Monolix benefits from external modules to manage complex ODE

Illustration with a population analysis of Irinotecan and its metabolites

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Background

The development of molecular targeting therapies may require the use of "**systems biology**" approaches in PK/PD modelling.

As a consequence, structural models may be complex, composed by stiff **ordinary differential equations** (ODE) and characterized by multiscale dynamics.

Their evaluation in the context of parameter estimation requires **sophisticated ODE solvers.**

Monolix proposes, in its last version 2.3.1, two ODE C++ solvers.

Objectives

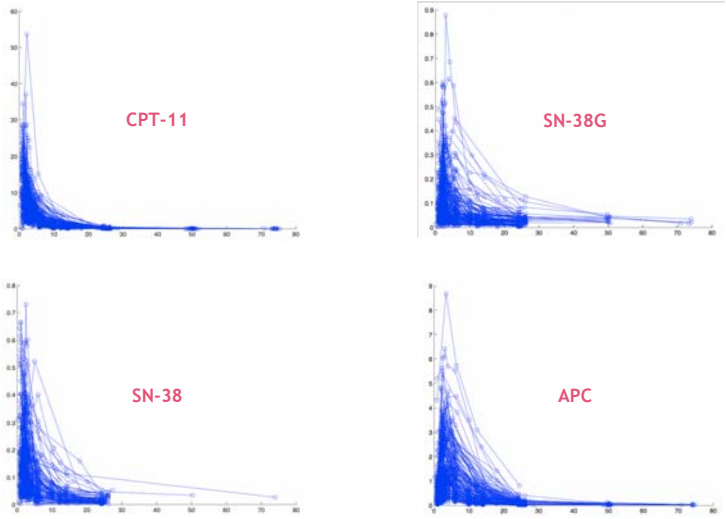
• To test the efficiency of the **coupling Monolix/ODE C++ solvers** to characterize complex PK models of Irinotecan and its metabolites.

Material and Methods

- Data -

• Irinotecan (CPT-11) and three of main metabolites (SN-38, SN-38G, APC) plasma concentrations:

- CPT-11 infusion over 90 minutes
- 162 patients, phase I and II pediatric clinical trials
- 5345 observations (33 on average per patients: 9.3 for CPT-11, 7.1 for SN38, 7.7 for SN38G, and 8.9 for APC)



Plasma concentrations of CPT-11 (top left), SN-38 (bottom left), SN-38G (top right) and APC (bottom right) in micromolar over time in hours

- Monolix software -

• Monolix 2.3.1 / package C++ CVODE (SUNDIALS)

- ADAMS/Moulton method (recommended for non-stiff systems)
- can be switched to BDF (Backward Differentiation Formulas)

- Methodological approach -

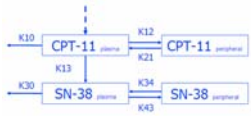
• Step-by-step approach

•Initial values of parameters set to 1

Results

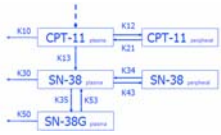
STEP I : CPT-11 and SN-38 data

- Linear 4 compartments model (residual error: additive)
- **Run duration: 13.5 minutes** (PC, 2 GHz Intel Core 2 Duo)



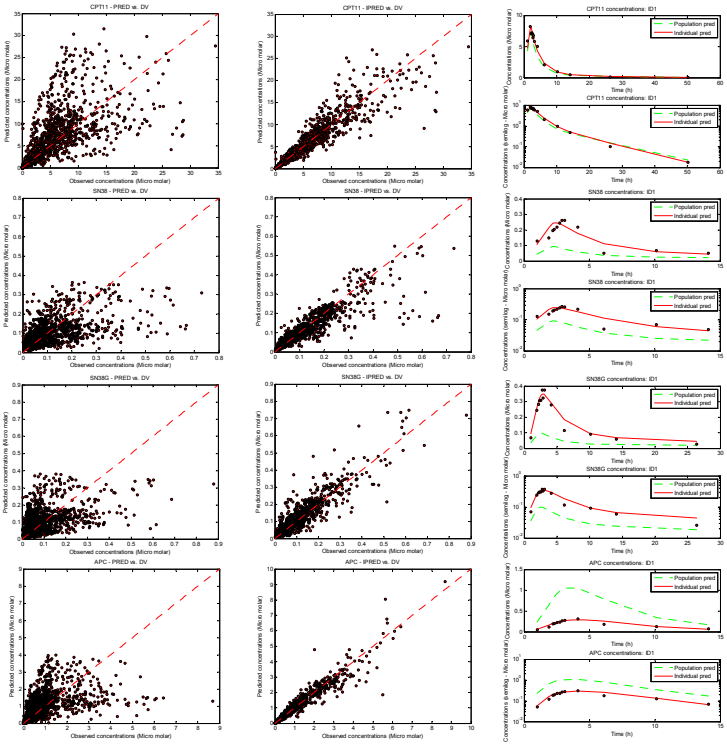
STEP II : CPT-11, SN-38 and SN-38G data

- Linear 5 compartments model (residual error: additive)
- **Run duration: 20 minutes**



STEP III : CPT-11, SN-38, SN-38G and APC data

- Linear 7 compartments model (residual error: additive)
- **Run duration: 33.3 minutes**



Goodness of fit plots for STEP III: IPRED vs DV (left column), PRED vs DV (centre) and individual/population fits of ID1 (right) for CPT-11 (top line), SN-38 (second), SN-38G (third), APC (bottom) plasma concentrations

- Comparison with NONMEM VI-

• STEP I: CPT-11 and SN38 data

- ADVAN7 and FO (analytic resolution): **Successful run in 19 minutes**
- ADVAN8 and FO (BDF method) : **Successful run in 45 minutes**
- Difficulties with ADVAN6 (Runge-Kutta-Verner order 5 and 6) and ADVAN9 (LSODA)

Conclusions

• Monolix 2.3.1 using external modules may constitute a very relevant tool to develop physiologically-based PK/PD models

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