

A Simulation Model of Glucose-Insulin Metabolism and Implementation on OSG

Milad Ghiasi Rad, Aditya Immaneni, Megan McCabe, Massimiliano Pierobon, Juan Cui*

Department of Computer Science & Engineering
University of Nebraska – Lincoln, Lincoln, NE, United States

ghiasirad.milad@huskers.unl.edu, aimmaneni@cse.unl.edu, megan.mccabe@huskers.unl.edu, pierobon@cse.unl.edu, jcui@unl.edu

* Corresponding author

Abstract — In this paper, we present the design and implementation of a stand-alone tool for metabolic simulation and its deployment on the Open Science Grid (OSG). The case study model of glucose-insulin metabolism aims at the development of a real-time monitoring system that can assist patients with diabetes to handle their blood glucose profile and maintain healthy diet habit. This system is able to integrate custom-built SBML models along with users' food intake information and produces the estimation of ATP, Glucose, and Insulin for the given duration using numerical analysis and simulation. The tool has also been generalized to take into consideration of temporal genomic information and be flexible for simulation of any given biochemical models. After implementation on OSG, the results have demonstrated the effectiveness of numerical optimization for model selection and the feasibility of the proposed tool for the given metabolic simulation. The ATP-glucose and glucose-insulin correlations revealed by this tool can be promising for a variety of different application cases.

Keywords: metabolic pathways, enzymes, chemical reactions, metabolic network simulation, OSG

I. INTRODUCTION

The metabolic pathways play important roles in the cell cycles. Cell metabolism can be described as a set of chemical reactions which genome data provides vast majority of information about it [1]. The chemical reaction chains inside the metabolic pathways are responsible for production of Adenosine triphosphate (ATP) which its presence shows the energy level inside the cell. More ATP means more free energy to start new crucial reactions. Therefore, ATP level is a good representation for energy force for many essential reactions inside the cell. ATP is also highly dependent to the glucose concentration as it is the factor that ignites the glucose compensation, which later ends up in producing more ATP in the process [2].

The simulation of the biochemical networks has been in the center of attentions for several years. This concept is not new and there are several tools have been developed for this purpose. Different programming languages have been used in these developments. For example, [3] used Fortran to develop a prediction tool for gas phase chemical kinetics using sensitivity analysis. Many more advanced and modern tools focused on the simulation of a series of chemical chain reactions. Spyder-Py3 is one of this kind to provide a command line interface and enables users, who can be the patients using this tool in a stand-alone platform for insulin level predictions, or the researchers focused on simulation purposes, to simulate the chemical reactions for

different instances. Another tool is COPASI [4] which uses a graphical user interface for importing and exporting data. While this tool benefits a lot of great features such as importing various file types and reaction definitions, it lacks flexibility needed for the metabolic networks analysis such as feeding and user characteristics compatibility.

Besides the development of the tools able to simulate the metabolic pathways, there are other tools developed to display genomic data onto diagrams of metabolic pathways [5]. This type of representation helps the user to consider the genomic data into account, e.g., through estimation of enzymatic activity to improve the metabolic model prediction.

The metabolic pathway databases are also important as their organization affects the performance of the simulation due to high data volume. [6], [7] introduced a universal database of metabolic pathways called MetaCyc to show the chemical reactions which are supported by experimental data. Other databases such as KEGG [8] and HMDB [9] are useful for the extraction of metabolic pathway models.

In this paper, we used the KEGG and HMDB metabolic databases to create a Systems Biology Markup Language (SBML) [10] model as the input of a stand-alone simulation tool that we designed and developed for simulation of the metabolic pathways and the behavior of the participating species. Although KEGG offers only a general model of metabolic networks, this model can be personalized using the samples taken from each test subject to consider the concentrations and reaction rates based on each case. This tool, compared to the other available tools, is more flexible, comprehensive, and is designed specifically for the analysis of metabolic networks.

Later in this paper, first we will discuss our methods and models we have used in section II by illustrating a case study on the glucose-insulin simulation. In section III we will discuss the challenges we had on implementing our proposed model and the tool development; in section IV the results will be discussed; and at section V we conclude this paper and our research.

II. THEORY AND MODELING

The tool developed in our research is capable to model and investigate any biochemical systems in which, the model is given by the user having all the needed arguments and initial concentrations. Considering a full knowledge on the basics of the model, the theory followed for this paper is summarized, as follows.

A Numerical Analysis of Biochemical Systems

In order to simulate the biochemical models, the models of chemical reactions need to be implemented in a proper form. There are different ways to implement them based on the user's

preference, while the most famous and standard model used by many researchers is SBML [10] which is a XML based model to represent the chemical reactions, substrates, products, rates, and so on in a form that are dependable in the machine language. The given model can represent even the biggest chemical models with such an ease that the data stored in the model can be directly accessed using different tools and programming languages in order to make computational models.

The general form of a standard chemical reaction can be defined as:



where, A and B are considered as substrates, C and D are the products both in $\frac{\text{mole}}{\text{liter}}$ or related scales, k_1 and k_{-1} are the forward and reverse reaction rates, and k_A to k_D are the coefficients of the species A to D .

The first-degree Taylor series derived in (3) using the general form in (2) [11] was used in this paper to do the numerical predictions and model the gradual change in the concentrations using the gradient of the concentration in each substrate or product in the previous step.

$$f(t + t_0) = \lim_{h \rightarrow 0^+} \sum_{n=0}^{\infty} \frac{t_0^n \Delta_h^n f(t)}{n! h^n} \quad (2)$$

$$f(t + t_0) = f(t) + f'(t) \times t_0 \quad (3)$$

where Δ_h^n is the n^{th} finite gradient operator, $f'(t)$ represents the rate of change which can be found using traditional classical chemical kinetics (CCK) at time t and $t + t_0$ is the next step in the time frame. $f'(t)$ can also be shown for a general specie (S) as $[S]'(t)$ in. Therefore, the concentration of S is demonstrated as $[S]$.

Another ability that is added to this tool is to generate the ordinary differential equation (ODE) data from the SBML file which is a new feature compared to the other tools. Other tools such as COPASI only provide a portion of the ODEs in a non-string form, while the tool we proposed, will give these entities in the string format, that is more reliable to check and verify. (4) shows the general form of ODE model for a general specie (S) derived from [12].

$$[S_i]'(t) = \sum_{j=1}^m v_{ij} V_j \quad (4)$$

where $v_{ij} = v_{ij}^1 - v_{ij}^{-1}$ while, v_{ij}^1 and v_{ij}^{-1} associating with the forward and reverse coefficients of the i^{th} specie in j^{th} reaction respectively, m is number of the reactions, and V_j is defined in (5) in which, n is the total number of species in all of the reactions [12].

$$V_j = k_1 \prod_{i=1}^n [S_i]^{v_{ij}^1} - k_{-1} \prod_{i=1}^n [S_i]^{v_{ij}^{-1}} \quad (5)$$

This formulation is the key to the modeling of the chemical networks as it represents the derivation of a specific concentration at any given time. In each step, every substrate or product in the list of reactions' species will be updated one by one using the ordinary differential equations and this updates the other metabolites accordingly which is demonstrated in Figure

1. The trace of changes in the concentrations can be stored to be visualized later or to be analyzed statically. In Figure 1, $C_1(i)$, $C_k(i)$, and $C_n(i)$ represent the concentrations of the metabolites 1 , k , and n at iteration i respectively, while their values are used to calculate the $i+1^{\text{th}}$ iteration of the C_1 , C_k , and C_n . For the metabolite k , the current values of the previous metabolites will be used to fasten the analysis process.

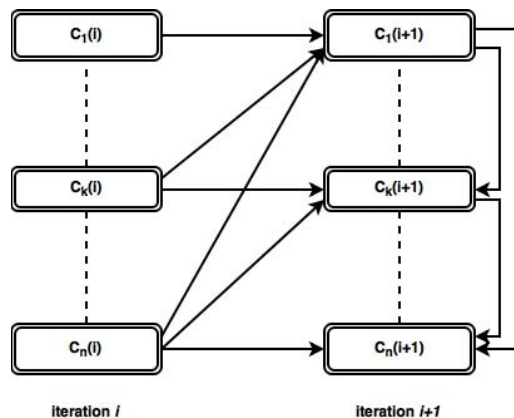


Figure 1: The iterations and the concentration updates

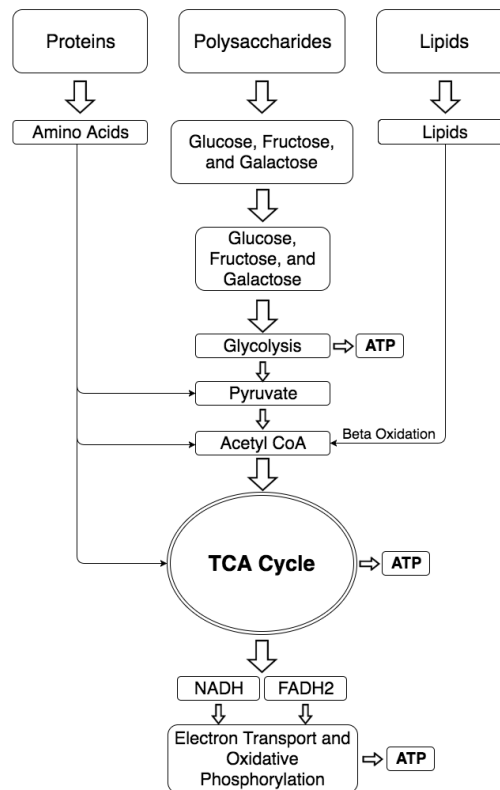


Figure 2: Major metabolic pathways participating in ATP production

B Modeling of Required Metabolic Pathways

The main metabolic pathways used in this paper are shown in Figure 2 which shows three main pathways of carbohydrates,

lipids and protein pathways. These pathways are highly interconnected and their intersection makes this network very complex.

The proposed model will be used to analyze different metabolites. The ATP concentration in the cell is one of the primary purposes of this model. In another project, we developed a mobile application to monitor the user's dietary intake [13]. The user is able to take the picture of their food and feed the nutrient information (including carbohydrates, protein, lipids, etc.) as the input to this model. Then the model can predict the probable effects of that specific meal on the concentration of ATP inside the cell as it can be a good measure of the energy level inside the cell and generally for the whole body.

The other application of the proposed model is to monitor and simulate the concentration of other metabolites such as glucose and insulin. Using this model, the glucose levels and insulin are able to be followed.

C Glucose-Insulin Model

In order to study the model described in the previous section, we add a glucose-insulin layer on top. The effects of insulin levels on the production of ATP is studied using this layer. Insulin was chosen because of its importance in the control of blood glucose and its implication in diabetes [14]. Therefore, this model will enable us to study the glucose-insulin response in cases of diabetic patients and possible generate advisory feedback on the dietary intake to the patients.

Two sub-models are required to model the uptake of glucose by a cell. Firstly, the variation of glucose and insulin levels in the blood needs to be modelled. Second, the model of glucose uptake by cells would need to be modelled. Glucose-insulin levels are obtained from [15]. Although the initial model is explained in rats, it can be easily adopted in humans. In order to utilize the model, some parameters are required to be estimated. There is an advantage of estimating the parameters individually for each case. As every person's response to food intake is different, estimating the parameters allows to account for these variations. Further, as described in [16] the glucose response varies based on the time of day. This can be incorporated into the model by estimating the parameters for different times of the day.

As it is a model of glucose-insulin metabolism, to estimate the parameters, blood glucose and blood insulin levels for up to 100 minutes after food intake at 15 minute intervals need to be considered. With the parameters estimated, the variation of blood glucose, blood insulin and intestinal glucose for each time step dt can be simulated.

The interaction of blood glucose with cells gives the uptake of glucose by cells. This interaction is studied in [17]. The model is simplified as a sigmoid function and fitted to the available data. Based on the blood glucose levels the cell glucose levels can then be estimated.

III. IMPLEMENTATION

Based on the methods described in Chapter II, a tool was implemented using Java programming language to perform a stand-alone tool for the simulation purposes. The main objective in the design of the program was to reduce the process time and maximize the flexibility of the tool compared to the commonly used simulation software such as COPASI [4] in which the user

is limited to general settings without being able to consider the food intakes easily.

The implemented model includes the SBML parser that extracts all the usable data for the simulations, including the reaction parameters, specie parameters, the forward and reverse reaction rates, the initial concentrations, the favorability of the reactions and so on, which is demonstrated in Figure 3. The data extracted from the SBML model will be used to generate the inputs required for the simulator. As Java was used to develop this tool, JSBML [18] library was used to extract the required data from the SBML model. The reactions in the model are extracted using the data gathered from KEGG metabolic pathways, while the user can use any other SBML-form models instead.

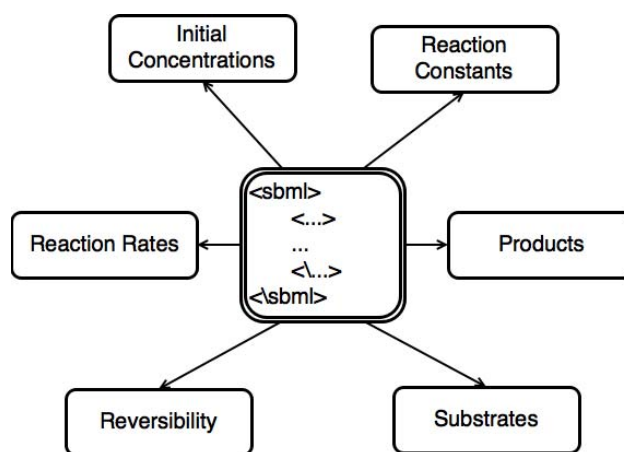


Figure 3: The structure of the extracted data from the SBML model for the proposed tool

The backbone of the model, developed in this paper, is the Glucose cycle which main pathways included in its model are the glycolysis and TCA cycle pathways. Using the other pathways such as protein and lipid pathways, the model was completed to be used in the developed tool.

Several other arguments were added to the program to make the user able to do variety of simulations based on the test cases. The simulation time and the number of steps will give the user this ability to change the simulation settings. The user is able to see each compartment separately as the specific output. Besides, the user can use his/her own initial concentrations for the given model as even for the same models, the initial concentrations may be different, reflecting the variations in the individual baseline metabolism. The user is also able to import the genomics data, e.g., gene expression data, to do the adjustments on the reactions according to the expression level of each gene in the samples. The gene expression levels generally do not represent all the protein levels, but their change can show a trend of change in some enzyme concentrations.

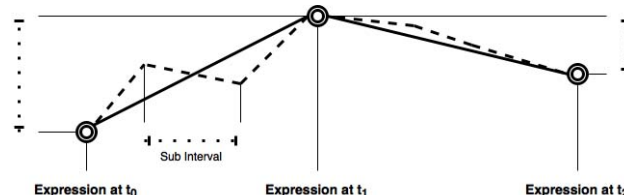


Figure 4: The gene expression level effect on the reaction rates

Figure 4 shows the model we used in this paper to consider the gene expression data into account to adjust the reaction rates, which are basically affected by the activity of the enzymes inside the cell. Based on the database, each gene can refer to one or more enzyme, which makes its analysis important. The expression data starts from a base and affects the rates gradually with some random behavior based on the user's preference until it reaches to the next time interval of the gene behavior simulation. A linear interpolation model was used to represent the change in the expression levels between the two different time frames. In between, based on the user's choice, the step sizes are implied to affect the rates with the semi-randomized behavior of %10 initially. The level of randomization used in this tool is adjustable by the user, which makes the tool able to analyze the high-level entropy analysis in some of the biochemical models. It is also visible in Figure 4 that, the lower gap between the expression levels end into lower distortion between the gene expression effect steps. Therefore, for the periods that there is no gene expression available, the model is still usable.

We also took the constant gene expressions or no expression into our considerations to give the user more flexibility on considering gene expressions into account.

Another argument was added to the tool to make it able to consider the food uptake into the cell. This feature has been added to the tool in order to make this tool viable for a variety of research studies to consider food intake in metabolic simulations like the tool that has been developed in [13]. Given the values for the amount of carbohydrate, lipids, sugar, and proteins in the given meal, alongside with the subject's weight, the tool can find the concentration change in each of the metabolites in the model. This was processed based on the assumption that blood makes almost 7% of the human and 5% of the mouse weight [19]. The added substrates into the blood stream will make a stepwise change in the concentration for each injection, which the number of injections for each meal is defined by the user. In this case, the user has the ability to change the behavior of the food consumption based on the problem description. The tool is developed in a way that it finds the related metabolites in the model to add the added concentrations directly in each specific step based on the user's preference. The protein uptake is more complex as the main amino acids should be considered based on their molecular weights to find the number of moles added to the system.

$$C_{i_{n+1}} = C_{i_n} + \frac{C_g}{MW_i \times W \times BP} \quad (6)$$

where, $C_{i_{n+1}}$ is the $n + 1^{\text{th}}$ iteration concentration of the metabolite i , C_{i_n} is the same parameter for iteration n , C_g is the gram weight of the injected metabolite, MW_i is the molecular weight of the metabolite, W is the body weight lb and BP is the blood percentage in the body for that specific specie found in [19].

As per the process described in [15] the parameters required to simulate the blood glucose levels need to be calculated. By utilizing the curve fitting tool in MatLab and the equations in [15], a script is written to estimate these parameters. The script takes the blood insulin and glucose curves as input and

calculates the required parameters. These parameters are then fixed into the simulation of the blood glucose curves.

From [20] it is seen that carbohydrates are readily converted to glucose in the blood stream. Therefore, the model focuses on the carbohydrates in the food ingested. The ingested food is translated to available glucose present in the intestines. The blood glucose, blood insulin and intestinal glucose are then simulated along with the kinetic simulation of the cellular state. The glucose uptake by the cell is taken as a sigmoid function of the blood glucose.

In order to run the kinetic model on OSG, a stand-alone jar file is created. The jar file and other required input files are then packaged into a tar file. A wrapper script is written to extract the files and execute the jar file with the required arguments. Based on the process number, the input files are selected and the simulation is run. Once the simulation is finished the output files are then compressed into a tar file and transferred back to the client system.

By utilizing the OSG, the simulation was run for model optimization by using various initial concentrations of cell compounds. As described, the example simulation is run for hundred different combinations of initial concentrations. A single run takes 48 seconds on a local system, therefore the total run time for 100 simulations is approximated to be 80 minutes. On the OSG, the total runtime after submission was measured to be a 1.2 minute, which gives an estimated speedup as 66.67.

IV. DISCUSSIONS AND RESULTS

The model implemented in the previous chapter, is now ready to be run on OSG. By running the tool in OSG, after designing and implementing the model of reactions, enzymes, and initial concentrations gathered from different databases such as HMDB and other references and literature, e.g., [21], various behaviors were observed from the output from different aspects of view.

As of the first implementation of the program, the tool was run using the given model and initial concentrations for the three different meals to observe and monitor the ATP level inside the cell as the measure of energy level.

Figure 5 illustrated the body's response to starvation and to the intake of three meals (breakfast, lunch and dinner) by the user with the moving window of 100 seconds. In this example, the user has consumed 118 grams of banana (1 medium size) with 244 grams of 2% milk (1 cup) as the breakfast at 8am, 185 grams of white rice with 100 grams of chicken breast for the lunch at 12pm, and 182 grams of apple with 178 grams of pear at 6pm as dinner. Here, we set 100 seconds as interval in a period of 1 hour for each small portion of the meal to be absorbed.

After running the simulations, the ATP and glucose concentrations are shown starting from 8am within a day. In Figure 5(a), the glucose concentration is shown for the entire day in the starvation state. Once starvation starts, the free glucose is consumed at first; then, glycogen starts to be consumed for the next 8 to 10 hours to maintain the glucose level in normal condition. If glycogen is completely burned, the third phase will start by consuming the fat resources. Figure 5(b) and (c) show the trend of glucose and ATP concentration with three different meals during a day, respectively. In Figure 5(d), an arbitrary periodic load was applied to the system to mimic the ATP consumption captured by the exercise tracker. At the end in

Figure 5(e), the overall ATP balance after applying the load has been demonstrated where the ATP concentration goes to the same level at 8am of the previous day. This information is helpful to alert the user to adjust his/her diet and exercise to manipulate the energy balance.

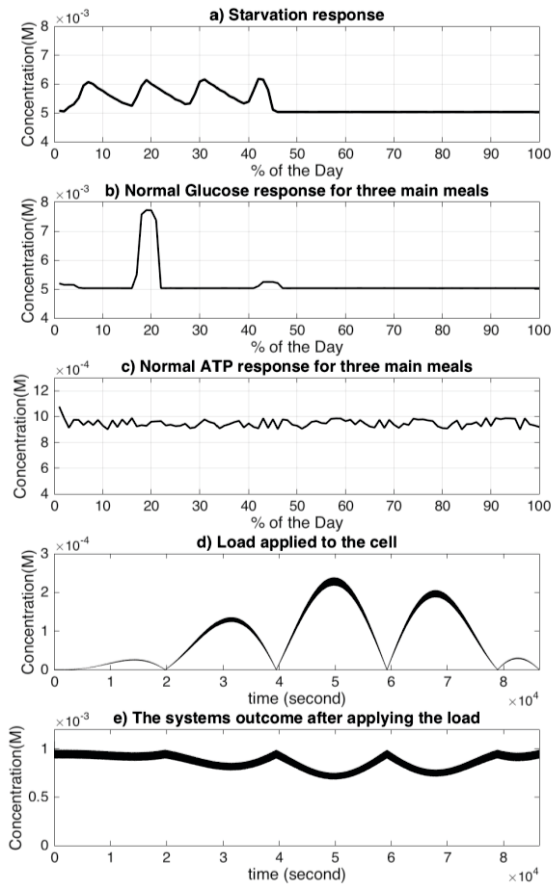


Figure 5: (a) Glucose concentration in starvation state, (b) Glucose concentration for a normal diet of three main meals within a day, (c) ATP concentration of the normal diet, (d) the load applied to mimic the activity (the ATP consumption) captured by exercise tracker, and (e) the ATP concentration for one day after applying the given load.

Figure 6 shows the glucose and ATP level correlations for the first 13 minutes. As it is demonstrated, there is a delay of almost one minute, until ATP level maintains and keeps in the same level as there is no external energy consumption. This shows the feasibility of the proposed model and ensures that the proposed tool is applicable for the other models and test cases.

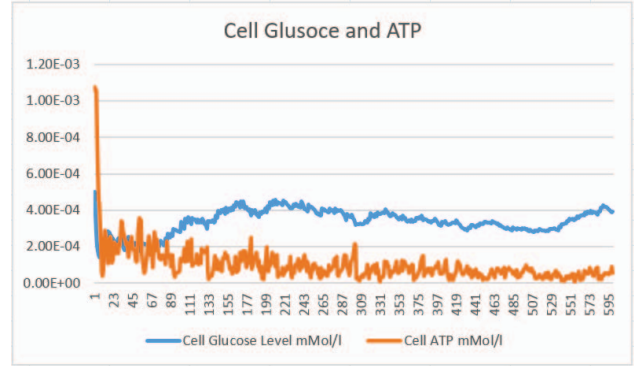


Figure 6: Glucose and ATP level change during the first 13 minutes

Figure 7 represents the systems input in terms of blood glucose that is fed to the cell. The simulation results are similar to [14] as the same mathematical model is used. Blood glucose levels obtained from human subjects can be seen in [16]. Its response is similar to the levels obtained here.

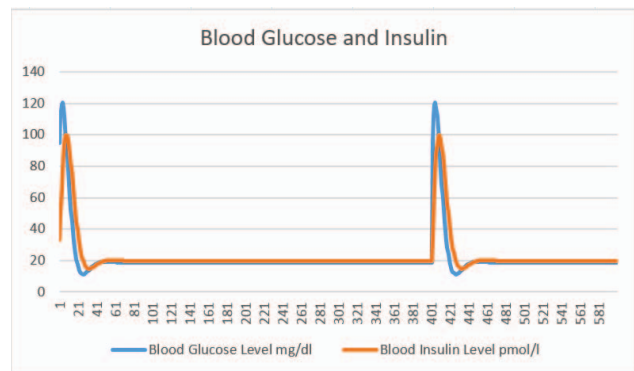


Figure 7: Glucose-Insulin correlation tested using the proposed model.

Below are results obtained from running the simulation for various initial concentrations. Figure 8 shows the typical glucose response when the initial glucose level is high. Both glucose and ATP respond well to the glucose input.

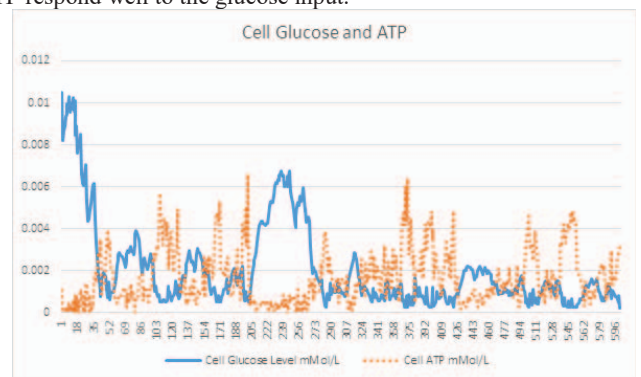


Fig 8 cont...

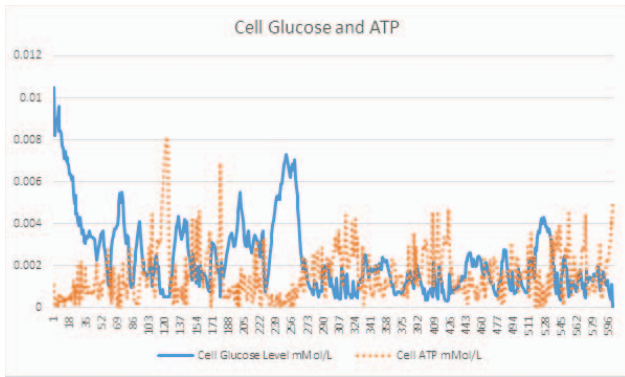


Figure 8: Graph showing Glucose and ATP response for two simulations with high initial glucose levels.

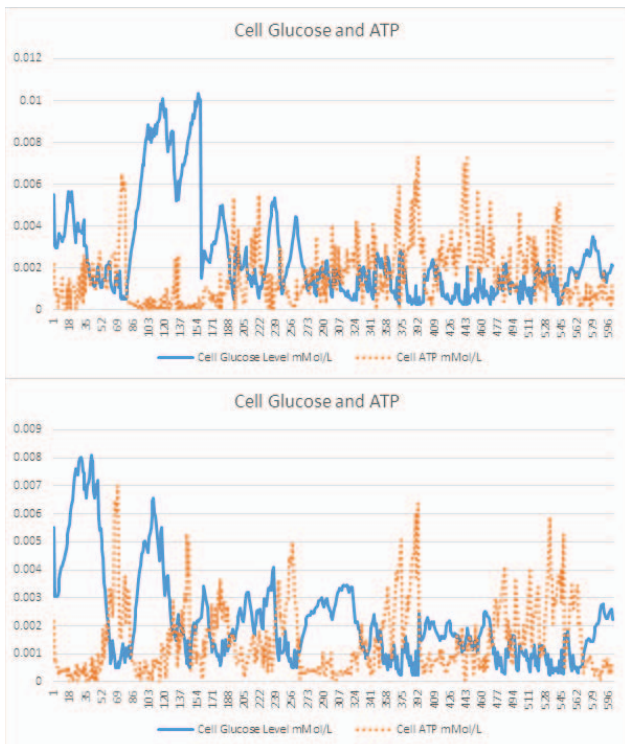


Figure 9: Graph showing Glucose and ATP response for two simulations with moderate initial glucose levels.

Figure 9 shows the glucose ATP response when initial glucose levels is moderately high. Although the overall glucose levels are lower, the ATP levels are high.

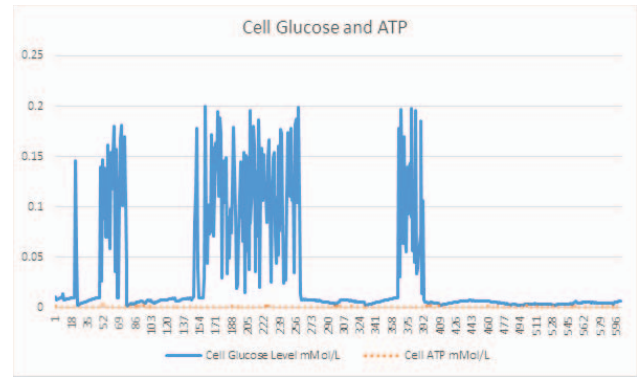
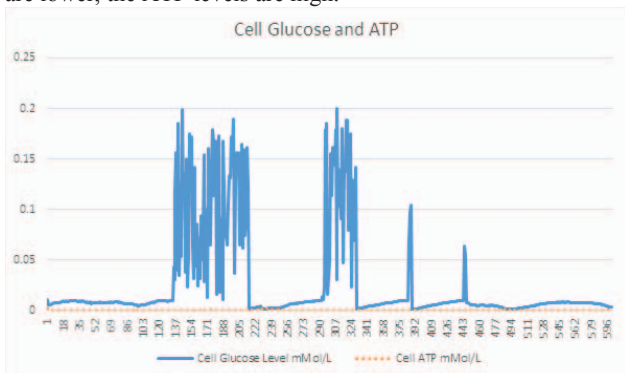


Figure 10: Graph showing Glucose and ATP response for two simulations with low initial glucose levels.

Figure 10 shows the response when the initial glucose concentrations are low. Due to low glucose, the ATP levels reach a stable level, causing them to not respond immediately when glucose levels increase.

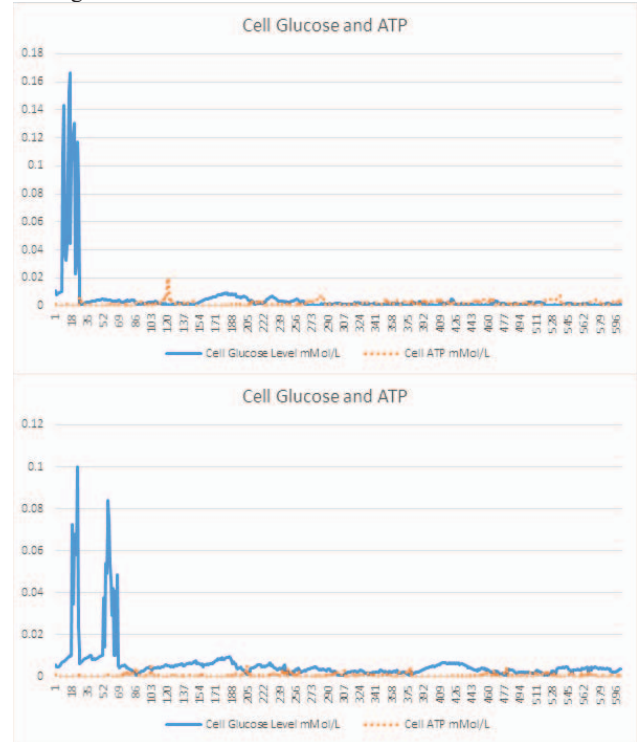


Figure 11: Graph showing Glucose and ATP response for two simulations with low start and ramped up initial glucose levels.

Figure 11 shows low initial glucose levels where the glucose levels are ramped at the initial steps, however the ATP levels do not respond. Once the glucose levels reach a stable value, the values do not respond well to the blood glucose input.

V. CONCLUSION

This paper presents a new tool to simulate the concentration of species participating in the metabolic pathways using the SBML model of the reactions. Using the current databases, the SBML model and the other required values were extracted to make a reliable model, while the user can import any modified

SBML model that satisfies the requirements of the metabolic pathways. Our proposed tool used this model to analyze the ATP level inside the cell as a measure of energy level. Then, this model was used to monitor the change of glucose level in parallel with insulin. This comparison gives a comprehensive understanding on the abilities of the proposed tool.

VI. FUTURE WORK

Our work in the design, implementation and test of the glucose-insulin stand-alone simulation tool is expandable to the other aspects of the research already performed in bioinformatics. Using other numerical simulation methods such as Runge-Kutta [22] will increase the stability of the given simulation accordingly. Besides, the proposed tool can be further modified by using a high-quality estimation of the enzymatic activity, e.g., from gene expression data or the metabolic profiles, to fully realize the simulation of customized metabolism.

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