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Quantitative modeling of human metabolism: A call for a community effort

Maria Masid and Vassily Hatzimanikatis

Abstract

Metabolism is the process by which cells and organisms obtain nutrients and energy to perform their functions. In the last years, many human diseases, including cancer, diabetes, and cardiac diseases, have been associated with altered metabolism. Understanding these metabolic alterations at a systems level will help to design better therapies and treatments. In this context, the human genome-scale metabolic models (GEMs) combined with mathematical methods and experimental data have been powerful tools to investigate cellular metabolism under different conditions. Here, we review current methods and models to study human metabolism, and we discuss future perspectives, including a community call for an agreement on how to use GEMs in a context-specific manner for quantitative analysis of human metabolism.

Addresses

Laboratory of Computational Systems Biotechnology, École Polytechnique Fédérale de Lausanne (EPFL), CH 1015, Lausanne, Switzerland

Corresponding author: Hatzimanikatis, Vassily (vassily.hatzimanikatis@epfl.ch)

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Human metabolism, Metabolic networks, Mathematical modeling, Biological networks.

Introduction

With the annotation of the human genome sequences in 2001 and 2004 [1,2], the scientific community reconstructed in 2007 the first genome-scale metabolic model (GEM) for human cells [3,4]. In 2010, within Systems Biology, there was a community effort to define the protocols required to reconstruct and curate high-level GEMs [5]. Since then, the human metabolic models were curated and refined over the years, and improved versions of the human GEMs were generated, including HMR [6], Recon 2 [7], HMR 2.0 [8], Recon 2.2 [9], iHsa [10], and the most recent versions Recon 3D [11] and Human1 [12].

Over the years, a phylogeny of constraint-based methods was developed to use GEMs to simulate the metabolic behavior of cells, such as perform a specific task, optimize the production of compounds of interest, or predict cellular phenotypes [13]. Some of these methods incorporate constraints at steady-state for mass balance [14], enzyme usage [15], and thermodynamic laws [16,17]. Such methods have been used to formulate biological hypotheses and guide experiments generating new sets of data used to improve the predictive capabilities of the metabolic models. GEMs and the methods developed are powerful platforms for integrating *omics* data, including transcriptomics, proteomics, metabolomics, and fluxomics.

As our knowledge of human metabolism increases, so does the size and complexity of the metabolic models in terms of genes, reactions, and metabolites. The ever-increasing size of the human metabolic models hinders their utilization for biological studies, as their increased complexity hampers the analysis of results and increases the computational cost. Furthermore, these networks are reconstructed based on the whole genome of human cells, while a specific cell type expresses only a portion of those genes. Thus, there is an apparent need to reduce GEMs to a more manageable size representing a particular cell type. To this end, a plethora of methods were developed to derive reduced-size context-specific models from the generic human models. Such context-specific models can capture the phenotype of a particular type of cell or tissue by reducing the generic GEM to the reactions catalyzed by enzymes expressed in the specific tissue. In the last years, several model-reduction methods were developed [18–20], including a human-centered specific network reduction [21]. These methods rely on transcriptomics or proteomics data and metabolic tasks to identify the set of reactions that will define the context-specific model [22–26]. The cell-type-specific and tissue-specific models have been successfully used to simulate metabolism in diseased and healthy cells, as well as to identify biomarkers and drug targets. Furthermore, personalized models that integrate *omics* data from patient samples have been

helpful for precision medicine [27–30]. Despite the large number of individual methods and workflows derived, up to date, there is not a consensus protocol to generate context-specific models.

In this review, we highlight the main methods and modeling approaches that have been used in the past years to model cellular phenotypes in a diversity of conditions. The focus of this review is to analyze the current applications and challenges of these methods and models and to provide future perspectives on how they can be extended to derive more quantitative approaches for the reconstruction of context-specific models (Figure 1).

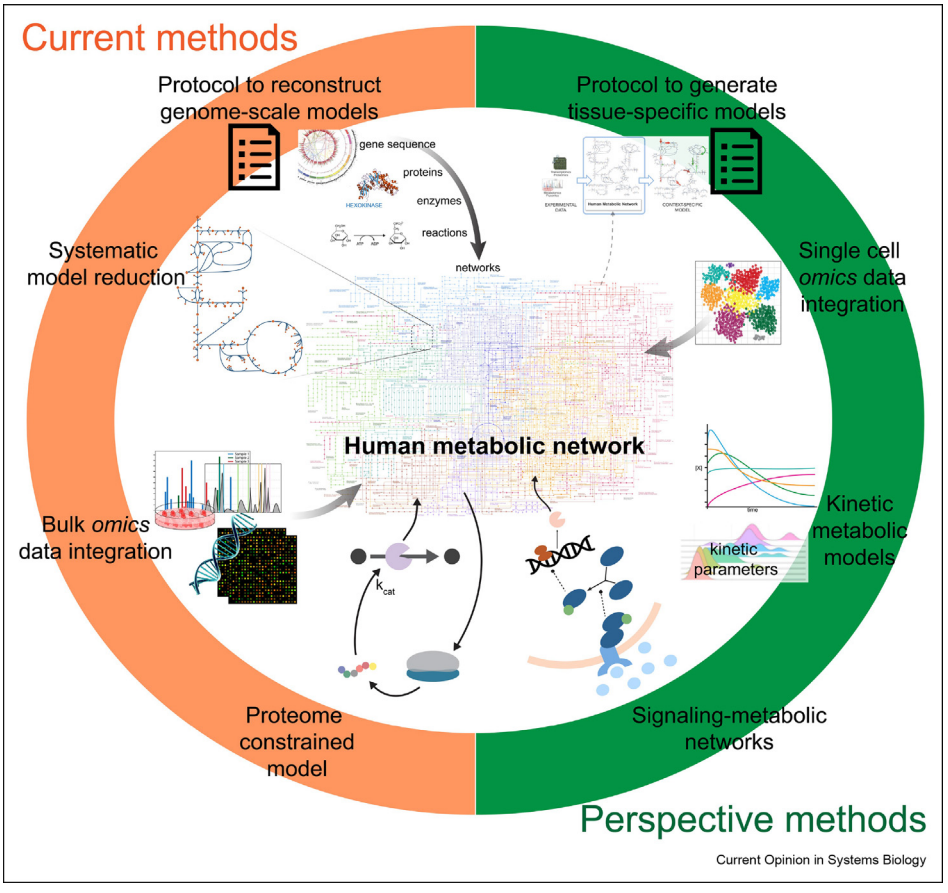
Current methods and perspectives

Model-based analysis with *omics* data integration in the human metabolic networks

Since the early 2010s, the era of big data allowed researchers to obtain and analyze huge amounts of genomics and transcriptomics data, leading to a community interest in integrating transcriptomics and proteomics data in GEMs toward the reconstruction of tissue-specific models. Nowadays, technological advances facilitated data extraction at a single-cell level [32], presenting the opportunity to integrate high-resolution data into GEMs. Although several groups have started to develop methods to integrate single-cell *omics* data into GEMs [33], it remains a challenge to systematically assess how the current methods can incorporate this type of data [34,35]. Overcoming this challenge is crucial to promote current modeling approaches toward personalized studies. Mirroring the knowledge on the methods developed to reconstruct tissue-specific models, the community can start integrating single-cell data and building single-cell models. Such models will better capture the metabolic features of a specific cell or single-cell population, leading to a better classification of the metabolic subtypes present in the population, as well as to characterize cooperation activities.

GEMs provide the relation between genes and metabolic reactions, enabling identifying the pathways, and

Figure 1



Current versus Perspective methods to investigate metabolic phenotypes using the human GEMs. In the center, the KEGG map [31] as a representation of the human metabolic network. To the left side, the current methods available to use GEMs to infer the metabolic state of the cells. To the right side, the perspective methods and models necessary to improve the predictive capabilities of GEMs by incorporating single-cell data and dynamic and signaling effects.

therefore the metabolites, involved in a specific process or condition. This mapping offers a unique opportunity to upgrade the value of *omics* data by interpreting the expression profile and the metabolomics at the same time. Moreover, GEMs are helpful to investigate alternative metabolic profiles in agreement with the observed phenotype and generate testable hypotheses both at the genomic and at the metabolomic level. Furthermore, GEMs, in combination with *omics* data, have been applied to identify cellular functions, such as growth, energy maintenance, and utilization and synthesis of metabolites, which are critical to correctly capture the metabolic states of the cell [36,37].

Recently, a method was developed to extract the metabolic pathways required to perform a set of metabolic tasks using GEMs, using the expression data to perform network enrichment analysis and assign functionality to the deregulated genes in the pathway [38]. This approach has allowed identifying the minimal network (minimum number of reactions) required to perform a metabolic task, such as the production of a metabolite, including not only the classical production pathway but also the additional reactions necessary for the activity of the main pathway (Figure 2).

Integrating the gene expression machinery in GEMs

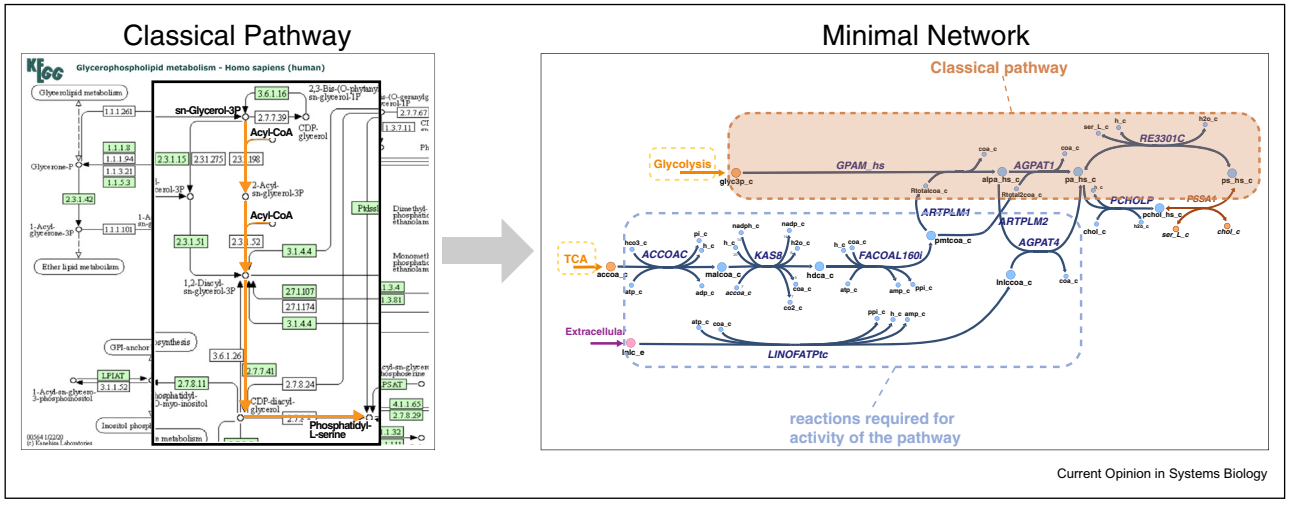
GEMs have been recently extended to include information on the concentration and availability of the enzymes [39] and to integrate the gene expression machinery [40–42]. These models, known as proteome constrained GEMs, can compute the optimal proteome allocation of the cell, improving the capabilities of GEMs to capture observed cellular phenotypes. Proteome constrained GEMs are currently being developed for a variety of organisms spamming from bacteria to human, and they can be readily used for the integration of *omics* data.

One of the challenges working with proteome constrained GEMs is the large number of parameters (k_{cat}) that are required. Currently, these are estimated based on databases such as BRENDA, SABIO-RK, and literature. However, the available data covers only a small fraction of the known metabolic reactions, highlighting the need to develop strategies to estimate them. Furthermore, as we refine the description of the mechanisms associated with the enzymes, we increase not only the quality of the GEMs but also their size, emphasizing once again the need to generate systematically reduced versions of these GEMs that correctly capture the biological state of the cells under study.

The cellular microenvironment

Human cells live in a complex environment where they constantly interchange metabolites with the medium surrounding them. The availability of nutrients and the ability of cells to use them determine the intracellular metabolism and, ultimately, their phenotype. Therefore, it is of great importance to correctly define the uptake of nutrients in GEMs while simulating cellular metabolism [43]. To this end, several studies have been performed to develop approaches that allow us to build a more biologically relevant environment in the GEMs [44]. While many of these studies and model development have been around cell lines [45,46], the environ-

Figure 2



Minimal networks versus classical pathway. Representation of the classical pathway in KEGG [31] for the synthesis of phosphatidyl-serine and the corresponding minimal network. The minimal network includes the classical pathway, the upstream pathways, in this case, glycolysis and TCA, and the set of reactions required to generate the precursor metabolites of the main pathway.

mental conditions change in *in vivo* systems. Thus, we should now use the *in vitro* and *in silico* learnings to estimate the *in vivo* environment of cells by combining the individual cellular metabolic states and functions with the information about the cell population in the microenvironment.

Drawing from the paradigms of the microbiome communities research, we can derive novel methods that will allow us to understand better the *in vivo* microenvironment of cells. We can benefit from the work done in microbial communities [47] to study the diverse populations of cells that are part of the microenvironment and their interactions [48,49]. It is worth noting here that in the case of human cells, the community of cells shares the same genome. The different cells in the population can be modeled using transcriptomics data, which will capture how differences in gene expression translate to different cellular phenotypes.

Recently, human GEMs have been used with a spatial modeling approach to reveal the heterogeneity in the tumor microenvironment [50], as well as to analyze the spatial and morphological dynamics of multicellular systems while modeling the metabolic activity of individual cells [51].

Signal transduction to metabolism

Cells not only cohabit in their microenvironment, but they also cross-communicate among them. The signals that cells sense in their immediate microenvironment are transmitted intracellularly and converted into responses that regulate and shape the phenotype of the cells. In certain cases, these signals regulate the expression of transcription factors and, therefore, of genes. In the case of metabolic genes, this process reprograms the metabolism of cells, affecting the activity of metabolic pathways.

Although the fields of signaling and metabolism have been widely studied independently, there is increasing evidence that metabolism is tightly regulated by signaling events, both in healthy and in diseased cellular states. This results in an emergent need to understand how the signals propagate from the receptors of the cells to the metabolic reactions. Toward this, we need to develop novel integrated models that connect metabolic and signaling networks and are able to simulate the flow of information from the receptors to the downstream metabolic pathways. Even though this remains a complex endeavor, the community is developing methods in this direction [52–54].

The need for dynamic models

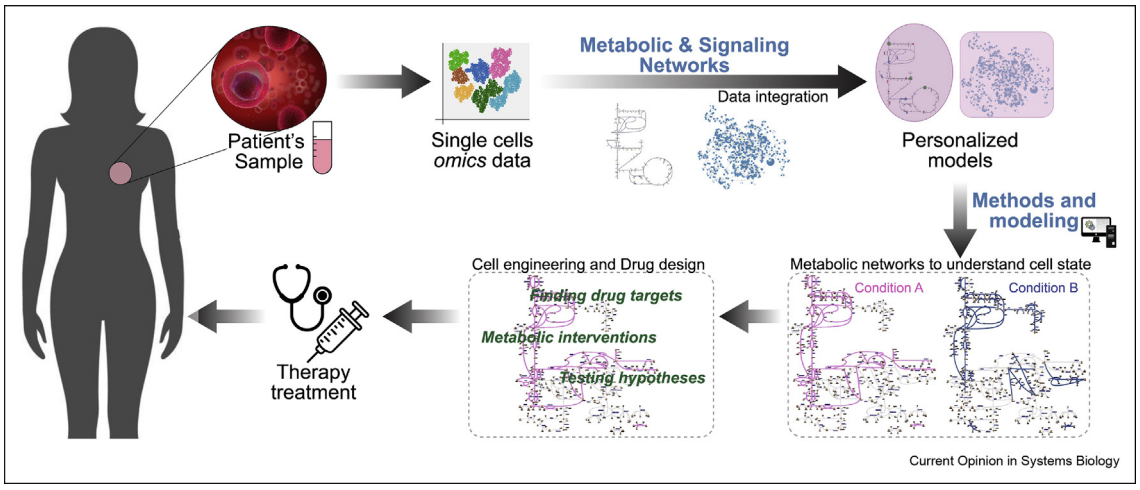
GEMs have been powerful tools to study and understand the metabolism of cells at a specific stage. Nevertheless, organisms and cells are dynamic systems continually adapting to their environmental conditions and regulation patterns. In order to capture and analyze this dynamic behavior, we need to develop kinetic models. While constraint-based models rely on the stoichiometric relation between reactions and metabolites using linear equations, kinetic models include ordinary differential equations that need dynamic or kinetic data to perform parameter identification. The outstanding limitation of current kinetic models of metabolism at the genome-scale, particularly in human metabolism, is the large number of kinetic parameters required and the uncertainty about their values. Numerous methods are currently being framed to overcome the lack of kinetic data [55–57] and perform parameter identifiability [58–61] in many organisms. All these previous methods have benefited from extensive fluxomic and metabolomic information, and while these methods and the associated frameworks could now be used for human metabolism, they will require more quantitative data, which currently is challenging in *in vitro* and *in vivo* models of mammalian systems.

Moreover, unlike other systems that operate in well-defined physiologies, such as bacteria or yeast, the mammalian and human metabolism are highly context-specific, e.g., tissue-specific and disease-specific conditions. This presents another challenge that can be addressed by a community effort to assess the variability across the representation of cellular conditions and cell types.

Personalized models

One of the biggest challenges of current therapies is the heterogeneity of the cell populations in the microenvironment and the heterogeneity among patients, leading to the need for personalized therapies and, therefore, personalized models [62]. Generating new approaches based on previous learnings from modeling human cells with GEMs will enhance the development of methods to integrate patient's specific metabolic and signaling data into metabolic and signaling networks to build personalized models. Deriving more accurate and robust human metabolic and signaling models that capture not only the intracellular events but also the interactions occurring in the cellular microenvironment will help to understand the alterations that lead to diseased states. Such models will provide a deeper understanding of the metabolic and signaling state of the patient's cells, enabling us to create engineering approaches to find effective drug targets, novel therapies, and treatments (Figure 3). Furthermore, the advance in models and methods will ultimately guide the steps required to achieve whole-cell modeling and whole-body modeling, which are already being investigated for the human gut microbiome [63].

Figure 3



Perspectives for personalized models. Applications of novel approaches toward personalized models to help in the design of novel therapies and treatments. The methods and models required to integrate patient-specific *omics* data will allow researchers to have a deeper understanding of the metabolic and signaling states of the patient's cells.

Conclusions

The reconstruction of these complex networks has benefited in the past from community efforts that allowed to improve their quality and applicability to understand the genotype−phenotype relationship of cells. The variability among physiological conditions such as different tissues, microenvironments, and the current access to more sophisticated protocols for data acquisition (whole cell, single-cell, and bulk populations), has given rise to many data integration methods. These methods, while similar in the objective they involve very different formulations and parameters. Although we understand that one method does not fit all purposes, the community should agree on the sets of methods to utilize as it has been done to develop protocols for experimental data.

Furthermore, the integration of signaling networks with metabolic networks and the associated quantitative analyses present new challenges. The reconstruction of signaling networks downstream a receptor or upstream a transcription factor can increase very fast in size due to the combinatorial complexity. This presents a challenging situation that will require the convergence toward a set of established community methods. While the community is developing methods to address some of these challenges, there is no consensus on the appropriate modeling and algorithmic formulations and associated assumptions. We suggest here that there is another opportunity as we move in the analysis and reconstruction of tissue-specific and cell-type-specific models for one or more parallel Systems Biology community efforts to establish protocols toward more quantitative modeling and analysis of human metabolism.

Conflict of interest statement

Nothing declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.coisb.2021.04.008.

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- • of special interest
- •• of outstanding interest

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