A COMPARISON OF SYSTEM DYNAMICS AND MARKOV MODELS FOR COST-EFFECTIVENESS ANALYSIS OF CHRONIC DISEASES

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ABSTRACT
To simulate chronic diseases Markov modeling is often used, but however the System Dynamics (SD) methodology is also applicable to this task. Both kinds of simulations can be used to analyse costs and effects of medical technologies for diseases. In this paper we perform an exemplary cost-effectiveness analysis for a smoking cessation programme for chronic obstructive pulmonary disease (COPD) patients with a simplified Markov model based on Menn (2009) as well as an analogue SD model. Such transformations from Markov models to SD models are always possible and lead to similar results. However, only the latter is of incorporating interactions between different patient groups.

Keywords: markov model, system dynamics model, cost-effectiveness analysis, ICER

1. INTRODUCTION

Cost-effectiveness analyses are often used as basis of decision making of different kinds of medical technologies (e.g. drugs, vaccination programmes, and other treatments). Such a cost-effectiveness analysis compares the effects and the costs of different treatments, for example by calculating the ICER (incremental cost-effectiveness ratio). Various types of models allow a cost-effectiveness analysis as long as they generate the cumulative costs and effects of an intervention as output.

The ICER is defined as:

$$ICER = \frac{C_1 - C_2}{E_1 - E_2} \quad (1)$$

C_1 describes the costs and E_1 the effects of treatment 1, e.g. the actual treatment. Accordingly C_2 and E_2 are the costs and effects for treatment 2, e.g. an alternative intervention (Briggs and Sculpher 1998).

One possible modelling methodology for cost-effectiveness analyses are the so called Markov models. They are common for modelling the progression of chronic diseases through several disease stages. But this type of model is not the only possibility to simulate such a chronic disease. The SD methodology, for example, is also applicable to this task. To show the similarities and differences of these two types of modelling as well as the generic transformation process from a Markov to a SD model we simulated the progress of the chronic disease COPD for a cohort of patients and calculated a cost-effectiveness analysis.

The basic model is a simplified version of the Markov model for COPD and two different treatments, the routine treatment on the one hand and a smoking cessation programme on the other hand, by Menn (2009). We transformed this model into a SD model such that advantages, disadvantages and various possibilities of expansions can be shown.

On PubMed we searched for other models which concern COPD in every possible way. There exist a lot of studies about COPD and a little bit less models. However, the cost-effectiveness analysis, which is realised in this paper, is very popular in the research of chronic diseases.

One model was very similar to the available model. The corresponding study performed a cost-effectiveness analysis with the help of a Markov model and a Monte Carlo simulation with the two cohorts “Smokers” and “Ex-Smokers”. There are some expansions like the possibility to change the state of smoking, another discounting rate and one additional state (Atsou et al. 2011).

One cost-effectiveness analysis was performed to see the differences between the two chronic diseases COPD and Asthma in the context of countries with low and middle income (Stanciole et al. 2011).

One cost-utility analysis has been realised to research a new method to test the arterial puncture of COPD patients again with the help of a Markov model (Oddershede et al. 2011).

One model which is really different from the others was a decision tree to analyse the advanced directives of COPD patients (Hajizadeh et al. 2010).

2. COPD

COPD is a common chronic disease of the lung. The different stages of the disease and therefore COPD itself are irreversible (GOLD 2010).

COPD can be divided into four different kinds of stages. Patients are classified after their forced expiratory volume in 1 second (FEV_1) that can be measured by spirometry (GOLD 2010).

Table 1: Classification of COPD Stages by GOLD

Severity of COPD	FEV_1
mild COPD	≥ 80%
moderate COPD	50% – 79.99%
severe COPD	30% – 49.99%
very sever COPD	< 30%

In our model mild COPD is "stage 1", moderate COPD "stage 2", severe COPD "stage 3" and very severe COPD is "stage 4". A fifth possible state is "death", which obviously is an absorbing state. The stages are distinguished by their expected life quality – these effects are quantified by QALYs (quality-adjusted life years) – and the costs of the patient's treatment. Another feature of the stages is that it is only possibly to leave a stage by progress into the next higher stage or by death. Patients cannot skip a stage or get better, because the decline of lung function is irreversible.

The reachability of the stages can be represented by a reachability graph, shown in figure 1.

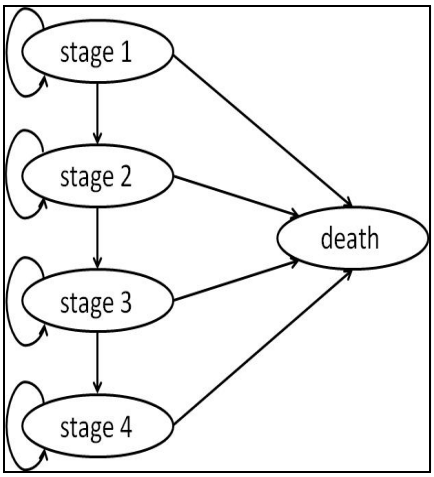

Figure 1: Reachability Graph of COPD

3. MARKOV MODEL

Markov models are based on the simulation of cohorts whose members transit through the states of the model. In this paper the simulated cohort, which contains only patients who suffer from COPD in stage 1 at the beginning, is subdivided into two different kinds of treatments: the routine treatment on the one hand and the intervention on the other hand. These cohorts are again divided into cohorts of smokers and persons who do not smoke anymore. For each of these cohorts a Markov model was calculated. The structure of the whole model is shown in figure 2, where COPD stands for the reachability graph of the different stages shown in figure 1.

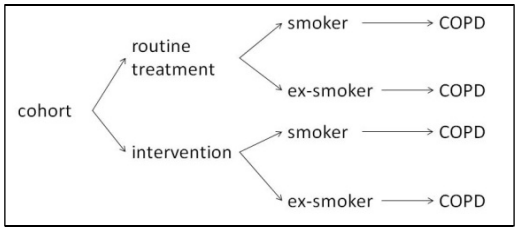

Figure 2: Structure of the Whole Model of COPD

In general, Markov models have different Markov states. These states are affiliated with each other by transition probabilities. Therefore Markov models are stochastic models (Briggs and Sculpher 1998). In our case these states correspond with the stages of COPD or the absorbing stage "death". "Stages 1-3" are all provided with three kinds of probabilities. The first one is the probability to stay at the same state as in the cycle before, the second one is the transition probability to move over to the next state, which means to get worse, and the third one describes the probability of dying. "Stage 4" has got only two probabilities, because the patient only can stay in the state or die, as no further progress is possible. "Death" does not have any transition probability which leads away from this state, because it is an absorbing state. Therefore people who die before the end of the simulation are not considered for the costs and effects anymore and furthermore do not influence the simulation any longer (Menn 2009). However, the feature that a person can stay in exactly one stage at any time of the simulation is characteristic of Markov models (Briggs and Sculpher 1998, Sonnenberg and Beck 1993).

Furthermore, an attribute of Markov models is that the operation time is not continuous, but discrete. This means that time is partitioned into time steps, the so called Markov cycles (Briggs and Sculpher 1998, Sonnenberg and Beck 1993). The cycle length of the model should be short enough so that multiple changes in pathology, symptoms, treatment decisions, or costs within a single cycle are unlikely (Weinstein et al. 2003). A patient can only change his/her stage between two cycles and not during a cycle. Therefore the model will be assumed as constant during the single Markov cycles (Briggs and Sculpher 1998).

Another defining property of Markov Models is that each Markov model fulfils the Markov property (Sonnenberg and Beck, 1993).

$$P\{N(t) = j \mid N(s) = i, N(s_n) = i_n, ..., N(s_0) = i_0\} = \\ = P\{N(t) = j \mid N(s) = i\} = P\{N(t) - N(s) = j - i\} \quad (2)$$

This formula means that the future state j at time t only depends on the actual state at time s. Therefore the probability of the future state does not depend on past states. Particularly, the probability of the progress of a person's disease is independent of the states in which the person has been in the past and of the states in which the person will be in the future (Fahrmeir et al. 2012).

After simulation the ICER for the cost-effectiveness analysis can be calculated. The ICER is defined in formula (1). C_1 and E_1 represent the costs and effects of the routine treatment (smokers and "ex-smokers" combined) of COPD and C_2 and E_2 the costs and effects for the intervention to stop smoking (smokers and "ex-smokers" combined too). The costs of the intervention are equal to the costs of the routine therapy. However, every person who receives the alternative treatment adds basic costs of 596 € at the beginning of the simulation (Menn 2009).

3.1. Simulation

All parameters values for the simulation were adopted from Menn (2009).

The running time of the simulation of the Markov model was 60 years. For the simulation the assumption that all patients start at the age of 45 in "stage 1" was made. A transition during simulation from smoker to ex-smoker was not possible. The cycle length was 3 months.

Because of the cost-effectiveness analysis the number of the persons, who receive the routine treatment, is the same as the number of the persons, who receive the intervention. If joining the routine treatment, the probability of being an ex-smoker will be 0.06 and on the other hand 0.22, if joining the intervention.

Table 2 shows the transition probabilities of reaching the next higher stage.

Table 2: Transition Probability from Each Stage to the Next Higher Stage (Menn 2009)

Stage	Smoker	Ex-smoker
1	0.014	0.0025
2	0.0103	0.003
3	0.023	0.0069

The mortality for smokers and ex-smokers is dependent on time. Therefore, there are different probabilities of dying for the different ages of the persons. The mortalities of smokers are shown in table 3, for ex-smokers in table 4.

Table 3: Probability of Dying for Smokers and the "Stages 1 – 4", Depending on Time (Menn 2009)

Age	Stage 1	Stage 2	Stage 3,4
45-49	0.0012	0.0012	0.0050
50-54	0.0021	0.0036	0.0085
55-59	0.0030	0.0052	0.0123
60-64	0.0047	0.0080	0.0190
65-69	0.0081	0.0138	0.0324
70-74	0.0136	0.0232	0.0542
75-79	0.0198	0.0335	0.078
80-84	0.0340	0.0576	0.1314
85-89	0.0473	0.0797	0.1790
≥90	0.0884	0.1467	0.3140

Table 4: Probability of Dying for Ex-smokers and the "Stages 1 – 4", Depending on Time (Menn 2009)

Age	Stage 1	Stage 2	Stage 3,4
45-49	0.0008	0.0014	0.0032
50-54	0.0014	0.0023	0.0056
55-59	0.0025	0.0043	0.0102
60-64	0.0039	0.0067	0.0158
65-69	0.0050	0.0086	0.0204
70-74	0.0085	0.0146	0.0342
75-79	0.0132	0.0225	0.0526
80-84	0.0228	0.0388	0.0896
85-89	0.0396	0.0669	0.1516
≥90	0.0742	0.1239	0.2695

The transition of persons from one stage to another stage can now be calculated with the help of formula (3).

$$A_{i,j} = A_{i-1,j} \cdot (1 - p_{j \to j+1} - d_{i,j}) + A_{i-i,j-1} \cdot p_{j-1 \to j} \qquad (3)$$

i stands for the cycle number and therefore for the time and j for the stage. $p_{j \to j+1}$ describes the probability of the possible transition from stage j to stage j+1 and $d_{i,j}$ stands for the mortality of stage j at time step i, $A_{i,j}$ contains the number of people in stage j at cycle i. This formula can be used to calculate all four stages for the simulation. But for "stage 1" the additional term $A_{i-1,j-1} \cdot p_{j-1 \to j}$ is 0 because there is no "stage -1". For "stage 4" $p_{j \to j+1}$ is 0 because the persons who are in this stage can only stay in this stage or die, therefore there is no transition probability to a higher stage. The number of persons of the stage "death" in cycle i now can be calculated by summing up all the people of the other stages at this cycle and then subtract this sum from the whole number of persons in the cohort.

The costs in Euros and effects in QALYs for each stage are listed in table 5 and formula (4) shows the calculation of the costs.

$$K_i = A_{i,1} \cdot C_1 + A_{i,2} \cdot C_2 + A_{i,3} \cdot C_3 + A_{i,4} \cdot C_4 \qquad (4)$$

K_i stands for the undiscounted costs of all persons of the cohort at cycle i. $A_{i,j}$ j=1,..4 are the number of people in stage j at cycle i. C_j j=1,..,4 are the costs for each stage j, which are listed in table 5. In analogy formula (4) can be used to calculate the effects for each time step.

Table 5: Cost and Effects of "Stage1 – 4" (Menn 2009)

Stage	Costs	Effects
1	103	0.2100
2	185	0.1975
3	367	0.1875
4	431	0.1625

Discounting of costs and effects is needed because the running time of the model is 60 years. The discounting rate is 3%. The discounted costs and effects are calculated with the help of formula (5).

$$C_d = \frac{C}{(1+d)^{(t/12)\cdot(i-1)}} \quad (5)$$

C stands for the undiscounted costs/effects, C_d for the discounted costs/effects, d for the discounting rate, t for the length of the Markov Cycle in months and i for the actual cycle of the process (Menn 2009).

4. SYSTEM DYNAMICS MODEL

As already mentioned in the introduction the SD model for COPD has been constructed on the base of the Markov model.

The general structure of a SD model consists of stocks and flows (Bossel 2004). For modelling COPD the four different stages of illness and the stage "death" were represented by stocks, which are the equivalent of the states in a Markov model.

The stage "death" could also be constructed as a "sink", because it is an absorbing stage (Brailsford 2008).

Accordingly, flows are the equivalent of the transitions of patients between the stages in the Markov model.

In our case, each stage has one flow to the next stage and one flow to the stage "death" which resembles the possible transitions of the Markov model. The transitions are influenced on the one hand by the number of people in a stage from which the transition is going away and on the other hand by the transition rates. The transition rates can be understood in analogy to the transition probabilities of the Markov model.

The System Dynamics model is not a stochastic, in contrast to the Markov model, but a deterministic model, so not probabilities but (fractional) rates are needed. The rates can be calculated from the probabilities of the Markov model with the following formula:

$$r = -\ln(1-p) \quad (6)$$

Here r defines the rate and p the probability (Menn 2009).

But if there is more than one possibility to change the state, as it is the case in our model (patients can die or transit to the next higher stage), it can be necessary to correct the probabilities before transforming them into rates. This is the case if the probabilities of one state represent mutually exclusive events. In our model, as people who die during one time unit reduce the number of people who can possibly transit to the next higher stage. Only the proportion $p_d+p_t\cdot(1-p_d)$ of patients would change the state in the SD model. However, formula (3) shows that in the Markov model the corresponding proportion simply equals p_d+p_t. To correct this, the transition probabilities have to be calculated in the following way:

$$p_t = \frac{p_t}{1-p_d} \quad (7)$$

p_t describes the transition probability and p_d the probability of dying. After that, the probabilites can be transformed with formula (6). This calculation leads to the following transition rates for the SD model:

Table 6: Transition rates for the ex-smokers of the SD model

Cycle	Transition 1	Transition 2	Transition 3
0	0.00250514	0.00300873	0.00694622
20	0.00250664	0.00301145	0.00696304
40	0.00250941	0.0030175	0.00699552
60	0.00251294	0.0030248	0.00703546
80	0.00251294	0.00303061	0.00706862
100	0.00252462	0.00304909	0.00716998
120	0.00253666	0.00307377	0.00730974
140	0.0025616	0.00312598	0.00760795
160	0.00260648	0.00322027	0.0081662
180	0.00270402	0.00343014	0.00949048

Table 7: Transition rates for the smokers of the SD model

Cycle	Transition 1	Transition 2	Transition 3
0	0.014116	0.0103753	0.0233869
20	0.0141288	0.010391	0.0234705
40	0.0141416	0.0104078	0.0235618
60	0.014166	0.0104373	0.0237247
80	0.0142149	0.010499	0.0240572
100	0.0142947	0.0106006	0.0246186
120	0.0143843	0.0107142	0.0252566
140	0.0145979	0.0109897	0.0268363
160	0.0148041	0.0112551	0.0284145
180	0.0154768	0.0121442	0.0341026

The transition rates and the death rates are inserted in the SD model as a lookup function.

In SD models the transitions are given by ordinary differential equations. Therefore, they are continuous time models. To calculate how many people are in which stage at a certain time step one has to integrate over time (Bossel 2004). Usually this is performed with numerical solving algorithms for differential equation systems and discrete time steps. However, theoretically these time steps get arbitrarily small.

The formula how to calculate the people in one stage is exemplary given in formula (8) for stage 2.

$$stage2(\mathrm{T}) = \int_0^T (transition1(t) - die2(t) - transition2(t))dt \quad (8)$$

Where "transition 1" describes the flow of the people from "stage 1" to "stage 2", "die 2" stands for the flow from "stage 2" to the stock "death" and "transition 2" represents the flow from "stage 2" to "stage 3".

The transitions, which are the flows in the model, are calculated in this way:

$$transition2 = stage2 \cdot transitionrate2 \quad (9)$$

"Stage 2" is the number of people in stage 2 and the "transition rate 2" is the rate for the flow of people from stage 2 to stage 3. Both depend on time.

The effects and the costs are two supplementary levels. They are calculated with the same formula (4) as in the Markov model. Only the discounting of costs and effects is different because the SD model is a continuous model. So it is not possible to discount in the same way as in the Markov model. In the SD model it is necessary to discount continuously. So, the costs and the effects are discounted with the help of the exponential function:

$$K(T) = \int_0^T k(t) \cdot e^{-rt} dt \quad (10)$$

K(T) describes the discounted and k(t) the undiscounted cost or effects and r the discounting rate and T the time.

The discounting rate for the discrete case corresponds to the discounting for one year. The rate of the Markov Model stands for a year. The formula to calculate the rate for one cycle is:

$$d_c = \left(1 + d_y\right)^{(m/12)} - 1 \quad (11)$$

d_c stands for the rate for one cycle and d_y for the rate for one year and m stands for the length of one cycle in months. One cycle in the SD model is like 3 months in the Markov model.

After that, it is necessary to calculate the rate for a continuous model with the following formula:

$$d = \ln(1 + d_c) \quad (12)$$

d stands for the discounting rate for the SD model.

The model has been constructed two times, once for the cohort "Smokers" and another time for the cohort "Ex-Smokers". The models are the same, except for the transition and mortality rates and the number of people.

It is also possible to simulate the model with each of the two possible treatments. Therefore an auxiliary variable exists for changing the number of people that are smokers or ex-smokers, because this is the only difference between the interventions.

The ICER is calculated the same way as in the Markov model. But the ICER is not calculated in the model itself.

In figure 3 a simplified stock and flow diagram of the stages of the SD model is shown as example. Figure 4 shows the stock and flow diagram for calculation of the costs end effects of the SD model.

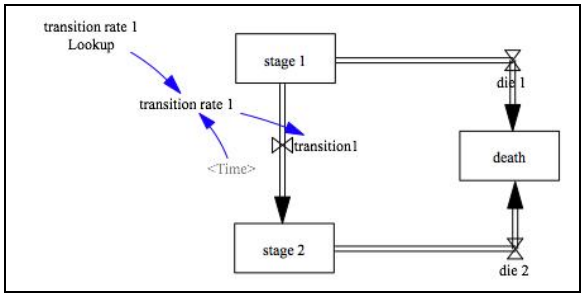

Figure 3: Stock and Flow – diagram of the stages

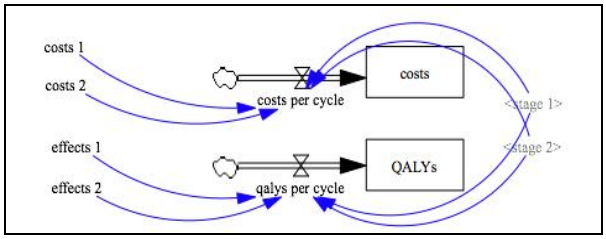

Figure 4: Stock and Flow – diagram of the costs and QALYs

5. THE DIFFERENCES

The Markov model needs probabilities to calculate the number of people in each stage (stochastic model) in contrast to the SD model (deterministic model), which needs rates.

The Markov model is a discrete time model because the transitions only can take place each time step. The SD model is a continuous-time model.

The SD model is constructed over stocks in opposition to the Markov model where the cohort is divided into states. But in spite of this, the stocks are equivalent to the states, which means that for each state there has to be a corresponding stock in the transformation of the model.

The discounting of the costs and effects in both models is different because we have on the one hand a discrete model and on the other hand a continuous model. However, the discounting factors are equal at each time step.

Table 1 shows the differences between the two models. These differences cause the different possibilities to expand the models.

Table 8: Differences/Equivalences between the Models

MARKOV	SYSTEM DYNAMICS
stochastic	deterministic
discrete time	continuous time
state	stock
transition probabilities	transition rates
discrete discounting	continuous discounting

5.1. Expansions

In both models, expansions are possible. In the SD model, one possible way is to include feedback and delays. In this research one possible expansion has been realised. People who are very ill, as in "stage 3" or "stage 4" of COPD, could influence people in "stage 1" or "stage 2". If many people are very ill, more people

with mild cases will stop smoking than before (deterrence). This scenario can be carried out with the help of the Smooth-function, which averages information (e.g. the value of a level) over time. Naturally, the influence on people does not take place immediately, but this process needs time, for example due to the politics and news. The Smooth function implements an Information Delay, in which the delay time is provided (Forrester 1969).

In this model the delay time was 12 month. A flow from the "stage 1 smokers" to the "stage 1 ex-smokers" was added, which depended from the smoothed "stage 4 smokers".

In the Markov model, this expansion is not possible because in a Markov model all patients are assumed to undergo an independent stochastic process. Therefore the amount of patients in one state cannot influence the stochastic process of another patient. However, it is possible to simulate a Markov model not as a cohort, but as a Monte Carlo simulation, because it is a stochastic model. In this case the patients run through the model individually and the transition probabilities are weighted in randomised probabilities. The Monte Carlo simulation also could be used as a sensitivity analysis (Briggs and Sculpher 1998).

6. RESULTS

The figures 5 and 6 show the division of the smokers and of the ex-smokers into the five stages in the SD model.

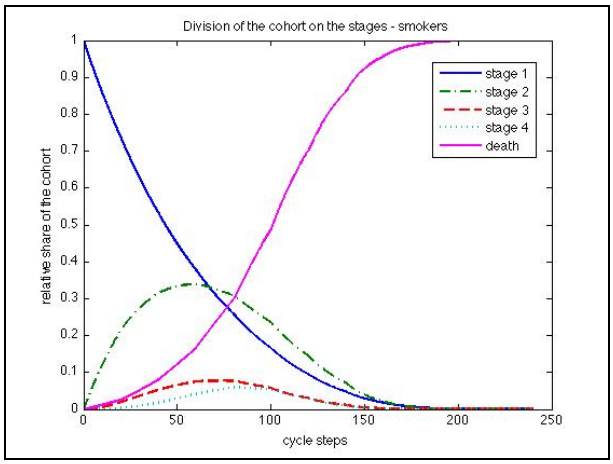

Figure 5: Division of the cohort into stages – smokers – System Dynamics model

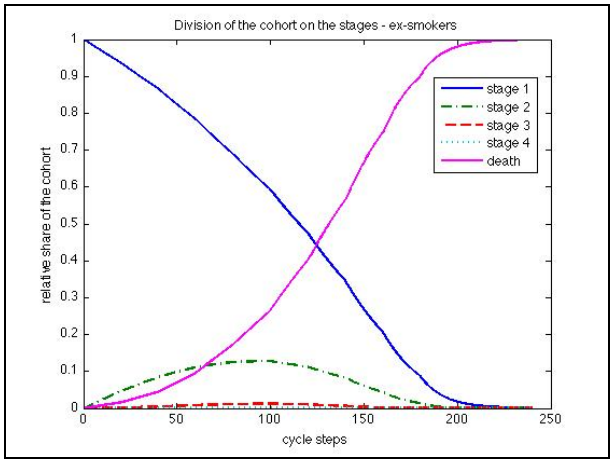

Figure 6: Division of the cohort into stages – ex-smokers – System Dynamics model

In the graphics of the SD model in opposite to the graphics of the Markov model no differences can be seen. But, in the analysis of the data are differences. The figures 7 and 8 show these differences of the division into the stages between the two models, because the absolute error of the two simulations is described. In both plots can be seen, that the biggest difference is in stage 2. In the cohort of the smokers, this difference is about 0.002 and in the cohort of the ex-smokers it is about 0.0003. Very noticeable is the oscillating behaviour of these differences, like in stage 1 in the beginning or the stage death in the end in both cohorts. Especially interesting as well is the drop of the stage 3 in both graphics and the fast increase of the stage 4 at the end in the cohort of the smokers

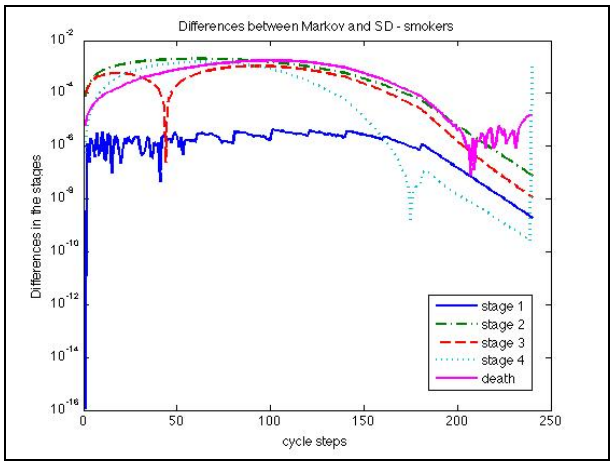

Figure 7: Differences between the Markov and SD model in the division into the stages – smokers

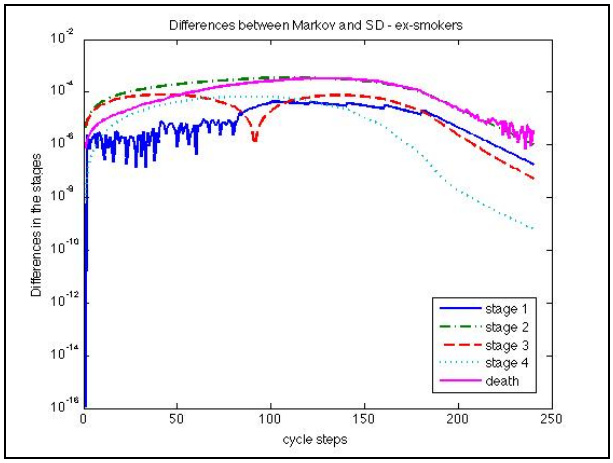

Figure 8: Differences between the Markov and SD model in the division into the stages – ex-smokers

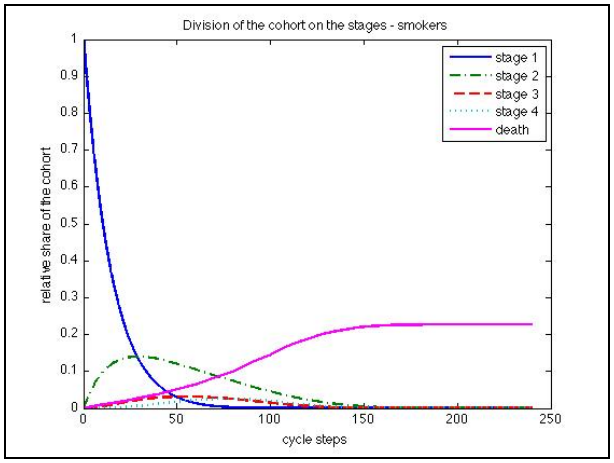

Figure 9: Division of the cohort into the stages – smokers – expanded System Dynamics model

The course of the costs and effects in the two models are very similar and no differences can be shown. But in the data are some small differences too, as for the division of the stages. The discounted values are more exactly than the undiscounted.

The ICER of the Markov model averages 838.4912 €/QUALY and the ICER of the SD model is 773.1253 €/QUALY. Why there are again some differences between the models is not yet analysed, as well not if only the differences of the stages cause the differences in the costs and effects and the ICER. Several factors could cause these deviations. Among them are the fact that although the two models should lead to equal values of states and levels at the discrete time steps, the continuous model calculates costs and effects also between these time points (and here also the discounting factor can differ), rounding errors and procedural errors of the numerical solver in the continuous case.

The following two graphics 9 and 10 show the division of the cohorts of smokers and ex-smokers in the expanded version of the SD model. It is easy to see that in the cohort of the ex-smokers are much more people than in the normal version and that they are coming from the cohort of the smokers. The people in "stage 1" of the ex-smokers increase very fast. After that, the course of the people through the stages is the same as in the normal version. In the cohort of the smokers "stage 1" shrinks in opposite to the ex-smokers and after the course is similar to the normal version.

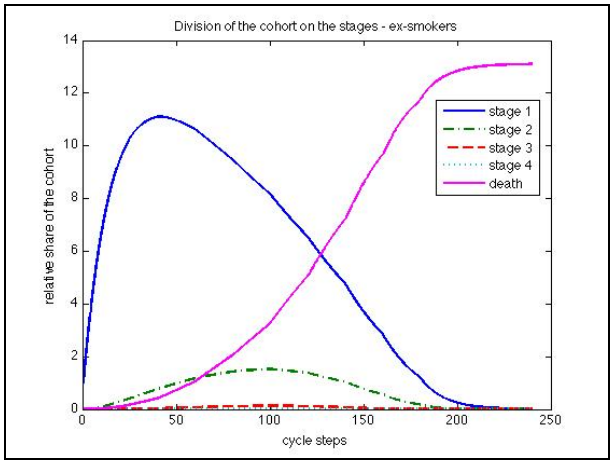

Figure 10: Division of the cohort into the stages – ex-smokers – expanded System Dynamics model

7. CONCLUSION

The approach shows that each Markov model can theoretically be transformed into an analogue SD model. In our example we got results that were slightly different, especially for the calculated ICER. There are a few possible explanations for these deviations, but this issue needs further and more detailed analyses. Naturally, there exist differences between the two methods, especially when it comes to possible expansions. For some research questions in the area of health care the limitations of Markov models are not a problem. However, a transformation of an existing Markov model into an SD formulation could allow for the incorporation of further aspects and influences, as was demonstrated in the case of deterrence for smokers in mild COPD stages.

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