Exploring inductive linearization in population pharmacokinetic and pharmacodynamic models

M Fidler[1,5], Y Xiong[2,5], R Schoemaker[3,5], J Wilkins[3,5], MN Trame[1,5], T Post[4,5], R Hooijmaijers[4,5], W Wang[1,5]

[1]Novartis Pharmaceuticals, USA, [2]Certara Strategic Consulting, USA, [3]Occams, The Netherlands, [4]LAP&P Consultants, The Netherlands, [5]The nlmixr team

Introduction

- PKPD models are commonly defined as a set of ordinary differential equations (ODEs) of the general form:

$$\frac{dy}{dt} = f(t,y) + A(t,y)\cdot y;\ y(t_0) = y_0 \qquad (1)$$

- The ODE represented in (1) can be approximated with a linear time-varying form by defining a sequence of observations $y[n]$ that conditionally depend on the previous iteration.

$$\frac{dy^{(n)}}{dt} = f\left(t, y^{(n-1)}\right) + A\left(t, y^{(n-1)}\right)\cdot y^{(n-1)};\ y^{(n)}(t_0) = y_0 \ (2)$$

- Since (2) no longer depends on $y[n]$ it is therefore a first-order linear system and can be solved by applying matrix exponentials.

- In this sequence the value of $y[n]$ is updated at each iteration and will converge rapidly to the exact solution. This ODE solving method is known as inductive linearization.

Goal

The viability of inductive linearization approach in parameter estimation problem is explored in this poster. Inductive linearization and the LSODA approach are compared in terms of speed and estimation precision using population PK data with Michaelis-Menten elimination.

Theory

- The speed of inductive linearization convergence depends critically on the choice of the initial solution.

- The structure of population analysis can be exploited to make inductive linearization efficient for ODE solving, at least when picking an initial solution:
  - Population approach assumes individual PKPD parameters are “similar”; they follow certain distributional constraints. If the design space is similar, one individual's solution would be just a perturbation of another’s. Therefore, we could use one individual’s solution as the starting solution for another when applying the inductive linearization.
  - Population approach fitting is typically iterative. Between iterations, there usually are small changes in the solved individual curves. Hence, another strategy is to use the solution of the last iteration as the starting solution of next iteration for inductive linearization.

Application - Methods

- We choose a simple two-compartment first-order input model with Michaelis-Menten elimination.
- The simulated data set has high-resolution PK sampling.
- We fit the data via the Stochastic Approximation EM (SAEM) algorithm.
- We compare and contrast the speed and precision of two ODE solving approaches: ODE solving by LSODA, and by inductive linearization.

Application - Results

- We solve the model ODEs once prior to the start of SAEM and use the solved solution as the initial solution for inductive linearization during SAEM iterations. We only iterate once of the inductive linearization when solving ODEs.
- Inductive linearization coupled with the matrix exponential method improved the overall model fitting speed by 50-60% over the LSODA method. Parameter estimates were comparable between methods.
- Table 1 shows the parameter estimate comparison.
- Figure 1 shows the prediction comparison and goodness-of-fit of the model fit.

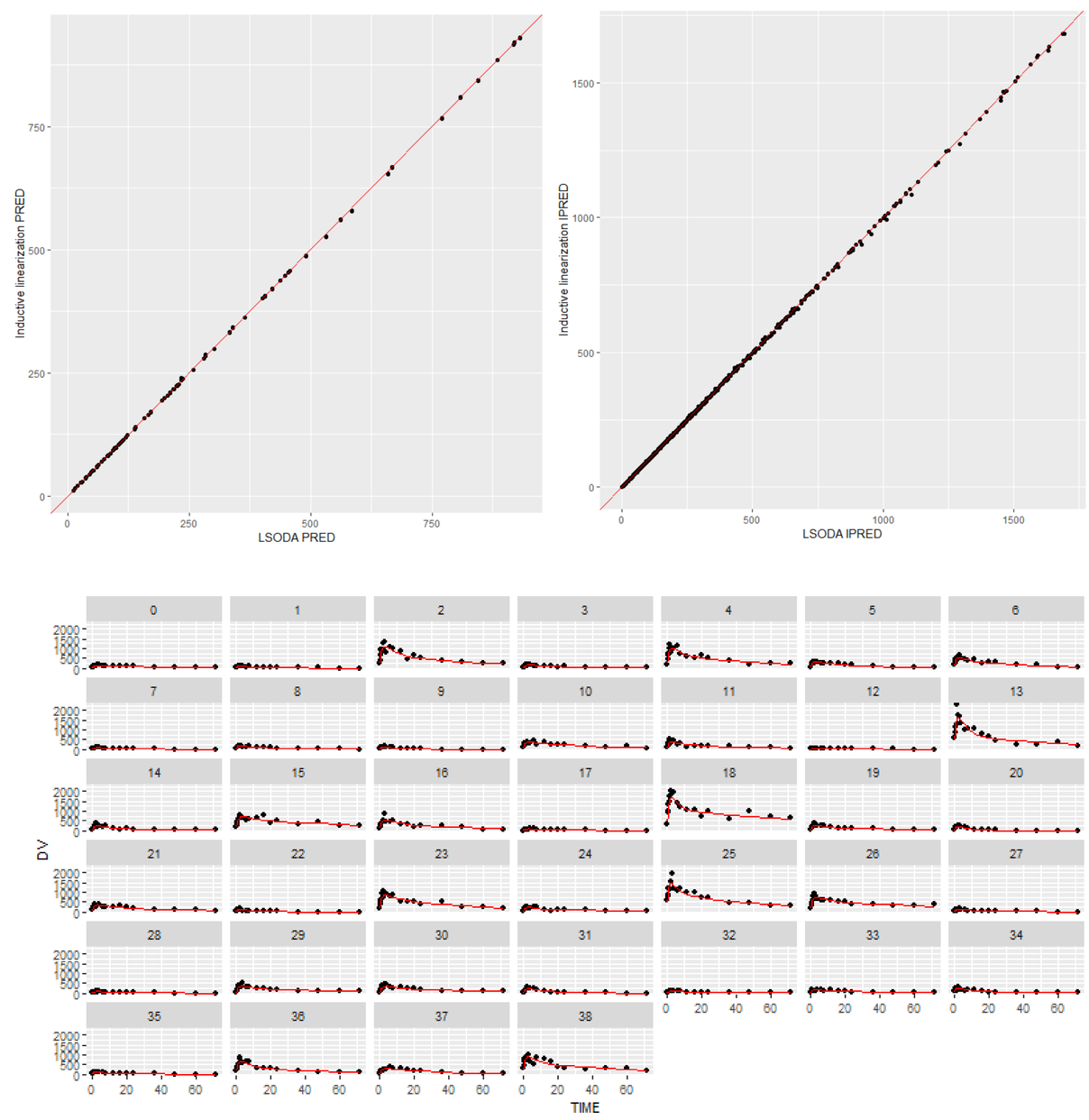

Figure 1: Goodness-of-fit plots by SAEM with inductive linearization for ODE solving

	LSODA			inductive linearization		
	Estimate	SE	OM	Estimate	SE	OM
IVM	7.119	0.059	0.089	7.132	0.053	0.081
IKM	5.843	0.056	0.038	5.829	0.059	0.084
IV	4.253	0.051	0.090	4.253	0.051	0.092
ICLD	1.362	0.040	0.017	1.461	0.037	0.022
IVT	3.929	0.060	0.084	3.982	0.059	0.084
IKA	-0.051	0.047	0.059	-0.056	0.048	0.059

Table 1: Parameter estimate comparison between inductive linearization and LSODA

Conclusions

Inductive linearization coupled with the matrix exponential method is a fast and stable method for population PK and PD models described by sets of nonlinear differential equations. This method offers an alternative to typical ODE solving methods in population PK and PD modeling.

References

1. Hasegawa C, Duffull SB (2018) J Pharmacokinet Pharmacodyn 45(1):35-47.
2. Sidje RB (1998). ACM Trans. Math. Softw. 24(1): 130-1569.