Development of a closed loop whole body (WB) physiologically based pharmacokinetic model (PBPK) of beta-blockers in the rat.

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Aim of study

- Estimate tissue to blood partition coefficients (K_p) using a WB-PBPK model
- Obtain open loop estimates to provide an informative prior for closed loop fitting
- Incorporation of permeability rate limited (PML) kinetics into the perfusion rate limited (PFL) model
- To compare steady state and closed loop estimates

Step 1: Obtain Steady state from rat data

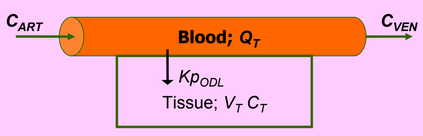
Steady State (SS) equations

$$Kp_{ss,i} = \frac{C_{T,ss,i}}{(1-E)\cdot C_{b,ss,i}}$$

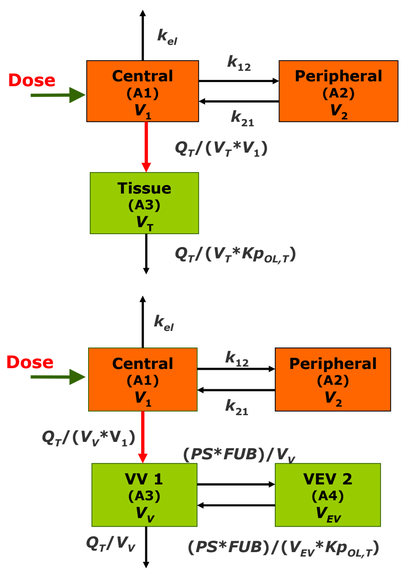
where
- *i* denotes adipose, bone, brain, gut, heart, lung, muscle, skin, testes, thymus, kidneys and liver
- $CT_{,ss,i}$ and $Cb_{,ss,i}$ are concentrations of drug in tissue and arterial blood at steady state respectively
- $E = 0$ for non-eliminating organs

Step 2: Determine PFL or PML tissues using open loop and collect K_p estimate and its %SE for prior subroutine in NONMEM

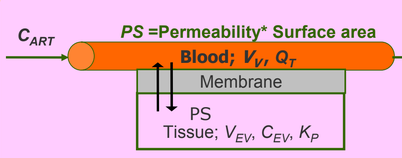
I) Open Loop: Perfusion Rate Limited (PFL) model



- Well Stirred
- C_{ART} simulated for concentration input (forcing function)



II) Open Loop: Pemeabilty Rate Limited (PML) model



- For some compounds, the tissue concentration equilibrated very slowly with arterial concentration
- Suggested permeability limited kinetics
- Obtained V_V (vascular) and V_{EV} (extra-vascular) from literature

- Kp estimated by least squares regression (NONMEM)

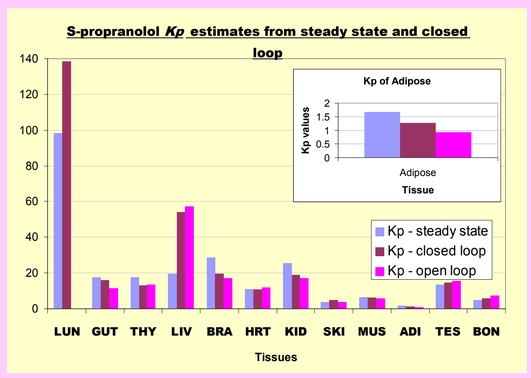
Conclusion

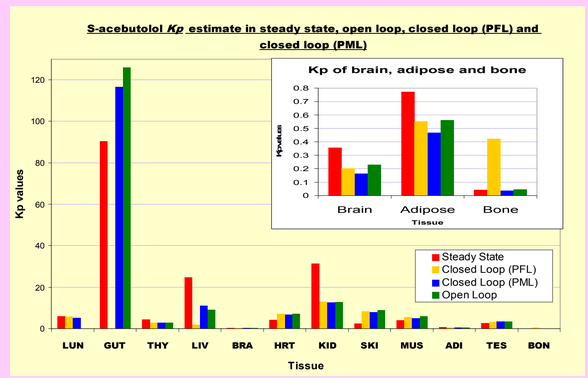
- OL finds the best fitting structural model to tissue data and gives basic PK parameters.
- Permeability limited model considered for some tissues
- K_p estimates change significantly from steady state estimate in some cases, especially if very permeability rate limited.

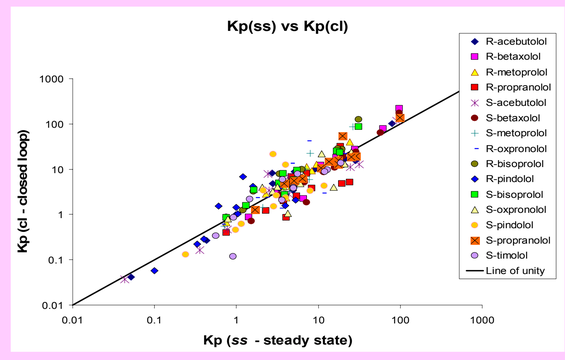
Results

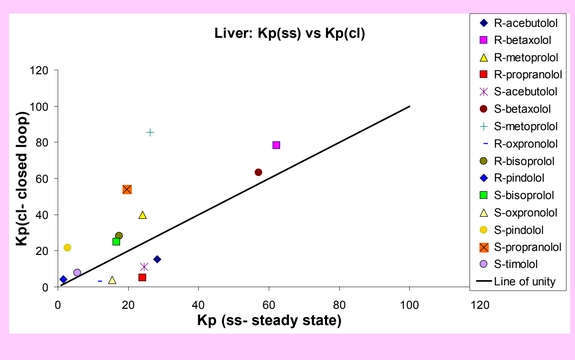
4 types of WBPBPK model

- **All tissues are PF.** → **S-propranolol.**
- All tissues are PF **except for gut (PM).** → R-metoprolol, S-oxprenolol, R-propranolol, R-,S-betaxolol.
- All tissues are PF **except for testes (PM).** → S-metoprolol, S-pindolol.
- All tissues are PF **except for gut (PM) and testes (PM).** → R-oxprenolol, R-,**S-acebutolol**, S-timolol, R-,S-bisoprolol, R-pindolol.



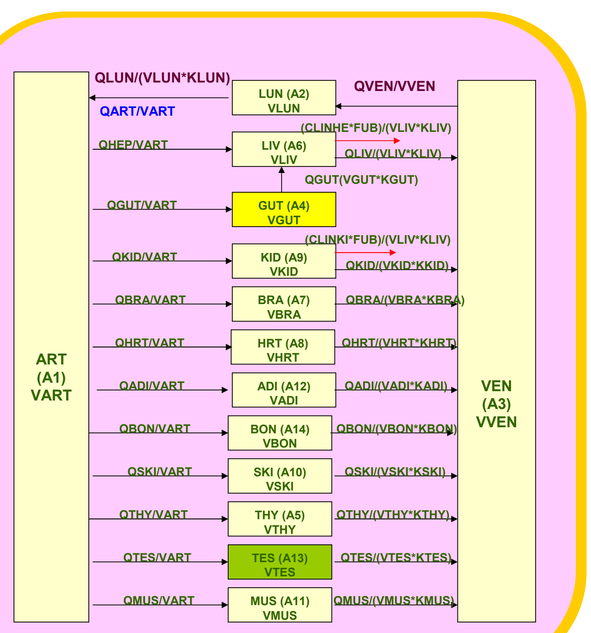


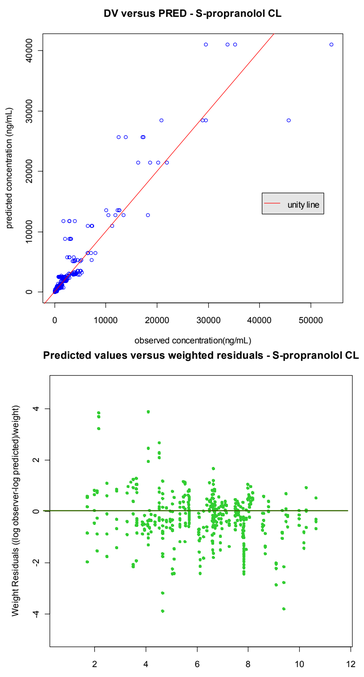


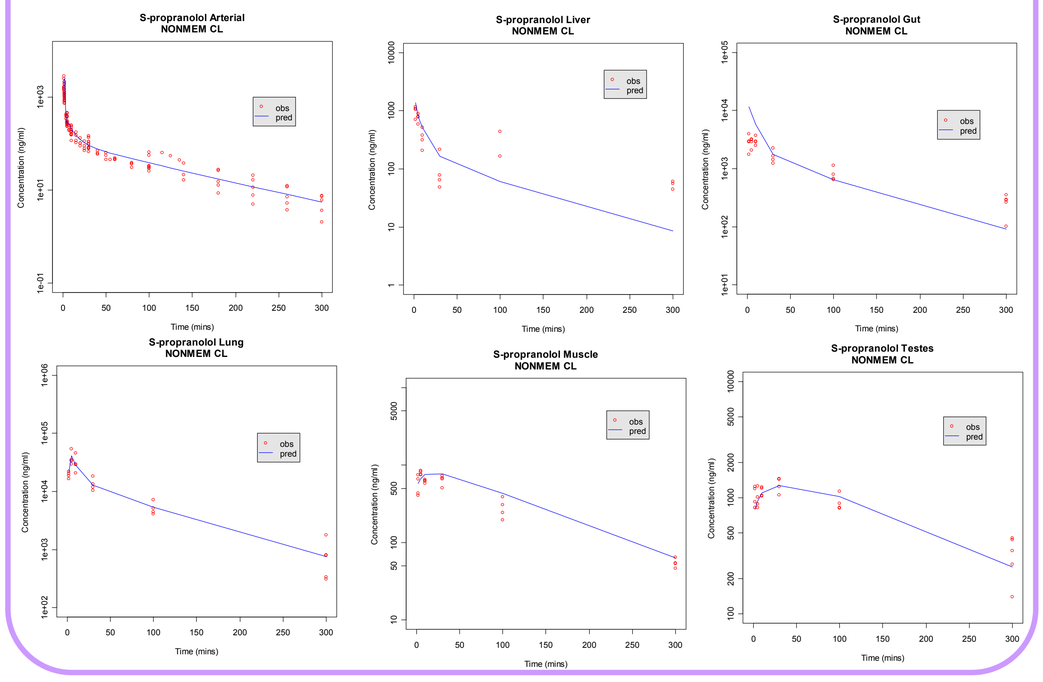


Step 3: Construct closed loop model based on open loop

I) Closed Loop: All perfusion rate limited – S - propranolol







II) Closed Loop: some permeability rate limited – S - acebutalol

- For closed loop modelling, all tissues and blood data are fitted simultaneously
- Q_{Tissue} and V_{Tissue} : physiological values from literature
- Kp (steady state) used for initial estimates
- Kp (open loop) used for informative prior mean
- 2*SE of Kp (open loop) used for prior uncertainty
- Incorporate appropriate PML tissue into the model

Open Loop