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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].

In this way, beta cells with different roles in the network could conceivably be compared with respect to their spatial relationship to alpha cells. However, genetic labeling can only be used in specific transgenic mouse strains and is not applicable to islets from other species. To circumvent this problem, Shuai et al. have recently introduced adenoviral vector based cell type specific promoter driven expression of fluorescent proteins mCherry or GFP [28].

Similarly, as suggested by Wedgwood and Satin [9] and Belgardt et al. [5], the dependence of a cell's role in the network on other characteristics of the same cell, its neighbors, or even mesenchymal structures, such as endothelial cells [29], can be investigated, given that calcium signals can be obtained from islets labeled for other structural or functional markers.

In this respect, one of the main challenges for the foreseeable future is to find out how some of the described functional properties of different beta cells, such as (i) the number of their functional connections (that determines their roles as hubs versus less well connected cells) [30–32] or (ii) the sequence in which they are activated during a calcium oscillation (that determines their role as pacemakers versus followers) [33,30,34–36] relate to recently described morphological subtypes of beta cells [37–42].

More specifically, Bader et al. recently described two molecularly and physiologically distinct populations of beta cells with regard to their Flattop (FLTP) expression profiles. $FLTP^{+}$ cells that constitute the majority of beta cells (80%) seem to be metabolically more active compared with $FLTP^{-}$ cells (20%) which display higher proliferation rates [43]. Similarly, by staining purified beta cells with antibodies against ST8SIA1 and CD9, Dorrell et al. found 4 distinct subpopulations of beta cells. The double negative subtype of cells displayed the lowest basal insulin secretion and the highest stimulation index [44]. Given that hub cells present a minority of beta cells and that they are metabolically highly active [15,30] but secretory less capable and slightly undifferentiated [30], it is tempting to speculate that they might at least partly overlap with $FLTP^{-}$ and non-$ST8SIA1^{-}$/$CD9^{-}$ cells, but this will have to be addressed in future studies. The understanding of the complex machinery in islets that governs the homeostatic control of glucose will definitely encompass further efforts in developing suitable experimental techniques for assessing simultaneously as many dynamical compounds as possible. Understanding and interpreting such complex and exhaustive data requires advanced computational tools and the MLN formalism definitely represents an excellent and promising possibility.

Belgardt et al. [5] and De Domenico [4] have evolved in their comments the idea of MLN and diabetes and other diseases research even further. De Domenico [4] emphasizes that the functioning of cells is governed by a set of molecular interactions and that all interactome types are interconnected. Because of this interdependency, the alteration of single genes can quickly propagate a perturbation to the protein–protein interaction network, causing abnormal functions in tissues and organs that culminate in diseases. Belgardt et al. [5] additionally underscore the relation of the disease network with the social network, especially in the relation with a lifestyle related pathogenesis. We acknowledge these ideas and believe that due to the interconnectedness of different networks, the identification of causes is a thrilling and very demanding mission that many times cannot be accomplished focusing only on single scales, i.e. network layers. Searching for such interdependencies is one of the main tasks of the recently emerging fields of network medicine [10] and network physiology [45]. However, probably the most vital and unresolved issue is to identify how different layers within an organism interact and, subsequently, how to formally describe and quantify such interactions. Interestingly, Belgardt et al. [5] have pointed out an interesting idea, relying on very recent studies [46], that exosomes might be the information carriers that interconnect different physiological networks and different scales of biological organization in an organism.

Nevertheless, the idea of having multiple layers of networks and/or interdependent networks is even older than the modern network science itself. Such systems were examined decades ago in disciplines like sociology and engineering, but in the last few years a tremendous progress has been made by providing a unified mathematical framework to study multilayer complex systems [47–50]. However, as nicely underscored by Muldoon [6], there are many open issues and possible inconsistencies especially by the definition of inter-layer connections based on multidimensional datasets. While the construction of connections within network layers has a long tradition and is well accepted within the community, the interlayer connections represent a different story. Currently, the choice for interconnecting nodes in different layers is set by the user. The nature and/or strength of these connections, however, impacts significantly the extracted network measures, especially the dynamic community detection. Buldú [3] shares the same concerns. In his comment he focuses predominantly on MLN brain networks, but the problems he raises are well applicable to tissues and other setting as well. While in general he agrees that the MLN perspective is a powerful technique to assess the multiple types of coordination and dynamic activities in the brain, he outlines some very important issues about the evaluation of interlayer connections. He stresses out that the same fundamental problems appear when studying the

interplay between anatomical and functional connectivity, tracking the network activity in time, and when focusing on specific frequency bands. We completely agree with both commentators and also encourage further endeavors to systematically explore the effects of various parameter choices. Finding objective and, most importantly, physiologically relevant criteria for the construction of inter-layer connections will be one of the most important future tasks in the MLN community, irrespective of the scale.

Wedgwood and Satin [9] as well as Pedersen [8] also suggest to combine phenomenological complex network approaches with mathematical models and computer simulations to gain more insight into the mechanism that support functional connectivity patterns. We strongly agree with this opinion and acknowledge their contributions and contributions by others in this regard [51,34,52,53,35]. Especially the recent study by Cappon and Pedersen has provided an interesting mechanistic explanation for the emergence of the small world functional network in our tissue slice preparation [31] due to a large degree of heterogeneity in intercellular coupling. Their simulation study also indirectly addressed an important problem of confocal microscopy based fMCI, namely that a 3D system is captured only with a 2D optical section. Their model was constructed in 3D and then a given 2D section was analyzed yielding functional connectivity patterns very similar with what we recorded in islets [52]. Moreover, we also employed a combination of computer simulations and experimental measurements to show that the most connected cells are the ones showing the highest degree of dissipativity [15] and to show that the spatiotemporal patterns of calcium dynamics upon stimulation with glucose display a phase transition from critical to supercritical behavior. In our model of coupled beta cells, in contrast with the study by Cappon and Pedersen [52], heterogeneity in intercellular coupling was not sufficient to explain the experimentally observed behavior, but a high degree of heterogeneity in some crucial parameters that govern beta cell behavior was also needed [33], as also noted by Loppini [2,54,55].

In sum, all contributors share our opinion and in a large extent also the enthusiasm about the network science and especially the MLN formalism being one of the key pillars for assessing the functional principles of various biological systems. We are all well aware that there are still limitations and open issues referring either to the theoretical part of network science or to the difficulties of acquiring and integrating data obtained from different sources and at different levels of biological organization. Since the network science is a rather young and intensively developing field, this should not be considered as a weakness, but rather as a motivation for researchers to critically interpret the current research and to develop new methods. This will in turn hopefully lead to more integrated perspectives on the functioning of biological systems and the evolution of complex diseases, thereby making the network science one of the major driving forces for the progress in human medicine.

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