

Network Medicine: New Paradigm in the -Omics Era

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The accurate assessment of disease progression and treatment response in individual patients is a critical prerequisite for personalized therapy. High-throughput microarray technologies have the potential to allow molecular diagnostics. To date, there have been few gene expression-based tests applied in clinics for disease intervention. This fact puts a premium on developing innovative methodologies to embed biological relevance into biomarker identification. With the completion of the Human Genome Project, the emphasis of genome-wide studies has shifted from cataloging a “parts list” of signature genes and proteins, to elucidating the networks of interactions that occur among them [1,2]. Molecular network analyses have been used to improve disease classification [3-11] and identify novel therapeutic targets [12-26]. Nevertheless, major challenges include the development of methods for efficiently constructing genome-scale interaction networks [27] and the identification, from among the enormous number of genes, of a particular set of markers with the highest capacity for molecular diagnostics/prognostics [28,29].

The emerging use of biomarkers may enable physicians to make treatment decisions based on the specific characteristics of individual patients and their tumors, instead of population statistics [30]. In current genome-wide association studies, genes are ranked according to their association with the clinical outcome, and the top-ranked genes are included in the classifier. To identify the most powerful biomarkers in individualized prognostication, state-of-the-art feature selection methods [31-33] should be widely applied. Attribute selection techniques can be categorized as those that rank individual attributes (filters) or those that rank subsets of attributes. Commonly used filtering methods include Cox models, ANOVA, Bhattacharyya distance, divergence-based methods [34] gain ratio, information gain, relief [35,36] linear discriminant analysis [37] and random forests [38-40]. Algorithms that evaluate subsets of features include correlation-based feature selection, consistency-based subset evaluation, wrapper [35,36] self-organizing maps (SOM) [41] independent component analysis [42-44] partial least squares [45] principal component analysis (PCA) [46-48] kernel PCA [49,50] sliced inverse regression [51] and logistic regression [52]. Exhaustive search, branch-and-bound search, sequential search (forward or backward), floating search, “plus *l*-take away *r*” selection [53] Tabu search [54] ant colony optimization [55,56] genetic algorithms [57,58] simulated annealing [59-61] and stochastic hill climbing [62] can be used as search strategies in feature selection. Only the first two search methods guarantee the optimal subset; the rest generate suboptimal results. However, the worst-case complexity of the first two search methods is exponential, and these two methods are not feasible for a large dataset. Some feature selection algorithms such as *significant analysis of microarray* (SAM) [63] and the *multivariate permutation test* (MPT) are designed specifically for gene filtering [64]. As the number of variables is much greater than the sample size in high-throughput applications, feature pre-selection using the *t*- or *F*-test [65] and nonparametric Wilcoxon statistics [66,67] are used in processing raw microarray data.

It has been noted that individual biomarkers showing strong association with disease outcome are not necessarily good classifiers [68-70]. Because genes and proteins do not function in isolation,

but rather interact with one another to form modular machines [71] understanding the interaction networks is critical to unraveling the molecular basis of disease. Molecular network analysis has led to promising applications in identifying new disease genes [72-89] and disease-related subnetworks [90-99] mapping cause-and-effect genetic perturbations [100-106] and classifying diseases [3-11]. The various computational models that have been developed for molecular network analysis can be roughly categorized into three classes [27]: logical models to demonstrate the state of entities (genes/proteins) at any time as a discrete level [107-110]; continuous models to represent real-valued network processes [111-120] and activities [121-135] and single-molecule models [136-138] to simulate small regulatory networks and mechanisms [139-143].

In the category of logical models, Boolean networks [107] were recently used to analyze the relationship between regulation functions and network stability in a yeast transcriptional network [144] and the dynamics of cell-cycle regulation [145]. The structure of Boolean networks can be learned from gene expression profiles [146-148]. Boolean networks can provide important biological insights into regulation functions and the existence and nature of steady states (i.e., polarity gene expression) [149] and network robustness. Nevertheless, as the number of global states is exponential in the number of entities and the analysis relies on an exhaustive enumeration of all possible trajectories, this method is computationally expensive and only practical for small networks [27]. Due to insufficient experimental data or incomplete understanding of a system, several candidate regulatory functions may be possible for an entity. To express uncertainty in regulatory logic, the Probabilistic Boolean Network (PBN) was developed [150] and used to model a 15-gene subnetwork inferred from human glioma expression data [151]. The synchronous dynamics of a Boolean network can be captured by a Petri net [152], which is a non-deterministic model widely used for detecting active pathways and state cycles [153] and for analyzing large metabolic pathways [154-157] and regulatory networks [158]. Another model, module networks, infers the regulation logic of gene modules as a decision tree, given gene expression data [159]. The Boolean implication networks presented by Sahoo et al. [160,161] used scatter plots of the expression between two genes to derive the implication relations in the whole genome. To date, Boolean implication networks have not been applied in biomarker discovery.

A recent formalism, Bayesian belief networks, is recognized as one

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of the most promising methodologies for prediction under uncertainty [62,162]. Bayesian networks express complex causal relations within the model and predict events based on partial or uncertain data computed by joint probability distributions and conditionals [163-166]. Bayesian networks have been utilized to aid clinical decision-making [167-176] and to model cellular networks [177] including genome-wide gene interactions [178] protein interactions [179-181] and causal influences in cellular signaling networks [182]. In modeling signal pathway interactions, Bayesian networks not only automatically elucidated most of the traditionally reported signaling relationships but also predicted novel inter-pathway network causalities, which were verified experimentally [182]. The acyclic structure of Bayesian networks clearly represents the primary cause in the directed graph, which is appealing in predictions. Nevertheless, the number of possible networks is exponential in the number of nodes under consideration, which makes it impossible to evaluate all possible networks. Thus, heuristic searches are used to construct Bayesian networks. Furthermore, it is not always possible to determine the causal relationships between nodes, i.e., the direction of the edges, owing to a property known as Markov equivalence [183,184]. More importantly, the acyclic Bayesian network structure was unable to model feedback loops, which are essential in signal pathways [182] and genetic networks [185-187]. To overcome this limitation, a more complex scheme, dynamic Bayesian networks, was explored for modeling temporal microarray data [188-195]. As an expansion of Bayesian networks, a probabilistic version of the MetaReg model [196] represented as a factor graph [197,198] was developed [199] to facilitate changes in the network structure (refinement) and inclusion of additional entities (expansion) [200].

As an alternative to Bayesian networks, an implication network model employs a *partial order knowledge structure* (POKS) for structural learning and uses the Bayesian theory for inference propagation [201,202]. When using Dempster-Shafer theory for belief updating, this implication network methodology is termed a Dempster-Shafer belief network [203,204]. An implication network is a general methodology for reasoning under uncertainty, as are other alternative formalisms such as neural networks [205,206], dependency networks [207], Gaussian networks [208], Mycin's certainty factors [209], Prospector's inference nets [210,211], and fuzzy sets [212]. POKSs are closed under union and intersection of implication relations, and have the formal properties of directed acyclic graphs. The constraints on the partial order can be entirely represented by AND/OR graphs [201,213]. When the constraints on the partial order are relaxed, the implication networks can represent cyclic relations among the nodes. In this condition, the implication network structure is a directed graph with nodes connected by implication (causal) rules, which can contain cycles such as feedback loops.

Recently, the implication networks have been used to model concurrent coexpression with major disease signaling hallmarks for lung cancer prognostic biomarker identification [214,215]. In these studies, genome-wide coexpression networks specifically associated with different prognostic groups were constructed using implication networks. Candidate genes co-expressed with 6 or 7 major lung cancer signaling hallmarks were identified from these disease-associated genome-wide coexpression networks. These candidate genes were further selected to form prognostic gene signatures using rank-based methods including Cox model, Relief and random forests [215]. The selected biomarker sets form biologically relevant networks when evaluated with curated databases of protein-protein interactions, chromosome locations, signaling pathways, cis-regulatory motifs/transcription factor binding sites, cancer related gene sets, and gene

ontology. This network-based approach identified extensive prognostic gene signatures outperforming existing ones that were identified using traditional rank-based methods. These results demonstrate that rather than using traditional methods to merely evaluate statistical association with disease outcome, embedding biological relevance into network modeling of human genome could identify clinically important disease biomarkers.

Unraveling complex molecular interactions and networks and incorporating clinical information in the modeling will present a paradigm shift in molecular medicine. In addition to innovative methodology development, open access to publications and original microarray data is crucial to facilitate the sharing of data, analytical tools and scientific findings. Other features of the OMICS publishing group including digital book, audio version-enhanced features of the journal website, language translation, and social networking will greatly expedite the knowledge sharing and dissemination in the -omic era.

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