Mechanism-based mathematical modelling as an alternative to animal experiments
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Mathematical modelling can be used in both Replacement, Reduction and Refinement. Some *in vivo* studies can be substituted with *in vitro* experiments in combination with a mathematical model. Biological hypothesises can be tested by models building on the current biological knowledge. A mathematical model can be used in prioritizing, which experiments are the most important in the further knowledge building and thereby help avoid unnecessary animal experiments.

I will give examples from my modelling works of the neuroendocrine system the Hypothalamus-Pituitary-Adrenal(HPA) axis. The HPA axis controls the level of cortisol in the body, which is changed in many normal and pathophysiological conditions.

In a mechanism-based, patient-specific ordinary differential equation (ODE) model presented in (Gudmand-Hoeyer et al, 2014), we identify three of the model parameters to be changed between groups with normal, high and low cortisol levels. In mechanism-based mathematical models, each of the parameters have a physiological interpretation. When comparing the model to data from different groups a change in the value of a given parameter indicates which mechanisms that have been changed between the groups.

Because of its hydrophobic properties most of cortisol in the blood is bound to transport proteins. Only free cortisol is considered bioactive, but in most clinical procedures only total cortisol is measured due to lower costs. Free cortisol is afterwards estimated. In (Gudmand-Hoeyer & Ottesen, 2018) we state a new equilibrium model for predicting the distribution of cortisol in plasma on free and bound forms. The model includes the activity of neutrophil elastase and competition from the steroids progesterone and testosterone. When changing the activity of the enzyme neutrophil elastase in the model in a physiological range, the model is able to fit data excellently. Further, analysis of the model shows that progesterone should be regarded when estimating free cortisol in women.

References

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