Solving sensitivity equations by inductive linearization and its applications in population pharmacokinetic and pharmacodynamic models via FOCEi

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Introduction

- Sensitivity equations are additional ancillary equations, typically derived by computers from the original user-specified model differential equations (ODEs), to evaluate derivatives of state variables with respect to model parameters. Derivatives are essential for population approach algorithms such as FOCEi [1]. Sensitivity equations are typically appended to the original model equations and solved by numerical ODEs solvers such as LSODA. The objective of this work was to explore the feasibility of solving sensitivity equations by inductive linearization (an iterative process to linearize nonlinear first order ODEs) [2] and the application of this methodology in population pharmacokinetic and pharmacodynamic model development.

- 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

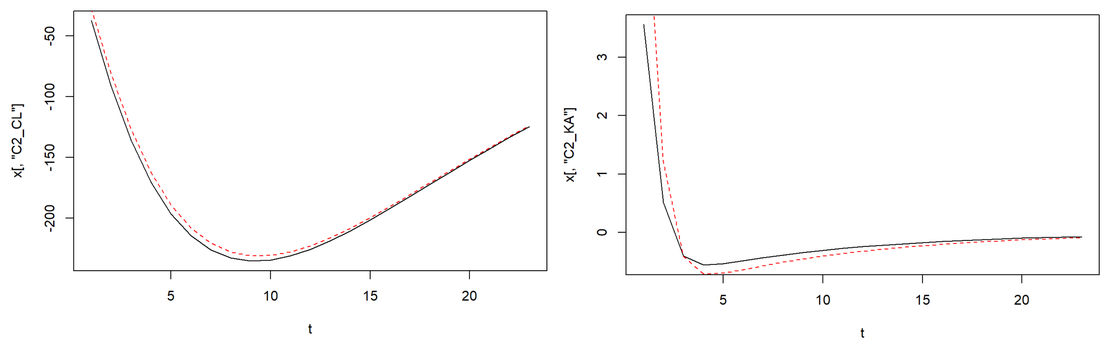
The inductive linearization of ODE solving are generalized to solving sensitivity equations. Inductive linearization approach and LSODA approach are compared in terms of speed and estimation precision with fitting a population PK model by FOCEi, whereas sensitivity information is necessary during optimization.

Theory

Theorem: If a set of ODEs can be written as the form (1), then sensitivity equations w.r.t. parameters can also be written as such a form.

- This important result implies that for a PKPD model that can be expressed as form (1), we can solve its sensitivity equations by coupling inductive linearization and matrix exponential. Since matrix exponential is numerically stable, this approach is expected to avoid some common numerical difficulties when fitting a large PKPD model which may result hundreds of ODEs and can be stiff when applying LSODA approach.

- In Figure 1, we show the proof-of-concept example of solving sensitivity equations with respect to KA, CL and Vc for a simple one-compartment model with first order absorption. Figure 1 suggests that there can small bias in sensitivity equations solved by inductive linearization. However, since sensitivity equations provide the general direction of iteration in FOCEi, some



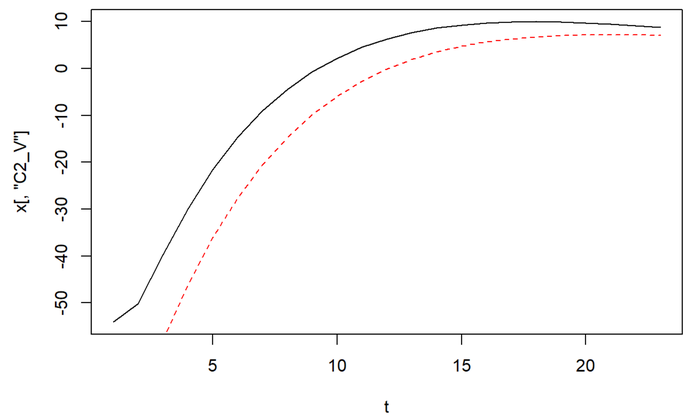


Figure 1:.Solving sensitivity equations by inductive linearization and matrix exponential. Black lines are from LSODA; red lines are from inductive linearization

Application - Methods

- We choose a simple one-compartment first-order input model.
- The simulated data set has high-resolution PK sampling.
- We fit the data via the First-Order Conditional Estimate with interaction as documented in [2].
- We compare and contrast the speed and precision of two ODE and sensitivity equation solving approaches: ODE solving by LSODA and by inductive linearization.

Application - Results

- Solving sensitivity equations by inductive linearization is an efficient and stable method when fitting a nonlinear pharmacokinetic model via FOCEi. This approach improves the speed of model fitting by about 50% over the LSODA method. Parameter estimates delivered by both approaches were comparable.

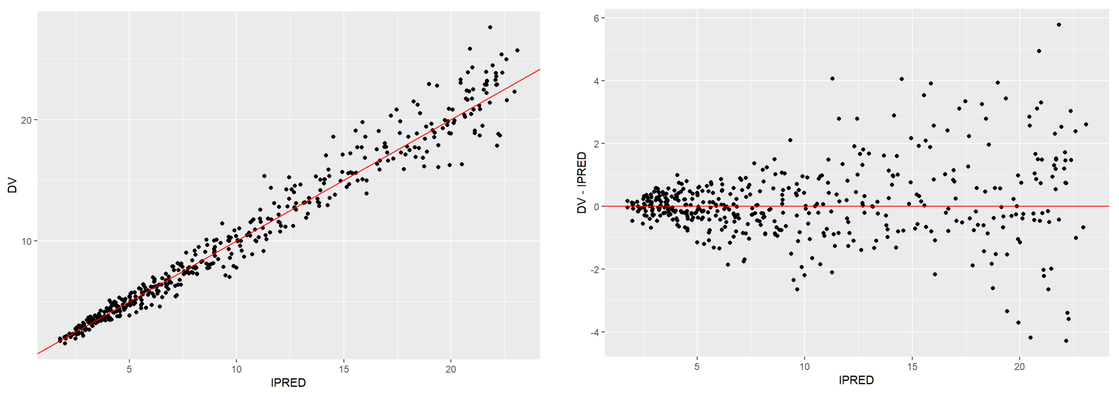


Figure 2: Goodness-of-fit plots by FOCEi with sensitivity equations solved by inductive linearization

Conclusions

Solving nonlinear ordinary differential equations (ODEs) by inductive linearization is promising when applied to fitting algorithms where derivative calculation is needed. This method offers a viable alternative to typical ODE solving methods in population PK and PD modeling.

References

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