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Order From Noise: What the Pacemaker Pays for Stochastic Resonance

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For more than a century, the origin of the heartbeat has remained stubbornly elusive. The classical view was deterministic: a dominant cluster of the fastest cells entrains its neighbors, and the sinoatrial (SA) node delivers a clean, periodic impulse through a coupled system of membrane and Ca^{2+} clocks¹. The paradigm has endured, in part, because of experimental limits of resolution. With conventional optical mapping, pacemaking at the node emerges and progresses smoothly and uniformly from an initiation site. At higher spatial and temporal resolution, cell-to-cell variability emerges, revealing the SA node as a loosely coupled, brain-like network of diversely firing and non-firing cells in which subthreshold Ca^{2+} and voltage fluctuations are dispersed throughout the node^{2,3}.

Within the traditional deterministic framework, variability is treated as disorder, an error term to be averaged away. In this issue of *Circulation Research*, Okamura *et al.*⁴ argue the opposite. Combining compelling experimental observations with theoretical analysis, they demonstrate that variability, in the form of stochastic resonance, is not merely tolerated by the pacemaker network but actively contributes to its function, providing a fundamental mechanism for the initiation and stabilization of cardiac rhythm.

Although the term may be unfamiliar to some readers in the cardiovascular field, stochastic resonance is a well-established concept in physics, neuroscience, and engineering. It describes the counterintuitive phenomenon whereby an optimal level of noise facilitates the activation of a system by enabling otherwise subthreshold signals to cross a critical threshold. Three ingredients are required: a *threshold* that must be crossed to generate an output; a *periodic, but subthreshold, signal* that on its own is insufficient to trigger activation; and a source of *noise*.⁵ On some cycles, noise combines with the weak signal and tips it over the threshold; and because the crossings are paced by the signal beneath them, the output inherits its rhythm. The hallmark is a “Goldilocks” scenario: too little noise and the signal stays silent, too much and the noise overwhelms; only at an intermediate level is noise “just right” for optimal signal transmission (Figure 1A). When performance is plotted as a function of noise intensity, it follows a characteristic bell-shaped, inverted-U

relationship—the signature that distinguishes stochastic resonance from simple stimulation (Figure 1B).

The mapping onto the pacemaker is precise: the critical threshold is the action potential threshold, subthreshold oscillations provide the weak periodic signal, biological variability supplies the noise, and the output is rhythmic firing. In their paper, using isolated rabbit cells, intact mouse tissue and multiscale models, Okamura *et al.*⁴ first demonstrate that noise is real, showing that heterogeneous local Ca^{2+} releases pervade the node. They then assign each cell a *resonance spectrum*: the band of frequencies it can follow—broad in fast cells, narrow in slow and dormant cells. They found that white-noise currents awakened every dormant cell tested and transformed sluggish, irregular activity into faster, more regular firing, tracing the characteristic inverted-U relationship that distinguishes true stochastic resonance from brute excitation.

What elevates the study beyond phenomenology is its mechanistic scope. Within each cell, noise is amplified by the coupled-clock system,⁶ as subthreshold depolarization recruits Ca^{2+} -release units, L-type Ca^{2+} current, and $\text{Na}^+/\text{Ca}^{2+}$ exchange in a positive-feedback cascade that drives small fluctuations toward threshold. At the tissue level, added noise prevents the phase transition into sinus arrest that otherwise occurs when dormant cells predominate. In this framework, noise is doing work precisely where the system is most vulnerable: at low firing rates bordering on failure.

The findings of Okamura *et al.*⁴ build on and decisively advance a growing body of work suggesting that biological noise contributes to pacemaker function. Exploiting rather than suppressing noise is well established in the nervous system,⁷ and the SA node is increasingly viewed as a brain-like network² in which a single dominant pacemaker may not be required.⁸ The application of stochastic resonance to cardiac pacemaking, first introduced by Clancy and Santana,⁹ is a framework that has gained indirect support by work demonstrating that the node's microvasculature varies regionally with myocyte excitability.³ Subsequent work has firmly tied biological noise to the reliability of pacemaking¹⁰, culminating in the mapping of its capillary-mitochondrial substrate onto the node's energetic hierarchy.¹¹ Against this backdrop, Okamura *et al.*⁴ provide an elegant, direct demonstration that stochastic fluctuations promote pacemaker activity. Their analysis focuses primarily on the single cell, where noise is generated and amplified, but the implications extend naturally to the tissue level. In a heterogeneous network, stochastic fluctuations arising in one subpopulation may facilitate excitation in neighboring cells, helping to coordinate activity across the node. Cellular and tissue level mechanisms plausibly represent complementary aspects of a single phenomenon.

A mechanistic demonstration still leaves a deeper question unresolved: Where does the physiological noise originate, and what determines whether one cell exploits it more effectively than another? In the Okamura experiments, noise is imposed through the recording pipette. In the living sinoatrial node, by contrast, it must be generated continuously from within. The spontaneous Ca^{2+} releases that constitute this noise require ongoing sarcoplasmic reticulum reloading by SERCA, among the most ATP-intensive pumps in the cell.¹¹ But the Ca^{2+} clock is dual-purpose. The same Ca^{2+} that drives diastolic

depolarization is taken up by mitochondria, where it stimulates oxidative phosphorylation, creating a beat-synchronized, just-in-time supply of ATP that matches energetic demand. The clock that sets the rhythm also funds it so the cell “pays as it goes”. ATP availability, in turn, depends not only on mitochondrial function but also on the vascular architecture that governs substrate and oxygen delivery. Thus, the noise a cell can make is, at root, an architectural quantity. Amplifying it—the second bill to be paid—costs more still, as coupled-clock feedback relies on that same Ca^{2+} cycling and $\text{Na}^+/\text{Ca}^{2+}$ exchanger flux. Crucially, this heavy metabolic premium is demanded under precisely the low-rate, high-noise conditions of vagal dominance and aging, when supply is least assured. Ultimately, the cellular capacity to convert noise into rhythm cannot exceed its capacity to generate ATP.

One possible answer to this deeper question is suggested by the capillary–mitochondria–ion channel (CMIC) model, which posits that excitability is an emergent property of a single energy supply chain.¹² In this framework, microvascular architecture sets the ceiling on oxygen and substrate supply; mitochondria set the bandwidth, converting substrate into beat-locked, just-in-time ATP; and ion channels and pumps translate local ATP into timing—and noise (Figure 1C). Because that chain varies from cell to cell, so does the noise each cell makes. At a larger scale, it grades across the node, from the superior region, densely vascularized and ATP-rich, to the inferior node, more sparsely perfused and ATP-poor.¹¹ Mitochondrial ATP synthesis is indispensable for pacemaker function. When mitochondria are uncoupled, the cells fall silent, and external pacing does not rescue them.

Viewed this way, Okamura’s findings invite broader interpretation. Instead of being distinct, the resonance spectrum the authors measure and the energetic bandwidth the node sets with its vasculature and mitochondria may be two readings of interlinked processes. If so, the generation and maintenance of physiological noise are themselves energetically constrained. Cells with greater metabolic reserve may therefore be better able to sustain the stochastic Ca^{2+} dynamics that confer robust pacemaking. Because Okamura *et al.*⁴ sorted cells by firing behavior rather than anatomical location, this metabolic interpretation is our own extension rather than a direct conclusion of their study. Nevertheless, it is consistent with evidence that regional variation in the node’s microvasculature parallels regional differences in excitability.³ The determining factor may be the cell’s position on the CMIC chain, with superior-to-inferior offering the most visible gradient, albeit not a hard line. By recruiting dormant cells and steadying slow ones, noise widens the band of rates over which the node fires reliably, thereby expanding the node’s functional bandwidth. Entrainment and stochastic resonance stand in opposite relation to heterogeneity: the first dissolves it into a common rhythm, the second requires it. The coexistence of these mechanisms suggests that heterogeneity is not just tolerated by the SA node, but may contribute directly to its functional resilience.

Importantly, the fluctuations that are amplified are unlikely to represent generic thermal noise alone but instead may emerge from the metabolic and Ca^{2+} -cycling processes that sustain pacemaker activity. The remaining gap is to identify the physiological origin, energetic cost, and regulation of this noise in the intact node. Okamura *et al.*⁴ deliver noise through a pipette and infer network-level behavior from computational models. Among the questions left unanswered is whether stochastic resonance emerges from within SA

node myocytes and discrete cellular endogenous noise, and whether it organizes rhythm in intact tissue. Both questions are now within reach using ultrafast genetically encoded voltage imaging, which can resolve subthreshold fluctuations and action potentials across the entire node. Future studies will be needed to determine whether stochastic resonance is primarily a single-cell phenomenon or also a tissue-level organizing principle, and whether its contribution varies with local energetic state.¹³

If the noise that supports pacemaking is metabolic in origin, then the concept of stochastic resonance carries potential therapeutic implications: energy-starved cells may be restored not by pacing alone but by restoring the ATP-dependent machinery that fails first when supply falls. One candidate is PIP₂ synthesis, as maintaining membrane PIP₂ is more ATP-sensitive than holding membrane potential, and PIP₂ sustains HCN channels and thus the “funny” current (I_f), needed for generating spontaneous depolarizing current in the SAN¹⁴. Parasympathetic slowing and aging may increase reliance on stochastic resonance while constraining energetic reserve, starving the very mechanism that could rescue a faltering node. Sick sinus syndrome may thus be, in part, a failure of energetic reserve, suggesting therapeutic opportunities that extend beyond device implantation to include restoration of microvascular supply and mitochondria–channel coupling.

Okamura *et al.*⁴ have shown that the pacemaker does not merely tolerate its own disorder; it recruits it for fail-safe timing. The deeper lesson lies in where that disorder is born: the noise is created by the pumps that constitute the Ca²⁺ clock, the mitochondria that fuel them, and the vascular architecture that sets how much fuel there is to spend. Noise is the active ingredient, and the ATP that makes and sustains it is the cost of rhythm that holds when the heart falters. Order from noise, in the end, is order the cell can afford.

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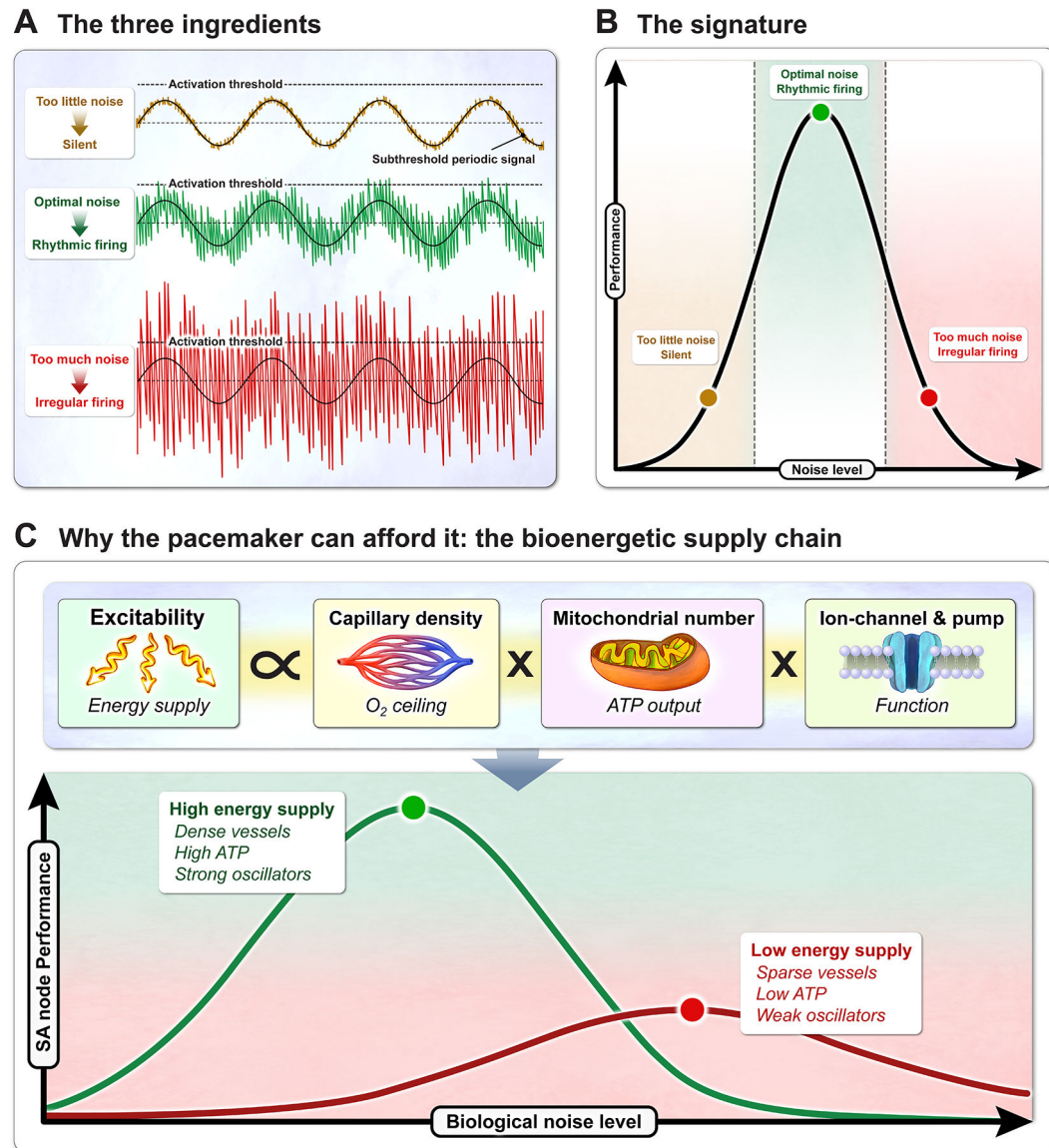


Figure 1. Stochastic resonance, and why the pacemaker can afford it.

(A) The three ingredients of stochastic resonance. A periodic but subthreshold signal never reaches the action-potential threshold on its own (top, silent). An optimal amount of noise lets random fluctuations occasionally sum with the signal to cross threshold, producing rhythmic firing that inherits the signal's periodicity (middle); too much noise scatters the crossings (bottom). (B) The signature: rhythm reliability (coherence) versus noise traces an inverted-U, peaking at an intermediate, optimal level. (C) Why it works in the SA node. Excitability scales with the bioenergetic supply chain: it is proportional to capillary density (which sets the O_2 ceiling) $\times$ mitochondrial number (ATP output) $\times$ ion-channel and pump function, which together set each cell's subthreshold noise and oscillator strength. Because that chain varies cell-to-cell and (more coarsely) region to region, each cell can occupy one of two idealized coherence-versus-noise curves (colored markers): an ATP-rich, high-supply cell (e.g., superior node) with strong oscillators that resonates near its optimum (high

coherence), and an ATP-poor, low-supply cell (e.g. inferior node) with weaker oscillators that runs noise-rich and off-optimum, so its coherence stays low.

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