MECHANISTIC MODELS FOR HEALTHCARE: A REVIEW OF CURRENT PRACTICE AND POSSIBILITIES

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ABSTRACT

Biomedical theory is often expressed in formal, usually dynamic mathematical models. However, these models rarely find their way into clinical practice. We review a number of projects where models of the underlying system are put to use to improve healthcare and find that such an approach can have advantages above alternative strategies. We discuss the obstacles to this approach and we conclude that it can fit in the paradigm of Evidence-Based Medicine.

KEYWORDS

prediction, decision support, modelling

1. INTRODUCTION

Mathematical models play a very modest role in clinical practice. In a 2008 review of 35 years of mathematical modelling of the medical condition of elevated intracranial pressure, the authors conclude that despite the large yield of 59 models 'virtually no tangible clinical impact has been reported' (Wakeland & Goldstein, 2008). In other bio-medical disciplines too, theory is, or could be, expressed in some formal way - but these expressions rarely find their way into clinical practice directly.

A way to put a mathematical model to use in clinical practice, is as a tool for decision support. This can be achieved by fitting the model with patient-specific parameters and exploring the outcomes of possible interventions. There are good a priori reasons for this approach:

- By modelling a specific patient, truly personalized advice and predictions can be given: tailor-made for this patient at this point in time.
- Decision-making (which weights the expected positive and negative consequences of an intervention) can be explicitly separated from diagnosis and prediction (which is based on scientific insights).
- The advice or prediction can be explained; after all the model is a representation of the theoretical background of the patient's condition and as such something the clinician is familiar with.
- The model should be able to answer a great many questions simply by simulating different situations. This includes questions the model designers have not thought of.

In this review we will discuss the ways in which a type of models we will call 'mechanistic models', can be of use to clinical practice. First we will look at some examples, and demonstrate the advantages of a model-based approach. We will then show that formal models at least partially meet the criteria to be considered reliable in the context of Evidence-Based Medicine (EBM). Then we explore properties of these models and the issues with their use. As more examples are now available we can provide a more elaborate review than Andreassen and Hejlesen (Andreassen & Hejlesen, 1994). We will further show how theoretical

and technological developments have decreased the obstacles for model use, as listed by Lehmann and Deutsch (Lehmann & Deutsch, 1998).

All the examples we consider in the next section are of models expressed as differential equations, i.e. mathematical models. However, the reasoning we will provide applies to any kind of formal model. To emphasize that the models we are interested in model dynamic, biological systems, we will from here on use the term ‘mechanistic models’.

2. MECHANISTIC MODELS: SHOWCASES AND PREREQUISITES

We will now illustrate the advantages of mechanistic models with applications from the following areas: mechanic ventilation, weight management and diabetes management.

The Intelligent Ventilator (INVENT) (Rees, 2011) project was set up to aid decision making about assisted breathing for Intensive Care (IC) patients. The system gives advice tailored to an individual patient by finding patient-specific parameters, indicating how well the parameters describe the patient and helping the clinician find the best ventilator settings by performing simulations.

The architecture of this system deliberately separates the several mathematical models, which represent current understanding of lung physiology, from the reasoning part of the system which represents current clinical preferences. The mathematical models of lung physiology used in the INVENT system have been established for a long time - some for decades. The novelty is that now they have been made available for use in a clinical setting.

The INVENT System as a whole is not yet in use clinically, but one of its models is: the Automatic Lung Parameter Estimator (ALPE) model is incorporated in a ventilator system. This combination enables clinicians to obtain clinically relevant pulmonary gas exchange parameters in 10 to 15 minutes in a non-invasive way (Rees, et al., 2002). The alternative is to proceed without reliable estimates because the traditional way of obtaining them is often considered too time-consuming (30—40 mins).

Our next example is a weight change model. This model can predict the course of weight change over time for a specific person because it takes into account personal factors (like age, sex, weight, height and physical activity) as well as physiological changes caused by changes in body weight (Hall, et al., 2011). In contrast, dieting advice based on heuristics is very general and can only provide a very rough expected weight loss estimate. The model can also be used to predict changes on population level. This is useful for policy-makers who for example consider taxing sweetened beverages.

One particularly prolific area for computational models of human physiology is diabetes. These modules can be very specific, like an algorithm to compute insulin sensitivity (Docherty, et al., 2011) or a method to anticipate the effects of a meal (Dalla Man, et al., 2007). A complete Decision Support Systems (DSS) that incorporates domain knowledge in the shape of a mechanistic model is KADIS (Salzsieder, et al., 2011). The model makes it possible to simulate a 24-h glucose profile of the patient and to test different therapies (insulin or oral hypoglycemic agents) and the effects of changes in meals or exercises, without burdening the patient. This replaces the usual trail-and-error approach for diabetic patients.

The input for the KADIS model is a ‘metabolic fingerprint’ of an individual patient consisting of attributes like: age, sex, weight etc., as well as 72h continuous glucose measurements in combination with self reported information on meals, exercise and medication during that period.

This system also illustrates the effort it takes to go from a reliable patient model to a usable DSS. The model output is translated into user-friendly information by visualising 24h simulated glucose in the same graph as the measured glucose, indicating weak-points in glucose control and other relevant information like food intake, exercise, medication and target ranges. Kadis does not run on either the diabetic’s or their physician's computer, instead the patient's data is sent to a `Diabetes Service Centre' where specialized operators interactively regulate the therapy according to established guidelines to find which adjustment best fits this individual. The resulting advice is put in a report which is sent to the patient's own physician.

Also from the field of diabetes, comes an example of another use for mathematical models: as a test-bed. The American Food and Drug Administration (FDA) has approved simulation software (Kovatchev, et al., 2009) to be used for pre-clinical testing of closed loop control systems of glucose, i.e. an insulin pump coupled with a control and continuous glucose measurements. The software models the patient, the insulin pump and a glucose sensor separately. The patient model takes its patient specific parameters from earlier

trails, making it possible to instantiate an entire population to run tests on. The advantage of this system is that it makes the testing phase that precedes clinical trials shorter and cheaper, it saves laboratory animals and enables exploration of the search space of the control algorithm. The stability of the algorithm can be tested to find what happens in extreme situations and to rule out inefficient scenarios.

2.1 Problems and Requirements

Several reasons have been put forward to explain why mechanistic models are not used more often. Wakeland and Goldstein (2008) name a few and Lehmann and Deutsch (1998) pointed to three unresolved issues with mechanistic models. It will become clear below that none of these issues pose insurmountable obstacles when we show how they are addressed by the models we discussed earlier.

We then turn to the issue of trust. A mathematical model that is intended to aid clinicians - either stand-alone or as part of some larger system - should be trustworthy. We discuss what it takes to be considered trustworthy in the context of medical practice, focusing on Evidence-Based Medicine, and show how mechanistic models fit in.

2.1.1 Obstacles for model use

The obstacles for model use found by Wakeland and Goldstein (2008) include models not answering clinically relevant questions, and being too complex and not intuitive enough for use. The first reason may be valid depending on what the model is intended to do. The second can be dealt with, if it is addressed properly: recall how the Kadis system bridges the gap between model and decision support by putting an operator between the model and the end user, and embedding the model in user-friendly software.

In a 1998 review Lehmann and Deutsch (1998) conclude[1] that while there is a place for mechanism-based models in education, research and as a test tool, such models are not suited for prediction and decision support for three reasons: 1) Current theory does not provide a sufficiently detailed explanation of the system to make a good enough simulation model. 2) Each part of the model has its own uncertainties, adding to the uncertainty of the outcome of the model as a whole. 3) It is not possible to obtain enough input-data, of sufficient quality, to instantiate a model for an individual.

Looking back at this review 15 years later, the above issues have not disappeared but they seem to be crumbling away slowly. Theory has progressed making the first two objections less of an issue, as exemplified by the decent fit of the models to data. Even so, the models from our examples are not ‘complete’. The diabetic patient model does not yet implement hormonal influences, diurnal variation and interactions of glucose metabolism with fatty acids (Dalla Man, et al., 2007). The weight change model (Hall, et al., 2011) generates reliable predictions for the average person but individual differences in physiological parameters may make prediction less reliable, especially on the long term. It has other sources of uncertainty too, like self reported food-intake, or the unimplemented influence of exercise on food intake.

As for the third objection: in terms of modelling mechanistic models fall between a ‘data-driven’ and ‘model-driven’ strategy, and good quality data is necessary to build a valid model. From our own experience we can say that as model builders we are always looking for suitable data-sets, and we depend on professionals from bio-medical fields to provide us with data. The limited availability of good quality data for model design has also been recognized as a problem by Wakeland and Goldstein, who propose the use of data repositories as a practical solution (Wakeland & Goldstein, 2008). As for the data necessary to tailor a model to an individual, this is easier now due to technological progress and social changes. The latter include increased internet access and the use of hand-held computers. It also helps to make pragmatic choices: for the Kadis system patients are asked to record and report specifics over a limited time-period only.

2.1.2 Trust and Evidence-Based Medicine

Evidence-Based Medicine (EBM) means that clinical reasoning and decision-making is substantiated with relevant literature whenever possible. Because it is not straightforward to go from literature to medical advice, several ranking schemas exist to help clinicians and guideline designers weight the separate and

[1] Their arguments are aimed at compartmental models (the kind of mathematical models used in the diabetes models we discussed and generally often used in diabetes modeling). However, none of them are really specific to that particular type of mechanistic models or to the field of diabetes.

overlapping bits of knowledge on the occurrence of a condition, reliability of tests, the prognosis, possible interventions, their benefits, and possible harms. Reviews of Randomized Controlled Trials (RCTs) are placed at the top end of the evidence hierarchy while reasoning from what is known of the underlying mechanisms of a disease is considered as the lowest quality of evidence (Levels of Evidence Working Group, 2011), if it is considered at all (Guyatt, et al., 2011).

There are good a priori reasons to criticize how little value is placed on mechanisms (Clarke, et al., 2013), including the fact that mechanistic models are part of the theoretical background of the setup of empirical studies. It is therefore unlikely that they will contradict each other, but if they do it is time to update the theory. However the main problem is that in EBM literature `mechanism-based reasoning' is used synonymously with `reasoning from first principles', even though the two expressions are not synonymous as mechanistic models are also subject to evaluation in the context of empirical finds. Our examples show that any one mechanistic model has probably undergone several iterations of validation.

The different equations and constants that form the theory from which the INVENT DSS for IC patients was built, have been empirically evaluated previously. The subsystem parts of the INVENT system have been evaluated against old and new data (Rees, 2011), and the predictions of the system as a whole were evaluated on a small number of patients. The weight change model makes use of mathematical descriptions of energy storage and expenditure that were empirically evaluated and published earlier. The model as a whole was built and then validated using separate data-sets (Hall, et al., 2011).

The Kadis DSS for diabetes management has seen many iterations of improvement and validation over several decades (Salzsieder & Augstein, 2011), the constituent parts of the system have been evaluated with data including tracer data and the whole system (the Kadis program in combination with the support provided by the `Diabetes Service Centre') has been the subject to trails with favourable outcome (Salzsieder, et al., 2011).

Finally the test-bed model makes use of a patient simulation model (Kovatchev, et al., 2009) which builds on earlier, empirically founded, mathematical descriptions and in addition has been tested on two (Dalla Man, et al., 2007) and validated on three different data-sets (Kovatchev, et al., 2009).

What is more, the authors of this model point to limitations in the current version and express the desire to incorporate more variables and mechanisms into the model and to extend it in order to make it applicable to another group of subjects. This means the current model is a stepping-stone for the next model. If the next model is to apply to a new subject group, it will be validated against a new set of data.

2.2 Future

In recent years a number of projects have started that use computer simulation to further our understanding of the workings of whole organs: the liver (Holzhütter, et al., 2012) and the brain (The Human Brain Project, 2013; Insel, et al., 2013; The Blue Brain Project, 2005). In addition, the Physiome Project (Hunter & Borg, 2003) is an international effort to describe the whole body by combining models across different levels. It is not to be expected that some kind of plug-and-play model of the liver or the brain will become available in the next few years, ready for use as a module (a ’library’ in software terms) in other programs. But mathematical models that describe parts of the whole will become available as a result of these projects, and can be put to use. Recall how the models we discussed in this paper build on earlier models. In addition, such projects provide new methodological insights.

There are many possibilities to combine mechanistic models with techniques from the field of artificial intelligence. These possibilities go beyond the use of patient-specific simulations. For example a mechanistic model can be used to generate system parameters or to create a synthetic dataset to train a decision support system (Montani, et al., 2003). Incorporating domain knowledge in the form a mathematical model can improve classification of patients (Cace, et al., 2013). It would be interesting to find further ways to leverage the potential of mechanistic domain models with machine learning techniques for data-mining purposes and for classification.

3. CONCLUSION

Mechanistic models have a place in clinical practice, and there are developments underway which will further their progress. We have shown that mechanistic models can be used to obtain patient-specific parameters and predictions, faster or easier than with alternative methods. Mechanistic models can also estimate the change of a parameter in time. Complete knowledge of biological systems is not available yet, but existing models are good enough to be usable. The question of usability should be addressed by having the model output be relevant and understandable.
Finally, mechanistic models have a firm empirical basis, and as such their predictions can be considered evidence-based.

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