Minimal Physiologically-based Pharmacokinetic Model for Monoclonal Antibodies

Phoenix Modeling Language School
November 16, 2017
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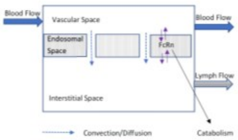
Agenda

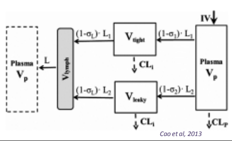
- Minimal PBPK Model Introduction: Theoretical and Objectives

  Cao, Yanguang; Balthasar, Joseph P.; Jusko, William J. (2013): Second-generation minimal physiologically-based pharmacokinetic model for monoclonal antibodies. In *Journal of pharmacokinetics and pharmacodynamics* 40 (5), pp. 597–607. DOI: 10.1007/s10928-013-9332-2. (Cao et al, 2013)

- A Stepwise Approach to Construct Phoenix WinNolin mPBPK Textual Model Using Built-in Model and Graphical Model Interface
- Demonstration
- Questions and Answers

mPBPK for Monoclonal Antibodies

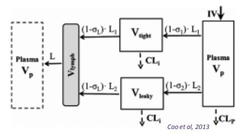




Theoretical

- Offers system-average rather than tissue specific
- mAbs are largely confined to plasma without distribution into blood cells
- Convection is the only distribution pathway
- Interstitial fluid (ISF) is the only extravascular distribution space (overall volume of vascular endothelial endosomes in adults ~0.4% plasma and < 0.1% of ISF volume)

mPBPK for Monoclonal Antibodies

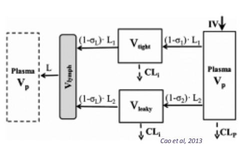


- Vtight = 0.65*ISF*Kp
- Vleaky = 0.35*ISF*Kp

Theoretical

- Cp: mAb concentration in Vp (plasma volume = 2.6L); CLp
- Tight tissue (muscle, skin, adipose and brain): Ctight, Vtight; CLi
- Leaky tissue (liver, kidney, heart, etc): Cleaky, Vleaky; CLi
- Vlymph; Clymph: lymph volume; mAb concentration in lymph. Vlymph = 2.6L
- L, L1, and L2: total lymph flow; lymph flow for tight tissue and leaky tissue: L = 2.9L/day ; L1 = 0.33*L; L2 = 0.67*L
- σ1 and σ2: vascular reflection coefficients for tight tissue and leaky tissue; σ1< 1; σ2<1
- σL: lymphatic capillary reflection coefficient = 0.2
- Kp: fraction of ISF for mAb distribution = 0.8
- ISF = 15.6 L

mPBPK for Monoclonal Antibodies



Objectives

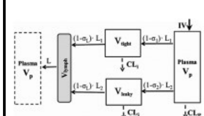
- Fitting only plasma concentration data
- To estimate σ1 and σ2 and clearance (CLp or Cli)
- To simulate mAb concentration vs time profiles in plasma, leaky and tight tissue

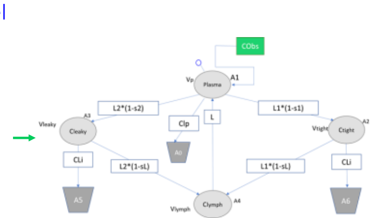
Model A has CLp from plasma

Model B has CLi from tight and leaky tissue

All initial conditions are concentration = 0

mPBPK Graphical Model





mPBPK for Monoclonal Antibodies

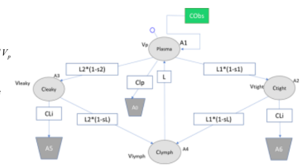
Differential equations (Model A +B)

$$\frac{dC_p}{d_t} = \frac{Input}{V_p} + [C_{lymph} \bullet L - C_p \bullet L_1 \bullet (1-\sigma_1) - C_p \bullet L_2 \bullet (1-\sigma_2) - C_p \bullet CL_p]/V_p$$

$$\frac{dC_{tight}}{d_t} = [L_1 \bullet (1-\sigma_1) \bullet C_p - L_1 \bullet (1-\sigma_L) \bullet C_{tight} - CL_i \bullet C_{tight}]/V_{tight}$$

$$\frac{dC_{leaky}}{d_t} = [L_2 \bullet (1-\sigma_2) \bullet C_p - L_2 \bullet (1-\sigma_L) \bullet C_{leaky} - CL_i \bullet C_{leaky}]/V_{leaky}$$

$$\frac{dC_{lymph}}{d_t} = [L_1 \bullet (1-\sigma_L) \bullet C_{tight} - L_2 \bullet (1-\sigma_L) \bullet C_{leaky} - C_{lymph} \bullet L]/V_{lymph}$$



mPBPK for Monoclonal Antibodies

Differential equations → **Phoenix Modeling Language**

$$\frac{dC_p}{d_t} = \frac{Input}{V_p} + [C_{lymph} \bullet L - C_p \bullet L_1 \bullet (1-\sigma_1) - C_p \bullet L_2 \bullet (1-\sigma_2) - C_p \bullet CL_p]/V_p$$

dosepoint(A1)

deriv(A1 = - (CLp * Cplasma)- (L1 * (1-s1)* Cplasma)- (L2 * (1-s2)* Cplasma) + (Clymph * L))

$$\frac{dC_{tight}}{d_t} = [L_1 \bullet (1-\sigma_1) \bullet C_p - L_1 \bullet (1-\sigma_L) \bullet C_{tight} - CL_i \bullet C_{tight}]/V_{tight}$$

deriv(A2 = (L1 * (1-s1)* Cplasma)- (Ctight * L1 * (1-sl))- (CLi * Ctight))

$$\frac{dC_{leaky}}{d_t} = [L_2 \bullet (1-\sigma_2) \bullet C_p - L_2 \bullet (1-\sigma_L) \bullet C_{leaky} - CL_i \bullet C_{leaky}]/V_{leaky}$$

deriv(A3 = (L2 * (1-s2)* Cplasma)- (Cleaky* (1-sl) * L2)- (CLi * Cleaky))

$$\frac{dC_{lymph}}{d_t} = [L_1 \bullet (1-\sigma_L) \bullet C_{tight} - L_2 \bullet (1-\sigma_L) \bullet C_{leaky} - C_{lymph} \bullet L]/V_{lymph}$$

deriv(A4 = (Ctight * L1 * (1-sl)) + (Cleaky * L2 * (1-sl))- (Clymph * L))

Examples

Published data were digitized from the following publications:

MEDI-528: humanized IgG1$_{\kappa}$ anti-IL-9 mAb

White, Barbara; Leon, Francisco; White, Wendy; Robbie, Gabriel (2009): Two first-in-human, open-label, phase I dose-escalation safety trials of MEDI-528, a monoclonal antibody against interleukin-9, in healthy adult volunteers. In *Clin Ther* 31 (4), pp. 728–740. DOI: 10.1016/j.clinthera.2009.04.019.

Gevokizumab: humanized IgG2 anti-IL-1β mAb

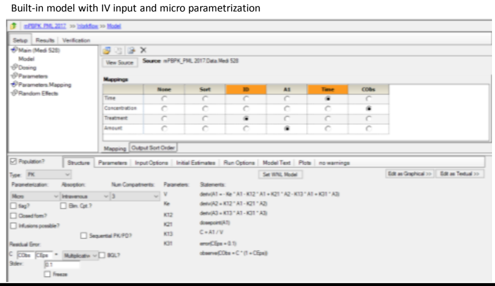
Cavelti-Weder, Claudia; Babians-Brunner, Andrea; Keller, Cornelia; Stahel, Marc A.; Kurz-Levin, Malaika; Zayed, Hany et al. (2012): Effects of gevokizumab on glycemia and inflammatory markers in type 2 diabetes. In *Diabetes Care* 35 (8), pp. 1654–1662. DOI: 10.2337/dc11-2219.

8C2: anti-topotecan mAb

Cao, Yanguang; Balthasar, Joseph P.; Jusko, William J. (2013): Second-generation minimal physiologically-based pharmacokinetic model for monoclonal antibodies. In *Journal of pharmacokinetics and pharmacodynamics* 40 (5), pp. 597–607. DOI: 10.1007/s10928-013-9332-2.

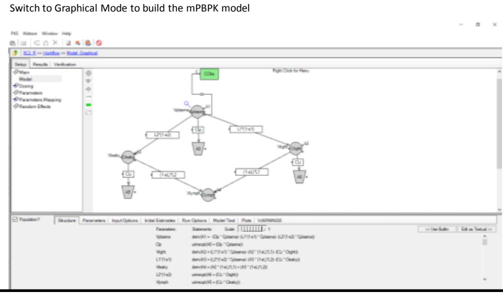
Stepwise to build up your model

Built-in model with IV input and micro parametrization



Stepwise to build up your model

Switch to Graphical Mode to build the mPBPK model



PML Textual Model (A and B)

```
test(){
# Insert parameter relationships here #
Vtight = 0.65 * ISF * Kp                    #Dose in mcg; Volume in mL; flow rate and# Clearance in#
Vleaky = 0.35 * ISF * Kp                    #L/day, time in day, concentration in mcg/mL#
L1 = 0.33 * L
L2 = 0.67 * L
# DE for the amount of plasma, tight tissue, leaky tissue and lymph  #
deriv(A1 = - (CLp * Cplasma)- (L1 * (1-s1)* Cplasma)- (L2 * (1-s2)* Cplasma) + (Clymph * L)) #omit –(CLp*Cplasma) if running model B#
deriv(A2 = (L1 * (1-s1)* Cplasma)- (Ctight * L1 * (1-sl))- (CLi * Ctight))      #omit –(CLi*Ctight) if running model A#
deriv(A3 = (L2 * (1-s2)* Cplasma)- (Cleaky* (1-sl) * L2)- (CLi * Cleaky))       #omit –(CLi*Cleaky) if running model A#
deriv(A4 = (Ctight * L1 * (1-sl)) + (Cleaky * L2 * (1-sl))- (Clymph * L))
#Dosepoint specifies drug input in plasma space#
dosepoint(A1)
#Convert amounts to concentrations#
Cplasma = A1 / Vp
Ctight = A2 / Vtight
Cleaky = A3 / Vleaky
Clymph = A4 / Vlymph
#using secondary statement to calculate TER; optional#
secondary(TER = L1 * (1-s1) + L2 * (1-s2))
```

PML Textual Model (A and B)

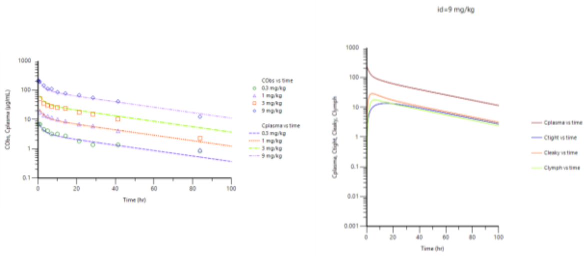
```
#Initial estimate of the within error  standard deviation#
error(CEps = 0.1)
#error model#
observe(CObs = Cplasma*(1+ CEps)) #multiplicative error model#

#fixed effects; parameter values are frozen#
fixef(L(freeze) = c(, 2900,))
fixef(ISF(freeze) = c(, 15600,))
fixef(Kp(freeze) = c(, 0.8,))
fixef(Vp(freeze) = c(, 2600, ))
fixef(sl(freeze) = c(, 0.2,))
fixef(Vlymph(freeze)  = c(, 2600, ))

#fixed effects; lower bound, initial estimate, upper bound; parameters to be estimated#
fixef(s1 = c(0, 0.5, 1))
fixef(s2 = c(0, 0.73,1))
fixef (CLi = c(,120,)) # model B#
#fixef(CLp=c(,120,))  # model A#
}
```

Demonstration

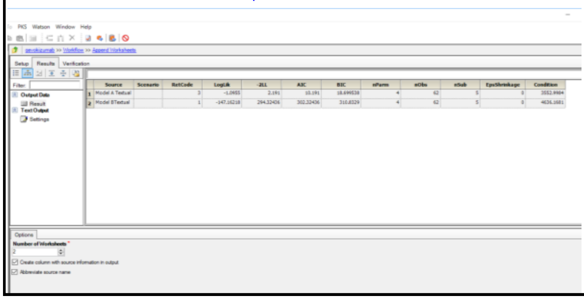
MEDI-528: Phase 1, healthy volunteers

- Humanized $IgG1_{K}$ anti-IL-9 mAb
- Single dose, 0.3, 1.0, 3.0, 9.0 mg/kg;
- IV infusion; 20 mg/min
- Infusion time: 1-40 min
- Sampling time points: up to 84 days

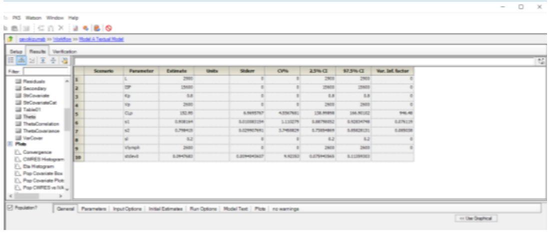
MEDI-528: Model Fitting and Simulation



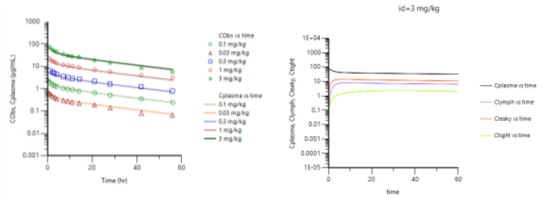
Gevokizumab: Model Comparison



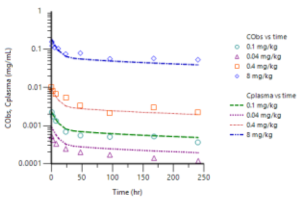
Gevokizumab (Model A)

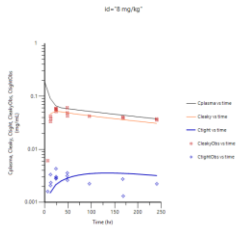


Gevokizumab: Model A Fitting and Simulation



8C2: Model B Fitting and Simulation





Conclusion

- mPBPK method by *Cao et al, 2013* including the major distributional characteristics of mAbs can serve as intermediate step when moving towards application of full PBPK models for mAbs.
- This model allows:
  - Estimation of mAb concentration versus time profiles in two different tissue groups (leaky and tight)
  - Estimation of mAb clearance

Questions?

Coming up…

Target-mediated Drug Disposition (TMDD) Modeling Using the Quasi-equilibrium Assumption
Write a textual model according to Gibiansky (2008), fit and simulate mAb profiles
November 30, 2017 | 10am EST
Presenter: Frank Striebel

Adaptive Simulations: Extending PML to Trial Simulations
A pre-clinical example to simulate a desired outcome
December 14, 2017 | 10am EST
Presenter: Bernd Wendt

Topics for 2018: NONMEM to PML Comparisons
- Popular Models using NONMEM software
  - 1:1 translation into Phoenix Modeling Language
  - Setup and run NONMEM models in Phoenix
  - Setup and Run same model in Phoenix NLME
  - Compare Results

CERTARA