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On the coherent behavior of pancreatic beta cell clusters

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ABSTRACT

Beta cells in pancreas represent an example of coupled biological oscillators which via communication pathways, are able to synchronize their electrical activity, giving rise to pulsatile insulin release. In this work we numerically analyze scale free self-similarity features of membrane voltage signal power density spectrum, through a stochastic dynamical model for beta cells in the islets of Langerhans fine tuned on mouse experimental data. Adopting the algebraic approach of coherent state formalism, we show how coherent molecular domains can arise from proper functional conditions leading to a parallelism with "phase transition" phenomena of field theory.

1. Introduction

Islets of Langerhans in the pancreas are ellipsoidal clusters of excitable endocrine cells that ensure blood glucose homeostasis. Alpha, beta, delta and PP cells form this particular structure. Specifically beta cells are able to lower glycemic level by releasing insulin [1]. In rodents, these cells are clustered in the central core of the islet surrounded by peripheral alpha cells, and are coupled through specific connections, the gap junctions [2–5]. In response to glucose uptake from extracellular space, beta cells within the islet modify their membrane potential, exhibiting slow oscillations with superimposed action potentials (bursting activity) [1]. This characteristic behavior leads to oscillations of the intracellular calcium concentration that triggers pulsatile insulin release [6,7]. On the other hand, isolated beta cells show an irregular spiking activity in response to glucose stimuli. Experimental measurements show moreover that beta cells electrical activity is synchronized over the islet [6,8,9]. Such an observed feature highlights that a coherent intercellular correlation extending over the islet's volume can be established under proper functional conditions and glucose concentrations, providing the motivation for the study presented in this paper. We indeed analyze such a behavioral property of the cells in the frame of a Hodgkin–Huxley [10] type model also considering the kinetics of the stochastic K–Ca channels [11] (calcium-dependent potassium channels; here Ca stands for the ion Ca^{2+}). We thus focus our study on the dynamics of the membrane potential in variable scale clusters in connection with intracellular calcium concentration and the activation of potassium and calcium channels. Our numerical simulations agree with the observed possibility of formation of coherent molecular domains and show how this depends on glucose concentrations and on the islet size. In particular, we find that the power density spectrum (PDS) of membrane voltage exhibits scale free self-similarity features with respect to frequency occurring with different self-similarity dimension in different frequency intervals and show how such a feature is indeed an evidence of coherent molecular dynamics. In our discussion, we use the algebraic approach of the coherent state formalism through which the isomorphism is shown to exist between the linear fit of the log–log plot of PDS/frequency and the squeezed coherent state algebraic structure. The plan of the paper is the following. The mathematical modeling is introduced in Section 2, while numerical simulations and results are presented in Section 3. The notions of (fractal) self-similarity dimension and squeezed coherent states are given in Section 4, where the algebraic isomorphism between self-similarity and coherent states is also discussed. Section 5 is devoted to conclusions.

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2. Mathematical modeling

An extended version of the stochastic multi-cell SRK (Sherman–Rinzel–Keizer) model [12], based on mouse electrophysiological data, was adopted to study bursting activity of beta cells cubic clusters of variable size for different glycemic levels. Such a Hodgkin–Huxley type model permits to reproduce isolated and coupled dynamics of beta cells. This is because of the stochastic formulation of the high conductance K–Ca channel gating. Single gating events of this specific type of channel can lead the cell to an active or a silent state, making possible to observe a spiking activity in an isolated cell. Thanks to "channel sharing", coupled cells are able to share the entire population of K–Ca channels [11,12], overcoming noise and giving rise to bursting behavior, a characteristic electrical pattern observed experimentally in beta cells within the islet. The model's equations for the i-th cell are:

$$C_m \frac{dV}{dt} = -I_{ion} - \bar{g}_{K\text{-}Ca} p (V - V_K) - g_c \sum_{j \in \Omega} (V - V_j)$$

$$\frac{dn}{dt} = \lambda \left[\frac{n_\infty - n}{\tau_n(V)} \right]$$

$$\frac{dCa}{dt} = f[-\alpha I_{Ca} - k_{Ca} Ca]$$

$$\langle p \rangle = \frac{Ca}{K_d + Ca}$$

$$I_{ion} = I_K + I_{Ca} = \bar{g}_K n (V - V_K) + \bar{g}_{Ca} m_\infty(V) h(V) (V - V_{Ca})$$

$$m_\infty(V) = \frac{1}{1 + \exp[(V_m - V)/S_m]}$$

$$h(V) = \frac{1}{1 + \exp[(V - V_h)/S_h]}$$

$$n_\infty(V) = \frac{1}{1 + \exp[(V_n - V)/S_n]}$$

$$\tau_n(V) = \frac{c}{\exp[(V - \bar{V})/a] + \exp[(V - \bar{V})/b]},$$

where the dynamical variables V, n, Ca have to be understood as V_i, n_i, Ca_i. The ODE system models the dynamics of the membrane potential V, the potassium channel activation level n and the intracellular calcium concentration Ca. C_m represents the membrane capacitance; $m_\infty(V)$ and $n_\infty(V)$ are sigmoid functions defined upon constant values of the voltage; in particular, they represent the steady states of the calcium and potassium currents, respectively, once a step function of the voltage is imposed; $h(V)$ is the inactivation curve of calcium channels; $\tau_n(V)$ is the voltage dependent time constant of potassium channels fine tuned by the parameter λ; $\bar{g}_K$, $\bar{g}_{Ca}$ and $\bar{g}_{K\text{-}Ca}$ represent the whole cell conductances of potassium, calcium and potassium–calcium dependent ionic channels, respectively; g_c is the strength (conductance) of coupling between two adjacent cells due to gap junctions, in a 3D Von Neumann neighborhood (Ω) of the cell modified to take account of different communication rules on the boundary region (in Fig. 1 is shown a $5 \times 5 \times 5$ cluster and the neighborhood considered for a central cell); p is the fraction of open K–Ca channels whose transition events are obtained as evolution of a stochastic process described in the following; V_K and V_{Ca} are the potassium and calcium equilibrium potentials; f is a fixed parameter which slows down intracellular calcium dynamics; the factor α converts current units in concentration units; k_{Ca} represents the rate at which calcium is pumped out from cytosol to extracellular space; K_d is a factor that depends on K–Ca channels kinetics; a, b, c, and $\bar{V}$ are parameters used to fine tune the dependence of the potassium channel time constant on the membrane voltage; V_n, V_m, V_h, S_n, S_m and S_h are parameters used to fit the activation and inactivation curves of the ion channels.

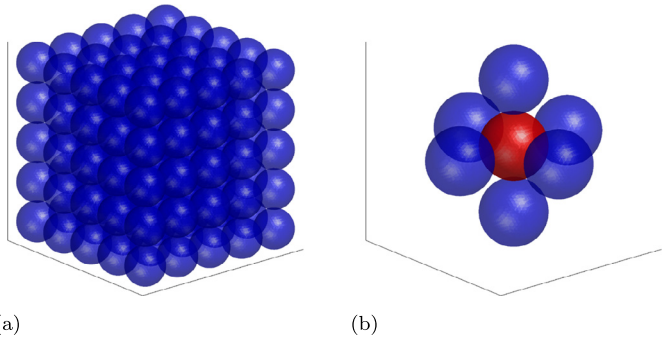

Fig. 1. 3D view of a $5 \times 5 \times 5$ cluster (a) and Von Neumann neighborhood (b) for a central cell, plotted in red. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.1. Stochastic gating of K–Ca channels

Transition events of the K–Ca channels were computed with the use of a two state Markov process for each ionic channel. Following [11], a two-state kinetics was adopted, i.e.:

$$\mathcal{C} \underset{1/\tau_o}{\overset{1/\tau_c}{\rightleftharpoons}} \mathcal{O}, \qquad \tau_o = \tau_c \frac{Ca_i}{K_d}.$$

Here τ_o and τ_c are the mean opening and closing times. Keeping τ_o fixed, τ_c varies as a function of intracellular calcium. The probabilities that a channel in a specific state makes a transition in a fixed time window are given by:

$$\frac{\Delta t}{\tau_c} = \text{Prob}\{s(t) = \mathcal{O}, t + \Delta t \mid s(t) = \mathcal{C}, t\},$$

$$\frac{\Delta t}{\tau_o} = \text{Prob}\{s(t) = \mathcal{C}, t + \Delta t \mid s(t) = \mathcal{O}, t\};$$

where $s(t) \in \{C, O\}$ is a stochastic variable and Δt is the considered time step [13]. Considering 600 channels of K–Ca type per cell, each two-state process was resolved with the use of a Monte Carlo simulation, computing the fraction of open channels at every integration time step of the model equations.

2.2. Glucose feedback

As in Ref. [14], glucose feedback was modeled tuning the calcium removal rate parameter in order to reproduce experimentally observed beta cells activity at specific blood glucose concentrations $[G]$. At about $[G] = 5.5$ mM and $[G] = 16.6$ mM, a silent-bursting and a bursting-continuous spiking transition, respectively, can be observed in beta cells membrane potential. These behaviors can be obtained in the model setting $k_{Ca} = 0.02\ \text{m s}^{-1}$ and $k_{Ca} = 0.09\ \text{m s}^{-1}$. Considering these observations, a simple linear function was adopted to achieve the feedback:

$$k_{Ca} = A[G] - B \quad \text{for } [G] \geq 2.33\ \text{mM},$$

where $A = 6.3 \cdot 10^{-3}\ \text{m s}^{-1}\,\text{mM}^{-1}$, $B = 0.0147\ \text{m s}^{-1}$ and $[G]$ is the glucose concentration. A full list of the adopted parameters is given in Appendix A.

3. Numerical simulations

A fourth order Runge–Kutta method with a fixed time step of 0.1 ms was adopted to solve the ODE system. The global model was implemented in a C++ code. Cells' voltage membrane signals