ODE solvers and stiffness issues for complex population PK models

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Background

Complex PK/PD models based on a **systems biology approach** are promising tools with a wide range of applications.

Nonetheless, their development will require **technical challenges**.

In particular, complex models are often stiff ordinary differential equations (ODE) characterized by **multiscale dynamics**. Their evaluation requires **sophisticated ODE solvers.**

Parameter estimation methods such as the ones used in PK/PD modeling require a large number of function evaluations thus need an appropriate ODE solver.

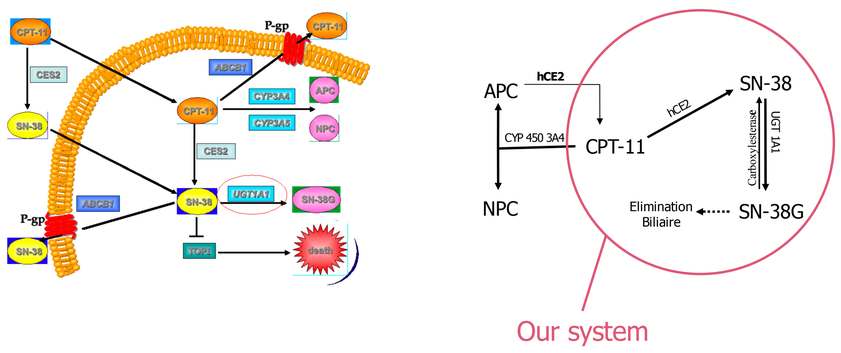
Objectives

• To fit **Irinotecan** (**CPT-11**) and two metabolites (**SN-38** and **SN-38G**) data collected from 177 patients with both sequential and simultaneous methods [1].

• In doing this, we analyze the behavior of **FO**, **FOCE INTER** (NONMEM), and **SAEM** (Monolix [2,3]) in terms of stiffness and ODE solver.

Material and Methods

- Biological system -



Our system

Left: Available knowledge from literature regarding CPT-11. **Right:** Our structural model

- Stiffness evaluation -

Stiffness is evaluated through the Jacobian of the linearized ODE model. The Eigen values (λi) of the Jacobian characterize the dynamics of the system.

$$\text{Stiffness Ratio} = \frac{\max(|\lambda i|)}{\min(|\lambda i|)}$$

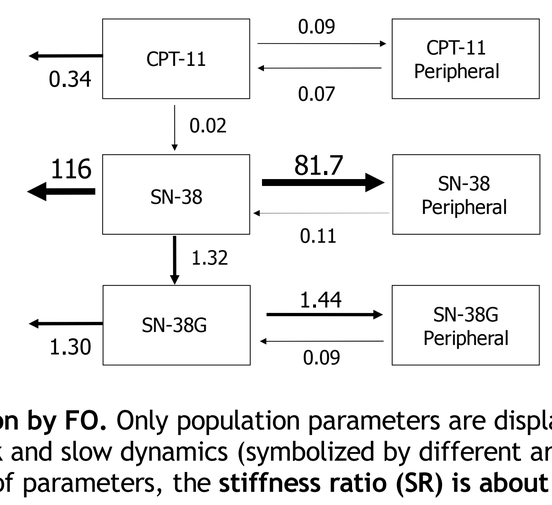


Illustration - Estimation by FO. Only population parameters are displayed. **The system is stiff** since it integrates quick and slow dynamics (symbolized by different arrows thickness). With this set of parameters, the **stiffness ratio (SR) is about 4000**.

[1] Zhang L, Beal S, Sheiner L. Simulatenous vs. Sequential Analysis for Population PK/PD Data I: Best-case Performance. J Pharmacokinet Pharmacodyn. 2003. 30(6):387-404; **[2] Kuhn E, Lavielle M.** Maximum likelihood estimation in nonlinear mixed effect models. Comp Stats Data Anal. 2005. 494):1020-38; **[3] Donnet S, Samson A.** Estimation of parameters in incomplete data models defined by dynamical systems. J Stat Plan Inf. 2007;

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Results

FO and FOCE INTER (NONMEM)

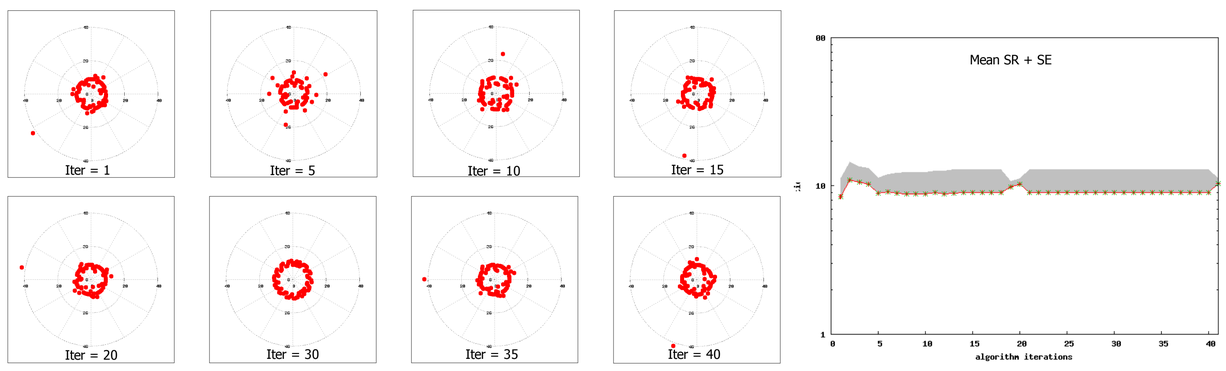
- **CPT-11 data:** Optimization procedure was successful (flag `MINIMIZATION SUCCESSFUL`) with **FO** and **FOCE INTER** (**ADVAN8** and **ADVAN9**)
- **CPT-11 + SN-38 data:** Optimization was successful with **FO** (**ADVAN8** **ADVAN9**) and with **FOCE INTER** (**ADVAN7** and **ADVAN9**)
  - **FOCE INTER** with **ADVAN8** failed at this point
- **CPT-11 + SN-38 + SN-38G** data: Optimization was successful with only **FO**

SAEM (Monolix)

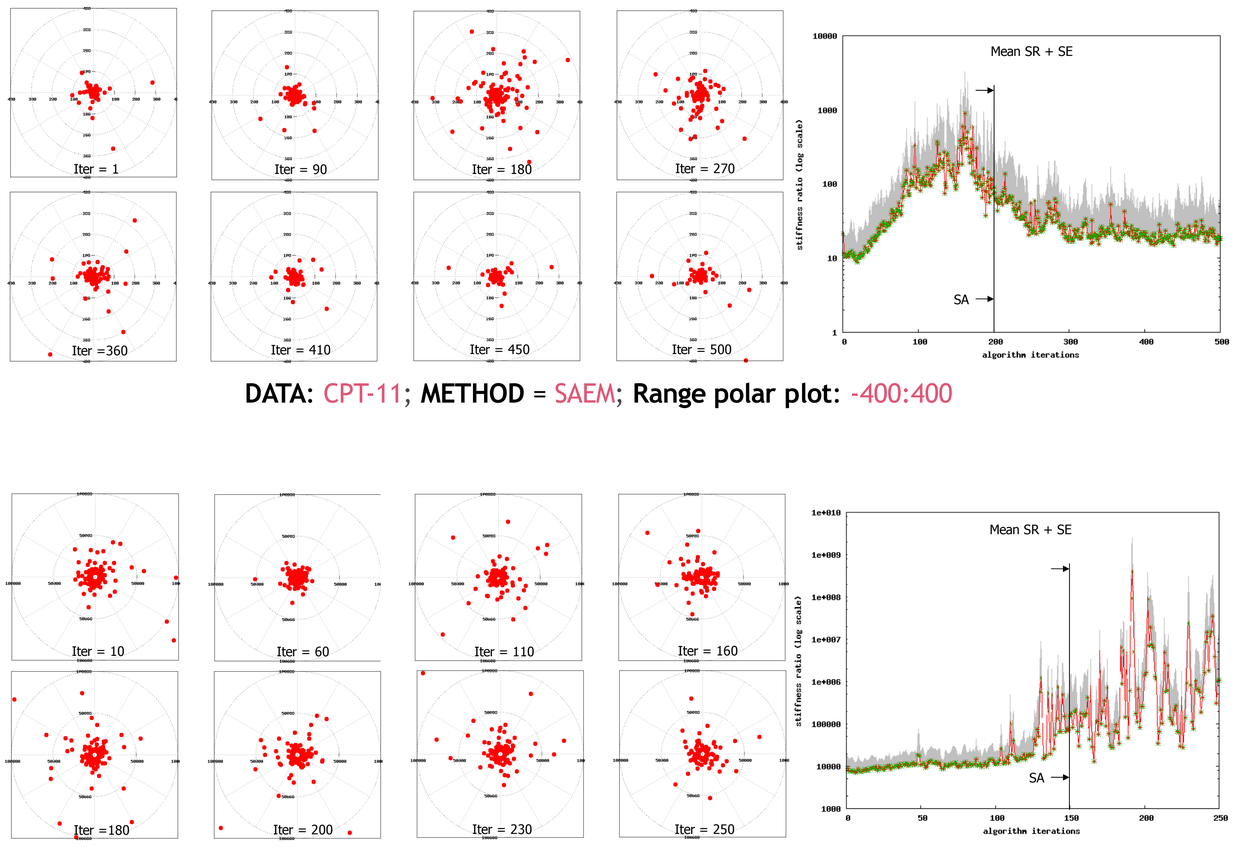
- **CPT-11 alone, CPT-11 + SN-38 data:** Optimization procedure was 'successful'
- However, standard algorithm settings (number of iterations, Markov chains, simulated annealing) could not be tested due to the computational time required by the MATLAB® ODE solver (ode15s).
- In consequence, runs did not converge while optimization was 'successfully' led.

Stiffness ratio (SR) for each individual at different iterations

Mean SR (+ SE) over iterations



DATA: CPT-11; **METHOD** = FOCE INTER; **Range polar plot:** -40:40



DATA: CPT-11 + SN-38; **METHOD** = SAEM; **Range polar plot:** -10^5:10^5

Conclusion and perspectives

	Global search	Coupled ODE solver
NONMEM	Poor	Robust (ADVAN9 only)
Monolix	Good	Not appropriated for large stiff problems

• Despite huge computational time, we're currently using Monolix with standard algorithm settings for CPT-11 + SN-38 + SN-38G data.

• We wish to design a new package in Monolix specially optimized for large stiff problems.