# Nutritional Systems Biology: Definitions and Approaches

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## Key Words

systems biology, nutrition, network biology, *Saccharomyces cerevisiae*

## Abstract

Nutrigenetics and nutrigenomics are nascent areas that are evolving quickly and riding on the wave of "personalized medicine" that is providing opportunities in the discovery and development of nutraceutical compounds. The human genome sequence and sequences of model organisms provide the equivalent of comprehensive blueprints and parts lists that describe dynamic networks and the bases for understanding their responses to external and internal perturbations. Unfolding the interrelationships among genes, gene products, and dietary habits is fundamental for identifying individuals who will benefit most from, or be placed at risk by, intervention strategies. More accurate assessment of the inputs to human health and the consequences of those inputs measured as accurate transcriptomic, proteomic, and metabolomic analyses would bring personalized health/diet to practice far faster than would waiting for a predictive knowledge of genetic variation. It is widely recognized that systems and network biology has the potential to increase our understanding of how nutrition influences metabolic pathways and homeostasis, how this regulation is disturbed in a diet-related disease, and to what extent individual genotypes contribute to such diseases.

## Contents



## INTRODUCTION

Practically all cellular processes, including every step in the flow of genetic information from gene expression to protein synthesis and degradation, can be affected by diet and lifestyle. Nutrients and nonnutrient components of foods alter the metabolic functions of the cells in complex ways. Similar to the role of pharmaceuticals, nutrients contain a number of different compounds that act as modifiers of network function and stability (41). However, there is still a limited understanding of the nutrient-related network characteristics and function, including robustness, regulation, and interaction. Exploiting roles of nutritional compounds for the rational design of strategies to manipulate cell functions and/or cell fates for benefit is severely restricted by this lack of information. A more complete knowledge of network function (**Figure 1**) will further enhance our abilities to predict quantitative or qualitative relationships between specific health outcomes and the diverse patterns and levels of nutrient intakes in genetically diverse individuals and populations (19, 43).

The significance of individual variations in gene sequences, particularly in single nucleotide polymorphisms (SNPs), has been accented since the completion of the Human Genome Project. Currently, focus is on the role of SNPs in chronic diseases and in predicting the response of individuals to different pharmaceuticals. A fruitful strategy in approaching and exploring the field of nutritional research is to borrow methods that are well established in medical and pharmacological research (11). For example, in analogy to pharmacology, nutrients can be considered as signaling molecules that are recognized by specific cellular-sensing mechanisms. However, the level of complexity in nutrition studies is further increased by the simultaneous presence of a variety of nutrients, with diverse chemical structures, that can have numerous targets with different affinities and specificities. In order to assess the metabolic responses to complex diets, it is therefore a necessity to look at hundreds of test compounds simultaneously and observe the diverse temporal and spatial responses. Obviously, this differentiates the nutritional from the pharmacological studies, where single elements are used at low concentrations and with a relatively high affinity and specificity in a small number of thoroughly selected targets. The way to face and successfully overcome the complexity of nutritional research is probably to dissect the research problems into smaller and more feasible challenges. This will allow defining of specific hypothesis that can be tested and evaluated using an appropriate model system (**Figure 1**) chosen to obtain correct and clear answers to the research question addressed (35, 39).

Nutritional genomics is a recent offshoot of the genetic revolution that we experienced over the past 10 years. It includes (*a*) nutrigenomics, which deals with the interactions between dietary components and the genome as well as the resulting changes in proteins and other metabolites, and (*b*) nutrigenetics, which has as its main goals to understand the gene-based differences in response to dietary components and to develop nutraceuticals that are the most compatible with the health status of individuals based on their genetic makeup (22). The birth of the specific fields of nutrigenomics and nutrigenetics has been propelled by the realization that

in order to prevent the onset of diseases, it is essential to take into consideration that

- nutritional habits that supply the body with inappropriate compounds can cause considerable levels of genome mutation, which subsequently will trigger alterations in gene expressions required for genome maintenance, and
- common SNPs may affect the activity of proteins that control the bioavailability of micronutrients and/or the affinity for micronutrient cofactors in key enzymes involved in DNA metabolism or repair.

Supplementation of the diet with appropriate nutraceuticals could, in some cases, help overcome inherited metabolic blocks in key DNA-maintenance pathways. For example, in cases where a polymorphism in a gene reduces the binding affinity for a micronutrient, resulting in a lower reaction rate, supplementation of the diet with the particular micronutrient is expected to be an effective strategy to modulate risk (4).

In this review, we discuss the integration of high-throughput techniques in nutrition research (**Figure 1**). We present examples that endeavor to quantify all the molecular elements of a biological system to assess their interactions and to integrate that information into graphical network models that serve as predictive hypotheses to explain emergent behaviors connected to diet.

## -OMICS IN NUTRITIONAL RESEARCH

Recent advances in high-throughput experimental techniques have resulted in rapid accumulation of a wide range of *x*-omics data of various forms, providing a foundation for in-depth understanding of biological processes. There are more than 450 different "omic flavors," ranging from arenayomics to xenobiomics (a complete list can be found at **http://www.omics.org/index.php/**). There are several examples of single *x*-ome approaches and combined analyses of these *x*-ome data for the development of improved strains and enhancement of metabolic engineering strategies (2, 9, 25, 31). However, recently we have witnessed the introduction of various omics technologies into nutritional research. As a result, many new disciplines have emerged, including nutrigenomics, which is defined as the interaction between nutrition and the individual's genome. Nutritranscriptomics, nutriproteomics, and nutrimetabolomics refer to the dependence of gene transcription, protein expression, and metabolite generation, respectively, on dietary changes (see New Technologies and Nutrition Research, sidebar below). An area of active research is the integration, interpretation, and application of these data, which should enable the identification of metabolic markers that can guide the assessment of the health status of humans and provide quantitative measures for diet-derived effects on human metabolism (19, 22).

The number of successful examples of transcriptome, proteome, and metabolome profiling, as stand-alone tools for capturing the cellular responses to nutrients and identifying their molecular targets, has grown significantly (6, 10, 16, 23, 27, 28, 34, 38, 47). The ultimate goal of these high-throughput studies was to enable nutrition scientists to make recommendations for personalized health maintenance based on molecular signatures of food-derived nutrients and nonnutrients that lead to a specific phenotype and subsequently to prevent the onset and progression of disease. A point worth touching upon is that the traditional medical world has often noted that, although many of the *x*-omes, particularly the younger disciplines, provide academically interesting research, they have not translated to methods or approaches with medicinal impact and value because the data integration when dealing with complex systems is not straightforward. Definitely one of the major challenges in the analysis and interpretation of these omic data is delivering models of causation from correlations (18, 37).

This has led to new questions and a radical rethinking about the way biological data are gathered, the value of "random-fishing" experiments versus hypothesis/target strategies,

## NEW TECHNOLOGIES AND NUTRITION RESEARCH

**Nutrigenomics:** the effect of diet on DNA stability and gene expression.

**Nutrigenetics:** the effect of genetic differences between individuals in their response to a specific dietary pattern, a functional food, or a supplement for a specific health outcome.

**Nutritranscriptomics:** the genome-wide study of mRNA expression levels in one cell or in a population of biological cells for a given set of nutritional conditions.

**Nutriproteomics:** the large-scale analysis of the structure and function of proteins as well as of protein-protein interactions in a cell to identify the molecular targets of diet components.

**Nutrimetabolomics:** the measurement of all metabolites to access the complete metabolic response of an organism to a nutritional stimulus.

**Systems biology:** the integrated approach for studying biological systems, at the level of cells, organs, or organisms, by measuring and integrating genomic, proteomic, and metabolic data. In this respect, it is the attempt to bring the existing knowledge about the various biological components onto a systemic level (with its unifying organizational principles) that determines the function of the organism.

**Bioinformatics:** in the context of systems biology, aims to interpret the large, disparate data sets and ultimately to provide insight into biological mechanisms that underpin the experimental observations. A classical bioinformatics approach is to begin by mapping experimental results onto a priori "known" biochemical pathways, as curated by previous research and literature. A complementary activity is to analyze results at a more granular level, namely, at the level of biochemical reactions, and to attempt to fit the observations into known reaction models. A third approach is to process the data in an empirical, statistical manner and generate de novo hypotheses about the mechanistic origins of the observations.

**Correlation networks:** useful approaches to examine the behavior of molecular systems. Such approaches generate graphs that represent the associations between molecules without preconception of their involvement in biochemical pathways.

and how we manipulate, analyze, and interpret the resulting information content in order to drive understanding and knowledge about complex biological processes and systems. The emergence of systems biology, also referred to as pathway, network, or integrative biology, has been one attempt to address such pressing issues.

## SYSTEMS-BASED THINKING OF NUTRITION

Even though a systems-based thinking has traditionally been used in medicine (physiology, nutrition, etc.), for many years the focus was on molecular mechanisms. But in the past century, the appearance of a holistic view across different scientific fields has been noticeable. Systems biology is a scientific field that endeavors to quantitatively characterize the genetic, transcription, protein, metabolic, signaling, and other informational pathway responses to a clearly defined perturbation of a biological system and to assess their interactions and integrate that information into graphical network models that serve as predictive hypothesis to explain emergent behaviors (45).

Human disorders and nutrient responses represent complex features that involve interactions among genes and between genes and environment, and also among genetic, genomic, proteomic, metabolomic, and signaling networks. Our need for fundamental understanding of the building blocks of the complex biological systems has been the main reason for the reductionist approach that was mainly applied in the past to elucidate these systems. The lack of analytical tools to allow a more holistic approach to dissect such systems was an additional obstacle. But the current boom in biological information propelled by large-scale high-throughput technologies has conduced a shift away from reductionism in favor of a systems-level view of biology (44).

To date, studies in mammalian systems have illustrated primarily the use of protein interaction and metabolomic data to describe topological properties of biological networks. However, an alternative approach to estimate correlations among genes, which in turn can become the basis of transcriptional networks, is the use of high-density microarrays. The widespread availability of microarrays for a

number of model systems allows the quantification of relative transcript abundances in a comprehensive fashion. Despite the relatively simplistic nature of correlation measurements, they reflect a plentitude of information regarding gene-gene interactions in any given system, pointing out general structure characteristics of transcriptional interaction networks (21).

The study of Rezzi et al. (33) represents one of the most recent examples of exploiting systems biology in the nutrition arena. In their work, they embraced systems-level thinking to unfold the complex interplay among genes, diet, lifestyle, and endogenous gut microflora. Their data suggest the occurrence of a metabolic imprinting of the basal metabolic phenotype in relation to a behavioral/psychological dietary preference that is characterized by "chocolate desiring" or "chocolate indifference." This imprinting is independent of the ingested food, as chocolate consumption versus placebo has no direct effect. The plasma metabotype variation with preference class is mainly characterized by differences in the lipoprotein profiles. In addition, the metabolic differences observed in urine suggest considerable differences in gut microbial metabolic activities that may be of long-term health significance to the host. By correlating the dietary preferences with measurements of the human plasma, urine postprandial lipoproteins, and gut microbial metabolites, the authors proposed their approach as a tool for the classification of dietary responses in populations and personalized nutritional management.

In another systems-level study conceived by Arbones-Mainar et al. (3), the effects of Picual and Arbequina olive oils, rich and poor in polyphenols, respectively, on plasma lipid and glucose metabolism, hepatic fat content, and the hepatic proteome were determined in *Apoe*$^{-/-}$ mice. Both extra virgin olive oils (EVOOs) decreased atherosclerosis in Apoe$^{-/-}$ mice despite an increase in plasma total cholesterol and the development of hepatic steatosis. Liver weight was significantly higher upon consumption of Picual EVOO, whereas the hepatic fat and hepatic acidophilin protein levels were substantially increased by the consumption of both EVOOs. These are conflicting findings, and it would be intriguing if olive oil consumption would affect the interaction between similar mechanisms in humans, as hepatic lipid loading over a longer period may have detrimental effects. The authors applied a systems biology approach to decipher the complex interactions between pathways that are on one hand involved in the beneficial reduction in plaque formation and on the other hand involved in the potentially less beneficial development of hepatic steatosis. The authors observed, for example, a significant up-regulation of a large array of antioxidant enzymes upon consumption of EVOO that may diminish oxidative stress instigated by hepatic steatosis and, in addition, may delay the development of atherosclerosis. Indeed, the accumulation of triglycerides may not pose a major challenge to the liver and represents a relatively safe way to store triglycerides as long as the antioxidant capacity is adequate to prevent lipotoxicity. In addition, the results of the proteomics analysis revealed for the first time that two different EVOOs instigated distinct effects on hepatic lipid metabolism by regulation of hepatic adipophilin. This mechanism may override any regulation by insulin or betaine homocysteine methyl transferase to enhance the production of very-low-density lipoprotein apolipoprotein B that is normally observed upon development of hepatic steatosis and early symptoms of insulin resistance.

Dieck et al. (8) conducted transcriptome and proteome analyses to identify the underlying molecular changes in hepatic lipid metabolism in zinc-deficient rats. When the hepatic genes/proteins identified as differentially regulated by zinc deficiency were arranged in the context of their biological functions, it became obvious that enzymes required for hepatic triacylglycerol turnover and β-oxidation of fatty acids uniquely showed reduced mRNA steady-state levels, whereas those of de novo lipogenesis displayed increased levels. Although not all genes encoding proteins

of these pathways were found on the array, altered transcript levels of a variety of enzymes as well as hepatic factor S14 argued for major changes in these metabolic routes. In summary, Dieck et al. (8) provided evidence for a rather complex regulatory network of zinc-dependent alterations in hepatic metabolism with gene groups functionally linked to hepatic lipolysis to show major changes in expression level. Their experimental findings and plausibilities provide support for the notion that an unbalanced gene transcription control via peroxisome proliferator-activator receptor-α, thyroid hormone, and sterol regulatory element-binding protein+-dependent pathways could explain most of the apparent pleiotropic effects of zinc deficiency on hepatic fat metabolism.

## NETWORK BIOLOGY APPLIED TO NUTRACEUTICAL DISCOVERY AND DEVELOPMENT

A major challenge for biologists today is the discovery of biomarkers for health benefits and disease diagnosis. Major advances in this area have arisen from the realization that focus should shift from the identification of single biomarkers to the identification of complex and dynamic biomarker patterns (**Figure 2**). Although this transition from single-biomarker blueprint to the investigation of biomarker patterns brings new levels of complexity to deciphering biological information, such a turnaround will be essential for answering biological questions related to the etiology and progression of disease states. This will be particularly important as different biomarker profiles are found at the healthy state, at the onset of disease, and at the late stage of disease, and only through analysis of the dynamic profiles will it be possible to elucidate the mechanisms and validation of transitional biomarker profiles. Network methods have been applied to identify and characterize various biological interactions and to assist in predicting gene functions in lower eukaryotes. Recently, gene network methods have been applied in the analysis of complex features in higher organisms (14, 20, 43).

Network biology provides the opportunity to gain further understanding of the structure and function of networks. Molecular interaction networks provide a convenient and practical scaffold to bridge the gap between individual genes and systems biology. Nodes with large numbers of edges, so-called hub nodes, which are highly connected, attract special attention because they represent the backbones of the network architecture. Despite the presence of key hub nodes in biological networks, these are typically so highly connected that they are resistant to the removal of single components and therefore are extremely robust to many different kinds of perturbations. The robustness, which is a very important principle of biological systems, can be established through network wiring or architecture and/or through network dynamics (i.e., interactions among a defined set of network components). Network wiring that includes structural redundancy or degeneracy provides multiple or alternative pathways, and such architectures avoid the need for dynamic responses to achieve robustness (1, 5). However, the significance of hubs in disease and intervention as well as the concept of scale-free networks are still the subjects of vigorous debate, and more convincing examples are needed to demonstrate their importance. Recently, Lum et al. (24) presented the integration of genotypic and gene expression data, offering to the scientific community one of the most comprehensive surveys of the brain coexpression network in a segregating mouse population. By describing the topological characterization of the whole-brain transcriptional network, the authors provided another example of biological "scale-free" networks with hierarchical structures. The modular structure of this network was found to be significantly enriched for pathways relating to splicing and RNA processing. These results are based on very basic correlation structures among the gene expression traits. Of particular interest is the observation that the key features in the whole-brain coexpression network in the BXH cross are highly

interconnected. This is significant when taking into account that brain is unambiguously one of the most transcriptionally complex tissues and the importance that RNA splicing and alternative splicing play in this tissue.

In the interplay of network biology and nutrition, there is already a noteworthy amount of promising results. In one of the most recent studies, Ferrara et al. (12) have taken advantage of the high heritability of mRNA abundance phenotypes and, via microarray technology, have mapped gene loci controlling gene expression at the genome-wide level in mice. By generating mRNA expression and metabolic profiles in liver samples obtained in an F2 intercross between the diabetes-resistant C57BL/6 *leptin*$^{ob/ob}$ and the diabetes-susceptible BTBR *leptin*$^{ob/ob}$, the authors could uncover genetic regions that coordinate groups of metabolites and transcripts and contain plausible genes. Their network identifies a specific metabolite glx (glutamate + glutamine) that regulates gene expression. In addition, glycine and serine are the two amino acids most highly correlated with glx, and the transcript most highly correlated with glx is alanine:glyoxylate aminotransferase (*Agxt*). The authors concluded that the upregulation by glx of *Agxt* is one mechanism by which glx is correlated with glycine and serine since *Agxt* catalyzes the transamination of glyoxalate to form glycine, which can then be converted to serine. The groups of metabolites and transcripts that are correlated or comap to physiological traits in the F2 sample used in this study may offer insight into metabolic pathways that are causal or reactive to diabetes pathology.

Schadt et al. (36) describe a multistep process to extract causal information from gene-expression data related to complex phenotypes such as obesity and gene expression. Central to this process is a likelihood-based test for causality that takes into account genotyping, RNA, and clinical data in a segregating mouse population to identify genes in the trait-specific transcriptional network that are under the control of multiple quantitative trait loci for the trait of interest but are still upstream of the trait. The authors applied the liquid chromatography-mass spectrometry procedure to a segregating mouse population phenotyped for omental fat pad mass and identified known genes (Hsd11b1) and new susceptibility genes (Tgfbr2, C3ar1 and Zfp90) for fat mass in this population in addition to significantly predicting the transcriptional response to perturbation of Hsd11b1. The three new susceptibility genes that they identified had not previously been directly associated with obesity-related traits. By focusing on the discovery of genes in the causal-reactive interval, the authors could identify those targets from the casual set that are optimally placed in the gene network associated with complex dietary traits.

## LESSONS FROM YEAST ON THE GENOME-NUTRIENT INTERACTION

The deletion of individual nodes has limited influence on disease networks in the majority of cases, as it is predicted by network biology analysis. In order to successfully perturb these robust networks, it is necessary to modulate multiple proteins. The perturbation of multiple nodes, leading to a diversity of phenotypes, has been demonstrated experimentally by synthetic behaviors as synthetic lethality, synthetic sickness, and synthetic rescue. In dual-knockout studies of many model organisms, the simultaneous deletion of two genes can be lethal (synthetic lethality) or deleterious (synthetic sickness) even though the isolated deletion of the two individual genes may not display any noticeable effect (20).

In one such large-scale study, where gene deletions were escalated by chemical interventions, Hillenmeyer et al. (17) demonstrated the magnitude of synthetic lethality in the budding yeast. Interestingly, lethality or sickness resulted in only 34% of single-gene deletions under ideal cultivation conditions of *Saccharomyces cerevisiae*. However, this percentage significantly increased when the applied stress was augmented by screening the whole genome panel of the yeast single-gene knockouts against a diverse small molecule library and then was

assayed against a wide range of environmental conditions. An additional 63% of gene knockouts then presented a growth phenotype; 97% of genes demonstrated a fitness defect when challenged with a small molecule under at least one environmental condition. Thus, although the majority of genes may be redundant under a wide range of environmental stimuli, significantly lower redundancy exists when a genetic perturbation is combined with a chemical insult across a spectrum of conditions.

A recent inspection of yeast metabolic networks applying an *in silico* model revealed that the cultivation conditions, especially in the case of nutrient-rich culture media, can counterbalance the disruption of 37% to 68% of the organism's genes (13, 30). Only 18% of dispensable genes are compensated for by gene duplicates, whereas other types of network buffering or robustness accounted for 4% to 17% of apparently "dispensable" genes. The maintenance of metabolic flux, under highly diverse environmental conditions, in microbial systems appears to be the primary selective pressure that maintains gene sequence, whereas starvation has been one of the most common environmental stresses.

As mentioned above, the budding yeast *S. cerevisiae* responds to various environmental perturbations by invoking specific adaptive mechanisms for its survival. Under nitrogen limitation, *S. cerevisiae* undergoes a dimorphic filamentous transition called pseudohyphae and is postulated to help the cells in foraging for nutrients and reaching an environment conducive for growth. This dimorphic transition involving different cellular processes is controlled by multiple signaling cascades, namely cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA), mitogen-activated protein kinase (MAPK), and target of rapamycin (TOR), which control the transcriptional activation of FLO11, a flocculin gene that encodes a cell wall protein. However, little is known about how these pathways coordinate to govern the conversion of nutritional availability into gene expression. Vinod et al. (46) have analyzed an integrative network composed of cAMP-PKA, MAPK, and TOR pathways with respect to the availability of nitrogen source using experimental and steady-state modeling approaches. The experiments demonstrate that the steady-state expression of FLO11 was bistable over the inducing concentration range of ammonium sulfate based on the preculturing condition. The steady-state analysis in tandem with experiments demonstrated how a complex signaling network interlinks various pathways to respond to changes in the nutritional status. Specific to the expression of FLO11, cAMP-PKA, MAPK, and TOR operated in parallel to decide the appropriate phenotypic response based on the degree of nutritional availability. Vinod et al. (46) demonstrated how these signaling pathways with specific sensitivity toward expression of FLO11 are integrated to respond under nitrogen starvation.

In summary, the studies of yeast biological networks have produced high-value information about the interplay of nutrition, genome, and phenotype. First, correlation networks demonstrate that nutrient-rich controlled environments can functionally compensate for a substantial proportion of genes. Second, the nutrient and nonnutrient compounds present in yeast's "diet" are driving the changes in transcript dosage, either by gene duplication or alterations in gene expression, in order to achieve network dynamics, reorganization, and ultimately survival. Of course, metabolite regulatory mechanisms (feedback loops), many of which are highly conserved, represent additional contributors to the network robustness. Last but not least, network robustness is also affected by redundancy and degeneracy, but the primary contributions come from environmental and internal sensing mechanisms that enable compensation through network dynamics (1, 15).

## THE FUTURE OF PRECLINICAL NUTRITION AND FOOD RESEARCH

The birth of new scientific disciplines was the response of the scientific world to concerns

about the dietary supplement and herbal industry (32). The field of nutritional genomics and genetics pledges information and knowledge for designing optimal diets that allow health maintenance and disease preventions for individuals. Personalized medicine and nutrition undoubtedly will have a tremendous impact on individuals, public health, and the economy. However, the human genetic heterogeneity poses a diversity of challenges in the research and applications of such a personalized approach. In addition, the complexity of foods and the variable physiological mechanisms that produce health or disease states increase the level of difficulty for accurate prediction of optimal diets for individuals. Adaptation to food availability and to individual nutrients requires fast but also sustained responses that simultaneously adjust the several interconnected metabolic processes. For their survival, cells need to regulate nutrient transport processes and storage capacity, tune the flux of intermediates through metabolic routes and branching points, and restructure the cellular transcriptome and proteome (7, 26, 42).

Yeast is the only eukaryotic organism in which large-scale screening methods, particularly DNA and protein microarrays, have been investigated in a whole-genome scale. In addition, yeast has several features that make it an ideal model for studying not only human disorders but also the effect of nutraceuticals in the prevention or progress of a disease. Heterologous expression of disease-causing protein in yeast has been successfully used to gain understanding of the normal functions of these proteins and to provide clues to the mechanisms of disease progression. Furthermore, examination of basic yeast physiology has revealed a striking conservation of biological processes between yeast and other eukaryotes. However, we should always remember that *S. cerevisiae* is a unicellular organism and, as such, is clearly deficient in some important attributes of multicellularity. Specifically, yeast has no immune system, tissues, or organs and requires only cell-to-cell communication for mating. Furthermore, yeast has closed mitosis and divides asymmetrically by budding, unlike human cells (29, 40).

In forward-looking systems science experiments, complex input perturbations followed by the monitoring of system-wide responses will be the new concept in experimental design. In addition, a desire to move to preventive health care and personalized diet and medicine will create an opportunity for a systems approach. Even though the concept and practice of targeting individuals may seem to be a new opportunity and a great challenge in Western society, such approaches have existed for centuries in the medical systems of other cultures. Bridging the gap between different philosophies and practical approaches to health care across various medical systems is definitely an attractive way to move forward. Eventually, food manufacturers will develop designer foods that target at least groups of individuals with similar metabolisms, if not individuals. Clearly, the examples presented in this review have highlighted the potential of systems and network biology to impact our understanding of nutrition as much as they have done in human health.



## DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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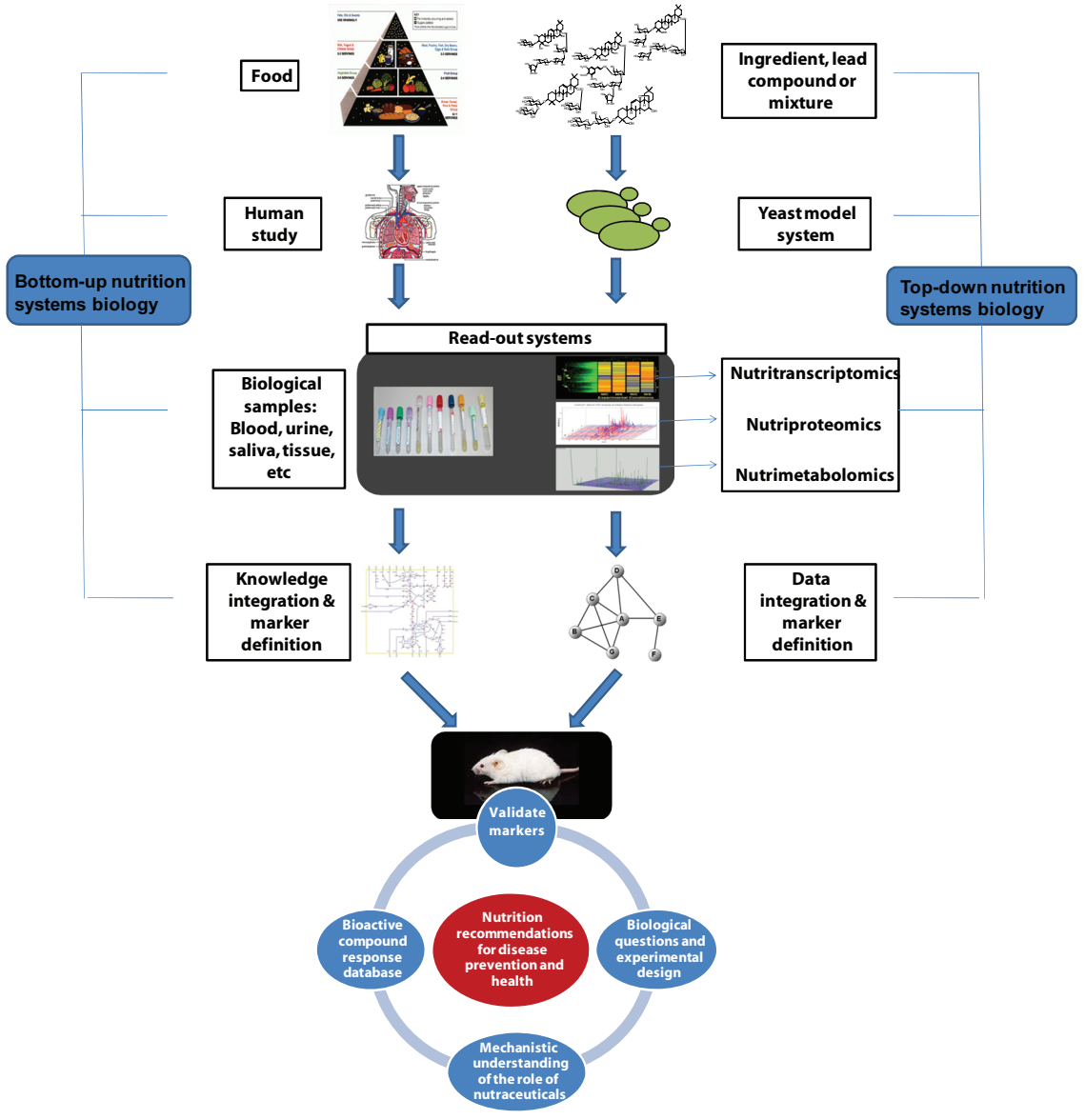


**Figure 1**

Application of bottom-up and top-down systems biology for the development of functional foods that target specific body functions through either individual ingredients or mixtures. A discovery process that derives molecular markers for the bioactivity of defined foods through a human intervention trial and the use of pathway models (bottom-up systems biology) should be followed by an animal model study to verify the markers in vivo. Similarly, the biomarker signature identification of specific nutrients using -omics technology in yeast (top-down systems biology) will eventually be tested by an intervention study in an animal model. The output of this process, which might well be iterative, includes new knowledge of the biological system as well as the potential for predictive understanding of that system; in the nutritional arena, this would lead to personalized nutrition.

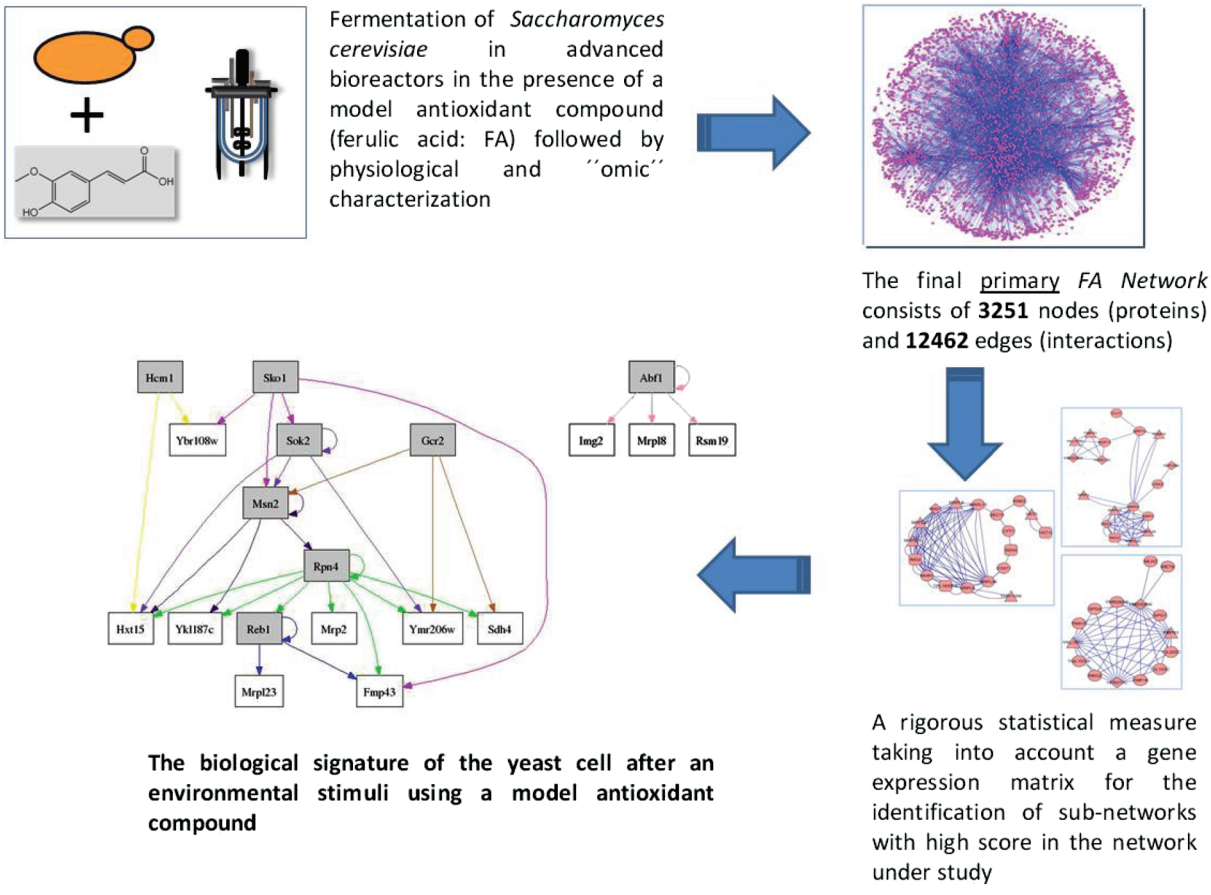


**Figure 2**

Abstracted flowchart for the elucidation of the role of a model antioxidant compound using *Saccharomyces cerevisiae* as a model system (unpublished data generated by our group). Methodology: Step one involves the physiological and transcriptome characterization of *S. cerevisiae* in the presence and absence of ferulic acid; step two, primary ferulic acid–specific network inference; step three, protein complexes (MCODE) and GO enrichment (BiNGO); step four, active modules; step five, intersection of active modules and clusters; and step six, transcription factor survey.

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**Indexes**



**Errata**

An online log of corrections to *Annual Review of Nutrition* articles may be found at http://nutr.annualreviews.org/errata.shtml