

Emergent global oscillations in heterogeneous excitable media: The example of pancreatic β cells

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Using the standard van der Pol–FitzHugh–Nagumo excitable medium model, I demonstrate a generic mechanism, diversity, that provokes the emergence of global oscillations from individually quiescent elements in heterogeneous excitable media. This mechanism may be operating in the mammalian pancreas, where excitable β cells, quiescent when isolated, are found to oscillate when coupled, despite the absence of a pacemaker region.

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I. EXCITABLE MEDIA

An excitable element is defined by its response to a perturbation: whereas a small disturbance causes merely an equally small response, a perturbation above a certain threshold in amplitude excites a quiescent element that then decays back to quiescence during a refractory period in which it is unresponsive to further excitation. Such elements, when coupled to their neighbors into an assembly, become an excitable medium [1]. These have attracted an enormous amount of interest from different areas of science: the Belousov-Zhabotinsky reaction [2], plankton populations [3], and the heart [4,5] are just a few well-known examples. Oscillations in excitable media such as the heart are produced by forcing the medium from a pacemaker region; in other cases all individual elements of the medium oscillate when isolated: they are all pacemakers, and the medium is then oscillatory rather than excitable. However, this need not necessarily be so. In this paper I present a generic mechanism for the production of global oscillations; the introduction of diversity amongst the elements leads to the destabilization of the quiescent state of an excitable medium and to the emergence of global oscillations even when each individual element of the medium is quiescent in isolation. I argue that an instance of such behavior may be found in a physiological example of an excitable medium without a pacemaker: the pancreatic β cells of mammals.

In the mammalian pancreas are encountered structures where insulin is produced. These, the islets of Langerhans, consist of several thousand spherical cells clustered together and electrically connected via resistive gap junctions [6]. The vast majority of these cells, those that produce insulin in response to the level of glucose in the blood, are of a type known as β cells. In many mammals, including humans, the electrical potentials of β cells in an islet are found by experiment to cycle synchronously in slow oscillations termed bursts [7]. On the other hand, an individual β cell when removed from the islet does not oscillate in this way [8], but rather is excitable. An islet of Langerhans, then, like the heart, is a physiological excitable medium. But in the pancreas, unlike in the heart, oscillations of the excitable me-

diu are not driven by pacemaking cells. The challenge is to understand the origin of these oscillations. Various detailed biophysical models of oscillations in networks of pancreatic β cells have been proposed, in which the importance of the heterogeneity of individual cells [9] and the emergence of oscillatory behavior upon coupling nonoscillatory cells [10,11] have been highlighted. Here I take a different approach in which I bring together these two ideas while simplifying the physics as far as possible to produce a minimal qualitative model for the phenomenon. I demonstrate that given diverse excitable elements, coupling these into a heterogeneous excitable medium can lead to the emergence of oscillations: that diversity is a generic mechanism for the emergence of global collective behavior not just in β cells, but in any heterogeneous excitable medium.

II. van der POL–FITZHUGH–NAGUMO MODEL

To illustrate the mechanism, and having in mind its application to pancreatic β cells, I take an electronic circuit model as a caricature of a physiological excitable medium and as representative of excitable media in general. Each element of the medium is a circuit shown in Fig. 1(a). In physiological terms, the capacitor C represents a cellular membrane charged by E , characterizing ion pumps, and drained by a nonlinear resistance n_1 across C . This nonlinear element, a device with a range of negative resistance, could be a tunnel diode, for example, and should have the cubic $i-v$ characteristic of Fig. 1(b). The inductance L models the finite switching time of the ion channels in the membrane. The circuit is then mathematically described by the van der Pol–

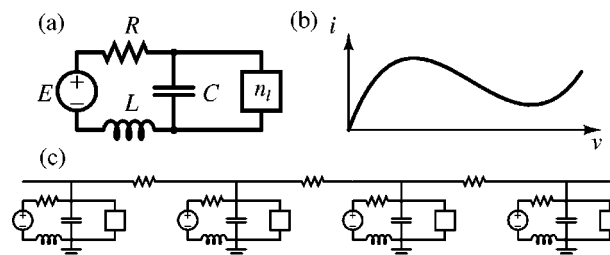


FIG. 1. An electronic excitable medium. (a) An element of the medium: the circuit and (b) the $i-v$ characteristic of the nonlinear element n_1 : the cubic function $i \propto v^3/3 - v$. (c) Resistive (diffusive) spatial coupling, illustrated for simplicity here in one dimension.

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FitzHugh–Nagumo equations [12–15]

$$\dot{\psi} = \gamma(\eta - \psi^3/3 + \psi), \quad (1a)$$

$$\dot{\eta} = -\gamma^{-1}(\psi + \nu + \beta\eta). \quad (1b)$$

Variables ψ and η are, respectively, proportional to the potential difference across the nonlinear device n_i and the current through the supply; the parameter ν is proportional to the potential E , β to the resistance R , and γ to the quotient L/C . The equations have an equilibrium point that is stable for $|\nu| > \Xi$ and unstable for $|\nu| < \Xi$, where

$$\Xi = \sqrt{\gamma^2 - \beta} \frac{3\gamma^2 - 2\gamma^2\beta - \beta^2}{3\gamma^3}, \quad (2)$$

so a circuit element is oscillatory for $|\nu| < \Xi$ and excitable for $|\nu| > \Xi$ in the vicinity of $|\nu| = \Xi$ [16]. In physiological terms, oscillatory behavior corresponds to bursting ($|\nu| < \Xi$), and excitability to silent and continuously active cells; one case being $\nu < -\Xi$ and the other $\nu > \Xi$.

Each of these elements is coupled to its nearest neighbors in one, two, or three dimensions to become an excitable medium. The coupling in biological and chemical excitable media is diffusive, though elastic excitable media that arise in electronics and rheology have also recently been considered [17,18]. Either or both of Eqs. (1) may host a coupling term, depending on the medium being modeled. Here, to imitate a cellular excitable medium, the circuits are coupled resistively as shown in Fig. 1(c). This leads to a diffusive term in Eq. (1a):

$$\dot{\psi} = \gamma \left[\eta - \psi^3/3 + \psi + \kappa \sum_{i=1}^n (\psi_i - \psi) \right], \quad (3)$$

where the i 's represent the n neighboring elements, and κ is the coupling strength or diffusion coefficient. In the continuum limit, the coupling term

$$\kappa \sum_{i=1}^n (\psi_i - \psi)$$

becomes the Laplacian $\kappa \nabla^2 \psi$; this is the classical van der Pol–FitzHugh–Nagumo model of an excitable medium, extensively analyzed in the excitable spiral-wave regime [16].

III. HETEROGENEOUS EXCITABLE MEDIA

Consider now what happens if we introduce a diversity of parameter values for the different elements of the medium. The position of the stable equilibrium point for Eqs. (1) depends on the parameters ν and β , so if we introduce a spread of parameter values across the medium, we change the equilibria of individual elements and the coupling between them

$$\kappa \sum_i (\psi_i - \psi)$$

will no longer be zero in the quiescent state. In such a heterogeneous medium, the dynamics of each element may be

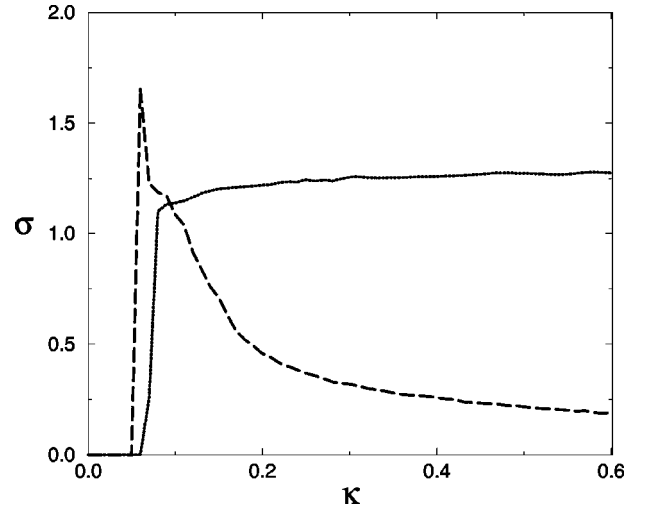


FIG. 2. Dotted line: Temporal standard deviation of ψ , σ_t [Eq. (4)], shows the emergence of oscillatory behavior from a heterogeneous excitable medium with increasing coupling κ . Dashed line: Standard deviation of times t_{\max} of maxima of ψ , σ_s [Eq. (6)], demonstrates increasing synchronization of the oscillations with increasing coupling κ . The numerical results are for a van der Pol–FitzHugh–Nagumo medium with $\beta=0.5$, and $\gamma=2$, with $4 \times 4 \times 4$ elements randomly assigned $\nu=0.76$ or $\nu=-0.76$, both of which are individually parameter values for which the medium is excitable rather than oscillatory, and thus quiescent unless excited.

analyzed to a good approximation by treating the influence of the rest of the medium as a type of external signal ε . This is equivalent to setting

$$\varepsilon = \kappa \sum_{i=1}^n (\psi_i - \psi)$$

whence the extra term ε may be removed from Eq. (3) by renormalizing ν , and the element is modeled by Eqs. (1) with an effective ν , $\nu' = \nu - \beta\varepsilon$; the medium is now oscillatory for $|\nu - \beta\varepsilon| < \Xi$. Hence a small ε can push an excitable element with $|\nu| > \Xi$ near to the excitable-oscillatory threshold over into the oscillatory regime. This diversity mechanism is not specific to the van der Pol–FitzHugh–Nagumo model, but rather is generic; it can be applied to any heterogeneous excitable medium in which the position of equilibrium is parameter dependent and there is an oscillatory regime reachable in the extended parameter space formed by an uncoupled element's parameters plus the extra term ε .

Let us examine the emergence of oscillations through diversity in a simple example using the van der Pol–FitzHugh–Nagumo model. In Fig. 2, plotted (dotted line) against coupling κ , is the temporal standard deviation of ψ_j for a sample element j ,

$$\sigma_t = \sqrt{\frac{1}{t_f - t_i} \sum_{t=t_i}^{t_f} \psi_j^2(t) - \bar{\psi}_j^2} \quad (4)$$

for a heterogeneous van der Pol–FitzHugh–Nagumo medium consisting of elements randomly assigned the parameter values $\nu=0.76$ or $\nu=-0.76$, together with the other parameters $\beta=0.5$, $\gamma=2$. Both of these parameter sets on their own, produce excitable rather than oscillatory elements,

which are quiescent without excitation, so at $\kappa=0$, σ_t is zero. But in Fig. 2, we see that as the coupling κ between elements passes a threshold, σ_t , which is measuring the temporal activity of the medium, increases from zero, meaning that the medium has spontaneously begun to oscillate; diversity has provoked the emergence of global oscillations from individually quiescent elements. In this example, each element is connected in a cubic lattice with six neighbors. Elements throughout the lattice are randomly assigned one of two parameter values: $\nu=0.76$ or $\nu=-0.76$. On average, any element will find that half its neighbors share the same parameter value, and half have the other value. At quiescence, the coupling between those with the same parameter values is zero, while between those with different parameter values it is

$$\varepsilon = \kappa \sum_{i=1}^m (\psi_i - \psi) = 3\kappa\Delta\psi,$$

since $m=3$ is the average number of neighbors with different parameter values. In the van der Pol–FitzHugh–Nagumo model, the change in the equilibrium value of ψ is $\Delta\psi \approx -\Delta\nu$. For our example, $\nu = \pm 0.76$, which makes $\Delta\nu = 2\nu$. In this case, then, the new effective ν is

$$|\nu'| = |\nu - \beta\varepsilon| = |\nu(1 - 6\beta\kappa)|. \quad (5)$$

We can see in Fig. 2 that the medium begins to oscillate when $\kappa \approx 0.06$. For the numerical values $\beta=0.5$, $\gamma=2$, $|\nu|=0.76$, used in Fig. 2, $|\nu'|=0.62$ when $\kappa=0.06$, which corresponds closely to the threshold for oscillation in a homogeneous van der Pol–FitzHugh–Nagumo medium given by Eq. (2) for these parameter values: $|\nu| = \Xi = 31/96\sqrt{7/2} = 0.60412$.

To simplify the above analysis as far as possible, I have considered a heterogeneous medium with just two states. The diversity mechanism works in the same way in a medium with a continuum of states, in which a proportion of elements—those whose uncoupled state falls within the parameter range for autonomous oscillation—may be intrinsic oscillators. However, such intrinsic oscillators do not act like the pacemaker region of a driven medium. Scattered randomly throughout a quiescent medium, they are neither sufficient nor necessary for global oscillations. Whether or not such intrinsic oscillators are found in a heterogeneous medium depends on whether an oscillatory regime exists within the parameter range of heterogeneity for an element when the system coupling term ε is zero. In the van der Pol–FitzHugh–Nagumo model this corresponds to whether the inequality $|\nu| < \Xi$ is satisfied without coupling. For β cells, the majority of experiments have found no evidence for intrinsic oscillations, and that isolated cells are exclusively excitable: either silent, or continuously active [19].

IV. SYNCHRONOUS AND ASYNCHRONOUS OSCILLATIONS

The diversity mechanism applies very naturally to physiological excitable media, since homogeneous cells are a mathematical fiction. The underlying dynamics is such that there is a threshold for a quiescent heterogeneous medium to

achieve criticality and cross the excitable-oscillatory boundary. This demands sufficient connectivity between neighboring elements in terms of the number of connections (dimensionality of the system) and the coupling strength (diffusion coefficient), together with sufficient heterogeneity between elements. While the threshold-crossing mechanism of diversity is generic, what happens on the other side of the threshold once the medium has become oscillatory is not. In some oscillatory media, synchronous global oscillations are stable, whereas in others these are unstable to spatial perturbations leading to the formation of propagating fronts or other spatial phenomena [20]. The standard deviation across the medium of times $t_{\max}(k)$ of maxima of ψ_k for elements k ,

$$\sigma_s = \sqrt{\frac{1}{N} \sum_{k=1}^N t_{\max}^2(k) - \bar{t}_{\max}^2}, \quad (6)$$

measures the spatial activity of the medium: the smaller this quantity, the greater the synchronization throughout the medium. In our example, σ_s plotted (dashed line) against coupling κ in Fig. 2 indicates that at the minimum coupling necessary for oscillatory behavior, the heterogeneous medium oscillates with little synchronization. As the coupling is increased, however, the synchronization rapidly improves, shown by the steep decay in the standard deviation of the maxima at larger κ .

If the synchronized state is an attractor for the homogeneous medium, then we might expect the behavior in the heterogeneous case to reflect this. Let us consider for a moment the related area of synchronization, phase and frequency locking, or entrainment of coupled oscillators, a vast field of study initiated by Huygens with his observations of synchronization of two pendulum clocks coupled by a common mounting [21–23]. Winfree [24] showed that synchronization emerges in a population of heterogeneous oscillators as coupling exceeds a critical threshold, in a manner reminiscent of a thermodynamic phase transition. Following this work Kuramoto *et al.* [25–27] developed his theoretical model whose tractability helped to advance significantly the study of coupled heterogeneous oscillators. This undergoes two transitions as the spread of natural frequencies is reduced, or the coupling is increased: first comes the onset of partial synchronization, which is followed by complete synchronization even with some residual heterogeneity among the elements. More recently a physically realizable version of the Kuramoto model has been proposed: an array of heterogeneous Josephson junctions [28]. Strong coupling between oscillators allows modification of the amplitude as well as the phase of an oscillator, which can give rise to phenomena such as amplitude death [29–31] (here however we are in the weak-coupling regime). Finally, if synchronous global oscillations are unstable in the homogeneous case, the addition of a certain amount of heterogeneity can even lead to an increase in synchronization, as studies with locally coupled limit-cycle oscillators have found [32,33].

We can obtain a theoretical understanding of synchronization in a homogeneous oscillatory medium by calculating analytically the Floquet exponents that indicate the linear stability of limit cycles against spatial perturbations. This I have done for the van der Pol–FitzHugh–Nagumo model in Fig. 3, where I show a family of dispersion relations for

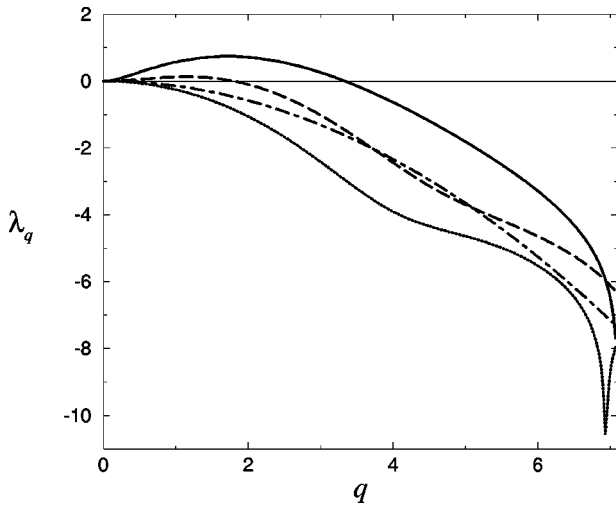


FIG. 3. Dispersion relations show destabilization of synchronous global oscillations in the van der Pol–FitzHugh–Nagumo model for a range of ν in the oscillatory regime. Here $\beta=0.5$, $\gamma=2$, $\kappa=0.09$: shown are curves for $\nu=0.592$ (dotted), $\nu=0.596$ (dashed), $\nu=0.600$ (solid), and $\nu=0.604$ (dot dashed). The maximal Floquet exponent λ_q gives the growth rate per period of a perturbation of wave number q (Ref. [17]). For $\nu=0.596$ and $\nu=0.600$, the dispersion relation λ_q as a function of q is positive for a range of q , meaning that there is a set of wavelengths for which perturbations grow exponentially. Outside this range of ν values, the dispersion relation is never positive, implying linear stability of synchronous global oscillations under perturbations of all wavelengths.

different values of ν . A positive value for the maximal Floquet exponent illustrates the destabilization of synchronous global oscillations of the medium for a range of ν for a particular value of β . In the case shown, for which, as in Fig. 2, $\beta=0.5$, $\gamma=2$, the dispersion relation λ_q is positive for a range of wave numbers $0 < q < q_c$ for ν values close to the excitable-oscillatory threshold of the medium. For these ν values, synchronous global oscillations are unstable to perturbations of wavelengths $1/q_c < \lambda < \infty$ when these wavelengths fit within the system size. For all other ν values in the oscillatory regime, global synchronous oscillations of the homogeneous medium are linearly stable. This is demonstrated numerically in Fig. 4 in which the measures of activity and spatial synchronization σ_t and σ_s for a homogeneous van der Pol–FitzHugh–Nagumo medium with $\beta=0.5$, $\gamma=2$, and $\kappa=0.09$ are plotted against ν . The dotted line σ_t shows that the medium is oscillatory up to $\nu=0.604$, then excitable, as Eq. (2) demands. The dashed line σ_s is positive near $\nu=0.6$, showing that global oscillations are unstable for a range of ν values; outside this range the standard deviation σ_s is zero, as the medium oscillates synchronously. The inset highlights the range of ν in which destabilization occurs.

In a homogeneous van der Pol–FitzHugh–Nagumo excitable medium we have seen that there are parameter ranges in which synchronous global oscillations are stable, and others in which they are not. The behavior of the homogeneous case helps us now to understand the heterogeneous medium. Figure 2 displays poor synchronization of the medium immediately following the emergence of oscillations, which then improves with increasing κ : σ_s peaks, then declines rapidly before leveling off. This can be seen as a combination of the

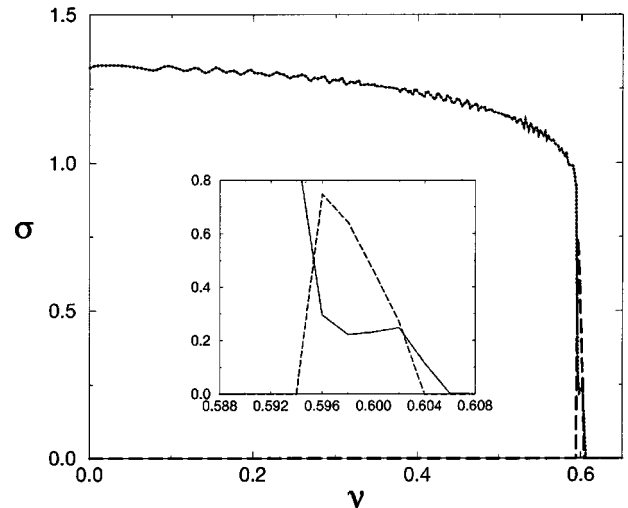


FIG. 4. Dotted line: Temporal standard deviation of ψ_j , σ_t [Eq. (4)], illustrates the transition to oscillatory behavior in a homogeneous excitable medium with decreasing ν . Dashed line: Standard deviation of times t_{\max} of maxima of ψ , σ_s [Eq. (6)], shows the destabilization of synchronous global oscillations in a range of ν just above the excitable-oscillatory threshold. The inset highlights the narrow range $0.588 < \nu < 0.608$ in which the destabilization occurs. Numerical results are for a van der Pol–FitzHugh–Nagumo medium with $4 \times 4 \times 4$ elements with $\beta=0.5$, $\gamma=2$, and $\kappa=0.09$. From Eq. (2), the medium is oscillatory for $|\nu| < \Xi = 0.060412 \dots$

intrinsic dynamics of the van der Pol–FitzHugh–Nagumo medium together with the synchronizing effect of coupling. Upon the emergence of oscillations in the heterogeneous medium, the effective ν , ν' [Eq. (5)], is within the range of values near to the excitable-oscillatory transition for which synchronous oscillations are unstable. As the coupling κ increases, ν' drops below this range and the synchronization immediately improves. The further slower decrease in σ_s is due to the additional synchronizing effect of coupling.

What might be the relevance of the synchronization of global oscillations for the β cells of the pancreas? The pancreas may be contrasted with another physiological excitable medium: the heart. While in the heart, synchronous oscillations are vital to the survival of the organism—the unsynchronized state of the fibrillating heart is fatal if not immediately resynchronized with an electric shock—it is not obvious why this should be so for β cells. Although in humans and in mice the oscillations are synchronous, in other mammals there is less evidence for this. While physiologists may yet provide a biological rationale for synchronization, it may be that it is not a physiological necessity but simply a byproduct of the emergence of oscillations: the pancreatic β cells of some species may be operating in a parameter range in which synchronous global oscillations are stable, while in others, less investigated up to now, spatial patterns may be found in the oscillations.

V. CONCLUSIONS

I have argued that diversity acts at a fundamental level in the dynamics of heterogeneous excitable media to produce global oscillations. Another related theme of study has sub-

jected excitable systems to various types of forcing. A periodically forced van der Pol–FitzHugh–Nagumo element shows behavior similar to a driven oscillator: phase locking, quasiperiodicity, period doubling, and chaos [34]. A quiescent excitable element may be excited by driving with a combination of a periodic subthreshold signal plus noise [35] or with an aperiodic subthreshold signal plus noise [36], phenomena which have been termed stochastic resonance, or with noise alone [37], when the phenomenon has been termed coherence resonance. Here, we have seen that even without any external forcing, either periodic or stochastic, a heterogeneous excitable medium can become self-excited to produce global oscillations.

To what extent is this general analysis applicable to pancreatic β cells? β cells are diffusively coupled excitable elements, although more complicated than van der Pol–FitzHugh–Nagumo elements, with more internal variables and parameters. Their heterogeneity has been made manifest in studies demonstrating differing rates among β cells of insulin synthesis and secretion [38–42], of glucose metabolism [43], of changes in calcium concentration [44,45], and of changes in electrical activity [46]. Physiologists have sus-

pected the importance of this variability [47]. β cell oscillations, or bursts, are more complex than the simple oscillations of a van der Pol–FitzHugh–Nagumo-type relaxation oscillator, but the basic mechanism that diversity provokes the emergence of oscillations, remains the same and provides a qualitative explanation for the emergence of global oscillations in the β cells of the mammalian pancreas. Heterogeneity is the norm in biological excitable media, so there may well be other instances awaiting discovery of this mechanism in operation.

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