Mechanistic mathematical modeling of body composition and energy turnover

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Introduction

Studies of drugs related to appetite, metabolism, and energy expenditure often require rigorous monitoring of food intake, body weight and sometimes energy expenditure. Obviously, such studies are laborious to administrate and costly. We explore how mechanistic dynamic mathematical models of energy balances and body composition can improve the study design and analysis of such experiments.

We consider the following general problem (Figure 1): Given energy intake (EI), and/or energy expenditure (EE) and /or body weight (BW) time series data, how to best quantitatively model the relationship between these variables and how to infer potential unobserved variables as well as system parameters?

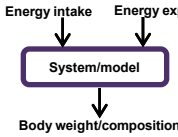

Figure 1. *System overview.*

The model class

We consider a class of ordinary differential equations (ODEs) models that are based on the law of energy conservation and explicitly connected to physiological variables (1-4). Together, this ensures that biophysical constraints are satisfied and facilitates potential extension of the scope of the models. Key model based predictions include time series of fat mass (FM), lean mass (LM), extra-cellular fluid (ECF), BW, fat mass (FM), EI and EE. Individual models within this class of models mainly differ in the level of resolution at which the system is modeled, see Table 1.

Species	Number of ODEs	Key variables	Reference
Human	2	LM, FM	1
Human	3	LM, FM, ECF	2
Human	8	PM, GM, FM, ECF	3
Mouse	2	LM, FM	4

TABLE 1. *Overview of common models. PM=protein mass, GM=glucogen mass.*

To exemplify, the moderately complex model proposed in (2) is detailed in Box 1.

BOX 1

The body weight (BW) is obtained as $BW = FM + LM + ECF$.

Key processes are represented by the following equations:

$$\rho_{FM}\frac{dFM}{dt} + \rho_{LM}\frac{dLM}{dt} = EI - EE$$

$$\frac{dECF}{dt} = \frac{\rho_W}{[Na]}\left(\Delta Na_{diet} - \xi_{Na}(ECF - ECF_b) - \xi_{Cl}\left(1 - \frac{Cl}{Cl_b}\right)\right)$$

where ρ_{FM} = 9400 kcal/kg and ρ_{LM} = 1800 kcal/kg are energy densities, ΔNa_{diet} is the change on sodium in mg/d from baseline, Cl_b is the baseline carbohydrate intake, [Na] is extra-cellular sodium concentration, ξ_{Na} and ξ_{Cl} are empirically determined constants, and ρ_w is the density of water. An empirical relationship, referred to as a Forbes curve, relates *dFM* to *dLM*. EI is taken from data if available, or alternatively, estimated based on typical feeding habits. EE can be estimated from empirical equations or modeled as

$$EE = \beta\Delta EI + \delta BW + K + \gamma_{LM}LM + \gamma_{FM}FM + \eta_{FM}\frac{dFM}{dt} + \eta_{LM}\frac{dLM}{dt}$$

where β is a coefficient for the thermic effect of feeding, δ a physical activity coefficient, γ and η are coefficients for the resting metabolic rate, and K ensures an initial steady-state.

Model selection

It is common that one system is modeled at different levels of resolution as the models in Table 1. The choice is typically based on the amount and quality of available data, prior information of the system, and the research question in focus. Hence, advantages and limitations of the different models in Table 1 are partly context dependent. In general, compared to a simple model, a more complex model enables more precise predictions but must be inferred from more reliable data (amount and/or quality).

Similar to the conclusion drawn in (2), our experience indicates that the simpler model presented in (1) is inferior (mainly with respect to flexibility) to the model presented in (2) when both EI and BW are observed. The choice between the models presented in (2) and (3) depends on what observations are available among the system variables present in the latter but not in the former. Furthermore, when modeling drug treatment data, inclusion of variables involved in the mechanism of action is natural.

A fundamental requirement of the models is flexibility to fit data generated for both EI and BW. Under- or overfitting of noisy body weight time profiles and uncertainty in empirical based estimation of energy expenditure are major issues. For application of any of the models in Table 1, choosing free parameters is central. Some general guidance is that sensitivity of parameters related to unobserved variables generally is high, i.e., it is natural to keep δ free when EE is unobserved (Box 1). Furthermore, the baseline EI before the study (affecting ΔNa_{diet} and Cl_b) is hard to infer empirically, and initial values for, e.g., FM and ECF, can be constrained around initial guesses from empirical equations (2).

Inference of EI using BW data

Observing EI is considerably more expensive than BW monitoring, and inference of EI from BW data is therefore valuable. Since models are represented by ODEs that are non-linear in the parameters, and since input data is incomplete, deconvolution methodologies designed for sparsely observed non-linear systems are required. In general, this problem can be defined by the following components: 1) available time-series data; 2) a model space representing the prior information of the input signal (e.g., feasible input model structures, parameter ranges and/or constraints); and 3) an error function that measures the feasibility of each tested model from the model space and works as a model selection criterion (e.g., AIC or cross-validation approaches). Together, these three components form an optimization problem – to optimize the error function over the model space given available data.

In practice, structural model identification problems of these types are very hard: representation of the model space is nontrivial, the size of the model space may be too large to allow an exhaustive search, and observing only few state variables makes structural identifiability a major issue. Therefore, a pragmatic approach is to apply non-parametric methods where a fixed structure of the input model is not assumed. To illustrate this, let some typical time-series BW data be represented by a smoothing spline function (spaps, Matlab), see Figure 2. EE is assumed unobserved but modeled as described in Box 1 with parameters taken from the literature. Then, EI can be identified non-parametrically by integrating the ODEs by Euler steps verifying at each step that simulated BW matches the smoothed BW data. Integration accuracy and precision is guaranteed by choosing sufficiently small step length. The resulting EI time series are depicted in Figure 2.

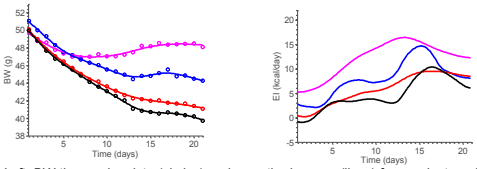

Figure 2. *Left: BW time-series data (circles) and smoothed curves (lines) from rodent models exposed to various diets or drugs affecting appetite. Right: inferred EI time courses using the model from (4).*

Naturally, the curvature but not the integral of the EI predictions is dependent on the curvature of the corresponding BW time-series data, and hence also on the choice of smoothing parameter. To validate the model alternative additional experiments may include body fat measures (e.g., by dual-energy x-ray absorptiometry).

An integrative PKPD modeling approach

In drug discovery/development, a natural extension is to connect the considered model class with PK of related drugs. Observations or predictions of EI and/or EE are then of major importance in order to identify a reasonable drug induced effect model based on the mechanism of action. Main advantages of a complete model include simulation of various dosing schedules, extrapolation over time, and improved understanding of the mechanism of action (drug targeting EI and/or EE). Concerning the latter, the main assumption in the analysis presented in Figure 2 is that treatment does not affect EE. However, the predicted EI depicted in black (Figure 2) exhibits negative values initially, something that may indicate an effect on EE. Another plausible explanation is an initially increased fecal elimination rate. Should the treatment affect EE, additional data in form of EI can help distinguish the effect on appetite from the effect on EE and in that way unraveling the mechanism of action.

Experimental design

Taken together, a framework containing the model class in Table 1, approaches for model selection and deconvolution, and integrative PKPD aspects enables new ways of analyzing experimental designs in the obesity area. As an example, a key question is how well a model can predict body weight change after a given period of time given data for an initial part of that period, when certain variables are observed. Since scenarios with no or only minor unmonitored drug tolerance development gives best predictions, proper translation of preclinical observations regarding tolerance is important.

Conclusions

Mechanistic mathematical models can describe the relationship between EI, EE, and BW. Deconvolution can be used to predict unobserved variables. Key advantages of a mechanistic model based analysis include improved understanding of the system dynamics, improved ability to predict beyond the data ranges, and potential to significantly improve the experimental design by reducing the study length. For the latter, the risk of tolerance development must be assessed.

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