# (?) 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, attentions have 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 was most originated from specific areas in physics or chemistry, to understand biology via a systems perspective, the new wave of catalysts actually come from areas of science that are far apart, as different as engineering, behavioral science, sociology, but centered on the concept of network [4].

Network is 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 are expanded to intertwined wiring diagrams. While many of us have been astonished by the complexity of such networks, few are able to gain any intuition from the hairballs [6]. While the term "biological network" is used rather loosely in literature for all networks originated from any subfields of biology, say food web, here in this essay, we focus our attention to molecular networks coming from genomics or systems biology because it is in general harder to gain intuitions in such networks. We want to argue that, intuitions as well as mathematical formalisms developed in commonplace networks from other disciplines are able to catalyze our understanding of biology, and therefore it is instructive to initiate comparison between biological networks with networks in other disciplines.

## Comparison depends on the nature of networks

Though underlying networks of various systems may resemble one another, comparing a bio-molecular network with a complex network from a distant field, say a social network, sounds like comparing apples to oranges. What kinds of comparison could truly deepen our understanding? We believe the focus of comparison should depend on the types of information captured in networks. 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. The essence of network is to describe the interactions between components of the parts-list (genes, proteins, small molecules etc.). For instance, many networks are defined based on various kinds of mechanistic interactions and specific goals of performance. These networks essentially capture 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. Such networks closely resemble, and should be compared with networks that perform specific functions like networks from engineering or technological systems. In this context, biologists could gain intuitions by examining the underlying skeletons of cross-disciplinary complex systems in the same ground as the interactions between molecular components in cells. Nevertheless, in many cases, an edge represents a certain level of coarse-graining. For example, a simple protein-protein interactions network usually does not capture the structural or temporal properties of binding. While more detailed mechanistic interactions could indeed be defined in this case [7][8], the framework may no longer be useful if too many details are incorporated. The scenario is analogous to classical mechanics; writing down the equations of all the particles is in principle possible but not really helpful. As a result, many networks are defined in a phenomenological sense. For instance, in a genetic interaction networks [9], two genes are connected based on the phenotypes of double knockout experiments; or in a disease networks [10], a gene and a disease are connected via the statistical association between analysis of genomic variants and the occurrence of the disease. It is useful for biologists to notice that such networks, which represent mathematical abstraction of complex relationships, share common graphical structures arise in many practical problems. For

instance, mathematical machinery used in the bipartite network between genes and diseases can resonate with movie recommendation scheme building on a similar bipartite network between users and movies. Toward this end, by comparing similar network formalisms, biologists will benefit from an algorithmic or method development standpoint.

**Comparison reveals common mechanisms and principles**
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 [11], which is essentially the same as the preferential attachment model proposed originally to explain the same pattern in many other networks [12]. 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) leading to the same power-law components-usage frequency distribution [13]. In general, the existence of such universal mechanisms is rather rare. Nevertheless, comparisons with commonplace networks do provide intuitions for biologists. For instance, many biological networks possess an intrinsic direction of information flow, such as signaling networks where information propagates from G-Protein coupled receptors to transcription factors [14], forming a hierarchical network organization. The hierarchical organization in biological networks resemble certain the chain of command in human society, like in military context and corporate hierarchy [15]. For instance, more influential transcription factors (regulators whose expression are more highly correlated with the expression of target genes) tend to be better connected and higher in the hierarchy [16]. Moreover, the cooperative regulatory factors in a transcriptional regulatory network tend to be in the middle layer [17]. This situation is well studied in management science, where in certain corporate settings middle managers interact the most with peers to manage subordinates below them [18]. Such observations reflect a democratic hierarchy as opposite to a conventional autocratic organization [19].

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 developmental genetic regulatory network, information propagates from genes controlling the initial stage of development (the input) to genes controlling detailed cell differentiation and morphogenesis (output) [20][21]. The intermediate layer refers to a small set of input-output genes integrating complex spatiotemporal information and trigger development of an entire program of cell differentiation [22]. In the networking architecture of the Internet, on the other hand, 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 IPv4, the primary protocols in the internet layer. A recent paper provided a first mechanism to understand its evolution by explicitly modeling information flow in feed-forward networks as a cascade of matrix multiplications (similar to neural networks in machine learning context) [23]. It showed that a bow-tie structure emerged if the goal matrix is rank deficient, i.e. the information can be compressed.

Lying at the heart of deciphering biological networks mediated by mechanistic interactions is the mapping between architecture and function. Toward this direction, comparison with various technological networks is particularly insightful. As an example, consider a biochemical oscillator. Two essential elements of an oscillator are a negative feedback loop and a source of time delay. Nevertheless, oscillators of various purposes (e.g. for circadian rhythms or for cell cycle) or from various organisms are not identical but have a certain level of variation because additional design objectives or strategies are involved. Just like not all electronic devices use the same oscillator design, the importance of design objectives is not new at all in engineering systems. 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 [24]. Robustness is

obviously a preferred design objective because it makes a system tolerate intrinsic or extrinsic stochastic fluctuations. 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 [25]. 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.

**Comparison highlights the commonality and difference 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" [24], 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 starting with bits and pieces and trying to connect random nodes, whereas technological networks are essentially blueprints drawn by engineers. 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 [26]. To a certain extent, an engineer is a tinkerer.

The parallel between tinkerer and engineer 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 [27]. 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 [28][29]. 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 facilitate the evolvability of these systems [30][31]. Indeed, it has been demonstrated that electronic circuits can be evolved to fulfill a fluctuating evolutionary goal [28]. Similarly, metabolic networks of bacteria living in multiple habitats are evolved to decompose multiple food sources [32][33]. Both of these networks show a level of modular organization. While both biological and technological networks are shaped by similar underlying design objectives that impose further constraints to the solutions, 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 [34][35].

Despite the similarity, tinkerers and engineers take different views in balancing different constraints and tradeoffs. Their optimal choices are exhibited 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 fashion of functions are updated often [36]. 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. 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. In the above 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 [37]. The observed rapid innovation at the top and bottom layers but constraint at the middle may shed light on a remarkably pattern in developmental genetic regulatory network. Different species exhibit different patterns at the early and late stages of embryo development, but highly similar during the phylotypic stage – the so-called hourglass phenomenon [38].

**Comparison leverages mathematical machineries**
Apart from networks mediated by mechanistic interactions, many networks in the literature are essentially two-dimensional projection of high-dimensional data. As big data across disciplines are often signified by the combinatorial explosion of high dimensional features, it is not surprising that network algorithms developed in one discipline can readily be applied in biology, for instance, the idea of "guilt by association" is widely used in genomics for inferring functions of a protein or a non-coding element based on the function of its neighbors in a network, the same idea is also widely used in social media like Facebook to suggest friends. Perhaps the best example is probably the PageRank algorithm. Idea originated from Katz centrality in social network analysis [39], 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 [40] and later in an algorithm called NetRank that rank prognostic relevance for patients with cancers [41]. More interestingly, the idea of PageRank was able to solve the global network alignment problem, which was applied in biological context in order to detect functional orthology across species [42].

Networks across disciplines, despite of different origins, actually present very similar challenges. For instance, being noisy and incomplete makes procedures like link prediction and denoising necessary. Difficulties lie at the proper learning of network organization. Generative models of networks, say stochastic block models [43], 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. Another trend of network analysis is the notion of multiplex networks where multiple layers of networks form an interconnected structure. The idea is 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. The same is true in biological context because of the existence of multiple relational connections (co-expression, genetic interactions etc.) between components in networks. A similar multiplex generalization in network analysis is the so-called temporal networks, which consider the slices of networks taking place at different time points together as a single mathematical structure [44]. Again, the current application focuses on online social networks because genome-wide data in biological systems are still not dynamics enough. However, as the number of time points increases, say in RNA-Seq experiments, algorithms developed in social contexts can be easily applied to integrate the slices of co-expression networks.

Nevertheless, biology motivates an alternate definition of temporal network. Networks from different species essentially capture a sense of temporal changes. In this definition, pairs of orthologous genes can be used to connect networks from different species, forming a multiplex structure. The notion has recently been used to integrate co-association across different species in order to detect conserved and specific functional modules [45]. Another mathematical formalism was developed to measure the evolutionary rewiring rate between networks across species in analogous to quantifying sequence evolution [46]. It was shown that metabolic networks rewire at a slower rate compared to various regulatory networks. The formalism can be applied to networks in social or technological contexts in general.

**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. Comparison of biological networks with technological networks, and the similarity between tinkerers and engineers point toward biological circuits that solve common functional problems – effectively a toolbox for synthetic biology [27]. Comparison of mathematical formalisms used in mining biological networks and various social networks point to further integration of two classes of data. Such integration is getting more and more important as datasets that combine genotypes, phenotypes and information like connections between individuals will become popular, for example, the Framingham study. Indeed, various scientific disciplines form a network in the intellectual universe where knowledge emerges when things connect.

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