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Isles within islets: The lattice origin of small-world networks in pancreatic tissues

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HIGHLIGHTS

- Gap junctions are known to synchronize pulsatile secretion in islets of Langerhans.
- Experiments have shown that islets are not, however, fully coordinated.
- Recent network analyses report functional small-world characteristics in islets.
- Here we reconcile all of these observations within a single theoretical framework.
- We propose islets are organized into independent clusters of coupled beta-cells.

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ABSTRACT

The traditional computational model of the pancreatic islets of Langerhans is a lattice of β-cells connected with gap junctions. Numerous studies have investigated the behavior of networks of coupled β-cells and have shown that gap junctions synchronize bursting strongly. This simplistic architecture of islets, however, seems increasingly untenable at the face of recent experimental advances. In a microfluidics experiment on isolated islets, Rocheleau et al. (2004) showed a failure of penetration of excitation when one end received high glucose and other end was not excited sufficiently; this suggested that gap junctions may not be efficient at inducing synchrony throughout the islet. Recently, Stozer et al. (2013) have argued that the functional networks of β-cells in an islet are small world. Their results implicate the existence of a few long-range connections among cells in the network. The physiological reason underlying this claim is not well understood. These studies cast doubt on the original lattice model that largely predict an all-or-none synchrony among the cells. Here we have attempted to reconcile these observations in a unified framework. We assume that cells in the islet are coupled randomly to their nearest neighbors with some probability, p. We simulated detailed β-cell bursting in such islets. By varying p systematically we were led to network parameters similar to those obtained by Stozer et al. (2013). We find that the networks within islets break up into components giving rise to smaller isles within the super structure—*isles-within-islets*, as it were. This structure can also account for the partial excitation seen by Rocheleau et al. (2004). Our updated view of islet architecture thus explains the paradox how islets can have strongly synchronizing gap junctions, and be weakly coordinated at the same time.

1. Introduction

Cellular networks often generate intense interest because tissue function is closely tied into their emergent properties. In the pancreas, for example, β-cells are organized into clusters named the islets of Langerhans; these networks are studied in detail because they regulate the production and secretion of insulin. It has long been thought that β-cells of an islet enjoy a robust coordination between them, which in turn is responsible for a phasic secretion of insulin. There is considerable evidence that points in this direction. The hypothesis of strong coupling rests on the observation that insulin secretion is known to be pulsatile in the blood, from which it is usually inferred that pulsatility arises directly at the level of secretion, that is, β-cells presumably secrete in a synchronous manner. This hypothesis is consistent with both experimental as well as computational studies. For one, islets are

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well known to express the connexin isoform, Cx36. Estimates place the effective gap junctional coupling between pairs of cells in the range of 50–300 pS, and this has been shown in several computational studies [1–5] to be very strongly synchronizing. Using the early Chay–Keizer model of β cells Sherman et al. [2] had shown that clusters of β-cells coupled with gap junctions displayed synchronized bursting at these strengths. Pedersen et al. [4] later studied synchronization using more modern models of β-cells physiology; their results show electrical coupling alone can synchronize not only membrane potential but also metabolic activity within β-cells. A further nuance is that diffusion of calcium and other metabolites within islets may actually cause oscillator death [5]. It would thus seem that a *sufficient* model for explaining pulsatile secretion is the following: β-cells in an islet are connected to their nearest neighbors via (electrical, and only weakly diffusive) gap-junctional coupling which synchronizes them rapidly. That is, a *lattice network* explains β-cell synchrony, and by extension, insulin pulsatility. In recent years, however, this viewpoint is being challenged by new experiments and simulation studies [6–8].

Rocheleau et al. [6] designed a novel microfluidic device to estimate the extent of intra-islet coupling. They were able to trap an isolated islet and stimulate two opposite ends differentially, with sub- and supra-threshold glucose concentrations. This resulted in a train of calcium activity emerging from the highly excited region, which failed to pass through the entire islet. One possible conclusion is that gap junctions do not synchronize islets completely. To explain these observations Benninger and co-workers have raised the possibility of "percolation-style" islet networks, that is, some gap junctions could be missing between neighbors, and so not all β-cells are connected. Using this argument they were able to simulate partial wave propagation in islets [9], although in their work they use not only an older (electrical-only) model of β-cells but also a widely variable gap junction strength; this is not likely to be physiologically plausible. Pedersen et al. [10] modeled the effects of a spatially varying glucose concentration on the emergent response of the islet using a model of Sherman and by linearly varying the parameter g_{KATP} (as an analogue of glucose). They showed wave block in a chain of 100 β-cells. However the gap junction strength in that study was 20 pS, which is somewhat lower than what is reported in the literature, about 50–300 pS. They found that for higher gap junctional strength waves penetrate deeper into the islet, thus raising the possibility that waves may propagate all the way to other end of the islet if gap junction values are raised sufficiently. Later, Hermann and Benninger [11] revisited the question of islet response to a gradient glucose excitation using models developed earlier in [12] and [9]. They were able to show that the propagation of excitation decays through the islet from the region of high excitation to low. They found, however, that this transition takes place gradually, unlike in experiments [6] where the transition takes place in a relatively narrow spatial region. They introduced a stochastic variability in K_{ATP} channels, and a varying expression of K_{ATP} channels between 50%–150% of the basal value to reproduce the sharp transition effect.

More recently, Stozer et al. [8] used a Ca^{2+} imaging of islets to construct so-called "functional networks" of β cells, that is, the *apparent connectivity* of an islet during bursting activity. They subjected these functional architectures to various network-theoretic measures and found that islets possesses small world characteristics. This is a startling result. On the one hand, it underlines that short-range connections are dominant in the network, which seems to correspond with the lattice picture. On the other hand, the small world topology also suggests that long-range connections do exist within the islet. In islet networks the emergence of the long range connection is puzzling from a gap junction lattice viewpoint. Although there are several possible candidates that can induce these long range connections, including diffusible factors such as extracellular potassium, the existence of long range connections contradicts the Rocheleau experiments because they would tend to facilitate synchrony across the islet. Gap junctions, on the other hand, are by far the strongest form of coupling between β-cells in the islet; however, because they occur only between neighboring pairs, they do not immediately account for small world behavior. It is therefore necessary to reconcile these various results within a coherent model of islet architecture.

Here we consider islet networks of β-cells that are coupled strongly, but sparsely. Based on percolation ideas, first suggested in [9], we assume a gap junction exists between two neighboring cells with a probability p. That is, a cell in a 3-dimensional network can have anywhere between 0 to 6 neighbors. We attach biophysically realistic dynamics to β-cells, run its dynamics, and following Stozer et al. [8] construct the emergent functional network. We are interested in asking what topology of the gap junction (percolation) lattice gives rise to functional networks with small world character. A second constraint is to verify whether the islets can simultaneously reproduce the Rocheleau results.

We show that sparsely connected islets, with low p values, exhibit networks parameters similar to those described in Stozer et al. [8], and are thus small-world at a functional level of description. Those same islets when subjected to high glucose concentration at one end and to low glucose at the other show activity that does not necessarily reach the end far from the excited region. These results reiterate the classical view that gap junctions between β-cells in islets primarily serve to synchronize, and update the picture of network architecture to be: cells clustered into small islands, apparently un-connected from each other.

2. Materials and methods

The construction and the analysis of the functional network has several building blocks. Firstly, for the β-cell model we chose the dual oscillator model (DOM) [13], an excellent biophysical model which includes not only electrical but also metabolic component in describing bursting. We simulated islet dynamics and obtained the functional connectivity information of the cells by constructing correlation matrices from the simulation results. Finally, we analyzed the networks generated from correlation matrices using the metrics from network theory following Stozer et al. [8]. We also describe the numerical setting that was used to investigate the failure of propagation within the islet.

2.1. The β-cell dual-oscillator model

The dynamics of β-cells in pancreatic islets were computed using the DOM proposed in Bertram et al. [13]. The details of the model equation as well as the parameter values are in Appendix. The DOM consists of two subsystems—an electrical and a glycolytic subsystem. The cell dynamics was captured by seven nonlinear, coupled differential equations each accounting for a variable of interest. These variables are the membrane potential (V), the potassium current activator (n), free cystolic calcium concentration (Ca), concentration of free calcium concentration in the endoplasmic reticulum (Ca_{er}), ADP concentration (ADP), Glucose-6 phosphate concentration ($G6P$) and Fructose 1,6-bisphosphate concentration (FBP). Of the seven, the first five correspond to electrical subsystem and last two to glycolytic subsystem and cross terms exist between the equations indicating the coupling between two mechanisms. Briefly, these equations are

$$C_m \frac{dV}{dt} = -I_{Ca}(V) - I_K(V, n) - I_{K(Ca)}(V, Ca) - I_{K(ATP)}(V, ADP), \tag{1}$$