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On the emergent dynamics and synchronization of β-cells networks in response to space-time varying glucose stimuli

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ABSTRACT

Recent findings based on calcium fluorescence imaging of pancreatic islets, also combined with optogenetic techniques, showed that β-cells synchronization underlie a small-world and scale-free functional organization, where specified hubs are responsible of the emergent coordination in electrical activity. Despite these features were suggested to be linked to an efficient spreading of information and calcium waves, it is still unclear from what they emerge, if they can still be observed when different dynamical variables are used to build functional networks, and how they vary upon changes in control parameters. In this work we investigate this aspect with a novel hybrid discrete-continuum mathematical model, coupling the stochastic electrical dynamics of β-cell clusters to nonlinear reaction–diffusion of glucose. By analyzing cells activity with the use of dynamical functional networks computed on the correlations between cells membrane voltage signals, we recover functional features in accordance to experimental observations. We further show that such properties are observed during specific phases of the complex electrical bursting oscillation, and are affected by glucose diffusion. These results suggest that functional properties derived from experimental calcium signals, on a time scale on the order of tens of seconds, are also recovered at a much faster time scale, i.e., on the order of hundreds of milliseconds. We finally describe how such functional features are strongly linked to synchronization patterns, in which coordinated sub-clusters of cells naturally emerge from the underlying dynamics.

1. Introduction

β-cells in the endocrine pancreatic islets respond to blood glucose stimulation by releasing insulin. Hormone release is driven by a cascade of biochemical processes leading to a calcium-driven secretion. Specifically, a complex electrical bursting activity drives a pulsatile release both at the single cell and at the islet level [1,2], thus implying a long-range synchronization [3,4]. A large amount of studies in rodents show that gap-junction electrical coupling has a key role in such coordination of cells activity, homogenizing the islet response to glucose stimuli [5,6], and filtering the noisy perturbations of the membrane voltage induced by the intrinsic stochastic activity of ion channels on cells surface [7–9], with significative effects on the emergent bursting robustness and insulin release [10]. In addition, another key factor in β-cell synchronization is represented by the glucose concentration to which is exposed each cell within the islet [11]. A homogeneous glucose stimulating concentration across the islet can lead to a full activation or to a globally silent response of the cellular population while stimulating glucose gradients can evoke wave-block phenomena [1,12,13]. More recent findings based on calcium fluorescence imaging of pancreatic islets [14–16], also combined with optogenetic techniques [16], further showed that cells synchronization underlie a small-world and scale-free functional organization, where specified hubs are responsible of the emergent coordination in electrical activity. However, despite these features were suggested to be linked to an efficient spreading of information and calcium waves, it is unclear their origin, if they can still be observed when different dynamical state variables are used to build functional networks, and how they vary upon changes in control parameters.

In this work we investigate the functional organization of β-cells aggregates by combining a discrete stochastic mathematical model of β-cell electrophysiology [8] to a continuum diffusive process of glucose [17,18]. Specifically, we study the emergent activity of cubic cell clusters stimulated by a heterogeneous glucose field whose space-time profiles are affected by spreading across

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the domain and by the cells uptake of metabolite. We model homogenous and gradient glucose stimuli with the aim to analyze synchronization patterns in presence of symmetric and asymmetric stimuli. Such hybrid modeling (discrete-continuum) represents a novelty in the investigation of β-cells dynamics. Coordination of cells population is then studied through a functional network approach, in line with experimental studies performed on mouse pancreatic islets [14–16]. However, while these experimental investigations analyze functional networks reconstructed from fluorescence calcium signals, in this work we construct such networks by using the computed membrane voltage time series. This choice permits to investigate synchronization by taking into account the complex bursting oscillations usually recorded from β-cells within islets or coupled clusters. Our results show that similar functional properties with respect to experiments are recovered, that they emerge within specific phases of the bursting oscillation cycle, and that they are modified by time-varying glucose stimuli. We finally highlight that the observed functional properties are closely related to phase-locking phenomena in the electrical oscillations of β-cells, therefore linking the emergent functional topology to the underlying dynamics of the system.

The paper is organized as follows. In Section 2 we introduce the mathematical model used to reproduce β-cell clusters electrophysiology and glucose diffusion across the clusters, describing the adopted implementation strategies. In Section 3 we describe the performed simulations and analyze the results. The outcomes and the effects of spatiotemporal inhomogeneous glucose stimulations on β-cells synchronization are discussed in Section 4. Section 5 is devoted to conclusions and future perspectives of the work.

2. Mathematical modeling

We have developed a new hybrid mathematical framework to investigate glucose diffusion and the evoked electrical behavior of β-cells assemblies by combining existing models of glucose diffusion and β-cells electrophysiology. Specifically, a continuum formulation was adopted to compute glucose space-time profiles across cell clusters by assuming that cells fill the entire 3D space and their membranes allow glucose uptake processes, i.e., every domain point is a portion of β-cell. We thus obtained a glucose field in the whole cubic domain, and we embedded in such domain a lattice of cells. We modeled cubic clusters formed by 1000 cells in line with the average β-cell number and their compact disposition in rodent islets [19–21]. Thus, the lattice sites are the β-cells centers (assumed as spherical in a first approximation) and the distance between sites is chosen by taking into account the typical radius of β-cells and assuming cell-cell contact between adjacent cells. Cells (considered as zero dimensional, i.e., points) are assumed to be stimulated by the glucose concentration computed on the lattice point on which they are located, i.e., their centers (Fig. 1).

Hybrid model. A generalized version of the stochastic SRK model [8,9] based on a Hodgkin–Huxley formulation was adopted to model β-cells activity. In particular, three coupled ordinary differential equations model the membrane voltage dynamics, the non-instantaneous activation of potassium ion channels and the slow dynamics of the intracellular calcium concentration which drives insulin secretion. The other ion currents taken into account are a voltage-sensitive calcium current which is supposed to activate and inactivate instantaneously, and a calcium-sensitive potassium current (K-Ca) whose macroscopic value is computed via the resolution of the underlying stochastic process of channels gating. The high conductance of such channels leads in fact to strong noise fluctuations of the membrane voltage that have a significant effect on the bursting robustness, permitting to obtain regular oscillations in case of sufficiently large coupled clusters as it was observed in experiments [22] and thus validating such an approach in spite of a classic deterministic formulation. In addition, gap-junction currents are considered. Glucose feedback is introduced in the calcium dynamics by scaling the removal rate based on the glucose stimulating concentration. Glucose dynamics is modeled via a reaction–diffusion (RD) partial differential equation which takes into account diffusion of glucose in the extracellular matrix of the islet and the β-cells uptake of glucose via the GLUT-2 transporter [17,18]. Intracellular glucose dynamics is computed based on such an uptake and used to fine-tune the calcium removal rate of the electrophysiological model, thus achieving the desired glucose feedback. To note that cells are point-like in the continuum formulation of glucose diffusion and morphological effects on extracellular glucose spreading is modeled through a porosity factor used to match the effective diffusion coefficient of the tissue [17]. The β-cell cluster is stimulated by exposing selected external surfaces to different glucose concentrations, discarding any intra-cluster source of glucose. This choice permits to match experimental *in vitro* conditions where only the external surface of the islet is exposed to glucose, neglecting glucose supply through blood vessels. The complete list of the equations of both the electrophysiological and the glucose diffusion models and a description of the numerical implementation can be found in Appendix.

Synchronization Measure. Synchronization of β-cells was investigated through the analysis of pairwise correlations in electrical activity. Specifically, functional networks were reconstructed filtering the more significant correlation coefficients R_{ij} computed on membrane potential signals, i.e., by considering cells as nodes which are coupled through links denoting a correlation in the electrical activity greater than a fixed threshold. In line with other studies we fixed such threshold to 0.75, and we analyzed synchronization pathways by studying the topology of functional networks [14,15]. A sensitivity analysis addressing the effect of threshold on the resulting network suggests that the results here presented are minimally affected by slight variations of this parameter. In addition, this cutoff value is also comparable with the one adopted in the investigations of functional networks in the brain [23,24].

Variation in time of cells correlation was analyzed by computing the coefficients R_{ij} in a moving time window $T_w = 200$ ms and by shifting such window with a step $\tau_s = 20$ ms:

$$R_{ij}(t') = \frac{\langle (V_i(t) - \langle V_i(t)\rangle_{t'}^{t''})(V_j(t) - \langle V_j(t)\rangle_{t'}^{t''})\rangle_{t'}^{t''}}{\sigma\,(V_i(t))_{t'}^{t''}\,\sigma\,(V_j(t))_{t'}^{t''}},$$

with $t'' = t' + T_w$, $t' = n\,\tau_s$, and $n = 0, 1, \ldots, (T_{sim} - T_w)/\tau_s$, where T_{sim} denotes the simulated time period. Thus, time dependence in the formula concerns the time interval over which are evaluated the statistical measures, i.e., mean values $\langle\cdot\rangle_{t'}^{t''}$ and standard deviations $\sigma\,(\cdot)_{t'}^{t''}$ are computed on windows of signals of length T_w so that the value $R_{ij}(t')$ quantifies the correlation between the ith and jth cells within the time interval $t \in [t', t' + T_w]$. We fixed the value of T_w based on the time duration of action potentials in β-cells ($\sim$100 ms), and we choose τ_s an order of magnitude lower than T_w to achieve a fine discretization of correlation dynamics. The functional network was studied by computing statistics and measures usually adopted in complex network analyses, i.e., degree distribution, local and global clustering coefficient, betweenness centrality, efficiency and small-worldness [25,26]. When computing small-worldness, the global clustering was obtained as the average of the local clustering coefficients computed on the nodes with degree greater than one, i.e., by considering the nodes for which the measure is actually defined (see Ref. [27].). This choice permitted to filter out the effects of isolated nodes and leafs. In addition, the functional network was compared to a null model obtained as the average behavior of 20 random networks computed by a degree-preserving random rewiring of the original graph. In partic-