## Computational modelling and analysis of brain metabolism in neurodegenerative diseases

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# Chapter 7

# Summary

Neurodegenerative diseases are disorders caused by the loss of neuronal structure and function. Two of the most widespread neurodegenerative diseases are Alzheimer's disease (AD) and Parkinson's disease (PD). The exact causes and mechanism of these diseases are unknown and there are presently no effective treatments to slow or reverse the disease progression. Disturbances of metabolism in the affected neurons, particularly in glucose and oxygen uptake and in the mitochondria, is a prominent feature in AD and PD. Understanding the change of metabolism in the disease process may be achieved through computational modelling and simulation and results from the analysis may aid in making predictions of which parts of the metabolic network in brain cells are changed under various conditions.

The study of brain metabolism is started by studying the brain in healthy subjects, at rest and during physical exertion when the brain shows substantially increased metabolism. A computational study of human metabolism during endurance sports event is described in **Chapter 2**. The analysis of changes in brain metabolism during exercise was part of a demonstration of 'virtual physiological human' modelling of human metabolism during exercise. Among others a whole body model was developed, which contains 25 compartments representing the head, trunk, arms, hands, legs and feet. We investigate energy conversion and heat transport, applied to a cyclist during a mountain time trial of the Tour de France, and the biochemical events during muscle contraction in the cyclist leg are predicted. We predicted that brain temperature may reach $39^0$C during a top performance in by a professional cyclist. In addition, the brain is exposed to increased levels of lactate in the blood. A model of brain central energy metabolism is introduced in this chapter. We calculate brain metabolism during normal resting conditions and during maximal exercise. During 15 minutes of exercise, glucose uptake into the brain doubles from the resting state, and a high amount of lactate is taken up. At the same time the increase in oxygen consumption is modest. To explain the dysbalance of carbon substrates and oxygen uptake, we hypothesize in this chapter that the carbon atoms in glucose and high lactate uptake, are partially directed to the synthesis of lipids in the brain. The model calculation shows that the ATP and carbon balance in the brain can be maintained in this way. The brain may therefore hypothetically contribute to the removal of lactate from the blood during intense exercise.

The calculations of brain metabolism during exercise and neurodegenerative disease make use of flux balance analysis (FBA), which is a mathematical method for calculating the distribution of metabolism in metabolic networks at steady-state by optimizing an objective function subject to a given constraints. A key assumption in FBA is that the concentrations of metabolites inside the organ or cell do not change. The fluxes (metabolic rates) into and out of each internal metabolite pools are assumed to be exactly balanced. This may be a good approximation for a slowly developing disease, but the assumption may not be valid under acute conditions, for instance if blood supply to the brain were acutely interrupted, glucose and oxygen are depleted and lactate accumulates.

To facilitate metabolic network construction and calculation of flux distribution based on the constraint-based modelling approach of FBA, we have developed a software package named BiGGR. This package used the R language and software environment which is used extensively in the genomics files. BiGGR is part of Bioconductor, a curated open source software repository for bioinformatics software. BiGGR allows the assembly of metabolic models from, among others, the BiGG database which contains metabolic reconstructions of many organism. Metabolic reactions can be retrieved by querying for pathways. The package can then be used for FBA computation and visualization of the computational results on the metabolic pathways model. An introduction to the first version of BiGGR is given in **Chapter 2**, and detailed explanation of an improved version of this software package as well as example of its application is given in **Chapter 3**.

FBA of a metabolic network usually involves optimizing an objective function such as ATP production, growth of biomass or product formation. However, it is subject to debate what is the suitable and correct objective function in a cell or organ. For the healthy brain we assumed maximal ATP production for a given supply of substrate, and constrained the flux distribution at two important branch points according to experimental data.

Availability and advances in other 'omics' fields makes data available that can be integrated into FBA to improve flux estimates when the condition of the cell changes. Here we developed a new algorithm to integrate measured levels of mRNA that reflect gene expression, for instance during disease progression. This new algorithm is termed Least-squares with equalities and inequalities-FBA (Lsei-FBA) and is explained in **Chapter 3**.

The Lsei-FBA method takes gene expression data from patients as input and uses an improved version of the central carbon metabolism model developed in Chapter 2 to predict metabolic fluxes. As an example, we applied this new algorithm in Chapter 3 to one Alzheimer's disease data set, where the gene expression is measured post-mortem in the hippocampus, the region most affected during early stages of the disease. The predictions for glucose and oxygen uptake agree reasonably well with experimental measurements in AD patients. This correspondence with measured uptake supports the idea that the predictions for the internal flux distribution in the full network are valuable (see below).

We applied the Lsei-FBA algorithm on the central carbon metabolism model to predict flux changes in various brain regions in Parkinson's disease in **Chapter 4**, and Alzheimer's disease in **Chapter 5**. In Parkinson's disease, we predicted reduction in metabolic fluxes through central carbon metabolism particularly in glycolysis, TCA cycle and oxidative phosphorylation pathways in the substantia nigra and other brain regions including frontal cortex, cerebellum and putamen. We also predicted an increase of lactate production and shifts in redox shuttles. Reduced metabolism via alpha

ketoglutarate dehydrogenase in the middle of the TCA cycle is compensated via the GABA shunt. In contrast to the decreases in metabolism in substantia nigra and most other brain regions, increases in metabolic fluxes are predicted in the globus pallidus internus part of the brain compared to normal controls. This corresponds with the electrophysiological activity in this region which is increased during Parkinson's disease.

For Alzheimer's disease, we predict reduced fluxes in the glycolytic pathways, oxygen consumption and ATP synthesis in most brain regions. The GABA shunt is activated to compensate for reduced alpha-ketoglutarate dehydrogenase activity. Changes in metabolic fluxes can be associated with specific brain regions: predicted changes in the middle temporal gyrus and the hippocampus, posterior cingulate cortex and entorhinal cortex are substantial while changes in the frontal gyrus and primary visual cortex are minimal.

In conclusion, metabolic network modelling has allowed computational predictions to be made about the complex changes in the metabolic network in the brain which presently cannot yet be measured directly. The results are promising, and the approach may be developed and tested further. It may also be tested for other diseases.