# Brain centered whole-body model of the energy metabolism

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# Outline

# Project group


- **Matthias Chung**
  Department of Mathematics
  Texas State University, San Marcos, TX, USA
- **Britta Göbel**
  Institute of Mathematics and Image Computing, Graduate School for Computing in Medicine and Life Sciences
  University of Lübeck, Germany
- **Kerstin M. Oltmanns**
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  University of Lübeck, Germany

# Selfish brain project

**Selfish brain** group, University of Lübeck

- Interdisciplinary clinical research group with about 25 scientists from medicine, psychiatry, biochemistry, physics, math
- Investigates the decisive role of the human brain in the regulation of the energy metabolism
- Obesity, diabetes mellitus, metabolic syndrome, anorexia, depression, metabolic learning
- Supported by the German Research Foundation, KFO-126

`www.selfish-brain.org`

# Selfish brain theory

The uniqueness of the **brain** is characterized by its

1. physical barrier properties,
2. high energy consumption,
3. low energy storage capacity,
4. substrate specificity,
5. plasticity,
6. ability to control and to record information from peripheral organs,
7. almost uninfluenced energy level by disturbances.

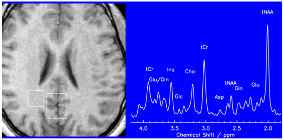
# Selfish brain theory

- aims at the systemic understanding of the human whole-body energy metabolism.
- regards the brain as heavy energy consumer **and** as superior regulatory instance.
  - The brain has the strongest position in the competition for energy.
  - The brain has two principal mechanisms to secure its energy supply:
    1. *allocation* of available energy resources,
    2. *ingestion*.
- explains metabolic diseases like diabetes mellitus and obesity as mistuning of energy allocation.

Peters, A., Oltmanns, K.M., Conrad, M. et al. (2004), Neurosci. Biobehav. Rev.

# Data acquisition

1. $^{31}$phosphorus MRS measurements of brain metabolites that are centrally involved in the energy metabolism (e.g. ATP, phosphocreatine)
2. Simultaneous monitoring of the peripheral glucose metabolism




- Influence on brain activity by transcranial direct current stimulation and hypoxia
- Examination of normal weight and obese subjects

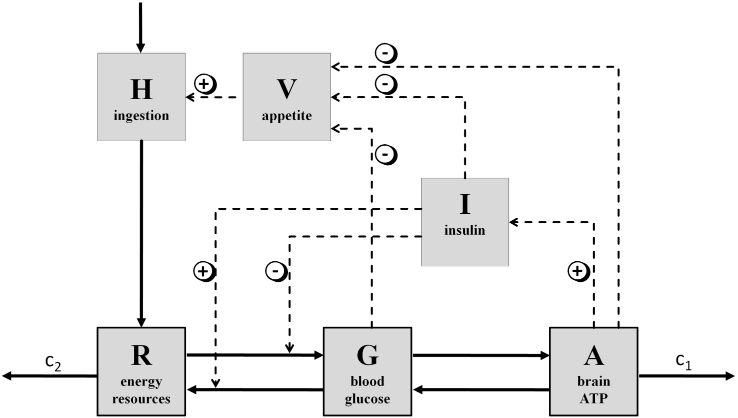
# Brain-centred energy metabolism model

**Aim:** Mathematical model of the human energy metabolism regarding the brain as superior regulatory instance and as energy consumer.

- Hypothesis: The regulation of the human glucose metabolism is tightly linked to cerebral energy supply.
- General model realistically describing the fundamental behaviour of the whole-body energy metabolism in healthy humans.
- Compact low-dimensional dynamical system.

$\hookrightarrow$ ODE compartment model

# Compartment model




Energy fluxes between compartments (solid) and control signals directing the energy fluxes in the organism (dashed).

Göbel, B., Langemann, D., Oltmanns, K.M., Chung, M. (2010), J Theor Biol

# Short-term energy metabolism model

**brain ATP:** $$\frac{\mathrm{d}}{\mathrm{d}t}A = p_1 \frac{G}{A} - c_1$$

**blood glucose:** $$\frac{\mathrm{d}}{\mathrm{d}t}G = -p_1 \frac{G}{A} - p_2 G I + p_3 \frac{R}{G}$$

**insulin:** $$\frac{\mathrm{d}}{\mathrm{d}t}I = p_4 A - p_5 I$$

**energy resources:** $$\frac{\mathrm{d}}{\mathrm{d}t}R = p_2 G I - p_3 \frac{R}{G} + p_6 H - c_2$$

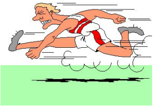
**ingestion:** $$\frac{\mathrm{d}}{\mathrm{d}t}H = p_7 \left(f\left(V\right) - H\right)$$

with **appetite:** $$V(A, G, I) = \frac{p_8}{AGI}$$

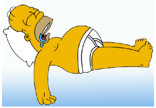
# Simulations

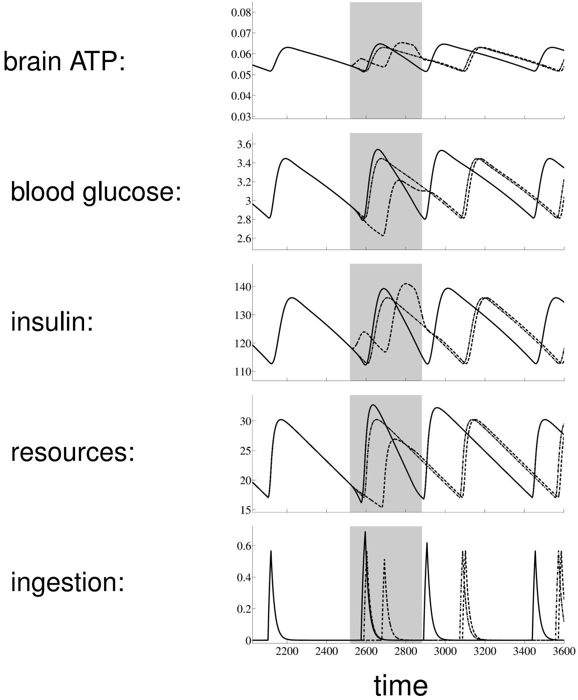
Simulation of the healthy human energy metabolism and the effects of two physiological interventions:

**1. Exercise:** temporarily increased peripheral energy consumption $c_2$, e.g. marathon



**2. Exhaustion:** temporarily decreased brain energy consumption $c_1$ and temporarily reduced peripheral energy consumption $c_2$






**solid:** exercise
**dashed:** exhaustion
**dash-dot:** resting state

**Circadian ingestive behaviour leads to oscillating energy levels in the compartments with the typical blood glucose and insulin variations.**

# Long-term model

$$\textbf{ingestion}: \quad \frac{\mathrm{d}}{\mathrm{d}t} H = p_7 \left( f\left(V\right) - H \right)$$

- $p_7$: sensitivity of the organism in food intake consistent with its need for energy
- *Low values $p_7$:* slow adaption to the energy needs
- *High values $p_7$:* fast adaption to the energy needs, ingestion $H$ is strongly regulated
- Short-time scale (daily): mild regulation = slow adaption
- Long-time scale (months to years): strict regulation = fast adaption

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# Long-term energy metabolism model

Transition $p_7 \to \infty$ leads to a description of the long-term behaviour with mean regulation of food intake:

$$
\begin{aligned}
\textbf{brain ATP}: \quad \frac{\mathrm{d}}{\mathrm{d}t}A &= p_1 \frac{G}{A} - c_1 \\
\textbf{blood glucose}: \quad \frac{\mathrm{d}}{\mathrm{d}t}G &= -p_1 \frac{G}{A} - p_2 GI + p_3 \frac{R}{G} \\
\textbf{insulin}: \quad \frac{\mathrm{d}}{\mathrm{d}t}I &= p_4 A - p_5 I \\
\textbf{energy resources}: \quad \frac{\mathrm{d}}{\mathrm{d}t}R &= p_2 GI - p_3 \frac{R}{G} + p_6 f(V) - c_2
\end{aligned}
$$

Göbel, B., Langemann, D., Oltmanns, K.M., Chung, M. (2010), J Theor Biol

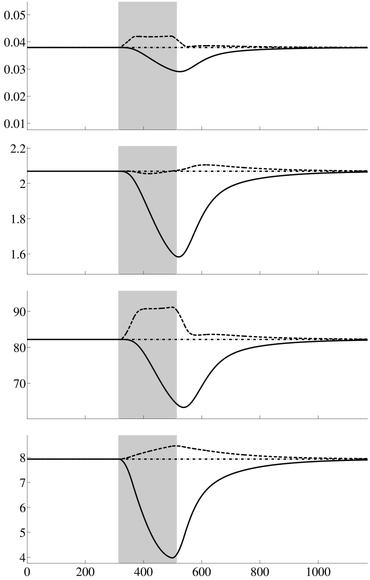
# Simulations

brain ATP:

blood glucose:

insulin:

resources:




time

**solid:** exercise
**dashed:** exhaustion
**dash-dot:** resting state

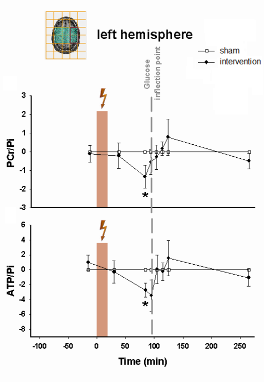
**Stable long-term behaviour in accordance with homeostatic regulation of the energy metabolism.**

# Conclusion

- The model contains the two central roles of the brain in the energy metabolism.
- Key elements like the preeminence of the brain's energy supply are reflected.
- Realistic description of the whole-body energy metabolism on a short and long time scale - even with a large class of physiological interventions.
- The presented dynamical system is a step towards a systemic understanding of the human energy metabolism, and thus may shed light on defects causing metabolic diseases.

# Ongoing work and outlook

- Solution of the inverse problem to generate insight into underlying mechanisms
- Model validation
- Extension of the model by further sub-compartments
- Interaction of the model to other regulatory systems, e.g. stress axis, memory




Oltmanns, K.M. et al. (2011),

Biol Psychiatry

# Thanks

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- **Bernd Fischer**
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