Figure 1 **[\*\*AU: It is the author's responsibility to obtain permissions for figures being adapted or reprinted from previous publications. Please obtain permissions as necessary and add permissions verbiage to figure captions where applicable.\*\*] [\*\*ED: All permissions have been obtained and permission verbiage is included in figure captions as applicable.\*\*]**Network representations.(*a*)Molecular networks form a functional base layer for several higher-order biological networks, including networks of organelles (e.g., vesicular transport), cellular networks (e.g., neural), and population-scale networks (e.g., disease transmission). (*b*)Abstract network representations can be built through a progressive layering of information and logic, according to the network under study. For instance, the addition of directional information to a network may be particularly important when representing a gene regulatory network. (*c*)Matrices are useful for representing certain network variables, like the pattern of connections and connection weights.

Figure 2Glycolysis and the citric acid cycle.Despite the complexity of the complete human metabolic network, the core subgraphs of glycolysis and the citric acid cycle can be appreciated in their global context through selective focus. The network structure of glycolysis is linear, while that of the citric acid cycle is cyclical. The two subgraphs are deeply enmeshed within the other processes of metabolism. Adapted with permission from Reference 154.

Figure 3Pictorial glossary of common network concepts and measures. Many of these metrics (such as degree, clustering coefficient, and betweenness centrality) are used as measures of node importance or influence. Node and edge metrics may be used by algorithms to elucidate higher-order topological features of networks (such as modules and diameter). Hierarchical structures have been used to organize many types of systems, including regulatory networks.

Figure 4The molecular interaction network of the RNA (ribonucleic acid) polymerase II elongation complex in *Saccharomyces cerevisiae* can be represented structurally (*a*) or as an abstract molecular interaction network (*b*). The molecular structure information lost in an abstract network representation may be important for interpreting certain observed molecular network phenomena. Panel *a* adapted with permission from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (identifier 1I6H), visualized with NGL Viewer. Panel *b* adapted with permission from STRING v10 protein–protein interaction database, showing experimentally determined interactions (76). (*c*) Three-dimensional protein structure data can be mapped onto protein–protein interaction networks (PPI) to construct structural interaction networks (SINs). SINs provide physical intuition and nuance for the interactions in a PPI. For instance, a SIN can help distinguish interactions involving single or multiple interfaces. This can be helpful for identifying permanent and transient interactions in the network. High-resolution definitions of various interactions are helpful when prioritizing disease-associated variants to gain mechanistic insights. For example, disease-associated nonsynonymous variants can either create or destroy a binding interface of an individual protein. This, in turn, will influence its interaction with other proteins in the network, which can drive disease progression. Furthermore, variants influencing core and surface of proteins will affect interactions in different ways. For example, for a given protein, mutations on its surface will mostly affect interactions involving a particular interface, whereas those in the core will disrupt all interactions equally.

Figure 5Network rewiring.(*a*)A schematic diagram illustrates the progression of a regulatory network from normal to a diseased state. The state of the regulatory network at a specific point in time is depicted as a snapshot. (*b*)Binding profiles of regulatory proteins can be used to infer both gain and loss of interaction in different cell states. (*c*)By reconstituting the time progression of the regulatory network, the resulting network rewiring can summarize the dynamic changes in regulatory elements.

Figure 6 **[\*\*AU: Please check capitalization and italicization (genes in italics, proteins roman) for all gene/protein names in this figure and caption.\*\*] [\*\*ED: A revised version of Figure 6 is attached consistent with the capitalizations and italicizations used in this figure caption.\*\*]**Feedforward loops (FFLs) are a frequently observed motif in molecular networks. (*a*)An example of a coherent FFL active in the regulation of flagellar protein production in *Escherichia**coli*. The *FlhDC* promoter directs the production of *FliA*, which activates class 2 operon genes*fliMNOPQR*. *FlhDC* also acts additively to activate *fliMNOPQR*. (*b*) Also in *E. coli*, the presenceof arabinose induces the formation of the AraC-arabinose complex, which is essential totranscribe the *ara* operon. CRP and cyclic AMP are required in this process. (c)**[\*\*AU: Is panel c necessary? Your readers are unlikely to need a visual definition of AND and OR.\*\*] [\*\*ED: Yes, we agree that panel c may be unnecessary for our readers. We have attached a revised version of Figure 6 with panel c removed.\*\*]**The presence of either of the two input elements is sufficient to generate the output in an OR gate FFL, whereas the presence of both inputs is required to produce the output in an AND gate FFL.**[\*\*AU: Rearranged sentence to reflect left/right orientation of these in panel *c* and “typical” was removed, OK?\*\*] [\*\*ED: Yes. However, agree with your suggestion to remove panel c.\*\*]**

Figure 7Network algorithms.(*a*)The general structure of a convolutional neural network with sample input and output (similar to DeepBind). Here we are trying to detect transcription factor (TF) binding sites. If we have high-throughput sequencing data containing sequences of potential TF binding sites, we can produce as output the probability that a particular sequence is a TF binding site. Training data consist of sequences with experimentally determined binding scores. The convolution layer performs feature extraction by convolving the input matrix with a convolution matrix called a kernel or feature detector. The resulting matrix is the feature map, which in this example would be sequence motifs. An activation function operation (e.g., rectified linear unit) introduces nonlinearity into the model. Pooling and subsampling reduce the dimensionality of the feature map; the depth of the feature map corresponds to the number of kernels used in the convolution step. The fully connected layer uses the feature maps to make predictions about the input. **[\*\*AU: Deleted for redundancy with above.\*\*] [\*\*ED: Agree that this is redundant and can be removed.\*\*]** (*b*) A series of steps by which information (sometimes termed “heat” in networks literature) propagates through a network (*left to right*). This information originates in node 4 (often a gene believed to be disease-associated with high confidence) and subsequently flows to neighboring nodes 2, 3, 5, and 6. In the next step, this signal may partially flow back into node 4, as well as neighboring nodes 1 and 7, before eventually reaching node 8. Matrices represent the propagation of heat from source to sink nodes.**[\*\*AU: OK?\*\*] [\*\*ED: Yes.\*\*]** When applied to large networks, the resultant distribution of heat throughout the network may enable one to assign well-defined modules.

Figure 8Cancer gene networks.(*a*,*b*)Gene interactions from multiple regulatory levels may be integrated together to form a metanetwork*.* (*c*)By pooling variants from multiple patients and mapping these mutations to extended gene regulatory regions, an aggregated mutational burden score can be defined. (*d*)Through techniques like network propagation, highly mutated subnetworks and key genes can be identified. **[\*\*AU: Please confirm abbreviations are correct.\*\*] [\*\*ED: Yes, all abbreviations here are correct here. Thank you for adding them to this figure caption.\*\*]**Abbreviations: G, gene; miRNA, microRNA; RBP, RNA-binding protein; TF, transcription factor; UTR, untranslated region.

Figure 9Cross-disciplinary network comparisons.By comparing networks across disciplines, we may learn more about the structure and function of both biological and human-made networks. For example, by comparing airline flight routes to the human metabolic network, we have learned that both follow a scale-free distribution (136, 137). A similar rich-get-richer evolutionary process may apply to both networks. Just as flight options are most easily expanded by connecting to an already well-connected airport, pyruvate and acetyl-CoA (acetyl coenzyme A) may function as hub metabolites, facilitating molecular transitions between biochemical pathways.