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Research Article

Biophysical modeling of β-cells networks: Realistic architectures and heterogeneity effects

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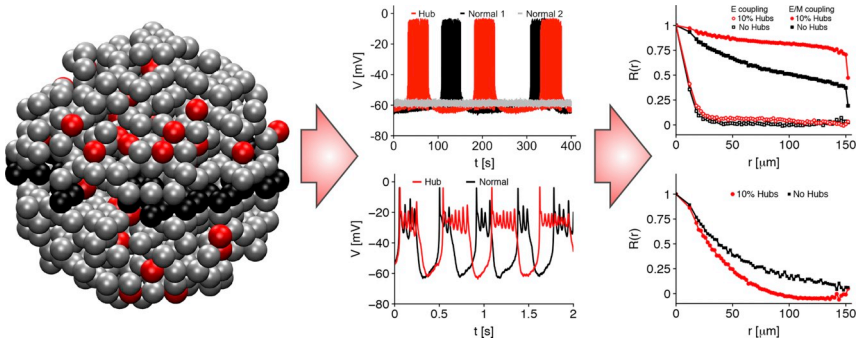
HIGHLIGHTS

- The synchronization among β-cells in islets is crucial for insulin pulsatile release
- The architecture of the islet and cells heterogeneity determines the functional connections among cells
- In specific conditions, β-cells very sensitive to glucose (hubs) can drive the electrical activity of neighboring cells
- Hubs induce compartmentalization of cells activity during fast oscillations
- Hubs enhance cells synchronization in slow glycolytic bursting

GRAPHICAL ABSTRACT



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ABSTRACT

The *β*-cells dynamics is the regulator of insulin secretion in the pancreas, and its investigation is a central aspect in designing effective treatment strategies for diabetes. Despite great efforts, much is still unknown about the complex organization of such endocrine cells and realistic mathematical modeling represents a useful tool to elucidate key aspects of glucose control in humans. In this contribution, we study the human *β*-cells collective behaviour, by modeling their electric and metabolic coupling in a cluster, of size and architecture similar to human islets of Langerhans. We focus on the effect of coupling on various dynamics regimes observed in the islets, that are spiking and bursting on multiple timescales. In particular, we test the effect of hubs, that are highly glucose-sensitive *β*-cells, on the overall network dynamics, observing different modulation depending on the timescale of the dynamics. By properly taking into account the role of cells heterogeneity, recently emerged, our model effectively describes the effect of hubs on the synchronization of the islet response and the correlation of *β*-cells activity.

1. Introduction

Great efforts are continuously devoted to the study of endocrine *β*-cells physiology and the understanding of the glucose-stimulated insulin secretion, being these aspects central for blood glucose homeostasis. The studies dedicated to this subject have a significant impact, especially considering the growing global problem of diabetes [1], i.e., the metabolic disorders with impaired *β*-cells functioning. In particular, special attention was paid to the investigation of *β*-cells electrical activity. Within this field, decades of studies have enlightened the main cellular processes involved in glucose sensing, cells activation and calcium-dependent insulin release [2–9].

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β-cells are the most numerous endocrine cells in pancreatic islets. They can exhibit a heterogeneous electrical response, triggered by enhanced intracellular ATP levels that are evoked by glucose metabolism. This electrical activity usually consists of spiking or bursting oscillations at multiple time-scales, as observed both in mouse and human pancreatic islets [7,10–13]. A characteristic feature of their collective electrical response is the synchronization of both the electrical activity and the related intracellular calcium oscillations all over the islet, as observed in mouse [4,14–22], with small phase differences which are linked to experimentally recorded calcium waves [19,23–27].

The cells synchronization is indeed crucial to achieve a pulsatile insulin release, which guarantees stronger hypoglycemic effects compared to constant secretion [28,29]. In the functioning of cells coordination and synchronization, the gap-junctions between adjacent cells play a fundamental role [23,30,31]. They are essential in confining biological noise and heterogeneity, and in achieving a robust activation of β-cells population within the islet [32,33]. Indeed, gap-junctions were found to affect significantly β-cells activity not only in mice but also in humans [34–38].

Recent experimental studies [24,39,40], based on calcium imaging and the monitoring of large populations of cells, further enriched the knowledge about the dynamics of β-cell networks. In particular, a specialized small subpopulation of cells (called hubs) was found to be more sensitive to glucose and to drive the response of the remaining cells, through cellular coupling [39]. Surprisingly, this heterogeneity in cells activity seems to be conserved across species, as stated by similar observations obtained from mouse and human islets [39]. The finding that hubs are the most metabolically active cells is also supported by Gosak et al. [41]. However, some debate exists in the literature about the role of hubs as pacemakers for the islet activity. Indeed, Benninger's group identified a group of less excitable β-cells acting as pacemakers in mouse islets [42], contrary to results reported by Johnston et al. [39]. Therefore, despite most recent advances [39,40,42], much is still unknown about the complex regulation of the islet, especially concerning the whole-islet β-cells activity. In particular, the effects induced by hubs, constituting a subpopulation of specialized cells highly sensitive to glucose, deserve detailed investigation, with particular regards to the human case. To gain more insight into the understanding of collective β-cells activity, biophysical models represent a necessary tool for comprehensive investigations. Advanced models, fine-tuned to reproduce cells electrical and metabolic activity, have been developed and used in pioneering studies of mouse β-cells dynamics [10,43,44] and in more recent investigations focused on the modeling of human β-cells [37,45,46]. It is worth to note that a modeling approach was recently used to investigate the effect of hubs on whole-islet behavior [47,48]. However, that model is built on mouse data and therefore, is not suited to reproduce electrical patterns as observed in human β-cells.

In this paper, we adopt a detailed mathematical description of β-cells activity, specifically fine-tuned on human data [45], to investigate the effect of a specialized subpopulation of cells on the whole-islet dynamics. In particular, we build a virtual islet, based on human islet cytoarchitecture [49–51], and analyzed the activity of the resulting β-cell network. We investigate the response of the network in different dynamics regimes, including spiking and fast bursting oscillations, as well as slow glycolytic bursting, both in the presence and in the absence of the highly active sub-population of cells used to model hubs. Simulation results confirm the differences, in the collective dynamics, among spiking, fast bursting and slow bursting electrical activity, and establish the effects of the metabolic activity, depending on the presence or absence of hub cells.

With this study, we want to overcome limitations of previous studies, by including in a human-like β-cells network both electric and metabolic coupling, and cells heterogeneity (normal β-cells and hubs), a key ingredient of the islet synchronous activity.

The paper is organized as detailed below. In the Methods section, we describe the main features of the model: biophysical description of cells activity, human architecture construction and cells heterogeneity. In Results, we analyze simulation outcomes. In Discussion and Conclusion sections, we comment on our observations in relation to experiments and other modeling studies, and we outline future perspectives in the modeling of whole-islet activity.

2. Methods

We rely on the biophysical model of human β-cells recently developed by Pedersen et al. [37,45,46], able to reproduce spiking, fast bursting and slow glycolytic bursting electrical patterns. For the reader most convenience, we report here the main equations describing the model, and refer the reader to the corresponding references for the full model details.

Our model is based on the combination of three key ingredients: a realistic reconstruction of β-cell aggregates in human islets, a reliable and well assessed Hodgkin-Huxley description of the human β-cell electrical activity [45,46], in the presence of both electric and metabolic coupling among cells [37], and, as a new ingredient, the heterogeneity of β-cells, which are diversified in normally and highly sensitive cells in response to glucose stimulation, in line with recent observations on mouse and human pancreatic islets [39].

The single-cell system is composed by an electrical and a metabolic component and is able to reproduce fast spiking, fast bursting and slow bursting electrical oscillations. In particular, slow bursting results from the interaction between the two components, electrical and metabolic.

The main model equations for the i-th cell are:

$$\frac{dV_i}{dt} = -I^i_{ion} - \sum_{j\in\Omega_i} g_c(V_i - V_j) + \varepsilon\Gamma^i_t \tag{1}$$

$$\frac{dx}{dt} = V_{GK} - V_{PFK} - \sum_{j\in\Omega_i} p_x(x_i - x_j) \tag{2}$$

$$\frac{dy}{dt} = V_{PFK} - V_{FBA} \tag{3}$$

$$\frac{dz}{dt} = 2V_{FBA} - V_{GAPDH} \tag{4}$$

$$\frac{da}{dt} = V_{GAPDH} - k_A \tag{5}$$

$$g_{KATP} = \hat{g}_{KATP}/(1 + a), \tag{6}$$

where I_{ion} includes various channel contributions: voltage-sensitive potassium, calcium and sodium channels, small and big conductance calcium-sensitive potassium channels, and ATP-sensitive potassium channels. The electrical subsystem (Eq. 1) further takes into account gap-junction coupling, and a white noise term Γ_t, used to model stochastic effects related to channels dynamics. The noise process has zero mean and covariance $\langle\Gamma(t)\Gamma(t')\rangle = \delta(t - t')$. Concerning the metabolic component, Eqs. 2–5 model main steps of glycolysis and are described in details in Refs [46, 52]. In particular, the variables x, y, z and a model the intracellular concentrations of glucose-6-phosphate/fructose-6-phosphate (G6P/FBP), fructose-1,6-bisphosphate (F6P), dihydroxyacetone-phosphate/glyceraldehyde-3-phosphate (DHAP/G3P), and ATP, respectively. The variable a ensures the feedback with the electrical component, directly tuning the activation level of ATP-sensitive potassium channels (Eq. 6). We further consider metabolic coupling, assuming that metabolites such as G6P and F6P can diffuse through gap-junctions. Finally, cells are assumed to communicate with adjacent cells in specific local neighborhoods Ω_i, defined by the β-cell cluster architecture.

The complete model description, including all equations and parameters, can be found in Refs [37,46]. Coupling conductance and permeability are set to $g_c = 0.01\,\mathrm{nS/pF}$ and $p_x = 0.01\,\mathrm{ms}^{-1}$, white noise strength is set to $\varepsilon = 0.2$. In the case of fast oscillations, the glycolytic

component is not taken into account, and cells activation is directly tuned by opportunely setting the conductance values of the ATP-regulated potassium channels.

The β-cells, modeled as described above, are assembled in a network built to simulate their arrangement in human islets. The structure of human islets, especially in comparison with mouse islets, has been widely investigated [53–57]. In mice, β-cells are located within the core of the islet, surrounded by a mantle of α and δ-cells [53]. In human islets, it is well assessed [55] that β-cells are intermixed with other cell types. On this basis, a two-dimensional analysis could bring to the conclusion that β-cells are not connected in a unique structure. However, a three-dimensional interpolation of such intermixed planes can probably generate a connected syncytium. At increasing islet size, the β-cells region is still covered by the mantle, forming trilaminar epithelial plates [53]. The mantle also extends along vessels, penetrating and branching in the islet, and the trilayer is folded, with different degrees of complexity, to guarantee both the contact among β-cells and their connection with α-cells. In both mice and humans, smaller islets ($<100\mu$m in diameter) are of the core-mantle type, while larger islets display the folded organization [57].

We rely on experimental evidences [49,50,51,53] on human islets to build a human-like β-cells network. In particular, we build a three-dimensional compact spheroidal cluster of cells with hexagonal packing [58], with a radius of 150μm (comparable with typical pancreatic islets size). We model the heterotypic islet composition and the β-cells dispersion via a site percolation on the cluster, with a probability $p_s = 0.5$, obtaining a connected network of $\sim$600 β-cells with heterogeneous local connectivity. Each β-cell is modeled as a spheroidal shaped cell, with a radius of 6.5μm. It is worth to note that the size of the cells is only taken into account to build the architecture and the connectivity matrix of the network, while it is not considered in the biophysical model, where cells are point-like, as done in other modeling studies on β-cells dynamics [37,38,58].

Overall, we simulate three different dynamical regimes, spiking, fast and slow bursting, in heterogeneous clusters. In the description of these three regimes, the metabolic coupling is included only in the glycolytic-driven slow bursting. Indeed, in this case, the metabolites are dynamical variables acting on the intracellular ATP and are affected by fluxes through gap junctions. On the other hand, the dynamics of metabolites is not taken into account in fast oscillation modes because of the different time scale. In this case, cells are assumed to be metabolically synchronized and within an active glycolytic phase, while heterogeneously responding based on KATP channels density and sensitivity. Electrical oscillations are still able to synchronize through ions exchange via gap junctions.

Cells heterogeneity is modeled by randomly sorting selected parameters. In particular, for fast spiking and bursting dynamics, we normally distribute voltage- and ATP-sensitive potassium channels conductance, the two parameters that mostly affect single-cell response to glucose. In the case of slow bursting, we normally distribute the voltage-sensitive potassium channels conductance and the glucokinase maximal reaction rate. Further, for each studied dynamics regime, we consider two sets of distribution parameters, in order to model two β-cell types, i.e. normal responding cells and highly sensitive cells (hubs). Hubs are assumed to be the 10% of all β-cells, in line with experimental observations and other modeling investigations [39,48]. A complete list of the adopted settings can be found in Table 1.

Finally, in our analyses we quantify cells synchronization by computing the two-point correlation index $R_{ij} = \langle (V_i - \langle V_i \rangle)(V_j - \langle V_j \rangle) \rangle / (\sigma_{V_i}\sigma_{V_j})$ over all β-cells pairs within the cluster, where V_i (V_j) represents the membrane potential signal for the i-th (j-th) cell, σ_{V_i} (σ_{V_j}) denotes the standard deviation of membrane potential signal for the i-th (j-th) cell, and the $\langle \cdot \rangle$ operator denotes the time average. It has to be noticed that experimental studies usually investigate cells correlation based on intracellular calcium signals [24,39,40], mostly because of the advantage of calcium imaging in simultaneously recording the activity of large cells populations. However, calcium dynamics has a slower time scale compared to membrane voltage and, although calcium variations are directly driven by membrane voltage oscillations, the use of calcium may not describe correctly electrical coordination of cells. Based on this premise, and also considering that the adopted electrophysiological model [37,45,46] was built by carefully fine-tuning on human membrane voltage data, we focus on voltage signals for the study of pairwise cells correlation.

3. Results

The reconstructed architecture of the β-cells network is shown in Fig. 1. The network is formed by a unique connected structure of $n = 618$ β-cells, built via the percolation procedure explained in Methods section, with no fragmentation in uncoupled sub-clusters (see Fig. 1A). On the other side, the architecture is characterized by significant heterogeneity in the local connectivity of cells (Fig. 1B). The average number of neighbors *per* cell is $\sim 5-6$, in agreement with experimental observations in human islets, measuring ethidium bromide diffusion among neighboring β-cells [34].

Relying on this architecture, we model and analyze the emergent activity and synchronization of the whole β-cells population for three cases of studies, representative of different electrical regimes recorded [46] in human β-cells: fast spiking, fast bursting and slow bursting activity. These regimes are analyzed both in the presence and in the absence of cells with enhanced metabolic activity, named hubs.

3.1. Spiking activity

The spiking activity of single β-cells, both normal cells and hubs, is shown in Fig. 2A. The spiking mode consists, in both cases, of periodic action potentials, fired from a resting potential of ~ -60 mV and with a peak of ~ -10 mV. Spiking period and signal amplitude both depend on the conductance of voltage-sensitive and ATP-sensitive potassium channels. In particular, the g_{KATP} parameter is used to model the β-cell exposure to glucose. The g_{KATP} values distribution is different for normal cells and hubs, ensuring a different characteristic response for the two cell families. In our simulations, normal cells (black curve) are mildly activated, exhibiting low amplitude action potentials and a spiking frequency of $\sim$3 Hz. The hubs (red curve) show instead higher action potentials amplitude and frequency ($\sim$7 Hz) compared to normal cells (Fig. 2A).

The emergent dynamics of the β-cells network, for islet models including or not the hubs, and with cells electrically coupled via gap junctions, is analyzed in Fig. 2B-C.

The response of the network, if composed only by normal β-cells, shows a significant level of synchronization, with a limited phase difference between cell membrane potential oscillations (see Fig. 2B-I). This phase difference is potentially related to wave-like propagation of action potentials, as stated by the geometry of the space-time plot in Fig. 2B, *i.e.* the active cell state propagates along lines within restricted bands of the diagram.

The behavior of the heterogeneous network, with the β-cells population composed of 90% normal cells and 10% hubs, is shown in Fig. 2B-II. The additional heterogeneity induced by hubs strongly affects cells synchronization, giving rise to a more intense, but less coordinated, spiking activity over the whole cluster with respect to the normal population case. Wave-like pattern is almost suppressed, and hubs drive and coordinate nearest neighboring cells activity (Fig. S1A-B in Supplementary Information). We also investigate the model behavior by varying the mean value and standard deviation of the normal distribution used to extract the g_{KATP} parameter for hubs. In particular, by using $\mu = 0.005, 0.01, 0.015$ nS/pF in combination with $\sigma = 1\%$, 10%, we obtain a marginal effect of the standard variation and a progressive shifting towards a coordinated behavior at mean values closer to normal cell g_{KATP} (not shown).

Table 1
Normal distribution parameters used to model β-cells heterogeneity. N: normal responding cell. H: hub, i.e. cell more sensitive to glucose. The parameters μ and σ denote mean value and standard deviation (expressed in percent respect to the mean) of the distributions.

Parameter	Fast spiking		Fast bursting		Slow bursting	
	N	H	N	H	N	H
g_{Kv} (nS/pF)	$\mu = 1$ $\sigma = 10\%$		$\mu = 0.2$ $\sigma = 1\%$		$\mu = 1$ $\sigma = 10\%$	
g_{KATP} (nS/pF)	$\mu = 0.017$ $\sigma = 1\%$	$\mu = 0.005$ $\sigma = 1\%$	$\mu = 0.015$ $\sigma = 1\%$	$\mu = 0.012$ $\sigma = 1\%$	see Eq. 6	
V_{GKmax} (mM/ms)	–		–		$\mu = 5.5 \cdot 10^{-5}$ $\sigma = 10\%$	$\mu = 7.5 \cdot 10^{-5}$ $\sigma = 3\%$

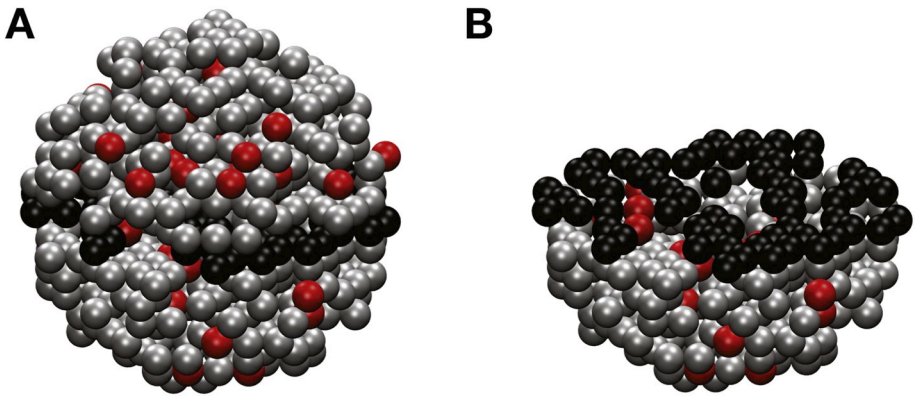

Fig. 1. Islet model.
A) Three-dimensional representation of the β-cells cluster used to model the islet dynamical behaviour. B) Cut of the spheroidal cluster in A) at the cross section highlighted in black. Gray and red spheres denote normal cells and hubs, respectively.

To quantify the loss in cells synchronization induced by hubs, we compute the correlation index R over cell pairs within the cluster. We finally average R based on the distance between cells, finally obtaining the function $R(r)$ (Fig. 2C). In the absence of hubs, cells show a significant correlation index (>0.5) within a 50μm radius, and a positive correlation can also be observed for peripheral and maximally separated cells ($R \sim 0.25$). In the presence of hubs, a clear drop in cells correlation is observed. In this case, a significant correlation ($R > 0.5$) is maintained only within a 25μm radius, and for $r > 50\mu$m the correlation goes to zero. Cells correlation computed on calcium signals shows similar values, over the whole distance range, as in the case of correlation evaluated from membrane potential signals (Fig. S2A in Supplementary Information).

3.2. Fast bursting activity

Previous studies pointed out that β-cells may show fast bursting activity, which is driven by at least two different cellular processes [45,46]. The two driving mechanisms are related to the activation/inactivation of two potassium channels: small conductance (SK) calcium-sensitive potassium channels and HERG potassium channels, respectively. SK-driven bursting is suppressed in electrically coupled cells at physiological coupling conductance values, and emergent activity is characterized by sustained high-voltage small amplitude membrane voltage oscillations [37], which are unlikely to drive insulin secretion in pancreatic islets. Instead, HERG-driven bursting is conserved in electrically coupled β-cells, showing, at physiological coupling conductance values, a bursting period larger than in the case of uncoupled cells.

This pattern is consistent with observations on mouse islets, and it may potentially act as an important regulator of whole-islet β-cells function in humans. On this basis, we test the effect of hubs inclusion in a β-cell population characterized by HERG-driven bursting activity. As in the case of the spiking regime, hubs are simulated by reducing the mean value of the g_{KATP} parameter distribution, thus assuming higher stimulating glucose concentrations compared to normal cells. Simulated fast bursting oscillations for both normal cells (black curve) and hubs (red curve) are shown in Fig. 3A. Results show a mean bursting period of ~0.5 s and ~0.4 s for hubs and normal cells, respectively. However, the bursting period alone does not fully describe the cells response. A reliable indicator of cells activation level in a fast bursting mode is the plateau fraction, i.e. the ratio between the time spent in an active state and time spent in a silent state within a bursting cycle. High plateau fraction values are correlated to enhanced intracellular calcium oscillations. The plateau fraction is ~0.6 and ~0.4 for hubs and normal cells, respectively, thus indicating a stronger activation for hubs than for normal cells.

We further test the effect of hubs on the emergent dynamics of coupled β-cells populations in a fast bursting mode. In the absence of hubs, the space-time plot of membrane voltage (Fig. 3B-I) suggests a strong synchronization of cells activity with limited phase differences at each bursting cycle due to cells heterogeneity. When including 10% of hubs in the cluster (Fig. 3B-II), the pattern becomes less synchronized, and a wave-like propagation scheme appears in different cells subclusters. However, contrary to the spiking regime, hubs do not anticipate and drive neighboring cells activity in fast bursting (Fig. S1C-D in Supplementary Information). Also for this case, we test the model behavior by varying the mean value and standard deviation of the normal distribution used to extract the g_{KATP} parameter for hubs ($\mu = 0.005, 0.01, 0.015$ nS/pF and $\sigma = 1\,\%, 10\%$). Computed results are in line to the observations obtained with the initial heterogeneity setting (see Table 1), with the only exception of $\mu = 0.005$ nS/pF, which induces sustained high-voltage small-amplitude membrane voltage oscillations in hubs, similarly to what is obtained in coupled cells driven by SK bursting mechanism. The correlation function $R(r)$ further shows a loss of correlation in cells activity at increasing distance from a reference cell, when hubs are included in the population (Fig. 3C). However, this drop in cells correlation is less severe compared to the one observed in spiking regimes, and, on average, cells show a positive

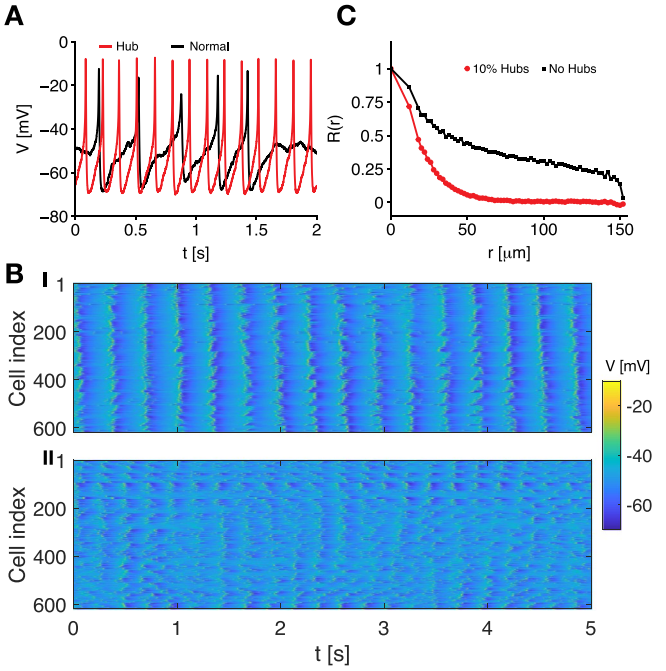

Fig. 2. Fast spiking regime.
A) Simulated electrical dynamics of representative normal (black curve) and hub (red curve) cells. Normal cell shows mild activation and a lower spiking frequency compared to the more active hub. B) Space-time plots showing membrane voltage dynamics of the whole β-cell population in the absence (I) and in the presence (II) of hubs (10% of the overall cells population). Color code denotes membrane voltage amplitude. Cells show strong synchronization in the absence of hubs and loss of coordination in the presence of hubs. C) Correlation function $R(r)$ computed by averaging the correlation index over all cells pairs within the cluster. Red line with circular symbols and black line with squared symbols denote the correlation function computed in the presence and absence of hubs, respectively.

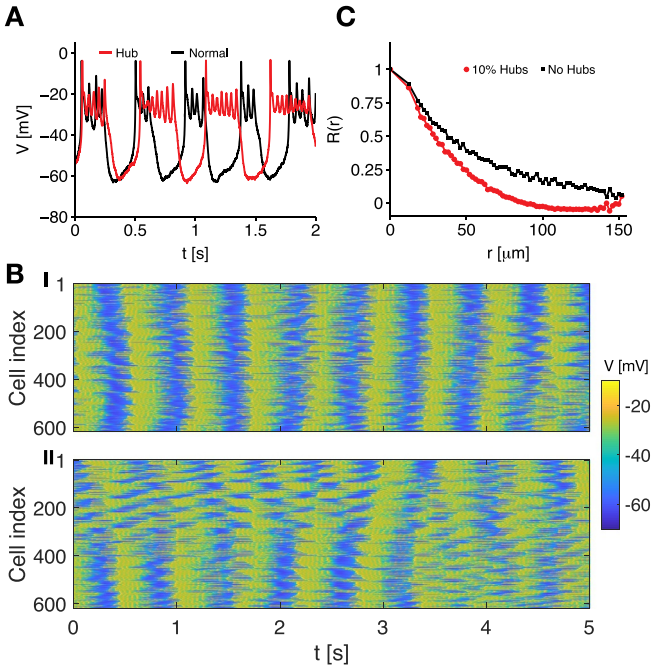

Fig. 3. Fast bursting regime.
A) Simulated electrical dynamics of representative normal cell (black curve) and hub cell (red curve). Normal cell shows reduced active phases of the burst compared to the more active hub. B) Space-time plots showing membrane voltage dynamics of the whole β-cell population in the absence (I) and in the presence (II) of 10% of hubs. Color code denotes membrane voltage amplitude. Cells show strong burst synchronization in the absence of hubs and loss of coordination and in the presence of hubs. Wave-like patterns can be observed in the latter case. C) Correlation function $R(r)$ computed by averaging the correlation index over all cells pairs within the cluster. Red line with circular symbols and black line with squared symbols denote the correlation function computed in the presence and absence of hubs, respectively.

correlation also when separated by a distance in the range 50–100 μm. Notably, when considering intracellular calcium for the computation of cell correlations, we do not observe significant differences induced by hubs, and cells have a high correlation index also at maximal distances ($R \sim 0.6$, Fig. S2B in Supplementary Information).

3.3. Slow bursting activity

The slow bursting mode in β-cells is characterized by a spiking activity alternating with silent phases, with a period on the order of minutes for the spiking-silent cycles. In this case, the bursting is driven by glycolytic oscillations, which induce ATP periodic variations and corresponding modulations of ATP-sensitive potassium channels. To model hubs, we consider that these cells show higher expressions of glucokinase (GK) compared to normal cells [39], suggesting their higher efficiency in glucose phosphorylation. Therefore, for hubs, we increase the mean value of the distribution of GK reaction rate compared to normal cells. In particular, simulations show that normal cells are characterized by a silent response or by an active response with a lower bursting period compared to hubs (Fig. 4A). Bursting period for hubs and active normal cells is ~150 s and ~200 s, respectively.

To analyze the effect of hubs in the case of coupled clusters, we model two cases: an electrically coupled β-cells cluster, and a cluster coupled both metabolically and electrically.

In the case of electric coupling only, cells activity is almost totally suppressed in the whole cluster due to negative entrainment of cells, both in the absence of hubs and in the presence of 10% of hubs (Fig. 4B-I,II). In particular, out of phase metabolic oscillations induce potentially active cells to be entrained in a silent state by neighboring cells, which are in a silent phase of the bursting cycle at the same time. Occasionally, when the active phase of the burst overlaps between neighbors, cells show action potential firing within narrow time windows. In the case of electric and metabolic coupling, glycolytic oscillators are able to synchronize all over the cluster, giving rise to a coordinated slow bursting mode (Fig. 4B-III). In this condition, the presence of hubs further enhances cells activity, through positive entrainment of normal silent cells, and synchronization (Fig. 4B-IV). These observations are also confirmed by analyzing the correlation function $R(r)$ (Fig. 4C) which rapidly goes to zero in the case of cells coupled only electrically ($R(r) \sim 0$ for $r > 25\mu$m), while it shows significant long-range correlations in the case of combined metabolic and electric coupling ($R(r) \sim 0.4$ at $r \sim 150\mu$m, in the absence of hubs). Strikingly, and contrary to spiking and fast bursting regimes, the presence of hubs promotes long-range correlations in the slow bursting regime. Correlation index computed with calcium data presents a similar behavior in the case of sole electrical coupling, while it reaches higher levels, compared to the ones obtained with membrane voltage data, in the case of electrical and metabolic coupling ($R \sim 0.8 - 0.9$ at maximal distances, Fig. S2C in Supplementary Information).

4. Discussion

The comparative analysis of the uncoupled normal cells and hubs, combined with the emergent dynamics of the cluster when coupled electrically and, for the slow bursting, metabolically, allows to draw an interesting scenario for the activity of human pancreatic islets.

Results for spiking and fast bursting activity are in agreement with recorded signals from human β-cells [46]. In particular, the electrical

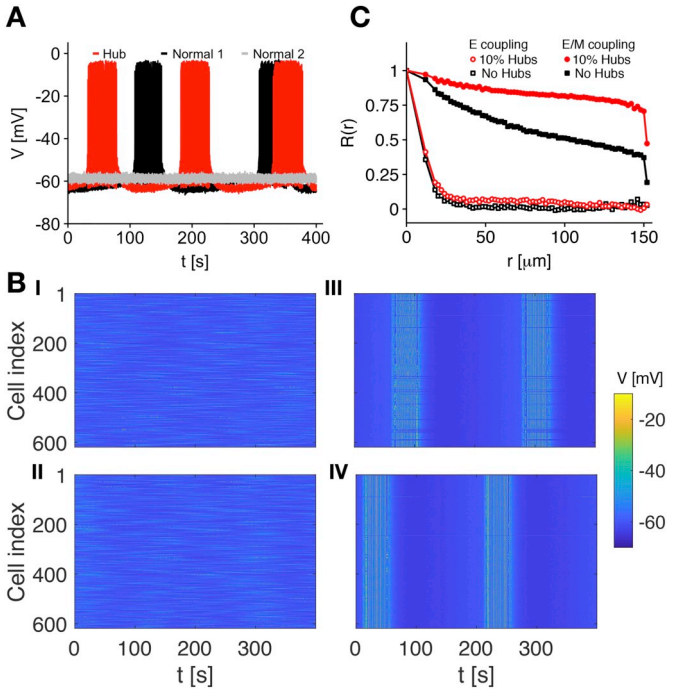

Fig. 4. Slow bursting regime.
A) Simulated electrical dynamics of representative normal (black and gray lines) and hub (red line) cells. Normal cells may show silent response (gray) or slow bursting (black) with lower frequency compared to hubs (red). B) Space-time plots showing membrane voltage dynamics of the whole β-cell population: (I) electric coupling in the absence of hubs; (II) electric coupling in the presence of 10% of hubs; (III) metabolic and electric coupling in the absence of hubs; (IV) metabolic and electric coupling in the presence of 10% of hubs. Color code denotes membrane voltage amplitude. C) Correlation function $R(r)$ computed by averaging the correlation index over all cells pairs within the cluster. Red and black lines denote the correlation function computed in the presence and absence of hubs, respectively. Empty and filled symbols denote electric coupling only and the combination of metabolic and electric coupling, respectively.

response of uncoupled hubs in our simulations preserves intrinsic spiking or bursting regime as observed in normal cells, but with increased levels of activation, related to the strong physiological response of hubs to glucose. The hubs spiking response is more intense and at higher frequencies than the normal cells behaviour. For fast bursting, hubs show a prolonged plateau phase, related to their stronger activation compared to normal cells. For slow bursting, hubs are characterized by higher bursting frequencies, driven by enhanced glycolytic oscillations, respect to normal cells.

It is in the coupled system that main differences arise when hubs are included in the model. For fast dynamics, the hubs tend to reduce cells correlation, acting as noise generators. A clear drop in the correlation index at increasing inter-cellular distance is obtained for both spiking and fast bursting in the presence of hubs. In contrast, normal cell populations show a significant correlation also at distances comparable with large portions of the islet. In this case, hubs tend to compartmentalize whole-islet activity, promoting the appearance of differently correlated sub-clusters. This effect is consistent with experimental evidence on human islets, which shows that cells tend to be correlated in subgroups, also in relation to the underlying architecture of the network [39]. In spiking mode hubs are also pacemaker of activity, driving and coordinating nearest neighboring cells. This is not the case for the fast bursting regime. It is worth to note that this can be related to the heterogeneity of cells here modeled. Indeed, we induce higher spiking frequencies and lower bursting frequencies in hubs, compared to normal cells. Assuming the pacemakers to be the fastest oscillators, as also suggested in the literature (see ref. [42]), explains why hubs drive neighboring cells only in a spiking regime in our model. Increased bursting frequencies for hubs could force this specific type of cells to lead other cells also in bursting regimes. To fully investigate this aspect, further studies devoted to a comprehensive electrophysiological characterization of hubs would be needed. Unfortunately, despite the appearance of wave-like patterns within small cells assemblies, we are not able to quantify such spatio-temporal dynamics due to the complexity of propagating fronts. However, results show that hubs tend to disrupt the coherent propagation of activity.

The effect of hubs inclusion on the collective dynamics is the opposite in the case of slow bursting. When considering both electrical and metabolic coupling, cells show increased correlation levels, which are significant also for peripheral and maximally separated cells. This behaviour is related to the almost full synchronization of glycolytic oscillators induced by metabolic coupling, which evokes positive entrainment of silent cells and coordination of electrical oscillations. This difference with respect to fast dynamical regimes may be related to a different functional organization between the two electrical patterns. However, it could be possible that the observed strong synchronization is due to the specific permeability used to model the metabolic coupling, estimated from mouse data [37,59]. Indeed, metabolic oscillators may be much more prone to synchronization compared to electrical oscillators, and may, therefore, require lower coupling strengths to guarantee partial coordination in the islet. Also, heterogeneity in coupling strength could contribute to achieving functional modularity. All our findings and conclusions still hold when calcium signals are used to evaluate cells correlation, despite obtaining higher correlation values in this case. Such increases in computed correlations are likely to depend on the slower time-scale of calcium dynamics. Our results overall support the idea that the presence of hubs is of key importance in regulating the synchronization of β-cells and their function.

5. Conclusions

In this work, we model the β-cells uncoupled and coupled behaviour in a percolated cluster architecture mimicking the network in human islets, including both structural and functional heterogeneity. The key role of functional heterogeneity, related to the presence of hubs (modeled via tuning of parameters describing the glucose sensing and ATP effects) is investigated in the three main dynamics regimes observed in islets. The hubs strongly affect the coherent dynamics, in a desynchronizing way for fast dynamics, and promoting synchronization in slow bursting dynamics. With respect to previous modeling works [37,48], our investigations improve the description of β-cells networks dynamics within islets, because it combines three key aspects for the islet functionality: a detailed topology of the cells network, based on experimental data for human islets, a biophysical model of human β-cells activity, and a comprehensive description of cells heterogeneity to reproduce hubs dynamics, whose fundamental role has also been recently studied in depth [39,40]. Our work, by modeling human islets structure, and by explicitly including the dynamics of cells extremely sensitive to glucose levels, goes towards a more realistic description of the complex dynamics underlying the release and control of insulin secretion, providing new insights in the understanding of pancreas islets functioning and diabetes disease mechanisms. On this basis, our results show that hubs may significantly alter the response of β-cells cluster with a potential impact on insulin release. Future studies on human islets should be devoted to the electrophysiological characterization of hubs, to a detailed description of metabolic pathways and to the modeling of gap-junction permeability to metabolites. These aspects constitute further necessary ingredients for increasingly realistic modeling of human islet functioning.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bpc.2019.106247.

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