Published in final edited form as:
Anat Physiol. ; 1(1): .

Network Medicine: New Paradigm in the -Omics Era

Nancy Lan Guo
Mary Babb Randolph Cancer Center/Department of Community Medicine, School of Medicine, West Virginia University, Morgantown, WV 26506-9300

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

Corresponding: Nancy Lan Guo, 2816 HSS, Mary Babb Randolph Cancer Center, Morgantown, WV 26506-9300, Tel: 304-293-6455, Fax: 304-293-4667, lguo@hsc.wvu.edu.

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 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.

Reference List

1. Ideker T, Sharan R. Protein networks in disease. Genome Res. 2008 Apr; 18(4):644–652. [PubMed: 18381899]

2. Han JD. Understanding biological functions through molecular networks. Cell Res. 2008 Feb; 18(2): 224–237. [PubMed: 18227860]

3. Chuang HY, Lee E, Liu YT, Lee D, Ideker T. Network-based classification of breast cancer metastasis. Mol.Syst.Biol. 2007; 3:140. [PubMed: 17940530]

4. Efroni S, Schaefer CF, Buetow KH. Identification of key processes underlying cancer phenotypes using biologic pathway analysis. PLoS.ONE. 2007; 2(5):e425. [PubMed: 17487280]

5. Ma X, Lee H, Wang L, Sun F. CGI: a new approach for prioritizing genes by combining gene expression and protein-protein interaction data. Bioinformatics. 2007 Jan 15; 23(2):215–221. [PubMed: 17098772]

6. Tuck DP, Kluger HM, Kluger Y. Characterizing disease states from topological properties of transcriptional regulatory networks. BMC.Bioinformatics. 2006; 7:236. [PubMed: 16670008]

7. Wachi S, Yoneda K, Wu R. Interactome-transcriptome analysis reveals the high centrality of genes differentially expressed in lung cancer tissues. Bioinformatics. 2005 Dec 1; 21(23):4205–4208. [PubMed: 16188928]

8. Muller FJ, Laurent LC, Kostka D, Ulitsky I, Williams R, Lu C, Park IH, Rao MS, Shamir R, Schwartz PH, Schmidt NO, Loring JF. Regulatory networks define phenotypic classes of human stem cell lines. Nature. 2008 Sep 18; 455(7211):401–405. [PubMed: 18724358]

9. Slavov N, Dawson KA. Correlation signature of the macroscopic states of the gene regulatory network in cancer. Proc.Natl.Acad.Sci.U.S.A. 2009 Feb 25.

10. Taylor IW, Linding R, Warde-Farley D, Liu Y, Pesquita C, Faria D, Bull S, Pawson T, Morris Q, Wrana JL. Dynamic modularity in protein interaction networks predicts breast cancer outcome. Nat Biotechnol. 2009 Feb; 27(2):199–204. [PubMed: 19182785]

11. Segal E, Friedman N, Kaminski N, Regev A, Koller D. From signatures to models: understanding cancer using microarrays. Nat Genet. 2005 Jun; 37(Suppl):S38–S45. [PubMed: 15920529]

12. Albert R, Jeong H, Barabasi AL. Error and attack tolerance of complex networks. Nature. 2000 Jul 27; 406(6794):378–382. [PubMed: 10935628]

13. Barabasi AL, Oltvai ZN. Network biology: understanding the cell's functional organization. Nat.Rev.Genet. 2004 Feb; 5(2):101–113. [PubMed: 14735121]

14. Chen Y, Zhu J, Lum PY, Yang X, Pinto S, MacNeil DJ, Zhang C, Lamb J, Edwards S, Sieberts SK, Leonardson A, Castellini LW, Wang S, Champy MF, Zhang B, Emilsson V, Doss S, Ghazalpour A, Horvath S, Drake TA, Lusis AJ, Schadt EE. Variations in DNA elucidate molecular networks that cause disease. Nature. 2008 Mar 27; 452(7186):429–435. [PubMed: 18344982]

15. Csermely P, Agoston V, Pongor S. The efficiency of multi-target drugs: the network approach might help drug design. Trends Pharmacol.Sci. 2005 Apr; 26(4):178–182. [PubMed: 15808341]

16. Kitano H. A robustness-based approach to systems-oriented drug design. Nat.Rev.Drug Discov. 2007 Mar; 6(3):202–210. [PubMed: 17318209]

17. Yildirim MA, Goh KI, Cusick ME, Barabasi AL, Vidal M. Drug-target network. Nat.Biotechnol. 2007 Oct; 25(10):1119–1126. [PubMed: 17921997]

18. Parsons AB, Brost RL, Ding H, Li Z, Zhang C, Sheikh B, Brown GW, Kane PM, Hughes TR, Boone C. Integration of chemical-genetic and genetic interaction data links bioactive compounds to cellular target pathways. Nat.Biotechnol. 2004 Jan; 22(1):62–69. [PubMed: 14661025]

19. Parsons AB, Lopez A, Givoni IE, Williams DE, Gray CA, Porter J, Chua G, Sopko R, Brost RL, Ho CH, Wang J, Ketela T, Brenner C, Brill JA, Fernandez GE, Lorenz TC, Payne GS, Ishihara S, Ohya Y, Andrews B, Hughes TR, Frey BJ, Graham TR, Andersen RJ, Boone C. Exploring the mode-of-action of bioactive compounds by chemical-genetic profiling in yeast. Cell. 2006 Aug 11; 126(3):611–625. [PubMed: 16901791]

20. Aguero F, Al-Lazikani B, Aslett M, Berriman M, Buckner FS, Campbell RK, Carmona S, Carruthers IM, Chan AW, Chen F, Crowther GJ, Doyle MA, Hertz-Fowler C, Hopkins AL, McAllister G, Nwaka S, Overington JP, Pain A, Paolini GV, Pieper U, Ralph SA, Riechers A, Roos DS, Sali A, Shanmugam D, Suzuki T, Van Voorhis WC, Verlinde CL. Genomic-scale prioritization of drug targets: the TDR Targets database. Nat.Rev.Drug Discov. 2008 Nov; 7(11): 900–907. [PubMed: 18927591]

21. Hopkins AL. Network pharmacology: the next paradigm in drug discovery. Nat.Chem.Biol. 2008 Nov; 4(11):682–690. [PubMed: 18936753]
22. Altieri DC. Survivin, cancer networks and pathway-directed drug discovery. Nat Rev Cancer. 2008 Jan; 8(1):61–70. [PubMed: 18075512]
23. Yang K, Bai H, Ouyang Q, Lai L, Tang C. Finding multiple target optimal intervention in disease-related molecular network. Mol.Syst.Biol. 2008; 4:228. [PubMed: 18985027]
24. Jia J, Zhu F, Ma X, Cao ZW, Li YX, Chen YZ. Mechanisms of drug combinations: interaction and network perspectives. Nat Rev Drug Discov. 2009 Feb; 8(2):111–128. [PubMed: 19180105]
25. Gardner TS, di BD, Lorenz D, Collins JJ. Inferring genetic networks and identifying compound mode of action via expression profiling. Science. 2003 Jul 4; 301(5629):102–105. [PubMed: 12843395]
26. Araujo RP, Liotta LA, Petricoin EF. Proteins, drug targets and the mechanisms they control: the simple truth about complex networks. Nat.Rev.Drug Discov. 2007 Nov; 6(11):871–880. [PubMed: 17932492]
27. Karlebach G, Shamir R. Modelling and analysis of gene regulatory networks. Nat.Rev.Mol.Cell Biol. 2008 Oct; 9(10):770–780. [PubMed: 18797474]
28. Sotiriou C, Piccart MJ. Taking gene-expression profiling to the clinic: when will molecular signatures become relevant to patient care? Nat.Rev.Cancer. 2007 Jul; 7(7):545–553. [PubMed: 17585334]
29. Quackenbush J. Microarray analysis and tumor classification. N.Engl.J Med. 2006 Jun 8; 354(23): 2463–2472. [PubMed: 16760446]
30. Dalton WS, Friend SH. Cancer biomarkers--an invitation to the table. Science. 2006 May 26; 312(5777):1165–1168. [PubMed: 16728629]
31. Gold C, Holub A, Sollich P. Bayesian approach to feature selection and parameter tuning for support vector machine classifiers. Neural Netw. 2005 Aug 16.
32. Huang TM, Kecman V. Gene extraction for cancer diagnosis by support vector machines-An improvement. Artif.Intell.Med. 2005 Jul 15.
33. Xiong M, Li W, Zhao J, Jin L, Boerwinkle E. Feature (gene) selection in gene expression-based tumor classification. Mol.Genet.Metab. 2001 Jul; 73(3):239–247. [PubMed: 11461191]
34. Theodoridis, S.; Koutroumbas, K. Pattern Recognition. 3rd ed.. Academic Press; 2006.
35. Hall MA, Holmes G. Benchmarking Attribute Selection Techniques for Discrete Class Data Mining. IEEE Transactions on Knowledge and Data Engineering. 2003; 15(3):1437–1447.
36. Witten, IH.; Frank, E. Data Mining: Practical Machine Learning Tools and Techniques. 2nd Edition. Morgan Kaufmann; 2005.
37. Kim, SJ.; Magnani, A.; Boyd, SP. Robust Fisher Discriminant Analysis. In: Weiss, Y.; Schoch, G.; Platt, J., editors. Advances in Neural Information Processing Systems 18. Cambridge, MA: MIT Press; 2006. p. 659-666.
38. Breiman L. Random Forests. Machine Learning. 2001; 45:5–32.
39. Jiang H, Deng Y, Chen HS, Tao L, Sha Q, Chen J, Tsai CJ, Zhang S. Joint analysis of two microarray gene-expression data sets to select lung adenocarcinoma marker genes. BMC.Bioinformatics. 2004 Jun 24.5:81. [PubMed: 15217521]
40. Diaz-Uriarte R, Alvarez dA. Gene selection and classification of microarray data using random forest. BMC.Bioinformatics. 2006; 7:3. [PubMed: 16398926]
41. Tamayo P, Slonim D, Mesirov J, Zhu Q, Kitareewan S, Dmitrovsky E, Lander ES, Golub TR. Interpreting patterns of gene expression with self-organizing maps: Methods and application to hematopoietic differentiation. PNAS. 1999 Mar 16; 96(6):2907–2912. [PubMed: 10077610]
42. Klampfl, S.; Legenstein, R.; Maass, W. Information Bottleneck Optimization and Independent Component Extraction with Spiking Neurons. In: Scholkopf, B.; Platt, J.; Hoffman, PC., editors. Advances in Neural Information Processing Systems 19. Cambridge, MA: MIT Press; 2007. p. 713-720.
43. Lindgren, JT.; Hyvärinen, A. Emergence of conjunctive visual features by quadratic independent component analysis. In: Scholkopf, B.; Platt, J.; Hoffman, PC., editors. Advances in Neural Information Processing Systems 19. Cambridge, MA: MIT Press; 2007. p. 897-904.

44. Theis, F. Towards a general independent subspace analysis. In: Scholkopf, B.; Platt, J.; Hoffman, PC., editors. Advances in Neural Information Processing Systems 19. Cambridge, MA: MIT Press; 2007. p. 1361-1368.
45. Nguyen DV, Rocke DM. Tumor classification by partial least squares using microarray gene expression data. Bioinformatics. 2002 Jan; 18(1):39–50. [PubMed: 11836210]
46. Braun, M.; Buhmann, J.; Müller, K. Denoising and Dimension Reduction in Feature Space. In: Scholkopf, B.; Platt, J.; Hoffman, T., editors. Advances in Neural Information Processing Systems 19. MIT Press; 2007.
47. Moghaddam, B.; Weiss, Y.; Avidan, S. Spectral Bounds for Sparse PCA: Exact and Greedy Algorithms. In: Weiss, Y.; Schoch, G.; Platt, J., editors. Advances in Neural Information Processing Systems 18. Cambridge, MA: MIT Press; 2005. p. 915-922.
48. Opper, M. An Approximate Inference Approach for the PCA Reconstruction Error. In: Weiss, Y.; Schoch, G.; Platt, J., editors. Advances in Neural Information Processing Systems 18. Cambridge, MA: MIT Press; 2005. p. 1035-1042.
49. Schraudolph, NN.; Günter, S.; Viswanadhan, VN. Fast Iterative Kernel PCA. In: Schoch, G.; Platt, J.; Hoffman, T., editors. Advances in Neural Information Processing Systems 19. Cambridge, MA: MIT Press; 2007. In Press
50. Zwald, L.; Blanchard, G. On the convergence of eigenspaces in kernel principal components analysis. In: Weiss, Y.; Schoch, G.; Platt, J., editors. Advances in Neural Information Processing Systems 18. Cambridge, MA: MIT Press; 2005. p. 1649-1656.
51. Li K. Sliced inverse regression for dimension reduction. Journal of the American Statistical Association. 1991; 86:316–342.
52. Li W, Sun F, Grosse I. Extreme Value Distribution Based Gene Selection Criteria for Discriminant Microarray Data Analysis Using Logistic Regression. Journal of Computational Biology. 2006; 11(2–3):215–226. [PubMed: 15285889]
53. Jain AK, Duin RPW, Mao J. Statistical Pattern Recognition: A Review. IEEE Transaction on Pattern Analysis and Machine Intelligence. 2000; 22(1):4–37.
54. Good AC. Novel DOCK clique driven 3D similarity database search tools for molecule shape matching and beyond: Adding flexibility to the search for ligand kin. J Mol.Graph.Model. 2007 Apr 4.
55. Karpenko O, Shi J, Dai Y. Prediction of MHC class II binders using the ant colony search strategy. Artif.Intell.Med. 2005 Sep; 35(1–2):147–156. [PubMed: 16061368]
56. Pratt SC, Sumpter DJ. A tunable algorithm for collective decision-making. Proc.Natl.Acad.Sci.U.S.A. 2006 Oct 24; 103(43):15906–15910. [PubMed: 17038502]
57. Baluja, S. Genetic algorithms and explicit search statistics. In: Mozer, MC.; Jordan, M.; Petsche, T., editors. Advances in Neural Information Processing Systems 9. Cambridge, MA: MIT Press; 1997. p. 319-325.
58. Juels, A.; Wattenberg, M. Stochastic hillclimbing as a baseline method for evaluating generic algorithms. In: Touretzky, DS.; Mozer, MC.; Hasselmo, ME., editors. Advances in Neural Information Processing Systems 8. Cambridge, MA: MIT Press; 1996. p. 430-436.
59. Falk CT. Preliminary ordering of multiple linked loci using pairwise linkage data. Genet.Epidemiol. 1992; 9(5):367–375. [PubMed: 1427024]
60. Kirkpatrick S, Gelatt CD, Vecchi MP. Optimization by Simulated Annealing. Science. 1983; 220(4598):671–680. [PubMed: 17813860]
61. Rodrigo G, Carrera J, Jaramillo A. Genetdes: automatic design of transcriptional networks. Bioinformatics. 2007 May 7.
62. Russell, S.; Norvig, P. Artificial Intelligence: A Modern Approach. 2nd Edition. Prentice Hall; 2003.
63. Tusher VG, Tibshirani R, Chu G. Significance analysis of microarrays applied to the ionizing radiation response. Proc.Natl.Acad.Sci.U.S.A. 2001 Apr 24; 98(9):5116–5121. [PubMed: 11309499]
64. Raza M, Gondal I, Green D, Coppel RL. Feature Selection and Classification of Gene Expression Profile in Hereditary Breast Cancer. Proceedings of the Fourth International Conference on Hybrid Intelligent Systems (HIS'04). 2004

65. Dudoit S, Shafer JP, Boldrick JC. Multiple Hypothesis Testing in Microarray Experiments. Statistical Science. 2003; 18(1):71–103.
66. Dettling M, Buhlmann P. Boosting for tumor classification with gene expression data. Bioinformatics. 2003 Jun 12; 19(9):1061–1069. [PubMed: 12801866]
67. Dudoit S, Yang Y, Callow MJ, Speed TP. Statistical methods for identifying differentially expressed genes in replicated cDNA microarray experiments. Statistica Sinica. 2002; 12:111–139.
68. Baker SG, Kramer BS, Srivastava S. Markers for early detection of cancer: statistical guidelines for nested case-control studies. BMC.Med.Res.Methodol. 2002; 2:4. [PubMed: 11914137]
69. Emir B, Wieand S, Su JQ, Cha S. Analysis of repeated markers used to predict progression of cancer. Stat.Med. 1998 Nov 30; 17(22):2563–2578. [PubMed: 9839348]
70. Pepe MS, Janes H, Longton G, Leisenring W, Newcomb P. Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker. Am.J.Epidemiol. 2004 May 1; 159(9):882–890. [PubMed: 15105181]
71. Hartwell LH, Hopfield JJ, Leibler S, Murray AW. From molecular to modular cell biology. Nature. 1999 Dec 2; 402(6761 Suppl):C47–C52. [PubMed: 10591225]
72. Franke L, van BH, Fokkens L, de Jong ED, Egmont-Petersen M, Wijmenga C. Reconstruction of a functional human gene network, with an application for prioritizing positional candidate genes. Am.J Hum.Genet. 2006 Jun; 78(6):1011–1025. [PubMed: 16685651]
73. Lage K, Karlberg EO, Storling ZM, Olason PI, Pedersen AG, Rigina O, Hinsby AM, Tumer Z, Pociot F, Tommerup N, Moreau Y, Brunak S. A human phenome-interactome network of protein complexes implicated in genetic disorders. Nat.Biotechnol. 2007 Mar; 25(3):309–316. [PubMed: 17344885]
74. Oti M, Snel B, Huynen MA, Brunner HG. Predicting disease genes using protein-protein interactions. J Med.Genet. 2006 Aug; 43(8):691–698. [PubMed: 16611749]
75. Oti M, Brunner HG. The modular nature of genetic diseases. Clin Genet. 2007 Jan; 71(1):1–11. [PubMed: 17204041]
76. Jonsson PF, Bates PA. Global topological features of cancer proteins in the human interactome. Bioinformatics. 2006 Sep 15; 22(18):2291–2297. [PubMed: 16844706]
77. Mani KM, Lefebvre C, Wang K, Lim WK, Basso K, la-Favera R, Califano A. A systems biology approach to prediction of oncogenes and molecular perturbation targets in B-cell lymphomas. Mol.Syst.Biol. 2008; 4:169. [PubMed: 18277385]
78. Cui Q, Ma Y, Jaramillo M, Bari H, Awan A, Yang S, Zhang S, Liu L, Lu M, O'Connor-McCourt M, Purisima EO, Wang E. A map of human cancer signaling. Mol.Syst.Biol. 2007; 3:152. [PubMed: 18091723]
79. Feldman I, Rzhetsky A, Vitkup D. Network properties of genes harboring inherited disease mutations. Proc.Natl.Acad.Sci.U.S.A. 2008 Mar 18; 105(11):4323–4328. [PubMed: 18326631]
80. Harbison ST, Carbone MA, Ayroles JF, Stone EA, Lyman RF, Mackay TF. Co-regulated transcriptional networks contribute to natural genetic variation in Drosophila sleep. Nat Genet. 2009 Mar; 41(3):371–375. [PubMed: 19234472]
81. Ortutay C, Vihinen M. Identification of candidate disease genes by integrating Gene Ontologies and protein-interaction networks: case study of primary immunodeficiencies. Nucleic Acids Res. 2009 Feb; 37(2):622–628. [PubMed: 19073697]
82. Quigley DA, To MD, Perez-Losada J, Pelorosso FG, Mao JH, Nagase H, Ginzinger DG, Balmain A. Genetic architecture of mouse skin inflammation and tumour susceptibility. Nature. 2009 Jan 11.
83. Liu J, Ghanim M, Xue L, Brown CD, Iossifov I, Angeletti C, Hua S, Negre N, Ludwig M, Stricker T, Al-Ahmadie HA, Tretiakova M, Camp RL, Perera-Alberto M, Rimm DL, Xu T, Rzhetsky A, White KP. Analysis of Drosophila segmentation network identifies a JNK pathway factor overexpressed in kidney cancer. Science. 2009 Feb 27; 323(5918):1218–1222. [PubMed: 19164706]
84. Wu X, Jiang R, Zhang MQ, Li S. Network-based global inference of human disease genes. Mol.Syst.Biol. 2008; 4:189. [PubMed: 18463613]

85. Ramani AK, Li Z, Hart GT, Carlson MW, Boutz DR, Marcotte EM. A map of human protein interactions derived from co-expression of human mRNAs and their orthologs. Mol.Syst.Biol. 2008; 4:180. [PubMed: 18414481]
86. Zhou Q, Chipperfield H, Melton DA, Wong WH. A gene regulatory network in mouse embryonic stem cells. Proc.Natl.Acad.Sci.U.S.A. 2007 Oct 16; 104(42):16438–16443. [PubMed: 17940043]
87. Emilsson V, Thorleifsson G, Zhang B, Leonardson AS, Zink F, Zhu J, Carlson S, Helgason A, Walters GB, Gunnarsdottir S, Mouy M, Steinthorsdottir V, Eiriksdottir GH, Bjornsdottir G, Reynisdottir I, Gudbjartsson D, Helgadottir A, Jonasdottir A, Jonasdottir A, Styrkarsdottir U, Gretarsdottir S, Magnusson KP, Stefansson H, Fossdal R, Kristjansson K, Gislason HG, Stefansson T, Leifsson BG, Thorsteinsdottir U, Lamb JR, Gulcher JR, Reitman ML, Kong A, Schadt EE, Stefansson K. Genetics of gene expression and its effect on disease. Nature. 2008 Mar 27; 452(7186):423–428. [PubMed: 18344981]
88. Wei Z, Li H. A Markov random field model for network-based analysis of genomic data. Bioinformatics. 2007 Jun 15; 23(12):1537–1544. [PubMed: 17483504]
89. Tong AH, Drees B, Nardelli G, Bader GD, Brannetti B, Castagnoli L, Evangelista M, Ferracuti S, Nelson B, Paoluzi S, Quondam M, Zucconi A, Hogue CW, Fields S, Boone C, Cesareni G. A combined experimental and computational strategy to define protein interaction networks for peptide recognition modules. Science. 2002 Jan 11; 295(5553):321–324. [PubMed: 11743162]
90. Calvano SE, Xiao W, Richards DR, Felciano RM, Baker HV, Cho RJ, Chen RO, Brownstein BH, Cobb JP, Tschoeke SK, Miller-Graziano C, Moldawer LL, Mindrinos MN, Davis RW, Tompkins RG, Lowry SF. A network-based analysis of systemic inflammation in humans. Nature. 2005 Oct 13; 437(7061):1032–1037. [PubMed: 16136080]
91. Ghazalpour A, Doss S, Zhang B, Wang S, Plaisier C, Castellanos R, Brozell A, Schadt EE, Drake TA, Lusis AJ, Horvath S. Integrating genetic and network analysis to characterize genes related to mouse weight. PLoS.Genet. 2006 Aug 18.2(8):e130. [PubMed: 16934000]
92. Goehler H, Lalowski M, Stelzl U, Waelter S, Stroedicke M, Worm U, Droege A, Lindenberg KS, Knoblich M, Haenig C, Herbst M, Suopanki J, Scherzinger E, Abraham C, Bauer B, Hasenbank R, Fritzsche A, Ludewig AH, Bussow K, Coleman SH, Gutekunst CA, Landwehrmeyer BG, Lehrach H, Wanker EE. A protein interaction network links GIT1, an enhancer of huntingtin aggregation, to Huntington's disease. Mol.Cell. 2004 Sep 24; 15(6):853–865. [PubMed: 15383276]
93. Lim J, Hao T, Shaw C, Patel AJ, Szabo G, Rual JF, Fisk CJ, Li N, Smolyar A, Hill DE, Barabasi AL, Vidal M, Zoghbi HY. A protein-protein interaction network for human inherited ataxias and disorders of Purkinje cell degeneration. Cell. 2006 May 19; 125(4):801–814. [PubMed: 16713569]
94. Pujana MA, Han JD, Starita LM, Stevens KN, Tewari M, Ahn JS, Rennert G, Moreno V, Kirchhoff T, Gold B, Assmann V, Elshamy WM, Rual JF, Levine D, Rozek LS, Gelman RS, Gunsalus KC, Greenberg RA, Sobhian B, Bertin N, Venkatesan K, yivi-Guedehoussou N, Sole X, Hernandez P, Lazaro C, Nathanson KL, Weber BL, Cusick ME, Hill DE, Offit K, Livingston DM, Gruber SB, Parvin JD, Vidal M. Network modeling links breast cancer susceptibility and centrosome dysfunction. Nat.Genet. 2007 Nov; 39(11):1338–1349. [PubMed: 17922014]
95. Sanchez I, Mahlke C, Yuan J. Pivotal role of oligomerization in expanded polyglutamine neurodegenerative disorders. Nature. 2003 Jan 23; 421(6921):373–379. [PubMed: 12540902]
96. Limviphuvadh V, Tanaka S, Goto S, Ueda K, Kanehisa M. The commonality of protein interaction networks determined in neurodegenerative disorders (NDDs). Bioinformatics. 2007 Aug 15; 23(16):2129–2138. [PubMed: 17553855]
97. Li CY, Mao X, Wei L. Genes and (common) pathways underlying drug addiction. PLoS.Comput.Biol. 2008 Jan.4(1):e2. [PubMed: 18179280]
98. Guo Z, Li Y, Gong X, Yao C, Ma W, Wang D, Li Y, Zhu J, Zhang M, Yang D, Wang J. Edge-based scoring and searching method for identifying condition-responsive protein-protein interaction sub-network. Bioinformatics. 2007 Aug 15; 23(16):2121–2128. [PubMed: 17545181]
99. He L, He X, Lim LP, de SE, Xuan Z, Liang Y, Xue W, Zender L, Magnus J, Ridzon D, Jackson AL, Linsley PS, Chen C, Lowe SW, Cleary MA, Hannon GJ. A microRNA component of the p53 tumour suppressor network. Nature. 2007 Jun 28; 447(7148):1130–1134. [PubMed: 17554337]
100. Dixon AL, Liang L, Moffatt MF, Chen W, Heath S, Wong KC, Taylor J, Burnett E, Gut I, Farrall M, Lathrop GM, Abecasis GR, Cookson WO. A genome-wide association study of global gene expression. Nat.Genet. 2007 Oct; 39(10):1202–1207. [PubMed: 17873877]

101. Goring HH, Curran JE, Johnson MP, Dyer TD, Charlesworth J, Cole SA, Jowett JB, Abraham LJ, Rainwater DL, Comuzzie AG, Mahaney MC, Almasy L, MacCluer JW, Kissebah AH, Collier GR, Moses EK, Blangero J. Discovery of expression QTLs using large-scale transcriptional profiling in human lymphocytes. Nat.Genet. 2007 Oct; 39(10):1208–1216. [PubMed: 17873875]
102. Stranger BE, Nica AC, Forrest MS, Dimas A, Bird CP, Beazley C, Ingle CE, Dunning M, Flicek P, Koller D, Montgomery S, Tavare S, Deloukas P, Dermitzakis ET. Population genomics of human gene expression. Nat.Genet. 2007 Oct; 39(10):1217–1224. [PubMed: 17873874]
103. Ourfali O, Shlomi T, Ideker T, Ruppin E, Sharan R. SPINE: a framework for signaling-regulatory pathway inference from cause-effect experiments. Bioinformatics. 2007 Jul 1; 23(13):i359–i366. [PubMed: 17646318]
104. Shachar R, Ungar L, Kupiec M, Ruppin E, Sharan R. A systems-level approach to mapping the telomere length maintenance gene circuitry. Mol.Syst.Biol. 2008; 4:172. [PubMed: 18319724]
105. Yeang CH, Mak HC, McCuine S, Workman C, Jaakkola T, Ideker T. Validation and refinement of gene-regulatory pathways on a network of physical interactions. Genome Biol. 2005; 6(7):R62. [PubMed: 15998451]
106. Cookson W, Liang L, Abecasis G, Moffatt M, Lathrop M. Mapping complex disease traits with global gene expression. Nat Rev Genet. 2009 Mar; 10(3):184–194. [PubMed: 19223927]
107. Glass L, Kauffman SA. The logical analysis of continuous, non-linear biochemical control networks. J Theor.Biol. 1973 Apr; 39(1):103–129. [PubMed: 4741704]
108. Thomas R. Boolean formalization of genetic control circuits. J Theor.Biol. 1973 Dec; 42(3):563–585. [PubMed: 4588055]
109. Davidson EH, Rast JP, Oliveri P, Ransick A, Calestani C, Yuh CH, Minokawa T, Amore G, Hinman V, renas-Mena C, Otim O, Brown CT, Livi CB, Lee PY, Revilla R, Rust AG, Pan Z, Schilstra MJ, Clarke PJ, Arnone MI, Rowen L, Cameron RA, McClay DR, Hood L, Bolouri H. A genomic regulatory network for development. Science. 2002 Mar 1; 295(5560):1669–1678. [PubMed: 11872831]
110. Smith J, Theodoris C, Davidson EH. A gene regulatory network subcircuit drives a dynamic pattern of gene expression. Science. 2007 Nov 2; 318(5851):794–797. [PubMed: 17975065]
111. Hellerstein MK. In vivo measurement of fluxes through metabolic pathways: the missing link in functional genomics and pharmaceutical research. Annu.Rev Nutr. 2003; 23:379–402. [PubMed: 12704218]
112. Kingsmore SF. Multiplexed protein measurement: technologies and applications of protein and antibody arrays. Nat Rev Drug Discov. 2006 Apr; 5(4):310–321. [PubMed: 16582876]
113. Ness SA. Basic microarray analysis: strategies for successful experiments. Methods Mol.Biol. 2006; 316:13–33. [PubMed: 16671398]
114. Sauer U, Hatzimanikatis V, Hohmann HP, Manneberg M, van Loon AP, Bailey JE. Physiology and metabolic fluxes of wild-type and riboflavin-producing Bacillus subtilis. Appl.Environ.Microbiol. 1996 Oct; 62(10):3687–3696. [PubMed: 8837424]
115. Yeung MK, Tegner J, Collins JJ. Reverse engineering gene networks using singular value decomposition and robust regression. Proc.Natl.Acad.Sci.U.S.A. 2002 Apr 30; 99(9):6163–6168. [PubMed: 11983907]
116. Bansal M, Gatta GD, di BD. Inference of gene regulatory networks and compound mode of action from time course gene expression profiles. Bioinformatics. 2006 Apr 1; 22(7):815–822. [PubMed: 16418235]
117. Ernst J, Vainas O, Harbison CT, Simon I, Bar-Joseph Z. Reconstructing dynamic regulatory maps. Mol.Syst.Biol. 2007; 3:74. [PubMed: 17224918]
118. Ciliberti S, Martin OC, Wagner A. Innovation and robustness in complex regulatory gene networks. Proc.Natl.Acad.Sci.U.S.A. 2007 Aug 21; 104(34):13591–13596. [PubMed: 17690244]
119. Shi Y, Klustein M, Simon I, Mitchell T, Bar-Joseph Z. Continuous hidden process model for time series expression experiments. Bioinformatics. 2007 Jul 1; 23(13):i459–i467. [PubMed: 17646331]
120. Cao Y, Liang J. Optimal enumeration of state space of finitely buffered stochastic molecular networks and exact computation of steady state landscape probability. BMC.Syst.Biol. 2008; 2:30. [PubMed: 18373871]

121. Nachman I, Regev A, Friedman N. Inferring quantitative models of regulatory networks from expression data. Bioinformatics. 2004 Aug 4; 20(suppl_1):i248–i256. [PubMed: 15262806]
122. Li S, Brazhnik P, Sobral B, Tyson JJ. A quantitative study of the division cycle of Caulobacter crescentus stalked cells. PLoS.Comput.Biol. 2008 Jan.4(1):e9. [PubMed: 18225942]
123. Chen KC, Calzone L, Csikasz-Nagy A, Cross FR, Novak B, Tyson JJ. Integrative analysis of cell cycle control in budding yeast. Mol.Biol.Cell. 2004 Aug; 15(8):3841–3862. [PubMed: 15169868]
124. Locke JC, Southern MM, Kozma-Bognar L, Hibberd V, Brown PE, Turner MS, Millar AJ. Extension of a genetic network model by iterative experimentation and mathematical analysis. Mol.Syst.Biol. 2005; 1:2005. [PubMed: 16729048]
125. Klipp E, Nordlander B, Kruger R, Gennemark P, Hohmann S. Integrative model of the response of yeast to osmotic shock. Nat Biotechnol. 2005 Aug; 23(8):975–982. [PubMed: 16025103]
126. Covert MW, Knight EM, Reed JL, Herrgard MJ, Palsson BO. Integrating high-throughput and computational data elucidates bacterial networks. Nature. 2004 May 6; 429(6987):92–96. [PubMed: 15129285]
127. Duarte NC, Herrgard MJ, Palsson BO. Reconstruction and validation of Saccharomyces cerevisiae iND750, a fully compartmentalized genome-scale metabolic model. Genome Res. 2004 Jul; 14(7):1298–1309. [PubMed: 15197165]
128. Feist AM, Henry CS, Reed JL, Krummenacker M, Joyce AR, Karp PD, Broadbelt LJ, Hatzimanikatis V, Palsson BO. A genome-scale metabolic reconstruction for Escherichia coli K-12 MG1655 that accounts for 1260 ORFs and thermodynamic information. Mol.Syst.Biol. 2007; 3:121. [PubMed: 17593909]
129. Resendis-Antonio O, Reed JL, Encarnacion S, Collado-Vides J, Palsson BO. Metabolic reconstruction and modeling of nitrogen fixation in Rhizobium etli. PLoS.Comput.Biol. 2007 Oct; 3(10):1887–1895. [PubMed: 17922569]
130. Barrett CL, Palsson BO. Iterative reconstruction of transcriptional regulatory networks: an algorithmic approach. PLoS.Comput.Biol. 2006 May.2(5):e52. [PubMed: 16710450]
131. Gianchandani EP, Papin JA, Price ND, Joyce AR, Palsson BO. Matrix formalism to describe functional states of transcriptional regulatory systems. PLoS.Comput.Biol. 2006 Aug 11.2(8):e101. [PubMed: 16895435]
132. Herrgard MJ, Lee BS, Portnoy V, Palsson BO. Integrated analysis of regulatory and metabolic networks reveals novel regulatory mechanisms in Saccharomyces cerevisiae. Genome Res. 2006 May; 16(5):627–635. [PubMed: 16606697]
133. Shlomi T, Eisenberg Y, Sharan R, Ruppin E. A genome-scale computational study of the interplay between transcriptional regulation and metabolism. Mol.Syst.Biol. 2007; 3:101. [PubMed: 17437026]
134. Chechik G, Oh E, Rando O, Weissman J, Regev A, Koller D. Activity motifs reveal principles of timing in transcriptional control of the yeast metabolic network. Nat Biotechnol. 2008 Nov; 26(11):1251–1259. [PubMed: 18953355]
135. Dunlop MJ, Cox RS III, Levine JH, Murray RM, Elowitz MB. Regulatory activity revealed by dynamic correlations in gene expression noise. Nat Genet. 2008 Dec; 40(12):1493–1498. [PubMed: 19029898]
136. Gibson M, Bruck J. Efficient exact stochastic simulation of chemical systems with many species and many channels. J.Phys.Chem. 1999; 104:1876–1889.
137. Gillespie D. A general method for numerically simulating the stochastic time evolution of coupled chemical reactions. J.Comp.Phys. 1976; 22:403–434.
138. Gillespie D. Exact stochastic simulation of coupled chemical reactions. J.Phys.Chem. 1977; 81:2340–2361.
139. Arkin A, Ross J, McAdams HH. Stochastic kinetic analysis of developmental pathway bifurcation in phage lambda-infected Escherichia coli cells. Genetics. 1998 Aug; 149(4):1633–1648. [PubMed: 9691025]
140. Gonze D, Goldbeter A. Circadian rhythms and molecular noise. Chaos. 2006 Jun.16(2):026110. [PubMed: 16822042]

141. Niemitalo O, Neubauer A, Liebal U, Myllyharju J, Juffer AH, Neubauer P. Modelling of translation of human protein disulfide isomerase in Escherichia coli-A case study of gene optimisation. J Biotechnol. 2005 Oct 17; 120(1):11–24. [PubMed: 16111781]
142. Schultz D, Ben JE, Onuchic JN, Wolynes PG. Molecular level stochastic model for competence cycles in Bacillus subtilis. Proc.Natl.Acad.Sci.U.S.A. 2007 Nov 6; 104(45):17582–17587. [PubMed: 17962411]
143. Weinberger LS, Burnett JC, Toettcher JE, Arkin AP, Schaffer DV. Stochastic gene expression in a lentiviral positive-feedback loop: HIV-1 Tat fluctuations drive phenotypic diversity. Cell. 2005 Jul 29; 122(2):169–182. [PubMed: 16051143]
144. Kauffman S, Peterson C, Samuelsson B, Troein C. Random Boolean network models and the yeast transcriptional network. Proc.Natl.Acad.Sci.U.S.A. 2003 Dec 9; 100(25):14796–14799. [PubMed: 14657375]
145. Li F, Long T, Lu Y, Ouyang Q, Tang C. The yeast cell-cycle network is robustly designed. Proc.Natl.Acad.Sci.U.S.A. 2004 Apr 6; 101(14):4781–4786. [PubMed: 15037758]
146. Akutsu T, Miyano S, Kuhara S. Identification of genetic networks from a small number of gene expression patterns under the Boolean network model. Pac Symp.Biocomput. 1999:17–28. [PubMed: 10380182]
147. Lähdesmäki H, Shmulevich I, Yli-Harja O. On learning gene regulatory networks under the Boolean network model. Machine Learning. 2003; 52:147–167.
148. Spellman PT, Sherlock G, Zhang MQ, Iyer VR, Anders K, Eisen MB, Brown PO, Botstein D, Futcher B. Comprehensive identification of cell cycle-regulated genes of the yeast Saccharomyces cerevisiae by microarray hybridization. Mol.Biol.Cell. 1998 Dec; 9(12):3273–3297. [PubMed: 9843569]
149. Albert R, Othmer HG. The topology of the regulatory interactions predicts the expression pattern of the segment polarity genes in Drosophila melanogaster. J Theor.Biol. 2003 Jul 7; 223(1):1–18. [PubMed: 12782112]
150. Shmulevich I, Dougherty ER, Kim S, Zhang W. Probabilistic Boolean Networks: a rule-based uncertainty model for gene regulatory networks. Bioinformatics. 2002 Feb; 18(2):261–274. [PubMed: 11847074]
151. Shmulevich I, Gluhovsky I, Hashimoto RF, Dougherty ER, Zhang W. Steady-state analysis of genetic regulatory networks modelled by probabilistic boolean networks. Comp Funct.Genomics. 2003; 4(6):601–608. [PubMed: 18629023]
152. Steggles LJ, Banks R, Shaw O, Wipat A. Qualitatively modelling and analysing genetic regulatory networks: a Petri net approach. Bioinformatics. 2007 Feb 1; 23(3):336–343. [PubMed: 17121774]
153. Peterson, J. Petri Net Theory and the Modeling of Systems. New Jersey: Prentice Hall PTR; 1981.
154. Koch I, Schueler M, Heiner M. STEPP--Search Tool for Exploration of Petri net Paths: a new tool for Petri net-based path analysis in biochemical networks. In Silico.Biol. 2005; 5(2):129–137. [PubMed: 15972017]
155. Kuffner R, Zimmer R, Lengauer T. Pathway analysis in metabolic databases via differential metabolic display (DMD). Bioinformatics. 2000 Sep; 16(9):825–836. [PubMed: 11108705]
156. Reddy VN, Liebman MN, Mavrovouniotis ML. Qualitative analysis of biochemical reaction systems. Comput.Biol.Med. 1996 Jan; 26(1):9–24. [PubMed: 8654057]
157. Simao E, Remy E, Thieffry D, Chaouiya C. Qualitative modelling of regulated metabolic pathways: application to the tryptophan biosynthesis in E.Coli. Bioinformatics. 2005 Sep 1; 21(suppl_2):ii190–ii196. [PubMed: 16204102]
158. Chaouiya, C.; Remy, E.; Ruet, P.; Thieffry, D. Proceedings of the 25th International Conference on Applications and Theory of Petri Nets. Berlin: Springer; 2004.
159. Segal E, Shapira M, Regev A, Pe'er D, Botstein D, Koller D, Friedman N. Module networks: identifying regulatory modules and their condition-specific regulators from gene expression data. Nat Genet. 2003 Jun; 34(2):166–176. [PubMed: 12740579]
160. Sahoo D, Dill DL, Gentles AJ, Tibshirani R, Plevritis SK. Boolean implication networks derived from large scale, whole genome microarray datasets. Genome Biol. 2008; 9(10):R157. [PubMed: 18973690]

161. Sahoo D, Seita J, Bhattacharya D, Inlay MA, Weissman IL, Plevritis SK, Dill DL. MiDReG: a method of mining developmentally regulated genes using Boolean implications. Proc.Natl.Acad.Sci.U.S.A. 2010 Mar 30; 107(13):5732–5737. [PubMed: 20231483]

162. Fenton NE, Neil M. A Critique of Software Defect Prediction Models. IEEE Transactions on Software Engineering. 1999; 25(5):675–689.

163. Heckerman, D. Probabilistic similarity networks. Cambridge, MA: The MIT Press; 1991.

164. Henrion M. Propagating uncertainty in Bayesian networks by probabilistic logic sampling. Proceedings of Uncertainty in Artificial Intelligence 4. 1988:149–163.

165. Lauritzen S, Spiegelhalter D. Local computations with probabilities on graphical structures and their applications to expert systems. Journal of the Royal Statistical Society B. 1988; 50(157): 224.

166. Pearl, J. Probabilistic Reasoning in Intelligent Systems: Networks of Plausible Inference. San Mateo, CA: Morgan Kaufmann; 1988.

167. Antal P, Fannes G, Timmerman D, Moreau Y, De MB. Bayesian applications of belief networks and multilayer perceptrons for ovarian tumor classification with rejection. Artif.Intell.Med. 2003 Sep; 29(1–2):39–60. [PubMed: 12957780]

168. Aronsky D, Haug PJ. Diagnosing community-acquired pneumonia with a Bayesian network. Proc.AMIA.Symp. 1998:632–636. [PubMed: 9929296]

169. Haddawy P, Kahn CE Jr, Butarbutar M. A Bayesian network model for radiological diagnosis and procedure selection: work-up of suspected gallbladder disease. Med Phys. 1994 Jul; 21(7):1185–1192. [PubMed: 7968852]

170. Hamilton PW, Anderson N, Bartels PH, Thompson D. Expert system support using Bayesian belief networks in the diagnosis of fine needle aspiration biopsy specimens of the breast. J Clin Pathol. 1994 Apr; 47(4):329–336. [PubMed: 8027370]

171. Kazi JI, Furness PN, Nicholson M. Diagnosis of early acute renal allograft rejection by evaluation of multiple histological features using a Bayesian belief network. J Clin Pathol. 1998 Feb; 51(2): 108–113. [PubMed: 9602682]

172. Kronqvist P, Montironi R, Kuopio T, Collan YU. Subjective breast cancer grading. Analyses of reproducibility after application of Bayesian belief networks. Anal.Quant.Cytol.Histol. 1997 Oct; 19(5):423–429. [PubMed: 9349902]

173. Mazzucchelli R, Santinelli A, Colanzi P, Streccioni M, Lopez-Beltran A, Scarpelli M, Montironi R. Urothelial papillary lesions. Development of a Bayesian Belief Network for diagnosis and grading. Anticancer Res. 2001 Mar; 21(2A):1157–1162. [PubMed: 11396156]

174. Ramoni M, Riva A, Stefanelli M, Patel V. An ignorant belief network to forecast glucose concentration from clinical databases. Artif.Intell.Med. 1995 Dec; 7(6):541–559. [PubMed: 8963375]

175. Rodin AS, Boerwinkle E. Mining genetic epidemiology data with Bayesian networks I: Bayesian networks and example application (plasma apoE levels). Bioinformatics. 2005 Aug 1; 21(15): 3273–3278. [PubMed: 15914545]

176. Wied GL, Dytch H, Bibbo M, Bartels PH, Thompson D. Artificial intelligence-guided analysis of cytologic data. Anal.Quant.Cytol.Histol. 1990 Dec; 12(6):417–428. [PubMed: 2078264]

177. Friedman N. Inferring cellular networks using probabilistic graphical models. Science. 2004 Feb 6; 303(5659):799–805. [PubMed: 14764868]

178. Friedman N, Linial M, Nachman I, Pe'er D. Using Bayesian networks to analyze expression data. J Comput.Biol. 2000; 7(3–4):601–620. [PubMed: 11108481]

179. Jansen R, Yu H, Greenbaum D, Kluger Y, Krogan NJ, Chung S, Emili A, Snyder M, Greenblatt JF, Gerstein M. A Bayesian networks approach for predicting protein-protein interactions from genomic data. Science. 2003 Oct 17; 302(5644):449–453. [PubMed: 14564010]

180. Yeang CH, Ideker T, Jaakkola T. Physical network models. J Comput.Biol. 2004; 11(2–3):243–262. [PubMed: 15285891]

181. Yeang CH, Vingron M. A joint model of regulatory and metabolic networks. BMC.Bioinformatics. 2006; 7:332. [PubMed: 16820044]

182. Sachs K, Perez O, Pe'er D, Lauffenburger DA, Nolan GP. Causal protein-signaling networks derived from multiparameter single-cell data. Science. 2005 Apr 22; 308(5721):523–529. [PubMed: 15845847]

183. Zhu J, Wiener MC, Zhang C, Fridman A, Minch E, Lum PY, Sachs JR, Schadt EE. Increasing the power to detect causal associations by combining genotypic and expression data in segregating populations. PLoS.Comput.Biol. 2007 Apr 13.3(4):e69. [PubMed: 17432931]

184. Zhu J, Zhang B, Smith EN, Drees B, Brem RB, Kruglyak L, Bumgarner RE, Schadt EE. Integrating large-scale functional genomic data to dissect the complexity of yeast regulatory networks. Nat Genet. 2008 Jul; 40(7):854–861. [PubMed: 18552845]

185. Milo R, Shen-Orr S, Itzkovitz S, Kashtan N, Chklovskii D, Alon U. Network motifs: simple building blocks of complex networks. Science. 2002 Oct 25; 298(5594):824–827. [PubMed: 12399590]

186. Milo R, Itzkovitz S, Kashtan N, Levitt R, Shen-Orr S, Ayzenshtat I, Sheffer M, Alon U. Superfamilies of evolved and designed networks. Science. 2004 Mar 5; 303(5663):1538–1542. [PubMed: 15001784]

187. Wuchty S, Oltvai ZN, Barabasi AL. Evolutionary conservation of motif constituents in the yeast protein interaction network. Nat Genet. 2003 Oct; 35(2):176–179. [PubMed: 12973352]

188. Dojer N, Gambin A, Mizera A, Wilczynski B, Tiuryn J. Applying dynamic Bayesian networks to perturbed gene expression data. BMC.Bioinformatics. 2006; 7:249. [PubMed: 16681847]

189. Kim SY, Imoto S, Miyano S. Inferring gene networks from time series microarray data using dynamic Bayesian networks. Brief.Bioinform. 2003 Sep; 4(3):228–235. [PubMed: 14582517]

190. Perrin BE, Ralaivola L, Mazurie A, Bottani S, Mallet J, D'Alche-Buc F. Gene networks inference using dynamic Bayesian networks. Bioinformatics. 2003; 19(Suppl 2):II138–II148. [PubMed: 14534183]

191. Husmeier D. Sensitivity and specificity of inferring genetic regulatory interactions from microarray experiments with dynamic Bayesian networks. Bioinformatics. 2003 Nov 22; 19(17): 2271–2282. [PubMed: 14630656]

192. Imoto S, Kim S, Goto T, Miyano S, Aburatani S, Tashiro K, Kuhara S. Bayesian network and nonparametric heteroscedastic regression for nonlinear modeling of genetic network. J.Bioinform.Comput.Biol. 2003 Jul; 1(2):231–252. [PubMed: 15290771]

193. Ong IM, Glasner JD, Page D. Modelling regulatory pathways in E. coli from time series expression profiles. Bioinformatics. 2002; 18(Suppl 1):S241–S248. [PubMed: 12169553]

194. Pe'er D, Regev A, Elidan G, Friedman N. Inferring subnetworks from perturbed expression profiles. Bioinformatics. 2001; 17(Suppl 1):S215–S224. [PubMed: 11473012]

195. Zou M, Conzen SD. A new dynamic Bayesian network (DBN) approach for identifying gene regulatory networks from time course microarray data. Bioinformatics. 2005 Jan 1; 21(1):71–79. [PubMed: 15308537]

196. Gat-Viks I, Tanay A, Shamir R. Modeling and analysis of heterogeneous regulation in biological networks. J Comput.Biol. 2004; 11(6):1034–1049. [PubMed: 15662196]

197. Kschischang FR, Frey BJ, Loeliger HA. Factor graphs and the sum-product algorithm. IEEE Trans.Info.Theory. 2001; 47:498–519.

198. MacKay, DJC. Introduction To Monte Carlo Methods In Learning In Graphical Models. New York: Kluwer Academic Press; 1998.

199. Gat-Viks I, Tanay A, Raijman D, Shamir R. A probabilistic methodology for integrating knowledge and experiments on biological networks. J Comput.Biol. 2006 Mar; 13(2):165–181. [PubMed: 16597233]

200. Gat-Viks I, Shamir R. Refinement and expansion of signaling pathways: the osmotic response network in yeast. Genome Res. 2007 Mar; 17(3):358–367. [PubMed: 17267811]

201. Desmarais MC, Maluf A, Liu J. User-expertise modeling with empirically derived probabilistic implication networks. User Modeling and User-Adapted Interaction. 1996; 5(3–4):283–315.

202. Desmarais MC, Meshkinfam P, Gagnon M. Learned Student Models with Item to Item Knowledge Structures. User Modeling and User-Adapted Interaction. 2006; 16(5):403–434.

203. Liu J, Desmarais MC. A Method of Learning Implication Networks from Empirical Data: Algorithm and Monte-Carlo Simulation-Based Validation. IEEE Transactions on Knowledge and Data Engineering. 1997; 9(6):990–1004.

204. Liu J, Maluf D, Desmarais MC. A New Uncertainty Measure for Belief Networks with Applications to Optimal Evidential Inferencing. IEEE Transactions on Knowledge and Data Engineering. 2001; 13(3):416–425.

205. Honavar, V.; Uhr, L. Artificial Intelligence and Neural Networks: Steps Toward Principled Integration. New York, NY: Academic Press; 1994.

206. O'Neill MC, Song L. Neural network analysis of lymphoma microarray data: prognosis and diagnosis near-perfect. BMC.Bioinformatics. 2003 Apr 10.4:13. [PubMed: 12697066]

207. Heckerman D, Chickering DM, Meek C, Rounthwaite R, Kadie C. Dependency Networks for Inference, Collaborative Filtering, and Data Visualization. Journal of Machine Learning Research. 2001; 1:49–175.

208. Kundu S, Sorensen DC, Phillips GN Jr. Automatic domain decomposition of proteins by a Gaussian Network Model. Proteins. 2004 Dec 1; 57(4):725–733. [PubMed: 15478120]

209. Cruz GP, Beliakov G. On the interpretation of certainty factors in expert systems. Artif.Intell.Med. 1996 Feb; 8(1):1–14. [PubMed: 8963377]

210. Campbell AN, Hollister VF, Duda RO, Hart PE. Recognition of a Hidden Mineral Deposit by an Artificial Intelligence Program. Science. 1982 Sep 3; 217(4563):927–929. [PubMed: 17747953]

211. Finlay AY, Sinclair J, Alty JL. Expert system diagnosis of ichthyosis. Clin Exp.Dermatol. 1987 May; 12(3):239–240. [PubMed: 3319297]

212. Desmarais MC, Maluf A, Liu J. User-expertise modeling with empirically derived probabilistic implication networks. User Modeling and User-Adapted Interaction. 1996; 5(3–4):283–315.

213. Falmagne JC, Doignon JP, Koppen M, Villano M, Johannesen L. Introduction to knowledge spaces: how to build, test and search them. Psychological Review. 1990; 97(2):201–224.

214. Guo NL, Wan YW, Bose S, Denvir J, Kashon ML, Andrew ME. A novel network model identified a 13-gene lung cancer prognostic signature. Int.J.Comput.Biol.Drug Des. 2011; 4(1): 19–39. [PubMed: 21330692]

215. Wan YW, Beer DG, Guo NL. Signaling pathway-based identification of extensive prognostic gene signatures for lung adenocarcinoma. Lung Cancer. 2011 Oct 31.