Compartment Modeling of Overweight in Toddler Age: Modeling and Simulating a Diets Effect with COPASI

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Abstract. Since overweight in toddler age has become an increasing problem in the last years it is an extensive and important topic. To counteract this, new diets are constantly being launched. But how effective are they really? To answer this question we present a system modeling approach for simulating the impact of an arbitrary diet. More precisely we design a simple model for the different body weight states and their transitions, model it in COPASI and do some simulations to discuss the impact of an arbitrary diet.

Introduction

Since overweight has become a problem in the last years it is an extensive and important topic. Increasingly it is already noticed in childhood too. In addition to limited quality of life, it also has enormous health consequences, such as coronary heart disease, type 2 diabetes mellitus and hypertension. Furthermore all these diseases cause high costs. Studies show that obesity is becoming more common in early childhood. This leads to many personal disadvantages, such as the impairment of the quality of life of the affected people. In addition, overweight causes public costs too, because overweight people have higher disease and accidents probabilities as well as higher unemployment rates.

Motivation. Modeling and simulating complex problems can answer many questions. Depending on the question, an abstract model of the system is needed. In order to answer such a question COPASI takes the abstract model as input and simulates its behaviour.

Thereby, it can be checked if the expected behaviour is observed, analysed how the desired behaviour can be reached or improved, as well as some specific questions according to the modelled problem can be answered.

Related Work. A number of related approaches in the area of modeling and simulating populations is available. For example, Levy et al. [2] compared different simulation models of obesity. In contrast to our approach, they discuss much more complex models. To the best of our knowledge, there is no related work on modeling this simulation model within COPASI.

Contribution. We define a simulation model and implement it by using COPASI. Furthermore, we analyse the impact of a diet by comparing two models (one with and one without diet states). With this simulation, we can determine if the diet has a positive effect and which arrangements should be done to improve people's body-weight conditions.

1 COPASI Modelling & Simulation

COPASI is a very powerful system simulator for reactions that convert a set of (any kind of) species into another set of species.

Following [1] and the COPASI webpage, in COPASI models each species is located in a compartment, which is a physical location with a size (volume, area, etc.). This maps directly to biochemical reaction networks, but can also represent other types of processes (for example, the species could be cell types). COPASI automatically converts the reaction network to a set of differential equations or to a system of stochastic reaction events.

Furthermore, COPASI models can have an almost unlimited number of species, reactions, and compartments, they can include arbitrary discrete events (also for model change), and arbitrary differential equations can be added explicitly and can be mapped to species, compartments, or generic variables. Compartments can have variable sizes, and for the reaction rates a large set of predefined kinetic functions are provided or can be defined by the user. COPASI not only comes along with a graphical modelling environment, it offers also data visualisation and result visualisation in 2D, in 3D, with animation, chart representation and others.

The key tool in COPASI is the multifaceted model analysis, not only in the time domain as many system simulators. COPASI provides (from [1]):

- stoichiometric analysis of reaction network, with mass conservation analysis and elementary flux modes,
- optimization of arbitrary components of the model,
- parameter estimation using a range of diverse optimization algorithms,
- local sensitivity analysis,
- metabolic control analysis,
- time scale separation analysis,
- analysis of stochasticity (linear noise approximation),
- cross section analysis (characterisation of nonlinear dynamics, as oscillations and chaos),
- and Lyapunov exponent calculation for chaos detection.

For these analysis methods, COPASI makes use of the following algorithms:

- LSODA for ODEs,
- RADAU5 for stiff ODEs,
- Stochastic Runge-Kutta (RI5) for stochastic ODEs,
- Gillespie's direct method for exact stochastic kinetics,
- Gibson & Bruck's version of Gillespie's algorithm for exact stochastic kinetics,
- τ-leap algorithm and adaptive SSA/τ-leap algorithm for faster stochastic kinetics,
- hybrid Runge-Kutta/SSA and hybrid LSODA/SSA algorithms for mixed stochastic kinetics and ODEs,
- and hybrid Runge-Kutta/SSA with arbitrary partition of reactions between stochastic kinetics and differential equations.

For the compartment modelling of overweight, we only use very basic features of COPASI: compartments (group with certain overweight status), with flow due to linear kinetics (1st order kinetics).

2 Method

In this section, we show how we designed the model and how this model can be applied for simulating the system behaviour. This approach is demonstrated by a simple example of a body weight condition model for toddlers.

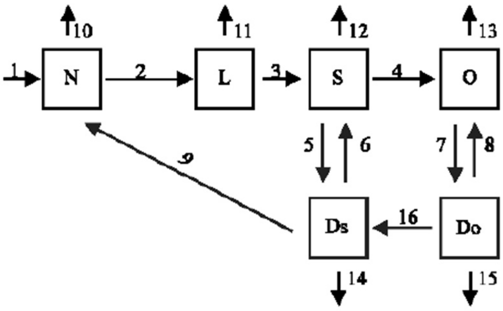

Figure 1: Model of typical body weight conditions and their diet states.

Model. First we designed the model in Figure 1. At the beginning every infant has normal body weight (state N). If the infant has unhealthy eating habits, its state changes to L. With bad eating habits, the probability for weight increase is high. Therefore the affected toddler changes to state S and if its weight is further increasing it gets obese (state O). If an infant improves its eating habits, it is on diet (DS for overweight toddlers on diet and Do for obese toddlers on diet) and can change back to its state before, because of weight loss. Furthermore, every state has his own transition for ending up within the state (transitions 10 to 15). Clearly, for getting a better diet effect, the rates of the transitions to normal weight should be maximized and minimized for staying on diet or stopping it without weight loss.

More mathematically the model above yields one differential equation per state. E.g. the differential equation for state S is defined as:

$$\frac{dS(t)}{dt} = t_3 L + t_6 Ds(t) - (t_4 + t_5 + t_{12}) S(t)$$

For the parameter S there are positive rates t_3 and t_6 for the incoming transitions, depending on the population size of state L and Ds, and negative for the outgoing ones (t_4, t_5, and t_{12}), depending on S. Analogous the five remaining differential equations could be built.

Using COPASI, all these ODEs are generated automatically via the GUI using the model as in Figure 1.

For simulation, we used classic time domain analysis by COPASI's ODE solvers (which are LSODA or

LSOAR [3] by default), and we used the steady state calculation algorithm method (for more details have a look at the user manual on the COPASI website [4]).

It is to be noted, that the model is a linear one, and that the above ODE for state S is equivalent to a transfer function model with

$$\mathbf{S}(s) = \frac{1}{s + (t_4 + t_5 + t_{12})} \cdot (t_3 \cdot \mathbf{L}(s) + t_6 \cdot \mathbf{Ds}(s))$$

Here $\mathbf{S}(s)$, $\mathbf{L}(s)$, and $\mathbf{Ds}(s)$ are the Laplace trasformations of $S(t)$, $L(t)$, and $Ds(t)$.

This equivalence – compart model with 1st order kinetics and 1st order transfer function allows the interpretation of the model in Figure 1 as (linear) network of 1st order transfer functions. Obviously, in this case also linear time domain analysis would have been sufficient.

Data. We got empirical data from fictitious hospital in Vienna of 1187 infants and their body weight progress. Based on that, the initial values for the transition probabilities are set as shown in Table 1.

var	value	var	value	var	value	var	value
t_1	6	t_2	0.02	t_3	0.0089	t_4	0.0029
t_5	0.0407	t_6	0.1274	t_7	0.0444	t_8	0.1598
t_9	0.0278	t_{10}	0.0006	t_{11}	0.0006	t_{10}	0.0006
t_{13}	0.0006	t_{14}	0.0006	t_{15}	0.0006	t_{14}	0.0042

Table 1: Calculated transition probabilities from log data (commercially rounded to four decimal places).

To see the course over time, we simulated 8000 time steps with interval size 1. Therefore, the integration and output intervals are from 1 to 8000. The initial values at time 0 are listed in Table 2.

Model with diet		Model without diet	
$N(0)$	255	$N(0)$	255
$L(0)$	226	$L(0)$	226
$S(0)$	273	$S(0)$	546
$O(0)$	95	$O(0)$	190
$Ds(0)$	273	$Ds(0)$	–
$Do(0)$	95	$Do(0)$	–
Sum	*1217*	*Sum*	*1217*

Table 2: Initial values at time 0 for both models. The model with the two diet states Ds and Do on the left and the model without diet states on the right.

Result. Figure 2 shows the simulation according to the input values. The numbers after 8000 time steps are almost the steady state numbers.

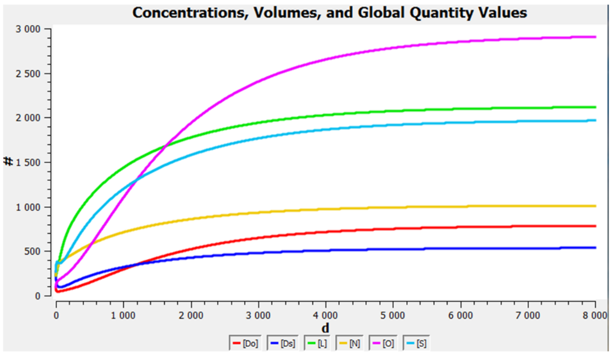

Figure 2: Course of the diet model over 8000 time steps.

To see the diets effect, analogous to our described model we built a second model without the two diet states Ds and Do. Hence this model is exactly the same, all parameters and methods are the same but without overweight and obese toddlers on diet. The states and transitions are sketched in Figure 3, which is a reduced model of the model with diet states (see Figure 1).

To keep the comparability we added the remaining initial values of Ds and Do to the initial values for the overweight and obese toddlers (see Table 2).

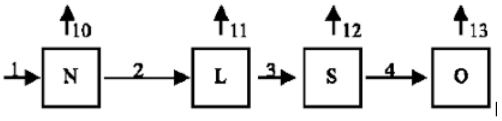

Figure 3: Model of typical body weight conditions without diet states.

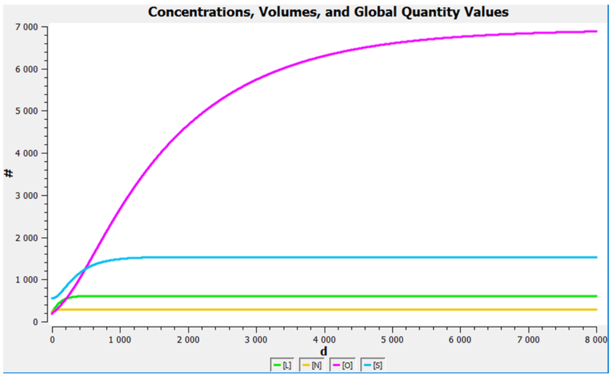

Figure 4: Time Course of the model without diet over 8000 time steps.

By comparing the two COPASI outputs (see Figure 2 and Figure 4) we can see that the diet led to a reduction of the adipose infants by more than 50% and while the overweight toddlers have increased slightly, the normal weights and the normal weights with bad eating habits increased too.

As result, by comparing the two models in their steady states we can conclude that the introduction of the diet was successful. Therefore, the diet should be applied to infants. Note that in reality, there are further reasons for overweight and weight loss in toddler age. To keep it simple we omitted them.

3 Conclusion

We have demonstrated how body weight conditions could be modelled and simulated with COPASI, and analysed if a given diet has a positive effect on body weight conditions of infants.

More general, with such a model it could be analysed how the parameters and variables affect the overall behaviour of a body weight condition system and answered different questions, e.g. which parameters or variables have the greatest effect on desired outcomes or how a specific variable influences the system flow.

The selected model implementation is very simplified, but it is good enough to show how a system could be modelled, simulated and analysed.

A big advantage of this ‘reduced’ compartment modeling is, that reality is sufficiently related to the modelled variables. Therefore it is not really important having all observed variables explicitly in the model, which simplifies the analysis a lot.

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