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Energy Storage and Transduction in Mitochondria

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1. Introduction

The processes of energy storage and dissipation in biological systems have been studied during the past few decades in search of alternative energy storage systems to the conventional ones. Based on these studies, living cells have proven to provide appropriate energy storage and consumption patterns for other areas of science and engineering (Alberty, 2003; Lehninger, 1984).

The ability of cells to store energy in an efficient manner and to release it to gain control over the system, has made them an important target for energy related studies and modeling efforts (Qian & Beard, 2006). Since bioenergetics and biochemical thermodynamics specifically deal with energy transductions in biochemical reactions, it would be necessary to investigate these processes from a thermodynamic point of view.

Living organisms usually operate at constant temperature and depend on energy from food consumption or exposure to sunlight for running their vital processes and maintaining their body temperature. Energy transduction takes place in the mitochondrion of animal cells, chloroplast of plant cells and cytoplasm of bacteria. This study focuses on bioenergetics of mitochondria, considering that membranes of mitochondria, chloroplasts and bacteria show many similarities in this regard.

Mitochondria have two types of complexes for obtaining energy from substrates. Complex I includes production of NADH from oxidation of fatty acids, TCA cycle, and glycolysis. Complex II includes $FADH_2$ production from TCA cycle. These complexes vary in different kinds of mitochondria (Cairns et al., 1998). The energy is eventually stored in the body in the form of high-energy molecules such as Adenosine Triphosphate (ATP). ATP molecules have three high-energy bonds which enable them to store energy and then release it as the bonds are broken according to the following equations (Hammes, 2000; Harper et al., 2000):

$$ATP + H_2O \rightarrow ADP + P_i \quad , \Delta G^{\circ\prime} = (-30.5)\ KJ/mol \tag{1}$$

$$ADP + H_2O \rightarrow AMP + P_i \quad , \Delta G^{\circ\prime} = (-27.6)\ KJ/mol \tag{2}$$

The change in Gibbs free energy for ATP hydrolysis in cells is estimated as follows:

$$\Delta G = \Delta G^{\circ\prime} + R.T.\ln(k) \tag{3}$$

The normal operating conditions of cells would be considered as T= 37°C and k=2300. By replacing these values into equation 3, the total amount of energy released from the hydrolysis of each mole of ATP will be 50 KJ. As a result, an average person with a body mass of 50 K, who needs at least 11700 KJ energy per day, will require over 125 K of ATP. The fact that this amount of energy is produced by only 50 g of this molecule in his body, confirms that ATP is constantly produced and consumed in cycles in the body (Datta, 2002; Haynie, 2003).

Oxidation of different substrates such as 3-hydroxybutyrate, glutamate plus malate (with equal mole fractions), 2-oxoglutarate, and succinate in mitochondria provides the energy that is required to phosphorylate molecules of ADP to form ATP molecules. This process is called "oxidative phosphorylation" and enables the aerobic organisms to obtain more energy from the substrates in comparison to anaerobic organisms (Haynie, 2003; Scheffler, 2000). The overall oxidative phosphorylation process in the mitochondria can be expressed as follows:

$$SH_2 + 0.5O_2 + nADP + nP_i \rightarrow S + H_2O + nATP \quad (4)$$

where S represents the substrate and the stoichiometric coefficient, n, is also determined by the type of substrate (Lemasters et al., 1984). The inner membrane operates very selectively and most of the metabolites and ions such as P_i, ADP, ATP and the respiratory substrates can only cross it through channels or by means of carrier proteins. The transport mechanism of these carriers is usually based on exchanging one substance for the other (Szewczyk & Wojtczak, 2002).

According to the chemiosmotic hypothesis, the electro-chemical driving force for transferring potassium ions into the matrix, leads to the opening of K_{ATP} channel which in turn results in osmotic swelling. In order to maintain electrical balance, the protons released by substrate oxidation are pumped from the matrix to the intermembrane space of mitochondrion. Subsequently, the concentration gradient drives these protons back to the matrix, where they will contribute to the phosphorylation process (Jin & Bethke, 2002; Mitchell, 1961, 1966, 1972). Therefore, proton flux causes a proton motive force (PMF) which is the key factor in energy transduction and ATP production. This process has been schematically shown in figure 1.

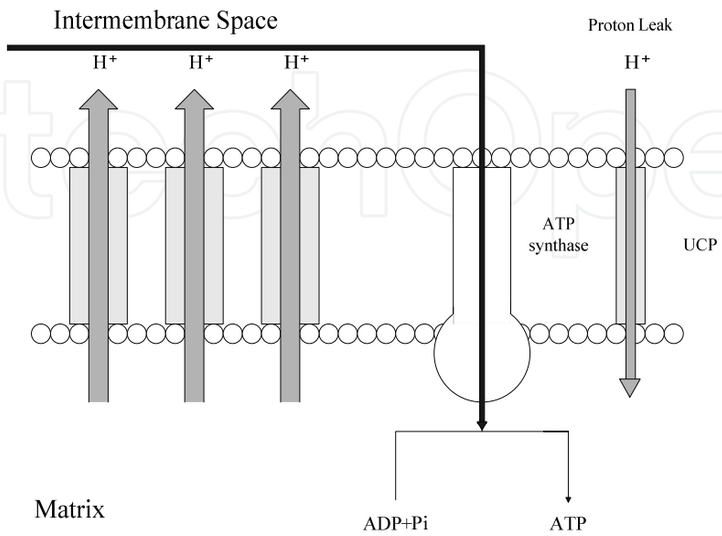

Fig. 1. Proton transport across the inner membrane of mitochondrion

However, coupling of oxidation and phosphorylation processes is not 100 percent complete. As can be observed in figure 1, the uncoupling proteins (UCPs) in the inner membrane let some protons back to the matrix without passing through ATPsynthase (Stuart et al., 2001). This proton leak reduces the coupling of processes and lowers the amount of ATP that is produced (Brand, 2005; Jezek et al., 1998; Jezek, 1999). The cycle of proton pumping and proton leaking across the membrane, also referred to as futile cycle, can release significant amounts of energy (Brand et al., 1999).

The efficiency of oxidative phosphorylation demonstrates the physiological role of mitochondria. In general, mitochondria are capable of taking on different roles to economize energy storage relevant to the current status of the body. These roles can be summarized as (Cairns et al., 1998):

- Maximizing ATP production
- Maximizing P_i production
- Minimizing the costs of energy storage
- A combination of the above

The overall rate of ATP production depends on substrate availability and cellular energy demand. Mitochondria of different tissues have various functions for matching the energy transductions with energy demands; based on these functions, mitochondria will be categorized as either "energetic" or "thermogenic" (Moyes, 2003). Mitochondria with energetic role, e.g. those of liver cells, are designed to maximize ATP production to provide the energy required for vital reactions. On the other hand, mitochondria with thermogenic role, e.g. those of brown adipose tissue (BAT) cells, release a considerable amount of energy as heat to maintain constant body temperature (Porter, 2001; Schrauwen & Hesselink, 2002).

Mitochondria within BAT cells differ from mitochondria of liver cells in that they have a limited rate of ATP synthesis, lower membrane potential, and higher respiratory rates (Kowaltowski, 2000). This is due to varying amounts of proton leak in different mitochondria and also dependents on the body mass (Hulbert, 2003; Else et al., 2004). The major characteristic of the membrane that distinguishes these two types of mitochondria is the property of membrane proton permeability (C_H) which can be used as a criterion for evaluation of proton leak across the membrane. The amounts of C_H are generally much higher in thermogenic mitochondria than the energetic ones (Nicholls, 1997). The main uncoupling protein in BAT is UCP1 which is activated by fatty acids and inhibited by nucleotides (Brand et al., 1999). These remarkable characteristics of BAT cell mitochondria have been a topic of interest among many researchers both from biological and thermodynamic point of views (Matthias et al., 2000).

In order to apply biological energy patterns to current industrial energy systems, an appropriate body of comprehensive models and criteria is required. Unfortunately most of the studies on energetic and thermogenic functions have so far focused on qualitative descriptions (Cadenas et al., 2001; Schrauwen & Hesselink, 2002) and little effort has been made to compare them from a quantitative point of view.

In this study we have proposed a thermodynamic model for ATP synthesis in systems that operate with some distance from equilibrium, by which the energy loss and the efficiency of oxidative phosphorylation can be calculated. Consequently, we have made a quantitative comparison between the rate of energy loss and efficiency of energetic and thermogenic mitochondria by means of this model. This quantitative evaluation of different mitochondria leads to a better understanding of their thermodynamic functions.

2. Non-equilibrium thermodynamics

Although thermodynamics is highly applied in studying biological systems, still many thermodynamic analyses are done based on equilibrium conditions. In other words, it is usually assumed that the systems tend to an equilibrium state after a while. This assumption is not very accurate for biological systems due to the fact that their survival depends on constant mass and energy exchange with their environment. As a result, it would be best to assume that such systems approach a non-equilibrium stationary state (NESS) (Qian & Beard, 2005).
The main difference between equilibrium steady state and non-equilibrium stationary state is that the system needs a constant supply of energy to maintain the latter state, which can be provided by cellular metabolism (Jou & Llebot, 1990). As a result, non-equilibrium thermodynamics (NET) govern such systems.
One of the simplifying assumptions in NET is the local equilibrium assumption, which states that in every small region within the system, thermodynamic properties can be related to state variables by means of equilibrium state equations. A small region is identified by enough number of molecules so that the macroscopic theory can be applied. Therefore, the entropy and specific internal energy can be obtained through the same calculations as in equilibrium state and Gibbs and Gibbs-Duhem relations are also applicable (Demirel & Sandler, 2001, 2004; Hill, 2002; Mazur, 1999).
When applying non-equilibrium thermodynamics to a process, it is important to take into account how far from equilibrium the process is (Demirel & Sandler, 2004). Distance from equilibrium conditions can be determined by the energy dissipation function (Φ) which gives the rate of free energy loss of a system (Caplan & Essig, 1969).
Entropy production in living systems can be viewed from three different aspects (Gnaiger, 1994):

- Stationary low entropy level:
  According to Prigogin, biological systems tend to produce the minimum amount of entropy and maintain almost constant entropy, so that it can be assumed:

$$dS/dt = 0 \tag{5}$$

- Entropy production within the system:
  Energy dissipation from irreversible processes in the system cause an increase in the entropy so that:

$$d_iS/dt > 0 \tag{6}$$

- Stream of negative entropy:
  In order to balance the entropy that is produced in the cell, some entropy is lost through interactions with the surrounding environment. This behavior can be expressed as follows:

$$d_eS/dt < 0 \tag{7}$$

Subsequently, the overall entropy balance of a biological system based on non-equilibrium thermodynamics can be regarded as:

$$dS/dt = d_iS/dt + d_eS/dt \tag{8}$$

Equation 8 suggests that entropy change in cells has two distinct components; d_eS which represents entropy exchange through system boundaries, and d_iS that corresponds to

entropy production within the system. For every small volume within the system (dv), energy dissipation function and entropy are related by (Demirel & Sandler, 2001):

$$\phi = T.\, d_i S/dt.\, dv \tag{9}$$

Since energy dissipation is directly proportional to the entropy production, Φ can be used to evaluate the amount of energy released during a process (Demirel & Sandler, 2004). Therefore, one of the main objectives of this study was to determine Φ for different mitochondria in order to compare their functions. However, a prerequisite for determination of Φ is the knowledge of the fluxes and forces in the system.
Based on Linear Non-equilibrium Thermodynamics theory (LNET) for processes with small values of Φ, the relationship between the driving forces (Potential gradients within the system) and thermodynamic fluxes are linear. LNET theory assumes local thermodynamic equilibrium within the system and is valid for many processes in biological systems (Demirel & Sandler, 2001). This can be stated as follows:

$$J_i = \sum_j (L_{ij}.X_i)\ ;\ (i,j = 1,2,\ldots,n) \tag{10}$$

In equation 10, J_i represent thermodynamic fluxes, and X_j stand for thermodynamic forces. The L_{ij} coefficients are phenomenological coefficients (PCs) that have the characteristics of conductance and contain some general information on the coupling mechanism of the processes (Aledo & Valle, 2004). According to the Onsager's theory, the matrix of PCs is symmetrical and positive definite. Therefore, the following relations exist (Stucki, 1980):

$$L_{ij} = L_{ji} \tag{11}$$

$$L_{ii} \geq 0 \tag{12}$$

$$L_{ii}.L_{jj} \geq L_{ij}^2 \tag{13}$$

Based on the information provided in this section, Φ can be determined for different processes if the relevant fluxes and forces are known. In the next section a thermodynamic model is developed to study oxidative phosphorylation processes and dissipation function.

3. Thermodynamic model

Although many studies have been carried out on ATP production in mitochondria, literature seems to be lacking reliable mathematical models in this area. Such models could be used to provide proper quantitative results on the amounts of energy being stored or released, as well as the entropy production and efficiency of oxidative phosphorylation processes.
In this section a thermodynamic model for determining energy dissipation, ATP production, and efficiency of oxidative phosphorylation processes is presented. This model is based on non-equilibrium thermodynamic equations, and chemiosmotic theory (Golfar et al., 2010).

3.1 Fluxes and forces

The first step is to determine the relationships between thermodynamic forces and fluxes. For oxidative phosphorylation, equation 10 is written as follows:

$$J_{Ox} = L_{OO}.A_{Ox} + L_{OH}.\Delta\mu_H + L_{OP}.A_{Ph} \tag{14}$$

$$J_H = L_{HO}.A_{Ox} + L_{HH}.\Delta\mu_H + L_{HP}.A_{Ph} \quad (15)$$

$$J_{Ph} = L_{PO}.A_{Ox} + L_{PH}.\Delta\mu_H + L_{PP}.A_{Ph} \quad (16)$$

In equations 14, 15 and 16, the subscripts Ox, H, and Ph refer to substrate oxidation, net H^+ flow and ADP phosphorylation. $\Delta\mu_H$ is the electrochemical potential difference across the inner membrane of mitochondrion and can be obtained from the following equation:

$$\Delta\mu_H = F\Delta\psi - 2.3(RT.\Delta pH) \quad (17)$$

where F is the Faraday constant and $\Delta\psi$ is the electrochemical potential difference across the membrane. The values of $\Delta\psi$ vary between 140 to 200 mV for different mitochondria.
A_{Ox} and A_{Ph} are the affinities of oxidation and phosphorylation processes which serve as thermodynamic forces. These affinities can generally be calculated by means of the following equation:

$$A_i = -\sum_j(\nu_{ji}.\mu_j) \quad (18)$$

where ν_{ji} is the stoichiometric coefficient of species j in the i^{th} reaction and μ_j is the electrochemical potential of j (Caplan & Essig, 1969). However, in the case of oxidative phosphorylation, the affinities of processes have been considered equal to Gibbs free energy difference (ΔG) with opposite signs (Lemasters et al., 1984).
In order to establish the phenomenological coefficients, the relationships among them should be verified. The following steps have been taken to determine which coefficients are independent and how to relate them to the dependent ones.
Although J_H can be calculated by equation 15, it can also be written as sum of the flux due to oxidation and the fluxes through ATPsynthase and passive channels (proton leak) as follows:

$$J_H = (-m_O.J_{Ox}) + C_H.\Delta\mu_H + m_P.J_{Ph} \quad (19)$$

where m_O and m_P are the stoichiometric coefficients of the respective pumps and C_H is the proton permeability of the membrane per unit area (Jou & Llebot, 1990). By replacing equations 14 and 16 into equation 19 and its comparison with equation 15 results in the following set of equations:

$$L_{OH} = (-m_O).L_{OO} + m_P.L_{PO} \quad (20)$$

$$L_{PH} = (-m_O).L_{OP} + m_P.L_{PP} \quad (21)$$

$$L_{HH} = (-m_O).L_{OH} + C_H + m_P.L_{PH} \quad (22)$$

Equations 20 to 22 enable us to calculate the desired phenomenological coefficients.
Since mitochondria operate at steady state conditions, all of the protons that are pumped to the intermembrane space will return to the inner membrane either by means of ATPsynthase or other enzymes. Otherwise, the electrochemical potential difference between the two sides of the membrane would increase. Therefore, the total proton flux is equal to zero at steady state ($J_H = 0$). Setting equation 15 equal to zero, $\Delta\mu_H$ will be calculated from the next equation:

$$\Delta\mu_H = ((-L_{PH})/L_{HH}).A_{Ph} + ((-L_{OH})/L_{HH}).A_{Ox} \quad (23)$$

Substituting equation 23 into equations 14 and 16, the fluxes J_{Ox} and J_{Ph} will appear as:

$$J_{Ox} = [L_{OO} - (L_{OH}^2/L_{HH})].A_{Ox} + [L_{OP} - (L_{OH}.L_{PH}/L_{HH})].A_{Ph} \quad (24)$$

$$L_{Ph} = [L_{PO} - (L_{PH}.L_{OH}/L_{HH})].A_{Ox} + [L_{PP} - (L_{PH}^2/L_{HH})].A_{Ph} \quad (25)$$

Now that we are able to determine the values of oxidation and phosphorylation fluxes by means of equations 24 and 25, we can proceed to the next step to evaluate energy dissipation function in mitochondria.

3.2 Energy dissipation function

Under isothermal conditions, Φ can be generally expressed as follows (Caplan & Essig, 1969):

$$\phi = \left[-\sum_j(\dot{n}_j^{in}.\Delta\mu_j) + \sum_j(J_i.A_i^{ex})\right] \quad (26)$$

where n_j represents the number of moles of species j, and $\dot{n}_j$ is defined as:

$$\dot{n}_j = (dn_j)/(dt) \quad (27)$$

The superscripts "in" and "ex" refer to the interior and exterior of the inner membrane of mitochondrion. In case of oxidative phosphorylation the following relation exists for net H^+ flow:

$$\dot{n}_H^{in} = (-)J_H \quad (28)$$

Therefore, the general equation for energy dissipation function (equation 26) takes the following form:

$$\phi = J_{Ox}.A_{Ox} + J_H.\Delta\mu_H + J_{Ph}.A_{Ph} \quad (29)$$

At the steady state the net proton flux is set to zero so that Φ is as follows:

$$\phi = J_{Ox}.A_{Ox} + J_{Ph}.A_{Ph} \quad (30)$$

Substituting equations 24 and 25 into equation 30, the dissipation function for oxidative phosphorylation at steady state will appear as:

$$\phi = \left\{\begin{matrix}[L_{OO} - (L_{OH}^2/L_{HH})] + 2[L_{OP} - (L_{OH}.L_{HP}/L_{HH})].(A_{Ph}/A_{Ox}) \\ +[L_{PP} - (L_{PH}^2/L_{HH})].(A_{Ph}/A_{Ox})^2\end{matrix}\right\}.A_{Ox}^2 \quad (31)$$

In equation 31, L_{OO} (influence of substrate availability on oxygen consumption), L_{PP} (feedback of phosphate potential on ATP production), and C_H (membrane proton permeability) depend on the nature of the inner membrane and are available for various mitochondria. Similarly, the values of m_O and m_P for different substrates are available from the literature. Knowing the amounts of these parameters, L_{OH}, L_{PH}, and L_{HH} can be obtained from equations 20 to 22. L_{OP} (substrate dependency of ATP production) can be determined according to degree of coupling of oxidation and phosphorylation reactions (q) by means of the following relation (Cairns et al., 1998):

$$q = L_{OP}/[(L_{OO}.L_{PP})^{0.5}] \quad (32)$$

q is a dimensionless scale that represents how well the process of oxidation is coupled with phosphorylation. In case of complete coupling, q is equal to one and if the processes are independent from each other, q is equal to zero. For any pair of coupled reactions, q can be viewed as follows:

$$q = \sqrt[N]{\prod L_{ij}/\prod L_{ii}} \quad (33)$$

When the value of q is close to one, the stoichiometric coefficients can be applied with an appropriate precision. As the values of q deviate from one, it would be best to use phenomenological stoichiometric coefficients (Z) that are defined as (Stucki, 1980):

$$Z = \sqrt{L_{PP}/L_{OO}} \quad (34)$$

As q tends to one, values of Z tend to real values of stoichiometric coefficients. The relationship between q and Z is as follows (Lemasters et al., 1984):

$$Z = (-q).(\Delta G_R/\Delta G_P) \quad (35)$$

where ΔG_R and ΔG_P are the Gibbs free energy change for phosphorylation and oxidation reactions respectively.

The degree of coupling has been experimentally determined for some energetic mitochondria (Lemasters et al., 1984; Stucki, 1980), but as for thermogenic ones the data is more limited. Therefore, we have considered the full range of variations of q from 0 to 1. Based on equation 32, for fixed values of L_{OO} and L_{PP}, L_{OP} is minimum at q = 0 and maximum at q = 1. Therefore the range of variations of L_{OP} can be determined for any kind of mitochondrion. After determination of the related parameters, Φ can be calculated for any given A_{Ph}/A_{Ox} using equation 31.

Although Φ is a very useful criterion for comparing different mitochondrial functions, evaluating the efficiency of oxidative phosphorylation processes will provide more insight into these missions and operating regimes.

3.3 Efficiency

The efficiency of oxidative phosphorylation is defined as the percentage of released energy by oxidation process that is consumed by phosphorylation process as follows (Kedem & Caplan, 1965):

$$\eta = (-J_{Ph}.A_{Ph})/(J_{Ox}.A_{Ox}) \quad (36)$$

The J_{Ph}/J_{Ox} ratio (or P/O ratio, in brief) can be theoretically determined from equations 24 and 25 and consequently, the efficiency of oxidative phosphorylation can be easily obtained from equation 36. The J_{Ph}/J_{Ox} ratio is an important criterion in biological systems (Hinkle, 2005) and represents the number of moles of ATP that are produced per consumed moles of oxygen. High values of this ratio imply high efficiency for energy storage processes. Furthermore, the optimum efficiency (η_{opt}) could be determined by means of the following equation (Stucki, 1980):

$$\eta_{opt} = q^2/\left(1+\sqrt{1-q^2}\right)^2 \quad (37)$$

From equation 37 it can be concluded that optimum efficiency happens when phosphorylation flux is not zero and the priority for the mitochondrion is to maximize ATP production. Clearly, complete coupling of oxidation and phosphorylation processes leads to maximum efficiency.

Such phenomenological thermodynamic models as the present one deal with the role of mitochondria of different organs in utilization and storage of biological energy (or ATP). As a result they could be used to determine energy dissipation function and efficiency of oxidative phosphorylation processes in mitochondria with different thermodynamic functions. The output of these theoretical approaches could be compared with experimental data, if any, to evaluate the model.

4. Results and discussion

In this section, the thermodynamic model is applied to two different types of mitochondria to compare their behaviors based on energy dissipation and efficiency of oxidative phosphorylation processes. We have focused on types of mitochondria for which there is sufficient experimental data available in literature. This will provide the chance to evaluate the theoretical results generated by the model by comparing them against the experimental results.

In order to investigate mitochondria with different thermodynamic roles, rat liver cell mitochondrion with energetic role and BAT cell mitochondrion with thermogenic function have been chosen. Calculations have been carried out for 3-hydroxybutyrate, glutamate plus malate (with equal mole fractions), 2-oxoglutarate and succinate as substrate, all of which have been widely used in previous investigations in this field. The values of different parameters for these two tissues (Jou & Llebot, 1990) and four substrates (Copenhaver & Lardy, 1952; Lee et al., 1996) are listed in tables 1 and 2 respectively. Table 1 includes the parameters related to the structure of the membranes, whereas table 2 contains the parameters corresponding to different substrates.

Parameter	Rat Liver Mitochondrion	Brown adipose tissue Mitochondrion
L_{OO}	1.9 $nmolO_2/(mgP.min.mV)$	0.5 $nmolO_2/(mgP.min.mV)$
L_{PP}	7.9 $nmolH^+/(mgP.min.mV)$	0.4 $nmolH^+/(mgP.min.mV)$
C_H	3.2 $nmolH^+/(mgP.min.mV)$	35 $nmolH^+/(mgP.min.mV)$

Table 1. Parameters related to rat liver and brown adipose tissue mitochondria (Jou & Llebot, 1990).

Energy dissipation function has been calculated in each case by means of equation 31. Since q is approximately 0.98 in rat liver cell mitochondria (Lemasters, 1984), L_{OP} is equal to 3.8 according to equation 32. As for BAT cell mitochondria, data on values of q were not sufficient. As a result, we assigned different values between 0 and 1 to q which lead to values of L_{OP} varying between 0 and 0.4 based on equation 32. The proton gradient across

the inner membrane is taken equal to 200 mV in calculations but the results still hold for a large range of affinity ratios for proton gradients from 140 to 200 mV.

Substrate	m_P	m_O	A_O
3-Hydroxybutyrate	4 nmolH^+/nmolATP	12 nmolH^+/nmolO_2	209 KJ/mol
Glutamate+Malate	4 nmolH^+/nmolATP	12 nmolH^+/nmolO_2	220 KJ/mol
2-Oxoglutarate	4 nmolH^+/nmolATP	12 nmolH^+/nmolO_2	307 KJ/mol
Succinate	4 nmolH^+/nmolATP	6 nmolH^+/nmolO_2	151 KJ/mol

Table 2. Parameters related to different substrates (Copenhaver & Lardy, 1952; Lee et al., 1996).

By replacing these values into equation 31, the rate of free energy loss (Φ) has been determined and plotted versus the affinity ratio (A_{Ph}/A_{Ox}) for both energetic and thermogenic mitochondria with 3-hydroxybutyrate, glutamate plus malate, 2-oxoglutarate and succinate respectively. Figures 2 to 5 correspond to these plots.

It is clearly seen that the values of Φ in BAT mitochondria are two to four times greater than rat liver mitochondria, indicating higher amounts of proton leak in BAT mitochondria. These results are in complete agreement with the qualitative descriptions based on biological functions of the two types of tissues and indicate the validity of the proposed model for such calculations.

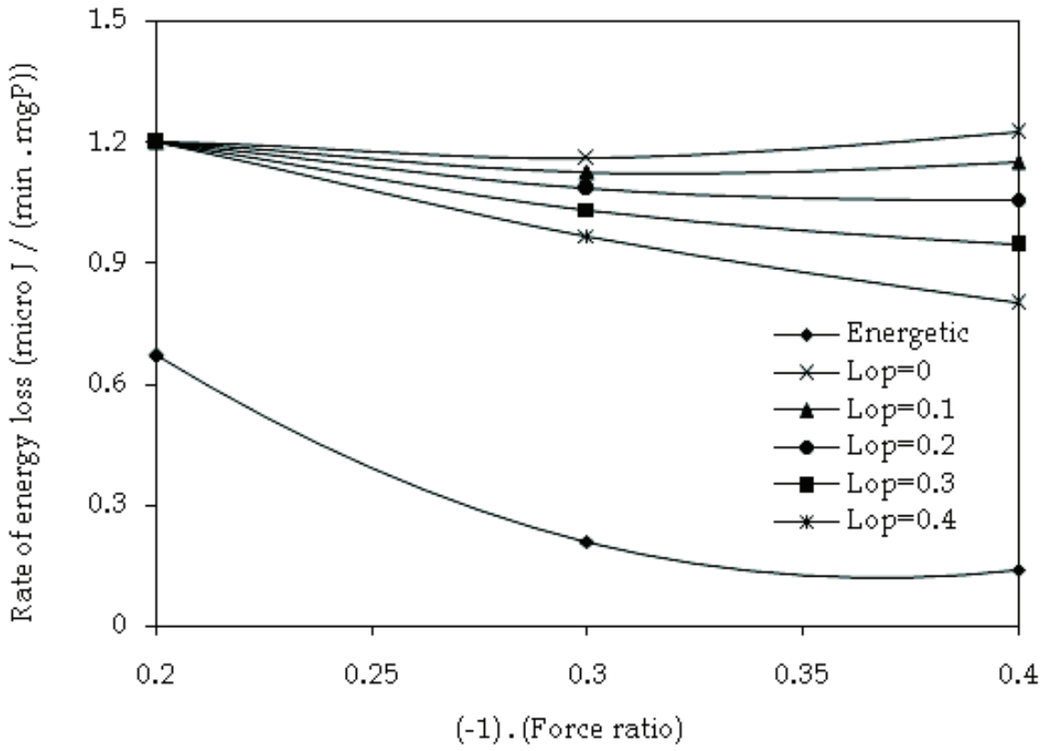

Fig. 2. Rate of energy loss (micro joules/(mgP.min)) vs. force ratio in rat liver and BAT mitochondria with 3-hydroxybutyrate as substrate.

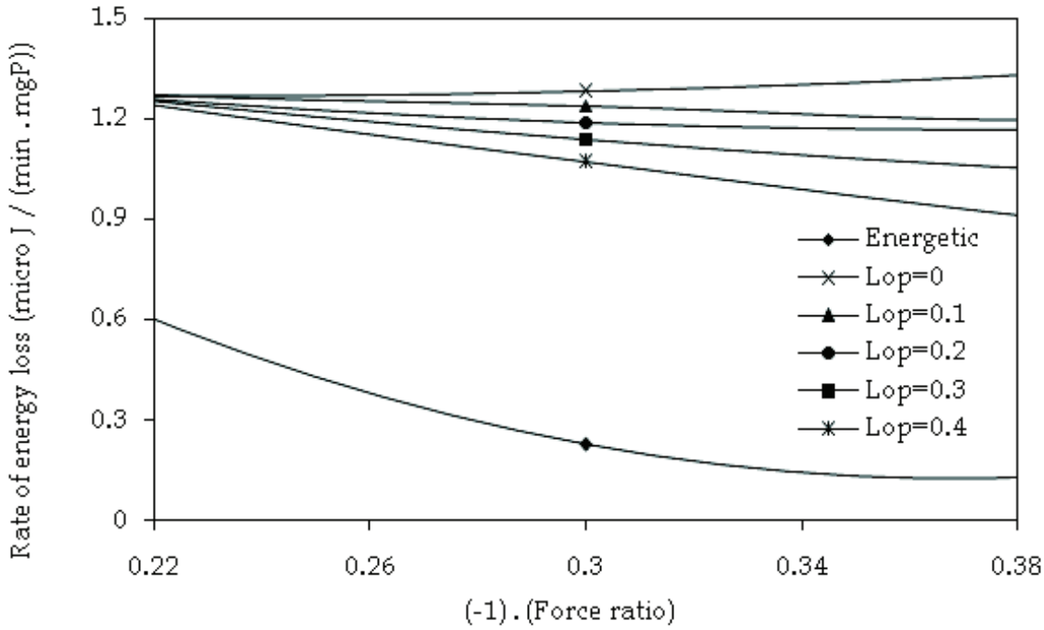

Fig. 3. Rate of energy loss (micro joules/(mgP.min)) vs. force ratio in rat liver and BAT mitochondria with glutamate+malate as substrate.

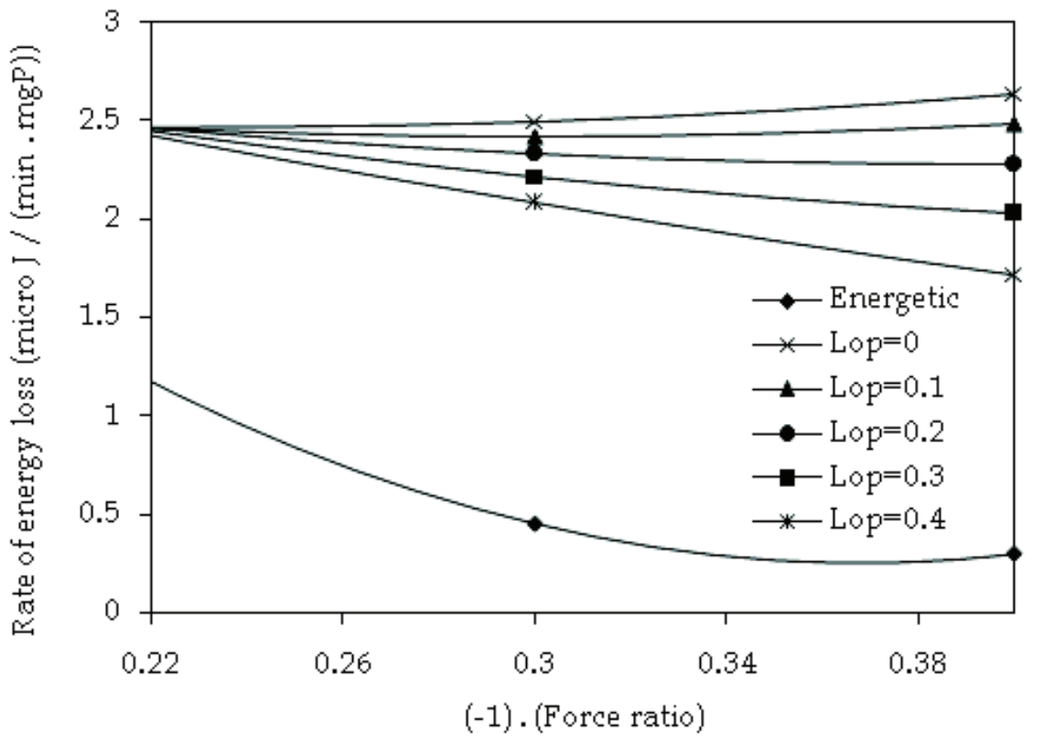

Fig. 4. Rate of energy loss (micro joules/(mgP.min)) vs. force ratio in rat liver and BAT mitochondria with 2-oxoglutarate as substrate.

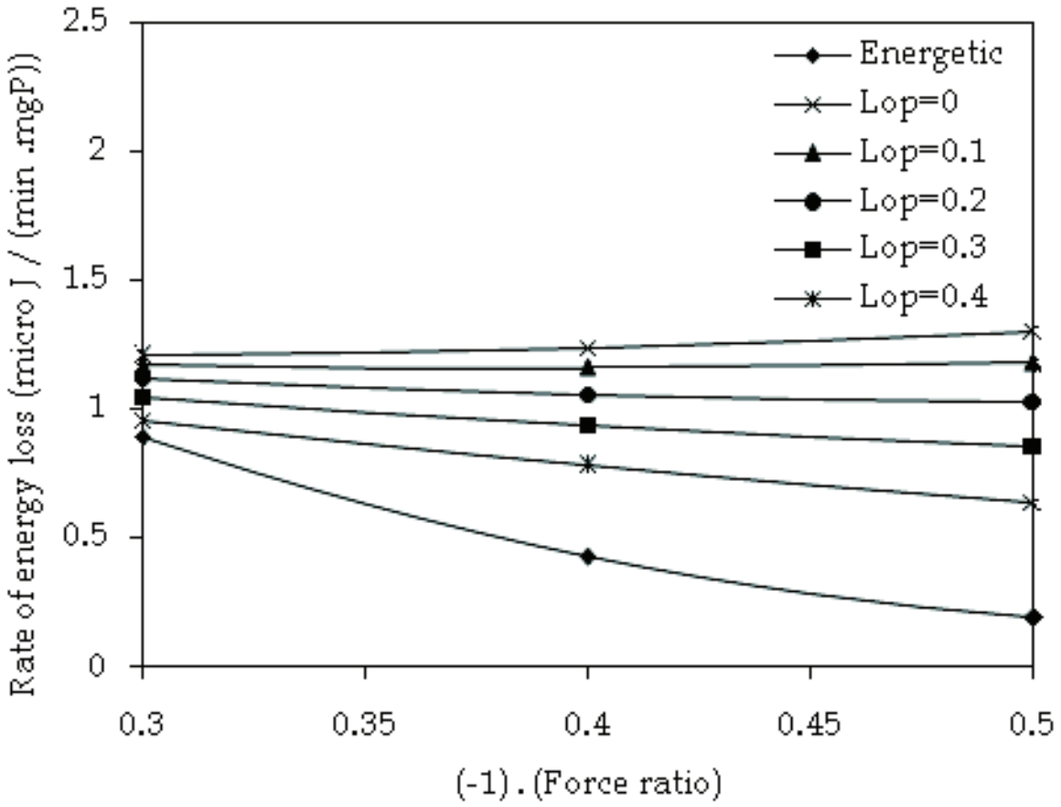

Fig. 5. Rate of energy loss (micro joules/(mgP.min)) vs. force ratio in rat liver and BAT mitochondria with succinate as substrate.

The efficiency of oxidative phosphorylation processes have also been calculated for these mitochondria for different values of L_{OP} with the four selected substrates, and plotted against Φ in figures 6 to 9. The curves in these figures show theoretical results while separate points show some experimental results (Hinkle et al., 1991; Lehninger, 1955; Lemasters, 1984; Nath, 1998; Nicholls, 1974).

From figures 6 to 9 three main points can be made:

- As expected, the efficiency of oxidative phosphorylation is much higher in rat liver than in BAT mitochondria. Lower efficiency is an advantage for BAT mitochondria since it enables them to release heat, conduct thermogenesis and regulate body temperature (Cannon & Nedergaard, 2003).
- In both energetic and thermogenic tissues the values of Φ are low considering the high values of efficiency. Furthermore, in rat liver mitochondria, selection of parameters leads to minimum entropy production with high efficiency. This operating regime in biological systems complies neither with minimum entropy production (MEP) nor maximum power output (MPO) regimes. In fact this conclusion supports the idea that biological systems follow the ecological regime, which involves producing little entropy together with considerable efficiency (Sanitillan et al., 1997).
- Once more the results obtained from the presented model comply with the earlier experimental outcomes. As can be seen in figures, the amounts of efficiency calculated in this model for rat liver mitochondria are close to the experimental results. Therefore,

we are convinced that the predicted values for the efficiency in thermogenic mitochondria will also comply with experimental results. This could be a challenge for further research in order to find proper data for the efficiency in thermogenic mitochondria.

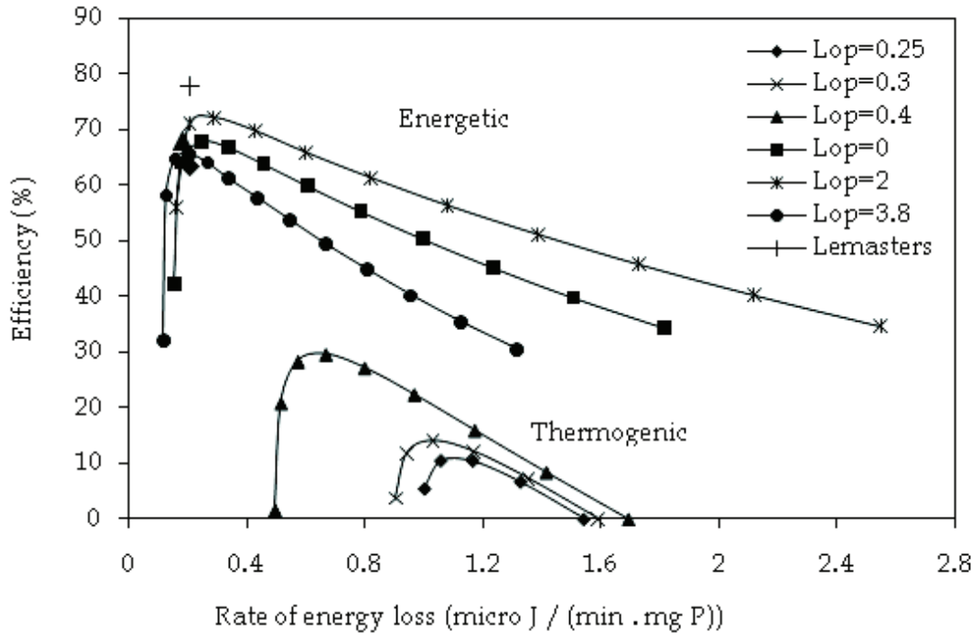

Fig. 6. Efficiency of oxidative phosphorylation vs. rate of energy loss in rat liver and BAT mitochondria with 3-hydroxybutyrate as substrate.

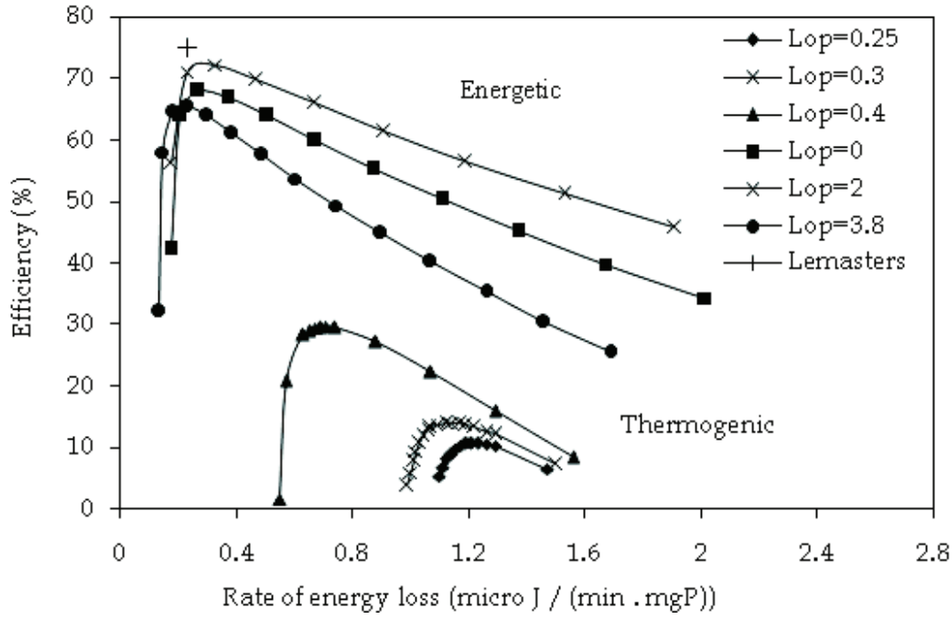

Fig. 7. Efficiency of oxidative phosphorylation vs. rate of energy loss in rat liver and BAT mitochondria with glutamate+malate as substrate.

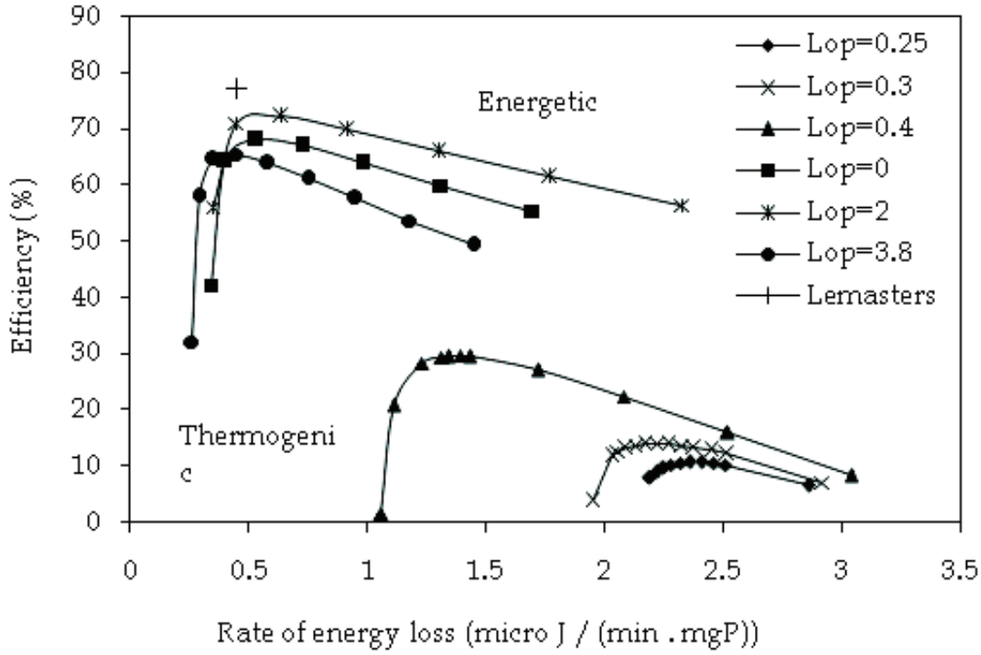

Fig. 8. Efficiency of oxidative phosphorylation vs. rate of energy loss in rat liver and BAT mitochondria with 2-oxoglutarate as substrate.

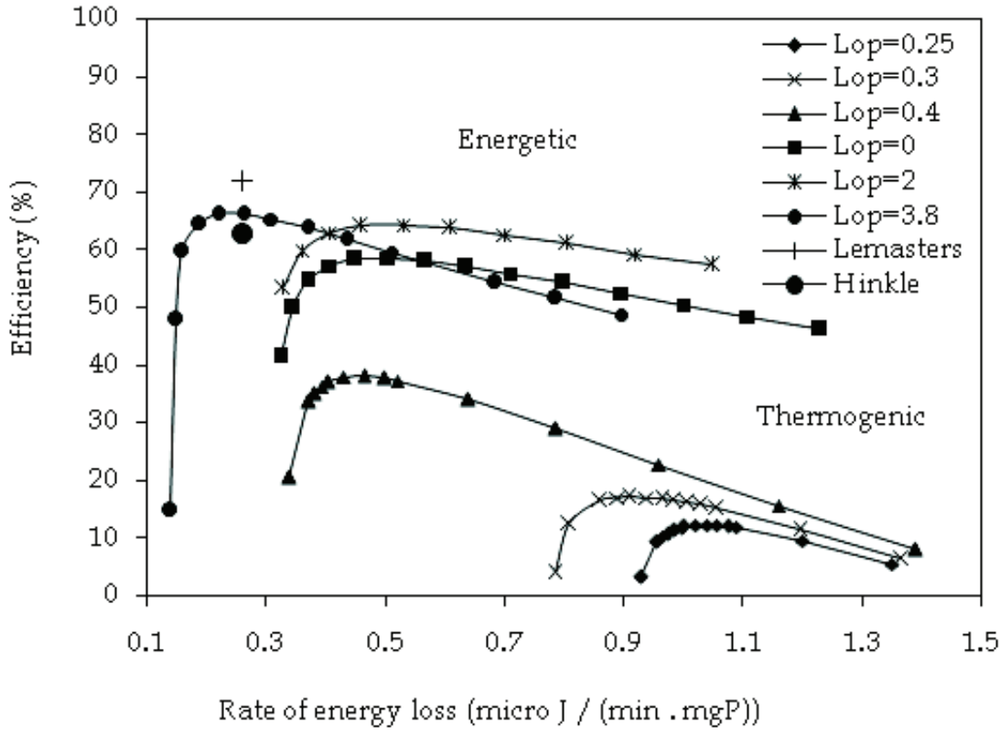

Fig. 9. Efficiency of oxidative phosphorylation vs. rate of energy loss in rat liver and BAT mitochondria with succinate as substrate.

5. Conclusion

Since biological systems are reasonably efficient in energy storage, they can be regarded as appropriate patterns for science and engineering. Thermodynamic models on energy transductions in such systems could play a key role in applying these patterns in industry and other relevant areas. In developing models for energy transductions in biological systems, it is important to apply non-equilibrium thermodynamics since the survival of these systems depend on constant mass and energy exchange with their surroundings, which requires operating at some distance from the equilibrium state.

Energy dissipation function (Φ), along with efficiency of oxidative phosphorylation processes can be viewed as useful criteria in studying the energy storage capabilities of a system and its operating regime. They can also be used to explain different mitochondrial functions.

Mitochondria of various tissues have different functions for matching the energy transductions with energy demands. The rate of energy dissipation and efficiency of energy storage in mitochondria is set according to their roles. In the previous sections, rate of free energy dissipation and efficiency of ATP production were determined for both energetic and thermogenic mitochondria by means of the proposed model and plotted in figures 2 to 9. These plots suggest that mitochondria with energetic function dissipate less energy as heat and store more energy in form of ATP molecules. As a result, the efficiency of oxidative phosphorylation is high in these cases (about 60 to 70 percent in rat liver mitochondria). On the contrary, thermogenic mitochondria release a great deal of energy due to more proton leak across the inner membrane. Therefore, the maximum amount of efficiency in BAT mitochondria is about 30 percent. These theoretical results comply with the experimental results for rat liver mitochondria.

Furthermore, comparison of efficiency values of two types of mitochondria with the rate of their energy dissipation indicates that such systems tend to produce less entropy and store energy in an efficient manner. This conclusion supports the theory of ecological regime in biological systems.

6. Further research

Based on the results of this research as well as the previous works on the subject, developing models for energy transductions in living organisms is of great importance in applying these energy patterns in industry. Therefore, it would be beneficial to figure out such models for other microbial cells such as bacteria and fungi. Studying ATP storage in animals with special characteristics such as hibernating animals or those with high resistance against thirst or starvation might also provide a better insight in this regard.

As mentioned earlier, there is not sufficient experimental data on different kinds of organs and substrates in the literature. Performing such experiments is essential for further research in this field. Furthermore, since Φ and η can be determined for different mitochondria by means of the model, they can be used in diagnosing mitochondrial dysfunctions. Moreover, they could assist in producing therapeutic drugs with mitochondria as their first or secondary target (Szewczyk & Wojtczak, 2002). These amounts can be changed synthetically, to help overcome mitochondrial diseases (Roussel, 2004). But for this to be practically possible, the range of values of Φ and η should be found for different organs.

Such thermodynamic models can also be used in assessing the effect of some drugs used for weight loss or doping. In fact weight loss through reducing the efficiency of ATP production (also reoffered to as "increased metabolic inefficiency") is a topic of interest in nutritional studies (Fine et al., 2004). The underlying mechanism of such drugs is usually based on affecting the mitochondrial membrane and changing the amounts of energy storage or dissipation. Measuring Φ before and after drug injection helps to study the effect of the drug and determine a healthy dosage. Similarly, if the range of Φ is known for an ordinary person, an increase in this function in athletes might be a sign of doping.
We believe the model presented in this chapter has the potential to be applied in various areas of science, pharmaceuticals and industry. Expanding and generalization of this model could be a challenge for further research.

7. Nomenclatures

A affinity of reaction or ΔG of reaction (KJ/mol)
A_i affinity of the i^{th} reaction (KJ/mol)
A_{Ox} affinity of oxidation reaction (KJ/mol)
A_{Ph} affinity of phosphorylation reaction (KJ/mol)
ADP adenosine diphosphate
ATP adenosine triphosphate
BAT brown adipose tissue
C_H membrane proton permeability [nmol H^+/(mg protein. min. mV)]
I subscript for reaction
J subscript for flux
J_H flux of proton transfer [nmol H^+/(mg protein. min)]
J_i thermodynamic flux for i^{th} reaction
J_{Ox} flux of oxidation reaction [nmol O_2/(mg protein. min)]
J_{Ph} flux of phosphorylation reaction [nmol ATP/(mg protein. min)]
L_{HH} phenomenological coefficient of proton (H^+) in proton transfer [nmol H^+/(mg protein. min. mV)]
L_{ij} phenomenological coefficient of j species in i^{th} reaction [nmol of j species /(mg protein. min. mV)]
L_{OH} phenomenological coefficient of proton (H^+) in oxidation reaction [nmol H^+/(mg protein. min. mV)]
L_{OO} phenomenological coefficient of O_2 in oxidation reaction [nmol O_2/(mg protein. min. mV)]
L_{OP} phenomenological coefficient of ATP in oxidation reaction [nmol ATP/(mg protein. min. mV)]
L_{PH} phenomenological coefficient of proton (H^+) in phosphorylation reaction [nmol H^+/(mg protein. min.mV)]
L_{PP} phenomenological coefficient of ATP in phosphorylation reaction [nmol ATP/(mg protein. min.mV)]
LNET linear non-equilibrium thermodynamics
m_O stoichiometric coefficient of pumps for oxidation reaction (nmol H^+/nmol O_2)
m_P stoichiometric coefficient of pumps for phosphorylation reaction (nmol H^+/nmol ATP)
n_j number of moles of species j

P protein (ATPsynthase)
PCs phenomenological coefficients (see L_{ij})
q degree of coupling of oxidation and phosphorylation reactions (dimensionless)
UCP uncoupling proteins
$\mathbf{X_j}$ thermodynamic forces for species j (KJ/mol)
η overall efficiency of oxidative phosphorylation
μ electrochemical potential (KJ/mol)
$\mathbf{\Delta\mu_H}$ electrochemical potential difference (KJ/mol)
$\mathbf{v_{ji}}$ stoichiometric coefficient of species j in the i^{th} reaction
Φ energy dissipation function [micro J/(mg protein. min)]

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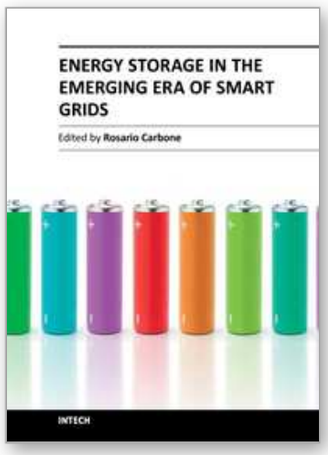

Energy Storage in the Emerging Era of Smart Grids

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