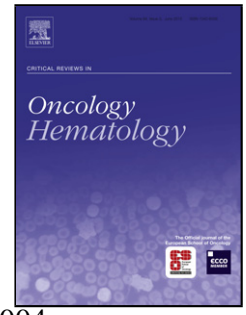

Title: Mathematical modeling of cancer metabolism

Author: Miguel Ángel Medina

PII: S1040-8428(17)30396-7
DOI: https://doi.org/10.1016/j.critrevonc.2018.02.004
Reference: ONCH 2501

To appear in: *Critical Reviews in Oncology/Hematology*

Received date: 16-8-2017
Revised date: 15-12-2017
Accepted date: 1-2-2018

Please cite this article as: Medina Miguel Ángel.Mathematical modeling of cancer metabolism.*Critical Reviews in Oncology and Hematology* https://doi.org/10.1016/j.critrevonc.2018.02.004

Mathematical modeling of cancer metabolism

Miguel Ángel Medina[1,2 *]

[1]Universidad de Málaga, Andalucía Tech, Departamento de Biología Molecular y Bioquímica, Facultad de Ciencias, and IBIMA (Biomedical Research Institute of Málaga), and [2]CIBER de Enfermedades Raras (CIBERER), E-29071 Málaga, Spain

[*]**Corresponding author:** Dr. Miguel Ángel Medina, Departamento de Biología Molecular y Bioquímica, Facultad de Ciencias, Universidad de Málaga, E-29071, Málaga. Phone: +34-952137132. Fax. +34-952131674. E-Mail: medina@uma.es

ABSTRACT

Systemic approaches are needed and useful for the study of the very complex issue of cancer. Modeling has a central position in these systemic approaches. Metabolic reprogramming is nowadays acknowledged as an essential hallmark of cancer. Mathematical modeling could contribute to a better understanding of cancer metabolic reprogramming and to identify new potential ways of therapeutic intervention. Herein, I review several alternative approaches to metabolic modeling and their current and future impact in oncology.

Keywords: mathematical model; cancer; tumor microenvironment; systems biology; metabolism

1. Introduction

Globally cancer represents one of the greatest challenges of the 21st century biomedicine, since cancer is one of the three main causes of death in the developed world. In fact, it is estimated that up to almost a half of population will develop some kind of cancer along life (World Health Organization cancer factsheet, www.who.int/mediacentre/factsheets/fs297/en/). Nonetheless, cancer is a very complex system, since the term "cancer" integrates around two hundred different diseases with very different etiology, evolution, diagnosis, prognosis and treatments loosely coupled by the emerging and integrating concept of *hallmarks of cancer* (Hanahan and Weinberg, 2000, 2011). Furthermore, every kind of cancer is an intrinsically heterogeneous and complex disease at different scales (Burrell et al., 2013). Firstly, in spite of the popular clonal theory of the origin of cancer, not all the tumor cells within a tumor mass have the same genetic landscape or exhibit the same biological behavior. For instance, within a cancer mass there are many highly proliferative tumor cells but also a small subpopulation of undifferentiated cancer stem cells with very low proliferative potential and exhibiting the property of self-renewal (Kaiser, 2015). On the other hand, in a tumor mass with a diameter greater than a few mm, the biological and metabolic behaviors of tumor cells within its core are extremely different from those exhibited by tumor cells at the surface of the tumor mass (Floor et al., 2012). Secondly, it is frequent that most of the cells within a tumor mass are not cancer cells, but a complex set of accompanying non-tumor cells, including endothelial cells, fibroblasts, T cells and macrophages, among other, linked by complex signaling and metabolic cross-talks supporting the properties of the so-called cancer microenvironment (Vaupel et al., 1989; Quesada et al., 2007; Balkwill et al, 2012; Hanahan and Coussens, 2013; Ghesquière et al., 2014). Third, cancers grow within the context of specific tissues and organs of the host and complex inter-relationships between cancer cells and the host are key not only in the carcinogenesis process but also in cancer progression, invasion and metastasis (Medina, 2014; Ruiz-Pérez et al., 2014; Ocaña et al., 2017).

Therefore, cancers as a whole are complex systems amenable to the systemic approaches provided by modern systems biology (Oltvai and Barabasi, 2002; Medina, 2013). Systems

biology understands the emergence of complex cellular, tissue and organismic functions as systems-level properties that arise from the dynamic interactions of many biomolecules, both gene-derived products and their low molecular weight substrates, ligands and modulators (Alberghina and Westerhoff, 2005). As a matter of fact, it has been proposed that cancer cell properties can be redefined from a systems biology approach (Alberghina et al., 2012). The aim of this and other systems biology approaches is to get insight of the behavior of the studied system as a whole.

2. Modeling at the heart of systems biology

From its beginning, the efforts to build a conceptual framework for systems biology have assumed that the study of a biological system as a whole entails the goals established by Kitano (Kitano, 2002), namely, to know the structure and the dynamics of the system, to identify the design principles that can justify both the structure and the dynamics of the system and to identify the rules governing the regulation of the behavior of the system. This conceptual framework places the modeling process at the heart of systems biology and, in general, at the center position in bioscience research (for a recent review, see Torres and Santos, 2015). From this systemic viewpoint, the main activities involved in the process are observation and experimentation, followed by modeling, simulation, analysis and optimization, leading back to observation and experimentation. According to Torres and Santos (2015), this spiral-wise procedure to build useful models follows three steps of conceptualization, formalization and management and optimization. There are many types of models, but all of them -explicitly or implicitly- involve mathematical formalizations, although with many alternative approaches.

3. Metabolic reprogramming as a pervading hallmark of cancer

Traditionally metabolism was understood as the whole set of biochemical reactions within a cell allowing the transformation of certain metabolites in others. This view is no longer acceptable, since a modern view of metabolism also integrates the whole set of physicochemical processes

allowing the exchange of matter (transport) and energy (bioenergetics) of every cell or alive being with their environment as an open thermodynamic system.

During the first half of the 20th century, an important part of the research efforts to elucidate the biological basis of cancer was centered on the particular features of cancer metabolism (Shapot, 1980), as clearly illustrated by the identification by Otto Warburg of aerobic glycolysis as a common feature of many types of tumors (Warburg, 1956). Later on, along the second half of the 20th century this metabolic approach to the basic study of cancer became old-fashioned with "genocentric" approaches dominating the scientific efforts to understand the molecular biology of cancer (Weinberg, 2014). This explains -at least, partially- that the first description of the hallmarks of cancer in 2000 ignored a role for metabolism (Hanahan and Weinberg, 2000). In contrast, when the same two authors revisited the concept of hallmarks of cancer eleven years later the previous list of 6 hallmarks of cancer was extended to 10 (Hanahan and Weinberg, 2011), one of the "new" ones being the so-called metabolic reprogramming of cancer cells. This is currently understood as a pervading hallmark of cancer involving changes in the metabolic fluxes through carbohydrate, lipid and nitrogen compound metabolic pathways, as well as through the tricarboxylic acid cycle and OXPHOS (Medina, 2014; Ruiz-Pérez et al., 2014).

4. Mathematical modeling of metabolism: bottom-up and top-down approaches

As other tasks within the systems biology framework, mathematical modeling can be carried out by either top-down or bottom-up approaches. According to Shahzad and Loor (Shahzad and Loor, 2012), the top-down approach involves a workflow in five stages: i) Sample collection and laboratory experiments to obtain the initial set of data. ii) High-throughput "omic" assays to expand the set of data to be analyzed. iii) Statistical analysis of the collected data. iv) The use of bioinformatics application for functional enrichment and modeling. v) The final critical step of data interpretation and extraction/inference of new discovered knowledge. In this top-down approach, there is a directional flow of information from "omes" (transcriptome, proteome, metabolome...) to flux-balanced metabolic pathways. On the other hand, the bottom-up approach is a four step bioinformatics-driven process that makes use of detailed information

extracted from biochemical, kinetic and metabolic databases, from literature searches ("bibliomics"), and new results from biochemical assays as the input set from which in the first stage a draft reconstruction of the model is carried out. After an extensive work of manual curation in the second stage, the third stage converts the curated set into mathematical models. Finally, in the fourth step the model should be validated or refined leading to a final computational model. These mathematical models of metabolism can be built at different scales with different degrees of detail, form very detailed models of defined metabolic pathways based on the acquired detailed knowledge of the kinetic data of each individual reaction taking part in the pathway, to not so detailed middle scale models based on fluxomics (with the use of flux balance analysis), to global genome-scale metabolic models.

An example of a mathematical model of a metabolic pathway based on detailed kinetic information is the model of mammalian polyamine metabolism (Rodríguez-Caso et al., 2006). This model captured the main features of this bicyclic pathway and the predictions from its simulations regarding the key regulatory and regulated enzymes of the pathway were later confirmed by other groups in experiments with transgenic mice and with pharmacological intervention (Marques et al., 2008; Agostinelli et al., 2010). In addition to these expected observations that confirmed what was previously known on the regulatory features of the polyamine bicycle, the model unveiled unexpected new knowledge on the key regulatory roles of acetyl-CoA/CoA recycling and S-adenosyl methionine availability for polyamine metabolism. Shortly after the publication of this model, the use of mice with genetically altered expression of spermidine/spermine N1-acetyltransferase allowed to experimentally confirm the prediction on the key role assigned to acetyl-CoA/CoA recycling (Jell et al., 2007). The prediction regarding the role of S-adenosyl methionine availability had already been confirmed experimentally by the same research group (Kramer et al., 1988). These predictions and observations have important implications for cancer metabolism and reinforce the option of targeting polyamine metabolism as an anticancer strategy (Murray-Stewart et al., 2016). Furthermore, a recent integrative metabolomics study has uncovered the regulation of S-

adenosyl methionine decarboxylase downstream mTORC1 to reprogram prostate cancer metabolism (Zabala-Letona et al., 2017).

An alternative approach for the kinetic modeling of metabolic pathways is based on the use of the coefficients and theorems of metabolic control analysis theory (Fell, 1997). With this approach, the metabolic adaptations of carbon metabolism underlying K-Ras transformation have been modeled (De Atauri et al., 2011).

Kinetic modeling of cancer metabolic pathways assisted with fluxomics (Cascante and Marín, 2008) is relatively frequent, as well illustrated by the kinetic model of glycolysis in HeLa tumor cells (Marín-Hernández et al., 2011). This model allowed for the simulation of different steady-state conditions (including low glucose concentration and hypoxic conditions), as well as the identification of the potentially best drug targets by enzyme titration simulations. At the mesoscale, a combination of transcriptomics and fluxomics allowed for the formulation of a metabolic model describing how K-Ras decouples glucose and glutamine metabolism to support cancer growth (Gaglio et al., 2011).

A first global reconstruction of the human metabolic network based on a combination of "bibliomic" and genomic data known as Recon 1 was made available ten years ago (Duarte et al., 2007). Several years later, a systems biology roadmap integrating conventional biochemical, molecular biology and post-genomic analyses along with different types of mathematical models was proposed as an efficient procedure for drug discovery in connection with cancer cell metabolism (Alberghina et al., 2014). More recently, Recon 2 was launched as a community-driven "consensus reconstruction" of human metabolism (Thiele et al., 2013). The main findings and importance of this Recon 2 paper has been reviewed elsewhere (Swainston et al., 2013). Very recently, genome scale metabolic modeling of cancer has been critically reviewed, stressing the requirements for successful flux-balance analysis simulations of cancer metabolism and discussing the similarities of the methods used for the modeling of both cancer and microbial metabolism (Nilsson and Nielsen, 2017).

5. The modularity of metabolism

Network science offers new approaches that have become increasingly popular and have demonstrated to be useful within the framework of systems biology. Metabolism is the paradigm of a biological network. The metabolic network has been shown to be hierarchical and modular (Ravasz et al., 2002). The modularity of metabolism opens the possibility to "grow" mathematical models of metabolic pathways by connecting independent model of pathways sharing at least a metabolite or a biochemical reaction. Such an approach was used to integrate the polyamine metabolism model with those of methyl cycle and sulfur amino acid metabolism (Rodríguez-Caso et al., 2006; Reed et al., 2008; Reyes-Palomares et al., 2012). This combined model illustrates the usefulness and convenience of bottom-up approaches for the construction of kinetic metabolic models. Furthermore, this model could predict the importance of S-adenosyl methionine availability on liver polyamine metabolism in pathophysiological situations, such as hepatocellular carcinoma. However, this “growing” of mathematical models of metabolic pathways based on the modularity of metabolism is far from being a simple task and in many cases may fail due to incompatibilities of the original models, the absence of critical data for integration or even the lack of sufficient modularity.

6. Tools and data sources

An ever-increasing number of biocomputational tools are made available to help researchers in the task of metabolic modeling. They include BioPP (Viswanathan et al., 2007), CellDesigner, (Funahashi et al., 2003), COPASI (Hoops et al., 2006), Payao (Matsuoka et al., 2010), sycamore (Weidermann et al., 2008), SBMM Assistant (Reyes-Palomares et al., 2009) and WikiPathways (Kutmon et al., 2016), among many others. There are also several useful databases containing valuable data regarding metabolic pathways, such as UNIPROT, KEGG, CHEBI, BRENDA and SABIO-RK. The CellML model repository is part of the international Physiome Project, containing hundreds of models covering a wide range of cellular processes (Lloyd and Yu, 2013). Biomodels is a very popular free, centralized database of curated, published kinetic models (Le Novère et al., 2006). With another different approach, JWS Online is a popular

systems biology tool for the construction, modification and simulation of kinetic models, serving additionally as a database for the storage of curated models (Olivier and Snoep, 2004). Many of these tools and databases were commented elsewhere (Navas-Delgado et al., 2010). Recently, *kpath*, a database that integrates information related to metabolic pathways that also provides a navigational interface for the building of metabolic networks, has been launched (Navas-Delgado et al., 2015).

Most of the tools mentioned in this section work under the Systems Biology Markup Language (SBML) standard. They and many other tools are listed in and available from the SBML URL (http://www.sbml.org).

7. Modeling metabolic interchanges in tumor microenvironment and other future challenges

As mentioned above, tumor cells are in a continuous exchange with other cell types within its microenvironment. The metabolic features of these cells are being studied extensively in the last few years, as reviewed elsewhere (De Bock et al., 2013; Ghesquiére et al. 2014; Ho et al., 2016). A number of models of tumor microenvironment signaling and biological features are already currently available (for instance, see Hartung et al., 2014; Norton and Popel, 2014; Shirinifard et al., 2009; Tran et al., 2011). In contrast, a bibliomic search clearly shows that there is an essential lack of models of the metabolic interchanges in tumor microenvironment. This should be a priority challenge for the near future.

When detailed kinetic data are not available, it has been shown that S-system analysis is a robust mathematical approach to model metabolism (Voit, 2000). This mathematical approach was introduced in the sixties by Michael Savageau. (Savageau, 1969). One of the advantages of this approach is that takes into account very naturally the key point of metabolic regulation. It could be expected that this blind approach could also be useful for modeling cancer metabolism and metabolic interchanges in tumor microenvironment.

Mathematical models of global metabolic landscapes exhibiting differential metabolic features of different types and subtypes of cancer will contribute with very useful supplementary

information to that provided by genetic and epigenetic landscape studies, such as those boosted by the cancer genome atlas initiative (TCGA, URL: cancergenome.nih.gov).

Much more effort should be devoted to the analysis of, and the potential correlations associated with, metabolic changes during cancer progression and metastasis.

Finally, other challenges for the future should be the implementation of models to simulate the metabolic interaction between cancer stem cells and non-stem tumor cells, as well as those able to simulate the complex metabolic interchanges between the cancer mass and tissues and organs of the host.

Conflicts of interest

I declare that I have no actual or potential competing financial interest.

Acknowledgements

Supported by grants BIO2014-56092-R (MINECO and FEDER), P12-CTS-1507 (Andalusian Government and FEDER) and funds from group BIO-267 (Andalusian Government). The "CIBER de Enfermedades Raras" is an initiative from the ISCIII (Spain). The funders had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

REFERENCES

Agostinelli, E., Marques, M P. M., Calheiros, R., Gil, F. P. S. C., Tempera, G., Viceconte, N., et al. (2010). Polyamines: fundamental characters in chemistry and biology. Amino Acids 38, 393-403. doi: 10.1007/s00726-009-0396-7

Alberghina, L., Westerhoff, H. (2005). Systems Biology: Definitions and Perspectives. Heidelberg: Springer

Alberghina, L., Gaglio, D., Gelfi, C., Moresco, R. M., Mauri, G., Bertolazzi, P., et al. (2012). Cancer cell growth and survival as a system-level property sustained by enhanced glycolysis and mitochondrial Front. Physiol. 3, 362. doi: 10.3389/fphys.2012.00362

Alberghina, L., Gaglio, D., Moresco, R. M., Gilardi, M. C., Messa, C., Vanoni, M. (2014). A systems biology roadmap for the discovery of drugs targeting cancer cell metabolism. Curr. Pharm. Design 20, 2648-66. doi: 10.2174/13816128113199990490

Balkwill, F.R., Capasso, M., Hagemann, T. (2012). The tumor microenvironment at a glance. J. Cell Sci. 125, 5591-6. doi: 10.1242/jcs.116392

Burrell, R.A., McGranahan, N., Bartek, J., Swanton, C. (2013). The causes and consequences of genetic heterogeneity in cancer evolution. Nature 501, 338-45. doi: 10.1038/nature12625

Cascante, M., Marín, S. (2008). Metabolomics and fluxomics approaches. Essays Biochem 45, 67-81. doi: 10.1042/BSE0450067

De Atauri, P., Benito, A., Vizán, P., Zanuy, M., Mangues, R., Marín, S., Cascante, M. (2011). Carbon metabolism and the sign of control coefficients in metabolic adaptations underlying K-ras transformation. Biochim. Biophys. Acta 1807, 746-54. doi: 10.1016/j.bbabio.2010.11.015

De Bock, K., Georgiadou, M., Carmeliet, P. (2013). Role of endothelial cell metabolism in vessel sprouting. Cell Metab. 18, 634-47. doi: 10.1016/j.cmet.2013.08.001

Duarte, N. C., Becker, S. A., Jamshidi, N., Thiele, I., Mo, M. L., Vo, T. D., et al. (2007). Global reconstruction of the human metabolic network based on genomic and bibliomic data. Proc. Natl. Acad. Sci. USA 104, 1777-82. doi: 10.1073/pnas.0610772104

Fell, D. (1997). Understanding the Control of Metabolism. London: Portland Press

Floor, S. L., Dumont, J. E., Maenhaut, C., Raspe, E. (2012). Hallmarks of cancer: Of all cancer cells, all the time? Trends Mol. Med. 18, 509–15. http://doi.org/10.1016/j.molmed.2012.06.005

Funahashi, A., Tanimura, N., Morohashi, M., Kitano, H. (2003). CellDesigner: a process diagram editor for gene-regulatory and biochemical networks. Biosilico 1, 159-62

Gaglio, D., Metallo, C. M., Gameiro, P. A., Hiller, K., Danna, L. S., Balestrieri, C., et al. (2011).Oncogenic K-Ras decouples glucose and glutamine metabolism to support cancer cell growth. Mol. Systems Biol. 7, 523. doi: 10.1038/msb.2011.56

Ghesquière, B., Wong, B. W., Kuchnio, A., Carmeliet, P. (2014). Metabolism of stromal and immune cells in health and disease. Nature 511, 167-76. doi: 10.1038/nature13312

Hanahan, D., Coussens, L.M. (2012). Accesories to the crime: functions of cells recruited to the tumor microenvironment. Cancer Cell 21, 309-22. doi: 10.1016/j.ccr.2012.02.022

Hanahan, D., Weinberg, R. A. (2000). Hallmarks of cancer. Cell 100, 57-70. doi: 10.1016/S0092-8674(00)81683-9

Hanahan, D., Weinberg, R. A. (2011). Hallmarks of cancer: the next generation. Cell 144, 646-74. doi: 10.1016/j.cell.2011.02.013

Hartung, N., Mollard, S., Barbolosi, D., Benabdallah, A., Chapuisat, G., Henri, G., et al. (2014). Mathematical modeling of tumor growth and metastatic spreading: validation in tumor-bearing mice. Cancer Res 74, 6397-407. doi: 10.1158/0008-5472.CAN-14-0721

Ho, P. C., Liu, P. S. (2016). Metabolic communication in tumors: a new layer of immunoregulation for immune evasion. J. Immunother. Cancer 4: 1. doi: 10.1186/s40425-016-0109-1

Hoops, S., Sahle, S., Gauges, R., Lee, C., Pahle, J., Simus, N., et al. (2006). COPASI: a COmplex PAthway SImulator. Bioinformatics 22, 3067-74. doi: 10.1093/bioinformatics/btl485

Jell, J., Merali, S., Hensen, M. I., Mazurchuk, R., Spernyak, J. A., Diegelman, P., et al. (2007). Genetically altered expression of spermidine/spermine N1-acetyltransferase affects fat

metabolism in mice via acetyl-CoA. J. Biol. Chem. 282, 8404-13. doi: 10.1074/jbc.M610265200

Kaiser, J. (2015). The cáncer stem cell gamble. Science 347, 226-9. doi: 10.1126/science.347.6219.226

Kitano, H. (2002). Systems biology: a brief overview. Science 295, 1662-4. doi: 1 0.1126/science.1069492

Kramer, D. L., Sufrin, J. R., Porter, C. W. (1988). Modulation of polyamine biosynthetic activity by S-adenosylmethionine depletion. Biochem. J. 249, 581-6. doi: 10.1042/bj2490581

Kutmon, M., Riutta, A., Nunes, N., Hanspers, K., Willighagen, E.L., Bohler, A., et al. (2016). WikiPathways: capturing the full diversity of pathway knowledge. Nucl. Acids Res. 44, D488-94. doi: doi:10.1093/nar/gkv1024

Le Novère, N., Bornstein, B., Broicher, A., Courtot, M., Donizelli, M., Dharuri, H., et al. (2006). BioModels Database: a free, centralized database of curated, published, quantitative kinetic models of biochemical and cellular systems. Nucleic Acids Res. 34, D689-1. doi: 10.1093/nar/gkj092

Lloyd C.M., Yu T. (2013). CellML Model Repository. In: Dubitzky W., Wolkenhauer O., Cho KH., Yokota H. (eds) Encyclopedia of Systems Biology. Springer: New York

Marín-Hernández, A., Gallardo-Pérez, J. C., Rodríguez-Enríquez, S., Encalada, R., Moreno-Sánchez, R., Saavedra, E. (2011). Modeling cancer glycolysis. Biochim. Biophys. Acta 1807, 755-67. doi: 10.1016/j.bbabio.2010.11.006

Marques, M. P. M., Gil, F. P. S. C., Calheiros, R., Battaglia, V., Brunati, A. M., Agostinelli, E., Toninello, A. (2008). Biological activity of antitumoural MGBG: the structural variable. Amino Acids 34, 555-64. doi: 10.1007/s00726-007-0009-2

Matsuoka, Y., Ghosh, S., Kikuchi, N., Kitano, H. (2010). Payao: a community platform for SBML pathway model curation. Bioinformatics 26, 1381-3. doi: 10.1093/bioinformatics/btq143

Medina, M. A. (2013). Systems biology for molecular life sciences and its impact in biomedicine. Cell. Mol. Life Sci. 70, 1035-53. doi: 10.1007/s00018-012-1109-z

Medina, M. A. (2014). Targeting the metabolism of cancer cells. A foreword. Curr. Pharm. Design 20, 2555-6. doi: 10.2174/13816128113199990491

Murray-Stewart, T. R., Woster, P. M., Casero, Jr., R. A. (2016). Targeting polyamine metabolism for cancer therapy and prevention. Biochem. J. 473, 2937-53. doi: 10.1042/BCJ20160383

Navas-Delgado, I., García-Godoy, M.J., López-Camacho, E., Rybinski, M., Reyes-Palomares, A., Medina, M.A., Aldana-Montes, J.F. (2015). kpath: integration of metabolic pathway linked data. Database 2015: bav083. doi: 10.1093/database/bav053

Navas-Delgado, I., Real-Chicharro, A., Medina, M. A., Sánchez-Jiménez, F., Aldana-Montes, J. F. (2010). Social pathway annotation: extensions of the systems biology metabolic modelling assistant. Brief. Bioinformatics 12, 576-87. doi: 10.1093/bib/bbq061

Nilsson, A., Nielsen, J. (2017). Genome scale metabolic modeling of cancer. Metab. Eng. 43, 103-12. doi: 10.1016/j.ymben.2016.10.022

Norton, K.A., Popel, A.S. (2014). An agent-based model of cancer stem cell initiated avascular tumour growth and metastasis: the effect of seeding frequency and location**.** J. R. Soc. Interface 11, 1-13. doi: 10.1098/rsif.2014.0640

Ocaña, M.C., Martínez-Poveda, B., Quesada, A.R., Medina, M.A. (2017). Metabolism in the tumor microenvironment: what is known about stromal and immune cells? Clin. Immunol. Endocrine Metab. Drugs, in press. doi: 10.2174/2212707004666170818164513

Olivier, B. G., Snoep, J. L. (2004). Web-based kinetic modelling using JWS Online. Bioinformatics 20: 2143-4. doi: 10.1093/bioinformatics/bth200

Oltvai, Z.N., Barabasi, A.L. (2002). Life's complexity pyramid. Science 298, 763-4. doi: 10.1126/science.1078563

Quesada, A.R., Medina, M.A., Alba, E. (2007). Playing only one instrument may be not enough: limitations and future of the antiangiogenic treatment of cancer. BioEssays 29, 1159-68. doi: 10.1002/bies.20655

Ravasz, E., Somera, A. L., Mongru, D. A., Oltvai, Z. N., Barabasi, A. L. (2002). Hierarchical organization of modulatity in metabolic networks. Science 297, 1551-5. doi: 10.1126/science.1073374

Reed, M. C., Thomas, R. L., Pavisic, J., James, S. J., Ulrich, C- M., Nijhout, H. F. (2008). A mathematical model of glutathione metabolism. Theor. Biol. Med. Model. 5: 8. doi: 10.1186/1742-4682-5-8

Reyes-Palomares, A., Montañez, R., Sánchez-Jiménez, F., Medina, M. A. (2012). A combined model of hepatic polyamine and sulfur amino acid metabolism to analyze S-adenosyl methionine availability. Amino Acids 42, 597-610. doi: 10.1007/s00726-011-1035-7

Reyes-Palomares, A., Montañez, R., Real-Chicharro, A., Chniber, O., Kerzazi, A., Navas-Delgado, I., et al. (2009). Systems biology metabolic modeling assistant: an ontology-based tool for the integration of metabolic data in kinetic modeling. Bioinformatics 25, 834-5. doi: 10.1093/bioinformatics/btp061

Rodríguez-Caso, C., Montañez, R., Cascante, M., Sánchez-Jiménez, F., Medina, M.A. Mathematical modeling of polyamine metabolism in mammals. J. Biol. Chem. 281, 21799-812.doi: 10.1074/jbc.M602756200

Ruiz-Pérez, M. V., Sánchez-Jiménez, F., Alonso, F. J., Segura, J. A., Márquez, J., Medina, M.A. Glutamine, glucose and other fuels for cancer. Curr. Pharm. Design 20, 2557-79. doi: 10.2174/1381612811319990482

Savageau, M.A. (1969). Biochemical systems analysis, I. Some mathematical properties of the rate law for the components enzymatic reactions. J. Theor. Biol. 25, 365-9. doi: 10.1016/S0022-5193(69)80026-3

Shahzad, K., Loor, J. J. Application of top-down and bottom-up systems approaches in ruminant physiology and metabolism. Curr. Genet. 13, 379-94. doi: 10.2174/138920212801619269

Shapot, V.S. (1980). Biochemical Aspects of Tumour Growth. Moscow: Mir

Shirinifard, A., Gens, J.S., Zaitlen, B.L., Poplawski, N.J., Swat, M., Glazier, J.A. (2009). 3D Multi-cell simulation of tumor growth and angiogenesis. Plos ONE 4, e7190. doi: 10.1371/journal.pone.0007190

Swainston, N., Mendes, P., Kell, D.B. (2013). An analysis of a "community-driven" reconstruction of the human metabolic network. Metabolomics 9, 77-64. doi: 10.1007/s11306-013-0564-3

Thiele, I., Swainston, N., Fleming, R. M. T., Hoppe, A., Sahoo, S., Aurich, M. K., et al. (2013). A community-driven global reconstruction of human metabolism. Nat. Biotech. 31, 419-25. doi: 10.1038/nbt.2488

Torres, N.V., Santos, G. (2015). The (mathematical) modleing process in biosciences. Front. Genet. 6, 354. doi: 10.3389/fgen.2015.00354

Tran, P.T., Bendapudi, P.K., LIn, H.J., Choi, P., Koh, S., Chen, J., et al. (2011). Survival and death signals can predict tumor response to therapy after oncogene inactivation. Sci. Transl. Med. 3, 103ra99. doi: 10.1126/scitranslmed.3002018

Vaupel, P., Kallinowski, F., Okunieff, P. (1989). Blood flow, oxygen and nutrient supply, a metabolic microenvironment of human tumors: a review. Cancer Res. 49, 6449-65.

Viswanathan, G.A., Nudelman, G., Patil, S., Sealfon, S.C. (2007). BioPP: a tool for web-publication of biological networks. BMC Bioinformatics 8, 168. doi: 10.1186/1471-2105-8-168

Voit, E. O. (2000). Computational Analysis of Biochemical Systems. Cambridge: Cambridge University Press

Warburg, O. (1956). On the origin of cancer. Science 123, 309-14. doi: 10.1126/science.123.3191.309

Weidermann, A., Richter, S., Stein, M., Sahle, S., Gauges, R., Gabdoulline, R., et al. (2008). SYCAMORE - a systems biology computational analysis and modelling research environment. Bioinformatics 24, 1463-4. doi: 10.1093/bioinformatics/btn207

Weinberg, R.A. (2014). The Biology of Cancer (2nd edition). New York: Garland Science

Zabala-Letona, A., Arruabarrena-Aristotena, A., Martín-Martín, N., Fernández-Ruiz, S., Sutherland, J.D., Clasquin, M., et al. (2017). mTORC1-dependent AMD1 regulation sustains polyamine metabolism in prostate cancer. Nature 547, 109-113. doi: 10.1038/nature22964