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Reply to comment

Loosening the shackles of scientific disciplines with network science Reply to comments on "Network science of biological systems at different scales: A review"

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We would like to thank all the experts for their insightful and very interesting comments that have been submitted in response to our review "Network science of biological systems at different scales" [1]. We are delighted with the number of comments that have been written, and even more so with the positive opinions that these comments communicate to the wider audience [2–9]. Although methods of network science have long proven their value in relevantly addressing various challenges in the biological sciences, such interdisciplinary research often still struggles for funding and recognition at many academic levels.

In this reply, we would like to highlight the coming of age of network science, as well as data science, applied to biological systems in the broadest possible sense. We would also like to emphasize that the theoretical and modeling tools that have been developed by physicists, mathematicians, and computer scientists have reached the maturity to effectively address the many challenges of our time, not least aiding the diagnosis and treatment of disease [10]. In

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what follows, we briefly discuss the comments on our review in the light of this fact, and we also point out the many outstanding challenges as well as opportunities for future research.

De Domenico [4] has raised concerns about the lack of objective measures for statistical similarities, either for dealing with simplex or multiplex networks. Along this line, Jalili [7] also puts emphasis on the existence of different similarity measures, such as the linear cross-correlation or the synchronization likelihood that captures nonlinear relationships, and similar concerns have been expressed by Wedgwood and Satin [9] as well as by Loppini who also suggested the use of partial correlations or transfer entropy as possible means of network construction [2]. Moreover, De Domenico, Jalili, and Pedersen [4,7,8] underline methodological drawbacks related to the thresholding of similarity matrices. Fixing the network density seems to be a good alternative, especially when multiple groups are compared [11]. We agree with this remark. For example, in islets the beta cell activity and the resulting synchronization patterns gradually depend on the stimulus concentration and also possible pharmacological interventions. Studying in depth the resulting network structures requires a proper compensation for such intrinsic biases. Perhaps even more remarkably, De Domenico highlights some advanced alternative approaches for bridling differences in densities that are based on the random matrix theory [12] or on optimization principles [13]. We would like to additionally point out that also prior steps preceding the application of similarity measure algorithms require a rigorous treatment. In particular, complex calcium signals captured with confocal microscope entail a baseline activity, noise and other artifacts. The processing of time series and the extraction of the desired dynamical components should therefore be performed with care.

Jalili [7] emphasized that the majority of functional brain network studies are based on undirected networks, although the information flow is in general directed. Even more, directionality of connections may reveal different architectural properties that are not observed in undirected networks [11]. We do not only agree with the comment but also argue that considering bidirectional connections can be even more relevant in intercellular than in brain networks. Often, the cells are directly coupled and the resulting collective activity is mediated by calcium wave propagation. As a matter of fact, Pires et al. [14] have already implemented a directed network approach to track the calcium signal in a culture of astrocytes, whereas we used a similar method to simultaneously track the depolarization and calcium wave propagation in islets and represented the intercellular communication pattern as a multiplex network [15]. In both studies the time lag was used as the main determinant for directionality. We believe that mapping and examining signal propagation in tissues and other settings by means of a directed network is a promising approach and signifies a physiologically relevant alternative for the more traditional functional connectivity patterns.

Loppini [2] has excellently pointed out the idea to use the multilayer network (MLN) formalism by means of including also other cell types, i.e. alpha and delta cells, as well as other intercellular signaling mechanism, such as autocrine and paracrine signaling. We very much agree with the idea. A complete understanding of islet functionality and hormone regulation requires a holistic approach beyond the beta cell physiology. While indeed a few recent studies have addresses this issue theoretically [16] and even in part experimentally [17], the technology to acquire simultaneously the dynamics of multiple cell types in situ with a good spatio-temporal resolution, which would facilitate such MLN-based endeavors, still needs to be developed. However, one of the most fundamental and the most problematic issues is the discrimination of different cell types in islets in a manner compatible with functional multicellular calcium imaging (fMCI). Relying on differences in the inactivation properties of voltage gated sodium channels between alpha and beta cells [18] or other electrophysiological properties of alpha, beta, and delta cells is limited to a single cell at a time and is therefore not compatible with fMCI. More promising are specific stimulation protocols with the help of which the cells can be classified with regard to their characteristic response to high glucose and glutamate [19] or adrenaline [20]. However, this approach is limited by the length of the protocol itself and therefore not suited for screening purposes followed by a battery of tests. Another option is immunolabeling which enables identification of cell types after recording the calcium response [21–23]. Immunolabeling is specific and a large number of cells can be characterized. Its major drawbacks are the fact that it is applicable only post festum, i.e., after the functional imaging and that during immunolabeling, the same optical section needs to be maintained to ensure an exact overlap between structural and functional data and this can be technically demanding and time consuming [21–23]. At present, the most straightforward approach to discriminate between the two most prevalent cell types, alpha and beta cells, would be to use GluCre-ROSA26EYFP (or GYY) mice that express the enhanced yellow fluorescent protein specifically in alpha cells [24] and that have previously helped to electrophysiologically characterize alpha cells in tissue slices [25]. Beta cells could then be discriminated from other non-alpha cells by their characteristic response to glucose. Additionally, transgenic somatostatin-Cre mice crossed with fluorescent reporter strains could be used to identify delta cells [26,27].

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