UPPSALA UNIVERSITET

A pharmacodynamic model for Scandinavian Stroke Scale data

Fredrik Jonsson and E. Niclas Jonsson

Division of Pharmacokinetics and Drug Therapy
Department of Pharmaceutical Biosciences
Uppsala University

UPPSALA UNIVERSITET

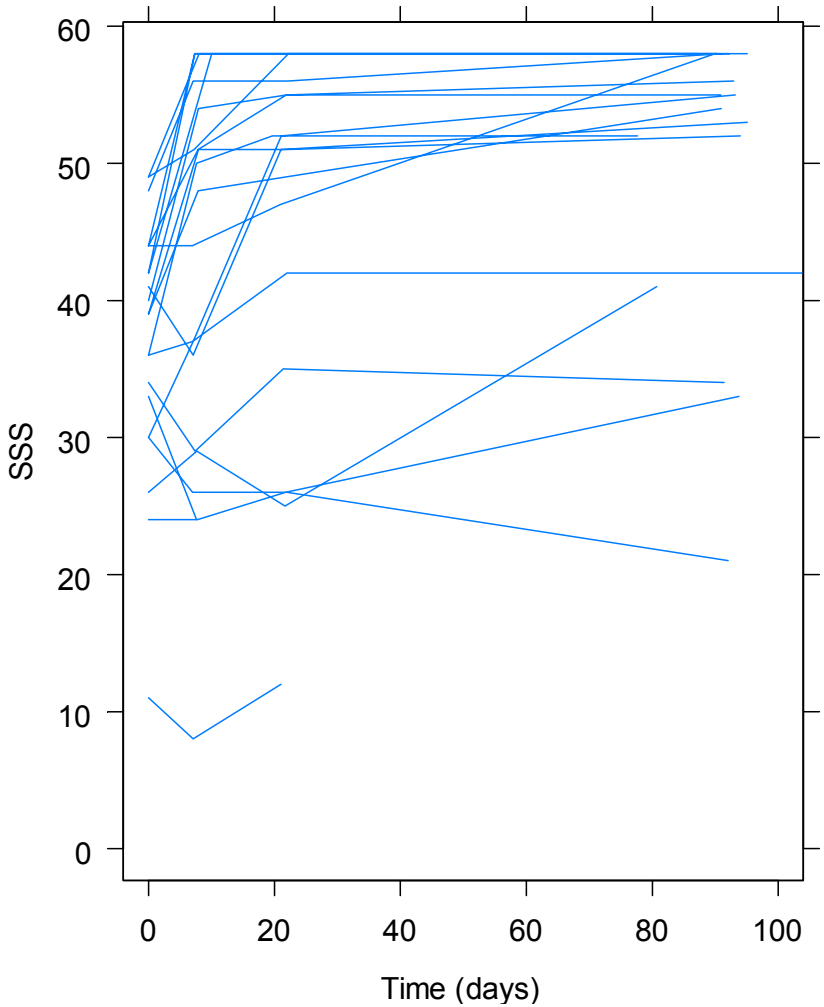
The Scandinavian Stroke Scale (SSS)

- Ordered categorical scale
- Often encountered in data from stroke studies
- Sum of several endpoints for neurological performance *(i.e.* speech, orientation, motor power, consciousness, etc).
- A total score of 58 denotes a healthy subject, a score lower than 10 denotes a severe neurological state
- Tends to exhibit both continuous and categorical properties – problematic!

UPPSALA UNIVERSITET

Features of SSS scale data

- SSS tends to increase with time
- Transition events complicate:
  - Score decline (Recurrent stroke)
  - Dropout
  - Transition to max score (Healing)



UPPSALA UNIVERSITET

Modeling strategies to consider for SSS data

- Modeling of Δscore between start and end of study
  - Ignores time course
  - Neglects systemic properties and transition events
- Modeling of cumulative probabilites
  - Too many categories
- Disease progression modeling
  - Disease progression not monotonous
  - Data too sparse

UPPSALA UNIVERSITET

Adapted modeling strategy

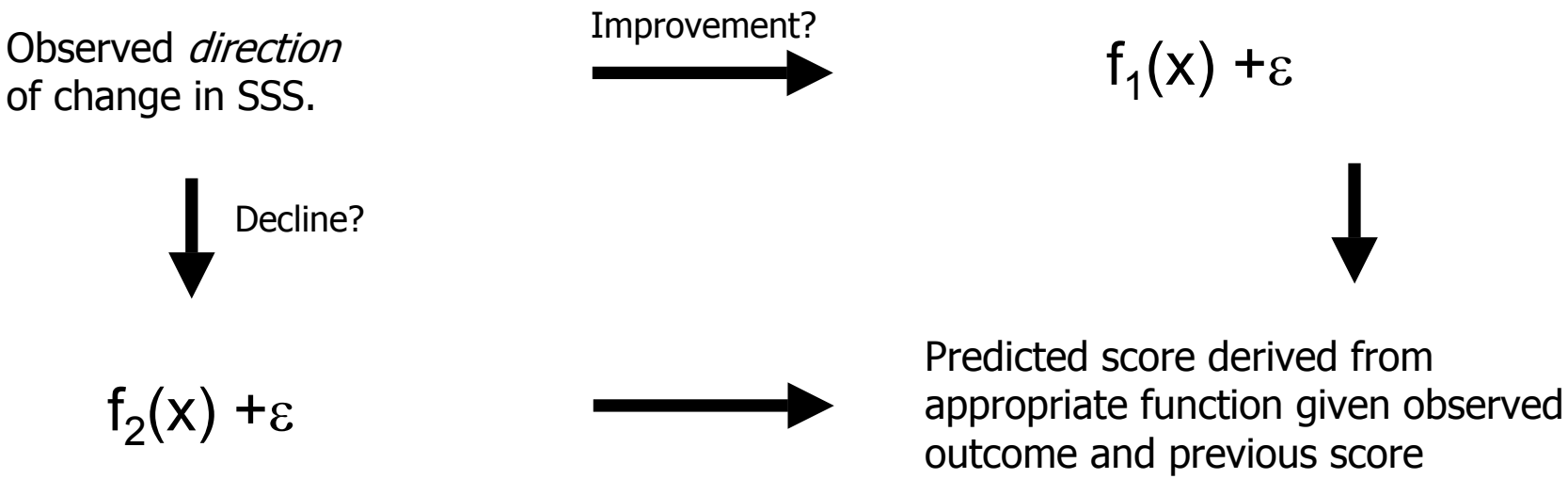
A two-part modeling approach:

1. Markov models for the probabilities of the transition events:
   - Healing (transition to maximum score)
   - Dropout
   - Decline of the SSS score.
2. Conditional linear models for the changes in SSS in either direction, given an observed increase or decline.

Similar to the approach in:
"A two-part random effects model for Semi-Continuous longitudinal data", MK Olsen and JL Schafer, JASA 96 (730-745).

UPPSALA UNIVERSITET

Flowchart for linear models



UPPSALA UNIVERSITET

Example

- SSS scores from a clinical study (n=166)
- Seven dose levels, including placebo
- SSS score recorded on admission and on days 7, 21 and 90.
- Drug exposure summarized by AUC derived from previous PK model

UPPSALA UNIVERSITET

Methods

- Predictors tested: cumulative AUC, demographic covariates, stroke severity, time between stroke and admission, previous SSS score
- Probabilistic outcomes modeled: Healing, Score decline, Dropout
- The probabilities were treated as random uncorrelated events and did not sum up to 1

UPPSALA UNIVERSITET

Methods

- Continuous outcomes modeled: Relative score improvement, relative score decline
- Observed score changes were transformed to fall between zero and one by division by maximum possible change
- Observed improvements/declines were used for conditioning in the predictions of SSS
- The set of probabilistic and continuous models were fit simultaneously using NONMEM 5 and a Fortran subroutine[1]

[1]N. Holford, available in the NONMEM user's repository

UPPSALA UNIVERSITET

Results: Probabilistic models

- Healing dependent on stroke severity
- Dropout dependent on model-predicted SSS and AUC
- No predictors of SSS score decline probability were found

UPPSALA UNIVERSITET

Results: Relative score improvement

- The magnitude of positive change best described as a function of stroke severity and observed previous SSS score
- No predictors of the size of negative change were found

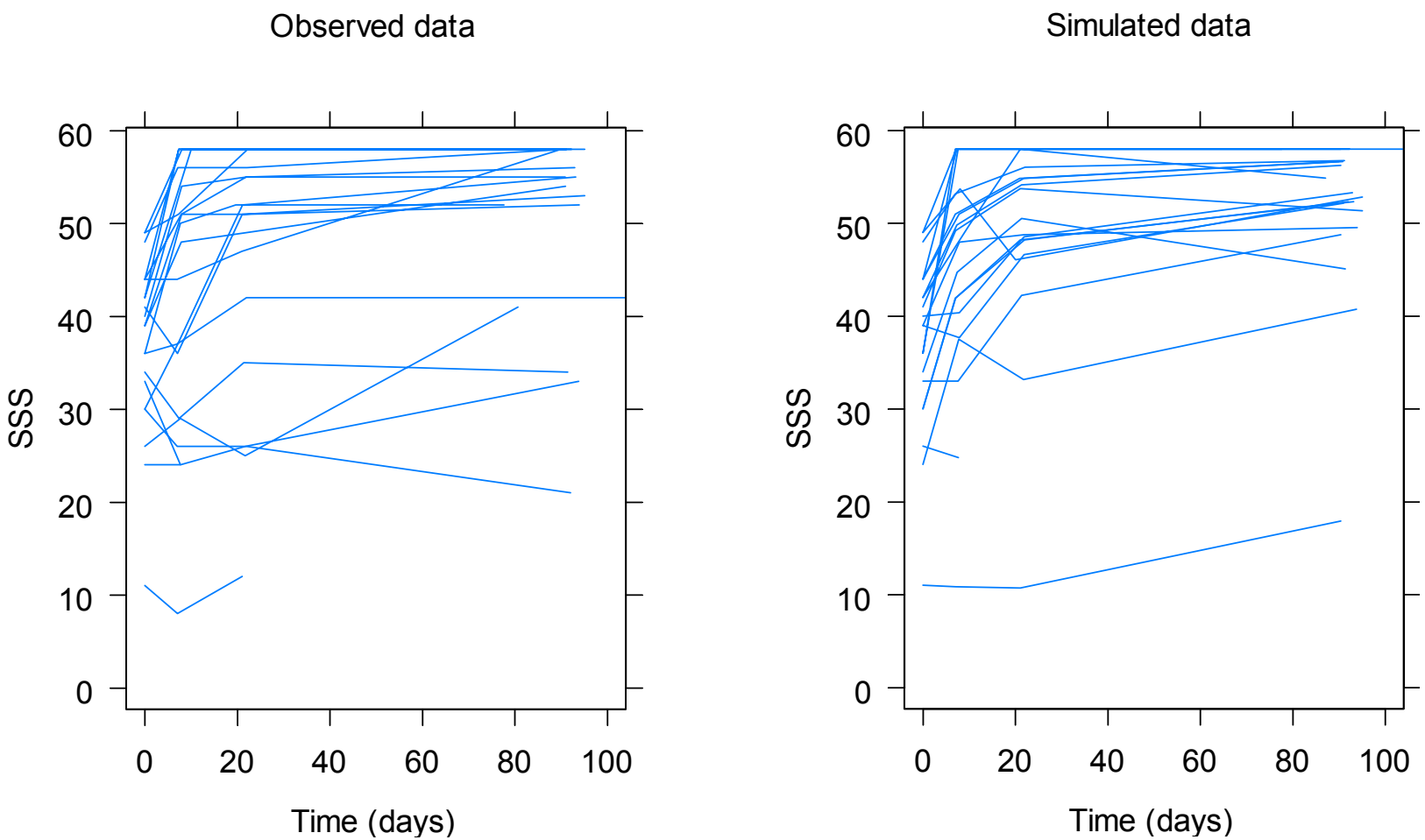
UPPSALA UNIVERSITET

Goodness of fit

- 1000 data sets were simulated and compared to observed SSS score distributions
- Simulations were performed while conditioning on the observed covariate distribution
- For Markovian model elements, simulated rather than observed SSS scores were used as model input

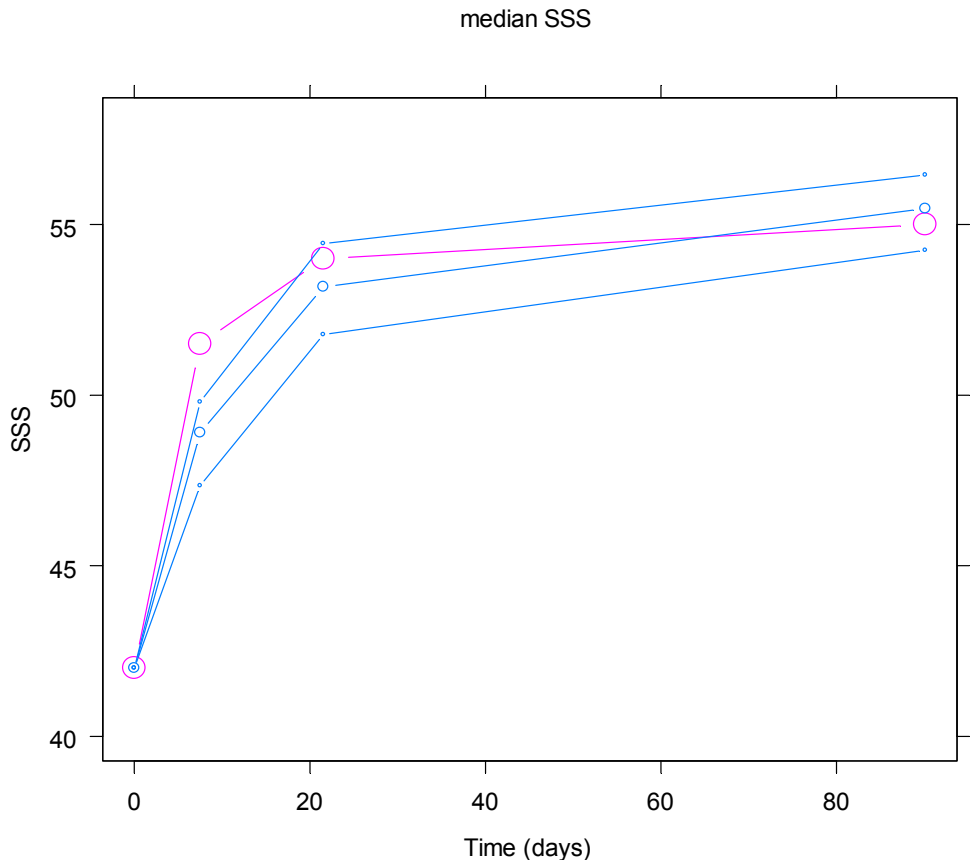
UPPSALA UNIVERSITET

Observed and simulated SSS



UPPSALA UNIVERSITET

Goodness of fit: Score distribution



- Pink: Median SSS in observed data
- Blue: Distribution of medians among 1000 simulated data sets (mean and 95% CI)

UPPSALA UNIVERSITET

Conclusions

- It was possible to describe observed SSS data over time using a two-part modeling approach
- The model fits the data well
- This approach has potential in modeling of data of this sort