(?) Comparative Netomics - lessons from cross-disciplinary network comparison

Throughout the history of science, advancements of biology were catalyzed by discoveries in other disciplines. For instance, the maturation of X-ray diffraction facilitated the discovery of the double helix, and later on the characterization of structures of thousands of different proteins. In the era of systems biology, attention has shifted from individual molecular components to their interactions at a system level. New functional genomics assays, in particular ones based on high-throughput sequencing (*Seq) [1], enables biologists to probe thousands of 'omes [2] – the comprehensive collections of constituents. One may wonder which discipline will contribute the most to biology in this new scientific paradigm [3]. While the influx of ideas in the age of reductionism mostly originated from specific areas in physics or chemistry, to understand biology via a systems perspective, the new wave of catalysts come from areas of science that are far apart, as diverse as engineering, behavioral science, sociology, but are centered on the concept of network [4].

Networks are by no mean new to biologists [5]. Metabolic pathways have been studied for decades. But more recently, as a result of the advancements of high-throughput techniques, simple pathways have been expanded to intertwined wiring diagrams. While many of us have been astonished by the complexity of such networks found in genomics or systems biology, few are able to gain any intuition from the hairballs [6]. In this essay, we argue that, by cross-disciplinary network comparison, algorithms or mathematical techniques as well as intuitions developed in commonplace networks can be able to catalyze our understanding of biology. One may wonder, however, comparing a bio-molecular network with a complex network from a disparate field, say a social network, sounds like comparing apples to oranges. So what kinds of comparison could truly deepen our understanding? We believe that it is useful to think of different descriptions of a cellular system as a spectrum (Figure 1).

A spectrum of cellular descriptions
Given the complexity of a cell, a certain level of simplification is necessary for useful discussion. We could picture the description of cellular systems as a spectrum (Figure 1). On one hand, there's a simple parts list that just enumerates each component without specifying any relationships. On the other hand, there is a complete three or even four-dimensional picture of how cellular molecules interact in space and time. It is well regarded that the characteristics of a cellular system cannot be explained by the characteristics of individual components – the whole is greater than the sum of its parts. Therefore, while the full picture is often too ambitious for current data acquisition, the parts list description is not fully informative. Network description sits conveniently between these extremes by capturing the relationships between components of the parts list. There are broadly two ways to define relationships based on the nature of experimental data. Firstly, networks could be defined in a phenomenological sense; meaning entries are connected via abstract mathematical relationship derived from phenomenological observables. Perhaps the most important phenomenological networks are built on the mapping between genotypes and phenotypes. An example is the disease networks [7]; a gene (genotype) and a disease (phenotype) are connected via the statistical association between the existence of genomic variants and the occurrence of the disease. While phenomenological networks offer a mathematical abstraction far away from the complete picture in the spectrum, there are networks defined to capture the mechanistic interactions happening inside a living system. Such networks are built on experimental knowledge on different facets of the complex organization of an organism, for instance, a regulatory network describes part of the cellular information processing, a metabolic network traces the chemistry of metabolites, and the protein-protein interaction network captures cell signaling as well as providing a manual on how to assemble molecular machines. The integration of such mechanistic networks provides a description reasonably close to the complete picture along the spectrum. The process could be visually regarded as the decoration of edges with directionality, color, thickness etc. Nevertheless, the incorporation of too much detail makes the system intractable, and network formalism generally breaks down if spatial or temporal details as well as higher-order interactions are included. At certain point, the actual four-dimensional picture is required.

Underlying mechanistic networks serve as the skeletons of different complex systems. Comparison of such networks allow biologists to gain intuitions by examining interactions in cross-disciplinary complex systems in the same ground as the interactions between molecular components in cells. Nevertheless, because of systems-specific details, not everything could be transferred from one discipline to another, and it is important to focus on the conceptual resemblance instead of merely topological resemblance. On the other hand, phenomenological networks are rather abstract connections between entities, and thus mathematical formalisms are easily transferrable. Toward this end, by comparing similar network-based mathematical formalisms across disciplines, biologists will benefit in terms of algorithms or method development.

Comparing phenomenological networks to leverages mathematical machineries
Phenomenological networks are typical products dealing with big data; they are essentially two-dimensional projection of high-dimensional data. As it is extremely common to have data with many features in the era of Big Data, especially in computational social science, networks across disciplines actually present very similar challenges. Here, we highlight a few areas where different questions arise in genomics and social science could be formulated by the very same approach. By the same token, network algorithms developed in one discipline can readily be applied in biology.

Approaches focusing on network topology
Even though the evolutionary process involves random changes at the molecular level, it is not surprising that natural selection organizes biological networks in an ordered fashion. Comparison of biological networks with different social and technological networks have provided valuable insights into the organizing principles of biological networks. One striking outcome of the comparison is that these natural and man made networks organize into scale free networks in which a majority of the nodes contain very few connections (edges) while a few nodes in the network are highly connected. Changes to the sequences of the centrally connected nodes (also called hubs) in biological networks are predictive of lethal and disease causing changes and have proven to be valuable in interpreting the genotype to phenotype network.

Another striking insight from these comparisons is these networks are organized in the form of modules such that nodes within the same module have a larger number of connections with each other as compared to nodes belonging to different modules. Evolutionarily this makes sense because connections within a module can be reused in a different functional context. Naturally, genes within the same module have similar biological properties. For example, the cellular components within the same module are more closely associated with the same set of cellular phenotypes than components belonging to different modules. Similarly, the modules within gene coexpression networks also tend to contain genes with similar functions and genes within the same module are often involved in the same biological pathway.

Due to rapid advancements in data acquisition, the structure of biological data goes beyond a single layer of network to multiplex structure common found in different technological and social networks. Multiplex networks contain multiple layers of interconnected networks - the multiple layers in these networks could either be formed by different categories of relationships (co-expression, genetic interactions, etc.) or they could be formed by relationships observed at different timepoints. The idea originated in social network analysis because an individual may participate in multiple social circles: family, friends, colleagues, or in online setting: Facebook, LinkedIn and Twitter. Similarly, the different layers in a temporal network contain parts of the network that are connected at different timepoints [28]. As dynamic data in genomic information becomes available, we think that valuable insights can be gleaned by the analysis of these data using algorithms developed in the context of multiplex social networks.

Nevertheless, biology motivates an alternate definition of temporal network. While they exist together at the same time-point, networks from different species essentially capture the

evolutionary changes to a common core. In this definition, pairs of orthologous genes can be used to connect networks from different species, forming a multi-layers structure. The notion has recently been used to integrate co-association across different species in order to detect conserved and specific functional modules [29]. Based on the same notion, a mathematical formalism was developed to measure the evolutionary rewiring rate between networks across species in analogous to quantifying sequence evolution [30]. It was shown that metabolic networks rewire at a slower rate compared to various regulatory networks.

Approaches focusing on the properties of nodes and edges
Lots of interesting questions as well as many machine-learning formalisms arise when we start to map properties of individual nodes to a network. In both biology and computational social science, very often the properties of nodes are incomplete, and we are interested to infer the missing data. The essence of these methods is the idea of "guilt by association" or the idea that nodes that have similar associations in the network tend to be more similar in nature. For example, if your friends in Facebook use Product Y, you are more likely to use product Y and the advertisements you view online are personalized based on these recommendation systems. In genomics, for example, one could infer the functions of a protein or a non-coding element based on the function of its neighbors in the underlying network. The same is true for predicting disease-associated genes: if the neighbors of a gene are all associated with Disease X, it is very likely that the gene is associated with disease X. Of course, the influence of a node may not be restricted to its nearest neighbors; network flow algorithms are widely used to examine the long-range influence.

Nodes association is closely related to nodes prioritization, in which the PageRank algorithm plays an important role. Originated from Katz centrality in social network analysis [22], PageRank algorithm was first used by Google to rank documents based on linkages in a self-consistent way. The algorithm was then adopted in food webs to determine extinction [23] and later in an algorithm called NetRank that rank prognostic relevance for patients with cancers [24]. Generally speaking, in addition to algorithms like PageRank that prioritize nodes by network topology, expression data, sequence information, functional annotation and biomedical literature are required for further filtering [25]. In applications like disease gene discovery, nodes prioritization is an essential process because of limited resources. Similarly, social networks can be utilized to identify the people that need to be vaccinated so that the spread of a disease can be avoided.

Very often whether two nodes are connected depend on their intrinsic properties. Therefore the inference or prioritization of nodes leads to prediction and denoising of links. Difficulties lie at the proper learning of network organization based on observable data. Recently, generative models of networks, say stochastic block models [27], are very popular in computational social science. Nevertheless, such models are not widely used in biological context yet, presumably because of the lack of gold standard for validation. Interestingly, because of the availability of datasets, for instance the Framingham study, there is an increase of attention on the connection between genomics information and sociological information. Biologists and sociologists have started to examine the hypothesis on whether phenotypes or genotypes are correlated in friendship networks [21].

Approaches focusing on causal relationships and dynamics
The construction of various phenomenological and social networks an active area of research for both biology and computational social science. While correlational relationships could potentially be easily calculated with the appropriate data, a fundamental question is the distinction between direct and indirect interactions. For instance, a statistical analysis on many cancer samples can easily identify the correlation between various somatic mutations (indirect), but the key is in fact to identify the driver mutations (direct). Established mathematical machineries like Bayesian networks or Markov random fields have been used for this purpose. The inference of causal relationships could be greatly benefited by time-series data. In social science, online retailers are interested to use purchase records to study how customers influence each other. On the other hand, the same question is extremely common in biology, under the term "reverse engineering".

For example, how can we infer the embryonic developmental gene regulatory network from temporal gene expression dynamics? Ideally, one could write differential equations to fit the temporal data; nevertheless, temporal data in most genomics experiments do not have enough time-points. To overcome the drawback, for instance, given the genome-wide expression profile of at different time-points, one could perform project the high-dimensional gene expression data to low dimensional space by data mining techniques such as SVD, and write differential equations to model the dynamics of the projections [26]. The inference of casual and direct relationships from statistical data points to the study of mechanistic networks.

Comparison of Mechanistic networks for gaining intuition
From a biologist standpoint, comparing various mechanistic networks between biology and other disciplines can bring intuition from other disciplines into biology. In spite of the disparate fields, we believe there is several aspects biologists could find inspiration.

Looking for universal mechanisms
Since the burgeoning of studying networks in various disciplines, efforts have been made on explaining some of the striking similarity in terms of organization of underlying networks in biological and other complex systems. An early example is the emergence of the scale-free degree distribution in a protein-protein interactions network. The pattern of organization could be explained by the duplication divergence model [10], a simple stochastic process describing how a protein network grows by gene duplication. As a hub protein has many interactions, its number of interactions is likely to increase further simply because one of its neighbors got duplicated. The same "richer get richer" model was proposed originally to explain the same pattern in many other networks [11]. More recently, it has been shown that components in both bacterial genomes as well as large-scale computer software projects form multilayered dependency networks (enzyme A is used to decompose the output metabolites of enzyme B; the installation of package A depends on the installation of package B). The common underlying dependency networks leads to the same power-law components-usage frequency distribution (how often a enzyme is present in a bacterial genome; how often a certain package is installed in a computer) [12].
While it is elegant to explain the topology of disparate networks by simple stochastic models, such universal mechanisms are rather rare. To a certain extent, the existence of such models underlines the importance of randomness in biology. Remarkably, the same duplication-divergence mechanism has been applied to describe the patterns of "memes" in online media [13]. As biologists, we love to think about functions and selection; it is interesting to see that, by network comparison, network organization could be a manifestation of stochasticity.

Looking for common design principles
Of course, biological networks are not random, and so do networks from other disciplines. Most observed similarities in terms of network organization are not easy to explain by simple mechanisms or principles, for instance, the so-called network hierarchy (see Box 1). The reason is because, for most networks, it is in general very hard to define a "function". In fact, lying at the heart of deciphering biological networks mediated by mechanistic interactions is the mapping between architecture and function. The mapping points to biological circuits that solve common functional problems – effectively a toolbox for synthetic biology [14]. Toward this direction, comparison with various technological or engineering networks with well-defined functions is particularly insightful. As an example, consider a biochemical oscillator. Two essential elements of an oscillator are a source of negative feedback and a source of time delay. Nevertheless, different oscillators (e.g. for circadian rhythms, for cell cycle, or from various organisms) have a certain level of variation because of additional design objectives or strategies. This is just like the case that not all electronic devices use the same oscillator design because of other design objectives. The striking similarity between biological systems and technological systems has long been identified. A decade ago, Uri Alon pointed out several common design principles in biological and engineering networks such as modular organization and robustness to perturbation [15]. Robustness is obviously a preferred design objective because it makes a system tolerate stochastic fluctuations, either intrinsically or from external sources. Modularity, on the other hand, makes a system more evolvable. For instance in software design, modular programming that

separates functionality of a program into independent modules connected by interface is widely practiced [16]. The same is for biological networks because modules can be readily reused to adapt new functions. Because of the fundamental importance of such design objectives, an insightful network comparison should be rooted in the common design objectives rather than merely network topology.

Looking for the commonalities and differences between tinkerer and engineer
The comparison of biological networks and technological networks should best be performed under the light of evolution. As Alon highlighted by the phase "the tinkerer as an engineer" [15], it is remarkable that "good-engineering solutions" are found in biological systems evolved by random tinkering. Indeed, comparison between biological and technological networks should manifest the nature of the two very different approaches: evolution as a tinkerer neither designs things nor builds systems— it settles on systems that, historically, conveyed a survival benefit (and if a better way comes along, it will adopt that). On the other hand, technological networks are essentially blueprints drawn by engineers who have a grand plan that makes sure everything work harmoniously. Biologists often tend to distinguish the two approaches cautiously so as to avoid the notion of intelligent design – the existence of an intelligent cause that construct living organisms on purpose. Nevertheless, the distinction is not clear-cut. Both biological networks and man-made technological networks like roadways and circuits are complex adaptive systems, there are plenty of examples showing that many great innovations are results of trial and error, and all technological systems are subjected to selection like users requirements. In a recent review, Wagner summarized nine commonalities between biological and technological innovation, such as descent with modification, extinction and replacement, and horizontal transfer [17]. To a certain extent, an engineer is a tinkerer (see Box 2).

Under such a united framework, we could picture that both engineer and tinkerer are working on an optimization problem with similar underlying design objectives. Like all optimization problems, there is no way to optimize all objectives and thus tradeoffs are unavoidable in both biological and technological systems. This is essentially the conventional wisdom – there's no free lunch [18][19]. Despite the similarity, tinkerers and engineers take different views in balancing different constraints and tradeoffs. Their optimal choices are exhibited in the topology of their corresponding networks. Taking software engineering as an example, software engineers tend to reuse certain code. However, the robustness of software will be reduced if a piece of code is highly called by many different processes. Analysis of the evolution of a canonical software system, the Linux kernel, revealed that the rate of evolution of functions (routines) is distributed in a bimodal fashion and thus a significant fraction of functions are updated often [20]. Therefore, unlike biological systems in which the majority of components are rather conserved and thus prefer a more independent organization to maintain robustness, software engineers pay the price of reusability and robustness by constantly tweaking the system. Indeed, further analysis of the underlying network of Linux kernel, the so-called call graph, showed that more central components at the call graph require more fine-tuning. The patterns seems to be hold for other software systems like the organization of packages in the statistical computing language R (Figure 2). In other words, unlike biological networks whose hubs tend to evolve slowly because of the number of constraints, software system is very similar to a roadway system; bottlenecks under high usage like George Washington Bridge require more upgrade and more construction. While intentional tweaking on bottlenecks sounds obvious for technological systems, it is not always possible (see Box 2).

Conclusion
Biology is a subject with a strong tradition of doing comparison. One hundred years ago, biologist compared the phenotypes of different species. Since the discovery of DNA, biologists have been comparing the sequences of different genes, and then all sorts of 'omes across species. To nourish a system-level understanding and to leverage the tremendous amount of high-throughput data, may be it is a time to extend our tradition even further to compare with networks from other complex systems as well as other disciplines. Indeed, various scientific disciplines form a network in the intellectual universe where knowledge emerges when things connect.

More Potential exhibits:
A table showing examples of the two types networks.
(Give more examples of phenomenological networks, like genetic interaction networks.)

A table highlighting problems studied in the framework of phenomenological networks, and the corresponding problems arise in computational social science.

Box 1 Hierarchical organization of networks
Many biological networks possess an intrinsic direction of information flow, forming a hierarchical network organization. The hierarchical organization in biological networks resemble the chain of command in human society, like in military context and corporate hierarchy [8]. For instance, in a transcriptional regulatory network more influential transcription factors (regulators whose expression are more highly correlated with the expression of target genes) tend to be better connected (have more interacting partners) and higher in the hierarchy [32]. Moreover, the transcription factors in the middle layer tend to be more cooperative [33]. Such a situation has been well studied in management science, where in certain corporate settings middle managers interact the most with peers to manage subordinates below them [34]. These observations reflect a democratic hierarchy as opposite to a conventional autocratic organization [35].

Of particular interest for hierarchical organization is the so-called bow-tie structure, meaning the intermediate layers have fewer components than the input and output layers. For example, in a signaling network, a large number of receptors corresponding to diverse stimuli and many transcription factors form the input and output layers, whereas the intermediate layer refers to a few key molecules like calcium and cAMP that mediate the inputs and outputs [31]. Similarly, in the networking architecture of the Internet, various protocols in the input/link layer (ARP, RARP, NDP etc) and various application protocols in the application/output layer (HTTP, FTP,DHCP etc) are essentially connected by only IPv4, the primary protocols in the internet layer. The reason for the emergence of such a common pattern is still widely open, a recent paper suggested bow-tie is a result of information compression [47].

Box 2 Tinkerer versus engineer
Despite the apparent differences, the similarity between biological systems and technological systems draws a parallel between tinkerer and engineer, and the parallel points to a common framework to unite them. Wagner further proposed an analogy between the genotype space for a biological system and the design space for a technological system. These spaces contain all the possible networks in the corresponding systems. In biology, many attempts have been made to search for solutions of common functional problems such as adaptation, oscillation and cell polarization [14]. Similar studies were performed in the context of circuit design, where a set of logic gates was evolved via rewiring in order to perform a predefined computational task [36][37]. These studies suggested that in both kinds of systems, the solution networks are close together in the genotype/design space. As each solution in genotype/design has multiple neighbors, robustness of a solution to mutation facilitates the evolvability of these systems [38][39]. Indeed, it has been demonstrated that electronic circuits can be evolved to fulfill a fluctuating evolutionary goal [36]. Similarly, metabolic networks of bacteria living in multiple habitats are evolved to decompose multiple food sources [40][41]. Both of these networks show a level of modular organization.

Very often we picture engineers design things from scratch. In reality, as a technological system evolves, engineers are subjected to various constraints like tinkerer. In the example of internet architecture, while there are frequent innovations at the input layer that interact with a variety of networking hardware and output layers that connect with many different software applications, the internet layer with very few protocols is the bottleneck under heavy constraints and such protocols can hardly be replaced [42]. The observed rapid innovation at the top and bottom layers but constraint at the middle is very common in biological system. Consider the metabolic

networks of different bacteria, the anabolic and catabolic components are much more diverse whereas there are less variations between central pathways \cite{2}.

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