A Multi-Scale Model of the Whole Human Body based on Dynamic Parsimonious Flux Balance Analysis

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Abstract: The multi-scale modelling approach is a powerful mathematical technique for simulating and analyzing complex biological systems such as the human body. This tool can help study the interactions of the various networks in a living organism, from the cellular level up to the population scale, in one framework. In this paper, a generic mathematical model is developed that describes human metabolism with 237 serum metabolites integrated with a chosen set of human metabolic networks. A new computational approach is presented for solving the resulting dynamic problem using parsimonious flux balance analysis (pFBA). To illustrate the performance of the proposed approach, the human hepatocyte genome scale model is selected for the metabolic network to be included. The simulation results show that the proposed approach has promise with respect to both computational efficiency and convergence. To demonstrate the potential application of the developed model, prediction of amino acid biomarkers for a set of inborn errors of metabolism (IEM) is considered as an example. All the simulations are performed using MATLAB and the COBRA toolbox. This framework has the potential to simulate various human metabolic disorders to help with the diagnosis of associated human diseases and to suggest novel treatment strategies. In addition, it opens the door to new opportunities for personalized medicine.

Keywords: Multi-scale modelling, whole-body model, metabolic network, flux balance analysis, personalized medicine.

1. INTRODUCTION

The multi-scale modelling approach is a powerful technique to analyze complex processes in a wide variety of engineering problems (Vlachos [2005]). It is a rapidly evolving area of research that has a fundamental impact on computational and applied science. This integrative modelling technique has also become a well-known tool in the systems biology research area (Dada and Mendes [2011]); it can help elucidate the complex interactions in different networks in a living organism, from the cellular level to the population scale in a single modelling framework. This framework can be used in a wide range of applications from biochemical production to human disease studies. Research has shown that the multi-scale modelling technique can lead to significant improvement in medical treatments and pharmaceutical research (Eissing et al. [2011]). For instance, Schaller et al. [2013] developed a multi-scale model of the whole human body, including three physiologically based pharmacokinetic models (PBPK) integrated with the liver insulin receptor model, to predict the dynamic behavior of the insulin-glucose-glucagon regulatory network. These authors have shown that the integrated model can be applied to the development and validation of novel diabetes treatment strategies. Also, Krauss et al. [2012] integrated the genome-scale model of the human hepatocyte with a PBPK model of the human body. These authors have illustrated that the model has potential applications to support a mechanistic understanding in diagnostics and drug development. Along with the multi-scale modelling technique, constraint-based models have become a widely used tool to study the human cell metabolism and help diagnose human diseases; these models contain important metabolic pathways that occur in the human body. In fact, cellular models are useful for an in-depth understanding of human metabolism, metabolic disorders, in-born errors of metabolism and drug mechanisms ([Kim et al., 2012, Hirano et al., 2009, Shlomi et al., 2009]). The advanced technology in the field of human metabolomics helps develop and validate these types of metabolic models ([Shulam, 2006, Wishart et al., 2007, Schellenberger et al., 2010]).

In spite of the rapid development and growing research in the fields of human metabolic modelling and metabolomics, a dynamic computational model is still lacking that can integrate the human metabolic networks with human metabolomics data. Hence, the objective of
this paper is to present such a framework and to demonstrate its computational efficiency and potential application in the field of human metabolism. In Section 2, the model development procedure and integration algorithm are elucidated. In Section 3, the computational efficiency of the modelling framework is illustrated and one potential application of the integrated model is described. Finally, conclusions are presented in Section 4.

2. MODEL DEVELOPMENT

To establish the modelling framework, the whole-body model (WBM) is developed. This model consists of 15 compartments representing 14 human organs along with human serum. This WBM contains a series of mass balance differential equations describing the concentration of human metabolites in various compartments (organs) that are connected by the blood stream as shown in Fig. 1 and described by the following equations:

**Kidney compartment:**
\[ \dot{C}_k = \frac{Q_k}{V_k} (C_{art} - \frac{C_g}{K_g}) - R_2, \]  

**Muscle compartment:**
\[ \dot{C}_m = \frac{Q_m}{V_m}(C_{art} - \frac{C_m}{K_m}) - R_3, \]

**Brain compartment:**
\[ \dot{C}_b = \frac{Q_b}{V_b} (C_{art} - \frac{C_b}{K_b}) - R_4, \]

**Heart compartment:**
\[ \dot{C}_h = \frac{Q_h}{V_h} (C_{art} - \frac{C_h}{K_h}) - R_5, \]

**Pancreas compartment:**
\[ \dot{C}_p = \frac{Q_p}{V_p} (C_{art} - \frac{C_p}{K_p}) - R_6, \]

**Stomach compartment:**
\[ \dot{C}_s = \frac{Q_s}{V_s} (C_{art} - \frac{C_s}{K_s}) - R_7, \]

**Liver compartment:**
\[ \dot{C}_l = \frac{Q_l}{V_l} (C_{l,inlet} - \frac{C_l}{K_l}) - R_8, \]

**Adipose tissue:**
\[ \dot{C}_a = \frac{Q_a}{V_a} (C_{art} - \frac{C_a}{K_a}) - R_9, \]

**Skin compartment:**
\[ \dot{C}_{sk} = \frac{Q_{sk}}{V_{sk}} (C_{art} - \frac{C_{sk}}{K_{sk}}) - R_{10}, \]

**Spleen compartment:**
\[ \dot{C}_{sp} = \frac{Q_{sp}}{V_{sp}} (C_{art} - \frac{C_{sp}}{K_{sp}}) - R_{11}, \]

**Lung compartment:**
\[ \dot{C}_{lu} = \frac{Q_{lu}}{V_{lu}} (C_{ven} - \frac{C_{lu}}{K_{lu}}) - R_{12}, \]

**Bone compartment:**
\[ \dot{C}_{bo} = \frac{Q_{bo}}{V_{bo}} (C_{art} - \frac{C_{bo}}{K_{bo}}) - R_{13}, \]

**Adrenal compartment:**
\[ \dot{C}_{adr} = \frac{Q_{adr}}{V_{adr}} (C_{art} - \frac{C_{adr}}{K_{adr}}) - R_{14}, \]

**Blood compartment:**
\[ \dot{C}_{art} = \frac{Q_{lu}}{V_{lu}} (\frac{C_{lu}}{K_{lu}} - C_{art}) + Q_{ext}, \]

\[ C_{ven} = \sum_{i=1}^{8} \frac{Q_i C_i}{K_i}, \]

\[ Q_l = Q_s + Q_p + Q_{sp} + Q_{g} + Q_{l,art}, \]
Michaelis—Menten kinetic model:

\[ R_i = \frac{V_{m,i} C_i}{K_m,i + C_i}, \]

Here, \( C_i \) represents the concentration of a specific metabolite which is present in human serum. In these equations, \( V_i \), organ volume, and \( Q_i \), blood flow rate to the organ, are physiological properties of the human body, and \( K_i \), called the tissue-partition coefficient, represents pharmacokinetics properties that could be determined by a specific estimation method (Poulin and Theil [1999]). \( R_i \) is the production rate or consumption rate of a metabolite in the body organ. \( Q_{ext} \) represents the exogenous appearance rate of a metabolite in the body and \( Q_{l,art} \) is the arterial blood flow rate to the liver. To estimate the physiological properties of the human body in the WBM, the developed models are adapted from the literature (Young et al. [2009], Brown et al. [1997], N.Johnson et al. [2005]). Here, the entire model contains 237 identified human metabolites in each compartment, including different types of lipids, fatty acids, amino acids and sugar sources. Therefore, the WBM consists of 3555 ordinary differential equations (ODEs) (i.e., 15 \times 237). The pharmacokinetic parameters used in the WBM and normal metabolite concentrations in the human serum are extracted from the Human Metabolome Database (HMDB) (Wishart et al. [2007]). In the WBM, all physiological and physicochemical properties are assumed to be constant and time-invariant. Also, we assume that blood is a homogenous mixture of plasma and serum.

In order to incorporate the biochemical reactions that occur in human cells into the modelling framework, the previously developed metabolic networks (e.g., Duarte et al. [2007]) are used. These models are represented by a stoichiometric matrix \( S \) and intercellular fluxes \( \nu \) indicating the reaction rates. To find the flux distribution, an algorithm called parsimonious Flux Balance Analysis (pFBA) is employed (Lewis et al. [2010]). The network is constrained by imposing lower and upper bounds for the flux of each reaction in the network. The steady-state fluxes for reactions are calculated by solving the following optimization problem

\[
\begin{align*}
\max & \quad c^T \nu, \\
\min & \quad \sum |\nu|, \\
\text{st} & \quad S \nu = 0, \\
& \quad \nu_{\min} \leq \nu \leq \nu_{\max}.
\end{align*}
\]

Here, \( c^T \) corresponds to the objective function and \( c \) is a vector of weights, indicating how much each reaction contributes to the objective function.

To complete the construction of the modelling framework, we need to integrate the metabolic models with the WBM. To do so, the transport reactions associated with the metabolic networks are used to couple with the WBM. The transport reactions allow the metabolites to enter in or exit from the organ cells as illustrated in Fig. 2. The rate of the metabolite exchanges depends on kinetic parameters associated with these reactions and metabolite concentrations in the human serum.

In order to solve the integrated model, a static optimization dynamic flux balance analysis approach (dFBA) proposed by Mahadevan et al. [2002] and Varma and Palsson [1994] is applied. Based on this algorithm, the WBM is solved to estimate all metabolite concentrations in the entire body. Then, estimated concentrations are used to calculate the reaction rates. The estimated reaction rates are set as lower-bound constraints for the pFBA problem. Solving the pFBA model leads to calculating the flux distribution through the whole metabolic network. Finally, estimated exchange fluxes update the metabolite concentrations in the whole-body model for the next time step.

The algorithm used to solve this integrated model assumes that the fluxes are constant over each time interval and they are updated at the beginning of each time interval (i.e., dynamic parsimonious flux balance analysis (dpFBA)). Therefore, the time step must be chosen properly to guarantee the accuracy of the results. In the next section, to demonstrate the performance of the computational algorithm, the WBM is integrated with the human hepatocyte metabolic network developed by Gille et al. [2010].

3. SIMULATION RESULTS

In this section, to illustrate the computational efficiency of the modelling framework, the dynamic parsimonious flux balance analysis (dpFBA) algorithm is implemented and the results are compared with dFBA (Mahadevan et al. [2002]) for urea production in the liver cell. Then, to demonstrate the application of the integrated model, the prediction of biomarker concentration for a set of in-born errors of amino acid metabolism in the body is simulated. One minute is used as the time interval in the simulations. All the simulations are implemented using MATLAB (MathWorks, Inc), COBRA toolbox, and ILOG/CPLEX solver (IBM, Inc).
3.1 Urea Production

Urea is the end product of amino acid degradation and metabolism in the human body. Here, we focus on the production of this metabolite in the liver based on the availability of substrates in the human serum. To do so, maximization of urea is considered as an objective function for the pFBA problem. As seen in Fig. 3.a, the urea concentration in the blood compartment increases since it is produced in the liver from ammonia and other nitrogen sources available in the human serum. Also, Fig. 3.b shows that after 60 minutes, the production rate of the urea becomes negligible since the required substrates (e.g., amino acids) are depleted from the human serum. In addition, the result shows that the concentration of urea in the blood compartment after a period of time does not change and it converges to a steady-state condition.

The simulation results show the consistency between flux and concentration profiles. This means that flux changes in the liver lead to concentration changes in the human serum, and eventually in the WBM. In addition, the simulation evidence demonstrates that all variables in the model (i.e., concentrations and fluxes), finally converge to the steady-state condition as expected. To elaborate, when the uptake rate of the substrates by the liver cell approaches zero, the production rate in the liver converges to zero as well which leads to steady-state concentration profiles in the WBM. To show the computational efficiency of the integrated model, dFBA is implemented with the same objective function (i.e., urea production). However, the use of dFBA results in significant variation in the metabolic fluxes due to present of alternative optimal solutions. The simulation evidence depicted in Fig. 4 indicates that dpFBA is more computationally efficient than dFBA in this framework since it is able to minimize the number of alternative solutions and to solve the numerical problem illustrated in the dFBA results.

3.2 Biomarker Prediction

A biomarker is a measurable metabolite indicating the severity or presence of some metabolic disorders in the human body. The identification of biomarkers is of major importance to biomedical research and is usually conducted using data analysis of metabolite data. Shlomi et al. [2009] developed a computational approach for predicting metabolic biomarker using metabolic models. These authors have shown that the proposed algorithm is able to predict the potential biomarkers for a set of inborn error of metabolisms in a qualitative way (i.e., increase or decrease in biomarker concentration in the blood compartment), based on flux balance analysis results. However, the proposed model is not able to show the biomarker concentration changes in the blood compartment quantitatively. Here, we apply our computational framework to predict biomarker concentration changes for a set of inborn errors of metabolism (IEM) whose causative genes are included in the hepatocyte model. To do so, we manually extract biomarker data from the OMIM database (McKusick [2007]) for a set of 10 inborn errors of amino acid metabolism. To further validate our prediction results, we extract biomarker concentrations for that set of metabolic disorders from the HMDB in healthy and unhealthy conditions.

To perform the simulations (i.e., one simulation per metabolic disorder), based on the information extracted from the databases, we remove the specific reactions associated with certain genes named in Fig. 5 and Table 1 at a specific time (i.e., $t = 300$ minutes) from the hepatocyte genome-scale model. Also, urea production is considered as an objective function at the cellular level for the pFBA problem. The simulation results show that the biomarker concentration associated with each inborn error of metabolism starts increasing at the time of deletion (See Fig. 5) and converges to higher levels of concentration. These results show that the model has the ability to identify the biomarker associated with a specific metabolic disorder properly. Also, the results indicate that the direction of the biomarker concentration changes is consistent with clinical evidence. Fig. 6 illus-
trates the comparison between predicted and experimental fold in the presence of inborn errors of metabolism. As seen, model prediction has relatively good agreement with experimental data. This indicates that the model is able to predict the change in biomarker concentration with acceptable accuracy. Although this example focuses on predicting the metabolic biomarker for known inborn errors of metabolism, the developed modeling framework is capable of predicting novel biomarkers for the knockouts of other genes present in the metabolic model including those that are not known at present to cause metabolic disorders but may be discovered in the future.

Fig. 6. Comparison of predicted and experimental fold for a set of 10 biomarkers associated with amino acid metabolic disorder. The results show that the model prediction has relatively good agreement with clinical data.

Table 1. Enzyme Names

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Name</th>
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<tbody>
<tr>
<td>AMT</td>
<td>Amino Methyl Transferase</td>
</tr>
<tr>
<td>GCSH</td>
<td>Glycine Cleavage System H Protein</td>
</tr>
<tr>
<td>GLDC</td>
<td>Glycine Decarboxylase</td>
</tr>
<tr>
<td>DBT</td>
<td>Dihydrolipoamide Branched-Chain Transferase</td>
</tr>
<tr>
<td>DLD</td>
<td>Dihydrolipoamide Dehydrogenase</td>
</tr>
<tr>
<td>BCKDHA</td>
<td>Branched-Chain Keto Acid Dehydrogenase E1,A</td>
</tr>
<tr>
<td>BCKDHB</td>
<td>Branched-Chain Keto Acid Dehydrogenase E1,B</td>
</tr>
<tr>
<td>HAL</td>
<td>Histidine Ammonia-Lyase</td>
</tr>
<tr>
<td>CPS1</td>
<td>Carbamoyl Phosphate Synthetase I</td>
</tr>
<tr>
<td>PRODH</td>
<td>Proline Dehydrogenase I</td>
</tr>
<tr>
<td>ARG1</td>
<td>Arginase I</td>
</tr>
<tr>
<td>FAH</td>
<td>FumarylAcetoacetate Hydrolase</td>
</tr>
<tr>
<td>MAT1A</td>
<td>Methionine AdenosylTransferase I</td>
</tr>
<tr>
<td>TRPO</td>
<td>Tryptophan Oxidoreductase I</td>
</tr>
</tbody>
</table>

Fig. 5. Prediction of amino acid biomarker blood concentration for different inborn errors of amino-acid metabolism. The title represents the name of inborn error of metabolism in each graph. The causative gene’s name is also indicated in each graph. ’...’ and ‘...’ represent biomarker concentration level in unhealthy and healthy individual extracted from clinical databases, and model prediction, respectively. The gene deletions occur at time= 300 minutes. The results show that the model is able to predict the identified biomarker and to demonstrate the right direction of changes in all simulations.

4. CONCLUSION

In this study, we have established a multi-scale computational modelling framework that includes a WBM with 237 human serum metabolites and metabolic models of human cells. These models have been integrated using the dynamic parsimonious flux balance analysis algorithm. To illustrate the computational efficiency of the proposed approach, the human hepatocyte genome-scale model was combined with WBM. The simulations indicated that the integrated model has great promise when it comes to computational efficiency. Also, a biomarker prediction
example has shown that the modelling framework can be utilized to simulate different human metabolic problems to help diagnose human diseases and identify novel biomarkers. Moreover, this framework opens new opportunities in personalized medicine to help analyze individual and population-based metabolism mechanisms since it includes the individual physiological properties of the human body and it has the capability to capture the genetic information. Although identifying a large number of parameters is one of the main challenges with this modelling approach, the availability of experimental and physiological evidence and databases related to human beings makes this possible. In the future, to enhance to generality of this modelling framework, other organ cell metabolic networks need to be integrated into the WBM. The hope here is that this expanded model will enable a much larger number of human metabolic diseases to be studied and will provide insight into novel treatment strategies.

REFERENCES


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