superior to AM in sound quality. The transmission of biological information seems to follow the same principle, exemplified by the activation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), an enzymatic complex consisting of dimers of hexameric rings. CaMKII is highly sensitive to the frequency of intracellular Ca^{2+} oscillations – only high frequency enables consecutive and autonomous activation of individual catalytic domains – but not to pulse duration or amplitude (De Koninck & Schulman, 1998).

Oscillations reconcile incompatible biological processes. As early as 1980, Boiteaux, Hess, and Sel'kov suggested that oscillation is the preferred mode of operation when it is necessary to reconcile incompatible conditions (Boiteux et al., 1980). Like the sleep–wake cycle in the

circadian rhythm, or the longer-term hibernation cycle through seasons, many fine-scale biological oscillations serve to accommodate processes that cannot occur simultaneously.

Cell cycle. The cell cycle progresses through distinct phases to achieve cell division and proliferation: DNA synthesis, cell growth, mitosis and various checkpoints (Alberts, 2015). Obviously, DNA synthesis cannot happen during mitosis, during which the chromatin condenses and DNA become inaccessible. Therefore, the cell cycle must accommodate incompatible conditions, by cycling among them. The engine driving the cell cycle oscillation is the negative feedback loop of cyclin and cdc2/APC, acting with time delays (Ferrell et al., 2011; Tyson, 1991). The negative feedback loop serves as the mechanism to enforce the overall strategy of reconciling these incompatible processes through oscillation.

Yeast metabolic cycle. Another excellent example is the yeast metabolic cycle, as studied by Tu et al. (2005). Their research uncovered a temporal profile of gene expression in yeast cultures that was highly periodic, synchronized to the respiratory oscillation (∼5 h). Even more remarkably, the overall cycle was clearly divided into three distinct phases, with a closely coordinated group of genes being expressed in each phase. For example, genes for amino acid synthesis were expressed during the 'oxidative' phase, genes for mitochondrial processes were expressed during the 'reductive/building' phase, and genes for heat shock proteins were expressed during the 'reductive/charging' phase. The authors referred to this alternating arrangement as 'temporal compartmentalization', a concept that was echoed by a synthetic design of a gene-metabolic oscillator in *E. coli* (Fung et al., 2005). Ultradian gene expression oscillations were later found in mammalian systems, in both nocturnal (Hughes et al., 2009) and diurnal (Mure et al., 2018) animals.

Energetic oscillations in mitochondria. At a finer time scale, mitochondrial function is characterized by oscillation in redox state, alternating between an oxidative and a reductive environment. Indeed, the aforementioned yeast metabolic cycle is built upon cycles of reduction and oxidation of the intracellular pool of nicotinamide nucleotides with periods of 45 s to 1 min (Aon et al., 1991). In guinea pig cardiomyocytes, mitochondrial redox transitions were shown to oscillate with a period of 1–3 min (O'Rourke et al., 1994; Romashko et al., 1998), as measured by the fluorescence of flavoproteins, which are closely linked to mitochondrial NADH levels. Oxidative processes (such as the TCA cycle) accumulate NADH, increasing fluorescence levels; while reductive processes (including the electron transport chain) use NADH, diminishing fluorescence. The oxidative/reductive oscillation is closely linked to oscillation in mitochondrial membrane potential ($\Delta\Psi_m$), which is a two-stage alternation, separating the build-up of the proton gradient in one phase from the draining of the proton gradient (for ATP synthesis) in the other (Aon et al., 2003; Romashko et al., 1998).

Proliferation versus *commitment in development.* Oscillatory behaviours also dominate developmental processes, where alternation between proliferation and differentiation is required (Beets et al., 2013). In developing vasculature, for example, proliferation and differentiation alternate over a 24-h cycle to achieve morphogenesis (Guihard et al., 2020). The clock driving the cycle is the negative feedback loop between bone morphogenic proteins (BMPs) 4 and 9 and their inhibitors matrix Gla protein (MGP) and crossveinless 2 (CV2), respectively. Each cycle has a proliferative phase of BMP4 dominance–BMP9 inhibition, and a differentiation-and-commitment phase of BMP4 inhibition–BMP 9 dominance. Another example of developmental oscillations is the extracellular signal-regulated kinase (ERK) oscillation that is downstream of epidermal growth factor/fibroblast growth factor stimulation and mitogen-activated protein kinase pathway activation. The temporal dynamics of ERK are known to govern cellular proliferation and differentiation (Marshall, 1995; York et al., 1998), not only seen in embryonic development (Kholodenko et al., 2010; Raina et al., 2022), but also in tissue regeneration (De Simone et al., 2021) and tumour microenvironment (Davies et al., 2020; Gillies et al., 2020). Oscillations in Wnt and Notch signalling can play a similar role (Diaz-Cuadros et al., 2020; Sonnen et al., 2018).

Oscillations allow for synchronization of coupled biological processes. One of the most important functions of oscillation in biology is that systems that are time-varying can lend themselves to synchronization of their time-varying processes, thereby combining many small outputs into one large one. This is seen in the cellular slime mold *D. discoideum*: individual cells synchronize their pulsations of cAMP to achieve macroscopic quantities of the chemoattractant, which produces aggregation (reviewed in Goldbeter & Berridge, 2010). In a striking example of the benefits of oscillation, mitochondria across the cell were also found to synchronize their oscillatory metabolic activities for maximum ATP output in cardiac tissues (Aon et al., 2003, 2006).

Similarly, in all secretory organs of the body, including the pituitary and pancreas, cells secreting a given hormone must synchronize their microscopic pulsations to achieve the macroscopic output necessary for

physiological function. In response to elevated glucose levels in the blood, the pancreas secretes insulin in an oscillatory fashion, with an amplitude of up to 600 pmol/L and a period of ∼5 min, a phenomenon that has been observed in rodents, canines and humans (Lang et al., 1979; Matveyenko et al., 2008). The liver's response to insulin seems to depend on this high-frequency oscillation of insulin release into the blood; its disruption could contribute to type 2 diabetes (Satin et al., 2015).

The intracellular oscillator in the pancreatic β-cell. Several important studies have elucidated the intracellular mechanisms of oscillatory insulin release in the pancreatic β-cell (McKenna et al., 2016; Merrins et al., 2016), highlighting the pivotal role of glycolytic oscillations (O'Rourke et al., 1994). In particular, a rise in glycolytic activity has been shown to precede membrane depolarization and calcium influx, which in turn triggers oxidative phosphorylation and ATP depletion (Fig. 6). While some authors have proposed that 'pulsatile basal insulin secretion is driven by glycolytic oscillations' (Fletcher et al., 2022) or metabolic cycles (Merrins et al., 2022), increasing evidence suggests that glycolytic oscillations are coupled to oscillations in intracellular Ca^{2+} and metabolic oscillations in the mitochondria. It is the synchronization of these oscillatory activities that drives pulsatile insulin release, which we summarize as the following.

The coupling of glycolytic oscillations to mitochondrial and intracellular Ca^{2+} oscillations cycle through the following four stages to secrete insulin in a pulsatile fashion (Fig. 7):

(1) As glucose is imported into the cell, it feeds into glycolysis in the cytosol, producing ATP and pyruvate. In the mitochondria, pyruvate propels the TCA cycle, generating NADH for charging the electron transport chain, which pumps H^+ into the intermembrane space, thus increasing mitochondrial membrane potential ($\Delta\Psi_m$) (Merrins et al., 2016).
(2) As glycolysis continues, ATP accumulates. When the ATP/ADP ratio reaches a critical value, the ATP-sensitive K^+ channels (K_{ATP} channels) on the cell membrane become inhibited, causing membrane depolarization (Craig et al., 2008). In turn, this triggers Ca^{2+} influx through the voltage-dependent Ca^{2+} channel (Satin, 2000).
(3) Influx of Ca^{2+} then plays numerous roles inside the cell, including ramping up mitochondrial ATP

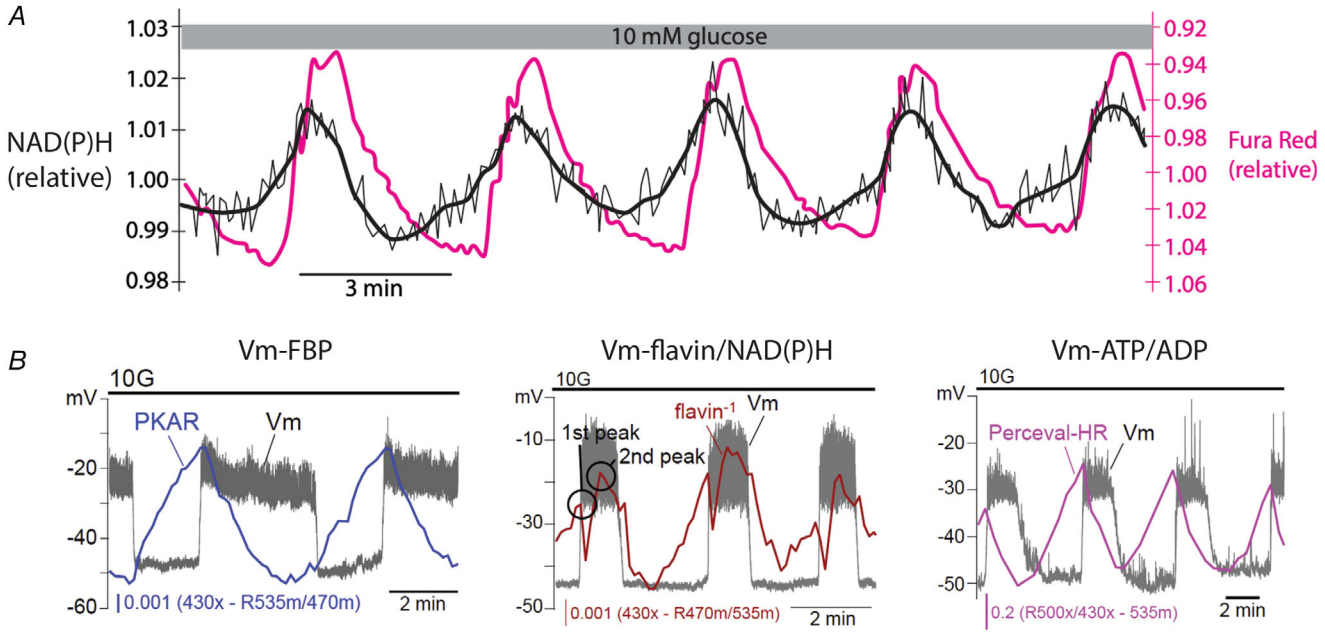

Figure 6. Intracellular processes are coupled in pancreatic β-cells to release insulin in an oscillatory fashion
A, metabolic oscillations (NAD(P)H) are synchronized to oscillations in intracellular Ca^{2+} (Fura Red) in mouse pancreatic β-cells. Redrawn from 'Ca^{2+} controls slow NAD(P)H oscillations in glucose-stimulated mouse pancreatic islets' by D.S. Luciani, S. Misler, and K.S. Polonsky (2006), *Journal of Physiology* 572(2), 379–392, and reprinted from 'Modelling Life' by Garfinkel et al. (2017), with permission of Springer. *B*, coupling of metabolic intermediates to membrane potential (V_m) oscillations in mouse pancreatic β-cells. Example recordings of V_m–fructose 1,6-biphosphate (FBP) (left), V_m–flavin/NAD(P)H (middle), and V_m–ATP/ADP ratio (right). Reprinted from 'Phase analysis of metabolic oscillations and membrane potential in pancreatic islet β-cells' by Merrins et al. (2016), *Biophysical Journal* 110, 691–699, with permission of Elsevier.

production (Jouaville et al., 1999) and triggering insulin release through exocytosis (Kesavan et al., 2007), a process that rapidly consumes ATP.

(4) Decreased ATP/ADP ratio then re-activates the K_{ATP} channels, therefore restoring the membrane potential and stalling Ca^{2+} influx, which allows for glycolysis to build up ATP again.

Tissue-level synchronization. Like in cardiac tissue (see section 'Mechanism no. 3: oscillatory emergence in tissue'), these cellular oscillators must then be coupled into a synchronous macroscopic oscillation, to achieve their physiological effects. The process by which this synchronization takes place has been well studied: pancreatic β-cells within the islets of Langerhans are connected by gap junctions (Fig. 7), which creates synchronous insulin release within the islet (Benninger et al., 2011; Sherman et al., 1988). On a higher level, inter-islet synchronization could be guided by the shared glucose-rich environment (Bier et al., 2000; Bruce et al., 2022) and/or neuronal input (Fendler et al., 2009; Imai et al., 2008).

In addition, intracellular responses to extracellular calcium are also characterized by frequency modulation of transcription factor bursts in the nuclei (Cai et al., 2008), suggesting that oscillations are better suited than steady levels for synchronizing tissues that have heterogeneous sensitivities to calcium.

Oscillatory processes across different organ systems. At still higher levels of organization, oscillatory processes must often be regulated and synchronized from organ to organ. As mentioned above, many hormones released by the pituitary show ultradian rhythms in humans, including luteinizing hormone (LH) (Bäckström et al., 1982), follicle-stimulating hormone (Bäckström et al., 1982), adrenocorticotropic hormone (ACTH) (Brandenberger et al., 1987), thyroid-stimulating hormone (TSH) (Romijn et al., 1990), growth hormone (Goji, 1993) and prolactin (Bäckström et al., 1982; Veldhuis & Johnson, 1988). The role of the HPG, hypothalamus–pituitary–thyroid, and HPA axes in regulating the oscillatory release of these hormones has been shown (Grant et al., 2018). Studies have also revealed that the ultradian oscillation in leptin, an

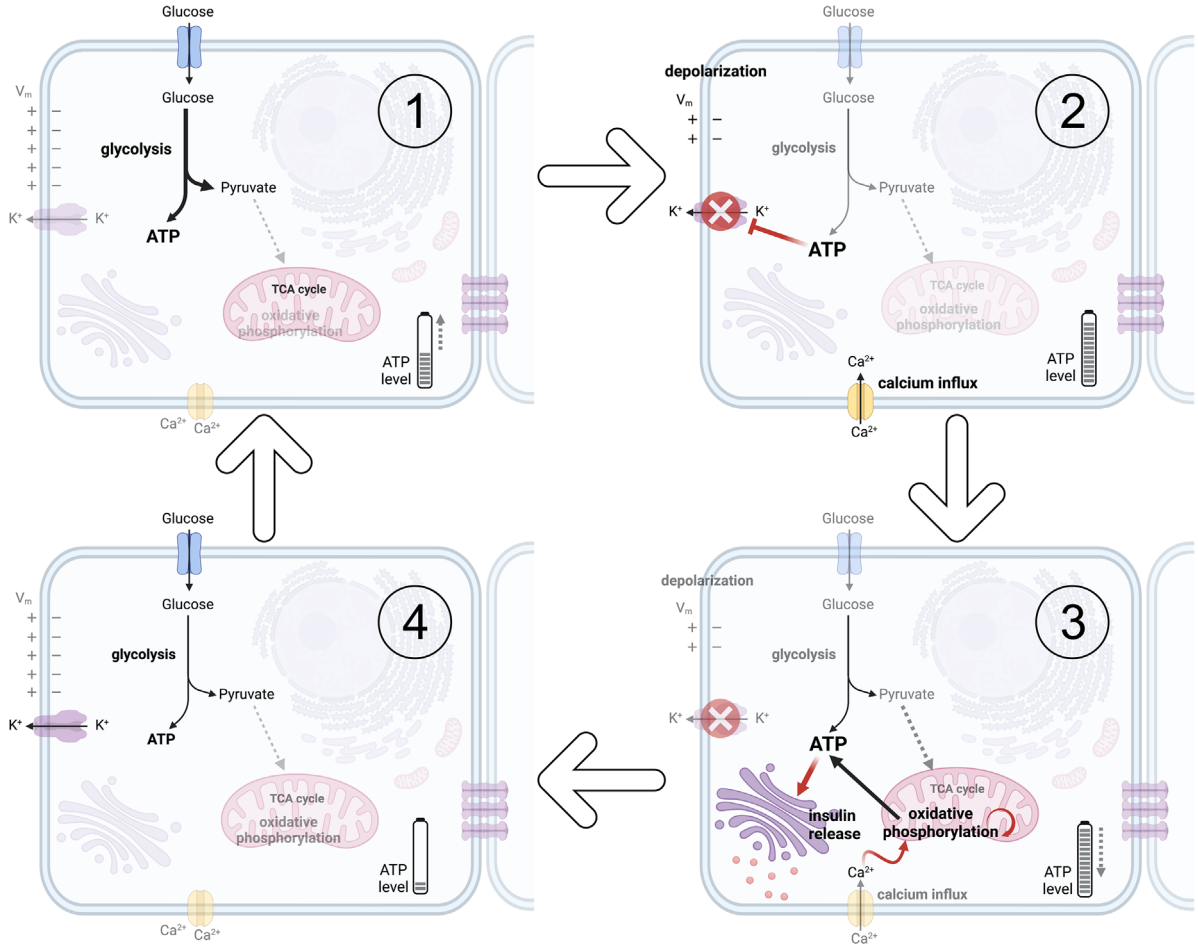

Figure 7. The four stages of oscillatory insulin release in pancreatic β-cells (see text)

adipocyte hormone (Sinha et al., 1996), showed pattern synchrony with those of LH and oestradiol in healthy women (Licinio et al., 1998), and with those of TSH in healthy adults (Mantzoros et al., 2001), but is inversely related to ACTH (Licinio et al., 1997). These synchronized actions could represent a general strategy for organ–organ communication.

And, at the highest level, since virtually all organs show rhythmic behaviours that are autonomous to that organ, there is clearly a need to regulate these peripheral oscillations to the overall circadian cycle (Guzmán et al., 2017), a need for 'one ring to rule them all…and in the darkness bind them'. It has been suggested that oscillations in core body temperature could serve as this universal entrainer (Brown et al., 2002; Buhr et al., 2010; Qian et al., 2022).

Oscillations promote cell diversity and pattern formation. Early studies demonstrated how biodiversity can be achieved by species oscillations (Huisman & Weissing, 1999; May & Leonard, 1975). Population oscillations make it possible for antagonistic organisms to share the same space, by cycling their populations in time, as demonstrated by the real-life game of rock-paper-scissors (Kerr et al., 2002; Sinervo & Lively, 1996) and the repressilator model (Elowitz & Leibler, 2000), together with recent studies of biofilm dynamics (Liu et al., 2017). This notion turned out to have wide implications beyond ecology. Oscillations facilitate biodiversity by enabling time-sharing or 'temporal compartmentalization' by multiple species, in the phrase of Tu et al. (2005), which is analogous to the alternation strategy by incompatible biological processes (see section 'Yeast metabolic cycle').

The segmentation clock in mammalian embryonic development has been studied since the 1990s (Lewis, 2003; Monk, 2003; Palmeirim et al., 1997), where the highly conserved oscillatory behaviour in Hes1 protein level is known to keep biological time for coordinated somite formation (Diaz-Cuadros et al., 2020; Matsuda et al., 2020). Hes1 represses downstream target Dll1, a ligand for the Notch signalling pathway (Kobayashi et al., 2009). Notch signalling in embryonic stem cells favours neural differentiation, whereas its inactivation tilts towards cardiac mesoderm differentiation. Here, Hes1 oscillations could generate cell populations that are heterogeneous in their differentiation competency, thus creating diverse cell lineages for somitogenesis (Kobayashi & Kageyama, 2010). Through ligand–receptor interactions, the segmentation clock also gives rise to spatial organization of diverse cell populations during somitogenesis and other processes of pattern formation (Bocci et al., 2020; Oates et al., 2012).

Discussion

Equilibrium-centric dynamics and the doctrine of homeostasis have long dominated biological thinking. It is increasingly recognized that this view is far from complete. Here, we studied examples of physiological oscillation and summarized their mechanisms and the mathematics required to understand them. Importantly, these oscillations play key functional roles, by being the preferred mode of communication in cell signalling, reconciling incompatible processes, synchronizing coupled processes, keeping biological time, and promoting diversity and pattern formation (Abstract Figure).

As new oscillatory behaviours are being discovered in physiological systems, additional functions may emerge. For example, high frequency voltage oscillations, as recorded by contact electrodes in the cortex, have been suggested to be critical in intracortical communication in the brain (Engel et al., 2009). It has been proposed that these oscillations can synchronize neuronal activity over long distances, thereby providing a basis for how different regions of the brain, say auditory and visual, can combine ('bind') their information into a single object (Buzsáki, 2006). Researchers have found that these high-frequency oscillations ('ripples') phase-synchronize, with definite phase-offsets, over long distances in the brain. This phase-synchrony, they suggest, 'may help to 'bind' different aspects of a mental event encoded in widespread cortical areas into a coherent representation' (Dickey et al., 2022).

Beyond homeostasis: homeodynamics? If oscillatory processes are central to physiology, then we will need to take a fresh look at the doctrine of homeostasis. We suggest that the concept of homeostasis needs to be parsed into two separate components. The first component is the idea that physiological processes are regulated and must respond to environmental changes. This is obviously critical and true. The second component is that this physiological regulation takes the form of control to a static equilibrium point, a view which we believe is largely mistaken. 'Homeodynamics' is a term that has been used in the past to try to combine regulation with the idea that physiological processes are oscillatory (Lloyd et al., 2001; Soodak & Iberall, 1978; Yates, 1994). It may be time to revive this terminology.

In past decades, the idea of homeostasis has been tacitly supported by forms of data acquisition that consisted in taking snapshots of cell activity, such as in single-cell RNA-seq experiments (Lähnemann et al., 2020). With new data modalities such as single-cell live imaging of gene expression (Phillips et al., 2017) and time-series RNA-seq (Smith et al., 2020) as well as emerging computational methods like Oscope (Leng et al., 2015)

and advanced analytic protocols (Cortassa & Aon, 2022), we will soon be able to detect oscillatory behaviours in a high-throughput manner, to survey dynamic processes in biology systematically.

Oscillation in health and disease. The dynamic paradigm offers a new approach to our concepts of health and disease. In homeostasis, 'levels' are the goal of the system and the target of therapies. Health is having the right levels, and disease is marked by levels that are either too low or too high. Therapy consists of supplying agonists (if levels are too low) or antagonists (if levels are too high). By contrast, the dynamical conception of health looks at the body's oscillatory processes and asks if they are in the right dynamical ranges, and whether they are properly synchronized or anti-synchronized to other oscillatory processes. In this view, disease can manifest as a loss of oscillation (Knobil et al., 1980; Xiong & Garfinkel, 2022) and/or a loss of synchronization (Glass, 2001; Goldbeter, 2002; Noble, 2006; Tu et al., 2005).

An excellent example of the conflict between the homeostatic and dynamic views of health and disease can be found in recent thinking about psychiatric depression. The homeostatic focus on 'levels', when applied to depression, led to the serotonin hypothesis, which held that depression was caused by low levels of serotonin, and that selective serotonin reuptake inhibitors (SSRIs) would restore this 'imbalance'.

But recent work has cast doubt on the 'serotonin levels' hypothesis. A recent exhaustive meta-analysis of serotonin studies in depression concluded that 'The main areas of serotonin research provide no consistent evidence of there being an association between serotonin and depression, and no support for the hypothesis that depression is caused by lowered serotonin activity or concentrations'. *The New York Times*, reporting this study, noted that 'The most commonly prescribed medications for depression are somewhat effective—but not because they correct a "chemical imbalance"' (Moncrieff et al., 2022; Smith, 2022).

In contrast with this static view, we saw above a radically different picture of depression as caused by a synchronization of bursting oscillations in a certain brain region. The mechanistically derived therapy for this was to abolish the bursting oscillations by blocking the negative-slope resistance region of the neuronal NMDA receptor. However, the causal relationship between synchronization of bursting behaviour and depression is unknown.

Bad vibrations. As we have already seen in the case of depression, not all oscillations serve a positive physiological function. Oscillations in physiology can also be pathological and dysfunctional. One important example of 'bad oscillations' is the onset of seizure, which presents in the EEG as large well-formed oscillatory behaviour (Marten et al., 2009). Bad oscillations also include the onset of muscle tremor in Parkinsonism, stroke and demyelinating diseases. In the latter two cases, the onset of oscillation can be attributed to the destabilization of the negative feedback stretch reflex, which normally maintains positional homeostasis in the limbs. Stroke patients suffer from 'hyperreflexia', increasing the steepness of the negative feedback loop, and patients with demyelinating diseases like MS suffer from increased time delays in those feedback loops, due to lowered axonal conduction velocity.

One significant application of Hopf bifurcation theory in cardiac electrophysiology was to uncover the mechanism of ventricular fibrillation, driven by 're-entrant' waves of excitation. Cardiologists were familiar with re-entry that was guided by anatomical pathways or scar tissue, but had speculated about what anatomically unconfined re-entrant waves might look like: did the activation wavefront rotate with a straight edge, like a radar beacon? Early theoreticians like Weiner and Rosenbluth, Krinsky and Winfree had demonstrated that the form of open-field re-entry in an excitable medium must be a spiral wave. But it was not until the advent of whole-heart computer mapping studies in the 1970s that the first spiral waves in cardiac tissue were recorded (Allessie et al., 1977; Grey et al., 1998). The mapping studies also documented that ventricular fibrillation consisted of multiple meandering spiral waves, continually breaking up and re-forming (Chen et al., 1988; Garfinkel et al., 1997).

The question was then: what causes the transition from a single spiral wave to the multi-wave spiral breakup regime? Theoreticians had demonstrated that a spiral wave can be destabilized by developing a secondary oscillation, caused by a steeply sloped negative feedback loop called the 'restitution curve' (Nolasco & Dahlen, 1968; Qu et al., 1999). The restitution curve gives the duration of the next action potential as a function of the previous diastolic interval. As Nolasco and Dahlen pointed out, this establishes a negative feedback loop: a long action potential duration makes for a shorter following diastolic interval, which makes for a shorter next action potential duration. If the feedback is steep (slope >1) then small differences are magnified, leading to unstable oscillations that break up the wavefront. Therefore, drugs or conditions that lower the slope of the curve to below 1 should have anti-fibrillatory action. A similar link between steeply sloped restitution curves and fibrillation was found to hold for atrial fibrillation as well (B.-S. Kim et al., 2002; Krummen et al., 2012).

This theoretical prediction was validated experimentally: drugs that lowered the slope of the restitution curve, acting through diverse ionic pathways,

prevented spiral wave breakup and the transition to fibrillation (Garfinkel et al., 2000; Riccio et al., 1999).

Glycolysis revisited. Oscillations in glycolysis have recently become a point of debate between the homeostatic and the dynamic worldview. The controversy is about whether these oscillations play a physiological role. A number of authorities have suggested that oscillations in glycolysis are merely an accidental and unwanted side effect of homeostatic negative feedback regulation: 'oscillations become inevitable' (Alberts, 2015), simply because there are many negative feedback loops (Chandra et al., 2011; El-Samad, 2021).

The paradigm of homeostasis, when applied to glycolysis, assumes that the purpose of glycolysis is to maintain constant ATP levels (Chandra et al., 2011). And yet all the available data suggest that glycolysis is oscillatory, and *needs* to be oscillatory, in order to couple to mitochondrial oscillations and to oscillations in intracellular Ca^{2+}. Indeed, as we saw, it has even been suggested that glycolytic oscillations are the engine driving pulsatile insulin secretion in the pancreas (see section 'The intracellular oscillator in the pancreatic β-cell').

In the face of all the data indicating both the fact of oscillatory glycolysis and its functional role, the idea that glycolysis *must* be maintaining constant ATP levels comes therefore not from data, but from a philosophical belief, that control *means* equilibrium control. The virtues of oscillation do not appeal to this control-theory mindset. Rather, oscillation is viewed as highly undesirable, and is disparaged as 'fragility' (seven times in Chandra et al., 2011). But oscillation, as we have seen, is an important functional mode of operation in physiological systems. And oscillatory behaviours are governed by limit cycle attractors that are stable and robust to perturbation, making them responsive, and not at all 'fragile'. Indeed, recent work has suggested that glycolytic oscillations are 'thermodynamically optimal' (Kim & Hyeon, 2021). If the purpose of glycolytic regulation is in fact to produce a (regulated) *oscillatory* response, then glycolytic oscillations may not be just an inevitable side effect of the feedback loops. Instead, they could well be the design principle of glycolytic physiology (Goldbeter, 2018).

'The cell is swell, but the issue is tissue'. The term 'pacemaker' is generally associated with cellular level mechanisms, modelled by ordinary differential equations (ODEs). However, as we have seen, in many cases, pacemaking emerges only at the tissue level. This is the case for both functional oscillations, as in pancreatic islets and the cardiac SAN, and dysfunctional oscillations, as in cardiac Premature Ventricular Complexes. Understanding the mechanism of these tissue-level oscillations will require the use of PDEs, in addition to the usual ODE models found in many studies of pacemaking.

Outlook. It is now over 50 years since the appearance of P.W. Anderson's visionary 'More is different: Broken symmetry and the nature of the hierarchical structure of science' (Anderson, 1972; Stumpf, 2022). Among the broken symmetries that Anderson discussed is the emergence of 'oscillators', which violate time-invariance symmetry. He asserts that 'Temporal regularity [i.e. oscillation] is very commonly observed in living objects', and that the role of this 'regular pulsing' is, first, in 'extracting energy from the environment in order to set up a continuing, quasi-stable process'; second, as a means of 'handling information'; and third, to use 'phase relationships of temporal pulses' to regulate physiological processes. It is time to bring this conception of physiological oscillations to the centre of biological discourse.

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Additional information

Competing interests

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L.X. and A.G.: conception or design of the work; acquisition, analysis or interpretation of data for the work; drafting the work or revising it critically for important intellectual content. Both authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Author's present address

L. Xiong: Department of Integrative Biology and Physiology, University of California, Los Angeles, CA, USA. Email: ivyxiong@ucla.edu

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