

Energy conservation and maximal entropy production in enzyme reactions



Andrej Dobovišek^{a,b,*}, Marko Vitas^e, Milan Brumen^{a,b,c,d}, Aleš Fajmut^{a,c}

^a University of Maribor, Faculty of Natural Sciences and Mathematics, Koroška cesta 160, 2000 Maribor, Slovenia

^b University of Maribor, Faculty of Medicine, Taborska 8, 2000 Maribor, Slovenia

^c University of Maribor, Faculty of Health Sciences, Žitna ulica 15, 2000 Maribor, Slovenia

^d Jožef Stefan Institute, Jamova cesta 39, 1000 Ljubljana, Slovenia

^e Laze pri Borovnici 38, 1353 Borovnica, Slovenia

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ABSTRACT

A procedure for maximization of the density of entropy production in a single stationary two-step enzyme reaction is developed. Under the constraints of mass conservation, fixed equilibrium constant of a reaction and fixed products of forward and backward enzyme rate constants the existence of maximum in the density of entropy production is demonstrated. In the state with maximal density of entropy production the optimal enzyme rate constants, the stationary concentrations of the substrate and the product, the stationary product yield as well as the stationary reaction flux are calculated. The test, whether these calculated values of the reaction parameters are consistent with their corresponding measured values, is performed for the enzyme Glucose Isomerase. It is found that calculated and measured rate constants agree within an order of magnitude, whereas the calculated reaction flux and the product yield differ from their corresponding measured values for less than 20 % and 5 %, respectively. This indicates that the enzyme Glucose Isomerase, considered in a non-equilibrium stationary state, as found in experiments using the continuous stirred tank reactors, possibly operates close to the state with the maximum in the density of entropy production.

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1. Introduction

The maximum entropy production principle (MEPP) is an important principle of non-equilibrium thermodynamics. The principle states that an open thermodynamic system, which is initially in a non-equilibrium non-stationary state, under the conditions of mass and energy conservations, spontaneously approaches to a stationary non-equilibrium state characterised with a maximum in the entropy production (MEP) (Dyke and Kleidon, 2010; Martyushev and Seleznev, 2006; Martyushev, 2010). Basic formulation of MEPP states that maximum in the entropy production of a system in a stationary state is achieved by maximal thermodynamic flux at given thermodynamic force (Martyushev and Seleznev, 2006; Martyushev, 2010). MEPP is extensively used in the research within different fields of science. Its applications account for the study of nanoparticle systems (Belkin et al., 2015; Hubler et al., 2014),

enzyme reactions (Dewar et al., 2006; Dobovišek et al., 2011, 2014; Županović et al., 2004), photosynthesis (Juretić and Županović, 2003), crystal growth (Martyushev et al., 2000; Martyushev, 2014), electric circuits (Županović et al., 2004; Botrić et al., 2005), ecosystems (Meysman and Bruers, 2010) etc. For a complete review see literature (Martyushev and Seleznev 2006; Dewar et al., 2014).

MEPP is not the only optimization principle of non-equilibrium thermodynamics. There is also well known Prigogine's minimum entropy production principle. Since the two principles include different constraints, variables and parameters and they are used under different conditions, they should not be considered as conflicting principles (Martyushev and Seleznev, 2006). The minimum entropy production principle is a consequence of Onsager's linear relationships between fluxes and forces (Martyushev and Seleznev, 2006; Onsager, 1931a,b), which is valid approximation close to the thermodynamic equilibrium. In the book Modern thermodynamics (Kondepudi and Prigogine, 1998), Prigogine defined the minimum entropy production principle by introducing two fluxes v_1 , v_2 and the corresponding thermodynamic forces X_1 and X_2 . Linear relationships between forces and fluxes and the reciprocal nature of Onsager's coefficients are assumed in this definition. Moreover, the

* Corresponding author at: University of Maribor, Faculty of Natural Sciences and Mathematics, Koroška cesta 160, 2000 Maribor, Slovenia.

E-mail address: andrej.dobovisek@um.si (A. Dobovišek).

force X_1 is assumed to be a fixed value yielding constant flux v_1 . The only variable within the optimization procedure is then the second output force X_2 , which is adjusted during the optimization procedure in such a way that the induced flux v_2 is equal to zero. Hence, the final result is a minimum in the entropy production. This optimization procedure has been critically discussed (Županović et al., 2004; Martyushev, 2013). Especially, it was argued that Prigogine's theorem defines special stationary state with zero induced flux (Županović et al., 2004). This in fact is a quasi-equilibrium state established very close to equilibrium, in which energy conversion is terminated since the induced flux vanishes and it is unable to perform any work. In such state the transfer of energy needed to drive processes is blocked (Županović et al., 2004). It is doubtful that such state could be found in biological systems, where processes naturally take place far from equilibrium and blockages of the free energy transduction are not allowed. In addition to that, it is also questionable, how the minimum entropy production principle could be applied to a single biochemical cycle, since two fluxes and two forces are required according to its formal definition. In fact, the mass conservation law in a single biochemical cycle in a stationary state requires only one net flux (Županović et al., 2004). MEPP, which was proposed by H. Ziegler in 1963 (Ziegler, 1963), is formulated in more general manner and allows either linear or non-linear relationships between the thermodynamic fluxes and forces (Martyushev, 2013). In linear non-equilibrium thermodynamics MEPP is an accepted optimization principle, while in non-linear non-equilibrium thermodynamics it is considered as a working hypothesis (Martyushev and Seleznev, 2014). Recent theoretical investigations attempt to justify MEPP on the basis of Jaynes's maximization of the information entropy (Jaynes, 1980) applied to non-equilibrium systems in a stationary state by using the mass and the energy conservation constraints (Kleidon et al., 2003; Kleidon, 2010). The basic idea is to show that under these constraints the stationary state with maximal entropy production in open thermodynamic systems is also statistically the most probable state (Dewar, 2003, 2005; Attard, 2006; Niven, 2009; Županović et al., 2010). It has been also demonstrated that the most likely state of the metabolic network in a *Thermoanaerobacterium saccharolyticum* operating with a reduced metabolic functionality is consistent with maximal entropy production (Unrein and Srienc, 2011).

Enzymatic reactions are typical examples of biochemical processes with non-linear flux-force relationship of the form $v \propto (e^{X/RT} - 1)$ (Martyushev and Seleznev, 2015). For them the applicability of MEPP is still under question. Enzymes are the key regulators of biochemical reactions in living cells and are strongly involved in almost all metabolic pathways due to their capability to speed up biochemical reactions and the ability to regulate and to be regulated. From the same reasons enzymes are also in the core of biotechnology and are indispensable in a multitude of biotechnological processes. In living cells as well as in certain types of chemical reactors enzymes operate in open reaction systems with incoming and outgoing fluxes of matter. Such systems spontaneously evolve towards non-equilibrium stationary states, where thermodynamic forces and fluxes are constant. This results in continuous energy dissipation and entropy production (Nicolis and Prigogine, 1977; Qian 2006, 2007). Such idealised view holds mainly for the biotechnological processes, where enzymes operate in a controlled stationary environment. In a living cell an enzyme is in constant interaction with a large number of other processes and thus its environment could be changeable throughout the cell life-time. In such cases it is often assumed that enzymes operate on a much shorter time scales compared with the cell life-time. Thus, an enzyme reaction could be considered as a fast process, during which a quasi-stationary state is achieved after a short transient (Klipp et al., 2005). Slowly changing environment in which the

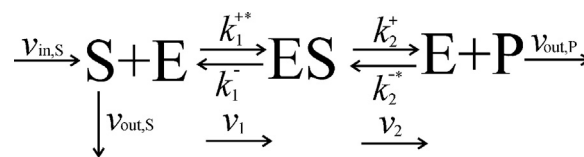


Fig. 1. Kinetic scheme of a reversible two-step enzyme reaction in an open reaction system considered for analysis with MEPP. External fluxes are: $v_{in,S}$ – incoming flux of substrate (S), $v_{out,S}$ – outgoing flux of substrate (S), $v_{out,P}$ – outgoing flux of product (P). Fluxes v_1 and v_2 are the net reaction fluxes in reaction steps $S + E \leftrightarrow ES$ and $ES \leftrightarrow E + P$, respectively. $S + E$ and $E + P$ represent macromolecular unbound states of enzyme (E) with ligands, which are substrate (S) and product (P), respectively. ES represents a complex of enzyme (E) bound with substrate (S). k_1^+ and k_2^+ are the first order rate constants, and k_1^{++} and k_2^{--} are the second order rate constants.

non-stationary enzyme reaction might take place could also be considered as approximately stationary within an appropriate short time interval. Thermodynamics of stationary states thus play an important role in understanding the metabolic processes in living cells and in biotechnology.

The aim of our work is to investigate applicability of MEPP on a single reversible two-step enzyme reaction presented in Fig. 1. An example of the enzyme family that corresponds with this kinetic scheme is the isomerase enzyme family. Isomerases are the enzymes that transform the substrate molecules into the product molecules, which possess the same atomic composition but have different arrangement as substrate molecules. The enzyme, which is explicitly considered in our study is Glucose Isomerase (GI) classified as D-xylose ketolisinomerase (EC 5.3.1.5) (Converti et al., 1997; Converti and Del Borghi 1998; Meilleur et al., 2006). This enzyme converts D-glucose into D-fructose and plays an important role in biotechnological industrial processes of high fructose corn syrup production (Converti et al., 1997; Converti and Del Borghi 1998; Meilleur et al., 2006). The model calculations based on MEPP are evaluated with experimental results obtained in a continuous stirred tank reactor, whereby the reactor with immobile GI was fed with the glucose solution (Converti et al., 1997; Converti and Del Borghi, 1998).

Though several authors argue against the validity of MEPP in the field of chemical kinetics (Andresen et al., 1984; Nicolis and Nicolis, 2010; Ross et al., 2012; Vellela and Qian, 2009), MEPP has been already successfully used in this field. For example, Dewar et al. (2006) used MEPP to study the properties of the rotary enzyme ATP synthase and showed that values of two key functional kinetic parameters of the ATP synthase, the gearing ratio and the relative angular position of the catalytic dwell, predicted with MEPP, are compatible with biologically optimal function of that enzyme. Juretić and Županović (2003) studied bacterial photosynthesis as a cyclic chemical reaction and concluded that proton pumps operate close to the maximum in entropy production. A general proof that entropy production can be maximized with respect to the kinetic parameters in any of the single enzymatic reaction steps has been previously shown (Dobovišek et al., 2011) and that result has been applied for the theoretical prediction of a single rate constant in an internal reaction step of the enzyme reaction catalysed by β -lactamase (Dobovišek et al., 2011, 2014). In previous studies (Dewar et al., 2006; Dobovišek et al., 2011, 2014; Juretić and Županović, 2003) MEPP was used for the optimization of those selected reaction steps in an enzyme reaction that were considered as most important and sensitive for the effective development of the enzyme function during biological evolution. An important and open question remains, how to apply MEPP to maximize the density of entropy production for the entire enzyme reaction, whereby all individual enzymatic reaction steps would be considered in maximization procedure.

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