(?) 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, intuitions as well as algorithms or mathematical techniques 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. 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. We could thus picture the description of individual components (parts list: genes, proteins and elements from genome annotation), and the full three or even four-dimensional picture of how molecules interact in space and time form the two ends of a spectrum. In this sense, the network perspective provides a useful middle ground by capturing the relationships between components of the parts list. A natural way to define relationships is by using various kinds of mechanistic interactions. Such 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. The integration of such mechanistic networks and various spatial and temporal quantities, visually as the decoration of arrows with directionality, color, thickness etc., provides a description reasonably close to the complete picture along the spectrum. While the incorporation of details offers physical intuition, it could be intractable. The scenario is analogous to classical physics; writing down the equations of all the particles is intractable, and thus physicists turn to a phenomenological and macroscopic formalism, i.e. thermodynamics. Similarly, certain networks defined in a phenomenological sense are useful. These networks do not capture the details of biological processes happening inside a living system, but provide a mathematical abstraction farther away from the complete picture in the spectrum. 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.

The underlying mechanistic network aims to serve as the skeleton of a complex system. Depending on the nature of interactions, mechanistic networks resemble, and could be compared

with various commonplace networks. For instance, signaling networks resembles certain chains of command in human society (e.g. corporate hierarchy) in terms of information transmission [8]. Developmental transcriptional regulatory networks, on the other hand, resemble technological systems like circuits in terms of the emergence of functions (specific input-output responses) [9]. The comparison thus allows 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, the systems-specific details make the framework not easy to transfer from one discipline to another. 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 algorithmic or method development.

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 areas 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 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 [15]. 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 [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 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 [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. 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).

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.

Formalisms for association and prioritization of nodes
In both biology and computational social science, networks are often used as a map for integrating various features. A general question of interest is to infer the properties of certain nodes. Though various kernel methods have been introduced, the essence of all solutions is the idea of "guilt by association". In genomics, a widely used approach to infer the functions of a protein or a non-coding element is 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. Online advertisers use the same trick. If your friends in Facebook use Product Y, you are more likely to use product Y and thus will be targeted. 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].

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. In social science setting, the same is true for applications like online advertising.

Formalisms for inference of edges
The construction of various phenomenological 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. This is of particular importance for biology in terms of identifying the master regulator of a disease. The same application is true for social networks for identifying the source of influence. Established mathematical machineries like Bayesian networks or Markov random fields have been used for this purpose. The inference of casual relationships could be greatly benefited by time-series data. The question is extremely common in biology, under the term "reverse engineering". 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].

Many networks in biology and social science are noisy and incomplete, leading to common challenges like link prediction and denoising. 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.

Formalisms for multi-layers network structure
A recent 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. While different layers of networks are categorical in this formalism, a similar multi-layers generalization in network analysis is the so-called temporal networks. In short, a temporal network considers the slices of networks taking place at different time points together as a single mathematical structure [28]. 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. 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.

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.

[[KKY2MG: the texts here are just snippets extracted from pervious writing, not coherent]]

Box 1 Hierarchical organization of networks

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 [31], 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 [8]. 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 [32]. Moreover, the cooperative regulatory factors in a transcriptional regulatory network tend to be in the middle layer [33]. 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 [34]. Such observations reflect a democratic hierarchy as opposite to a conventional autocratic organization [35].

Box 2 Tinkerer versus engineer

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 [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 facilitate 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.

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 [42]. 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 [43].

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 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) [44][45]. 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 [46]. 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) [47]. It showed that a bow-tie structure emerged if the goal matrix is rank deficient, i.e. the information can be compressed.

Box 3

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

May be giving a few more examples of phenomenological networks, like genetic interaction networks.

[1] L. Pachter, "*Seq: functional genomics assays based on high-througphput 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. Barabasi, *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] 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.

[8] 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.

[9] E. H. Davidson, *The Regulatory Genome: Gene Regulatory Networks In Development And Evolution*, 1 edition. Burlington, MA ; San Diego: Academic Press, 2006.
[10] A. Vázquez, A. Flammini, A. Maritan, and A. Vespignani, "Modeling of Protein Interaction Networks," *Complexus*, vol. 1, no. 1, pp. 38–44, 2003.
[11] A.-L. Barabási and R. Albert, "Emergence of Scaling in Random Networks," *Science*, vol. 286, no. 5439, pp. 509–512, Oct. 1999.
[12] T. Y. Pang and S. Maslov, "Universal distribution of component frequencies in biological and technological systems," *Proc. Natl. Acad. Sci.*, vol. 110, no. 15, pp. 6235–6239, Mar. 2013.
[13] M. P. Simmons, L. A. Adamic, and E. Adar, "Memes online: Extracted, subtracted, injected, and recollected," in *In Proceedings of the Fifth International AAAI Conference on Weblogs and Social Media*, 2011.
[14] 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.
[15] U. Alon, "Biological Networks: The Tinkerer as an Engineer," *Science*, vol. 301, no. 5641, pp. 1866–1867, Sep. 2003.
[16] 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.
[17] 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.
[18] A. D. Lander, "Pattern, growth, and control," *Cell*, vol. 144, no. 6, pp. 955–969, Mar. 2011.
[19] 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.
[20] 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.
[21] J. H. Fowler, J. E. Settle, and N. A. Christakis, "Correlated genotypes in friendship networks," *Proc. Natl. Acad. Sci.*, p. 201011687, Jan. 2011.
[22] L. Katz, "A new status index derived from sociometric analysis," *Psychometrika*, vol. 18, no. 1, pp. 39–43, Mar. 1953.
[23] 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.
[24] 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. Schlitt, 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.

[25] Y. Moreau and L.-C. Tranchevent, “Computational tools for prioritizing candidate genes: boosting disease gene discovery,” *Nat. Rev. Genet.*, vol. 13, no. 8, pp. 523–536, Jul. 2012.
[26] D. Wang, A. Arapostathis, C. O. Wilke, and M. K. Markey, “Principal-Oscillation-Pattern Analysis of Gene Expression,” *PLoS ONE*, vol. 7, no. 1, p. e28805, Jan. 2012.
[27] 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.
[28] P. Holme and J. Saramäki, “Temporal networks,” *Phys. Rep.*, vol. 519, no. 3, pp. 97–125, Oct. 2012.
[29] 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.
[30] C. Shou, N. Bhardwaj, H. Y. K. Lam, K.-K. Yan, P. M. Kim, M. Snyder, and M. B. Gerstein, “Measuring the Evolutionary Rewiring of Biological Networks,” *PLoS Comput Biol*, vol. 7, no. 1, p. e1001050, Jan. 2011.
[31] 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.
[32] 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. Frietze, Y. Fu, J. Gertz, F. Grubert, A. Harmanci, P. Jain, M. Kasowski, P. Lacroute, 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.
[33] 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.
[34] 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.
[35] Y. Bar-Yam, D. Harmon, and B. de Bivort, “Attractors and Democratic Dynamics,” *Science*, vol. 323, no. 5917, pp. 1016–1017, Feb. 2009.
[36] 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.
[37] K. Raman and A. Wagner, “The evolvability of programmable hardware,” *J. R. Soc. Interface*, vol. 8, no. 55, pp. 269 –281, Feb. 2011.
[38] A. Wagner, “Neutralism and selectionism: a network-based reconciliation,” *Nat. Rev. Genet.*, vol. 9, no. 12, pp. 965–974, Dec. 2008.

[39] J. Masel and M. V. Trotter, “Robustness and Evolvability,” *Trends Genet.*, vol. 26, no. 9, pp. 406–414, Sep. 2010.
[40] 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.
[41] 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.
[42] 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.
[43] B. Prud’homme and N. Gompel, “Evolutionary biology: Genomic hourglass,” *Nature*, vol. 468, no. 7325, pp. 768–769, Dec. 2010.
[44] 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.
[45] 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.
[46] D. L. Stern and V. Orgogozo, “Is Genetic Evolution Predictable?,” *Science*, vol. 323, no. 5915, pp. 746–751, Feb. 2009.
[47] T. Friedlander, A. E. Mayo, T. Tlusty, and U. Alon, “Evolution of bow-tie architectures in biology,” *ArXiv14047715 Q-Bio*, Apr. 2014.