



COMBINED TOP-DOWN AND BOTTOM-UP MODELLING PROVIDES INTERNALLY CONSISTENT EXPLANATIONS OF WHOLE-BODY GLUCOSE HOMEOSTASIS THROUGH THE IDENTIFICATION AND ELIMINATION OF DATA INCONSISTENCIES AND MISSING REGULATIONS

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Type 2 diabetes is caused by the failure of a complex interplay between insulin responding and insulin producing organs, leading to increased glucose concentration in the blood. The complexity of the system argues for a systems biology approach when investigating the disease, integrating experiments with mathematical modelling. Furthermore, the different time-scales demand an open and systematic multi-scale modelling framework, which currently is not available. We here present a combined top-down/bottom-up approach and illustrate the usefulness for providing internally consistent explanations and data. In our approach, organ module constraints are extracted from a hierarchically formulated whole-body model, and detailed organ models are fitted both to these constraints and to new cell and organ-level data. We illustrate this through the development of a detailed adipose tissue module, using data from isolated human adipocytes. A main finding is that the insulin stimulated increase in glucose uptake by isolated cells accounts for less than 50% of the total increase in adipose tissue glucose uptake in response to a meal. The resulting zoomable whole-body model translates mechanistically oriented simulations at the biochemical level, which is the level where drugs act, to the whole-body level, which is of clinical and diagnostic relevance. Our approach and pilot study opens the door to hierarchical modelling as a tool in drug certification and in finding new treatments of insulin resistance and type 2 diabetes.

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