Biblid: 1821-4487 (2019) 23; 1; p 32-37
UDK: 591.133.1

Original Scientific Paper
Originalni naučni rad

APPLICATION OF CELLDESIGNER PROGRAM FOR NUTRITION PLANNING AND FOOD SAFETY CONTROL

PRIMJENA CELLDESIGNER-A ZA PLANIRANJE PREHRANE I KONTROLU SIGURNOSTI HRANE

Lucija MARIĆ, Elena MALEŠIĆ, Katarina ŠANKO, Tamara JURINA, Davor VALINGER, Jasenka GAJDOŠ KLJUSURIĆ, Maja BENKOVIĆ, Ana JURINJAK TUŠEK
University of Zagreb, Faculty of Food Technology and Biotechnology, Pierottijeva 6, 10000 Zagreb, Croatia
e-mail: mbenkovic@pbf.hr

ABSTRACT

In this work the application of CellDesigner 4.0 (Systems Biology Institute, Tokyo, Japan) for nutrition planning and food safety control was tested using three models: (i) metabolic model ofglycolysis, (ii) folate-mediated 1-carbon metabolism and (iii) metabolism of arsenic in humanliver. Each model was simulated with a few different initial nutrient concentrations and enzyme activities. After model design and simulations in CellDesigner, it can be concluded that the use of computational tools enablefast and reproducible analysis of different input concentrations and different enzyme activity effects on specific metabolic process in the human organism. Application of computational modelling for nutrient related pathway analysis ensures a detail insight in metabolic process and simple control of the metabolic reaction affectedby nutrient intake. Computational approach also simplifies prediction of potential hazards in foods, as demonstratedby metabolism ofarsenicexample.

Key words:*CellDesigner, mathematical modelling, nutrition planning, food safety.*

REZIME

U ovom radu istražena je primjena programa CellDesigner 4.0 (Systems Biology Institute, Tokio, Japan) u svrhu planiranja prehrane i kontrole sigurnosti hrane na tri različita primjera: (i) modelu metabolizma glikolize, (ii) modelu metabolizma 1-C ugljikovih spojeva potpomognutih folatom i (iii) modelu metabolizma arsena u jetri. Provedena je simulacija modelakorištenjem različitih početnih koncentracijanutrijenata terazličitih aktivnosti ključnih enzima. Na temelju rezultata dobivenih simulacijom modela u programu CellDesigner može se zaključiti da upotreba računalnih alata omogućuje brze i ponovljive rezultate analiza primjenom različitih ulaznih koncentracija, kao i utjecajem različitih enzimskih aktivnosti na specifični metabolički put u ljudskom organizmu. Upotreba računalnog modeliranja za metaboličke puteve nutrijenata osigurava detaljan uvid u metaboličke procese i jednostavnu kontrolu metaboličkih reakcija koje se temeljena unosu nutrijenata. Matematičko modeliranje također omogućavapraćenje promjena, ovisno o unosu nutrijenata u stanicu, dajući uvid u ono što se događa u situacijama kada je pojedini nutrijent dominantan. Računalni pristup također pojednostavljuje predviđanjepotencijalnih kontaminanata u hrani, što je vidljivo iz primjera metabolizma arsena u jetri.

Ključne riječi:*CellDesigner, matematičko modeliranje, planiranje prehrane, sigurnost hrane.*

INTRODUCTION

Over the last few years, the implementation of systems biology in nutrition research has proven to be a very powerful tool for understanding the mechanisms by which food components influence health and/or prevent diseases. Also, systems biology simplifies the detection of biologically active molecules involved in metabolic mechanisms. Systems biology creates large data sets using and combining genomics, proteomics and metabolomics knowledgeand enables a more extensive analysis of individual responses to individual nutritional interventions thus providing a comprehensive understanding of how a particular diet can affect both health and disease (*Badimon et al*., 2017).It is anticipated that this approach will further enlighten the molecular and biochemical interactions that take place in the cell. Acquired knowledge will lead to an improved understanding of how cellular dynamics affect tissues and the entire organism. Computer modelling provides an alternative way of solving statedcomplexity of interactions in the cell and facilitates the representation of metabolic processes for different nutrients. There are open model-oriented databases such as the BioModels Database that contains models in SBML(Systems Biology Markup Language) format that enable the exchange in computationalmodels (*Hucka et al.*, 2004).

Almost all cellular processes, ranging from gene expression to synthesis and protein degradation, may be prejudiced by diet and lifestyle. Nutritive and non-nutritive components affectmetabolic changes in the cellin a complex way. Similar to the mechanism of drugaction, each food component affects the setof metabolic reactions acting differently depending on the components. Researches in this field are still at the beginning, and emphasis has been placedon designing strategies to explain the effects of individual food components on the cell functions. Manipulating effects of individual food components on the cell functions could make significant improvement in the prevention and/or treatment of some chronic diseases today (Panagiotou *and Nielsen*, 2009).

Complementing knowledge will enable a better understanding and prediction of qualitative and quantitative correlations between a particular dietary pattern or nutrients input and their impact on health..

One of the key roles of this promising area within nutrition field is the principle of personalized nutrition according tonutritional (national) recommendations which greatly affect the treatment or prevention of metabolic disorders. Precise individual guidelines would provide a dynamic approach to classical dietary recommendations that would include parameters of the inner and outer human system that are almost constant in interactions (*de Toro-Martín et al*., 2017). In addition to the genetic effect, such recommendations would also includethe effect of nutritional habits, nutritional behavior, physical activity, a set of microbiota and metabolic reactions.

In this work the application of CellDesigner 4.4 (Systems Biology Institute (SBI), Tokyo, Japan) for nutrition planning and

food safety control was tested usingthree models: (i) *metabolic model ofglycolysis*, (ii) folate-mediated 1-carbon metabolism and (iii) *metabolism of arsenic in human liver*. Each model was simulated with different initial nutrient concentrations and with different enzyme activities.

MATERIALS AND METHODS

Materials

Programe

CellDesigner version 4.4 and MS Excel 2016 (Microsoft, USA) were used in this work. CellDesigner is a computer program used to illustratebiological processes in the cell, such as graphically displaying biochemical and gene regulated networks (*Klipp et al.,* 2010). The main features of the program include: description of biochemical semantics, detailed description of the protein state change, support of SBLM (SBLM, Systems Biology Markup Language) format which describes models of biochemical reactions, an integration with SBW (SBW, Systems Biology Workbench) simulations and SBLM simulation library and possibility to browse and modify models converted from exiting databases (*Funahashi et al., 2003*).

Model of the glycolysis metabolism

Mathematical model of glucose metabolism in liver cells developed by *König et al*., 2012 was analysed. The model includes 36 biochemical reactions, 44 metabolites, and 185 kinetic parameters.

Model of the folate-mediated 1-carbon metabolism

In this paper, a mathematical model describing folate mediated 1-carbon metabolism was analysed (*Reed et al*., 2004). Model is based on information of folate - enzymatic kinetics and regulatory mechanisms that predict the influence of genetic and nutritional variationsand describes processes in cellular cytosol. The model includes 19 biochemical reactions, 10 metabolites and 60 kinetic parameters.

Model of arsenic metabolism in the liver

To analyse the processes occurring in liver cells in the presence of the arsenic atom, a semi mechanistic mathematical model including the toxic-kinetic phenomena developed by *Stamatelos et al*. (2011) was used. The model describes the transport of arsenic via the cell membrane and arsenic metabolism in liver cells.

Methods

Construction and simulation of the glycolysis metabolism model in CellDesigner

Simulations of glycolysis metabolism were performed using the model constructed in the CellDesigner program. The effect of different initial glucose concentrations ($c_{0,GLC}$ = 4.0, 5.0, 6.0, 7.0 and 7.7 mmol/L) on the degradation rate of glucose in the glycolysis was investigated, as well as the effect of reduction (for 3 %, 5 % and 10 %) of the maximum reaction rates of the key enzymes included into the glycolysis pathway (glucokinase, phosphofructokinase, pyruvate kinase) on the degradation rate of glucose ($c_{0,GLC}$ = 5 mmol/L). The results obtained by computer simulation in CellDesigner were graphically displayed using the Microsoft Excel 2016 program.

Construction and simulation of folate-mediated 1-carbon metabolism model in CellDesigner

Simulations of folate mediated 1-carbon metabolism were performed usingthe CellDesigner program. During the experiment, the initial folate concentration in the cell ($c_{0,FOLATE}$ = 3, 30 and 60 nmol /L) has been varied as the input parameter. According to *Reed et al*., 2006 the initial folate concentration is comprised of concentrations of THF (tetrahydrofolate), SAM (S-adenosyl-L-homocysteine) and 5mTHF (5-methyltetrahydrofolate).The effect of reducing the maximum reaction rate (for 10 %) of the key enzyme included into folate metabolism, methionine synthase on the concentration of tetrahydrofolate and methionine was also investigated. The values obtained by computer simulation in CellDesigner were graphically displayed using the Microsoft Excel 2016 program.

Construction and simulation of arsenic metabolism in liver model in CellDesigner

Simulations of the arsenic metabolism model were carried out, with different initial amounts of arsenic based on the concentrations of arsenic in groundwater in the Republic of Croatia. Considering the average daily water intake of 2 L, using the data on arsenic concentration in drinking water in Slavonia (*Habuda-Stanić et al.*, 2006, *Ćavar et al*., 2004), the initial arsenic amountsfor simulation of arsenic metabolism in the liver were calculated. Simulations were performed for four initial amounts of $n_{0,As}$ = 0.10 mmol, $n_{0,As}$ = 1.010 mmol, $n_{0,As}$ = 4.576 mmol and $n_{0,As}$ = 16.317 mmol in a time interval of t = 4000 min.

RESULTS AND DISCUSSION

Analysis of glycolysis metabolism model in CellDesigner

The use of CellDesigner for biochemical simulation is very widespread due to simple visualization and presentation of the logic and dynamics of complex reactions involved in most metabolic pathways (*Funahashi et al*., 2003).Theliverglycolysis modelconstructed in CellDesigner is given in Figure 1. The degree of glycolysis can be determined based on measurements of the enzyme activity that catalyses the irreversible, one-way reaction: hexokinase (in the liver glucokinase), phosphofructokinase and pyruvate kinase. According to*Mali et al*. 2016,the activity of mentioned enzymes in diabetic patients decreases and returns to normal 24 hours after insulin therapy. Patients suffering from type II diabetes, have lower levels of insulin hormone which is a key to glucose homeostasis regulation thus leading to the conclusion that glycolysis enzymes are not completely inhibited.Their activity is reduced as much as necessary for the metabolism of smaller amounts of glucose that try to enter the cell (*Lee et al*., 2014). The effect of different initial glucose concentrations ($c_{0,GLC}$ = 4, 5, 6, 7 and 7.7 mmol/L) at the glucose degradation rate in the glycolysis was investigated. After a meal rich in carbohydrates, blood glucose concentrations increased to about $c_{0,\ GLC}$ = 5mmol/L, which is also a reference value for the period of hunger. The diagnosis of diabetes mellitus is established if glucose in the blood is overc$_{GLC}$ = 7 mmol/L after overnight starving or if at any time during the day the value was greater than c_{GLC} = 11.1 mmol/L (*Bergman Marković*, 2014). Results obtained fromCellDesigner simulation arepresented in Figure 2, from which is apparent that the glucose concentration decreased over time.

The most significant decrease was observed for simulation with $c_{0,GLC}$ = 4 mmol/L within the first hour. The glucose concentration decreased under c= 3 mmol/L showing the conditions when the hypoglycaemia occurs.

The glucose value of $c_{0,\ GLC}$ = 7 mmol/L declined within t = 2.5 hours to the value of c_{GLC} = 5 mmol/L, which is in consistency with the literature (*Bergman Marković*, 2014). The results of the glycolysis simulation with the maximum glucokinase reaction rates reduced for 3%, 5% and 10% showed that reducing the maximum reaction rate slows down the glucose degradation. On the other hand, simulation results also determined that by reducing the maximum reaction rate ofphosphofructokinaseas well aspyruvate kinase for 3%, 5% and 10%, glucose degradation occurredfaster. Phosphofructokinase is allosterically regulated by a series of effectors (ADP, AMP, cAMP, fructose-1, 6-bisphosphate, fructose-2,6-bisphosphate, ATP, citrate, phosphoenolpyruvate).

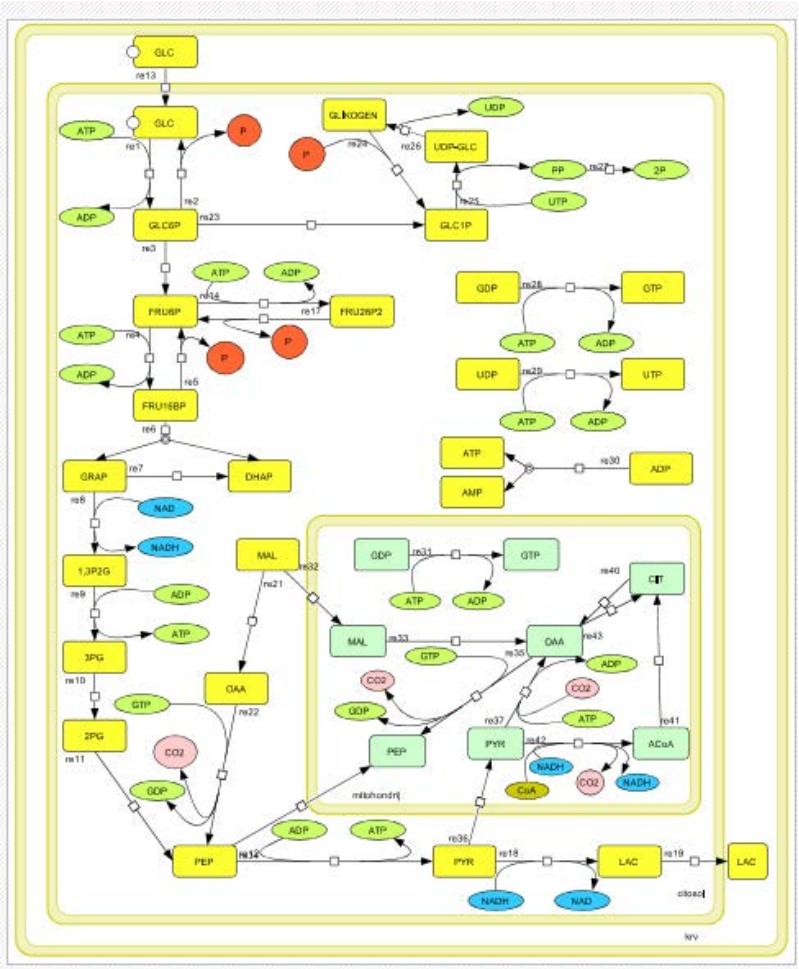

Fig. 1. Glycolysis model constructed in CellDesigner ((1,3P2G) 1,3-bisphospho glycerate,(2PG) 2-phospho glycerate, (3PG) 3-phospho glycerate, (ACoA) acetyl-coA, (CIT) citrate, (CoA) coenzyme A, (DHAP) dihydroxyacetone phosphate,(FRU16P2) fructose-1,6 bisphosphate, (FRU26P2) fructose-2,6 bisphosphate, (FRU6P) fructose-6 phosphate, (GLC) glucose, (GLC1P) glucose-1 phosphate,(GLC6P) glucose-6 phosphate, (GRAP) glyceraldehyde 3-phosphate, (LAC) lactate, (OA) oxalacetate, (MAL) malate, (P) phosphate, (PEP)phosphoenolpyruvate, (PP) pyrophosphate, (PYR) pyruvate, (UDP-GLC) UDP-glucose, (ATP) adenosine 5'-triphosphate, (ADP) adenosine 5'-diphosphate, (AMP) adenosine 5'-monophosphate, (GTP) guanosine-5'-triphosphate, (GDP) guanosine-5'-diphosphate, (UTP) uridine-5'-triphosphate, (UDP) uridine-5'-diphosphate, (NAD) nicotinamide adenine dinucleotide

The rate of glycolysis depends on the concentration of all listed effectors. Glucose from glycogen in muscles directly enters glycolysis. The liver stores a large amount of glycogen, which is broken down as needed, and sends glucose to other parts of the body where it is missing. At a certain glucose concentration, saturating the active sites on the substrate-binding enzyme results in the substrate being no longer able to bind, thereby making the maximum reaction rate constant. The effect of reducing the maximum reaction rate (3%, 5% and 10%) of the key glycolysis enzymes (glucokinase, phosphofructokinase, pyruvate kinase) on the glucose degradation rate ($c_{0,GLC}$ = 5 mmol/L) was also analysed (Figure 3).

Analysis of folate-mediated 1-carbon metabolism model in CellDesigner

Model of folate-mediated 1-carbon metabolism in the cellular cytosol constructed in the CellDesigner program is given in Figure 4.In this study, computer program CellDesigner was used for analysis of folate metabolism which is a mediator in many other key metabolic processes such as nucleotide synthesis, DNA methylation andreplication, amino acid metabolism, etc. The folate concentration is closely related to other metabolic components, whose concentration changes are dependent on the amount of folate in the cell and the metabolic activity of the responsible enzymes. Also, complexity of this metabolism is manifested in the presence of allosteric inhibition, activation and mutually interconnected reactions of two cycles (folate and methionine). Namely, many substrates within these two cycles have the role of inhibitors of their metabolic enzymes despite the fact that they do not participate directly in some chemical reactions, therefore the reaction rate and substrate concentration were not directly proportional to the cellular concentration of folate. The effect of different initialfolate concentrations ($c_{0,FOLATE}$ = 3, 30 and 60 nmol/L) on the concentration of formed homocysteine, tetrahydrofolate and 5-methyltetrahydrofolate was investigated. Although the concentrationof serum folate is variable and dependsondietary intake, a reference interval of serum folate is $c_{0,FOLATE}$ = 11-57 nmol/L (*Pagana and Pagana*, 2013) thus the values of initial concentrations of folate $c_{0,FOLATE}$ = 3 nmol/L were used for the case of extreme folate deficiency, $c_{0,FOLATE}$ = 30 nmol/L for normal folate level and $c_{0,FOLATE}$ = 60 nmol/L for serum folate values slightly higher than recommended. The changes of homocysteine concentration with respect to three different initial folate values are presented in Figure 5. In the first case ($c_{0,FOLATE}$ = 3 nmol/L) concentration of homocysteine grows to approximately c_{HCY} = 0.55 nmol/L and after a time period of t = 20 h its concentration continues to grow. In the second ($c_{0,\ FOLATE}$ = 30 nmol/L) and third ($c_{0,\ FOLATE}$ = 60 nmol/L) case, the level of homocysteine reaches the highest value after an hour after which it decreases and achieves a constant value of c_{HCY} = 0.198 nmol/L and c_{HCY} = 0.174 nmol/L respectively.According to *Ganguly and Alam, 2015*homocysteine is known to mediate cardiovascular problems by its adverse effects on cardiovascular endothelium and smooth muscle cells with resultant alterations in subclinical arterial structure and function.Elevated plasma homocysteine concentration is considered a risk factor for cardiovascular disease.

Given that vitamin B_{12} is a critical cofactor of methionine synthase enzymes, the effect of B_{12} deficit on the metabolism rate and the amount of its metabolites was analysed by reducing methionine synthesis activity by 10%, consistent with patients with a serious vitamin B_{12} deficiency.

The effect of maximum reaction rate of methionine synthesisreduction (by 10%) on concentration of produced tetrahydrofolate and is given in Figure 6.After t = 20 h, the concentration of the produced tetrahydrofolate was84% lower than the concentration of produced tetrahydrofolate under normal conditions, whatcan be compared toa change of 73% (*Reed et al*., 2004).

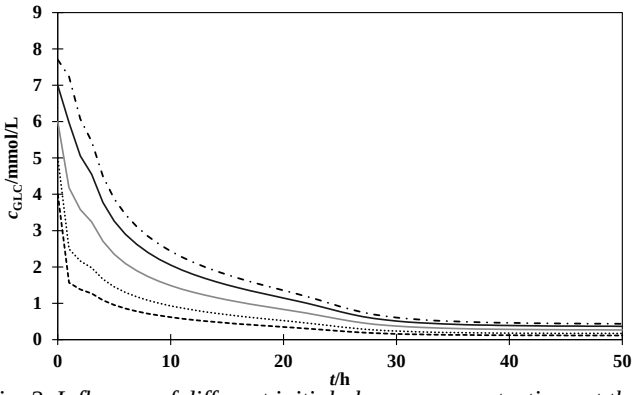

Fig. 2. Influence of different initial glucose concentrations at the rate of glucose degradation. (---) $c_{0,GLC}$ = 4 mmol/L, (···) $c_{0,GLC}$ = 5 mmol/L, (—) $c_{0,GLC}$ = 6 mmol/L, (—) $c_{0,GLC}$ = 7 mmol/L, (-·-·-) $c_{0,GLC}$ = 7.7 mmol/L

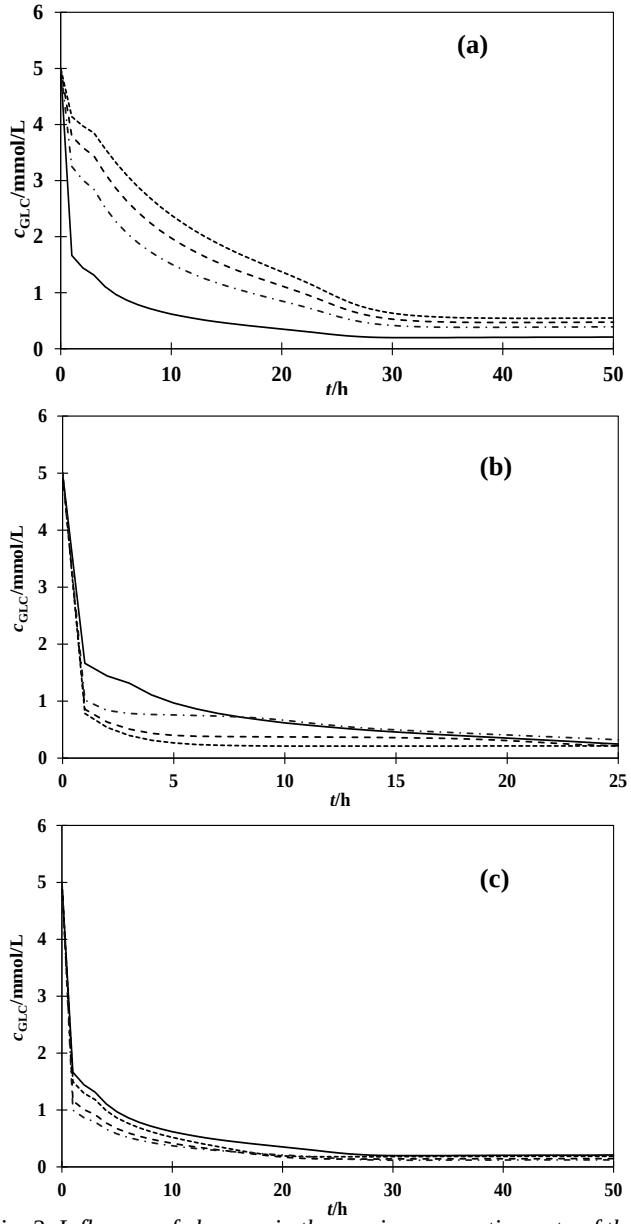

Fig. 3. Influence of changes in the maximum reaction rate of the enzymes: (a) glucokinase, (b) phosphofructokinase and (c) pyruvate kinase on the glucose degradation rate. (—) v_{max} according to König et al., 2012, (···)v_{max} reduction for 3 %, (---) v_{max} reduction for 5 %, (-·-·-)v_{max} reduction for 10 %. $c_{0,GLC}$ = 5 mmol/L

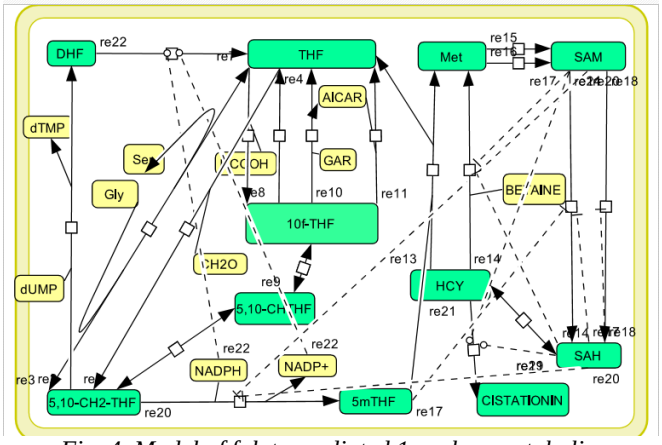

Fig. 4. Model of folate-mediated 1-carbon metabolism constructed in the CellDesigner((5,10-CH2-THF) 5,10-methylenetrahydrofolate,(5mTHF) 5-methyltetrahydrofolate (AICAR) aminoimidazolecarboxamide ribonucleotide, (SAH)S-adenosylhomocysteine,(SAM) S-adenosylmethionine,(THF) tetrahydrofolate, (HYC) homocysteine, (UMP) uridine-5'-monophosphate, (NADP) nicotinamide adenine dinucleotidephosphate, (Ser) serine, (Gly) glycine

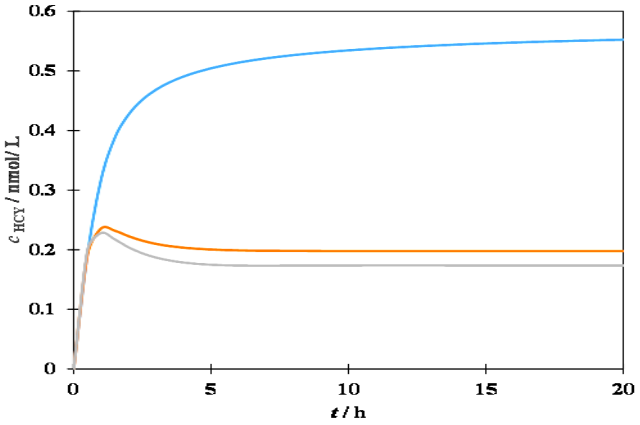

Fig. 5. The effect of folate concentration change on homocysteine level (blue-initial folate concentration: $c_{0,FOLATE}$ = 3 nmol/L, orange-initial folate concentration: $c_{0,FOLATE}$ = 30 nmol L^{-1}, gray-initial folate concentration: $c_{0,FOLATE}$ = 60 nmol/L)

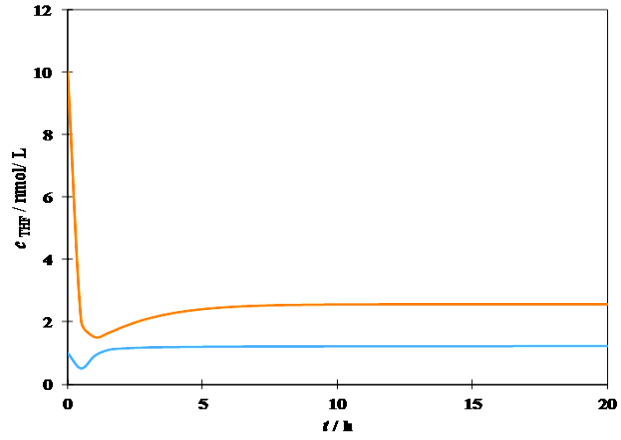

Fig. 6. The effect of the methionine synthesis maximum reaction rate reduction on the concentration of tetrahydrofolate (blue-reduced methionine synthesis activity by 10%, orange-normal methionine synthase activity)

Analysis of arsenic metabolism model in liver using CellDesigner

It is known from literature that arsenic represents a serious health problem and it is of great importance to increase knowledge about the impact of arsenic on the human body (*Cohen et al.*, 2013). The use of mathematical models ensures the reduction of necessary experiments on living cells and significantly helps in planning targeted experiments (*Tóth et al*., 2015). According to available literature, the largest share of arsenic in the human body is ingested through drinking water. In this paper, arsenic metabolic simulations were performed in liver cells with the initial amounts of arsenic obtained on the basis of measured arsenic concentrations in the waters of Slavonia.Eastern Croatia includes the area of Slavonia, the southern part of Baranja and western Srijem. The area extends between the Drava in the north, the Sava in the south, the Danube in the east. This area is one of the areas of the Pannonian Basin, which is known for its naturally increased concentrations of arsenic in groundwater. According to some estimates, approximately 500,000 people in the Pannonian basin (Hungary, Romania, Serbia and Croatia) are exposed to arsenic concentrations higher than the maximum permissible concentration prescribed by the European Union. The increased concentration of arsenic in these areas is not a consequence of desorption processes. Arsenic in the groundwater of the Pannonian basin is mainly derived from the period of the last ice age. Changes in concentrations of extracellular and intracellular arsenic, concentrations of extracellular and intracellular monomethylated arsenic and concentrations of extracellular and intracellular dimethylated arsenite were observed over a 4000 minute time interval using CellDesigner model of the arsenic metabolism in liver, given in Figure 7. At the smallest initial amount of arsenic of n_{As0} = 0.1 μmol, according to the literature there is no activation of the mechanism of oxidative stress in the cell (*Ruiz-Ramos et al*., 2009). From the simulation results, it was apparent that the fastest transfer of arsenic takes place during the first t = 100 min of the process. It has also been observed that the amount of intracellular arsenic increases in this time interval and after that time the consumption phase occurs. A time period of t = 100 min is probably needed to activate the enzymatic digestion/conversion of the introduced arsenic. From the simulation results for the extracellular arsenic it is apparent that after t = 4000 min all the arsenic is located in the liver cell.The transfer of arsenic to the liver cells is carried out through the aquaporin 9 on the basis of the difference in electrochemical potential, and it is assumed that the transmission slows down as more arsenic is introduced into the cell (*Liuet al*., 2006).

CONCLUSIONS

After model design and conducted simulations in CellDesigner, it can be concluded that the use of computational tools allows fast and reproducible analysis of different input concentrations and different enzyme activity effect on specific metabolic process in human organisms. Application of computational modelling for nutrient based pathway ensures a detail insight in metabolic process and simple control of the metabolic reaction influenced by nutrient intake. Computational approach also simplifies prediction of potential hazards in foods, as demonstrated by the arsenic example.

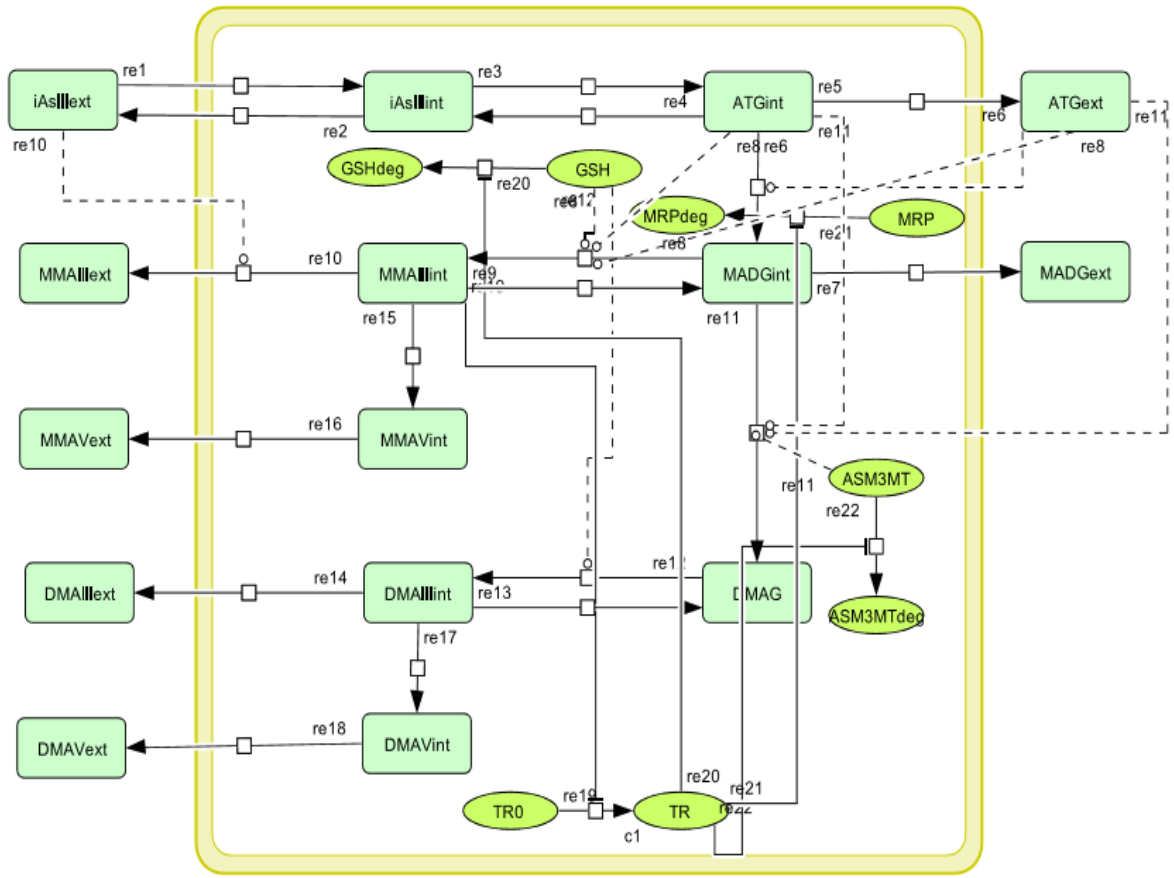

Fig. 7. CellDesigner model of the arsenic metabolism in liver. ((iAsIII) arsenite, (GSH) glutathione (MMA) monomethylatedarsenicals, (DMA) dimethylated arsenicals, (ATG) arsenic triglutathione, (MADG) monomethylarsenic diglutathione, (ASM3MT) arsenic methyltransferase.

REFRENCES

Badimon, L., Vilahur, G., Padro, T. (2017). Systems biology approaches to understand the effects of nutrition and promote health. British Journal of Clinical Pharmacology, 83, 38-45.

Bergman Marković, B. (2014). Šećerna bolest u obiteljskoj medicini. Alfa d.d., Zagreb, Croatia.

Cohen, S.M., Arnold, L.L., Beck, B.D., Lewis, A.S., Eldan, M. (2013). Evaluation of the carcinogenicity of inorganic arsen. Critial Reviews in Toxicology, 43, 711-752.

Ćavar, S., Kuleš, M., Plavšić, F. (2004). The relationship of hair arsenic concentration and different drinking water arsenic levels in eastern Croatia-pilot study. Final program and abstract book of the 3rd Croatian congress of toxicology with international participation. Plitvice, Hrvatska, 26.05.2004, 115.

de Toro-Martín, J., Arsenault, B.J., Després, J.P., Vohl, M.C. (2017). Precision Nutrition: A Review of Personalized Nutritional Approaches for the Prevention and Management of Metabolic Syndrome. Nutrients, 22, 9-18.

Funahashi A., MorohashiM., KitanoH. (2003) CellDesigner: a process diagram editor for gene-regulatory and biochemical networks. Biosilico, 1, 159-162.

Ganguly P., Alam S.F. (2015) role of homocysteine in the development of caridovasculare disease. Nutrition Journal, 14, 6-15.

Habuda-Stanić M., Kuleš M., Kalajdžić B., Romić Ž. (2006) Quality of groundwater in eastern Croatia. The problem of arsenic pollution. Desalination, 1-3, 157-162.

Hucka, M., Finney, A., Bornstein, B.J., Keating, S.M., Shapiro, B.E., Matthews, J., Kovitz, B.L., Schilstra, M.J., Funahashi, A., Doyle, J.C., Kitano, H. (2004) Evolving a lingua franca and associated software infrastructure for computational systems biology: the Systems Biology Markup Language (SBML) project. Systems Biology, 1, 41-53.

Klipp E., Wade R.C., Kummer U. (2010) Biochemical network-based drug-target prediction. Current Opinion in Biotechnology, 21, 511-516.

König M., Bulik S.,Holzhütter H.G. (2012) Quantifying the Contribution of the Liver to Glucose Homeostasis: A Detailed Kinetic Model of Human Hepatic Glucose Metabolism. Computational Biology, 8, 6-12.

Lee D. W., Gardner R., Porter D. L., Louis C. U., Ahmed N., Jensen M., Grupp S. A., Mackall C. L. (2014) Current concepts in the diagnosis and management of cytokine release syndrome. Blood, 124, 188-195.

Liu, Z.J., Sanchez, M.A., Jiang, X., Boles, E., Landfear, S.M., Rosen, B.P. (2006) Mammalian glucose permease GLUT1 facilitates transport of arsenic trioxide and methylarsonous acid. Biochemical and Biophysical Reserach Communications, 351, 424-430.

Mali A. V., Bhise S. S., Hegde M. V., Katyare S. S. (2016) Altered erythrocyte glycolytic enzyme activities in type-II diabetes. Indian Journal of Clinical Biochemistry, 31, 321-325.

Pagana K. D., Pagana T. J. (2013) Mosby's Manual of Diagnostic and Laboratory Tests 4th Ed., Elsevier, pp. 445.

Panagiotou G., Nielsen J.(2009) Nutritional systems biology: definitions and approaches. Annual Review of Nutrition 29, 329-339.

Reed M. C., Nijhout H. F., Neuhouser M. L., Gregory J. F., Shane B., James S. J., Boynton A., Ulrich C. M. (2006) Amathematical model gives insights into nutritional and genetic aspects of folate-mediated one-carbon metabolism. The Journal of Nutrition 136, 2653 – 2661.

Reed M. C., Nijhout H. F., Sparks R., Ulrich C. M. (2004) A mathematical model of themethionine cycle. Journal of Theoretical Biology 226, 33 – 43.

Ruiz-Ramos, R., Lopez-Carrillo, L., Rios-Aperez, A.D., De Vizcaya-Ruíz, A., Cebrian, M.E. (2009) Sodium arsenite induces ROS generation, DNA oxidative damage, HO-1 and c-Myc proteins, NF-kappaB activation and cell proliferation in human breast cancer MCF-7 cells. Mutation Research 674, 109-115.

Stamatelos, S.K., Brinkerhoff1, C.J., Isukapalli1, S.S., Georgopoulos, P.G. (2011) Mathematical model of uptake and metabolism of arsenic(III) in human hepatocytes - Incorporation of cellular antioxidant response and threshold dependent behavior. BMC Systems Biology 5, 16-30.

Tóth, A., Brózik, A., Szakács, G., Sarkadi, B., Hegedűs, T. (2015) A Novel Mathematical Model Describing Adaptive Cellular Drug Metabolism and Toxicity in the Chemoimmune System. PLoS ONE 10(2): e0115533-e0115548.

Received: 20. 02. 2019. Accepted: 21. 03. 2019.