Theoretical Description of Metabolism Using Queueing Theory

Vladyslav P. Evstigneev · Marina G. Holyavka · Sergii V. Khrapatiy · Maxim P. Evstigneev

Received: 8 December 2013 / Accepted: 25 July 2014 / Published online: 21 August 2014

Abstract A theoretical description of the process of metabolism has been developed on the basis of the Pachinko model (see Nicholson and Wilson in Nat Rev Drug Discov 2:668–676, 2003) and the queueing theory. The suggested approach relies on the probabilistic nature of the metabolic events and the Poisson distribution of the incoming flow of substrate molecules. The main focus of the work is an output flow of metabolites or the effectiveness of metabolism process. Two simplest models have been analyzed: short- and long-living complexes of the source molecules with a metabolizing point (*Hole*) without queuing. It has been concluded that the approach based on queueing theory enables a very broad range of metabolic events to be described theoretically from a single probabilistic point of view.

Keywords Metabonomics · Metabolism · Queueing theory · Metabolites

V. P. Evstigneev · M. P. Evstigneev (✉)
Department of Physics, Sevastopol National Technical University, Universitetskaya str., 33, 299053 Sevastopol, Russia
e-mail: max_evstigneev@mail.ru

M. G. Holyavka
Department of Biophysics and Biotechnology, Voronezh State University, 394006 Voronezh, Russia

S. V. Khrapatiy
Department of Biophysics, ESC "Institute of Biology", Taras Shevchenko National University of Kyiv, 01601 Kyiv, Ukraine

M. P. Evstigneev
Department of Biology and Chemistry, Belgorod State University, 308015 Belgorod, Russia

1 Introduction

Metabolism is an undetachable property of any living organism on Earth which determines a life functionality of the living objects on any level of organization. To date, a major piece of attention has been focused on the development of experimental techniques and methodologies for investigation of metabolic processes and metabolites. A typical example is a rapidly growing area of research, called metabonomics, which specifically deals with metabolites and has a huge potential for identification of various human diseases on early stage (see Nicholson and Lindon 2008). A common approach in metabonomics is to measure the global, dynamic metabolic response of living systems to biological stimuli or genetic manipulation, and characterize/quantify metabolites' distribution using various experimental techniques (see Nicholson and Lindon 2008; Beckonert et al. 2010). Theoretical description of metabolism in complex multicellular system in terms of metabolites' distribution is extremely difficult task as it requires detailed knowledge of all metabolic pathways. Numerous approaches for analytical description of metabolism have so far been developed, all of them grounded on the use of concrete metabolic picture, e.g., the flux-based approaches (see Grimbs et al. 2007; Aldridge et al. 2006; Stelling et al. 2002), metabolic network analysis (Jeong et al. 2000; Lima-Mendez and Helden 2009), Petri net analysis (Chaouiya 2007; Peleg et al. 2002), stochastic approach (De Jong 2002), entropy approach (see Veselkov et al. 2010) and others.

In the present work, we develop an alternative theory specifically linked to the qualitative Pachinko model first suggested by Nicholson in (see Nicholson and Wilson 2003), and based on probabilistic approach to treat metabolism in terms of metabolites' distribution using the queueing theory. As a starting point in analysis, we used the work by Trenkenshu (Trenkenshu (1992)) reported the successful application of the queueing theory in biokinetics.

2 Results and Discussion

2.1 Pachinko Model for Metabolism

The process of metabolism may be considered in terms of a qualitative scheme named the Pachinko model (Fig. 1) (see Nicholson and Wilson 2003). The model is derived from a typical Pachinko machine (Japanese pinball), in which the outcome is determined by a probabilistic flow and collisions between the steel balls and pins. The Pachinko model diagram (Fig. 1) represents xenobiotic metabolism and interactions with endogenous, sym-endogenous, sym-xenobiotic and trans-xenobiotic elements. In this diagram, the *Pins* represent key metabolizing enzymes or transporter molecules, some of which are arranged in sequence to indicate probable pathways. A *Hole* represents an exit point from the system of an excreted metabolite. Some pathways through the machine are more probable than the others, dictated by a combination of the chemistry and enzyme–substrate interactions. A mutation at any point is the equivalent of moving or changing the size of a *Pin* that alters the probabilities of routes through the machine. The outcome is conditional on the sequence and sites

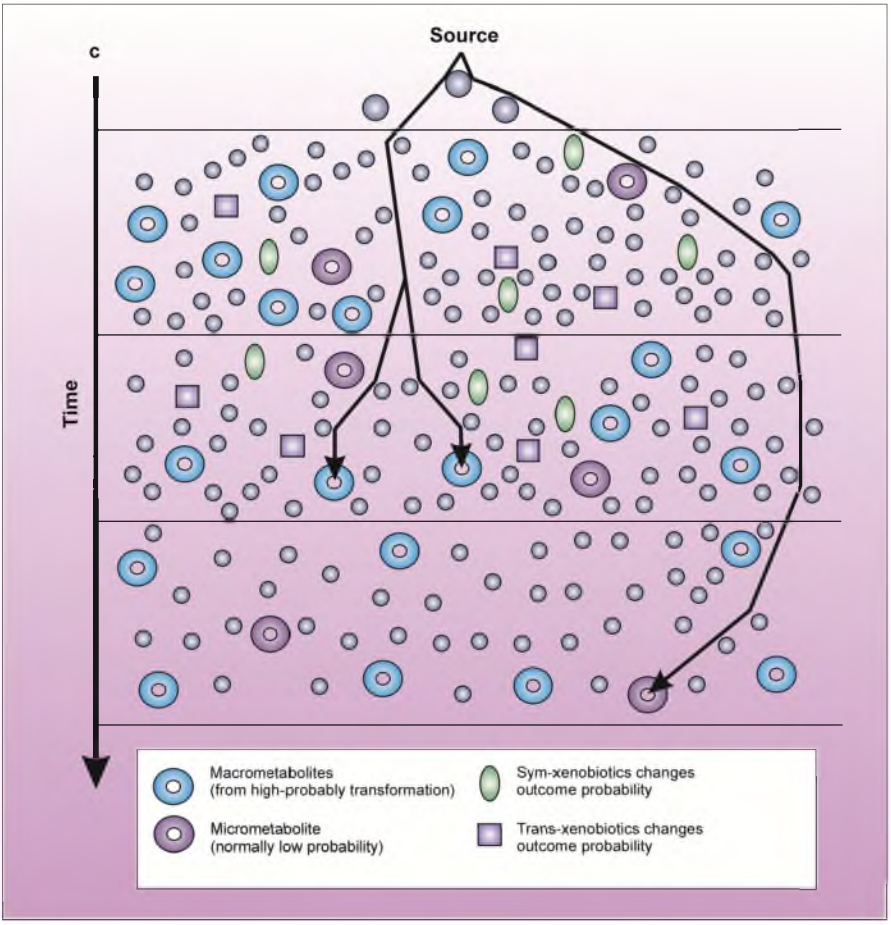

Fig. 1 Pachinko model diagram, redrawn by permission from Macmillan Publishers Ltd: Nature Rev. Drug Discov. (Nicholson and Wilson 2003), copyright (2003) (Color figure online)

of the previous metabolic events. Highly probable events lead to macrometabolites; low-probability events lead to the formation of micrometabolites. The activity of the system is influenced by the present numbers and types of other metabolites flowing through the system. This will result in a probabilistic interaction between the species and could lead to blocking some pathways normally used in drug metabolism.

2.2 General Formulations of the Theory

In the above described qualitative Pachinko model, the following three objects may be separated: an incoming flow; centers of metabolism (*Holes*); and transporter molecules or ferments (*Pins*). Such approach in general does not introduce new biophysical processes, but is fully probabilistic in its origin and therefore should be described by

the laws of probability. Its quantitative description may, in principle, be accomplished by any of the approaches currently developed in literature and cited in the introductory section, e.g., flux-based models (Grimbs et al. 2007; Aldridge et al. 2006; Stelling et al. 2002) or Petri net analysis (Chaouiya 2007; Peleg et al. 2002). However, the Pachinko approach introduces the incoming flow of metabolites in general case as a flow of discrete particles, which may create queues near the *Pins* and *Holes* and result in deviation from the common mass action law which is most often used in order to quantify the metabolic network by means of kinetic equations (see for example Wagner and Fell 2001; Aldridge et al. 2006; Covert et al. 2001). Analysis of the Pachinko model and its fundamental probabilistic origin results in the conclusion that it may be described in terms of mathematical queueing theory (QT), which has found extensive application in applied biokinetics (e.g., Kühl and Jobmann 2007; Trenkenshu 1992) and is most appropriate for description of statistical systems with queues. Let us further apply the queueing theory to quantitative description of the Pachinko metabolic model.

The key assumption of the QT approach is a Poisson character of the incoming flow of molecules

$$P_k(t) = \frac{(\lambda t)^k}{k!} \mathrm{e}^{-\lambda t}. \tag{1}$$

Let us suggest that a main property of the outcoming flow of metabolites is the relation of macrometabolite flow out of the system λ_{out} to the incoming flow (or substrate) λ_{in}:

$$\varphi = \frac{\lambda_{\text{out}}}{\lambda_{\text{in}}}$$

Let us term this quantity as the effectiveness of the metabolism process in a given biological system. In fact, the effectiveness of metabolism is proportional to the probability of interaction of molecules coming in the system with *Pins* and *Holes*. In the general case, this probability depends on time, on the parameters of interaction with *Pins* ($a_1, a_2, \ldots, a_m$) and *Holes* ($b_1, b_2, \ldots, b_l$):

$$\varphi = P(t; a_1, a_2, \ldots, a_m; b_1, b_2, \ldots, b_l) \tag{2}$$

Hence, the main task of modeling the process of metabolism in this work is the determination of the explicit form of the function (2).

2.3 Model with Fast Dissociation Between Molecule-Pin and Molecule-Hole

Let us assume that the incoming flow of molecules is uniform, containing only 'normal' molecules, which activate a metabolizing process. *Pins* and *Holes* are thought to be distributed randomly over the volume of the system, having the concentrations C_{P} and C_{H}, respectively. Random distribution implies that all routes in the system are equally probable. Let us consider a limiting case when the time of dissociation of *Molecule-Pin* (τ_{P}) and *Molecule-Hole* (τ_{H}) complexes is much shorter than compared with the time of entering of a new molecule into the system

$$\tau = 1/\lambda_{\text{in}} \gg \tau_{\text{P}}, \tau_{\text{H}}. \tag{3}$$

Apparently, a molecule entered in the system will interact with the *Pins* and *Holes* with probabilities p_{P} and p_{H}, respectively. In the equilibrium state, these probabilities will be proportional to the corresponding concentrations:

$$P_{\text{P}} = K_{\text{P}} \cdot C_{\text{P}}, \quad P_{\text{H}} = K_{\text{H}} \cdot C_{\text{H}}. \tag{4}$$

According to the formulation of the Pachinko model, a source molecule will undergo $(i-1)$ interactions with the *Pins*, and finally, an ith step will lead it to the *Hole*. The probability of such pathway is

$$p_i = p_P^{i-1} p_H$$

Assuming that the number of possible interactions is sufficiently big, the total probability to get a positive outcome in the form of macrometabolite should be written as a sum of all p_i

$$P = \sum_{i=1}^{\infty} p_P^{i-1} \cdot p_H = \frac{p_H}{1 - p_P}. \tag{5}$$

Taking into account Eq. (4), one finally gets

$$\varphi = P = \frac{K_H C_H}{1 - K_P C_P}$$

2.4 Model for Long-Living Complexes Molecule-Hole

The limiting condition (3) may be removed. It is expected that some *Holes* may be engaged with the processing of the first-captured molecule and are therefore inaccessible to other molecules. In order to evaluate this process, it is necessary to consider the interaction of the molecule with the hole in more detail. Let us assume that there is no queueing of the molecules in the vicinity of the *Holes*, waiting for their turn to be processed.

Following the previously described analysis, the probability to pass through a set of *Pins* and enter the reaction center in the *Hole* can be derived from (5)

$$P_P = \sum_{i=1}^{\infty} p_P^{i-1} = \frac{1}{1 - p_P}. \tag{6}$$

In case of a Poisson flow of molecules (1), the probability that during the time t no molecules will enter the *Hole* equals to

$$P_0(t) = \exp(-\lambda_{\text{in}} t).$$

Considering short times, the exponent may be simplified to

$$\exp(-\lambda_{\text{in}} t) \approx 1 - \lambda_{\text{in}} t \tag{7}$$

Recalling that the probability of entering the *Hole* also depends on the set of interactions with the *Pins* (6), one can write an expression for the probability $P_0(\Delta t)$ that during the short period of time Δt, no molecules will enter the *Hole*

$$P_0(\Delta t) = 1 - \lambda_{\text{in}} P_{\text{P}} \Delta t \tag{8}$$

Dealing with a short period of time that is much less than $1/\lambda_{\text{in}}$, one can assume that during this period, only one molecule can enter the reaction center. The corresponding probability may therefore be written as

$$P_1(\Delta t) = 1 - P_0(\Delta t) = \lambda_{\text{C}} \Delta t,$$

where $\lambda_{\text{C}} = \lambda_{\text{in}} P_{\text{P}}$ and represents a flow in the vicinity of the *Hole*.

Consider a system with n centers of metabolism (*Holes*). Let us calculate the probability that after a short period of time $(t, t + \Delta t)$, all centers are vacant. It may happen in the following circumstances:

- at the moment of time t, all *Holes* are vacant, and during the time Δt, no molecules had entered the reaction center, P_{00}

$$P_{00} = P_0(t) \cdot (1 - \lambda_{\text{C}} \Delta t) \tag{9}$$

- at the moment of time t, one *Hole* is engaged, but during the time Δt, the complex *Molecule-Hole* had dissociated, and no molecules had entered the reaction center, P_{10} (the piece of time Δt is thought to be too short to take into account the possibility that two or more *Holes* may be engaged to the moment of observation)

$$P_{10} = P_1(t) \cdot (1 - \lambda_{\text{C}} \cdot \Delta t) \cdot H(\Delta t), \tag{10}$$

where $H(t)$ is the probability that the complex *Molecule–Hole* had dissociated to the moment t.

Let us assume an exponential law for that (which is common in QT)

$$H(t) = 1 - \exp\left(-t \Big/ \tau_H\right).$$

For short Δt, $H(\Delta t) \approx \Delta t / \tau_{\text{H}} = \Delta t \cdot \nu_{\text{H}}$, where $\nu_{\text{H}} = 1/\tau_{\text{H}}$ and represents a frequency of processing the incoming molecules in the *Hole*. Thus, Eq. (10) adopts the form

$$P_{10} = P_1(t) \cdot (1 - \lambda_{\text{C}} \cdot \Delta t) \cdot \Delta t \cdot \nu_{\text{H}}, \tag{11}$$

Finally, to the end of Δt, the probability that all *Holes* are vacant equals to

$$P_0(t + \Delta t) = P_{00} + P_{10} = P_0(t) \cdot (1 - \lambda_{\text{C}} \Delta t) + P_1(t) \cdot (1 - \lambda_{\text{C}} \Delta t) \cdot \Delta t \cdot \nu_{\text{H}} \tag{12}$$

Evaluation of (12) results in

$$\frac{P_0(t+\Delta t)-P_0(t)}{\Delta t}=-\lambda_C P_0(t)+P_1(t)\left(1-\lambda_C \Delta t\right)\nu_H. \tag{13}$$

Equation (13) simplifies when $\Delta t \to 0$

$$\frac{\mathrm{d}p_0(t)}{\mathrm{d}t}=-\lambda_C P_0+P_1(t)\nu_H. \tag{14}$$

Similar thoughts allow to deduce a differential equation for the case when k centers are engaged

$$\frac{\mathrm{d}P_k(t)}{\mathrm{d}t}=\lambda_C P_{k-1}(t)-\left(\lambda_C+k\nu_H\right)P_k(t)+(k+1)\,\nu_H P_{k+1}(t). \tag{15}$$

When $k=n$

$$\frac{\mathrm{d}P_n(t)}{\mathrm{d}t}=\lambda_C P_{n-1}(t)-n\nu_H P_n(t). \tag{16}$$

Lets consider an equilibrium state. Apparently, the derivatives of probabilities in Eqs. (14)–(16) should be equal to zero, and we get a system of linear differential equations

$$\begin{cases} -\lambda_C P_0+P_1\nu_H=0 \\ \cdots \\ \lambda_C P_{k-1}-\left(\lambda_C+k\nu_H\right)P_k+(k+1)\,\nu_H P_{k+1}=0 \\ \cdots \\ \lambda_C P_{n-1}-n\nu_H P_n=0 \\ \sum\limits_{k=0}^{n} P_k=1 \end{cases}. \tag{17}$$

Sequential substitution of equations in (17) results in the solution of the system

$$P_k=\frac{\rho^k}{k!}P_0, \tag{18}$$

where $\rho=\lambda_C/\nu_H$ and represents a relation between the incoming flow of molecules in the vicinity of the *Hole* and the frequency of processing in the *Hole*. Substituting the last equation in (17) by (18)

$$P_0=\left[\sum_{k=0}^{n}\frac{\rho^k}{k!}\right]^{-1} \tag{19}$$

and combining (18) and (19)

$$P_k=\frac{\rho^k}{k!}\left[\sum_{i=0}^{n}\frac{\rho^i}{i!}\right]^{-1}. \tag{20}$$

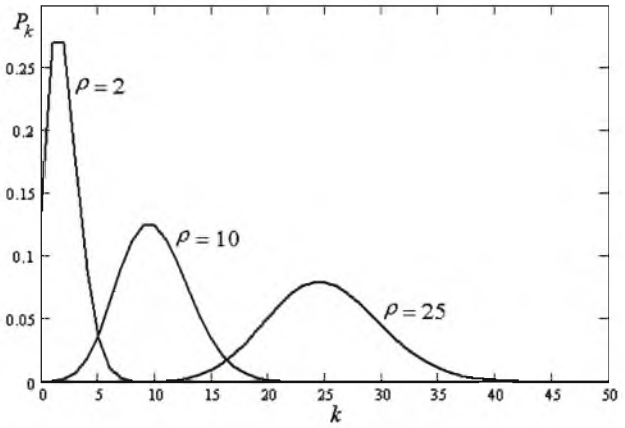

Fig. 2 The distribution of the probability P_k that k centers are engaged ($n = 50$)

At this point, it is interesting to look at the distribution of P_k values over the range of k (Fig. 2).

It is clearly seen from the Fig. 2 that there exists a maximum of distribution which corresponds to the number of the engaged *Holes* which appear under the given incoming flow of macrometabolites λ_{in}. On increasing the incoming flow with respect to the frequency of processing ν_{H} ($\rho = 2, 10, 25$), the maximum of distribution is being shifted right-hand thereby meaning that more *Holes* are engaged and the system is getting more busy. Apparently, each engaged *Hole* produces an outcoming macrometabolite, and hence, knowledge of the distribution of the engaged *Holes* (20) enables to calculate the outcoming flow λ_{out}

$$\lambda_{\text{out}} = P_H\,(P_1 \nu_H + 2P_2 \nu_H + \ldots + nP_n \nu_H) = P_H \nu_H \sum_{k=1}^{n} kP_k$$

$$= P_H \nu_H \sum_{k=1}^{n} \left(k \frac{\rho^k}{k!} \left[\sum_{i=0}^{n} \frac{\rho^i}{i!} \right]^{-1} \right)$$

and the effectiveness of metabolism

$$\varphi = \frac{\lambda_{\text{out}}}{\lambda_{\text{in}}} = \frac{P_P P_H}{\rho} \sum_{k=1}^{n} \left(k \frac{\rho^k}{k!} \left[\sum_{i=0}^{n} \frac{\rho^i}{i!} \right]^{-1} \right). \tag{21}$$

The function $\varphi(\rho)$ is depicted on the Fig. 3.

Very slow incoming flow of macrometabolites ($\rho \to 0$) being completely processed by the system of *Holes* results in maximum effectiveness of metabolism (~80 %, see Fig. 3). A relation $\rho \to 0$ is similar to Eq. (3) which means that the metabolism under such condition operates in accordance with the fast dissociation model (see above). An increasing of ρ leads to proportional (rough approximation, see Fig. 2) engaging

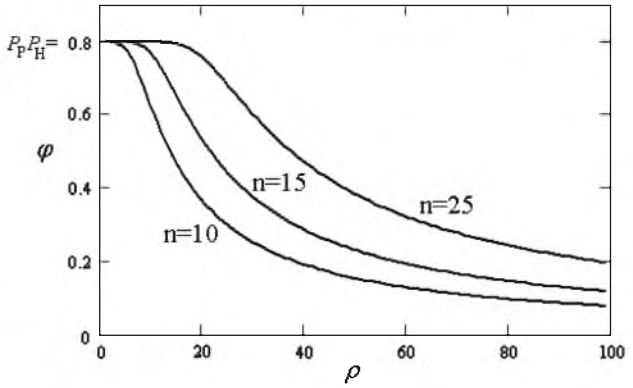

Fig. 3 Dependence of the effectiveness of metabolism on the incoming flow of molecules (ρ) for different total number of *Holes* n, and $P_P P_H = 0.8$

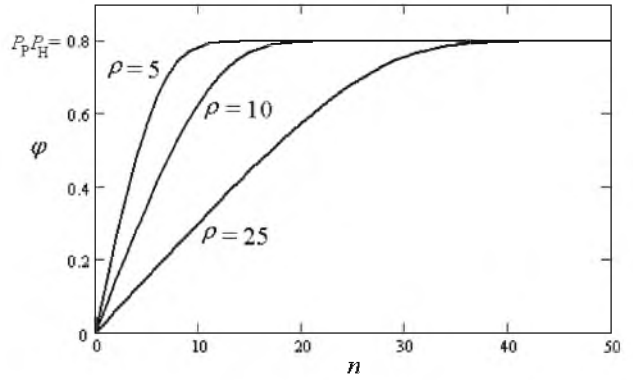

Fig. 4 Dependence of the effectiveness of metabolism φ on the total number of *Holes* in the system for different incoming flows ρ and $P_P P_H = 0.8$

of the *Holes*. Eventually, most of the *Holes* are becoming engaged, which means that the production of the outcoming metabolites is mainly determined by the rate of processing in the *Hole* (v_H) (which is maintained constant) and hence to a decreasing of φ. An increase of the number of metabolism centers (n) results in increasing of the number of processing points in the system and therefore to a greater φ (Fig. 3). Qualitatively, the same conclusions may be deduced from the Fig. 4. Very small n means that the system is not able to process all incoming molecules, whereas very high n allows it. An increasing of the incoming flow (ρ) under constant n decreases the effectiveness of metabolism (Fig. 4), as we have seen it on the Fig. 3.

3 Conclusions

The main aim of the work is to develop a new strategy of analysis of biological metabolism in terms of metabolites' flow by using the Pachinko model and a formalism

of queueing theory. The results presented here are a first step in pushing forward this approach and discuss only the simplest cases of the metabolizing system with different rates of interactions between the source molecules entering the system and the reaction center of the system (Hole) without queueing. Apparently, this approach allows the analysis to be extended to more complicated cases of the metabolizing processes, e.g., taking into consideration the non-uniformity of the incoming molecules (introduction of micrometabolites which block metabolism once being captured in the reaction center), subsequent consideration of a competition between macro- and micrometabolites for binding with the Holes, introduction of the queueing to the system and so forth. In fact, there are no limitations for applications of QT for the analysis of metabolism. One can just think about two fundamental assumptions behind the suggested theory of metabolism: an approach based on the probabilistic nature of the processes under investigation and consideration of the incoming molecules as a Poisson flow of events. In this respect, the suggested theory may be considered as a mixture of the flux-based and stochastic approaches, currently used for quantitative description of metabolic networks. We see the uniqueness of this theory in its ability to take into account the 'time structure' of the metabolites' flows, which includes different lifetimes of the metabolites' transformation/interaction/complexation in biological fluid and treatment of the effects of saturation as a consequence of statistical queueing of metabolites, using the well-elaborated instruments of the queueing theory. Further application of the developed theory to real biological systems, as well as inclusion of queues and competing fluxes into the QT approach, is currently under way in our laboratory.

Acknowledgments The work was supported by the Program of Strategic Development of VSU.

References

Aldridge BB, Burke JM, Lauffenburger DA, Sorger PK (2006) Physicochemical modeling of cell signaling pathways. Nat Cell Biol 8:1195–1203. doi:10.1038/ncb1497

Beckonert O, Coen M, Keun HC, Wang Y, Ebbels TMD, Holmes E, Lindon JC, Nicholson JK (2010) High-resolution magic-angle-spinning NMR spectroscopy for metabolic profiling of intact tissues. Nat Protoc 5:1019–1032. doi:10.1038/nprot.2010.45

Chaouiya C (2007) Petri net modeling of biological networks. Brief Bioinform 8:210–219. doi:10.1093/bib/bbm029

Covert MV, Schilling CH, Famili I, Edwards JS, Goryanin I, Selkov E, Palsson B (2001) Metabolic modeling of microbial strains in silico. Trends Biochem Sci 26:179–186. doi:10.1016/S0968-0004(00)01754-0

De Jong H (2002) Modeling and simulation of genetic regulatory systems: a literature review. J Comput Biol 9:67–103. doi:10.1089/10665270252833208

Grimbs S, Selbig J, Bulik S, Holzhütter H-G, Steuer R (2007) The stability and robustness of metabolic states: identifying stabilizing sites in metabolic networks. Mol Syst Biol 3:146–12. doi:10.1038/msb4100186

Jeong H, Tombor B, Albert R, Oltvai ZN, Barabási A-L (2000) The large-scale organization of metabolic networks. Nature 407:651–654. doi:10.1038/35036627

Kühl PW, Jobmann M (2007) Nonexponential time distributions in biocatalytic systems: Mass service replacing mass action. In: Deutsch A, Brusch L, Byrne H, de Vries G, Herzel H (eds) Mathematical modeling of biological systems, Volume I (Series: Modeling and simulation in science, engineering and technology), Birkhäuser, Boston, Basel, Berlin, pp 59–67. doi:10.1007/978-0-8176-4558-8_6

Lima-Mendez G, van Helden J (2009) The powerful law of the power law and other myths in network biology. Mol Biosyst 5:1482–1493. doi:10.1039/B908681A

Nicholson JK, Wilson ID (2003) Opinion: understanding 'Global' systems biology: metabonomics and the continuum of metabolism. Nat Rev Drug Discov 2:668–676. doi:10.1038/nrd1157

Nicholson JK, Lindon JC (2008) Systems biology: metabonomics. Nature 455:1054–1056. doi:10.1038/4551054a

Peleg M, Yeh I, Altman RB (2002) Modelling biological processes using workflow and Petri Net models. Bioinformatics 18:825–837. doi:10.1093/bioinformatics/18.6.825

Stelling J, Klamt S, Bettenbrock K, Schuster S, Gilles ED (2002) Metabolic network structure determines key aspects of functionality and regulation. Nature 420:190–193. doi:10.1038/nature01166

Trenkenshu RP (1992) Application of the queueing theory in biokinetics. In: Shokin YI (ed) Evolutionary modelling and kinetics. Nauka, Novosibirsk, pp 125–160 (in Russian)

Veselkov KA, Pahomov VI, Lindon JC, Volynkin VS, Crockford D, Osipenko GS, Davies DB, Barton RH, Bang J-W, Holmes E, Nicholson JK (2010) A metabolic entropy approach for measurements of systemic metabolic disruptions in patho-physiological states. J Proteome Res 9:3537–3544. doi:10.1021/pr1000576

Wagner A, Fell DA (2001) The small world inside large metabolic networks. Proc R Soc Lond B 268:1803–1810. doi:10.1098/rspb.2001.1711