Survey of the Modeling Brain Energy Metabolism and Function — Report of the work by Larisa. V et al.; in Bulletin of Mathematical Biology (2006) 68: 275-291

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Introduction

- Point-model (Spatial Free Model)
- Justification of the hidden variables and observable variables
- Pathophysiological applications

Previous Results

- Mathematical Model for metabolism in mammalian cell cycle (Hatzimanikatis et al., 1995)
- Mathematical Modeling for metabolism by stoichiometric method (Gombert and Nielson, 1999)
- Mathematical Model concerning oxidative metabolism in the cerebral cortex (Hudetz, 1999)
- Mathematical Models focusing on pathogenesis of tissue damage (Reggia et al., 1997; Revett et al., 1998)

Modeling Principles

- Consideration of the brain tissue in vivo as a whole
- Relationship between O_2 supply and demand
- Relationship between metabolic energy production and consumption
- A continuous supply of metabolic energy is needed for vital activities of the tissue (Mayevksy and Chance, 1982, Science)
- All tissue of the human body share the basic mechanism maintaining the energy balance

Metabolism Mechanism In Brain Tissue

- 50 % of the energy consumed by the brain is needed for a normal $Na^+ - K^+ - ATP$ activity (Erecinska and Silver,1989)
- Ratio between NAD and NADH.
- Significant decrease in O_2 supply to the brain will cause a decrease in ATP levels along with a rise in NADH.
- Rising in NADH follows by the inhibition of the active transport mechanisms and elevation of extracellular K^+ levels.
- Redox state of the mitochondria is a sensitive indicator of the intracellular metabolic state and used to evaluate the cellular energy status. (Mayevsky and Chance, 1982; measured by Kraut et al., 2003)

Metabolism Mechanism In Brain Tissue (Cont'd)

- Increase of NADH levels dues to pathological conditions, such as ischemia.
- conditions that activate brain metabolism, such as spreading depression and/or convulsions, decreased the level of NADH in brain tissue, i.e., NADH was oxidized to NAD (Mayevsky and Chance, 1975; Mayevsky, 1983a; Mayevsky and Sclarsky, 1983).
- Once the balance of energy production, supply, and demand is impaired, a cascade of events occurs that finally leads to tissue degeneration

Variables

Assumption: The tissue functional state is fully determined by the following metabolic variables

- Concentration of extracellular potassium (K)
- Rate of potassium reuptake (R)
- Blood flow (F)
- Oxygen (O)
- NADH (N)
- Partial impairment (P)

Equation of Concentration of extracellular potassium (K)

$$(1) \quad \frac{dK}{dt} = \underbrace{C_{K,K}(K - K_{rest})(K - K_\theta)(K - K_{max})}_{\text{regenerative process}}$$

$$+(\delta + P)\underbrace{(K_{max} - K)}_{\text{translation of intracellular potassium}}$$

$$\underbrace{-C_{K,R}\,KR}_{\text{reuptake due to Na/K pump}} \qquad \underbrace{+\,K_{inj}}_{\text{external injection}}$$

Equation of Rate of potassium reuptake (R)

$$(2) \quad \frac{dR}{dt} = \underbrace{C_{R,NOKE}\, NO(K - K_{rest})(R_{max} - R)}_{\text{increase of } R \text{ due to increase of NADH and } O_2} - \underbrace{C_{R,RK}\, R(K_{max} - K)}_{\text{Recover Na/K ATP activity to resting level when K's value restored}}$$

Equation of Rate of Blood flow (F)

$$(3) \quad \frac{dF}{dt} = \underbrace{C_{F,FO}\,(F_{max} - F)(O_{rest} - O)}_{\text{Dependence of Blood supply}}$$

$$+ C_{F,F} \underbrace{\left(\frac{F_{max}}{2} - F\right)}_{\text{self-regulation of blood flow} \longrightarrow \text{base rate}}$$

$$- \underbrace{C_{F,KF}\,(K - K_{rest})(F_{rest} - F)}_{\text{Variation caused by irregular extracellular } K \text{ rise}}$$

Equation of Oxygen (O)

Energy status of the tissue is determined by the Oxygen O.

$$(4) \quad \frac{dO}{dt} = \underbrace{C_{O,FO} F(O_{max} - O)}_{\text{supply term}} - \underbrace{C_{O,NRO} N(RO)^{1/2}}_{\text{demand / cost term}}$$

The power $\frac{1}{2}$ is because to oxidatize NADH, one NADH need one O atom, so $1/2$ of O_2.

Equation of NADH (N)

The rate of NADH change is determined by its level, while the consumption rate depends on the potassium reuptake as well as on oxygen:

$$\frac{dN}{dt} = C_{N,N}(N_{max} - N) - C_{N,NRO}N(RO)^{1/2} \quad (5)$$

Equation of Partial impairment (P)

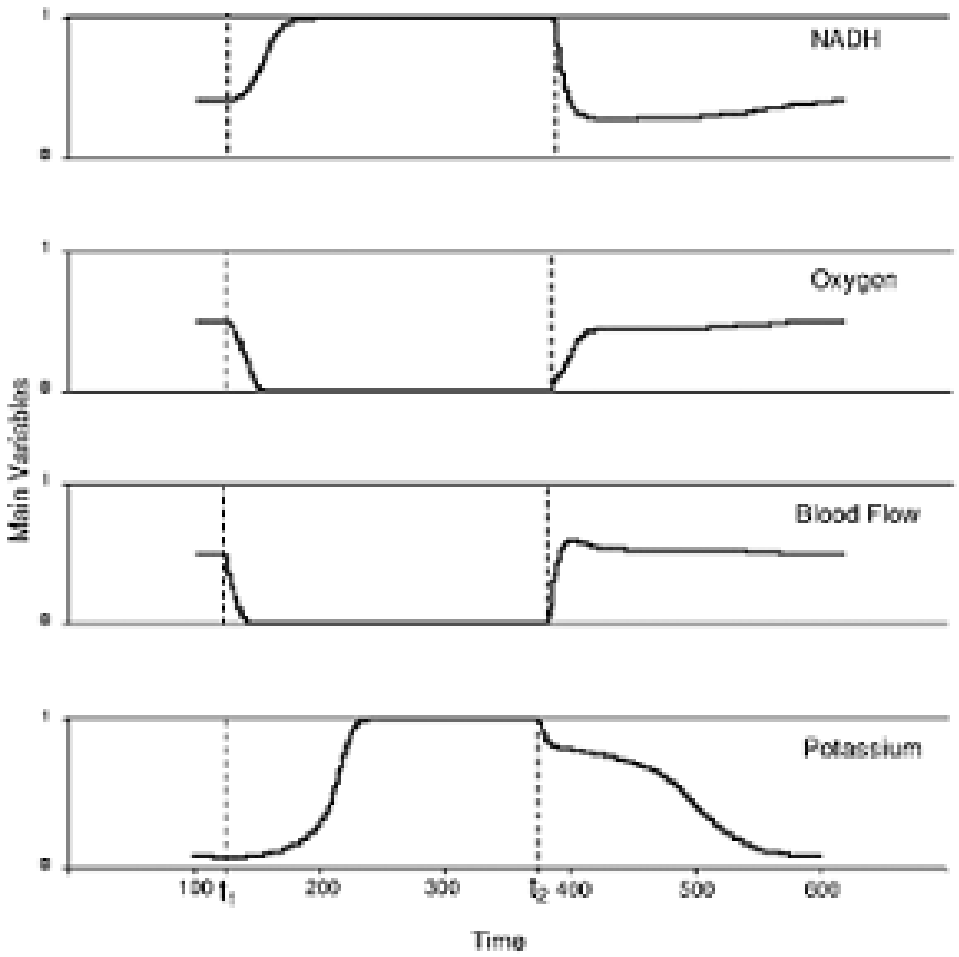
Level of stresses experienced by the tissue is represented by the partial impairment variable P. In (1), stresses upset the integrity of tissue cells, which results in increasing translation of the intracellular potassium to the extracellular space. In a damaging situation, the stores of oxygen deplete, and O becomes insufficient for Na/K pump functioning. The concentration of extracellular potassium rises and the partial impairment augments.

$$(6) \quad \frac{dP}{dt} = C_{P,OK}(O_{max} - O)(K - K_{rest})$$

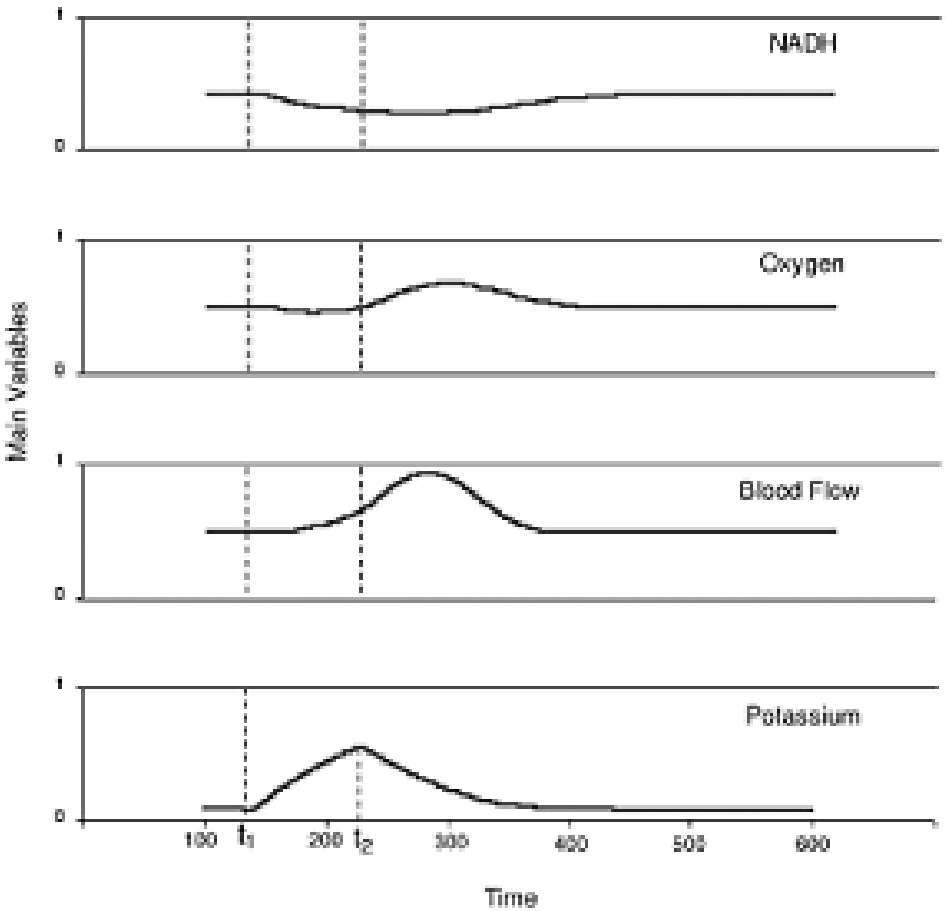
Numerical Remark

- The scheme applied to solve the dynamics system $(1) - (6)$ is a software "Stella". Actually, backward Euler method or Runge-Kutta is good enough to capture the solution, and they are stable. The initial condition of the variables in the model reflect normoxic tissue state.
- A variety of ischemic events produced below by setting $F_{max} < 1$ in (3) within a time interval $t_1 < t < t_2$. $K_{inj} \geq 0$. Numerically, 100 time units approximate 1 minute in real time.
- All of the constant parameters are estimated.

Global Ischemia



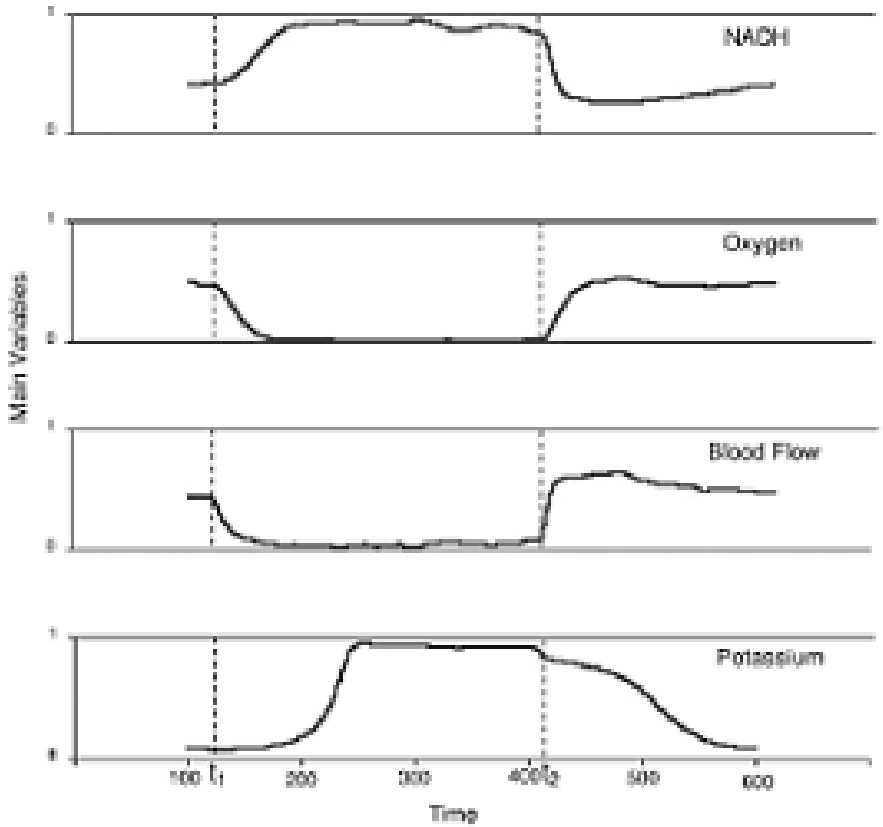
Spreading Depression with a Delay



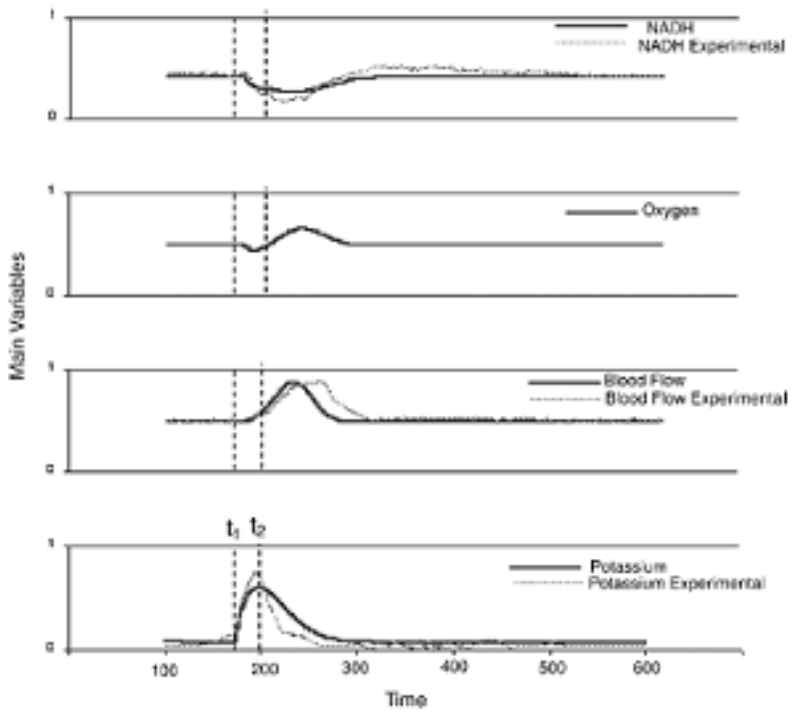
Pathological Scenario With Experimental Blood Flow

- Exclude equation (3) from the set of system and instead, used in (4) the experimental blood flow; with all the remaining variables computed according to the corresponding equations.

Global Ischemia simulated by using experimental data on Blood flow

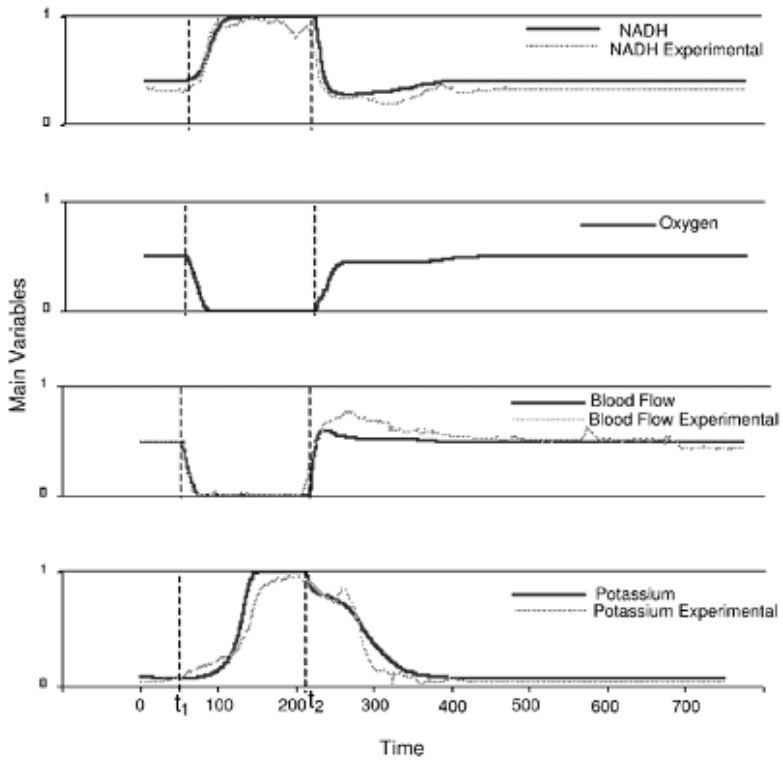


The comparison of the temporal behavior of the model to the corresponding clinical data for Spreading Depression



[1] Experimental Source: Mayevsky et al. (1996).

The comparison Global Ischemia (Oxygen from clinic)



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[2] Experimental Source: Mayevsky et al. (1992).

Conclusion

- Based on assumption, model the metabolism mechanism in Brain tissue by ODE instead of PDE
- Five pathophysiological tissue conditions were stimulated based on the model, which are biological reasonable.
- Using the model, a potentialities of minimizing the number of measured parameter is possible.
- In principle, the comparison of the computed and clinical data can be used to test the tissue state and predict the recovery process.

Reference

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THANK YOU!