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Six Degrees of Depolarization A Comment on Network Science of Biological Systems at Different Scales: A Review by Marko Gosak et al

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In 1967, the social psychologist Stanley Milgram asked how many intermediates would be required for a letter from participants in various U.S. states to be received by a contact in Boston, given that participants were given only basic information about the contact, and were instructed only to pass along the message to someone that might know the intended recipient (Milgram, 1967). The surprising answer was that, in spite of the social and geographical distances covered, on average, only 6 people were required for the message to reach its intended target.

Network science provides a means to interpret this result. This approach involves the construction of a mathematical *graph*: a collection of *nodes* and *edges* that connect them. Nodes typically represent physical entities, such as participants, while edges between nodes represent an interaction, such as the forwarding of the message. By representing the process as a graph, we can uncover which participants are most important with respect to message-passing. It should be noted that graph representations do not impose any properties on the nodes themselves, only on the links between them. Moreover, physical space does not necessarily play a role in defining the graph; it is the *means* of communication between the nodes that is important. Approaches from network science have previously been successfully applied to airline routes (Verma et al., 2015), human social networks (Borgatti et al., 2009), power grids (Pagani and Aiello, 2013), and food webs (Dunne et al., 2002). So, how can these ideas aid in understanding biology?

Gosak et al (2018) use networks of insulin-secreting beta cells within pancreatic islets, whose dysfunction is implicated in type 2 diabetes (Bonner-Weir and O'Brien, 2008), as an example for network analysis. While isolated beta cells exhibit a wide range of electrical responses, islets display robust synchronisation of electrical or Ca^{2+} activity (Bertram et al., 2010). Electrical activity is a key regulator of beta cell secretion (Rorsman and Braun, 2013), which suggests that network properties are key to islet function. Indeed, the existence of so-called *hub cells* that orchestrate islet activity, to the extent that silencing a single hub cell can disrupt the function of the entire network, has recently been proposed (Johnston et al., 2016). Hubs are a property of a special kind of network, a scale-free (a type of small world) network. In such a network, a small number of nodes are highly connected, while most have relatively few connections (Newman, 2003). (Johnston et al., 2016) demonstrate that islets possess scale-free properties. Thus, hub cells are a natural consequence of the

computed network structure and require no special *intrinsic* properties, further highlighting the need to understand the role of the *whole* network.

The hypothesis that beta cells within the islet form a scale-free network is a conundrum, however, as beta cell-beta cell communication is usually considered local, mediated by extensive gap junctional coupling (Benninger et al., 2011; Benninger and Piston, 2014; Le Gurun et al., 2003). A scale-free network is inconsistent with only local coupling, since at least some cells must be coupled over long distances. These incompatible viewpoints can be understood by noting that the methods applied by Gosak *et al.* (Markovi et al., 2015; Stožer et al., 2013) compute *functional connectivity*, i.e., how the cells are coupled is determined by their dynamic responses to stimuli. The network architecture imposed by gap junctional communication is, in contrast, a type of *structural connectivity*. Understanding how *structural connectivity* informs *functional connectivity*, and vice versa, is a great challenge in applying network science to biological systems (Friston, 2011; Huang and Ding, 2016).

This question has been partially addressed in a computational modelling study of gap junction-coupled beta cell networks (Cappon and Pedersen, 2016). Here, simulations could produce scale-free functional networks (using the same methods as (Gosak et al., 2018)) provided that cells were coupled *heterogeneously*, that is, different cells in the network were coupled to differing numbers of other cells and with different coupling strengths. Different cell properties of recently identified functional *subtypes* of beta cells may also contribute to differences in structural vs. functional connectivity (Avrahami et al., 2017; Bader et al., 2016; Dorrell et al., 2016; Gutierrez et al., 2017; van der Meulen et al., 2017), though it remains unclear how these intrinsic differences might relate to network structure; i.e. it is not a given that heterogeneous coupling structures (such as in the scale-free network) are linked to beta cell heterogeneity. In addition, it is also likely that incretin, paracrine, or juxtacrine signalling may also regulate network activity, which would not be captured by gap junction structural connectivity (Benninger et al., 2011; Caicedo, 2013; Rorsman and Braun, 2013).

While network analysis is a promising new approach to probe the function of biological networks, it has limitations. A core problem is extracting the putative network from the experimental data (Bastos and Schoffelen, 2016; Friston, 2011; Petersson et al., 1999; Phillips et al., 2015). Most approaches rely on pairwise correlation between cells using time series data: two nodes are regarded as coupled if their correlation, which measures how similar their time series are, exceeds a specified value. Gosak et al (2018) show that these approaches can be sensitive to the threshold chosen, and in particular, can overestimate the degree of coupling in a network, particularly if there is significant synchronisation between the time series, which is often the case in islets. These issues, however, can be mitigated by corrections made during network extraction (Ansmann and Lehnertz, 2012).

Although modern imaging techniques allow the activity of many cells to be collected simultaneously, not every beta cell in an islet can be imaged with sufficient temporal resolution to resolve individual electrical or Ca^{2+} events. Thus, networks must be constructed using only a *subset* of the population. Constructing networks from such subsets can lead to incorrect graphs and exacerbates the problem of false positives. In cases where the underlying mechanisms mediating cell activity are understood, network extraction from

time series data can be made more robust when combined with models that take this knowledge into account (Bastos and Schoffelen, 2016; Kadirvelu et al., 2017; Stevenson et al., 2009).

Multilayer networks (MLNs) provide a way to investigate interactions between nodes with respect to different variables, as well as to investigate how networks change over time. For example, islet insulin secretion lowers plasma glucose levels, in turn reducing the stimulatory signal for electrical activity, which may alter the functional network (Markovi et al., 2015). Moreover, it has also recently been demonstrated that beta cells with high metabolic rates can influence the electrical activity across the entire islet (Westacott et al., 2017). However, MLNs must be constructed carefully, especially if it is not known how different processes within the same node are connected. As before, this can be mitigated using complementary modelling techniques which describe specific interactions between these processes (Bertram et al., 2007).

As network science-based approaches are currently being adopted across a wide range of biological disciplines, including neuroscience (Bullmore and Sporns, 2009; Sporns, 2014; Stam, 2014), genetics (Costanzo et al., 2016; Mizrachi et al., 2017), epidemiology (Keeling and Eames, 2005; Leventhal et al., 2015), and endocrinology (Johnston et al., 2016; Markovi et al., 2015; Stožer et al., 2013), we agree with (Gosak et al., 2018) that they will generally prove to be very useful. However, some caution in interpreting results arising from these approaches is in order, and we stress that whenever possible, known physiological and/or mathematical models should be combined with network analysis to improve their robustness and provide more insight into the underlying mechanisms. Nonetheless, there is a bright future to the approach and we expect many new insights and breakthroughs to result from their implementation.

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