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Review

Network science of biological systems at different scales: A review

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Abstract

Network science is today established as a backbone for description of structure and function of various physical, chemical, biological, technological, and social systems. Here we review recent advances in the study of complex biological systems that were inspired and enabled by methods of network science. First, we present research highlights ranging from determination of the molecular interaction network within a cell to studies of architectural and functional properties of brain networks and biological transportation networks. Second, we focus on synergies between network science and data analysis, which enable us to determine functional connectivity patterns in multicellular systems. Until now, this intermediate scale of biological organization received the least attention from the network perspective. As an example, we review the methodology for the extraction of functional beta cell networks in pancreatic islets of Langerhans by means of advanced imaging techniques. Third, we concentrate on the emerging field of multilayer networks and review the first endeavors and novel perspectives offered by this framework in exploring biological complexity. We conclude by outlining challenges and directions for future research that encompass utilization of the multilayer network formalism in exploring intercellular communication patterns in tissues, and we advocate for network science being one of the key pillars for assessing physiological function of complex biological systems—from organelles to organs—in health and disease.

Keywords: Complex networks; Biological systems; Intercellular communication; Calcium signaling; Beta cells; Multilayer networks

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1. Introduction

The past two decades have witnessed the coming of age of network science as the central paradigm behind some of the most fascinating discoveries of the 21st century [1,2], from the mathematical formulation of small-world properties and their omnipresence in gene and transcriptional networks, protein networks, brain and social networks, food chains and electric power grids [3], to the universal scaling properties due to growth and preferential attachment that likewise pervade biological, social and technological networks [4]. The field of research today known as network science has been going from strength to strength, as evidenced by the many reviews devoted to and building upon networks [5–15]. Network science has provided models, methods, and algorithms that have revived not just statistical physics, arguably the parent to the field, but indeed many other fields of natural and social sciences, including of course the study of complex biological systems, to which we will attend to in this review.

In addition to the study of static networks that remain structurally unchanged, methods of network science allow us to study network evolution over time, for example due to changes in external factors, the onset of disease, targeted attack, or simply due to random failure. Such changes can be studied in the realm of temporal networks [16–18], where the theoretical framework accounts for addition or removal of nodes, or similarly for changes in links between nodes, over time. Also important is the fact that networks exist between different layers of each studied system, and this is particularly apparent in complex biological systems, where networks of organelles form cells, which then again form networks to form organs, and so on. This can be accommodated in the theoretical framework of multilayer or interdependent networks, or more generally networks of networks, which acknowledge that not only are the interactions in complex systems limited and thus inadequately described by well-mixed models, but also that the networks that should be an integral part of such models are often interconnected, thus making the processes that are unfolding on them interdependent [19–23]. From the world economy and transportation systems to social media, it is clear that processes taking place in one network can significantly affect what is happening in many other networks.

Before delving into networks in complex biological systems, we note that in addition to network science, technological breakthroughs in the acquisition and storage of vast amounts of digitized data have also aided the progress in all above-mentioned disciplines. The so-called big data revolution has had a particularly deep impact on social sciences and economics, where social and behavioral experiments in the past typically involved one-shot self-reported data on relationships and their outcomes in a small sample of people, while today the approach is to mine massive amounts of digitized data for both structure and content of relationships [24,25]. Importantly, however, also in biological and chemical systems, advanced imaging techniques and ever more sophisticated experimental equipment have led to the data deluge, thus playing into the hand of synergies with network science and advanced data analysis methods.

2. Biological systems as complex networks

For a complete understanding of complex biological systems, such as cells, tissues, whole organisms, or even ecosystems, it is not sufficient to identify and characterize individual building blocks in the system. It is also necessary to obtain a thorough insight into the interactions between molecules, pathways, cells, organs, and individual species. However, due to a nontrivial nature of interactions among components, large amount of data and inherent nonlinearities in the dynamics of individual elements, the interaction patterns and functional organization of biological systems are hard to assess. The modern complex network theory has proven to be a very effective key towards understanding these complex architectures. Network analysis is beneficial because it can facilitate identification of complex, and often emergent, patterns, and can provide hypotheses for relationships between structure and function in many systems and at different scales, as illustrated in Fig. 1.

At the subcellular level, it is now possible to characterize and examine different molecular networks, such as gene regulation networks [26], protein interaction [27,28] and metabolic regulation networks [29], in order to understand how different components and interactions between them determine the function of this enormously complex machinery. In this framework, nodes of a network signify for example proteins or metabolites, whereas the links stand for protein–protein and metabolic reactions or shared genes. Most of these networks were found to have a specific non-random structure exhibiting small-world properties, a power law degree distribution and a modular and hierarchical organization (for review see [30]). Most importantly, tools of network theory have not only proven to be able to successfully uncover the cell's normal internal organization and evolution, but can also gradually improve our understanding of disease pathogenesis. An abnormality in a specific gene spreads along the links of the molecu-

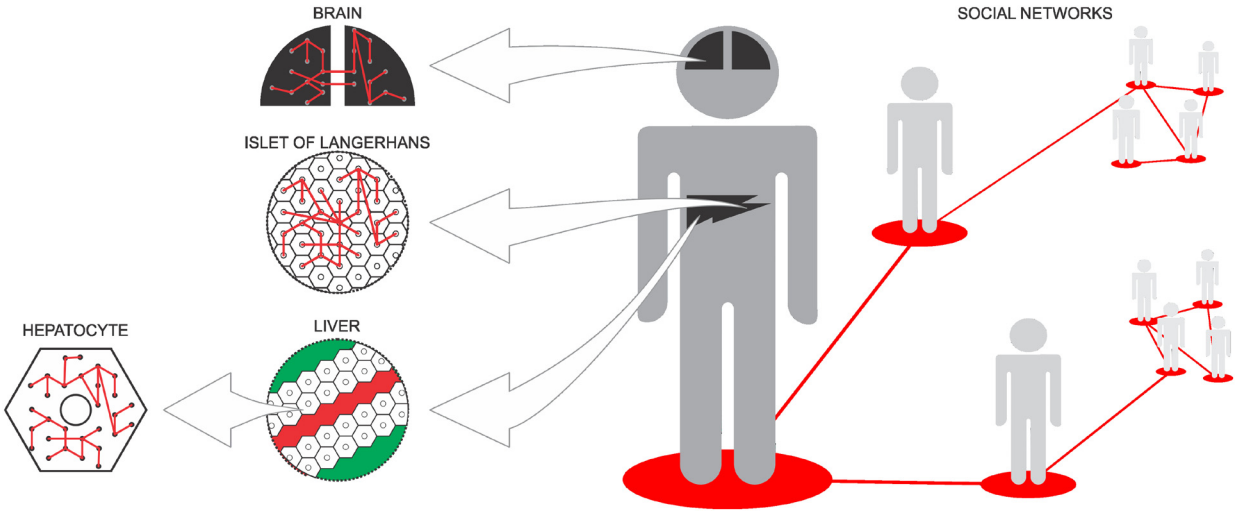


Fig. 1. Complex networks are found at all organizational levels in biological systems. At the subcellular level, networks between genes, proteins, and organelles orchestrate transcription, biochemical reactions, and intracellular transport in a transcriptionally and metabolically active cell, such as a hepatocyte (lower left panel). In this case, the links between nodes can be shared transcriptional regulation, common metabolic intermediates, or participation in a given process. At the tissue level, information transfer between different cells, such as beta cells within a pancreatic islet of Langerhans (middle left panel), is achieved via gap junctions and paracrine signaling. Here, links between cells are based on physical interaction (direct contact or contact via nerves or diffusible factors) or on similarities between signals produced in different cells (such as membrane potential or intracellular calcium concentration changes). At the organ level, different areas of the brain are activated simultaneously and cooperate during various activities and tasks (upper left panel). Again, links can be structural (via white matter association and commisural pathways) or based on similarities between signals obtained by functional brain activity recordings (fMRI for instance). At the level beyond an individual organism, humans interact with other persons in social and business networks (right), with other species in ecosystems, build transportation networks and power grids, and many of these networks are at least in part interdependent with financial and trading networks (not shown).

lar network and perturbs multiple molecular processes in the entire set of molecular interactions in a particular cell, or the so-called interactome [31,32]. In this regard, the methodology of network science offers a strong theoretical framework for identification of disease modules and pathways and molecular relationships among apparently distinct (patho)phenotypes [32,33] as well as for the design of drug–target networks [34].

Modern network theory is increasingly used in neuroscience to understand the neuronal physiology and anatomy at different scales and in the most physiological and pathophysiological conditions experimentally achievable at present [35]. First endeavors were undertaken at a microscopic anatomical level of individual neurons. Watts and Strogatz [3] analyzed the anatomical connectivity of the nervous system of *C. elegans*, whereby neurons represented the nodes and the synapses or gap junctions the links of the neuronal network. Their study has revealed a highly clustered and efficient network, thereby representing the first evidence of small-world architecture of a real nervous system. Later graph-theoretical approaches have focused on morphological characterization [36–39] or to dynamical correlations in electrical firing activity of neuronal networks [40–42].

Even more attention, also in the context of potential clinical applications, has been given to the study of brain network topology or connectomics [43–46]. The majority of existing studies restricted their attention to functional networks, which reflect statistical dependence between brain region activities. The construction of such macro-networks is based on modern brain mapping techniques, such as diffusion MRI, functional MRI, EEG, and MEG, whereby two functional domains of the brain are considered to be connected if their temporal correlation exceeds a given threshold. Some studies have also investigated the brain's structural connectivity, most frequently designated by the architecture of white matter tracts [47]. It has been shown that the neuroanatomical brain network bears many similarities with the functional connectivity patterns [48–50], although the precise interplay between the structural features and functional associations is still incompletely understood [51]. Irrespective of the imaging and the subsequent network extraction techniques, the extracted brain networks are inherently complex and share a number of common features with other real-life systems, such as small-worldness, heterogeneity in connectivity and a hierarchical and modular organization [43–45,52]. Noteworthy, the brain's connectivity measures are also emerging as prospective markers for discovering connectivity abnormalities in neurological and psychiatric disorders [53–58], for tracking changes associated with

developmental processes [59] and aging [60], and for exploring activity- and behavior-dependent structure of brain networks [61–63].

On large scales of observation, network-based analyses have been found very useful for addressing several questions in ecology and problems in conservation. First studies were conducted in the so-called context networks of species interactions. Food webs, one of the fundamental issues in ecological research, were reported to exhibit a complex topology, similar as in other types of real-world networks, even though a rather high level of variability in network structures was detected [64]. Moreover, the network concepts have also been applied to other types of species interactions, such as pollination networks [65] and host–parasitoid webs [66]. One of the main advantages of these methods is a straightforward evaluation of robustness and susceptibility of a given ecosystem to species loss or other types of perturbations [64,67,68]. Another type of widely used networks in ecology are mappings of connectivity across landscapes, where nodes typically represent patches on a landscape. The resulting spatial networks describe the link between processes and patterns of landscape features, thereby representing an efficient methodology for assessing important issues like species dispersal or the impact of habitat loss [69,70].

Finally, we mention branching patterns of blood vessels or the venation in plant leaves, which represent the foundation for one of the most prosperous theoretical frameworks of the effects of network structure on the behavior of networked systems, the theory of biological allometry [71]. Investigating these circulatory systems can benefit largely from a network-based perspective, not only through quantification and understanding of transport processes in these loopy hierarchical networks [72–76], but also through reconstruction of vascular architectures from imperfect data [77]. Recently, very similar methodological concepts have been applied to infer the structure of fibroblastic reticular cell networks, which serve as scaffolds for lymphocyte migration and provide key elements for proper immune responses [78]. The underlying structure of the FRC network has been identified as robust with small-world network topological features, analogous to many other biological networks.

3. Functional connectivity patterns in islets of Langerhans

While the network-based approaches are undoubtedly a successful and widely-used methodological approach to investigate biological systems at different scales, their application to study the functional interaction patterns between individual cells in tissues has been rather limited. This seems a bit counterintuitive, since several tissues are organized as networks, evolve in time and their cells can be regarded as dynamical entities, which interact with each other. As such, they represent excellent candidates for being studied and interpreted in terms of graph-theoretical approaches. However, until recently, the utilization of network concepts has not yet received very much attention in this area, mostly due to a lack of suitable experimental techniques.

The above also holds true for islets of Langerhans, microorgans in which around 10^3 beta cells are homotypically interconnected via gap junctions and paracrine signals to ensure a coordinated secretion of the most important anabolic hormone insulin [79–84]. Moreover, beta cells behave as cellular oscillators, displaying highly regulated and coordinated changes in intracellular ATP, cAMP, membrane potential (MP), intracellular calcium concentration ($[Ca^{2+}]_i$) changes, and insulin secretion [85,86]. Finally, beta cells seem an attractive candidate for application of complex network tools for another very important practical reason. Their dysfunction is one of the main pathophysiological factors for development of diabetes mellitus, a disease of epidemic proportions and with severe personal and health-system costs [87]. However, since the total beta cell volume is rather small (there are around 10^6 beta cells in mice and 10^9 in humans) and since they are positioned within the exocrine pancreatic tissue, which secretes digestive enzymes that potentially threaten the structural and functional integrity of beta cells, the development of techniques to study beta cells *in vitro* has followed a painstaking path. By microdissecting pancreatic tissue, researchers could record MP changes in individual beta cells within structurally preserved islets, but this way, functional information could be obtained from a single cell only are at most from two cells at a time [88]. In addition, microdissection is very time-consuming. An important step further in beta cell research was combining model mice with increased beta cell mass with isolation techniques that employ digestive degradation of the exocrine part of the tissue, enabling access to isolated islets, or after dispersion of islets, of suspended single beta cells, in which MP or intracellular calcium $[Ca^{2+}]_i$ recordings can be obtained upon loading with calcium- sensitive fluorescent dyes [89–92]. However, recordings on isolated cells do not permit any reliable conclusions as to the function of the intact beta-cell syncytium, and recordings of $[Ca^{2+}]_i$ changes have been limited by too low a spatial resolution of CCD cameras to enable reliable recordings

from single cells within islets [92,93] and upon advent of confocal microscopy, by the fact that uptake of fluorescent dyes is usually limited to the outermost layers of islets [94,95].

In 2003, Speier and Rupnik have introduced the pancreas tissue slice method, which does not employ enzymes and preserves the structure of the endocrine and surrounding exocrine tissue. Additionally, the slicing procedure exposes the islet core, which enables access to a large number of beta cells [96,97]. Using this method in combination with confocal microscopy, MP and $[Ca^{2+}]_i$ dynamics can be traced with single cell resolution over long periods of time in a large number of cells simultaneously [98,99]. In beta cells, stimuli, such as glucose, are coupled with exocytosis of insulin and it is reasonable to ask why study more proximal steps in the stimulus-secretion coupling, such as MP and $[Ca^{2+}]_i$ changes, and not exocytosis directly. Since beta cells are functionally polarized, with exocytosis being targeted towards vasculature, it is impossible to capture exocytotic events in all cells from a focal plane by confocal microscopy [100–102]. In contrast, both MP and $[Ca^{2+}]_i$ changes affect every part of the membrane and volume and are thus easier to capture [99]. Importantly, they are temporally tightly coupled to exocytosis of insulin-containing granules [91,92,103]. Therefore, they can serve not only to understand the propagation of MP and $[Ca^{2+}]_i$ signals between cells but also as a proxy for assessing exocytosis.

A graph-theoretical approach can be applied on the abovementioned MP and $[Ca^{2+}]_i$ recordings by extracting patterns of functional connectivity, i.e., identifying cell pairs with correlated activity [104,105]. First, the recorded time series are processed by a band-pass filter or by other advanced methods, such as Huang–Hilbert empirical model decomposition [105,106]. These are needed in order to remove noise, the effect of photo-bleaching, and the basal slow component of Ca^{2+} activity. The cross-correlation coefficient between calcium dynamics of cell pairs is used to form binary connectivity maps that, in turn, form basis of functional beta cell networks. In terms of the complex network theory, beta cells are nodes, and each and every pair of them are connected if their $[Ca^{2+}]_i$ signals are similar enough [104]. The methodology to extract functional connectivity patterns from $[Ca^{2+}]_i$ traces encompassing the calculation of pairwise cell-to-cell correlations and the thresholding of the obtained correlation matrix to achieve a binary description is demonstrated in Fig. 2 for two pancreas tissue slices that were subjected to stimulation by 8 mM and 12 mM glucose. A visual assessment indicates that a higher glucose concentration does not only provoke higher beta cell activity but also leads to more synchronized behavior and to more integrated functional network structures. It should be noted that despite the fact that the threshold parameter affects network density, within reasonable limits the result is qualitatively independent on its value. In practical terms, the threshold for correlation should be chosen low enough to yield a network whose density permits calculation of network parameters, and also high enough to explain the largest possible part of variance in data [104].

Once the functional network is established, it can be quantified by network statistics. Here we describe some commonly used metrics and the insights that they have offered into the complexity of beta cell signaling in islets: (i) average degree, (ii) average clustering coefficient, (iii) global efficiency, (iv) community structure, and (v) largest connected component. More specifically, by counting the number of connections that are attached to the i-th cell, we define its degree, k_i, and the average degree $\langle k \rangle$ is simply obtained by averaging over the whole population. Its value reflects the proportion of highly correlated cell pairs, i.e., cell pairs with highly synchronized $[Ca^{2+}]_i$ signals. To characterize segregation of the network, the so-called clustering coefficient is calculated. The local clustering coefficient, C_i, measures how well particular adjacent regions are interconnected, whereas the average clustering coefficient, $\langle C \rangle$, is defined as the average of all local clustering coefficients. A more advanced measure for segregation is the identification of communities, i.e., subsets of cells that are more densely connected among themselves than they are to the rest of the network. A popular method to arrange the nodes into individual communities is governed by an optimization process in which a measure called modularity, Q, is being maximized. Higher values of Q correspond to architectures that are more segregated. A conceptually different metrics that measures the functional integration of the network is the global efficiency $\langle E \rangle$. The measure is computed as the inverse sum of shortest path lengths between all pairs of cells in the network. Higher values of $\langle E \rangle$ signify short geodesic separation among cells and hence a better communication ability. Another measure for the degree of integration of islets is the largest component, which is also very informative with respect to susceptibility to perturbations. This metric reflects the fraction of cells that are interconnected either directly or indirectly and how many of them are isolated.

In Fig. 3 we illustrate the network metrics used to characterize the functional beta cell connectivity and the results quantifying the networks shown in Fig. 2. In the low stimulation regime (8 mM), the network is rather sparse and segregated into localized interconnected subcomponents, with very little inter-module connections. On the other hand, a much denser and more cohesive network is observed in the high stimulation regime (12 mM), yet with still

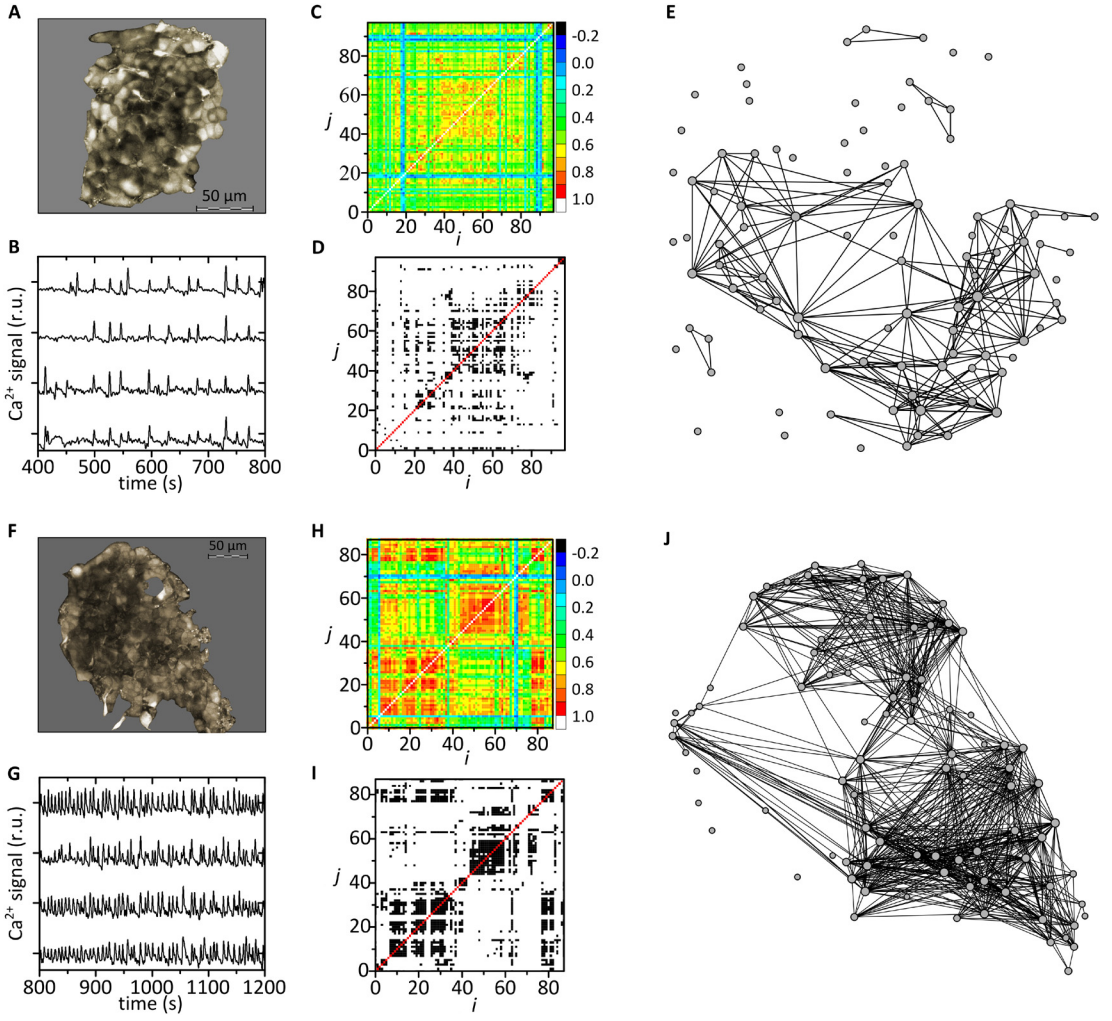
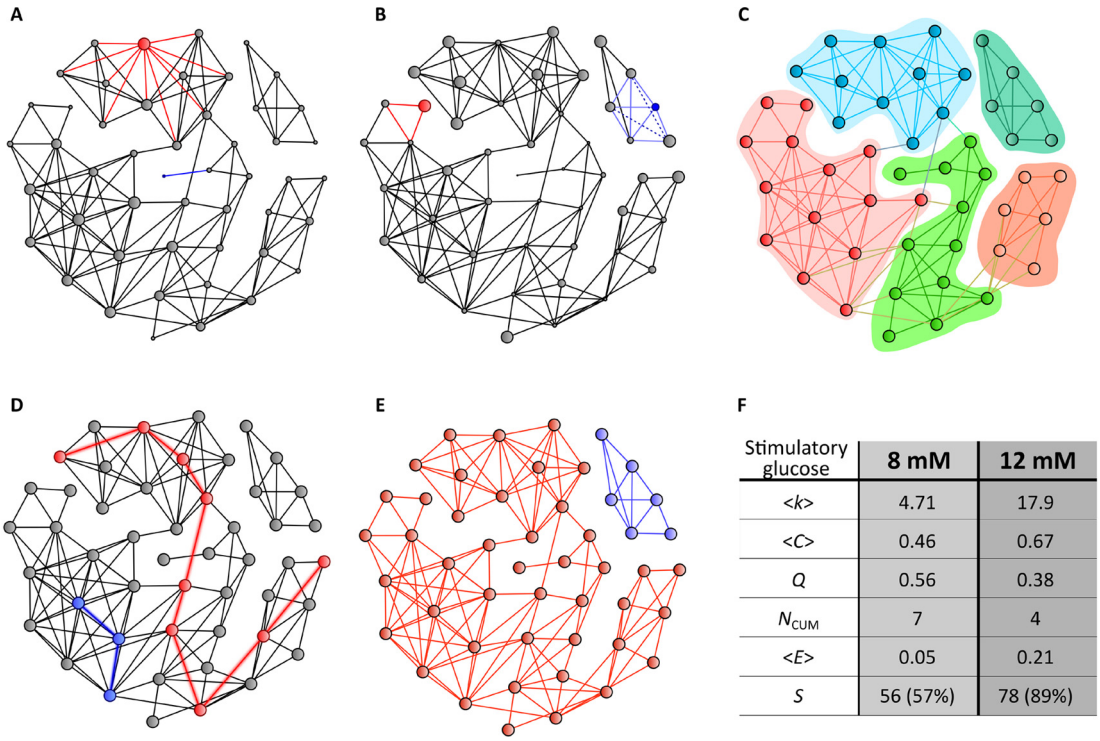


Fig. 2. Construction of functional beta cell networks. Confocal images of two pancreas tissue slices (A & F). Characteristic recorded $[Ca^{2+}]_i$ signals from four beta cells (B & G). Correlation matrices showing color-coded correlation coefficient values between all cells pairs, coding of the degree of correlation as indicated in the figure (C & H). Binary connectivity matrices with black ($d_{ij} = 1$) and white ($d_{ij} = 0$) elements obtained by thresholding the correlation matrix at $R_{th} = 0.75$ (D & I). Resulting functional networks with nodes corresponding to physical positions of individual cells in tissue slices (E & J). Upper panels (A–E) correspond to stimulation with 8 and lower panels (F–J) to stimulation with 12 mM glucose.

well-defined and localized subgroups [105,107]. Most importantly, the results indicate that beta cell networks are not homogeneous lattice-like structures, rather they form functionally more efficient and clustered networks. Especially the high glucose-provoked functional connectivity is characterized by a high global efficiency and a high clustering coefficient, thereby indicating small-world topological features [3]. In general, these properties reflect a very efficient design that ensures synchronizability, local redundancy of activating signals, robustness, as well as a balance between local and global processing [108]. Moreover, in our previous study we have demonstrated that the density of the beta cell network is highly influenced by glucose concentration, the main nutrient secretagogue [104]. The extent of segregation into functional sub-compartments as well as other network metrics were found to be non-linearly dependent on glucose concentration. They saturate to a plateau value at 9–10 mM glucose, thereby revealing the highest degree of network plasticity over physiological glucose concentrations below this plateau [105].

Employing an analogous experimental and analytical approach, as well as biophysical and mathematical modeling, others have largely confirmed our results [109,110] and provided a mathematical foundation for our findings and their seeming discordance with the general belief that islets are homogeneous lattices [81,111–114]. It has also been



Stimulatory glucose	8 mM	12 mM
<*k*>	4.71	17.9
<*C*>	0.46	0.67
Q	0.56	0.38
N_{CUM}	7	4
<*E*>	0.05	0.21
S	56 (57%)	78 (89%)

Fig. 3. Schematic overview of network metrics used for the characterization of beta cell functional networks. A) Average degree $\langle k \rangle$, B) average clustering coefficient $\langle C \rangle$, C) number of communities N_{cum} and modularity Q. D) global efficiency $\langle E \rangle$, E) relative largest component S, and F) summarized networks measures for beta cell networks under 8 mM and 12 mM glucose shown in Fig. 2.

suggested [115] and later demonstrated convincingly that the beta cell connectivity can be a target of diabetogenic insults, such as lipotoxicity [84,110] and cytokines [115], and may also play an important role in rare monogenic forms of neonatal diabetes [116,117]. Moreover, very recently it has also been shown that in a mouse model of prediabetes with a disrupted insulin secretion mechanism a reduced synchronicity in $[Ca^{2+}]_i$ dynamics was observed in comparison to wild-type littermates. As a result, functional beta networks were found to be more segregated, which was suggested to be associated with morphological and functional adaptations of islets, resulting from disruptions of the secretory apparatus, and leading in turn to a large-scale disorganization of hormone release activities [118].

Noteworthy, in the last years similar endeavors combining multicellular $[Ca^{2+}]_i$ imaging and graph-theoretical approaches have also been conducted on other multicellular systems. In particular, network analysis has been implemented to uncover the intercellular interaction patterns in pituitary endocrine cells [119], neural progenitor cells [120], cultures of astrocytes [121], neuronal assemblies [122–126], and human lens epithelium cells [127]. These methodologies have proven not only to successfully describe the nature of intercellular signaling pathways, but were also found to provide valuable insights into the evolution of intercellular networks during increasing stimulatory conditions [105], the entrainibility and stability of intercellular networks [122], the experience-dependent plasticity of tissue function [119], changes in connectivity during development [120,122], and to the modifications of cell-to-cell connectivity occurring in disease [110,123,127]. In all these studies, the network approach enabled the assessment of inherent dynamical dependencies between cells, offering thereby a principled framework for statistical inference, which would not be possible with conventional methodological tools.

4. Multilayer network approaches as the current frontier and their applicability to islets of Langerhans

Biological networks are in general nonstationary and evolve in time. Often, they are governed by multiple types of interactions and/or interact with other networks. Therefore, the standard network approach focusing on single networks in isolation might be insufficient to unveil the functional regulatory patterns originating from complex interactions across multiple layers of biological relationships and processes. For the description of such multi-dimensional

complex systems that exhibit multiple facets of complexity, the multilayer network (MLN) formalism has been proposed and is acquiring more and more prominence in terms of a new research direction [19–22,128–132]. First studies employing the MLN paradigm focused on describing transportation [133–135], social [136–139] and communication networks [140–142], and, as the big data movement advances, also in quantitative economics and financial networks [143–145]. Nevertheless, the integration of MLN theory into research of biological systems is recently also becoming a more and more contemporary topic [146–148].

The major biochemical networks that govern cellular activities, gene regulatory networks, and the network of biochemical reactions, are actually highly interdependent and are as such excellent candidates for being analyzed and visualized as MLN [23,131,149]. Moreover, the increased availability of genomic, proteomic and metabolomic data made the task of integrating multilayered complexity of biological systems auspicious, especially in the less complex biological systems, such as unicellular organisms or nematodes. For instance, constructing a MLN of protein–protein interactions (PPIs) of six different life stages of the nematode worm *C. elegans* revealed robustness of the PPI networks [150], whilst a large relative reactivity to perturbations was reported in the PPI and in the gene regulation networks in *E. coli* [149]. Further, an MLN based on gene expression similarities detected functional communities across layers that were linked to cell-specific processes (e.g., DNA damage reparation or endocytosis) in yeasts [151]. In more complex biological systems, e.g., humans, an early study of transcription and splicing networks demonstrated that strongly coupled modules are formed where strict regulation of data transfer from DNA to proteins is needed [152]. In recent years, the MLN approach was employed extensively to link human diseases with genetic, biochemical, and environmental factors. Interestingly, this approach demonstrated that most diseases are dominated by genetic risk factors, while environmental factors prevail in depression, cancer, and dermatitis, to name only a few [153], and that diseases that share common genes tend to share common symptoms [154]. Moreover, the MLN approach shows a promising socio-economic impact in the developing countries, where malnutrition and neglected diseases are often associated with poverty and for which there is lack of interest from the pharmaceutical industry. Novel pharmaceutical drugs providing treatment of neglected diseases [129] and targeted nutritional intervention [155] promise to improve the overall health status.

The utilization of MLN theory is becoming popular also at the macroscopic level of biological sciences. Especially the description of ecological systems could benefit from the application of this novel framework and is gaining popularity also due to the growing availability of ecological data (for review see [148]). Different layers can account for multiple interaction types between species [156–159], such as predation, competition, and facilitation, or for a more precise description of spatial and temporal evolution of ecological processes and interactions [160–162]. The methodology was proven successful by the description of reciprocal effects between ecological resources and social networks [163] and in movement ecology for the description of gene-flow patterns in discrete habitats [164]. It has been argued that formulating ecological systems as MLN does not only offer additional perspectives into the architecture and dynamics of ecological systems, but also more firmly evaluates their robustness to perturbations, which is a critical element in restoration management [148,165]. Furthermore, following the advances in the MLN theory, many endeavors were devoted to the description of epidemic-like spreading processes on top of multilayered interconnected complex networks [166]. Examples include competitive spreading [167], spreading on temporal networks [168], epidemic propagation in partially overlapped multiplex networks [169], the impact of immunization strategies [170] isolations [171], and vaccination [172] on the speeding of diseases within and across different layers, to name only a few.

The theoretical framework and computational tools from the realms of the MLN theory are recently also becoming a popular and developing trend in network neuroscience [58,146,173–175]. The first application of multilayer analysis addressed the temporal evolution of brain network dynamics [176]. In general, each layer represents a subsequent time window and the edges within that layer represent the existing functional relationships in the given time interval. Considering functional brain networks as dynamic rather than static entities has proved particularly powerful in characterizing reconfiguration of human brain networks during learning [61], performing tasks [177,178], and to track the development of seizures [179]. Beyond temporal networks, one can extend the MLN construct to represent frequency-band specific brain networks [180]. The calculation of several multiplex hub and connectivity metrics has revealed that networks obtained in different frequency bands do not act as independent entities and provides a more accurate map of brain's most important functional regions, allowing to distinguish between healthy and pathologic populations better than conventional network approaches [181–183]. Furthermore, researchers have also made use of possibilities offered by the multilayer framework to address the longstanding issue about the interplay between brain structure,

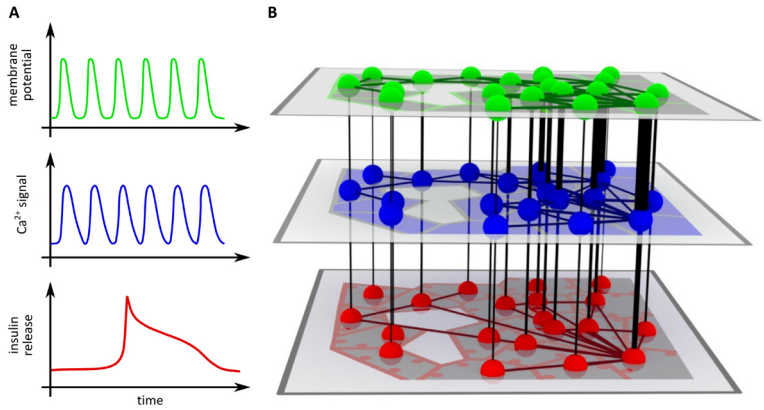


Fig. 4. A hypothetical activity (A) and the corresponding multiplex network representation (B) of functional interactions based on simultaneously recorded membrane potential (green), calcium (blue), and exocytotic event dynamics (red). The thickness of interlayer connections reflects the time lag between individual signals. (For interpretation of the colors in this figure, the reader is referred to the web version of this article.)

function, and dynamics. Specifically, the brain network can be represented by two layers: one reflecting anatomical connectivity, and the other encoding functional relationships [128,184]. Several network metrics, especially the multiplex motifs, were shown to be more informative than their single-layer counterparts taken separately [128].

Until now, very few studies have incorporated the MLN approach on the multicellular and tissue level with the aim to investigate the intercellular interaction patterns between individual cells. Nevertheless, many cell population types are governed by different oscillatory subsystems, are nonstationary, interact by different signaling mechanisms as well as with other cell types, and their function is morphology-dependent. Treating them by means of a multiplex network formalism could be therefore much more beneficial and informative than a single-layer projection. An interesting demonstration of this concept was performed on the famous neural network of *C. elegans*, where the two layers were associated either with electrical signals propagating through synapses and neuronal dendrites, or with diffusion of ions through gap junctions [131,185]. Later, Bentley et al. [186] expanded this representation by additionally integrating monoamine neuromodulator layers. It has been argued that the multilayer approach revealed significant differences between network layers and in the importance that individual neurons have in different layers, thereby providing important novel findings about the physiology of the neuronal network.

Recently, we used the MLN methodology for the description of the temporal information flow and interaction patterns between beta cells in islets [187]. In particular, we made use of simultaneous multicellular recordings of MP and Ca^{2+} dynamics which facilitated us to track the propagation of the depolarization and Ca^{2+} wave and to construct the corresponding two layers of the resulting node-aligned multiplex network. Interlayer connections were created only between the same cells located in different layers and their weight reflected the time lag of the Ca^{2+} signal with respect to the depolarization. Our results have revealed some discrepancies in the structure of both layers, which are attributed to cell-to-cell variability of time lags between MP and Ca^{2+} signal. More specifically, high-degree nodes in both layers were found to have a longer delay than nodes with less intralayer functional connections, which was speculated to be related with a higher activity of endoplasmic reticulum calcium pumps in hub cells. While representing the intercellular signalization in terms of a multiplex network gave us new insights into the physiology of the complex signaling processes in islets, there is plenty more room for upgrades and future development. Advances in imaging techniques nowadays facilitate simultaneous recordings of several cellular activities (metabolites, ATP, cAMP, NAD(P)H, pH, ROS, etc.).

In Fig. 4 we show a hypothetic multiplex network of cells constructed on the basis of MP (green), $[Ca^{2+}]_i$ (blue), and exocytic event (red) dynamics. The interlayer connections define the time lag between depolarization, Ca^{2+} increase and granule fusion events. While the MP and Ca^{2+} network layers have a very similar structure [187], the functional relationship between exocytic responses is probably less well coordinated and depends also on other factors, such as the proximity to the vasculature, etc. [102]. Nevertheless, investigating the exact relationship between the function the cells have in the exocytic (or other alternative) network layer and the most frequently utilized Ca^{2+} layer, remains a challenge for future work.

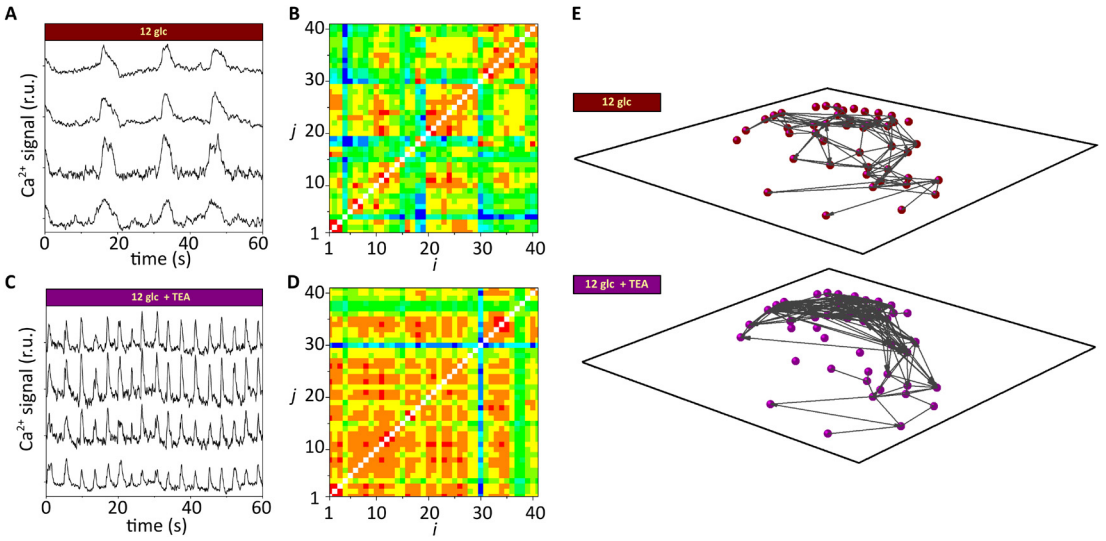


Fig. 5. Characteristic recorded $[Ca^{2+}]_i$ signals from four beta cells after stimulation with 12 mM glucose (A) and the subsequent stimulation with 12 mM glucose plus 10 mM tetraethylammonium (B) in the same islet. Panels (C) and (D) show the corresponding correlation matrices. The resulting node-aligned multiplex network is shown in panel (E).

The MLN formalism was recognized as particularly appealing in the context of understanding network structure and function across time or between experimental scenarios [16,176]. Typically, layers are to that purpose generated on the basis of a series of time windows and the nodes are linked only across sequential replicas to indicate identity. Such a framework seems to have a lot of potential also for the multilayer functional representation of tissues. Scenarios whose exploration would benefit from such approaches include investigations of prolonged or increasing stimulation of cells [105], functional adaptation and plasticity after repeated stimulations [119], tracking the network evolution after targeting the cells via optogenetic/photopharmacological strategies [109], and discovering the effect of pharmacological interventions, where the multicellular network structures are evaluated before and after the application. To illustrate an example of the latter, we show in Fig. 5 a two-layer multiplex network generated on the basis of functional correlations of Ca^{2+} dynamics in beta cells. The first layer corresponds to a 12 mM glucose stimulation only, whereas the second one represents the connectivity pattern after 10 mM tetraethylammonium have been subsequently applied. Evidently, the potassium channel blocker tetraethylammonium does not only shorten oscillations and rapidly increase their frequency, but also enhances correlation and densifies the functional network, which is most probably a result of higher Ca^{2+} wave velocities [99].

In general, MLN describing how functional connectivity changes across time provide a richer framework than traditional approaches. For example, the multilayer model for time-varying networks is not only suitable to explore the robustness and fluctuations in functional connectivity [141], but can also provide an improved characterization of modular units or central hubs [188,189]. While this methodological direction is still largely unexplored on the level of intercellular interactions, the number of potential applications is large. Future efforts incorporating multilayer representations will likely offer novel perspectives and insights into the architecture and dynamics of tissues, certainly even beyond the islets of Langerhans.

5. Conclusions

Over the past years, the network science has largely contributed to the analysis and to a functional understanding of the structure of complex real world networks [1,2]. It turned out that many of them share very similar global statistical features and structural design principles [1,2,6,32,190]. In this review, we focused specifically on the achievements in biological networks research, which has led to an enormous progress in systems biology and network medicine [191–194]. The fundamental premise in these emerging fields is to connect genomic, proteomic, and metabolic networks at the subcellular level with disease networks and epidemiology at the macroscopic level of the whole organism [130,195–198]. However, there is a gap of knowledge and many unexplored research potentials at the intermediate

scales about intercellular networks and cell-to-cell interactions in tissues [81,82,104,199], and this middle level should represent an important part in the holistic network medicine framework [197]. The motivation for this encompasses at least in part the recent discoveries about the involvement of cell-to-cell signaling pathways in the pathogenesis of several diseases [200–206].

The importance of intercellular coupling is becoming an increasingly popular topic also in beta cell and diabetes research [81,84,207–209]. It is a well-established fact that a coordinated activity of beta cell populations principally mediated by the strong electrical coupling via gap junctions is required to ensure a normal pulsatile release of insulin and glucose homeostasis at the level of the whole organism [80,81]. Moreover, disruptions of the intercellular communication pathways have been shown to induce desynchronization in beta cell activity and an impairment of normal oscillatory patterns of insulin secretion [80,110,118,208–213], the latter being a defining characteristic of type 2 diabetes [81,214]. This motivated us and others to study the beta cell syncytium by means of graph-theoretical approaches with the aim to quantify the intercellular interaction and information flow patterns in pancreatic islets [84,104,105,109–112,199,215,216]. Incorporating tools from the armamentarium of the network theory into beta cell research has not only revealed that beta cell networks share many similarities with several other real-life networks, such as small-worldness, heterogeneity, and modularity [104,105], but has also lead to important new insights into the relationship between cellular metabolic activity and energetics and the orchestration of collective behavior [109,215]. Understanding such regulations of islet function, especially in relation to aging [217] or during type 2 diabetes pathogenesis, when the secretory demand in beta cells increases [218], is crucial for the determination of new treatments founded on the restoration of insulin secretion by boosting cell communication [84].

To conclude, exploring and understanding complex biological systems through the lens of network language nowadays represents a very active interdisciplinary field of research and is acquiring more and more attention also at the level of intercellular interactions in multicellular systems, where important insights into the organizing principles of dynamics in tissues can be gathered. We strongly believe that future efforts will benefit from the emerging mathematical concept of MLN, which has several advantages with respect to the traditional network approaches. Especially at the multicellular level, the multilayer formalism offers a largely untapped potential to explore the complex organization of tissues in both health and disease, far beyond the islets of Langerhans.

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