Modeling and Simulation of the Human Exercise Metabolism

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Abstract: - This paper proposes a mathematical model of human exercise metabolism. For modeling object-oriented techniques are applied, resulting in a modular description of the system. The physical and biochemical structure of the energy metabolism is represented by the declarative module equations and the connection of modules. Simulation results show that the proposed model quite accurately reproduces dynamic effects observed in experiments.

Key-Words: - exercise metabolism; object-oriented modeling; performance diagnosis; metabolic regulation; simulation

1 Introduction

An important task within sports medicine is the diagnosis of metabolic performance in individuals. This diagnosis forms the basis for the development of effective training plans for the avoidance of injury and overtraining.

For ethical reasons the diagnosis has to depend on the measurement of a few readily accessible values, e.g. the concentration of lactate in peripheral blood. However, the values measured do not necessarily reflect the metabolic processes under analysis. In addition the performance tests are usually limited to a few standardized patterns which do not always stimulate the metabolic processes optimally. Therefore the measured data has to be interpreted by an expert with an extensive background in the behavior of complex biochemical systems.

In all domains of science, modeling and simulating are important methods for understanding the behavior of complex regulated systems. Applying these methods to the exercise metabolism provides an opportunity to observe the response of intra- and extramuscular intermediates to exercise. Thus insights into regulatory mechanisms are gained. In so doing, these methods can support the analysis of metabolic processes in qualitative and quantitative terms.

This article is structured in three parts. In the first section the biochemical basis of exercise metabolism is reviewed. In the second section the application of object-oriented techniques for modeling the exercise metabolism is discussed. The article ends with the presentation and discussion of a few simulation results obtained with the proposed model.

2 Biochemical Basis of Modeling

Earlier investigations [4] have shown that the application of deductive methods is reasonable for modeling metabolic processes. This modeling paradigm is based on a theoretical analysis of the system being studied. The aim of this section is to provide an overview of the exercise metabolism and its regulation. The presentation is based on standard biochemistry literature [3], [5] and [8].

2.1 Metabolic Processes During Exercise

During muscle contractions chemical-bond energy is transformed to mechanical energy by the hydrolysis of the metabolite adenosine triphosphate (ATP) in the muscular *cross-bridge cycle*

$$ATP + H_2O \longrightarrow ADP + P_i + H \qquad (1)$$

where H_2O is water, ADP is adenosine diphosphate, P_i is inorganic phosphate and H is a hydrogen ion.

Since the amount of intramuscular ATP is limited, prolonged muscle contractions require a continual re-synthesis of ATP. The metabolism of the skeletal muscle is specialized in covering arbitrary temporal courses of the ATP-demand by the degradation of different fuel reserves. When focusing on exercise of short and medium duration the sources for ATP re-synthesis are, on the one hand, compounds with a high phosphate group transfer potential and, on the other hand, glucose.

2.1.1 Phosphoryl Group Transfer Reactions

Rapid depletions in the muscular ATP-level are re-supplied by the transfer of a phosphoryl group from a substrate of high group-transfer potential to ADP. Due to their near to equilibrium nature the response of such

reactions to changes in the cellular ATP-level is without time delay.

The immediate substrate for ATP-re-synthesis is creatine phosphate (CP). The enzyme *creatine kinase* catalyses the reversible transfer of a phosphoryl group from CP to ADP to form ATP and creatine (Cr):

$$CP + ADP + H \iff ATP + Cr \qquad (2).$$

If ADP accumulates in the cell, the enzyme *adenylate kinase* catalyses the reversible phosphoryl group transfer of one ADP to another to form ATP and adenosine monophosphate (AMP):

$$2\ ADP \iff ATP + AMP \qquad (3).$$

2.1.2 Anaerobic and Aerobic Degradation of Glucose

During exercise, glucose is an important substrate for the regeneration of ATP. The metabolic pathways of the aerobic and anaerobic degradation of glucose and the related ATP re-synthesis are shown in Fig.1.

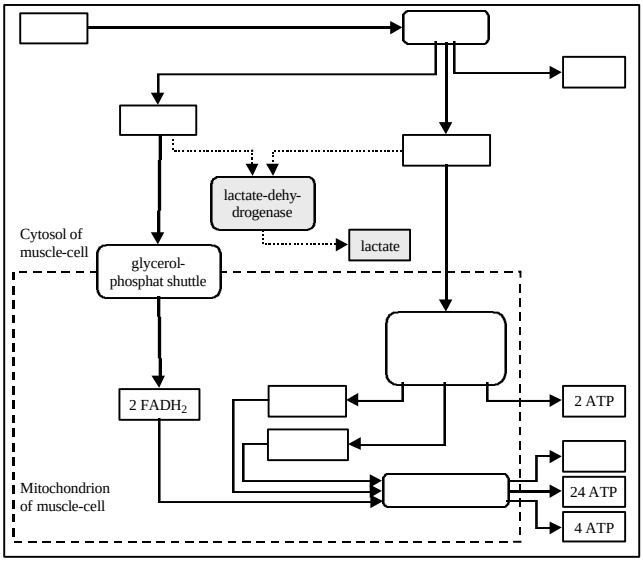

Fig.1: Degradation of Glucose

The breakdown of glucose starts with the *glycolysis* which is a sequence of 10 reactions. In this anaerobic pathway one molecule of glucose is irreversibly converted into two molecules of pyruvate

$$\text{glucose} + 2\ P_i + 2\ ADP + 2\ NAD \longrightarrow 2\ ATP + 2\ \text{pyruvate} + 2\ NADH + 2\ H + 2\ H_2O \qquad (4)$$

which involves the production of two ATP-molecules and the reduction of two electron-carriers nicotinamide adenine dinucleotide (NAD) to NADH.

The electron-carrier NAD has to be regenerated if *glycolysis* is to proceed. Under anaerobic conditions NAD is regenerated by the reversible transformation of pyruvate into lactate

$$\text{pyruvate} + NADH + H \iff \text{lactate} + NAD \qquad (6)$$

which is catalyzed by the enzyme *lactate dehydrogenase* (gray rectangles and punctuated lines in Fig.1).

The lactate which is formed during exercise partly diffuses out of the muscle into the blood. A major part of the lactate in the blood is transported either to the liver or to non-contracting muscle groups. In the liver, lactate is re-synthesized to glucose which enters the blood and is taken up by the skeletal muscle. This process is known as the *cori cycle*. The blood lactate which enters the non-contracting muscle groups is primarily stored during exercise.

Under aerobic conditions pyruvate is completely oxidized to carbon dioxide (CO_2) in the mitochondrial *TCA-cycle*

$$2\ \text{pyruvate} + 2\ ADP + 8\ NAD + 2\ FAD + 2\ Pi + 4\ H_2O \longrightarrow 2\ ATP + 6\ CO_2 + 8\ NADH + 2\ FADH_2 + 4\ H \qquad (7)$$

which involves a further production of 2 ATP and a reduction of 8 NAD as well as 2 flavin adenine dinucleotide (FAD).

The reduced electron-carriers NADH and $FADH_2$ have a high electron transfer potential which is used to regenerate ATP in the *respiratory chain*. The re-oxidation of two molecules NADH is coupled with a production of six ATP-molecules

$$\begin{aligned} 2\ NADH + O_2 + 2\ H &\longrightarrow 2\ NAD + 2\ H_2O \\ 6\ ADP + 6\ HP &\longrightarrow 6\ ATP + 6\ H_2O \end{aligned} \qquad (8)$$

whereas the re-oxidation of two molecules $FADH_2$ is coupled with the production of four ATP-molecules

$$\begin{aligned} 2\ FADH_2 + O_2 &\longrightarrow 2\ FAD + 2\ H_2O \\ 4\ ADP + 4\ HP &\longrightarrow 4\ ATP + 4\ H_2O \end{aligned} \qquad (9).$$

As shown in Fig.1 the cytosolic NADH-molecules which are formed in the *glycolysis* may be converted via *glycerol phosphate shuttle* into mitochondrial $FADH_2$ molecules

$$NADH_{cyt} + H + FAD_{mit} \longrightarrow NAD_{cyt} + FADH_{2\,mit} \qquad (10)$$

which are used in the *respiratory chain* for a further production of ATP.

Altogether the complete oxidation of one molecule glucose leads to a synthesis of 36 molecules ATP, of which 32 are formed in the respiratory chain.

2.2 Metabolic Regulation

Metabolic pathways such as the *glycolysis* consist of several successive reactions that serve a common function. As mentioned above the *glycolysis* for instance consists of 10 reactions which cause a breakdown of glucose to pyruvate involving the production of ATP. The total turnover of a pathway is regulated by controlling the amount of enzymes which catalyze single reactions and by controlling their activity. During exercise of short and medium duration the effect of the first regulatory mechanism is negligible. For this reason, the presentation focuses on the latter.

2.2.1 Regulation of Enzyme Activity

The rate limiting reaction which determines the total turnover rate of a pathway is usually catalyzed by a regulatory enzyme. The activity of such an enzyme depends on the concentrations of its substrates as well as on the concentration of its modulators. A modulator which lowers the activity of the enzyme and therefore lowers the rate of a whole pathway is called an inhibitor. Inhibitory effects are often suspended by the binding of activating modulators to the enzyme.

The functional relationship between the turnover of a reaction and the concentration of its modulators depends on the binding mechanisms of the modulators to the binding sites of the enzyme [8]. When modeling the kinetic properties of an enzyme a very careful analysis of these binding mechanisms is obligatory.

Metabolic systems consist of complex networks with a large number of intermediates and reactions, either equilibrium reactions or enzyme catalyzed reactions. On the lowest level such networks are regulated by the activity of enzymes as described above. The metabolic network is organized in control loops which form forward and backward inhibition and activation.

2.2.2 Regulation of the Breakdown of Glucose

A simple comparison between a 100m sprint and a 5km run shows that the temporal course of the muscular ATP-demand depends to a large extent on mode, intensity and duration of work. Complex regulatory mechanisms accomplish that the proportion of the ATP-production from different intramuscular fuel sources via the described pathways is co-ordinated to cover the current ATP-demand.

As explained in the previous section the contraction of muscles is associated with a decrease in the muscular ATP-level and a simultaneous increase in the ADP- and AMP-level (equ.1). The concentrations of these metabolites serve as intracellular signals for the regulation of the exercise metabolism: the enzymes of the rate limiting steps are inhibited by ATP or activated by both ADP or AMP.

The turnover of the *glycolysis* is regulated in the reaction which is catalyzed by the enzyme phosphofructokinase (PFK). A binding of the two substrates fructose 6 biphosphate and ATP to the catalytic site of the enzyme enables the formation of the products. A binding of the substrate ATP to the regulatory site of the enzyme inhibits its activity. The inhibitory action of ATP is reversed by AMP. Citrate, which is an intermediary product of the aerobic degradation of pyruvate, inhibits the enzyme PFK. Furthermore, rising levels of hydrogen ions inhibit the activity of the enzyme. Thus, a rising intramuscular pH-level suspends the inhibition of the enzyme and thereby increases the turnover of the *glycolysis*. This situation occurs for example in early stages of exercise when the H-production through the hydrolysis of ATP (equ.1) exceeds the H-consumption through the enzyme *creatine kinase* (equ.2).

In the *TCA-cycle* reduced electron-carriers for the *respiratory chain* and other substrates for biosynthesis pathways are produced. The presentation of the regulatory mechanisms of the *TCA-cycle* is focused on its primer function. The formation of the intermediary metabolite citrate from the substrates pyruvate and NAD is catalyzed by the enzymes *pyruvate dehydrogenase* and *citrate synthase*. Both are inhibited by ATP and NADH and activated by ADP (*pyruvate dehydrogenase*) resp. AMP (*citrate synthase*). The following degradation of citrate is regulated by the enzymes *isocitrate dehydrogenase* and *a-ketoglutarate dehydrogenase*. Besides the substrates, the metabolites NAD and ADP have an activating effect on these reactions whereas ADP and NADH have inhibiting effects. To summarize these effects: the turnover of the *TCA-cycle* is the higher the more ATP is needed and the more reduced electron-carriers are available in the cell.

3 The Model

In recent years, object-oriented methods are more and more applied for modeling complex systems in multidisciplinary areas [1]. Particularly for modeling biochemical processes these techniques seem to be well suited as they take into account the hierarchical and complex structure of such systems [6].

The object-oriented paradigm allows the modeling of large interconnected systems in a modular fashion. The physical and biochemical structure of the processes is represented by the declarative module equations and the connections of the modules. Essential steps of object-oriented modeling are:

1. the hierarchical decomposition of the system,
2. the mathematical description of elementary subsystems,
3. the aggregation of the overall mathematical model and
4. the generation of the simulation program code.

As the last two steps are automatically performed when using an appropriate modeling and simulation tool like *Dymola* [2] only the first two steps are discussed in the following subsections exemplary for chosen subsystems of the exercise metabolism.

3.1 Hierarchical Structure of the Exercise Metabolism

In the first step of object-oriented modeling the exercise metabolism is decomposed via top-down analysis on succeeding hierarchical levels. Starting from the system as a whole it is broken up into smaller and smaller

subsystems under topological and phenomenal points of view. The physical couplings between the subsystems are given by their interconnection via interfaces. This procedure is explained in the following two subsections by means of Fig.2 which shows a simplified object-diagram of the uppermost levels of the exercise metabolism.

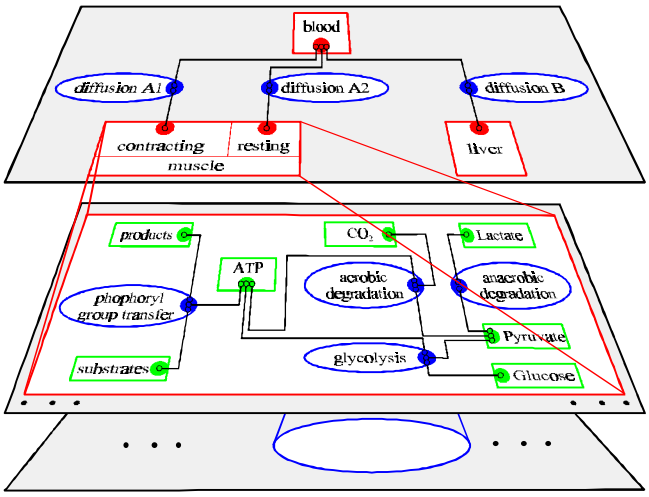

Fig.2.: Hierarchical structure of exercise metabolism

3.1.1. Topological Structure Representation of the Exercise Metabolism

The top hierarchical level of the model describes the exercise metabolism as a whole. As shown in Fig.2 the subsystems of the top level describe the topological structure of the exercise metabolism by a three-compartment model.

One compartment represents all muscles of the body. Within this subsystem the contracting muscle groups, i.e. in the case of cycling the musculature of the lower torso, are distinguished from the resting muscle groups, i.e the musculature of the upper torso. During exercise the ATP turnover within the contracting muscle groups is higher than the ATP turnover when at rest. However, the ATP turnover in the resting muscle groups during exercise is about the same as the ATP turnover when at rest. The phenomenal structure, i.e. the metabolic pathways, within the contracting and resting muscle groups are of course the same.

Referring to section 2 the blood compartment distributes lactate and other intermediates which are produced during exercise. For the proposed model the primarily task of the liver compartment is the removal of lactate.

An exchange of the metabolites between the compartments mentioned above is possible via reaction systems which represent the processes of diffusion between (a) muscle and blood and (b) liver and blood.

3.1.2 Phenomenal Structure of the Exercise Metabolism

The phenomenal structure of the metabolic processes within the compartments is analyzed in different levels of detail. The aim of the decomposition is the reduction of the module description to a minimal number of elementary modules on the lowest hierarchy level. These elementary modules inherit their properties from basic submodels, which are encoded in a library.

To explain this, the phenomenal structure of the muscle compartment as outlined in section 2 is illustrated in the second level of Fig.2. Already on this level the modules can be classified into two types: reaction modules, which are associated with elliptic symbols, and storage modules, which are associated with rectangular symbols. The spots within the graphical symbols represent the interconnection points of the modules and the lines represent their interconnections.

The metabolic pathways which are found on the second model level are finally decomposed into elementary modules like equilibrium reaction, regulated reactions, diffusions as well as different types of storages.

3.2 Mathematical Description of Elementary Modules

In the second step of modeling, the systems equations for the basic components are set by applying elementary physical and biochemical laws, e.g. mass balances and the Michaelis-Menten equation. This is elucidated by examples in the following subsections.

3.2.1 Storages

A storage module describes the behavior of the metabolite concentration c_M which is influenced by the turnover $\dot{c}_{M,i}$ of i=1 ,2, ...,N reactions. The derivation of the metabolite concentration $\dot{c}_M$ with respect to time is obtained by

$$\dot{c}_M = \sum_{i=1}^{N} \dot{c}_{M,i} \qquad (11).$$

According to the custom in object-oriented modeling the derivation of the metabolite concentration $\dot{c}_M$ and the turnover of the influencing reactions $\dot{c}_{M,i}$ are connected as *through variables* to the interconnection points of storage modules.

The concentration c_M is calculated by the model equation which integrates the derivation $\dot{c}_M$. The required initial value c_{M0} corresponds with the concentration of the metabolite during rest.

In the special case that the concentration of a metabolite M is assumed as constant c_M is explicitly set to the constant value.

3.2.2 Equilibrium Reaction

The mathematical description of a general equilibrium reaction between K substrates S and L products P

$$S_1 + S_2 + ... + S_K \quad \Longleftrightarrow \quad P_1 + P_2 + ... + P_L$$

is given by the algebraic equation

$$\prod_{k=1}^{K} c_{S,k} = K_e \cdot \prod_{l=1}^{L} c_{P,l} \tag{12}$$

where $c_{S,k}$ are the substrate concentrations, $c_{P,l}$ are the product concentrations and K_e is the equilibrium constant of the reaction.

The turnover of the reaction is gained by deriving eq.12 with respect to time. The additional constraints hereby are

$$-\dot{c}_{S,1} = -\dot{c}_{S,2} = ... = -\dot{c}_{S,K} = \dot{c}_{P,1} = \dot{c}_{P,2} = ... = \dot{c}_{P,L}\,. \tag{13}$$

3.2.3 Regulated Reactions

To gain the mathematical description of the turnover of regulated reactions, the effects of regulatory factors have to be analyzed in detail. Exemplary for such reactions the mathematical equation for the calculation of turnover the PFK-reaction (see subsection 2.2.2) is suggested. For the calculation it is assumed that

- The substrates F6P and ATP bind sequentially to the enzyme with the binding constants K_{F6P} resp. K_{ATP}.
- The binding of two inhibitory hydrogen ions to the enzyme is competitively to the substrates. The binding constant is denoted as K_H.
- ATP binds to the inhibitory binding site if and only if hydrogen ions were bound before. The binding to the inhibitory site of the enzyme is non-competitive with respect to the binding to the substrate site. The binding constant of ATP to the inhibitory is denoted as $K_{I,ATP}$.
- The inhibitor citrate binds to an inhibitory site of he enzyme (binding constant K_C) if and only if hydrogen ions and ATP molecules are already bound to the inhibitory sites of the enzyme. The activator AMP binds competitively to the substrates with the binding constant K_{AMP}.
- v_{PFK}^{max} is the maximal turnover of the reaction.

The turnover of the PFK is then given by

$$\dot{c}_{PFK} = \frac{v_{PFK}^{max} \frac{c_{ATP}}{K_{ATP}} \frac{c_{F6P}}{K_{F6P}}}{\left(1 + \frac{c_{ATP}}{K_{ATP}} + \frac{c_{F6P}}{K_{F6P}} + \frac{c_{ATP}}{K_{ATP}} \frac{c_{F6P}}{K_{F6P}}\right) + n} \tag{14.a}$$

where n is given by

$$n = \frac{c_H^2}{K_H} \frac{1 + \frac{c_{ATP}}{K_{I,ATP}}}{1 + \frac{c_{AMP}}{K_{AMP}}} \left(1 + \frac{c_{ATP}}{K_{I,ATP}} \left(1 + \frac{c_C}{K_C}\right)\right). \tag{14.b}$$

3.3 Individual Simulation Models

In the next steps of modeling the mathematical overall model is aggregated in a symbolic form. The aggregated mathematical overall model for the exercise metabolism takes the form of a differential-algebraic equation system (DAE). For simulating such models it is mandatory to determine the values of the model's parameters as well as the initial values of the state variables. Particularly with regard to DAEs the initial condition have to be consistent.

The exact values of the model set have to be determined from experimental data. As mentioned in the introduction it is not possible to measure the whole set of model values in experiments. Nevertheless, the acceptable range of many values can be determined from literature on biochemistry and on sports medicine. Based on these ranges experimental data is used for the identification of the model set. The data for this purpose is obtained from conventional exercise tests on a bicycle ergometer, during which the concentration of lactate is determined several times.

The routine applied for the identification iteratively adapts the values of the model set in order to minimize the deviation between the measured and simulated time course of output variables. In addition, it is guaranteed that the identified values are within an acceptable range.

Some of the values of the model set are nearly generic for all persons. Others reflect a person's metabolic standing and therefore have to be identified for each person individually from experimental data.

4 Simulation Results

The reliability of the model is examined by the analysis of simulation results. With regard to an implementation in performance diagnosis it has to be verified that the results obtained by simulations are in accordance with reality. This has to be proven for several persons whose metabolic performance is distinguishable. The results which are shown beneath result from simulations with the identified model set of two subjects.

In Fig.3 and Fig.4 the time course of blood lactate is presented for two selected types of exercise. This examination is accompanied by an experimental examination. A comparison of the measured and simulated time response of the blood lactate concentration shows a good quantitative and qualitative accordance for all types of exercise and for both persons. Moreover, the analysis of the dynamic behavior of intramuscular metabolites corresponds with reports on qualitative behavior in literature (data not shown). This can be shown for other exercise tests as well.

In Fig.5 the turnover of ATP molecules within the pathways of the contracting muscle compartment are shown. These values are calculated by simulation and

are not measurable. The qualitative behavior is in good accordance with the behavior reported in [3].

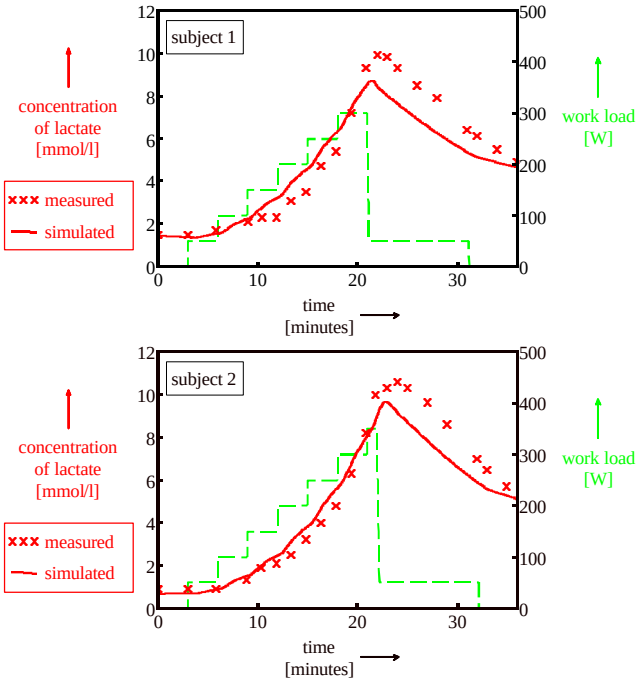

Fig.3: Time response of blood lactate for a step-like increase of work load (dashed line)

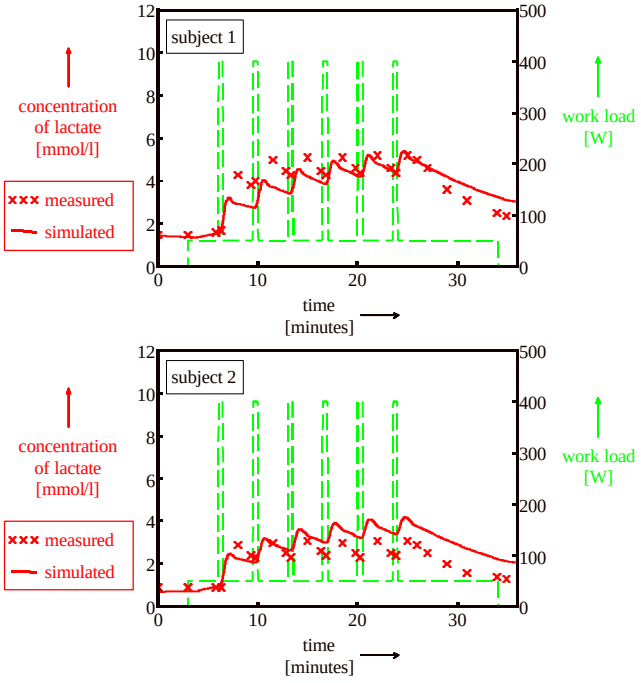

Fig.4: Time response of blood lactate for an impulse-like increase of work load (dashed line)

5 Conclusions

A model for the exercise metabolism is developed by means of an object-oriented modeling approach. This approach was found to be very powerful for representing the complex and hierarchical structure of metabolic processes.

The results obtained by simulating different input patterns with the data sets of two people are in accordance with the dynamic behavior measured in experiments and observed in literature. These results suggest that the model can be used to support the diagnosis of metabolic performance.

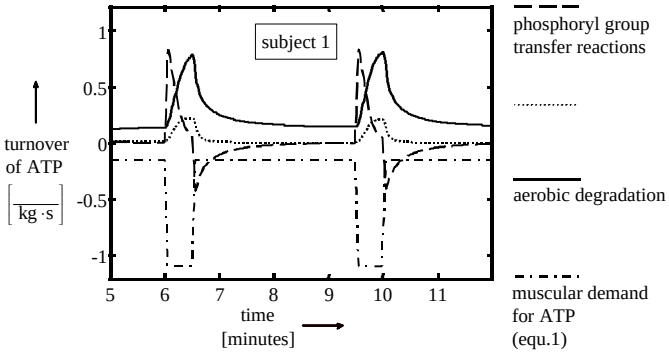

Fig.5: Time response of the turnover of ATP for an impulse-like increase of workload (see Fig.4)

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