Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Biotechnology

New paradigms for metabolic modeling of human cells

Adil Mardinoglu[1] and Jens Nielsen[1,2,3]

Abnormalities in cellular functions are associated with the progression of human diseases, often resulting in metabolic reprogramming. GEnome-scale metabolic Models (GEMs) have enabled studying global metabolic reprogramming in connection with disease development in a systematic manner. Here we review recent work on reconstruction of GEMs for human cell/tissue types and cancer, and the use of GEMs for identification of metabolic changes occurring in response to disease development. We further discuss how GEMs can be used for the development of efficient therapeutic strategies. Finally, challenges in integration of cell/tissue models for simulation of whole body functions as well as integration of GEMs with other biological networks for generating complete cell/tissue models are presented.

Addresses
[1] Department of Biology and Biological Engineering, Chalmers University of Technology, Gothenburg, Sweden
[2] Novo Nordisk Foundation Center for Biosustainability, Technical University of Denmark, Hørsholm, Denmark
[3] Science for Life Laboratory, KTH – Royal Institute of Technology, Stockholm, Sweden

Corresponding author: Nielsen, Jens (nielsenj@chalmers.se)

Current Opinion in Biotechnology 2015, **34**:91–97

This review comes from a themed issue on **Systems biotechnology**

Edited by **Sarah Maria Fendt** and **Costas Maranas**

http://dx.doi.org/10.1016/j.copbio.2014.12.013

0958-1669/

Introduction

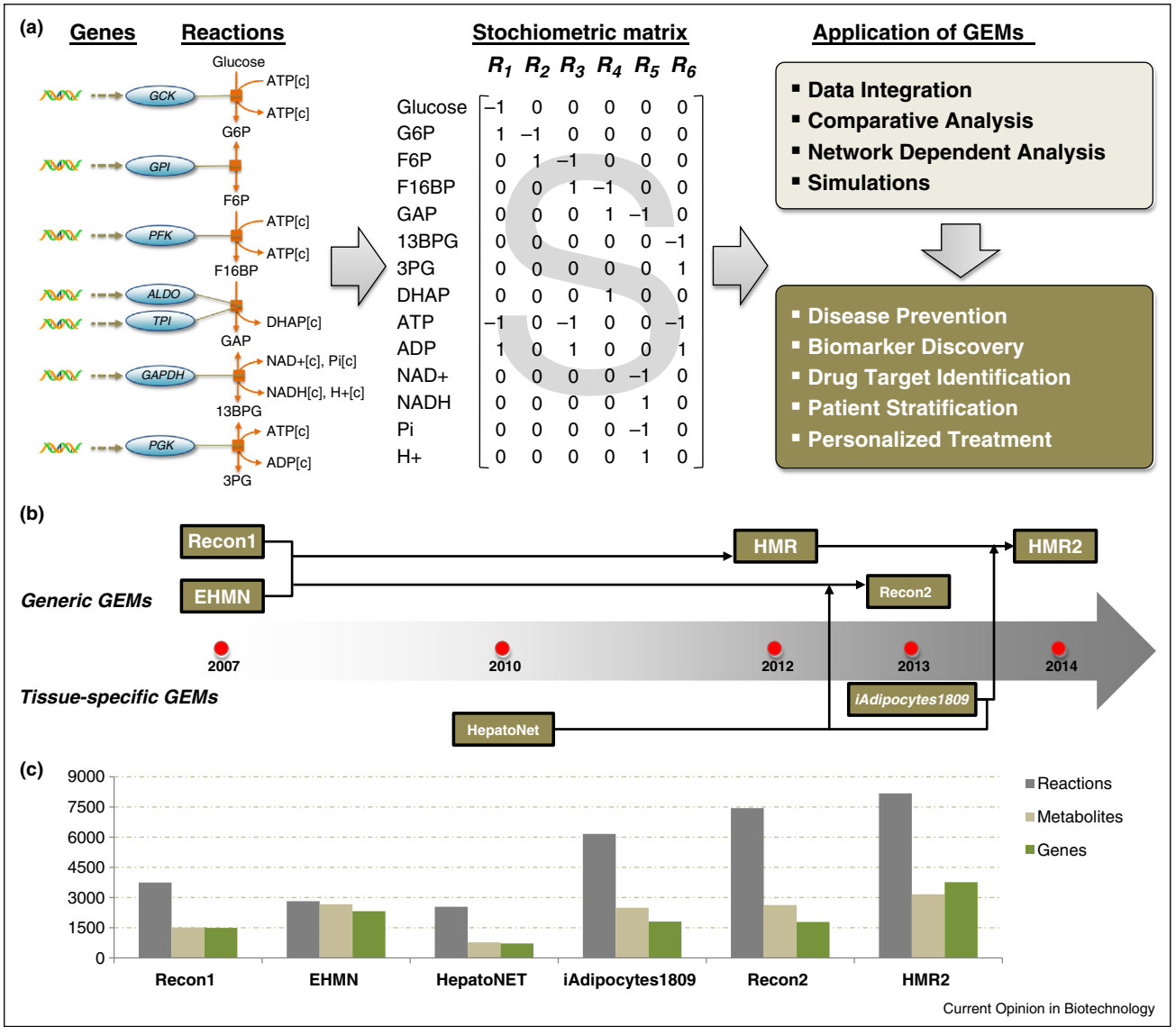
Type 2 diabetes (T2D), cardiovascular disease (CVD), non-alcoholic fatty liver disease (NAFLD) and cancer are caused by the abnormalities in cell/tissue functions and have become prevalent worldwide [1,2]. These chronic diseases are strongly linked to obesity that has reached epidemic proportions in almost all developed countries [3]. Currently used methods for development of drugs to treat these disorders are costly and inefficient, and unfortunately result in more failures than successes. For cancer, drug development is even more challenging due to the heterogeneous molecular mechanisms underlying human tumor progression [4]. Therefore, the development of innovative approaches is vital for accelerating the discovery of potentially effective products for the treatment of these disorders [5]. In this context, generation of computer models for cells/tissues in health and disease states may provide further insights for revealing the adaptations in cell/tissue functions in response to a chronic disease through the use of systems biology based approaches.

The specific application of systems biology for studying complex diseases is generally referred to as systems medicine. One of the key objectives of systems medicine is to understand biological processes of cells/tissues in health and disease states and gain new insights into what drives the appearance of the disease [6]. A principal tool of systems medicine is GEnome-scale metabolic Models (GEMs) which can aid in understanding the mechanistic relationship between genotype and phenotype and in revealing the underlying molecular mechanisms of complex diseases [7••]. GEMs are the collection of the annotated stoichiometric chemical reactions as well as enzymes associated to those reactions in a particular cell/tissue (Figure 1a). This network information can be converted into a computational model and analyzed using various algorithms. GEMs are powerful tools for dealing with the rising torrent of biological information and allow for sifting through huge datasets to look for emergent properties of enzymes and other metabolic functions as they interact in a cell/tissue. The harvested knowledge through the use of GEMs may be used for designing diets for disease prevention, discovery of novel biomarkers for stratification, identification of drug targets for designing effective treatment strategies, and prediction of the toxicity caused by the drugs, that is, personalized treatment [8••,9–11] (Figure 1a).

Global reconstructions of the human metabolism

Alterations in metabolism may be the cause or consequence of a disorder, and changes in metabolite concentrations can be used as biomarkers for diagnosis and monitoring of the diseases whereas enzymes can be targeted for disease treatment. GEMs allow for studying the interactions between metabolites and enzymes in a holistic manner rather than by more traditional reductionist, 'one metabolite and one enzyme', approaches. Two global reconstructions of the human metabolic network, Recon1 [12] and EHMN [13] were manually reconstructed through evaluation of bibliomic data and these networks revealed the existing gaps in understanding of human metabolism for further experimental investigations. These networks, which focus on different parts of the metabolism were merged with the knowledge databases for biochemical reactions resulting in Human Metabolic Reaction database (HMR) [14] (Figure 1b). Recon1

Figure 1



(a) GEMs contain the biochemical reactions as well as the associated genes in particular cells/tissues. This network information can be converted to computational models through the use of a stoichiometric matrix (**S**) and these models can be used in various translational medicine applications including: omics data integration, comparative and network dependent analysis, and simulations. **(b)** The timeline of generation and evaluation of global reconstructions of human metabolism. **(c)** Bar plot showing the number of the reactions, unique metabolites and genes incorporated to the generic human GEMs and cell-type specific GEMs used in their improvement.

and EHMN also formed the basis for a community-driven effort resulting in Recon2 [15•] that also incorporated information from metabolic reconstruction of the human hepatocyte (HepatoNet) [16]. Recently, a functional GEM for adipocytes, *iAdipocytes1809*, with a strong focus on lipid metabolism was reconstructed [17••] and integrated to HMR together with HepatoNet for the construction of HMR2 [18••]. The number of the reactions, associated genes and the unique metabolites incorporated in the generic human GEMs as well as in cell-type GEMs which are used in their improvement are presented in Figure 1c. From this, it is seen that HMR2 is currently the most comprehensive global reconstruction of the human metabolism.

Cell/tissue-type and cancer specific GEMs

Metabolism differs in each cell/tissue type and it is therefore necessary to reconstruct cell/tissue specific GEMs for simulation of their physiological and pathophysiological states. Hence, a number of algorithms which use gene expression and proteomics data as input, have been developed [8••] and systematically evaluated