Application of the SBTOOLBOX2 in drug discovery and development

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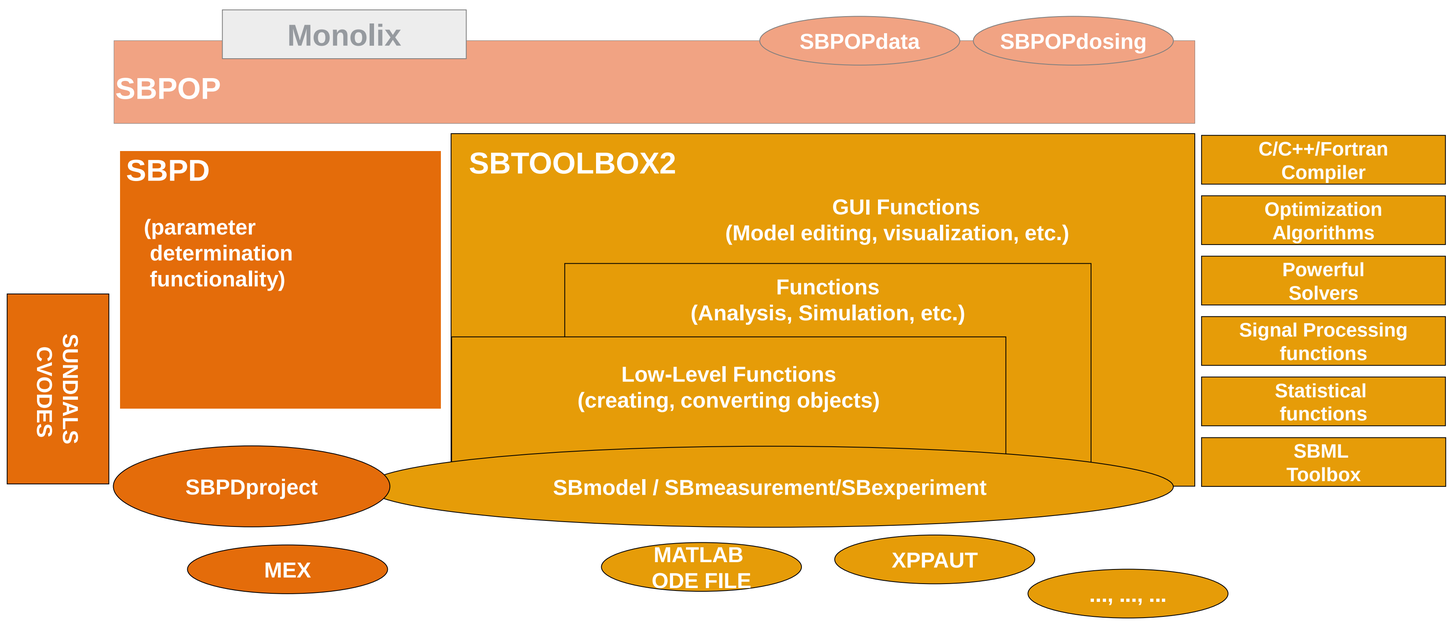
Background

- In modern Drug discovery and Development, mechanistic physiologically based and more traditional PKPD models all play an important role.
- The practical handling of mathematical drug and disease models and their analysis require powerful and flexible, yet user-friendly computational tools. Ease of modeling, analysis and subsequent bridging to population approaches is crucial.
- The Systems Biology Toolbox 2 (SBTOOLBOX2, [1]), is a publicly available, open-source tool aiming at simplifying the required modeling and simulation workflow (can be freely downloaded from - http://www.sbtoolbox2.org). At Novartis the SBTOOLBOX2 is used together with the SBPOP (see Figure 1), to enable a link to population modeling approaches in Monolix® (Lixoft, France). Currently, the SBPOP extension is not generally available.
- Here we focus on the SBTOOLBOX2 and exemplify its use based on an application to an early target feasibility assessment for a monoclonal antibody therapy. The link between the SBTOOLBOX2 and population estimation methods is out of scope of this poster.

SBTOOLBOX2

- The SBTOOLBOX2 is a Matlab toolbox. It uses multiple features available in Matlab® (The MathWorks, USA) and provides additional specific technical features for Drug development and Discovery.
- The Systems Biology platform consists of linked packages (Figure 1): 1) The SBTOOLBOX2 is used for model development; 2) The Systems Biology Parameter Determination (SBPD) is used for project-level representations.
- Automatic C-code generation while processing projects is useful for speeding up simulations, in a seamless manner to the user. By using the SBPD, the project simulation is very fast (30-200 times faster than normal Matlab Simulation).
- Within the SBTOOLBOX2 project, model coding is very easy. Model syntax can be ODE-based or biochemical reactions-based. The latter is most intuitive and simple (see in example)

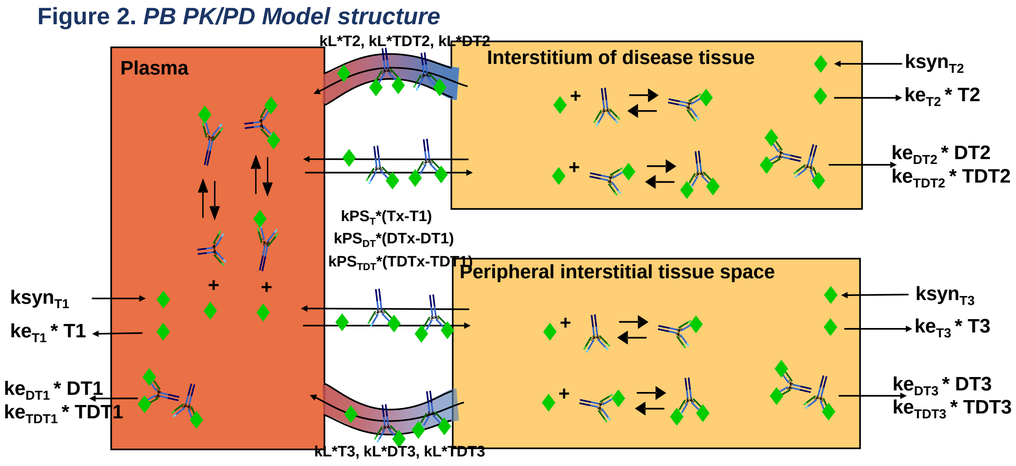
Figure 1. *Design of the Systems Biology Toolbox 2*



Example – Target feasibility analysis

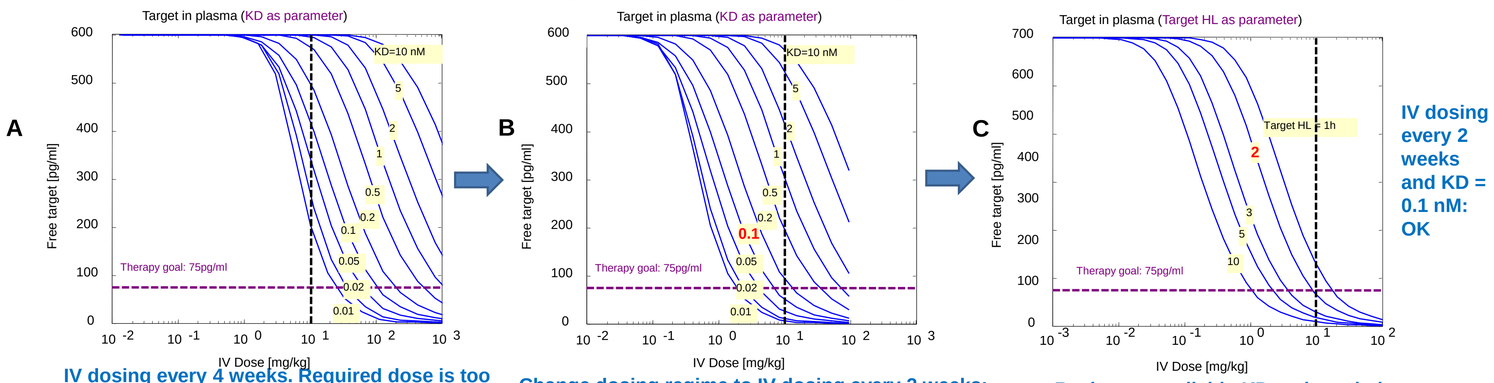
- Here we present a drug monoclonal Antibody (mAb) - target binding model [2], developed in the SBTOOLBOX2. Model describes mAb concentration in physiologically sized plasma and tissue compartments (Figure 2). PK part: Linear elimination; distribution between compartments modeled as diffusion and active transport through lymph flow. PD part: Target (green rhombs on the Figure 2) synthesis and elimination; drug-target binding reactions; target and drug-target complex transport reactions.
- Key aim is to assess dose-response relation for different assumptions on which gaps in knowledge exist and to test different properties of the mAb to support its design (estimation of KD with respect to dose regime and target half-life – see Figure 3). At the time of this analysis the mAb is not yet designed, so such an analysis helps in defining specifications for this mAb.

Figure 2. *PB PK/PD Model structure*



TQ = target concentration in compartment Q
TDTQ, DTQ = drug/target complex concentrations in compartment Q

Figure 3. *Simulation of dosing regimens and related dose-response curves in SBTOOLBOX2. A,B - Sensitivity analysis with respect to administration route and KD; C - Sensitivity analysis with respect to target half-life (HL)*



IV dosing every 4 weeks. Required dose is too high – we cannot reach therapy goal for target concentration with dosing regime like this

Change dosing regime to IV dosing every 2 weeks: ~10mg/kg with a appropriate KD=0.1 nM

Basing on available KD and needed therapy goal we assess Target half-life

IV dosing every 2 weeks and KD = 0.1 nM: OK

- ODE representation of the model is cumbersome, error prone, but within the SBTOOLBOX2, we can use the biochemical representation that allows a very good overview of the model, understandably coded, and easily re-usable for other projects. Here is the model syntax for Target synthesis, elimination and binding to mAb in plasma:
  - => T1 : Target_synthesis_1
    vf = ksyn$_{T1}$
  - T1 => : Target_elimination_1
    vf = ke$_{T1}$*T1*Vol1
  - D1+T1 <=> DT1 : Binding_1
    vf = (k$_{DT1}$*D1*T1)*Vol1
    vr = (k$_{DT1*}$KD$_{DT1}$*DT1)*Vol1
  - DT1+T1 <=> TDT1 : Doublebinding_1
    vf = (k$_{TDT1}$*DT1*T1)*Vol1
    vr = (k$_{TDT1}$*KD$_{TDT1}$*TDT1)*Vol1

Conclusions

- The SBTOOLBOX2 gives the user high flexibility and relative simplicity to work on PKPD and PBPK modeling activities, as compared to different popular software packages like Berkeley Madonna® (University of California at Berkeley, USA), CellDesigner® (Systems Biology Institute, Japan), etc.
- The SBTOOLBOX2 is easy to use, well documented and easily extensible. These qualities make the SBTOOLBOX2 a potential tool for Training and Education in the field of Systems biology and Drug Discovery and Development.
- The SBTOOLBOX2 provides a range of well-documented modeling techniques which may be used within Pharma projects.

References

1. Schmidt H. and Jirstrand M.: Systems Biology Toolbox for MATLAB: a computational platform for research in systems biology. Bioinformatics 22 (4): 514-515, 2006
2. Roskos L.: Handbook of Therapeutic Antibodies. 2008.

Acknowledgements

- We would like to thank all our colleagues from M&S at Novartis who provide an exciting and challenging work experience.

This study was supported by Novartis Pharma AG, Basel, Switzerland.

Poster presented at the Population Approach Group Europe (PAGE), June 5-8, 2012, Venice, Italy.