An interconnected multi-level mechanistic model of the human brain

Nicolas Sundqvist[1], Henrik Podéus[1], Sebastian Sten[1], Salvador Dura-Bernal[2], Fredrik Elinder[1], Soroush Safaei[3], Maria Engström[1], Gunnar Cedersund[1]

[1]Linköpings university, Sweden; [2]State University of New York, USA; [3]University of Auckland, New Zealand

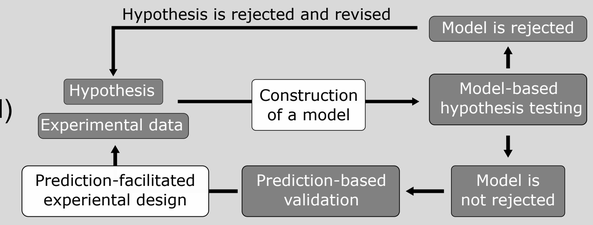
Introduction

We aim to expand and integrate a set of existing and newly developed mechanistic models that describe different aspects of the neuronal and hemodynamic functions of the brain. The goal is to have an interconnected multi-level, multi-time scale model that can explain mechanisms on different levels of the cerebral physiology. Starting with ion channel kinetics and zooming out to the scale of intracellular metabolic networks, large intraneuronal signalling networks, and ultimately describing the hemodynamic control of cerebral tissue.

Method

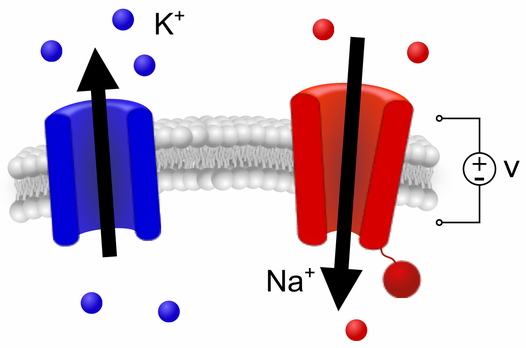
We use ordinary differential equations (ODEs) and large-scale neuronal network modelling structures (NEURON and NetPyNE). We utilize both qualitative and quantitative information in a data-driven modelling approach. We use experimental data from measurements such as:

- Action potentials (AP)
- Magnetic resonance spectroscopy (MRS)
- ^{13}C metabolic flux analysis (MFA)
- Functional magnetic resonance imaging (fMRI)
- Local field potential (LFP)
- Multi-unit activity (MUA)
- Electro-encephalography (EEG)

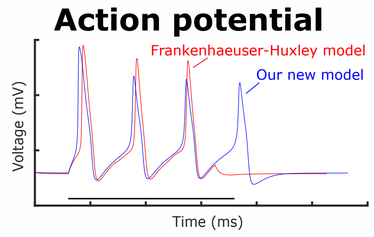


Ion channel kinetics

We have developed a generic and flexible model that can be adapted to different voltage-gated ion channels. The model can be used to accurately calculate action potentials, quantitatively describe and predict the role of disease-causing mutations, and predict the effect of pharmaceutical interventions.



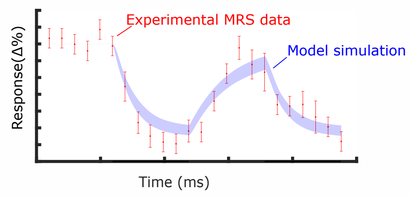
Action potential



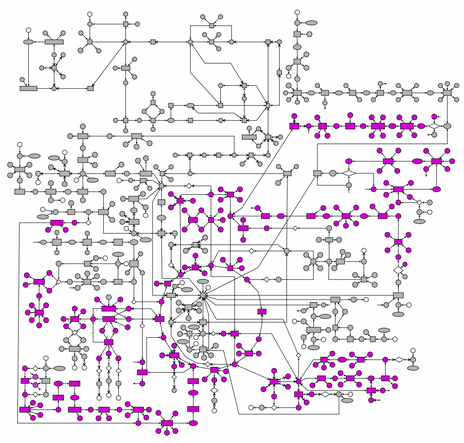
Intracellular metabolism

We have developed a new model that integrates mechanistic modelling of both MRS and blood oxygen level dependent (BOLD) measurements, thus connecting the BOLD- and metabolic responses. The metabolic model covers the central metabolism, on a detailed level. Statistical tests confirm that the model can describe both estimation data and predict independent validation data, not used for model training. Further, larger metabolic networks can be studied with ^{13}C MFA, where isotope labelling data and steady-state models are used to map the metabolic activity during different conditions.

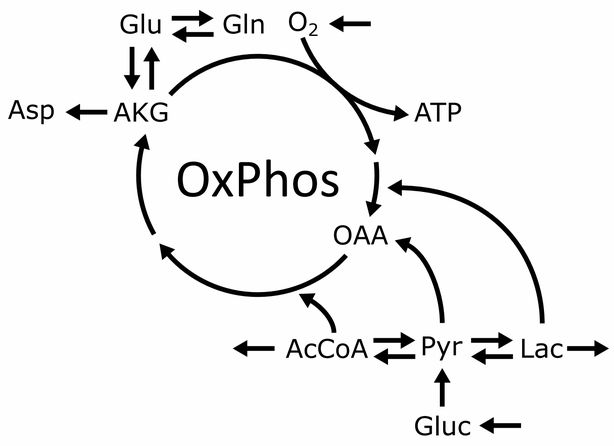
Metabolic dynamics



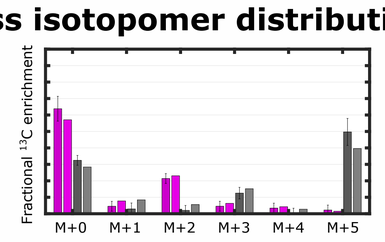
Large scale metabolic flux analysis



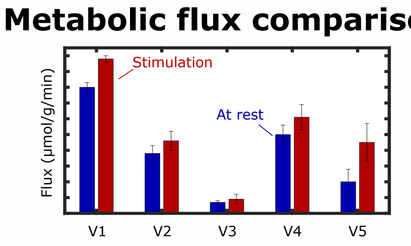
Detailed metabolic interactions



Mass isotopomer distributions

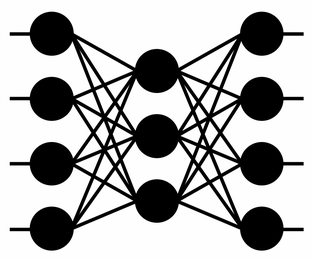


Metabolic flux comparison

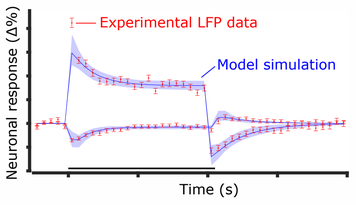


Neuronal interactions

We can also describe how different populations of neuronal cells interact with each other. Creating a spatially resolved model structure that can describe different neuronal populations and their interactions. To train these models LFP, MUA, and EEG measurements are used.



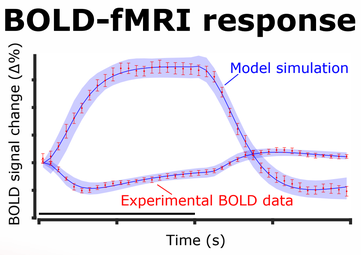
Neuronal local field potential



Neurovascular coupling

On the tissue level we have developed a comprehensive mathematical model of the neurovascular coupling. This model describes how neuronal activity affects the regulation of cerebral blood volume and flow, oxygen saturation, and the BOLD-response.

BOLD-fMRI response



Contact & bibliography
Nicolas Sundqvist
Linköping University
Nicolas.sundqvist@liu.se

LINKÖPING UNIVERSITY

Conclusion

We aim to develop an interconnected model of the brain that can describe a multitude of different aspects of the cerebral function. In this pursuit we have developed individual models that describes:

- **Voltage gated ion-channel kinetics.**
- **Intracellular metabolic responses to neuronal stimulation.**
- **Intracellular metabolic flux configurations during different conditions.**
- **Electrophysiological activity and spatially resolved interneuronal interactions.**
- **The neurovascular coupling i.e. how neuronal activity affects the hemodynamical control of the cerebral tissue.**