

Comparative Netomics - lessons from cross-disciplinary network comparison

Throughout the history of science, we have seen many examples in which the advancements of biology have been catalyzed by discoveries in other disciplines. For instance, the maturation of X-ray diffraction facilitated the discovery of double helix, and later on the characterization of structures of thousands of different proteins. In the era of systems biology, attentions have been shifted from individual molecular components to their interactions in 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 from which discipline will biology be benefited most, [in such a 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 [vary](#) 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](#) published in high profile journals. 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 methods developed in commonplace networks from other disciplines are able to catalyze our understanding of biology. Indeed, not only capturing the unique flavor of systems biology, the concept of network essentially describes the interactions between individual constituents-who is interacting with whom-in any complex system. The simple description thus enables one to examine the underlying skeletons of cross-disciplinary complex systems in the same ground as the interactions between molecular components in cells. [While biologists want to gain insights on the complex interactions between molecular components, the common network language makes ideas and methods developed to understand the organization of complex systems in diverse fields more accessible to biologists, and vice versa. To leverage the interdisciplinary connections, it is instructive to initiate comparison between biological networks with networks in other disciplines.](#)

Two classes of network comparison

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 comparing apples to oranges. What kinds of comparison could truly deepen our understanding? We believe [the focus of comparison](#) should [depend on the nature of](#) networks. [Transcriptional regulatory networks, metabolic networks or protein-protein interaction networks, are examples of widely studied molecular networks. They 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. [Despite the intrinsic difference,](#) they all refer to specific goals of performance mediated by actual mechanistic interactions. Such networks closely resemble, and should be compared with networks [that perform specific functions](#) like networks from engineering or technological systems. There is another class of biological networks with examples like genetic interaction networks [\[7\] or disease networks \[8\].](#) The former example is a sophisticated metrics summarizing results of double knockout experiments whereas the later describes the statistical association between genes and diseases as a result of GWAS and analysis of various genomics variants. Such networks do not show mechanistic interactions but a mathematical abstraction of complex relationships. From an algorithmic or method development standpoint, they share common graphical structures arise in computational social science, for instance mathematical

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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.

Comparison of design principles

Lying at the heart of deciphering biological networks mediated by mechanistic interactions is the mapping between architecture and function. 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 [9]. 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 [10]. 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. Nevertheless, in many cases, common topological patterns are the reflection of common underlying design objectives or strategies.

While networks originated from technological systems are particularly analogous to biological networks, under certain specific design objectives, comparison could be further broadened to include networks from other disciplines. An interesting example is related to how information is transferred between input and output nodes in a network. Many biological networks possess an intrinsic direction of information flow, for instance signaling networks where information propagates from G-Protein coupled receptors to transcription factors [11], and developmental gene regulatory networks where information propagates from genes controlling the initial stage of development to genes controlling detailed cell differentiation and morphogenesis [12][13]. The former example refers to the spatial organization, whereas the later is defined in a temporal fashion. The later is similar for the regulatory networks in general; 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 [14]. 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, cooperative regulatory factors in a transcriptional regulatory network tend to be in the middle layer [16]. The situation is well studied in management science, where in certain corporate settings middle managers interact the most with peers to manage subordinates below them [17]. Such observations reflect a democratic hierarchy as opposite to a conventional autocratic organization [18]. 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. 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) [19]. It showed that a bow-tie structure emerged if the goal matrix is rank deficient, i.e. the information can be compressed. Of course, there are still plenty of interesting observations without explanation. For example, in developmental genetic regulatory network, the intermediate layer refers to a small set of input-output genes integrating complex spatiotemporal information (the input) and trigger development of an entire program of cell differentiation (the output) [20]. 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, SMTP, DHCP etc) are essentially connected by IPv4, the primary protocols in the internet layer. 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

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Deleted: For instance, transcription regulation uses cooperative binding to arrive at a sigmoidal response curve whereas the same is achieved by an amplifier in circuit design. Analogies of this kind have inspired the advancement of synthetic biology. In terms of global network organization, a decade ago, Uri Alon pointed out several common design principles such as modularity and the usage of recurring elements (motifs) \cite{Alon Sci 2003}. These common topological patterns are in many cases the reflection of common underlying design objectives or strategies. For examples, modularity makes a system more evolvable, which is an advantage one would like to optimize. Therefore, an insightful network comparison should be rooted in the common design objectives. As Alon highlighted by the phrase "the tinkerer as an engineer",

internet layer is the bottleneck with under heavy constraints in which there are very few protocols and they can hardly be replaced [21]. Remarkably, the rapid innovation at the top and bottom layers but constraint at the middle happens 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 [22].

Revisiting tinkerer versus engineer

The parallel between biological networks and technological networks should best be examined under the light of evolution. As Alon highlighted by the phrase “the tinkerer as an engineer” [9], 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 [23]. [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 [24]. 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 [25][26]. 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 [27][28]. Indeed, it has been demonstrated that electronic circuits can be evolved to fulfill a fluctuating evolutionary goal [25]. Similarly, metabolic networks of bacteria living in multiple habitats are evolved to decompose multiple food sources [29][30]. 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 [31][32].

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 [33]. 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 like George Washington Bridge require more upgrade and more construction.

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Deleted: \cite{Wagner 2014}. In such a common framework, biological networks and networks with specific performance goals in other disciplines are shaped by similar underlying design objectives. However, as “there’s no free lunch”, there is no way to satisfy all objectives and thus tradeoffs are unavoidable. Networks in different disciplines are perhaps the optimal configurations subjected to different constraints and tradeoffs. Here, via a few specific examples, we want to illustrate how network comparison works in the broadened context. (~1000 words)

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Comparison in terms of mathematical approaches

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 [34], 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 [35] and later in an algorithm called NetRank that rank prognostic relevance for patients with cancers [36]. 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 [37].

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 [38], are very popular 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 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. The multi-layers notion has recently been used to integrate co-association across different species in order to detect conserved and specific functional modules [39]. A similar 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 [40]. 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 mine the resultant co-expression networks.

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 between 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 [24]. Comparison of methods in mining biological networks and networks in computational social science is bridging the two distant fields, whereas efforts have been spent on the interface [41]. Indeed, various scientific disciplines form a network in the intellectual universe in which knowledge emerge when things connect.

~2700 words

- [1] L. Pachter, "RNA-Seq: functional genomics assays based on high-throughput sequencing," *Bits of DNA: Reviews and commentary on computational biology*, 2014. .
- [2] M. Baker, "Big biology: The 'omes puzzle," *Nature*, vol. 494, no. 7438, pp. 416–419, Feb. 2013.

- [3] Tony Hey, Stewart Tansley, and Kristin Tolle, *4th Paradigm*. Microsoft Research, 2009.
- [4] A.-L. Barabási, *Linked: How Everything Is Connected to Everything Else and What It Means for Business, Science, and Everyday Life*. New York: Plume, 2003.
- [5] A.-L. Barabási and Z. N. Oltvai, "Network biology: understanding the cell's functional organization," *Nat. Rev. Genet.*, vol. 5, no. 2, pp. 101–113, Feb. 2004.
- [6] A. D. Lander, "The edges of understanding," *BMC Biol.*, vol. 8, no. 1, p. 40, Apr. 2010.
- [7] P. Beltrao, G. Cagney, and N. J. Krogan, "Quantitative Genetic Interactions Reveal Biological Modularity," *Cell*, vol. 141, no. 5, pp. 739–745, May 2010.
- [8] K.-I. Goh, M. E. Cusick, D. Valle, B. Childs, M. Vidal, and A.-L. Barabási, "The human disease network," *Proc. Natl. Acad. Sci.*, vol. 104, no. 21, pp. 8685–8690, May 2007.
- [9] U. Alon, "Biological Networks: The Tinkerer as an Engineer," *Science*, vol. 301, no. 5641, pp. 1866–1867, Sep. 2003.
- [10] M. A. Fortuna, J. A. Bonachela, and S. A. Levin, "Evolution of a modular software network," *Proc. Natl. Acad. Sci.*, vol. 108, no. 50, pp. 19985–19989, Dec. 2011.
- [11] N. Polouliakh, R. Nock, F. Nielsen, and H. Kitano, "G-Protein Coupled Receptor Signaling Architecture of Mammalian Immune Cells," *PLoS ONE*, vol. 4, no. 1, p. e4189, Jan. 2009.
- [12] D. H. Erwin and E. H. Davidson, "The evolution of hierarchical gene regulatory networks," *Nat. Rev. Genet.*, vol. 10, no. 2, pp. 141–148, Feb. 2009.
- [13] I. S. Peter and E. H. Davidson, "Evolution of Gene Regulatory Networks Controlling Body Plan Development," *Cell*, vol. 144, no. 6, pp. 970–985, Mar. 2011.
- [14] M. B. Gerstein, A. Kundaje, M. Hariharan, S. G. Landt, K.-K. Yan, C. Cheng, X. J. Mu, E. Khurana, J. Rozowsky, R. Alexander, R. Min, P. Alves, A. Abyzov, N. Addleman, N. Bhardwaj, A. P. Boyle, P. Cayting, A. Charos, D. Z. Chen, Y. Cheng, D. Clarke, C. Eastman, G. Euskirchen, S. Fietze, Y. Fu, J. Gertz, F. Grubert, A. Harman, P. Jain, M. Kasowski, P. Lacroite, J. Leng, J. Lian, H. Monahan, H. O'Geen, Z. Ouyang, E. C. Partridge, D. Patacsil, F. Pauli, D. Raha, L. Ramirez, T. E. Reddy, B. Reed, M. Shi, T. Slifer, J. Wang, L. Wu, X. Yang, K. Y. Yip, G. Zilberman-Schapira, S. Batzoglou, A. Sidow, P. J. Farnham, R. M. Myers, S. M. Weissman, and M. Snyder, "Architecture of the human regulatory network derived from ENCODE data," *Nature*, vol. 489, no. 7414, pp. 91–100, Sep. 2012.
- [15] H. Yu and M. Gerstein, "Genomic analysis of the hierarchical structure of regulatory networks," *Proc. Natl. Acad. Sci.*, vol. 103, no. 40, pp. 14724–14731, Oct. 2006.
- [16] N. Bhardwaj, K.-K. Yan, and M. B. Gerstein, "Analysis of diverse regulatory networks in a hierarchical context shows consistent tendencies for collaboration in the middle levels," *Proc. Natl. Acad. Sci.*, vol. 107, no. 15, pp. 6841–6846, Mar. 2010.
- [17] S. W. Floyd and B. Wooldridge, "Middle management involvement in strategy and its association with strategic type: A research note," *Strateg. Manag. J.*, vol. 13, no. S1, pp. 153–167, Jun. 1992.
- [18] Y. Bar-Yam, D. Harmon, and B. de Bivort, "Attractors and Democratic Dynamics," *Science*, vol. 323, no. 5917, pp. 1016–1017, Feb. 2009.
- [19] T. Friedlander, A. E. Mayo, T. Tlusty, and U. Alon, "Evolution of bow-tie architectures in biology," *ArXiv14047715 Q-Bio*, Apr. 2014.
- [20] D. L. Stern and V. Orgogozo, "Is Genetic Evolution Predictable?," *Science*, vol. 323, no. 5915, pp. 746–751, Feb. 2009.
- [21] S. Akhshabi and C. Dovrolis, "The Evolution of Layered Protocol Stacks Leads to an Hourglass-shaped Architecture," in *Proceedings of the ACM SIGCOMM 2011 Conference*, New York, NY, USA, 2011, pp. 206–217.
- [22] B. Prud'homme and N. Gompel, "Evolutionary biology: Genomic hourglass," *Nature*, vol. 468, no. 7325, pp. 768–769, Dec. 2010.
- [23] A. Wagner and W. Rosen, "Spaces of the possible: universal Darwinism and the wall between technological and biological innovation," *J. R. Soc. Interface*, vol. 11, no. 97, p. 20131190, Aug. 2014.
- [24] W. A. Lim, C. M. Lee, and C. Tang, "Design Principles of Regulatory Networks: Searching for the Molecular Algorithms of the Cell," *Mol. Cell*, vol. 49, no. 2, pp. 202–212, Jan. 2013.
- [25] N. Kashtan and U. Alon, "Spontaneous evolution of modularity and network motifs," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 102, no. 39, pp. 13773–13778, Sep. 2005.

- [26] K. Raman and A. Wagner, "The evolvability of programmable hardware," *J. R. Soc. Interface*, vol. 8, no. 55, pp. 269–281, Feb. 2011.
- [27] A. Wagner, "Neutralism and selectionism: a network-based reconciliation," *Nat. Rev. Genet.*, vol. 9, no. 12, pp. 965–974, Dec. 2008.
- [28] J. Masel and M. V. Trotter, "Robustness and Evolvability," *Trends Genet.*, vol. 26, no. 9, pp. 406–414, Sep. 2010.
- [29] A. Kreimer, E. Borenstein, U. Gophna, and E. Ruppin, "The evolution of modularity in bacterial metabolic networks," *Proc. Natl. Acad. Sci.*, vol. 105, no. 19, pp. 6976–6981, May 2008.
- [30] S. Maslov, S. Krishna, T. Y. Pang, and K. Sneppen, "Toolbox model of evolution of prokaryotic metabolic networks and their regulation," *Proc. Natl. Acad. Sci.*, vol. 106, no. 24, pp. 9743–9748, Jun. 2009.
- [31] A. D. Lander, "Pattern, growth, and control," *Cell*, vol. 144, no. 6, pp. 955–969, Mar. 2011.
- [32] O. Shoval, H. Sheftel, G. Shinar, Y. Hart, O. Ramote, A. Mayo, E. Dekel, K. Kavanagh, and U. Alon, "Evolutionary Trade-Offs, Pareto Optimality, and the Geometry of Phenotype Space," *Science*, vol. 336, no. 6085, pp. 1157–1160, Jun. 2012.
- [33] K.-K. Yan, G. Fang, N. Bhardwaj, R. P. Alexander, and M. Gerstein, "Comparing genomes to computer operating systems in terms of the topology and evolution of their regulatory control networks," *Proc. Natl. Acad. Sci.*, vol. 107, no. 20, pp. 9186–9191, May 2010.
- [34] L. Katz, "A new status index derived from sociometric analysis," *Psychometrika*, vol. 18, no. 1, pp. 39–43, Mar. 1953.
- [35] S. Allesina and M. Pascual, "Googling Food Webs: Can an Eigenvector Measure Species' Importance for Coextinctions?," *PLoS Comput Biol*, vol. 5, no. 9, p. e1000494, Sep. 2009.
- [36] C. Winter, G. Kristiansen, S. Kersting, J. Roy, D. Aust, T. Knösel, P. Rümmele, B. Jahnke, V. Hentrich, F. Rückert, M. Niedergethmann, W. Weichert, M. Bahra, H. J. Schliitt, U. Settmacher, H. Friess, M. Büchler, H.-D. Saeger, M. Schroeder, C. Pilarsky, and R. Grützmann, "Google Goes Cancer: Improving Outcome Prediction for Cancer Patients by Network-Based Ranking of Marker Genes," *PLoS Comput Biol*, vol. 8, no. 5, p. e1002511, May 2012.
- [37] R. Singh, J. Xu, and B. Berger, "Global alignment of multiple protein interaction networks with application to functional orthology detection," *Proc. Natl. Acad. Sci.*, vol. 105, no. 35, pp. 12763–12768, 2008.
- [38] E. M. Airoldi, D. M. Blei, S. E. Fienberg, and E. P. Xing, "Mixed Membership Stochastic Blockmodels," *J Mach Learn Res*, vol. 9, pp. 1981–2014, Jun. 2008.
- [39] K.-K. Yan, D. Wang, J. Rozowsky, H. Zheng, C. Cheng, and M. Gerstein, "OrthoClust: An orthology-based network framework for expression clustering across multiple species," *Genome Biol.*, vol. 15, p. R100.
- [40] P. Holme and J. Saramäki, "Temporal networks," *Phys. Rep.*, vol. 519, no. 3, pp. 97–125, Oct. 2012.
- [41] J. H. Fowler, J. E. Settle, and N. A. Christakis, "Correlated genotypes in friendship networks," *Proc. Natl. Acad. Sci.*, p. 201011687, Jan. 2011.