



SBPOP – A Computational Tool Supporting Model Based Drug Development

Application to the Renin-Angiotensin System

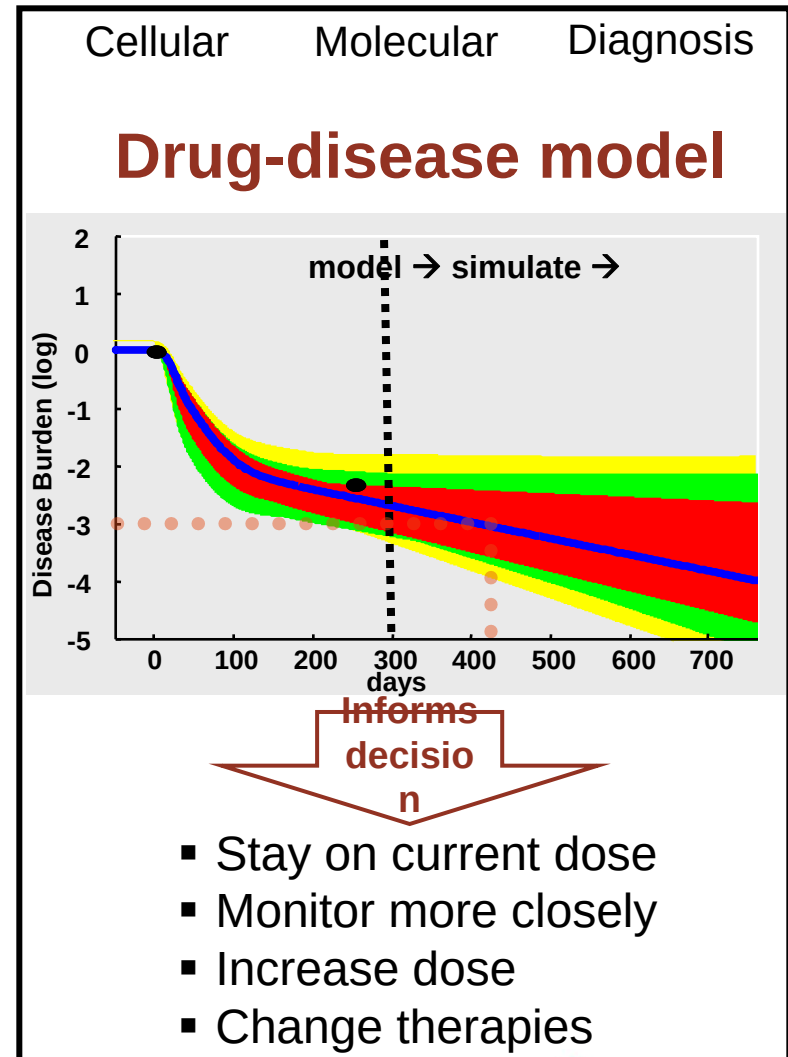
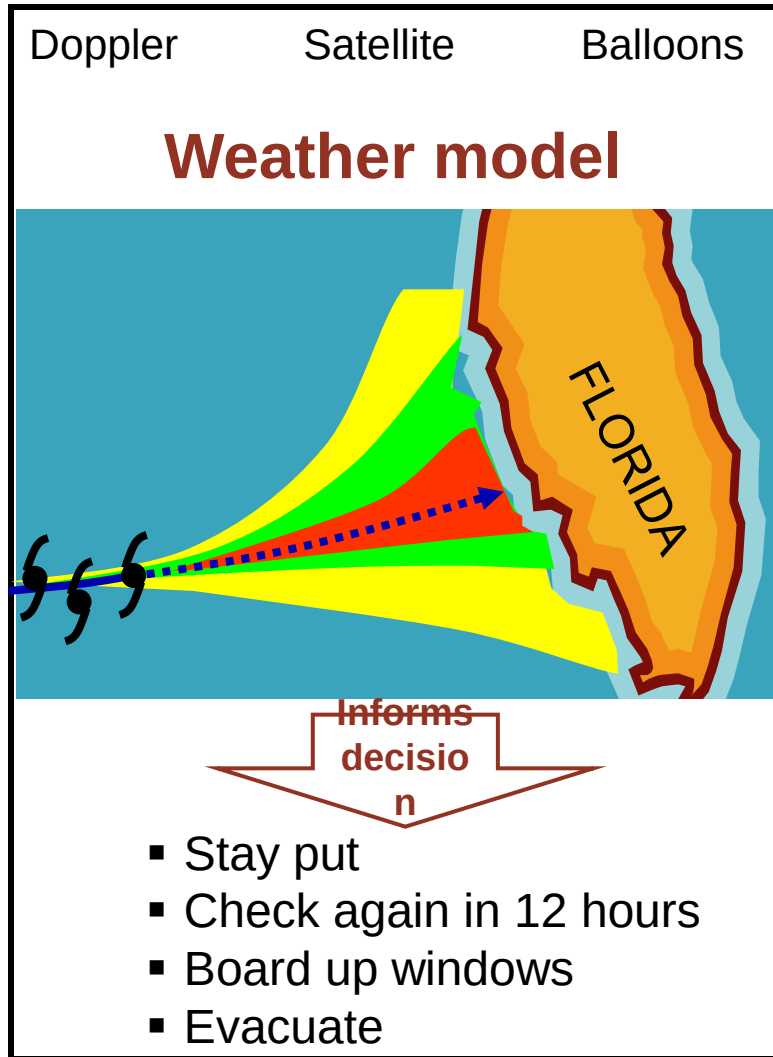
Bruno Bieth, Antoine Soubret, Henning Schmidt

Modeling & Simulation

Novartis Pharma AG



Drug Model: Modeling & Simulation



Outline

- Introduction to the **SBPOP platform**
- RAS Model
- Illustration of use
- Simulation

Terminology

SBPOP

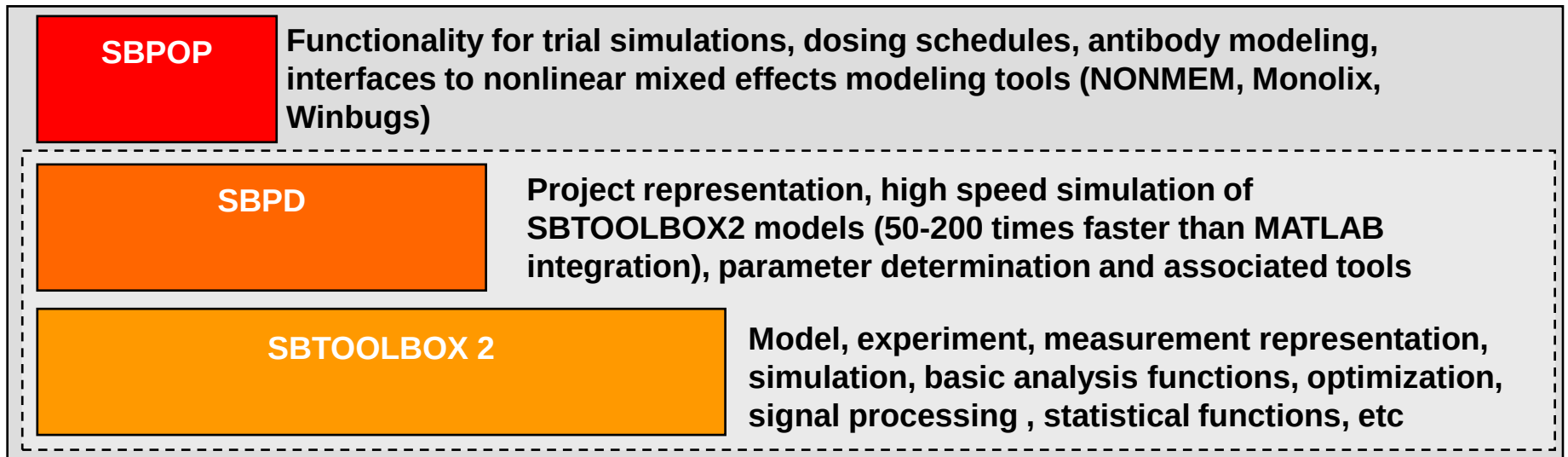
System Biology (SB)	Aims at understanding biology and physiology at the system level, by taking an engineering-like approach
Population PK/PD Modeling (Pop-PKPD)	Population pharmacokinetic (PK) and pharmacodynamic (PD) modeling aims at describing the time course of drug exposure and clinical response to a treatment in a framework taking into account patient variability and experimental uncertainties

SBPOP

- **Goal:** Modeling, Simulation, and Analysis of biochemical systems.
- **Powerful:** Capabilities for population modeling, early biologics antibody modeling and trial simulation.
- **User friendly:** Easily customizable and extensible (by the user!).
- Provides the means to focus on the biology and physiology behind a given project, rather than on re-implementing models, code, data, etc. for each task again.
- OS independent since based on MATLAB.
- Allows users to produce results with scripts that can easily be peer-reviewed.

SBPOP

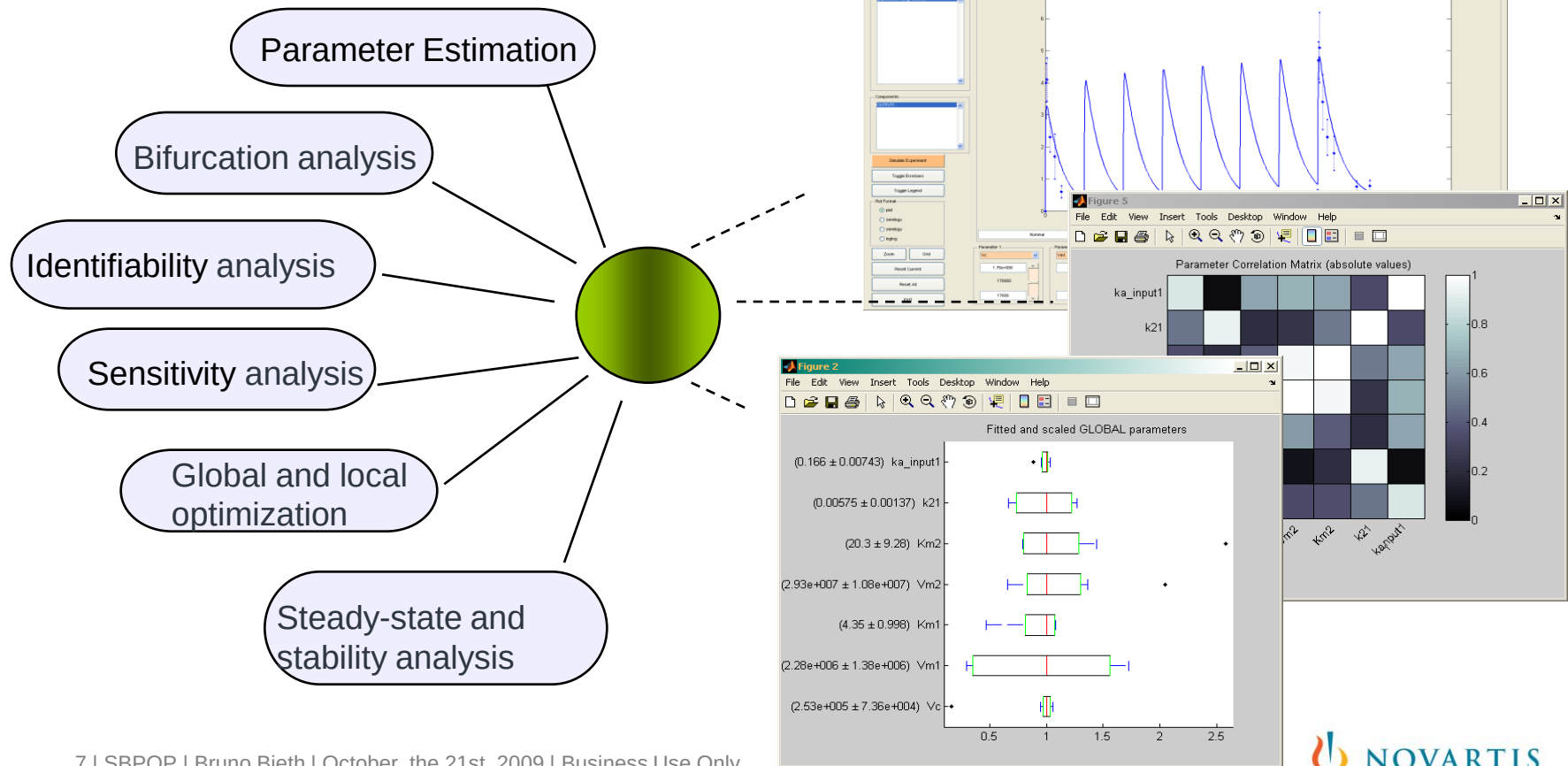
- Platform built on three nested components



SBPOP

Main Features SBTOOLBOX2

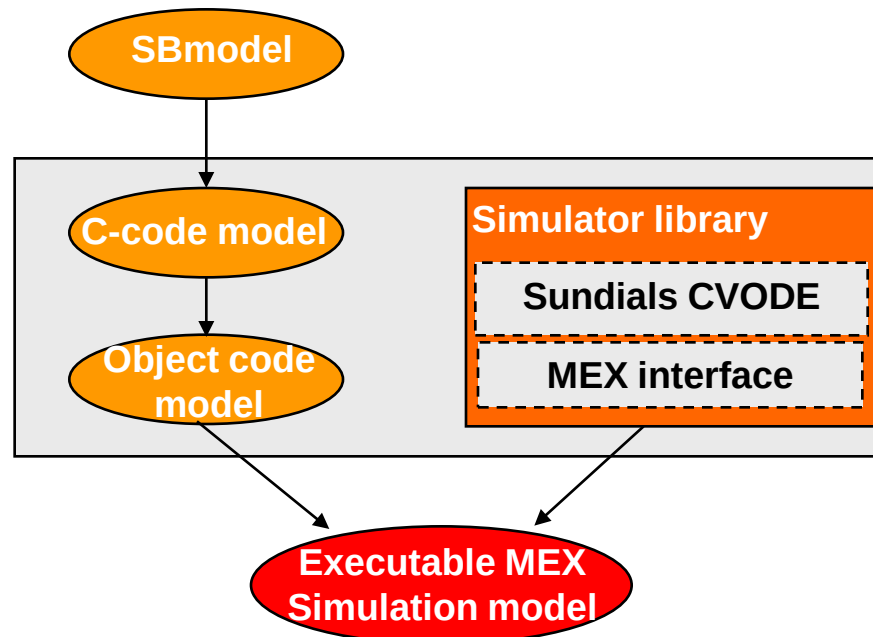
- Representation of models (ODE and biochemical reaction representation) - SBModel, measurement data, experiment descriptions.



SBPOP

Main Features SBPD

- Provide important functionality that is needed for parameter determination applications.
- Automatic conversion of SBmodels to compiled C-code MEX simulation functions, using the SUNDIALS CVODE ODE solver for simulation.
- Simulations are sped up by a factor roughly between 50 and 200.



SBPOP

Main Features SBPOP

- Handling of physiological PK/PD type of models for the feasibility analysis of antibody therapies, including affinity and dose prediction.
- Formal representation of **dosing schemes**, merging of dosing schemes with SBmodels to obtain simulation models, and simulation of dosing schemes on models.
- Simulation of clinical trials.
- Interface with NONMEM/ MONOLIX
 - Import and export of clinical data files, handling and transformation of data (SBPOPdata object).
 - Automatic generation of models from SBmodels, SBPOPdosing schemes, and information from SBPOPdata objects.

SBPOP

- The first two packages (SBTOOLBOX2 and SBPD) are publicly available
- SBTOOLBOX2: GNU License
- SBPD: Creative Commons License
- Matlab ($\geq$ R2006a)
- Matlab style help

```
>> help SBTOOLBOX2
>> help SBPD

>> help SBsimulate
>> help SBPDsimulate

>> helpSB SBsimulate
>> helpSBPD SBPDsimulate
```

- <http://www.sbtoolbox2.org>



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Application to the Renin-Angiotensin System

- The renin-angiotensin system (RAS) is a hormone system that regulates blood pressure and water (fluid) balance.
- Due to the high complexity of the physiological mechanisms involved in the regulation of blood pressure a model based approach has been employed in order to better understand the inner workings of the blood pressure regulation system.
- Simple SBPOP example model of the Renin-Angiotensin System (RAS), targeted by compounds under development
 - Model given by:
 - Pharmacokinetic/Pharmacodynamic Modeling of Renin Biomarkers in Subjects Treated With the Renin Inhibitor Aliskiren
Y Hong, J Dingemanse and DE Mager. *Clinical Pharmacology & Therapeutics* (2008); **84**, 1, 136–143
 - Mean PK/PD Data are extracted from study conducted by Nussberger *et al.*:
 - Angiotensin II suppression in humans by the orally active renin inhibitor aliskiren (SPP100).
Juerg Nussberger; Grégoire Wuerzner; Chris Jensen; Hans R. Brunner. *Hypertension*. 2002;39:e1.

Application to the Renin-Angiotensin System

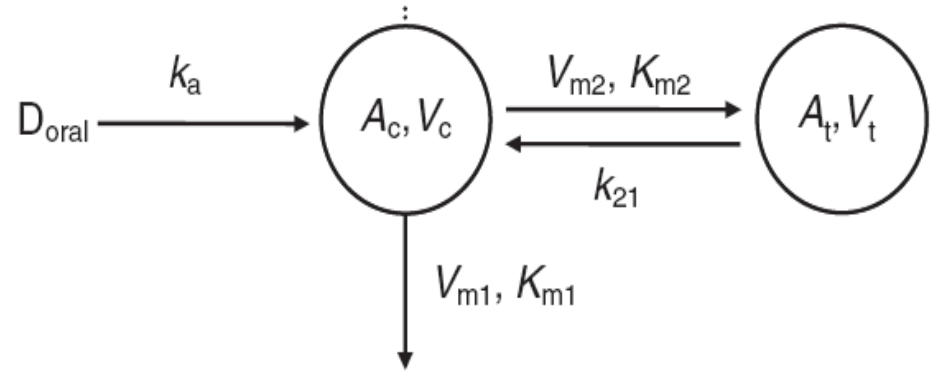
PK/PD Model

■ PK Model:

$$\frac{dA_p}{dt} = -k_a \cdot A_p$$

$$\frac{dA_c}{dt} = k_a \cdot A_p - \frac{V_{m1}}{K_{m1} \cdot V_c + A_c} \cdot A_c + k_{21} \cdot A_t - \frac{V_{m2}}{K_{m2} \cdot V_c + A_c}$$

$$\frac{dA_t}{dt} = \frac{V_{m2}}{K_{m2} \cdot V_c + A_c} \cdot A_c - k_{21} \cdot A_t$$



■ PD Model (AR: active renin)

$$\frac{dAR}{dt} = K_s(t) \cdot \left(1 + \frac{E_{\max} \cdot C_p^h}{EC_{50}^h + C_p^h} \right) - k_{out} \cdot AR$$

Outline

- Introduction to the SBPOP platform
- RAS Model
- **Illustration of use**
- Simulation

Model representation in SBPOP

$$\frac{dA_p}{dt} = -k_a \cdot A_p$$

$$\frac{dA_c}{dt} = k_a \cdot A_p - \frac{V_{m1}}{K_{m1} \cdot V_c + A_c} \cdot A_c + k_{21} \cdot A_t - \frac{V_{m2}}{K_{m2} \cdot V_c + A_c} \cdot A_c$$

$$\frac{dA_t}{dt} = \frac{V_{m2}}{K_{m2} \cdot V_c + A_c} \cdot A_c - k_{21} \cdot A_t$$



```

***** MODEL STATES
d/dt (Ap) = - R1                % ODE system
d/dt (Ac) = R1-R2+R3-R4
d/dt (At) = R4-R3
Ap(0) = 40                      % Initial condition for Ap (if 0, IC definition can be left out)
***** MODEL PARAMETERS
ka = 0.0748                     % /h    % Settings for the PK parameters
Vc = 176000                     % ml
Vm1 = 812000                    % ng/h
Km1 = 0.516                     % ng/ml
Vm2 = 87480000                  % ng/h
Km2 = 135                       % ng/ml
k21 = 0.00248                   % ^h-1
***** MODEL VARIABLES
Cp = Ac/Vc                      % Aliskiren concentration is the output of the simulation
***** MODEL REACTIONS
R1 = -ka*Ap                     % Definition of the reaction kinetic expressions
R2 = Vm1/(Km1*Vc+Ac)*Ac
R3 = k21*At
R4 = Vm2/(Km2*Vc+Ac)*Ac
    
```

Measurement Representation in SBPOP

TABLE 1. Plasma levels (Aliskiren), Aliskiren (L), Aliskiren (R), Aliskiren (S), and Drug Levels After Oral Administration of SBPOP (Aliskiren)

Time (h)	Aliskiren (L)	Aliskiren (R)	Aliskiren (S)	Aliskiren (S)	Aliskiren (S)
Day 1-1	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-2	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-3	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-4	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-5	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-6	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-7	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-8	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-9	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-10	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-11	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-12	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-13	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-14	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-15	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-16	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-17	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-18	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-19	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-20	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-21	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-22	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-23	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-24	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-25	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-26	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-27	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-28	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-29	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-30	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-31	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-32	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-33	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-34	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-35	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-36	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-37	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-38	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-39	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-40	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-41	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-42	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-43	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-44	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-45	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-46	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-47	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-48	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-49	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-50	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-51	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-52	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-53	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-54	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-55	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-56	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-57	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-58	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-59	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-60	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-61	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-62	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-63	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-64	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-65	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-66	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-67	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-68	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-69	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-70	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-71	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-72	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-73	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-74	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-75	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-76	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-77	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-78	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-79	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-80	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-81	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-82	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-83	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-84	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-85	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-86	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-87	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-88	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-89	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-90	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-91	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-92	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-93	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-94	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-95	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-96	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-97	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-98	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-99	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02
Day 1-100	1.00E+02	1.00E+02	1.00E+02	1.00E+02	1.00E+02

[Name]

Measurement Aliskiren

% Measurement name

[Notes]

% Notes about the measurement

[Components]

time, Cp, Cp+, Cp-

% Names of the measured components:

% time of measurement (time), aliskiren concentration (Cp),

% upper (Cp+) and lower bound (Cp-) of the concentration

[Componentnotes]

Cp: component Ac/Vc

% Aliskiren concentration

[Values]

0,0,0,0

0.5,4,4.6,3.4

1,4.1,4.77,3.43

3,2.3,2.75,1.85

6,1.7,2.4,1

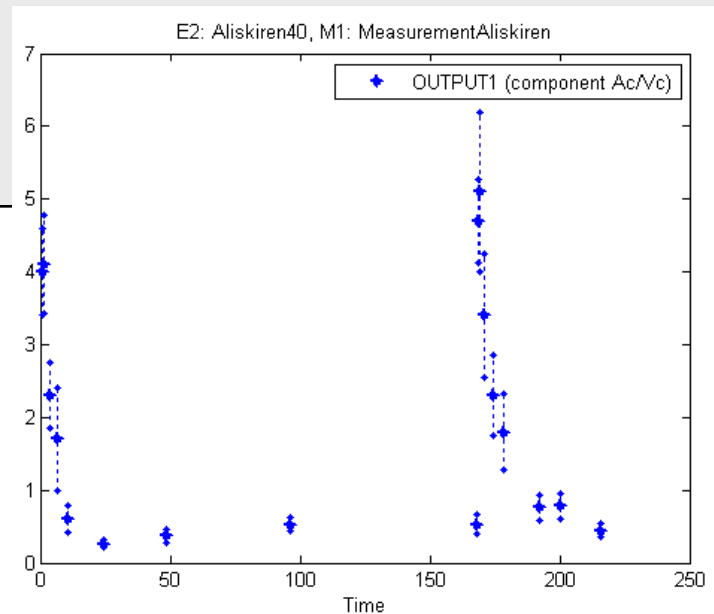
10,0.6,0.78,0.42

24,0.26,0.31,0.21

% Measurement data

```
>> data = SBmeasurement('measurement.csv')
```

```
>> SBvisualizedata(data)
```



Experiments Representation in SBPOP

- The dosing schedule is a dose of drug given every 24 hours for 8 days

```
***** EXPERIMENT NAME
Aliskiren PK Model
***** EXPERIMENT INITIAL PARAMETER AND STATE SETTINGS

***** EXPERIMENT PARAMETER CHANGES

***** EXPERIMENT STATE CHANGES
time=24, Ap=Ap+40           % At time =24, a new dose of aliskiren is given to the patient
                           % and added to the current value of the amount of drug at
                           % absorption site
time=48, Ap=Ap+40
...
```

Implementation of dosing scheme

- Alternative to represent the dosing scheme in terms of experiments. Allows the definition of clinical trials including cross-over studies.

```
***** INPUT1
type:                ABSORPTION1
time:                0          % (hr) time for first application
deltaT:              24        % (hr) time in-between applications
nr_repetitions:      8         % number of applications
D:                   40        % (unit) dose
ka:                  0.0748    % (1/hr) absorption rate coefficient
```

- ODE in SBmodel has to be replaced by

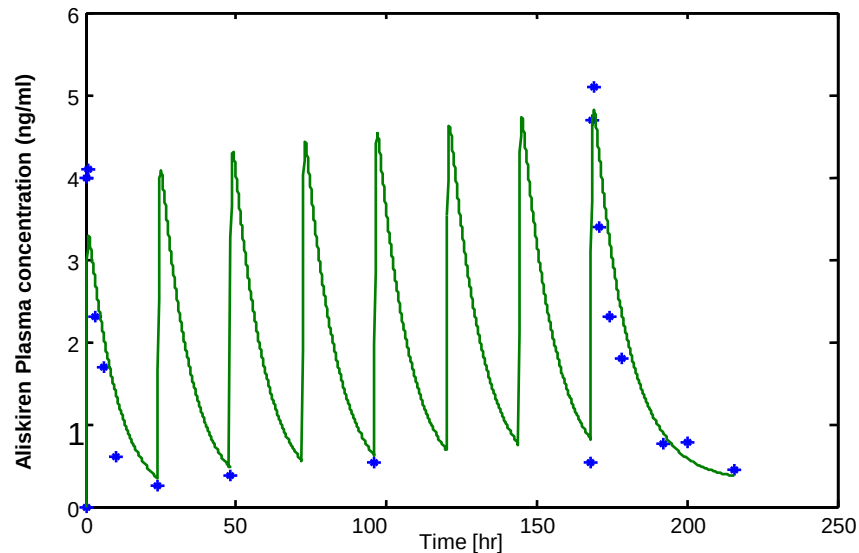
```
***** MODEL STATES
d/dt (Ap) = - R1          % ODE system (model reaction are written below)
d/dt (Ac) = R1-R2+R3-R4
d/dt (At) = R4-R3
```

Outline

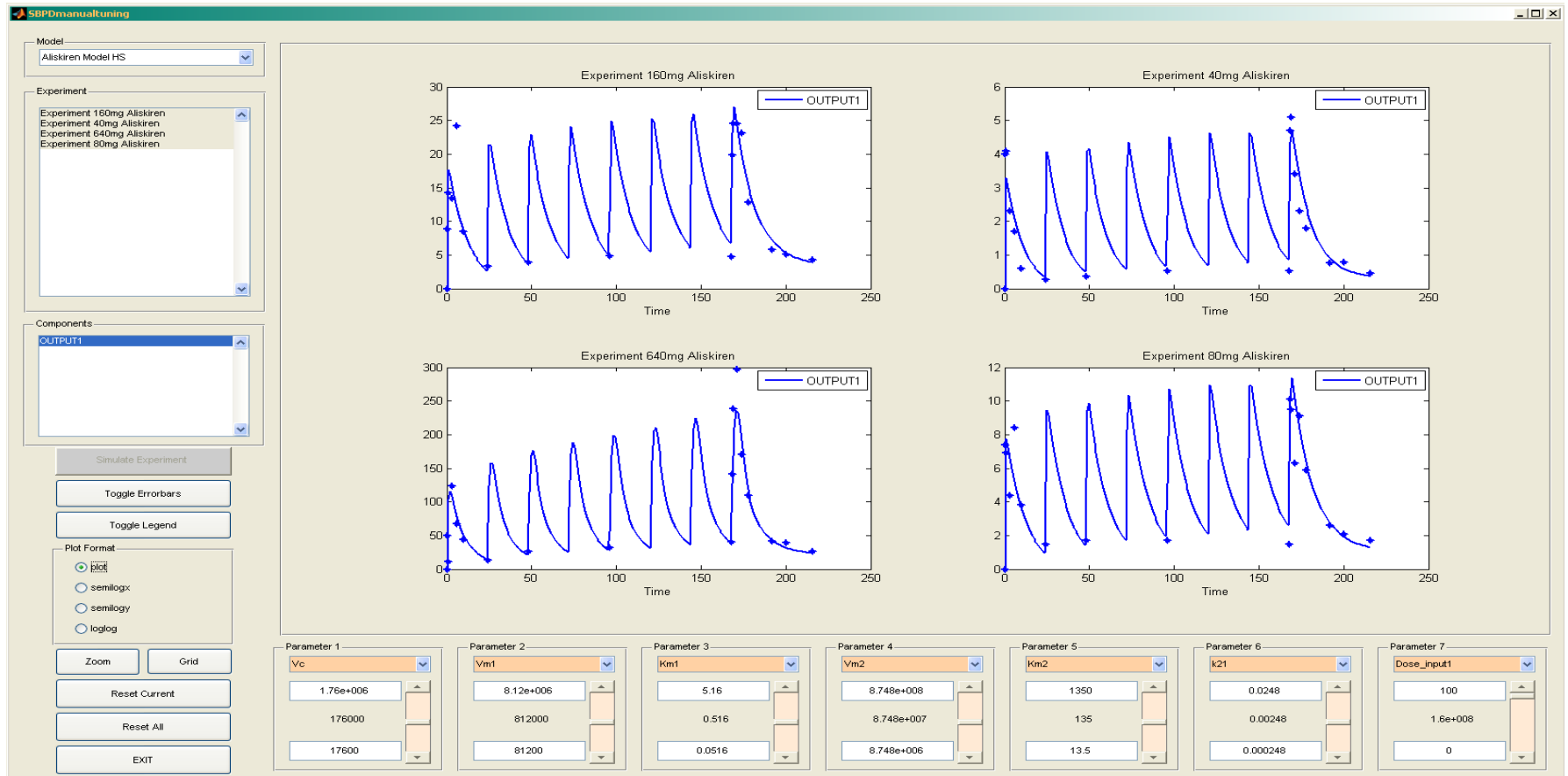
- Introduction to the SBPOP platform
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Simulation

```
>> model = SBmodel('Pkmodel.txt') % Import model
>> dosing = SBPOPdosing('dosing.dos'); % Import dosing scheme
>> measurement = SBmeasurement('Measurement.csv'); % Import Measurement
>> modeldosing = SBPOPmergemoddos(model,dosing); % Merge model and dosing description
>> simdata = SBsimulate(modeldosing,[0:1:216]); % Simulation
>> [time,name,data] = SBmeasurementdata(measurement); % Import time, name and data measurement
>> plot(time, data(:,1), Simdata.time,Simdata.statevalues(:,1)); % Plot
```



Simulation and Parameter Estimation



Comparison

PK Model

■ Hong et al.

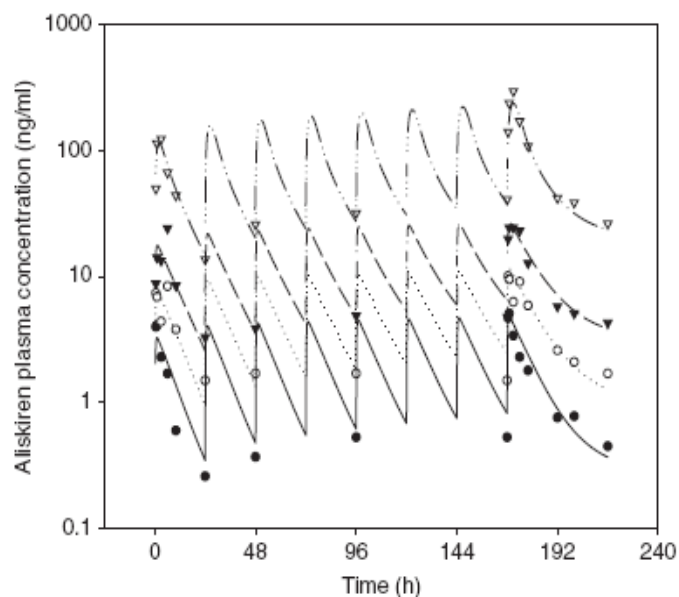
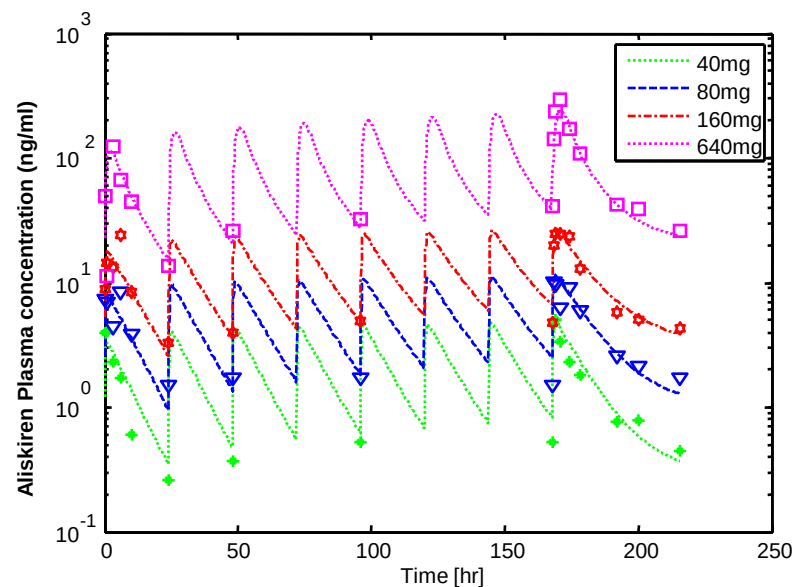


Figure 1 Time-course of mean aliskiren plasma concentrations after multiple dosing for 8 days. The symbols represent the data extracted from ref. 32, and the lines are model-predicted profiles. Doses are 40 (closed circle; solid line), 80 (open circle; dotted line), 160 (closed inverted triangle; broken line), and 640 mg (open inverted triangle; dash-dot-dot line).

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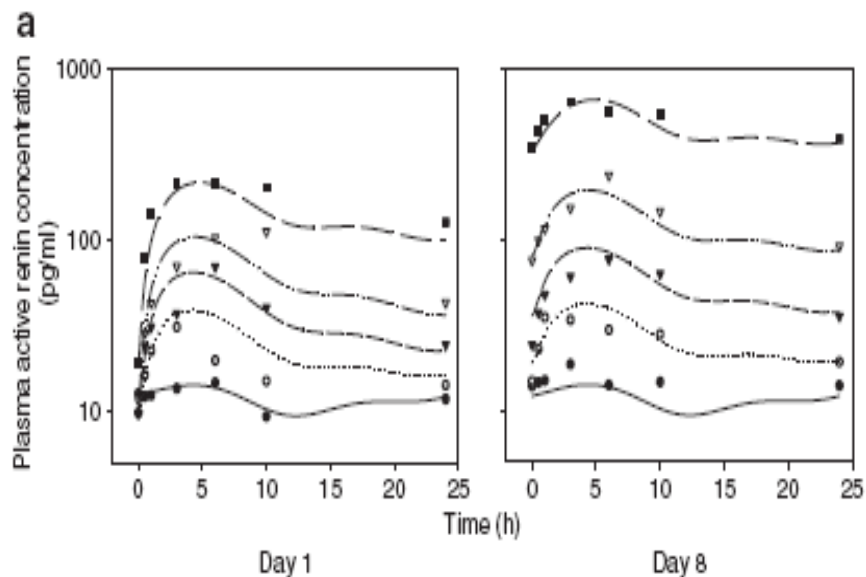


No discernable differences

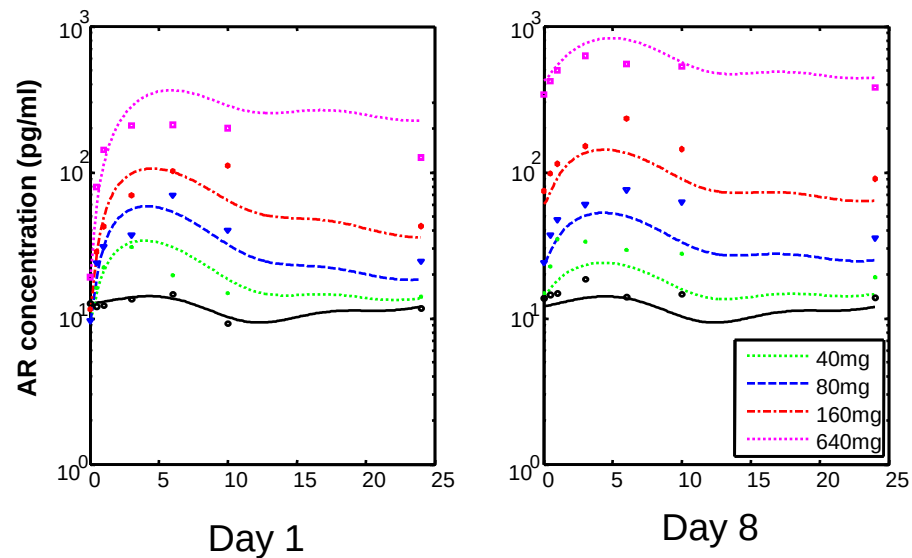
Comparison

PD Model

■ Hong et al.



SBPOP



Differences for low doses

Conclusions

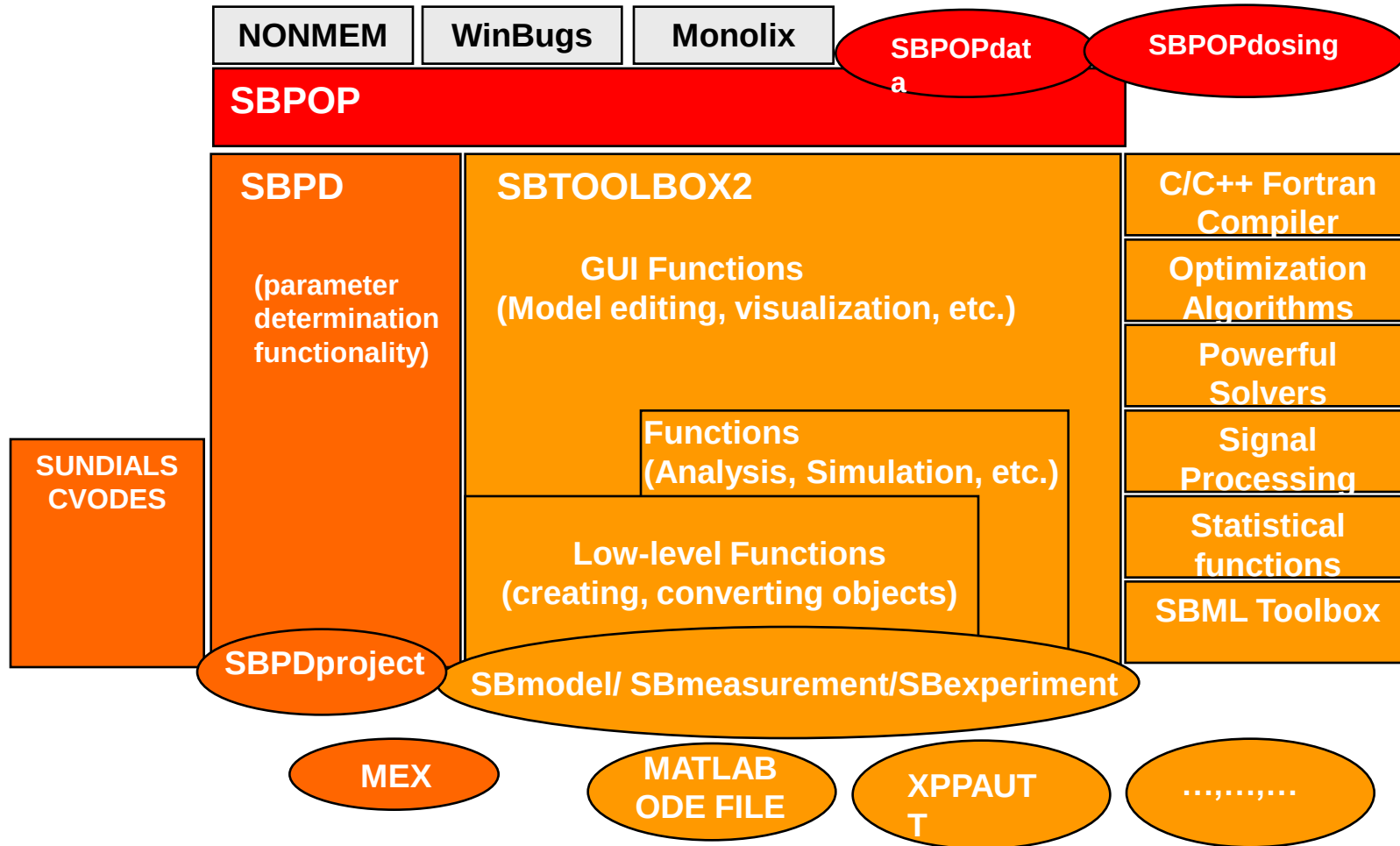
- SBPOP is well suited for modeling and simulation of kinetics (Systems Biology / Pharmacometrics)
- Systems biology can impact Pharma Development if tools exist (!they do!)
- Allows to focus on the biology / physiology rather than challenges on software implementation
- Experiment, dosing scheme settings enable clear description and auditability of the model
- Usefulness of user-friendly, intuitive, and extensible software
- <http://www.sbtoolbox2.org>

Title

Subtitle

- Backup slides

Design of SBPOP



Application to the Renin-Angiotensin System

- Model given by:

- Pharmacokinetic/Pharmacodynamic Modeling of Renin Biomarkers in Subjects Treated With the Renin Inhibitor Aliskiren

Y Hong, J Dingemanse and DE Mager

Clinical Pharmacology & Therapeutics (2008); **84**, 1, 136–143

- Mean PK/PD Data are extracted from study conducted by Nussberger *et al.*:

- Angiotensin II suppression in humans by the orally active renin inhibitor aliskiren (SPP100).

Juerg Nussberger; Grégoire Wuerzner; Chris Jensen; Hans R. Brunner

Hypertension. 2002;39:e1.