Journal of
Computer Science & Systems Biology

Nanda et al. J Comput Sci Syst Biol 2011, S13
DOI: 10.4172/jcsb.S13-003

Review Article Open Access

Metabolomics: The Future of Systems Biology

Tushar Nanda[1]*, Mausumi Das[1], Kadambini Tripathy[1] and Ravi Teja Y[2]

[1]Department of Bioscience and Biotechnology, Fakir Mohan University, Odisha-756020, India
[2]Department of Biochemistry, Andhra University, Andhra Pradesh- 530003, India

Abstract

The collection of global metabolic data and their interpretation (both spectral and biochemical) using modern spectroscopic techniques and appropriate statistical approaches, are known as `metabolomics'. This review covers research on metabolomics, ranging from the development of specialized chemical analytical techniques to the construction of databases and methods for metabolic simulation. Furthermore we have also outlined the recent developments in elucidating the system-level functions of the bioconstituents of living organisms. Metabolomics has the potential to serve an important role in diagnosis and management of human conditions. As such the purpose of this systematic review is to summarize existing literature on metabolomics and its various techniques in terms of diagnostic accuracies and distinguishing metabolites. This article has also highlighted the novelty of the field of metabolomics with various detection methods. Here metabolomic methodologies are discussed briefly followed by a more detailed review of the use of metabolomics in integrated applications where metabolomics information has been combined with other "omic" data sets (proteomics, transcriptomics) to enable greater understanding of a biological system.

Keywords: Metabolomics; Transcriptomics; Pharmacology; Genotype

Introduction

Metabolomicsis the "systematic study of the unique chemical fingerprints that specific cellular processes leave behind" - specifically, the study of their small-molecule metabolite profiles [1]. Metabolomics is the study of the small molecule, chemical fingerprint that specific cellular processes produce in metabolism, the chemical processes in a cell or organism that are necessary for life [2]. The metabolome represents the collection of all metabolites in a biological organism, which are the end products of its gene expression. Thus, while mRNA gene expression data and proteomic analyses do not tell the whole story of what might be happening in a cell, metabolic profiling can give an instantaneous snapshot of the physiology of that cell. One of the challenges of systems biology and functional genomics is to integrate proteomic, transcriptomic and metabolomic information to give a more complete picture of living organisms [3].

Metabolites are the small chemical components in every cell. Major traits such as food quality, taste, nutritional value, toxicity, allergenicity etc. are all directly correlated with the presence or absence of specific combinations of metabolites. Importantly, it is often this combination of metabolites, rather than the presence of individual compounds, which is of greatest biological relevance. In particular, complex traits such as flavor and nutritional value also inevitably have a complex biochemical background. Metabolomics technologies have therefore been developed to give us the broadest possible overview of the biochemical composition of biological materials without having to have prior metabolic knowledge [3].

Metabolomics is a newborn cousin to genomics and proteomics. It is a close counterpart to the genome, the transcriptome and the proteome. Together these four "omes" constitute the building blocks of systems biology [4]. Specifically, metabolomics involves the rapid, high throughput characterization of the small molecule metabolites found in an organism. Since the metabolome is closely tied to the genotype of an organism, its physiology and its environment (what the organism eats or breathes), metabolomics offers a unique opportunity to look at genotype-phenotype as well as genotype-envirotype relationships. Metabolomics is increasingly being used in a variety of health applications including pharmacology, pre-clinical drug trials, toxicology, transplant monitoring, newborn screening and clinical chemistry. However, a key limitation to metabolomics is the fact that the human metabolome is not at all well characterized. There are approximately 2900 endogenous or common metabolites that are detectable in the human body. Previous studies of properties of metabolic works have mainly focused on the statistic properties of networks, including the small world, and power-law distribution of node degree, and building block of network motifs [5]. The primary platforms in use for metabolomics are mass spectrometry and microarrays which associate tools to process data flows [6]. There is potential for the metabolome to have a multitude of uses in oncology, including the early detection and diagnosis of cancer and as both a predictive and pharmacodynamic marker of drug effect [7].

Overview of systems biology

A system-level understanding of a biological system can be derived from insight into four key properties [8] (Figure 1):

1) System structures: These include the network of gene interactions and biochemical pathways, as well as the mechanisms by which such interactions modulate the physical properties of intracellular and multicellular structures.

2) System dynamics: How a system behaves over time under various conditions can be understood through metabolic analysis, sensitivity analysis, dynamic analysis methods such as phase "portrait" and "bifurcation" analysis, and by identifying essential mechanisms underlying specific behaviors. Bifurcation analysis traces time-varying

***Corresponding author:** Tushar Nanda, Department of Bioscience and Biotechnology, FM University, Odisha, E-mail: ertusharnanda@gmail.com

Received April 15, 2011; **Accepted** May 20, 2011; **Published** May 23, 2011

Citation: Nanda T, Das M, Tripathy K, Ravi Teja Y (2011) Metabolomics: The Future of Systems Biology. J Comput Sci Syst Biol S13. doi:10.4172/jcsb.S13-003

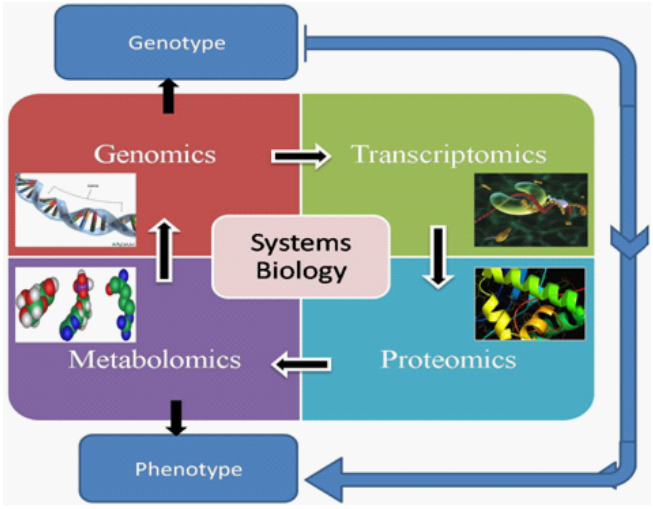

Figure 1: Overview of systems biology.

change(s) in the state of the system in a multidimensional space where each dimension represents a particular concentration of the biochemical factor involved.

3) The control method: Mechanisms that systematically control the state of the cell can be modulated to minimize malfunctions and provide potential therapeutic targets for treatment of disease.

4) The design method: Strategies to modify and construct biological systems having desired properties can be devised based on definite design principles and simulations instead of blind trial-and-error.

The genomic projects have provided a far wide amount of information which still needs to be implemented and further can be useful for the onset of metabolomics [9].

Techniques

There are two types of techniques discovered till now:

» **Separation methods**

- **Gas chromatography:** Especially when interfaced with mass spectrometry (GC-MS), is one of the most widely used and powerful methods. It offers very high chromatographic resolution, but requires chemical derivatization for many biomolecules: only volatile chemicals can be analyzed without derivatization [10].
- **High performance liquid chromatography:** Compared to GC, HPLC has lower chromatographic resolution, but it does have the advantage that a much wider range of analytes can potentially be measured [10].
- **Capillary Electrophoresis:** CE has a higher theoretical separation efficiency than HPLC, and is suitable for use with a wider range of metabolite classes [10] and has its niche to provide information mainly on polar or ionic compounds in biological fluids and CE-MS has demonstrated to be a powerful technique for the profiling of polar metabolites in biological samples [11,12].

» **Detection methods**

- **Mass Spectrometry:** Mass spectrometry (MS) is used to identify and to quantify metabolites after separation by GC, HPLC (LC-MS), or CE. GC-MS is the most 'natural' combination of the three, and was the first to be developed. In addition, mass spectral fingerprint libraries exist or can be developed that allow identification of a metabolite according to its fragmentation pattern [10,13].
- **Surface-based mass analysis:** Surface-based mass analysis has seen a resurgence in the past decade, with new MS technologies focused on increasing sensitivity, minimizing background, and reducing sample preparation [10].
- **Desorption Electrospray Ionization:** Desorption electrospray ionization (DESI) is a matrix-free technique for analyzing biological samples that uses a charged solvent spray to desorb ions from a surface. Advantages of DESI are that no special surface is required and the analysis is performed at ambient pressure with full access to the sample during acquisition. A limitation of DESI is spatial resolution because "focusing" the charged solvent spray is difficult [10].
- **MALDI:** MALDI is also used however, the application of a MALDI matrix can add significant background at <1000 Da that complicates analysis of the low-mass range (i.e., metabolites). In addition, the size of the resulting matrix crystals limits the spatial resolution that can be achieved in tissue imaging [9,10].
- **Secondary ion mass spectrometry:** SIMS was one of the first matrix-free desorption/ionization approaches used to analyze metabolites from biological samples. SIMS uses a high-energy primary ion beam to desorb and generate secondary ions from a surface. The primary advantage of SIMS is its high spatial resolution (as small as 50 nm), a powerful characteristic for tissue imaging with MS [10].
- **Ion-mobility spectrometry:** other methods of detection that have been used include ion-mobility spectrometry, electrochemical detection (coupled to HPLC) and radiolabel (when combined with thin-layer chromatography) [10].

Apart from these techniques there are a various number of techniques for further metabolomics studies: Microarray analysis enables one to determine the relative level of expression of practically all genes in a genome, allowing the prediction of cellular plans for protein synthesis to be established [14]. The relative rates of development of the high throughput computational methods for the detection of SNPs (Single Nucleotide Polymorphism) and small indels (insertion / deletion) has gained wide applications in the field of the molecular markers [15]. Advanced microscopy and corresponding image analysis have evolved in recent years as a compelling tool for studying molecular and morphological events in cells and tissues. Data mining approaches used in HCS are image descriptors,computations, normalization, quality control methods and classification algorithms [16]. High-throughput DNA sequencing has enabled systems biology to begin to address areas in health, agricultural and basic biological research. Concomitant with the opportunities is an absolute necessity to manage significant volumes of high-dimensional and inter-related data and analysis. *Alpheus* is an analysis pipeline, database and visualization software for use with massively parallel DNA sequencing technologies that feature multigigabase throughput characterized by relatively short reads, such as Illumina-Solexa (sequencing-by-synthesis), Roche-454 (pyrosequencing) and Applied Biosystem's SOLiD (sequencing-by-ligation) [17]. The analytical methods of

choice for the analysis of metabolites in search of disease biomarkers in biological specimens. Global metabolite analysis and profiling of two different sets of data results in a plethora of data that is difficult to manage or interpret manually because of their subtle differences [18]. Metabolomics attempts to systematically identify and quantitate metabolites from biological samples. The small molecules represent the end result of complexity of biological processes in a given cell, tissue, or organ, and thus form attractive candidates to understand disease phenotypes [19]. Understanding the role of human genetic differences in xenobiotic metabolism and its relationship to interindividual susceptibility to chemical toxicities and carcinogenesis is an area of intense interest [20]. During the previous decade, a new array of analytical methodologies and technologies were introduced related to the analysis of microbial, plant and animal metabolomes [21]. One of the research has been focused on metabolites that these are essential for the growth and survival of the relevant bacteria. To identify potential drug targets, they have to be further screened these metabolites to eliminate any found in the human host [22]. Short interfering RNAs (siRNAs) can be used to suppress gene expression and have a lot of potential applications in therapy, yet how to design an effective siRNA is still under consideration [23]. The availability of the complete sequence information of *Neisseria meningitides*serogroup B proteome has made it possible to carry out the *in silico* analysis of its genome for identification of potential vaccine and drug targets [24]. Virtual screening by molecular docking has become a largely used approach to lead discovery in the pharmaceutical industry when a high-resolution structure of the biological target of interest is available [25]. Applications covering phytochemistry, toxicology and clinical research in the field of metabonomics are presented with the latest developments with the techniques like capillary electrophoresis, and capillary electro chromatography normally hyphenated with MS [26]. DNA Micro arrays, In Vivo Expression Technology (IVET), Signature-Tagged Mutagenesis (STM), Differential Fluorescence Induction (DFI), etc., are some of the metabolomics applications [27]. Pathway Tools software were used to corroborate finding ten metabolites as potential candidates for developing novel antibiotics [22]. Molecular docking has been used for lead discovery in pharmaceutical industries for virtual screening [28] which will be helpful for further metabolomics studies in future.

Recent developments

This new analytical science has progressed within the last years particularly with regard to improvements in mass spectrometry based detection, now allowing highly robust, reproducible, selective and sensitive qualitative or quantitative analysis of endogenous metabolites [29]. The applicability of CE-MS in metabolomicsresearch is illustrated by examples of the analysis of biomedical and clinical samples, and for bacterial and plant extracts. . Future considerations such as challenges for large-scale and (quantitative) clinical metabolomics studies and the use of sheath less interfacing and different ionization techniques are to be discussed [30]. Report of the development of the most complete reconstruction of yeast metabolism to date that is based upon reliable literature evidence and richly annotated according to MIRIAM standards [31]. The combined approach of systems biology and large scale network models was applied to investigate the hypertensive side effect of the cholesteryl ester transfer protein inhibitor torcetrapib in the context of human renal function [32]. A new algorithm Pathway Activity Profiling (PAPi) with which we are able to compare metabolic pathway activities from metabolite profiles. The applicability and potential of PAPi was demonstrated using a previously published data from the yeast *Saccharomyces cerevisiae*. PAPi was able to support the biological interpretations of the previously published observations and in addition, generated new hypotheses in a straightforward manner [33]. The high sensitivity and resolution of mass spectrometry achieved with liquid or gas chromatography allows for detection and quantification of hundreds to thousands of molecules in a single measurement. Where homogenization-based sample preparation and extraction methods result in a loss of spatial information, mass spectrometry imaging technologies provide the in situ distribution profiles of metabolites and proteins within tissues [13]. The field of drug metabolism has changed dramatically, the advances in liquid chromatography-mass spectrometry (LC-MS) are extremely impressive, and the speed of analysis has been increased even more with the recent developments in ultra performance LC (UPLC) [34]. Micrometabolomics, dealing with sample preparation methods, with focus on laser-assisted microdissection, and the analytical technologies used. Mass spectrometry (MS) and nuclear magnetic resonance (NMR) are among the most emergent technologies in metabolomics [35]. The developments regarding environmental metabolomics have taken place to a larger extent compared to previous year [36]. Evolution of metabolomics from its predecessor, "Hmetabolite profiling" has been provided with some pointers to future methodological and technological direction. Also efforts in the field of "targeted metabolomics", namely, "steroidomics in the brain" have been highlighted [37]. A comparative modelling of the protein Hypoxanthin-guanine phosphoribosyltransferase is performed using the modeling program modeller9v3. The following structure validation programs PROCHECK, PROSA, VERIFY3D and WHATIF are used [38]. Data Mining, a tool for Systems Biology or a Systems Biology Tool [39]. A better understanding of the metabolic pathways may aid in the drug development and toxicity evaluation process [40]. Metabolites in safety testing (MIST) criterion is an approach to evaluate the Human Metabolites in a Drug that is Extensively Metabolized [41]. Specific neural (EEG) frequencies can be associated with visual perception. This can be adapted therapeutically i.e. to photostimulate inhibited protein-substrate reactions thereby regulating the function of each physiological system [42-44]. Various concepts are being introduced in industries for quick recovery [45]. Nowbreast cancer type is being decided with the help of computer added softwares [46] which will also be helpful for further studies of metabolomics. Damage analysis is of higher priority these days which utilizes various statistical methods e.g. graph analysis to study the damages in various metabolic pathways [47].

Applications

» **Disease diagnosis and treatment**

- Metabolomics is now used in evaluation of glucose disorders e.g. type-1 and type-2 diabetes both in human and animal models. Diabetic complications such as diabetic nephropathy diagnosis are demonstrated using the metabolomic approach [48-50].
- Metabolomics and systems biology is a pathway tool for investing cardiovascular diseases. The KEGG pathway database along with the application of Transcriptomics and lipidomics is playing the key role in controlling the cholesterol in the diet [51,52]. Micro RNA analysis is also playing the role in diagnosing the point of chronic heart failure [53].
- Diagnosis of head and neck cancer by Powerful OMICS

technologies [54]. New ideas are needed to explain the genetic equidistance result that must grant different mutation rates to different species and must be independently testable [50,55].

- Metabolomics in application for obstetrics and gynecology included a discussion of methodology, challenges, potential applications and current research [56].
- miRNAs are found to be the biomarkers for the induced liver injury [57].
- Metabolomics research highlights the identification of reliable biomarkers with emphasis on neuroAIDS [58]. Such identification of candidate markers will be advantageous for tracking the progression of human immunodeficiency virus/central nervous system (HIV/CNS) disease to gain maximal benefit from antiretroviral treatment and to provide insight into the mechanism of related neuropathogenesis.
- Metabolomics applications has been used to understand inflammatory bowel diseases (IBD) such as Crohn'sdisease (CD) and ulcerative colitis (UC) [59].
- Also urine metabolomics has great diagnostic potential for cystic renal disorders [60].

Drug discovery and biomarker discovery

Advances in the field of metabolomics applied to cancer research enabled the documenting of the generality of the Warburg effect in a broad variety of tumors [61,62]. Metabolite concentrations represent sensitive markers of both genomic and phenotypic changes [63]. Metabolomics has been an onset tool for the diagnosis of heart disease and diabetes research [64]. Mass spectrometry-based quantitative analysis and biomarker discovery using metabolomics approach represent one of the major platforms in clinical fields including for the prognosis or diagnosis, assessment of severity and response to therapy in a number of clinical disease states as well as therapeutic drug monitoring. Established strategy for the metabolomics investigation applies to samples from cells, animals and humans to separate groups based on altered patterns of metabolites in biological fluids and to identify metabolites as potential biomarkers discriminating groups [65]. Loss of metabolic homeostasis is common in critical illness, the metabolome could have many applications, including biomarker and drug target identification. Metabolomics could also significantly advance our understanding of the complex pathophysiology of acute illnesses like sepsis and acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) [66]. Metabolomics has shown a great advancement specifically in this sector.

Hypoxanthin-guanine phosphoribosyltransferase (HPRT) is responsible for catalyzing a reaction which breaks down uric acid in the body. The lack of this enzyme creates a build-up of uric-acid, leading to a neurological problem, joint pain and kidney problem [67]. The clinical study demonstrated that acute intake of 24 mg CHP plus 160 mg zinc did not show any clinical side effects or copper deficiency in healthy subjects [68]. In this view, the functions prediction of genomic sequences for hypothetical proteins will invigorate our knowledge with reference to the identification of new drugs for tuberculosis [69].

Future direction in metabolomics

- The Future of Metabolomics provides detailed insight into the effective use of metabolomics throughout drug discovery, preclinical development and clinical trials.
- Metabolomics can be applied in lifecycle management by identifying new indications for a marketed product, or by developing a test that will optimize dosing and help patients to receive a dose that is both efficacious and safe.
- Metabolomics can be used to uncover new drug targets, prioritize lead compounds, and assess toxicity non-invasively, enabling the development of novel, smarter and safer drugs.
- Within the next 10 years it is anticipated that metabolomics will become a standard tool in the pharma industry as validated metabolomic-based biomarkers begin to emerge and cost-effective screens are established.

Conclusion

Metabolomics has its roots in early metabolite profiling studies but is now a rapidly expanding area of scientific research in its own right. Metabolomics (or metabonomics) has been labeled one of the new "omics", joining genomics, transcriptomics, and proteomics as a science employed toward the understanding of global systems biology [70]. Metabolomics has its roots in early metabolite profiling studies but is now a rapidly expanding area of scientific research in its own right.

References

1. Metabolomics: PhD student of South Korea.
2. Solomon DJS, Fischer SM. Metabolomics at Agilent: Driving Value with Comprehensive Solutions.
3. Tyagi S, Raghvendra, Singh U, Kalra T, Munjal K (2010) Applications of Metabolomics - a systematic study of the unique Chemical fingerprints: an overview. 3: 083-086.
4. Wishart DS (2007) Computational approaches to metabolomics: an introduction, Pacific Symposium on Biocomputing. 12: 112-114.
5. Hua D, Yanghua X, Wei W, Li J, Momiao X (2008) Symmetry of Metabolic Network. J Comput Sci Syst Biol 1: 001- 020.
6. (2006) The Future of Metabolomics: Building Competitive Advantage in Drug Discovery, Clinical Development and Diagnostics. Business Insights 156.
7. Spratlin JL, Serkova NJ, Eckhardt SG (2009) Clinical applications of metabolomics in oncology. A Review. Clin Cancer Res 15: 431.
8. Hiroaki Kitano (2002) Systems Biology: A Brief Overview. 295: 1662-1664.
9. Valdes-Gonzalez T, Goto-Inoue N, Hayasaka T, Ishiyama H, Setou M, et al. (2011) Imaging Technology of Complex Lipid Molecular Species by a Combination of TLC-Blot and MALDI- TOF –Special Reference to Human Brain Ganglioside Molecular Species. J Glycom Lipidom 1:104.
10. http://en.wikipedia.org/wiki/Metabolomics.
11. Barbas C, Moraes EP, Villaseñor A (2011) Capillary electrophoresis as a metabolomics tool for non-targeted fingerprinting of biological samples. J Pharm Biomed Anal 55: 823-831.
12. Ramautar R, Somsen GW, de Jong GJ (2009) CE-MS in metabolomics. Electrophoresis 30: 276-291
13. Lee do Y, Bowen BP, Northen TR (2010) Mass spectrometry-based metabolomics, analysis of metabolite-protein interactions and imaging. Biotechniques 49: 557-565.
14. Allam AR, Shyambabu M, Srinubabu G (2008) Microarray Analysis of Differentially Expressed Genes Between Diabetes vs Healthy. J Proteomics Bioinform S1: S055-S084.
15. Sablok G, Shekhawat NS (2008) Bioinformatics Analysis of Distribution of Microsatellite Markers (SSRs) / Single Nucleotide Polymorphism (SNPs) in Expressed Transcripts of *Prosopis juliflora:* Frequency and Distribution. J Comput Sci Syst Biol 1: 087-091.

16. Kozak K, Agrawal A, Machuy N, Csucs G (2009) Data Mining Techniques in High Content Screening: A Survey. J Comput Sci Syst Biol 2: 219-239.

17. Miller NA, Kingsmore SF, Farmer AD, Langley RJ, Mudge J, et al. (2008) Management of High-Throughput DNA Sequencing Projects: *Alpheus*. J Comput Sci Syst Biol 1: 132-148.

18. Issaq HJ, Van QN, Waybright TJ, Muschik GM, Veenstra TJ (2009) Analytical and statistical approaches to metabolomics research. J Sep Sci 32: 2183–2199.

19. Wang JH, Byun J, Subramaniam Pennathur MD (2010) Analytical Approaches to Metabolomics and Applications to Systems Biology. Sem Neph 30: 500-511.

20. Wogan GN, Hecht SS, Felton JS, Conney AH, Loeb LA. Semin Cancer Biol 14**:** 473–486.

21. Dunn WB, Ellis DI (2005) Metabolomics: Current analytical platforms and methodologies. TrAC 24: 285-294.

22. Sarker M, Chopra S, Mortelmans K, Kodukula K, Talcott C, et al. (2011) In Silico Pathway Analysis Predicts Metabolites that are Potential Antimicrobial Targets. J Comput Sci Syst Biol 4: 021-026.

23. Gupta SK, Akhoon BA, Srivastava M, Gupta SK (2010) A Novel Algorithm to Design an Efficient siRNA by Combining the Pre Proposed Rules of siRNA Designing. J Comput Sci Syst Biol 3: 005-009.

24. Sarangi AN, Aggarwal R, Rahman Q, Trivedi N (2009) Subtractive Genomics Approach for *in Silico* Identification and Characterization of Novel Drug Targets in *Neisseria Meningitidis Serogroup B*. J Comput Sci Syst Biol 2: 255-258.

25. Jothi R, Parthasarathy S, Ganesan K (2008) Comparison of the Virulence Factors and Analysis of Hypothetical Sequences of the Strains TIGR4, D39, G54 and R6 of *Streptococcus Pneumoniae*. J Comput Sci Syst Biol 1: 103-118.

26. Xiayan L, Legido-Quigley C (2008) Advances in separation science applied to metabonomics. Electrophoresis 29: 3724-3736.

27. Sergio H, Antonio G, Juan C, Enrique Q (2009) OMICS Techniques and Identification of Pathogen Virulence Genes Application to the Analysis of Respiratory Pathogens. J Comput Sci Syst Biol 2: 124-132.

28. Abdelouahab C, Abderrahmane B (2008) Docking Efficiency Comparison of Surflex, a Commercial Package and Arguslab, a Licensable Freewar. J Comput Sci Syst Biol 1: 081-086.

29. Ramautar R, Mayboroda OA, Somsen GW, de Jong GJ (2011) CE-MS for metabolomics: Developments and applications in the period 2008-2010. Electrophoresis 32: 52-65.

30. Koal T, March DHP (2010) Challenges in Mass Spectrometry Based Targeted Metabolomics. Curr Mol Med 10: 216-226.

31. Dobson PD, Smallbone K, Jameson D, Simeonidis E, Lanthaler K, et al. (2010) Further developments towards a genome-scale metabolic model of yeast. BMC Syst Biol 28: 145.

32. Chang RL, Xie L, Xie L, Bourne PE, Palsson BØ (2010) Drug off-target effects predicted using structural analysis in the context of a metabolic network model. PLoS Comput Bio l6: e1000938.

33. Aggio RB, Ruggiero K, Villas-Bôas SG (2010) Pathway Activity Profiling (PAPi): from the metabolite profile to the metabolic pathway activity. Bioinform Epub 26: 2969-2976.

34. Guengerich FP, Rendic S (2010) Update information on drug metabolism systems. Curr Drug Metab. 11: 1-3.

35. Moco S, Schneider B, Vervoort J (2009) Plant micrometabolomics: the analysis of endogenous metabolites present in a plant cell or tissue. J Proteome Res 8:1694-1703.

36. Viant MR (2008) Recent developments in environmental metabolomics. Mol Biosyst 4: 980-986.

37. Griffiths WJ, Karu K, Hornshaw M, Woffendin G, Wang Y (2007) Metabolomics and metabolite profiling: past heroes and future developments. Eur J Mass Spectrom 13: 45-50

38. Choubey J, Patel A, Khatri S, Dewangan R, Gupta SK, et al. (2009) Homology Modell ing of Hypoxanthin-Guanine hosphoribosyltransferase, Enzyme Involved in Salvage Pathway of Purine Metabolism. J Comput Sci Syst Biol 2: 259-261.

39. Nicolas T (2009) Data Mining, a Tool for Systems Biology or a Systems Biology Tool. J Comput Sci Syst Biol 2: 216-218.

40. Grundmann O (2010) The Gut Microbiome and Pre-systemic Metabolism: Current State and Evolving Research. J Drug Metabol Toxicol 1: 105.

41. Griffini P, James AD, Roberts AD, Pellegatti M (2010) Metabolites in Safety Testing: Issues and Approaches to the Safety Evaluation of Human Metabolites in a Drug that is Extensively Metabolized. J Drug Metabol Toxicol 1: 102.

42. Ewing GW (2009) A Theoretical Framework for Photosensitivity: Evidence of Systemic Regulation. J Comput Sci Syst Biol 2: 287-297.

43. Ewing GW, Ewing EN (2009) Does an Improved Understanding of the Nature and Structure of the Physiological Systems Lead to a Better Understanding of the Therapeutic Scope of Complementary & Conventional Medicine? J Comput Sci Syst Biol 2: 174-179.

44. Brum IJB, Martins-de-Souza D, Smolka MB, Novello JC, Galembeck E (2009) Web Based Theoretical Protein pI MW and 2DE Map. J Comput Sci Syst Biol 2: 093-096.

45. Fernández A (2011) Pharmaceutical Industry at the Post-Genomic Junction. J Postgenom Drug Biomark Develop 1:103e.

46. Garg B, Sufian Beg MM, Ansari AQ (2009) Optimizing Number of Inputs to Classify Breast Cancer Using Artificial Neural Network. J Comput Sci Syst Biol 2: 247-254.

47. Lakshminarasimhan N, Tagore S (2009) Damages in Metabolic Pathways: Computational Approaches. J Comput Sci Syst Biol 2: 208-215.

48. Sébédio JL, Pujos-Guillot E, Ferrara M (2009) Metabolomics in evaluation of glucose disorders. Curr Opin Clin Nutr Metab Care 12: 412-418.

49. Gao S, Wang X (2009) Predicting Type 1 Diabetes Candidate Genes using Human Protein-Protein Interaction Networks. J Comput Sci Syst Biol 2: 133-146.

50. Yao L, Rongling W (2009) Modeling Host-Cancer Genetic Interactions with Multilocus Sequence Data. J Comput Sci Syst Biol 2: 024-043.

51. Wheelock CE, Wheelock AM, Kawashima S, Diez D, Kanehisa M, et al. (2009) Systems biology approaches and pathway tools for investigating cardiovascular disease. Mol Biosyst 5: 588-602.

52. Yeboah J (2011) Flaws in Current Clinical Trial Design: Need for Intermediate Markers. J Postgenom Drug Biomark Develop 1: 102e.

53. Shi G, Cui Q, Zhang Y (2009) MicroRNA Set : A Novel Way to Uncover the Potential Black Box of Chronic Heart Failure in MicroRNA Microarray Analysis. J Comput Sci Syst Biol 2: 240-246.

54. Nagaraj NS (2009) Evolving 'omics' technologies for diagnostics of head and neck cancer. Brief Funct Genomic Proteomic 8: 49-59.

55. Shi H (2008) The Genetic Equidistance Result of Molecular Evolution is Independent of Mutation Rates. J Comput Sci Syst Biol 1: 092-102.

56. Horgan RP, Clancy OH, Myers JE, Baker PN (2009) An overview of proteomic and metabolomic technologies and their application to pregnancy research. BJOG116:173-181.

57. Yang X, Li Z, Su Z, Davis K, Chen T, et al. (2011) Urinary Micrornas as Noninvasive Biomarkers for Acetaminophen-Induced Liver Injury. J Postgenom Drug Biomark Develop 1:101.

58. Pendyala G, Want EJ, Webb W, Siuzdak G, Fox HS (2007) Biomarkers for neuroAIDS: the widening scope of metabolomics. J NeuroimmunePharmacol2: 72-80.

59. Lin HM, Helsby NA, Rowan DD, Ferguson LR (2011) Using metabolomic analysis to understand inflammatory bowel diseases. Inflamm Bowel Dis 17: 1021-1029.

60. Taylor SL, Bukanov NO, Chapman A, Fiehn O, Osier M, et al. (2010) A metabolomics approach using juvenile cystic mice to identify urinary biomarkers and altered pathways in polycystic kidney disease. Renal Physiol 298: F909-F922.

61. D'Alessandro A, Zolla L (2011) Metabolomics and cancer drug discovery: let the cells do the talking.DrugDiscov Today.

62. Hang X, Wu FX (2009) L1 Least Square for Cancer Diagnosis using Gene Expression Data. J Comput Sci Syst Biol 2: 167-173.

63. Miroslava C, Culf U, Barnett DA, Culf AS, Chute I (2010) Cell culture metabolomics: applications and future directions. Drug discov today 15.

64. Dunn WB, Goodacre R, Neyses L, Mamas M (2011) Integration of metabolomics in heart disease and diabetes research: current achievements and future outlook. Bioanal 19: 2205-2222.

65. Suzuki NYZ (2011) Mass spectrometry-based quantitative analysis and biomarker discovery. 131: 1305-1309.

66. Serkova NJ, Standiford TJ, Stringer KA (2011) The Emerging Field of Quantitative Blood Metabolomics for Biomarker Discovery in Critical Illnesses. Am J Respir Crit Care Med.

67. Rao VS, Das SK, Umari EK (2009) Glycomics Data Mining. J Comput Sci Syst Biol 2: 262-265.

68. Uyemura K, Dhanani S, Yamaguchi DT, Song MK (2010) Metabolism and Toxicity of High Doses of Cyclo (his-pro) Plus Zinc in Healthy Human Subjects. J Drug Metabol Toxicol 1:105.

69. Anandakumar S, Shanmughavel P (2008) Computational Annotation for Hypothetical Proteins of *Mycobacterium Tuberculosis*. J Comput Sci Syst Biol 1: 050-062.

70. Rochfort S (2005) Metabolomics Reviewed:A New "Omics" Platform Technology for Systems Biology and Implications for Natural Products Research. J Nat Prod 68: 1813–1820.