# Modelling of postprandial glucose and insulin dynamics

# IMPACT PARAGRAPH

Computational modelling is a powerful tool that has greatly improved our understanding of the human system. Computational models can be combined with (biological) datasets to perform *in silico* predictions across different spatial and temporal scales. The increasing amount of data allows the development of models that link different levels of biological organization to study complex system behavior and provide insight into the processes underlying health and disease. In this thesis, "Modelling of postprandial glucose and insulin dynamics: the role of amino acids", we focused on personalizing computational models of the glucose-insulin regulatory system and investigating factors influencing this system, in particular the effects of amino acids (AAs).

## Personalized complex meal models

The increasing prevalence of obesity and overweight, defined as abnormal or excessive fat accumulation, has a large impact on health and well-being [1]. Obesity results from an imbalance between energy intake and energy expenditure and is one of the major causes of insulin resistance. An increased insulin secretion by the pancreatic β-cells can often compensate for insulin resistance. However, over time, the increased demand on the β-cells to produce more insulin may lead to β-cell dysfunction and the development of type 2 diabetes mellitus (T2DM), which is characterized by high blood glucose levels [2]. Type 2 diabetes mellitus (T2DM) may eventually lead to disorders of the circulatory, nervous, and immune system, adversely affecting the life of patients as well as causing a large socio-economic impact. Large efforts are being undertaken by governmental and public health bodies to educate the general public on the importance of a healthy lifestyle, including diet and physical activity [3, 4]. While nutritional and lifestyle interventions may improve glucose homeostasis, a large heterogeneity exists in an individual's response to such interventions, which can be attributed to differences in genetic, environmental, and lifestyle factors [5]. In this thesis, we transitioned from a population average glucose homeostasis model (E-DES) to a personalized model, enabling insight into inter-individual differences in glucose metabolism. Together with an extension made to the model that allows for description of AAs and protein (E-DES-PROT), we can now describe and simulate the response of a person to a complex meal. This makes our work interesting for both consumers as well as for the food industry. The mechanistic nature of the model allows study and comparison of physiological processes contributing to postprandial glucose and insulin dynamics. A better understanding of how individuals respond to various foods at the mechanistic level may lead to

personalized dietary advice as well as targeted nutritional interventions. It also provides the opportunity to adjust and develop new food products with varying macronutrient composition targeted for specific phenotypes. This might further contribute to improved healthcare and reduction of the socio-economic impact of metabolic diseases such as T2DM. In addition, mechanistic models can easily be modified and adapted for various conditions, allowing researchers to simulate their own experiments or procedures, potentially reducing costs and the use of animal experiments.

### Hybrid models

While the intra-individual variability in postprandial glucose and insulin responses can be largely explained by mechanisms of glucose regulation encoded in mechanistic models, it is known that other factors such as body composition, diet, physical activity, and cardio-metabolic health related parameters may also affect glucose regulation [6, 7]. Zeevi et al. [8] showed that large inter-individual differences exist in response to identical meals, and that a machine learning model trained on a wide variety of phenotypic information was able to accurately predict the magnitude of postprandial glucose excursions. Machine learning methods allow a convenient framework to integrate diverse data that may have relevance in glucose regulation without the need for a causal understanding. While machine learning based approaches are useful for prediction, they only provide limited insight into the biology underlying inter-individual differences in glucose homeostasis [9]. Thus, a hybrid approach in which machine learning is combined with mechanistic modelling may circumvent the disadvantages of these standalone methods. Such a hybrid approach may yield more insight into the biology underlying inter-individual differences in glucose homeostasis. In our work, we developed and applied, for the first time, a hybrid combination of a machine-learning model with the mechanistic E-DES model to identify factors predictive of inter-individual differences in glucose and insulin following a glucose drink in a large group of individuals with various glucometabolic status. Whilst, a naïve sequential combination may not be suitable when studying underlying factors of inter-individual variance, a parallel approach should be explored in glycemic responses following complex meals containing varying amount of macronutrients as well as meals in free-living conditions. In the future, hybrid models may play a crucial role in the advancement towards ‘digital twins’ by providing simulative decision-support.

### Open source data and software

Open science is the movement to make scientific research and its results accessible to allow verification of scientific claims by others, but also to allow data from many different sources to be integrated to obtain new insights. There is a growing realization that scientific research depends more and more on computer code for simulation, calculations, analysis, visualization, and general data processing. It is important to have access to this code as well as to usable datasets. This allows researchers, for example, to apply models to their own data and further build and improve upon them. In our work, we made the computational modelling code publically available and detailed the computational software with corresponding versions and libraries. Furthermore, the modelling individualization pipeline was made available and was constructed in a generalized manner, requiring no biological insight to implement. As such, these computational techniques can be readily applied to other systems or models for analysis. We extracted dynamic time-series data from papers spanning over multiple decades going back to the late 60's. We made this data reusable and publically available to support data-sharing and allowing other researchers to use and employ the data.

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