Extension of Continuous-Time PK/PD Markov Models to Published Count Data

IV-14

Doerthe Steller[1], Sven Mensing[1]
[1]Abbott, Ludwigshafen, Germany

Background & Objectives

- Availability of rich clinical data forms the basis of reliable PK/PD modeling but is limited in everyday practice.
- Incorporation of summarized or literature data has become an important goal whenever individual study data is sparse or missing.
- Modeling of multiple information sources helps to design subsequent studies and enhance clinical trial success.
- Continuous-time Markov models have been successfully applied to categorical PK/PD modeling problems for individual patient data (IPD).
- Aim of this work was to implement a Markov model in NONMEM that describes aggregated data (AD) obtained from literature.

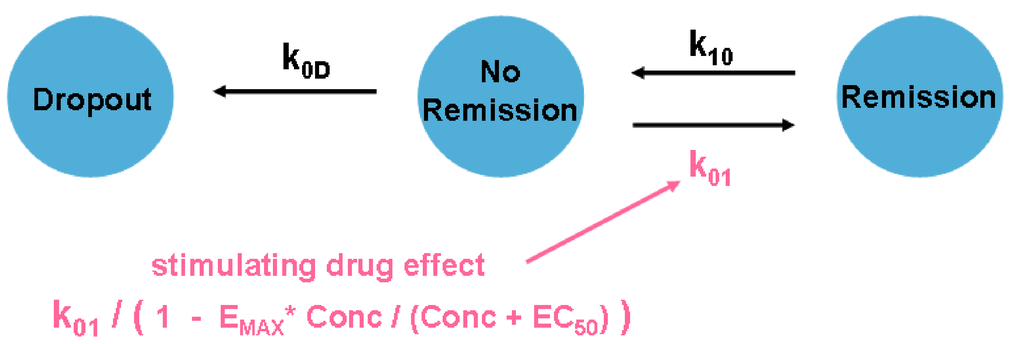
Methods

- Markov chain models provide an accessible mean to model categorical data showing temporal correlation in the observations.
- Here we present a continuous-time Markov model for published categorical data and exemplify its utility by fitting Infliximab literature data from the clinical trials ACT1 and ACT2 on Ulcerative Colitis (UC) [1, 2].
- The numbers of subjects in the states of “remission” (state 1), “no remission” (state 0) and “dropout” (state -1) were given in the publication at different time points (at week 8, 30 and 54).

Model structure

- A two-compartment IV model with first-order elimination was used to describe the concentration-time profile of ACT1 and ACT2 Infliximab data [2].
- Based on this a continuous-time 3-state Markov model was built with transition rates k_{ij} between the model states. The drug effect was incorporated as stimulating the rate to a better state (no remission to remission).

Figure 1. Schematic of 3-state Markov Model for UC



- The Markov model was implemented in NONMEM 7.1.2 via the Kolmogorov backward equations [3], yielding differential equations describing the transition probabilities P_{ij} at any time point.
- For each observation a likelihood of the current observed state is given based on the information of the previous state and the transition rates k_{ij} on which the model is optimized.
- These likelihoods P_{ij} for going from one state (i) to another (j) can be expressed as:

$$P'_{ij}(t) = \sum_{s \neq i} (k_{is} P_{sj}(t)) - \sum_{s \neq i} (k_{is})\, P_{ij}(t)$$

Adaptation to Literature Data

- The remission and dropout information obtained from literature consists in numbers of subjects in a certain state and hence requires adjustment in the likelihood calculations.
- Usually one would optimize the estimated likelihood (P_{ij}) for going from one state (i) to the other (j) given individual data.
- Due to the nature of published data the binomial likelihood of p (= P_{ij}) given y subjects out of a total of n was maximized. For numerical stability the binomial log-likelihood was implemented and approximated as follows:

$$log(L(p|n,y)) = log\left(\binom{n}{y} p^y (1-p)^{n-y}\right)$$

$$\approx log\left(\frac{\pi}{3}(6n+1)\right) + n \cdot log\left(\frac{n}{e}\right) + y \cdot log(p) + (n-y) \cdot log(1-p)$$

- Model quality was assessed by simulations with Trial Simulator software (Version 2.2.1, Pharsight Corporation, Mountain View, CA) and visual predictive checks (VPC’s) of respective model states.

Data Preparation

TIME	AMT	RATE	CMT	MDV	EVID	DV	ENDP	NPAT	PRE1
0	10	-2	2	1	1	.	.	122	0
7	10	-2	2	1	1	.	.	122	0
6	10	-2	2	1	1	.	.	122	0
8	.	0	4	0	0	39	1	122	0
8	.	0	-8	1	2	.	.	122	39
8	.	0	-7	1	2	.	.	122	39
8	.	0	-6	1	2	.	.	122	39
8	.	0	-5	1	2	.	.	122	39
8	.	0	5	1	2	.	.	122	39
8	.	0	6	1	2	.	.	122	39
8	.	0	7	1	2	.	.	122	39
8	.	0	8	1	2	.	.	122	39
14	10	-2	2	1	1	.	.	122	39
22	10	-2	2	1	1	.	.	122	39
30	10	-2	2	1	1	.	.	122	39
30	.	0	4	0	0	45	1	122	39
30	.	0	-8	1	2	.	.	122	45
30	.	0	-7	1	2	.	.	122	45
30	.	0	-6	1	2	.	.	122	45
30	.	0	-5	1	2	.	.	122	45
30	.	0	5	1	2	.	.	122	45
30	.	0	6	1	2	.	.	122	45
30	.	0	7	1	2	.	.	122	45
30	.	0	8	1	2	.	.	122	45
38	10	-2	2	1	1	.	.	122	45
46	10	-2	2	1	1	.	.	122	45
54	.	0	4	0	0	42	1	122	45

Table 1: Extract from NONMEM data set for the Markov PD model. DV=39, 45 and 42 from a total of NPAT=122 patients in the 10 mg/kg arm experienced remission (ENDP=1) at week 8, 30, 54. For utilizing the Markov model in NOMMEN, compartments are switched off and on (CMT = -8,-7,-6,-5, 5, 6, 7, 8 with EVID=2) after each observation. PRE1 denotes the number of patients previously in state 0 (no remission).

Results

- A 3-state Markov model on the basis of published data was built, adequately describing UC disease progression and treatment effect as shown by the VPC’s in figure 2.
- This comprehensive model may be used for simulations of different scenarios and comparison to other treatments of UC.
- By this, the process of drug development could be optimized regarding go/ no-go, dose and patient population selection and trial design.

Figure 2. Remission VPC’s of Final Markov Model

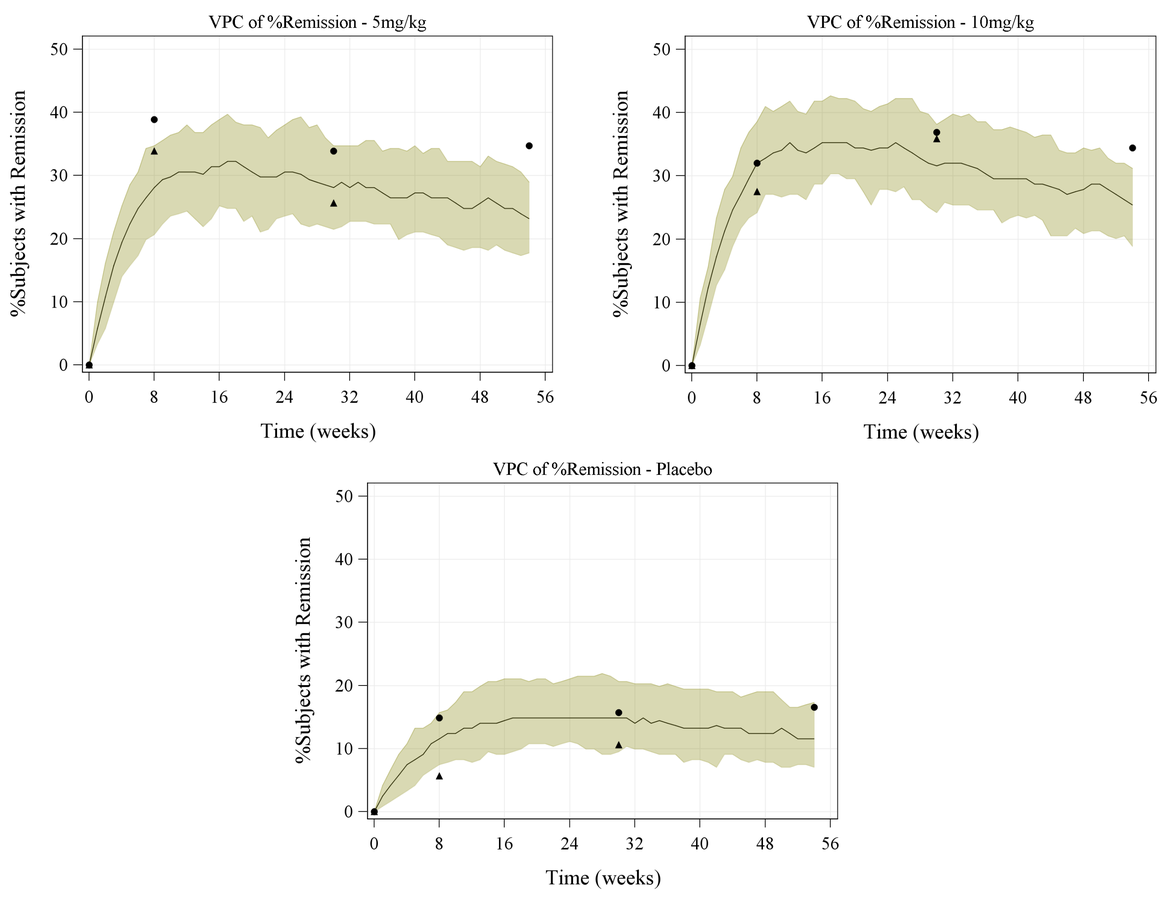


Figure 2: Remission VPC’s of final 3 state Markov model for the 5mg/kg (top left), the 10mg/kg treatment (top right) and the placebo arm (bottom). 90% prediction intervals with respective median remission rates are shaded in olive, observed remission rates from ACT1 depicted by black circles ●, from ACT2 by black triangles▲.

Conclusions

- A Markov model was successfully developed for the description of aggregated categorical data from literature.
- Due to the continuous-time implementation of the Markov model relevant clinical endpoints can be assessed at any time point.
- This enables predictions of success of different dosing scenarios in future trials.
- Extension of the model to include individual and aggregated data is straight forward and allows combined estimation.

References

[1] Rutgeerts P, Sandborn WJ, et al. Infliximab for Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med (2005);353:2462-2476.
[2] Fasanmade A et al. Population Pharmacokinetic Analysis of Infliximab in Patients with Ulcerative Colitis. Eur J Clin Pharmacol (2009);65:1211-1228.
[3] Welton NJ, Ades AE. Estimation of Markov Chain Transition Probabilities and Rates from Fully and Partially Observed Data: Uncertainty propagation, Evidence Synthesis, and Model Calibration, Med Decis Making (2005);25:633-645