A signature of biology in the “omic” era is the shift of attention from a few individual components to a collection of constituents. In the past structural biologists studied the binding of a few proteins, but now they are able to probe the interactions between thousands of proteins. Similarly, geneticists who would previously manipulate a single gene for functional characterization can now employ high-throughput functional genomic techniques to study the relationships between all genes. In many cases, genome-scale information describing how components interact is captured by a network representation. While the concept of metabolic pathways exists for decades and the study of regulatory networks was pioneered by researchers like Davidson and Kauffman, the paradigm of studying biological networks was arguably initiated by Barabasi’s efforts which began slightly more than a decade ago, in parallel with the advances in data acquisition and engineering techniques in systems biology.

Nevertheless, given the astonishing size and complexity of the cellular molecular networks probed by genomics or systems biology, gaining easy intuition about biology from these hairballs is not guaranteed.

[[move to crit block]]

Indeed, there are researchers who are more skeptical and quite a number of controversies have been publicized. A major concern of network analysis comes from the critic that statistical patterns observed in networks offer limited insights. For instance, while the enrichment of some of the so-called network motifs, small recurrent subgraphs in a network, suggests that the structures are potentially interesting, but understanding the actual functions relies on the actual dynamics \cite{Ingram BMC Genomics 2006}. Indeed, the topology of the underlying network is a coarse description of a complex system. One could incorporate different levels of details into the system, forming a spectrum of cellular descriptions (see Figure 1). In many cases, further details of a system bring further knowledge. For example, incorporating the details of binding interfaces into a protein-protein interactions network offers further insights on the nature of hubs in the network \cite{Kim et al. Science 2006, Clarke et al. JSB 2012}. Though it is tempting to go for as details as possible, creating a complete 3D or even 4D picture, it is worthwhile to note that too many details make the system intractable. In reality, a complete system-wide modeling of a cell is still in a very beginning phase, a coarse network description of a cell remains to be useful.

[[KKY: The previous version has a more elaborate description of the spectrum. I suggest making Figure 1 in a Box, and putting some of the remaining text into the box.]]

[[NO]]

[[Inporate the below]]

How could we make full use of the topological patterns observed in many biological networks? Or, more broadly, what approaches might help in deciphering hairballs? We believe there are two equally important thought processes in thinking about networks. The first way of thinking about networks focus on mathematical formalisms and algorithmic aspects for practical problems. Topological patterns, even though offer limited insights of the system, could be used as features in various machine-learning frameworks for all sorts of predictions.

[[cut below][

This thought process is particularly useful for systems whose mechanistic interactions between components are too complex to comprehend, but statistical association between components can be probed. For example, co-expression networks or genetic interactions networks capture association between components undergoing much more complex mechanistic interactions. Such approach leverages the simplicity of network framework. In particular, it allows one to transfer formalism readily between disciplines. This can beneficial for the biological science because formalisms developed elsewhere to easily find fruitful application in biology. The second way of thinking about networks assumes the underlying network is the skeleton of a complex system; understanding topological features are keys to decipher the organization principles behind the complex system. This is particularly the case for networks that capture the mechanistic interactions within systems, for instance protein-protein interactions network, transcriptional regulatory networks etc. In this approach, we argue that, apart from going into further details as explained above, we could gain intuition by comparing biological networks with underlying networks of complex systems for which we have more day-to-day experience. Therefore, in both thought processes, cross-disciplinary network comparison offers insights in deciphering biological networks.

Throughout the history of science, many advances in 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 this essay, we will explain how formalisms and ideas from disciplines as diverse as engineering, behavioral science and sociology could help us with the “hairball challenge”, and the potential challenges.

[[KKY: here follows many of the texts we wrote in “association networks” and “mechanistic networks” of the previous version. They should be trimmed, but I believe more subjective thoughts should be sprinkled around those texts in response to reviewer 2’s comment (ref.2.2 if you have the response letter I shared with you). Next, I provide another paragraph expressing our opinions on network critics toward the end of the essay.]].

[[move to conc]]

Seeking comparison between biological networks, social networks and technological networks may echo the long-time fantasy of finding universality in all complex systems. Indeed, the discovery of the scale-free degree distribution in many different networks initially hinted at such direction. Very soon researchers argued that a universal model never exists: there are biological networks whose degree distributions do not follow a simple power-law \cite{Clauset SIAM 2009, Tanaka et al. FEBS 2005}; there are simply too many ways to generate a network with a broad degree distribution \cite{Newman 2005}. Indeed, it is important to clarify certain myths for the advancement of network biology as a field \cite{Keller BioEssays 2005, Lima-Mendez Molecular BioSystems 2009}. While scale-free distribution is not universal (and the lack of fundamental laws of networks in general) sounds like a bad news, we believe that one should not be disappointed or simply turn away from network biology. As suggested by some of the examples in this essay, understanding the differences between biological networks and networks from other disciplines may be as rewarding as finding the commonality. Nevertheless, discouraging the search of fundamental laws is not healthy for science. The concept of universality has a long tradition in statistical physics literature, and the perspective of characterizing the underlying mechanisms of complex systems by a few scaling or critical exponents should very much be appreciated. In fact, apart from the degree distribution, there are still many relatively open questions. For examples, as building blocks of networks, different network motifs exhibit different occurrence frequencies \cite{Milo et al. Science 2002}. It is quite remarkable that under proper normalization, the transcriptional regulatory networks constructed by experiments in different cell lines as well as different species exhibit similar patterns \cite{Neph et al. Cell 2012, Boyle et al. Nature 2014}. Whether it is an interesting technical artifact or an insightful clue on cellular information processing is still unknown.

[[KKY: here follows one or two paragraphs for conclusion. I think the previous version is too long.]]

Keller BioEssays 2005

<http://onlinelibrary.wiley.com/doi/10.1002/bies.20294/abstract>

Ingram et al. BMC Genomics 2006

<http://www.biomedcentral.com/1471-2164/7/108>

Newman 2005

http://arxiv.org/abs/cond-mat/0412004

Lima-Mendez et al. Molecular BioSystems 2009

<http://pubs.rsc.org/en/content/articlehtml/2009/mb/b908681a>

Clauset et al. SIAM 2009

<http://epubs.siam.org/doi/abs/10.1137/070710111>

Tanaka et al. FEBS 2005

http://www.sciencedirect.com/science/article/pii/S0014579305010082

This paper is useful if we plan to discuss the internet, error attack…

[**http://www.pnas.org/content/102/41/14497.short%20Doyle**](http://www.pnas.org/content/102/41/14497.short%20Doyle)