Towards the implementation of the Markov property into a continuous-time transition state model in NONMEM.

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Background

- Repeated measures of ordered categorical data are typically described in NONMEM using proportional odds models. A limitation of proportional odds models is the underlying assumption that the observations are independent. As a result, simulations with these models result in individual profiles that are physiologically implausible [1]
- Markov models assume that future events depend on present events. The Markov property is currently implemented in a proportional odds model by making the probabilities dependent on the preceding stage [2]. However, as this model is discrete in time, the timing and frequency of the samples have a considerable influence on the parameter estimates
- Continuous-time Markov processes are defined by the Kolmogorov backward equations [3]. To our knowledge these equations have never been applied in a NONMEM model

Objective

- To develop a method for estimating transition probabilities on a continuous time scale, which should enable the simulation of physiologically plausible individual profiles

Outline

A stepwise approach was followed:

1. Implementation of a continuous-time Markov model in NONMEM
2. Analysis of actual data from a pain animal model to investigate the properties of the implemented model
3. Simulation of individual profiles to evaluating the physiologically plausibility of the outcome of the model

Animal model

Monosodium Iodoacetate (MIA) model

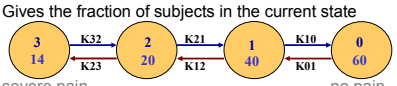
- Monosodium Iodoacetate is injected into knee joint resulting in destruction of chondrocytes
- Static allodynia (pain) is measured using the Von Frey hair (VFH) response test

Implementation in NONMEM

The NONMEM model code contains three sections:

1. Transition model

Gives the fraction of subjects in the current state



Set of 4 differential equation (1 for each state)

2. Kolmogorov backward equations

Give the transition probability at the current time

$$P_{ij}^{'}(t) = \sum_{s \neq i}(k_{is}P_{sj}(t)) - \sum_{s \neq i}(k_{is}) * P_{ij}(t)$$

In NONMEM: 1 differential eq. per transition probability

3. Likelihood

Gives the probability to be in a state at the next time point

$$P_j(t) = \sum_{0}^{i=j} P_i * P_{ij}$$

*Only the most likely transitions are plotted, but all transitions are theoretically possible

Analysis of actual data

Study design

- Observations at 0, 0.5, 1, 2, 3 and 4 hours after dose
- VFH scores: 14, 20, 40 and 60 g
- Dosages: vehicle, 0.01, 0.03 & 0.1 mg/kg
- 6 rats per treatment group

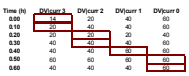
Effect

- Linear drug effect on K32, K21 and K10

Simulation of individual profiles

Individual profiles were simulated in three steps:

1. Creation of a simulation dataset with many obs. per hour
2. Simulation of the next state for all possible current states using Kolmogorov backward equations (NONMEM)
3. Selection of the path followed and reduction of the dataset to the original study design (S-PLUS):



Results

- The implemented continuous-time Markov model does not behave as expected as the profile of the probability of the next state doesn't follow the profile of the probability of the current state (compare e.g. the blue lines in figures 1 and 2). This is due to the fact that the Kolmogorov backward equations reach steady state rapidly
- The description of the VFH data from the MIA model is reasonable. However, the description of the probabilities after 3 hours could be improved (figure 3)
- After obtaining continuous-time transition probabilities individual profiles can be adequately simulated and are physiological plausible as the observation are depended (figure 4)

Implementation

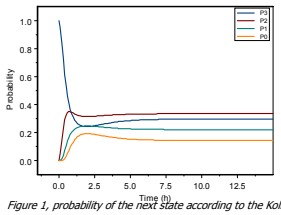


Figure 1, probability of the next state according to the Kolmogorov backward equations

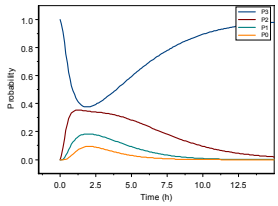


Figure 2, probability of the current state according to the transition model

Description

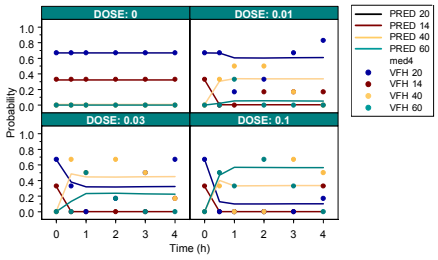


Figure 3, VPC of the probability of all VFH scores

Simulations

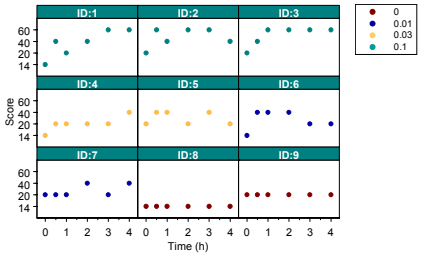


Figure 4, Example of simulated individual profiles

Conclusions & open ends

- The continuous-time Markov model, as currently implemented in NONMEM, has promising properties as it takes into account the dependency between observations. However, to benefit from these properties it needs to be further improved
- The major drawback is that the steady-state conditions of the Kolmogorov backward equations seem to be independent on the rate constants of the model. Therefore, when the model reaches steady-state the transition probabilities do not change anymore, even not after including a drug effect
- If it will be possible to overcome these drawbacks the continuous-time Markov model will have excellent simulation properties (physiologically plausible profiles)

References

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[2] Zingmark, P.H., Kågedal, M., Karlsson, M.O. J Pharmacokinet Pharmacodyn. 2005 Apr;32(2):261-81. Epub 2005 Nov 7.

[3] Sheldon M. Ross: Introduction to probability models. Seventh edition, 2000.