Multi-level multi-scale hybrid model for clinical decision support

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Keywords
digital twins, health informatics, mathematical modelling, hybrid models, personalized medicine.

1. Introduction

Most diseases develop over several years and do not show symptoms before they lead to more acute conditions. Furthermore, the disease mechanisms often involve multiple organs, time-scales, and control mechanisms, affected by several medical and environmental factors. The data relevant for a certain disease are therefore highly heterogenous, and require different analysis approaches. We therefore propose a multi-scale, multi-level, and hybrid model for predicting disease progression.

2. Methods

We use two kinds of models for two purposes: mechanistic for simulation of scenarios (how biomarker evolve over time given certain conditions, e.g. treatments), and machine learning (ML) for risk calculation.

Mechanistic models are based on ODE equations and describe the dynamics of biological systems, e.g. organs. These models can be connected with each other, describing how different biological systems interact. The resulting multi-level model can then be personalized by training and validating them on individual time-series data, and can as such be used to predict the progression of biomarkers for an individual.

ML models are trained on multidimensional data with known outcomes to get a risk score for that outcome within a specific time period. One such type of ML is Bayesian graphical networks (BGN), that are based on conditional dependencies between different biomarkers and outcome.

3. Results

Here, we present a first multi-scale and multi-level model of metabolism on both a cellular [1,2], organ/tissue [3], and whole-body level [4], for diabetics and non-diabetics. The whole-body model describes long term weight changes [4], and is connected with the other sub-models in a top-down fashion through glucose intake and amounts of body fat and lean tissue affecting glucose uptake. The two other sub-models - a model of postprandial glucose uptake, and a model of intracellular insulin signalling and glucose uptake in fat cells [1,2] - are connected in a cyclic manner, with insulin resistance in adipose tissue, which is correlated with fat mass, manifesting as a reduced glucose uptake in fat cells. Diabetes is modelled as a gradual change of parameters in the fat cell model. To describe atherosclerosis progression, these models will be further connected with models for e.g. whole-body fat flow [5,6], plaque formation, and thrombus formation [7].

For risk calculation, our developed BGN outperforms risk models currently used for cardiovascular risk prediction in health care [8] (ROC AUC 0.82 vs 0.71). This model can also take simulated biomarkers from the mechanistic models as input and then predict the risk for a different scenario.

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4. Conclusions

Our model can be used as decision support to evaluate different treatments. The hybrid approach offers a way to understand why and criticize the assessments made, while making use of different kinds of knowledge and data. The usage of these kinds of multilevel multiscale models therefore open up for a more personalised and participatory health care, were different kinds of knowledge generated by the clinical sector are combined and made available for the patients in a comprehensive manner.

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