# *In Silico* Liver

-- Finding the correlations between model parameters and hepatic pharmacokinetic behaviors

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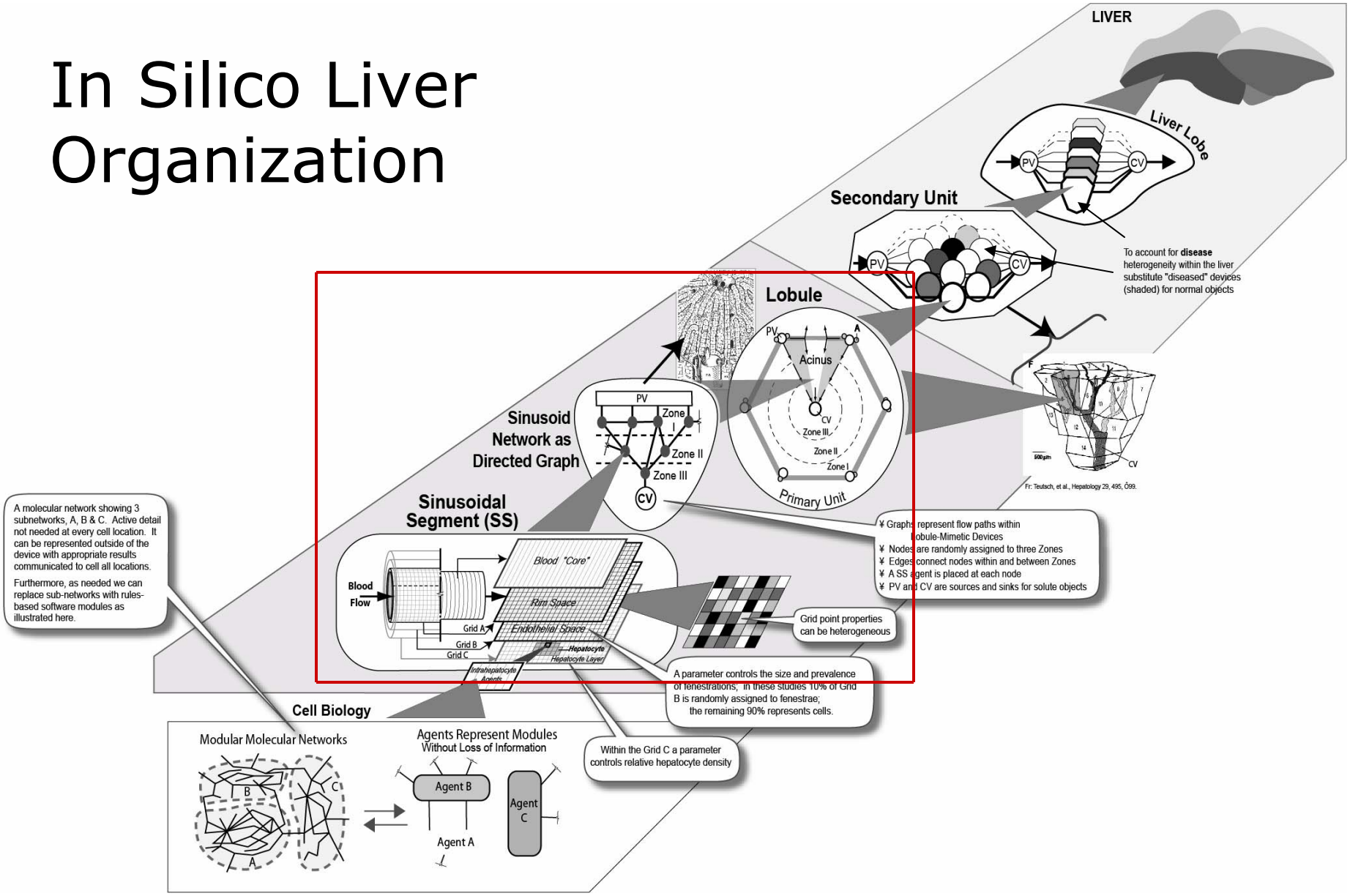
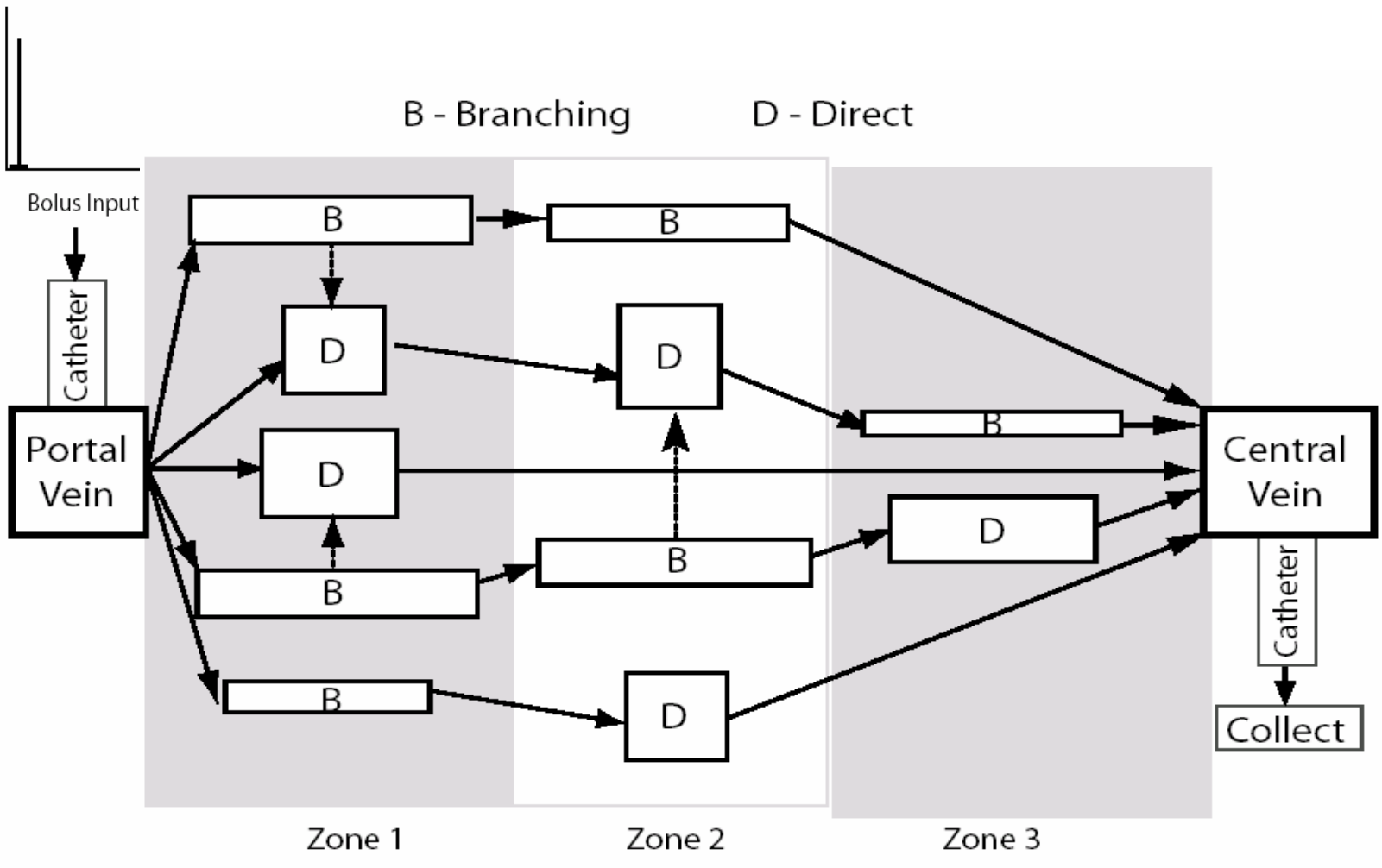
# I. Model Construction and Parameters

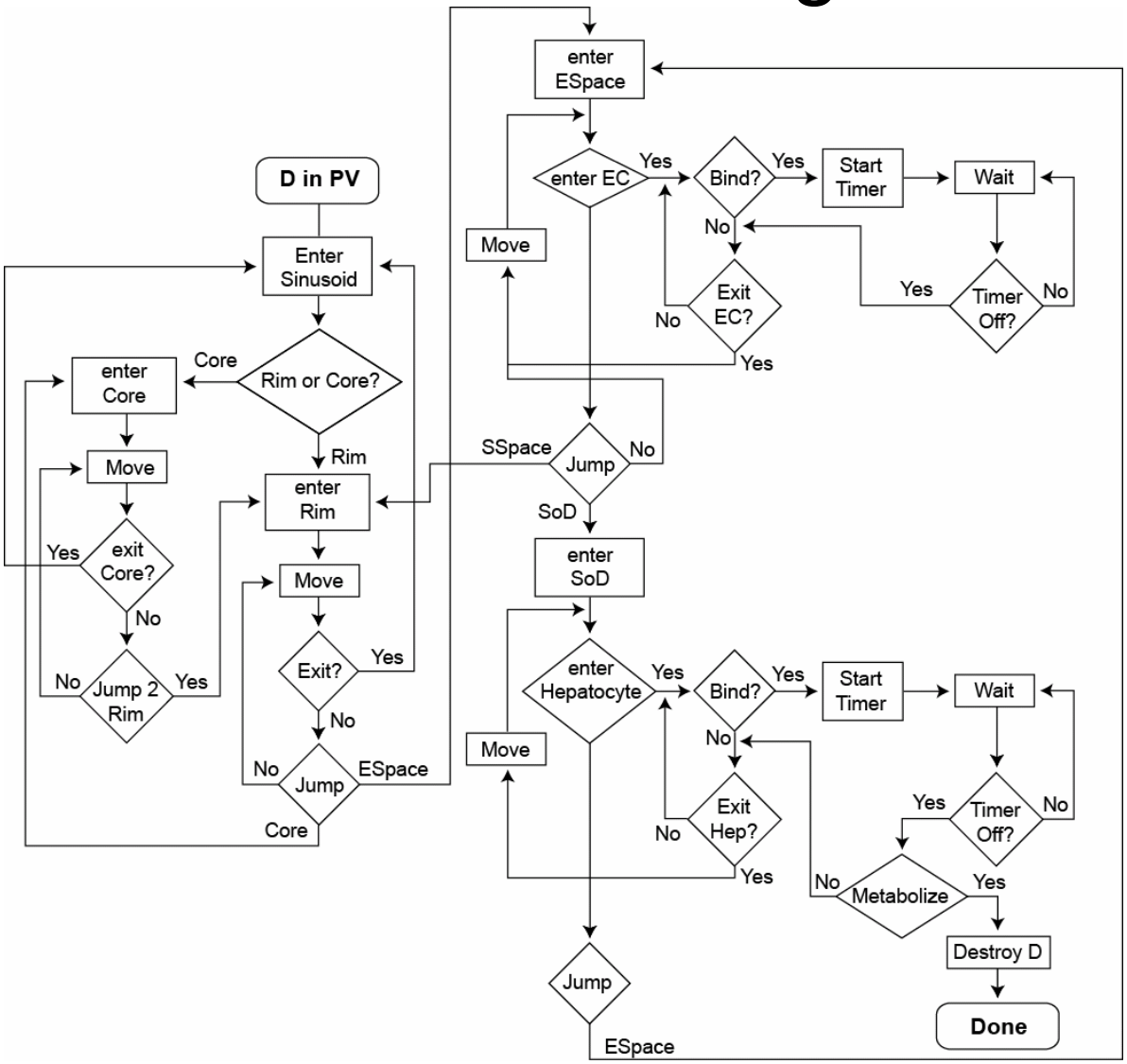
# In Silico Liver Organization



# Sinusoid Network



# Solute options within a sinusoidal segment




A solute object represents molecules moving through the model. In silico, solute behavior is dictated by rules specifying the relationships between *solute type*, *location*, and *proximity* to other objects and agents, as well as solute's *physicochemical properties*.

# Parameters

## Liver associated parameters

### Lobule Structure:

- Sinusoid Ratio (direct/branching)
- Sinusoid circumference
- Sinusoid length
- Density of endothelial wall
- Density of hepatocyte in the space of Disse

### Flow dynamic

- Turbo factor
- Core flow rate

## Drug-associated parameters:

- Space to space Jump probability
- Enzyme/transporter per cell
- - Probability of metabolization
- Solute binding probability
- Solute binding cycle

## Bolus Parameters:

- Bolus start time
- Dosage parameter A, B and C

Because the lag time due to the catheter effect, the bolus is not a pulse injection but a distribution similar to gamma distribution.

# Lobule Specification (Sinusoid network)

```
# number of nodes in each acinal zone
                45   21   3
# number of intra- and inter-zone edges
                22   21   0
                 0   10   3
                 0    0   0
```

- 22, 10, 0: intra-zone edges
- 21: inter-zone edges from zone I to zone II
- 0: inter-zone edges from zone I to zone III
- 3: inter-zone edges from zone II to zone III

# II. Result Analysis

# Hepatic Clearance ($CL_H$)

$CL_H$ is the volume of blood from which drug is removed completely by the liver per unit time. It is a function of *hepatic blood flow* ($Q_H$) and the *extraction efficiency* of the liver for the drug ($E_H$):

$$CL_H = Q_H \cdot E_H$$

"well-stirred" model: most popular hepatic drug clearance kinetic model

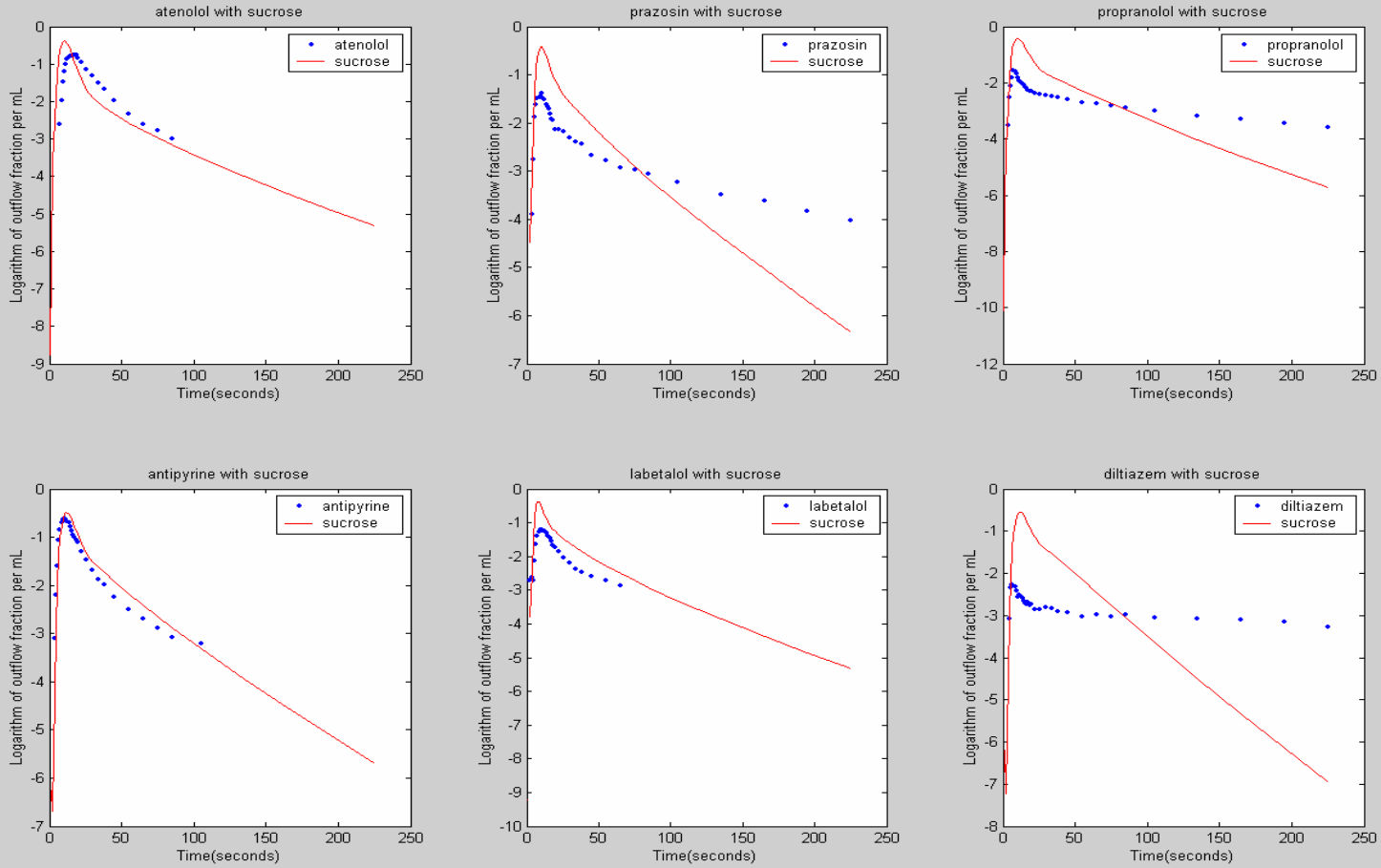
$$CL_H = Q_H \cdot \frac{f_{ub} \cdot CL_{u_{\text{int}}}}{Q_H + f_{ub} \cdot CL_{u_{\text{int}}}}$$

$f_{ub}$ : fraction of unbound drug in the blood

$CL_{u_{\text{int}}}$ : hepatic intrinsic clearance of unbound drug

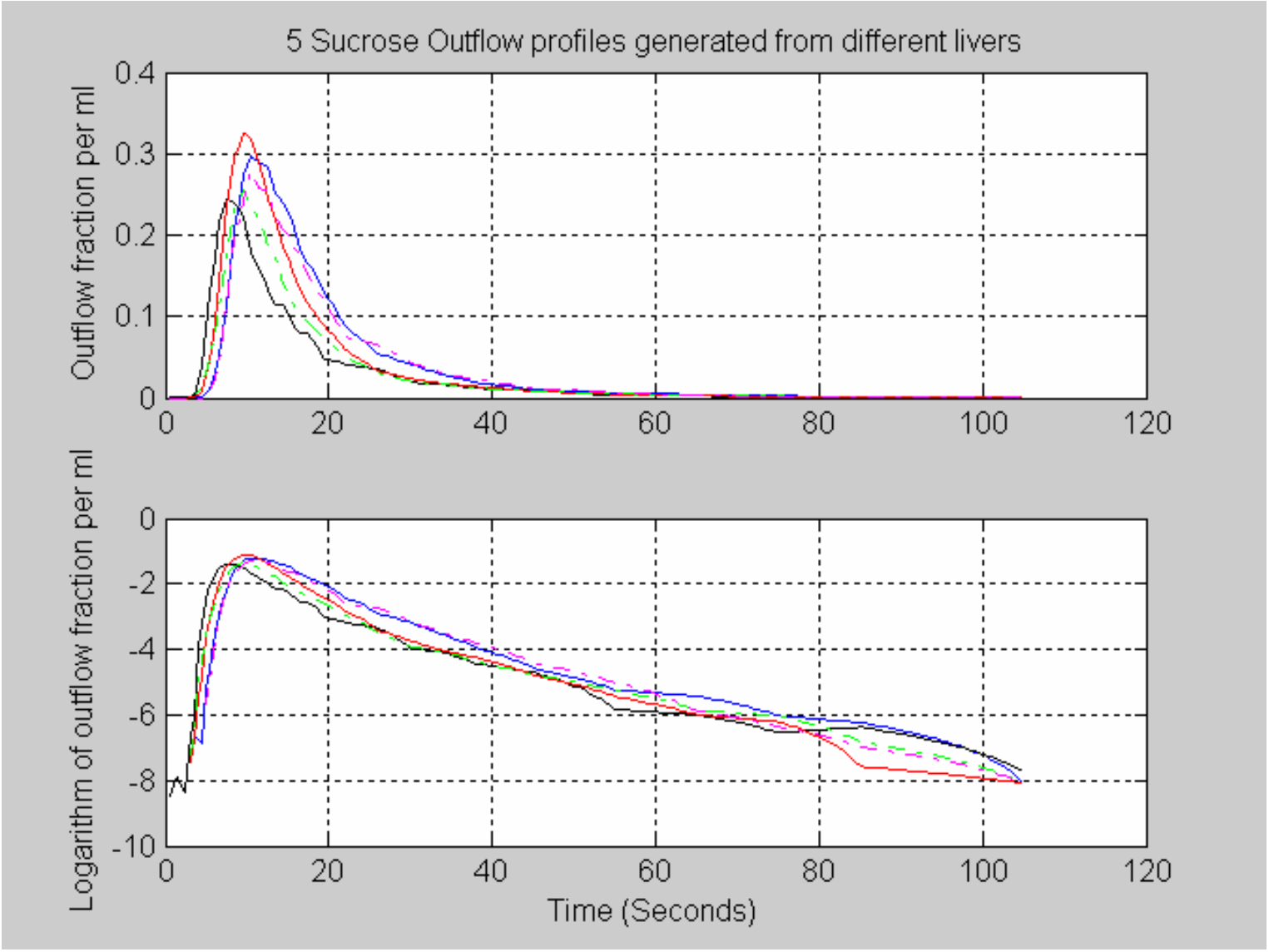
# Semi-log outflow profiles for 6 cationic drugs and sucrose

## ($CL_{u_{int}}$ increases with the increase of lipophilicity)




Hung, D *et al*, JPET297:780-789, 2001

# Liver Inter-individual Difference



# Parameters Contribute to Liver Inter-individual Difference

- *Direct sinusoid circumference:*

  Thicker direct sinusoid → $Q_H$ ↑→ higher peak high (lower $CL_H$)
- *Branching sinusoid length:*

  Short ones → $Q_H$ ↑→ higher peak high
- *Ratio of direct and branching sinusoid:*

  Higher percentage of direct sinusoid → $Q_H$ ↑→ higher peak high
- *Turbo factor:*

  Larger values → $Q_H$ ↑→ higher peak high
- *Core flow rate ($Q_H$):*

  Faster flow rate → $Q_H$ ↑→ higher peak high

All of those are liver-associated parameters

# Relationship between parameters and Hepatic clearance ($CL_H$)

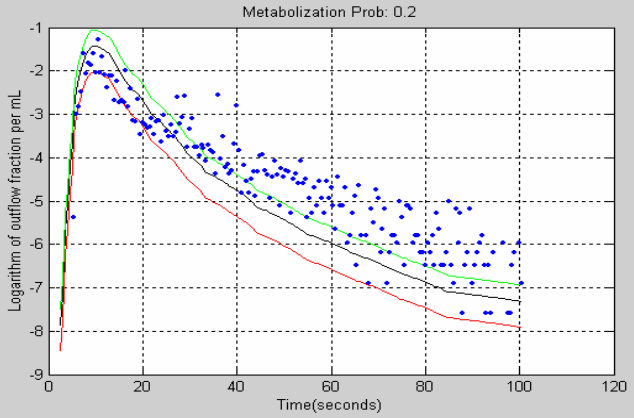
$CL_H$ increases with the increase of

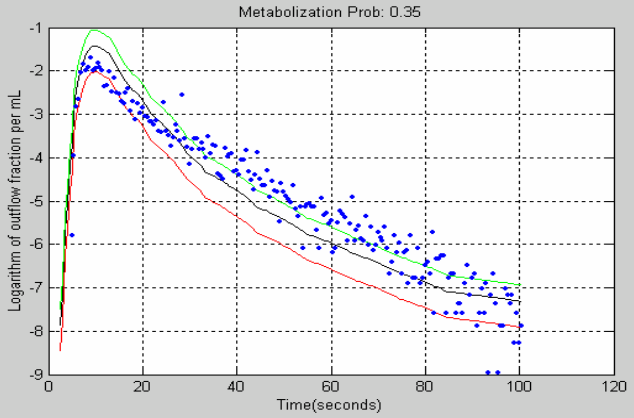
- Rate of metabolization ($CLu_{int}$)
- Net solute transported to space of Disse

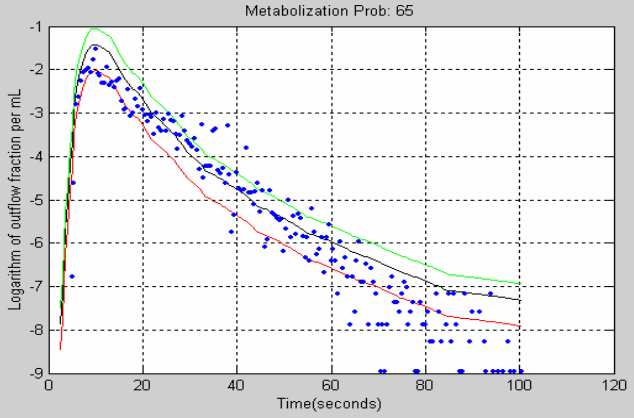
  ($f_{ub}$, $CLu_{int}$)
  - (Solute jumps from endothelial space to space of disse - Solute jumps back from space of disse to endothelial space)
  - Solute binding probability
  - Solute binding cycles (short cycle → more transported solutes)

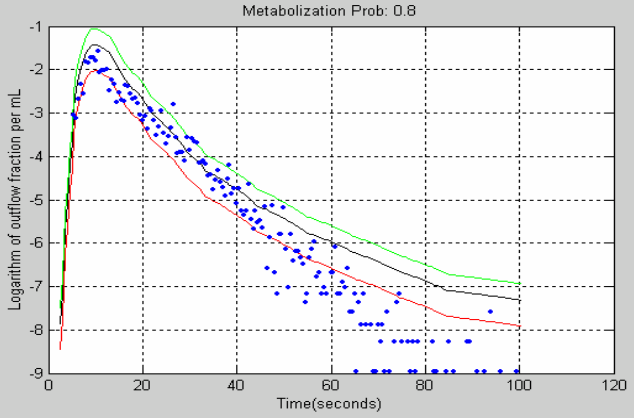
All of them are drug-associated parameters

# Rate of Metabolization

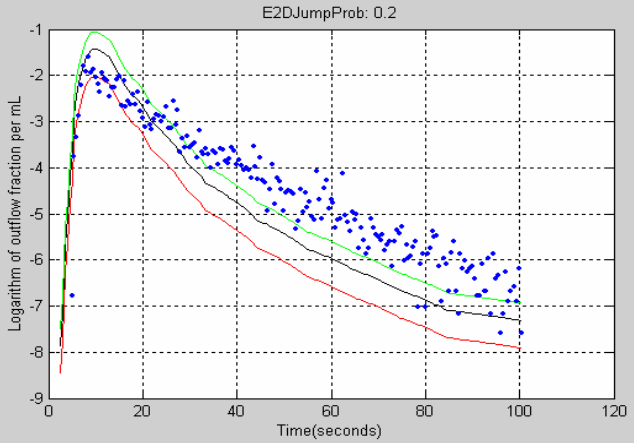


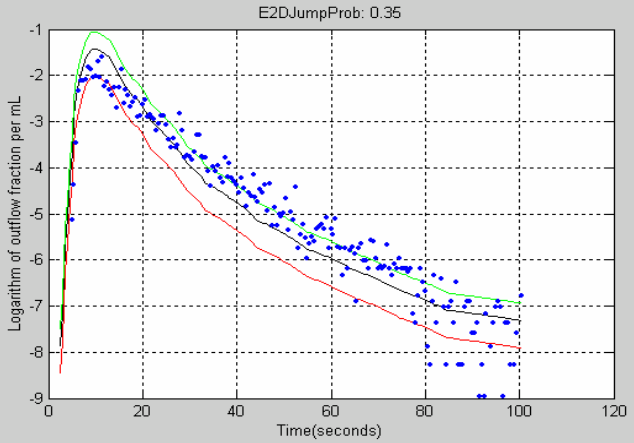



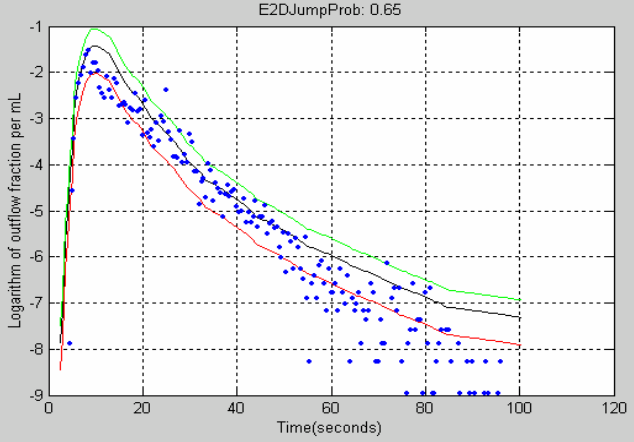



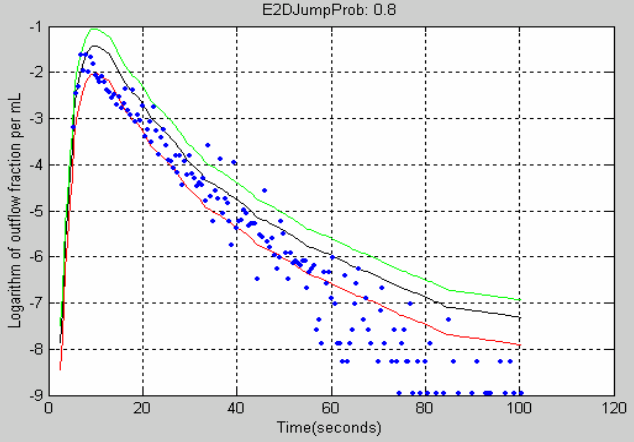



# Solute Jump Probability from Endothelial Space to Space of Disse

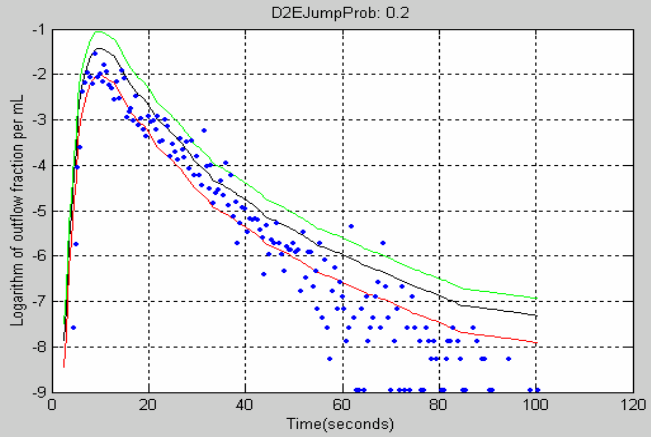


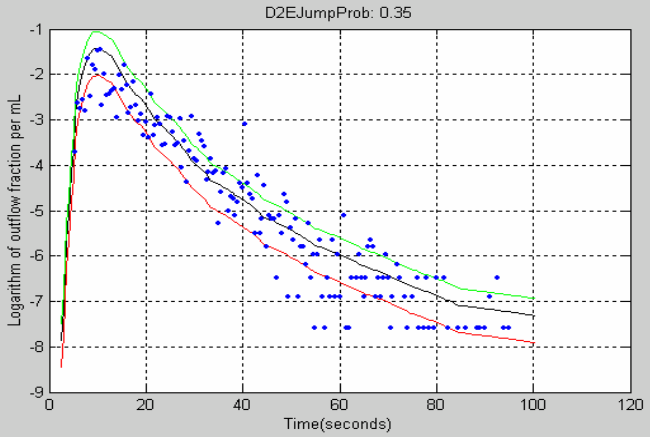



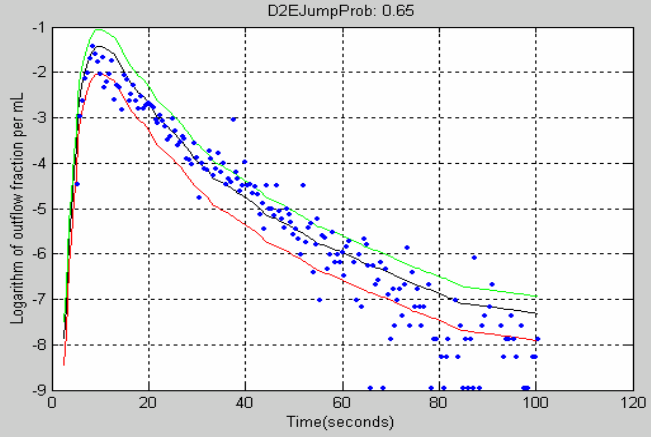



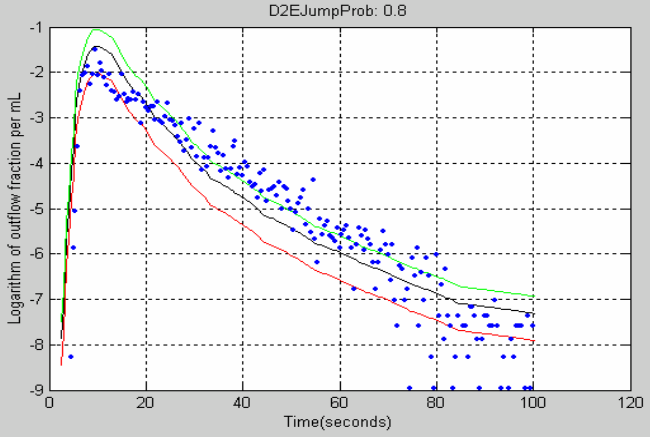



# Solute Jump Probability from Space of Disse to Endothelial Space

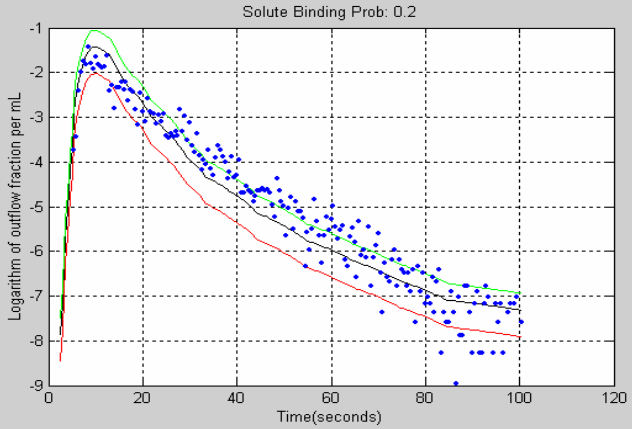


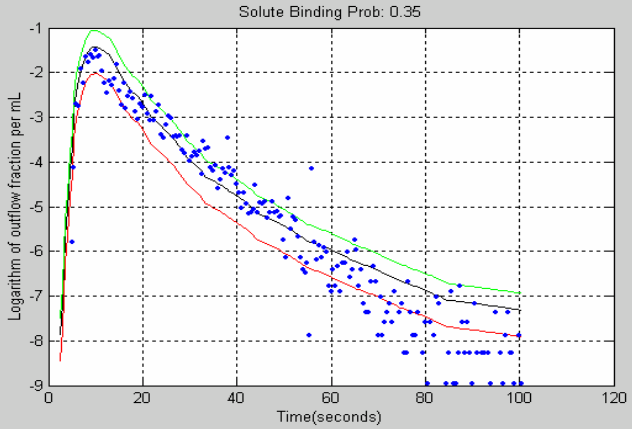



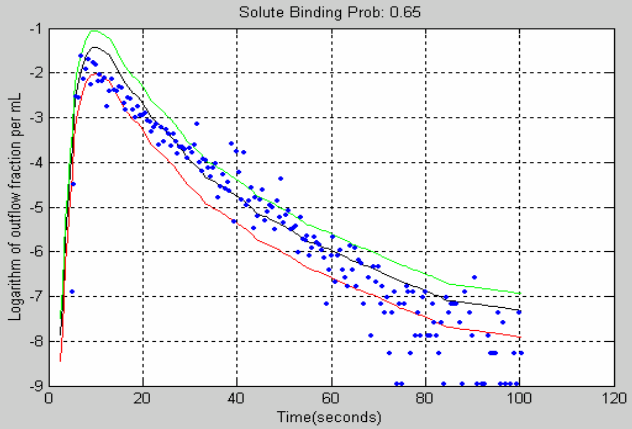



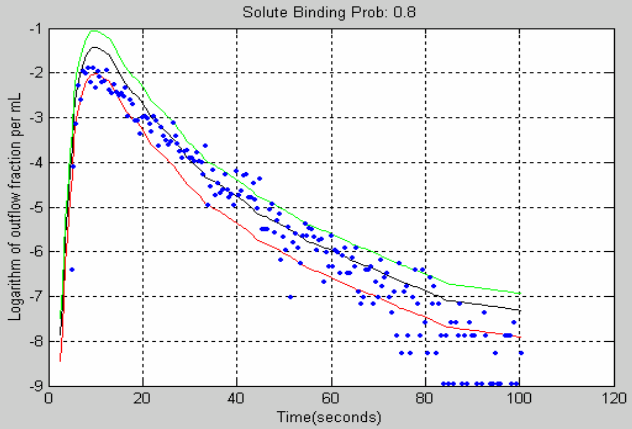



# Solute Binding Probability

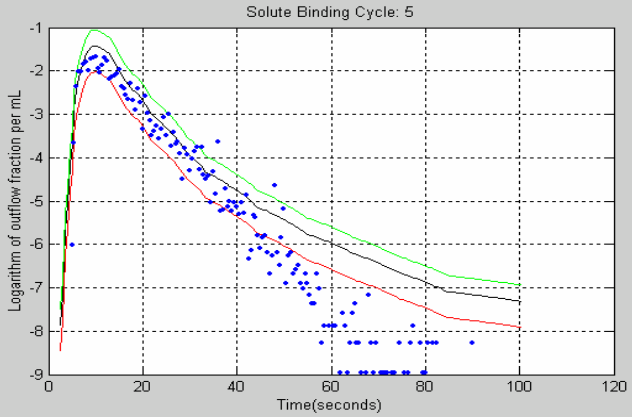


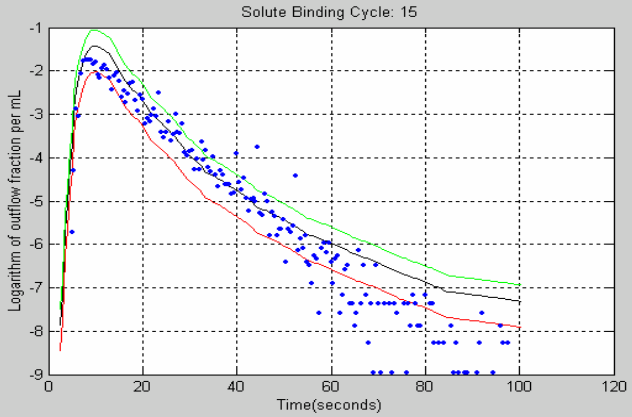



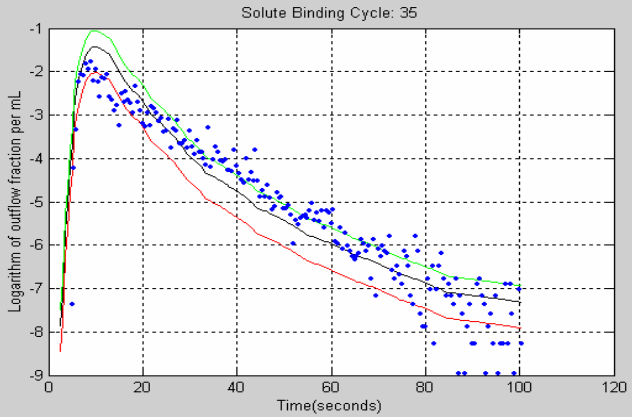



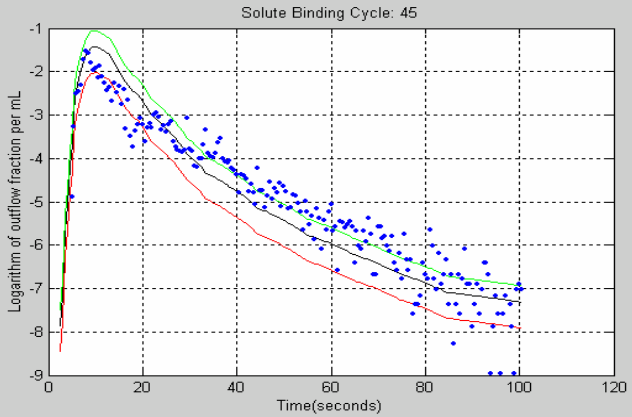



# Solute Binding Cycles

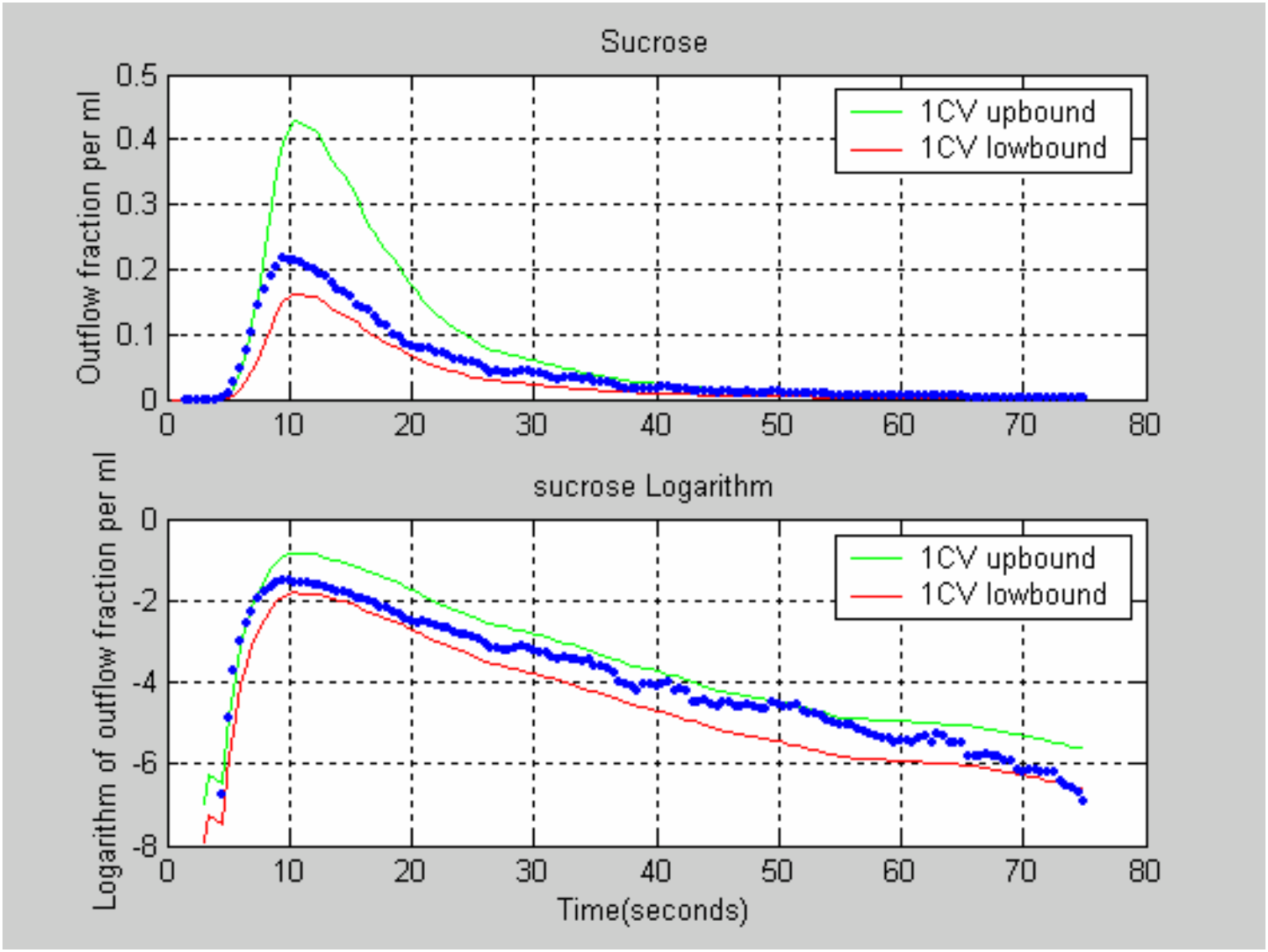


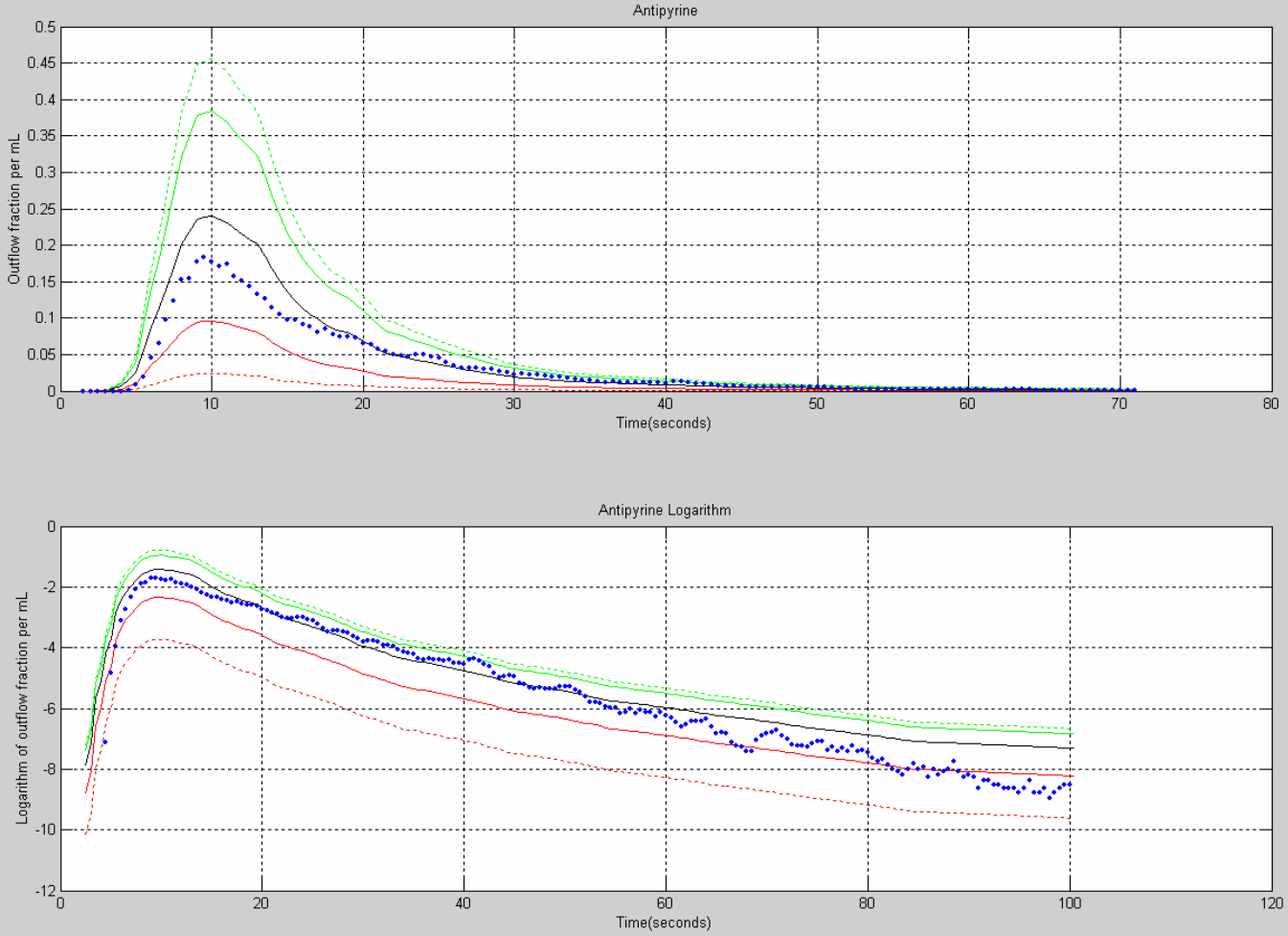



# Best matches -Sucrose



# Best matches -Antipyrine



# II. Improve model

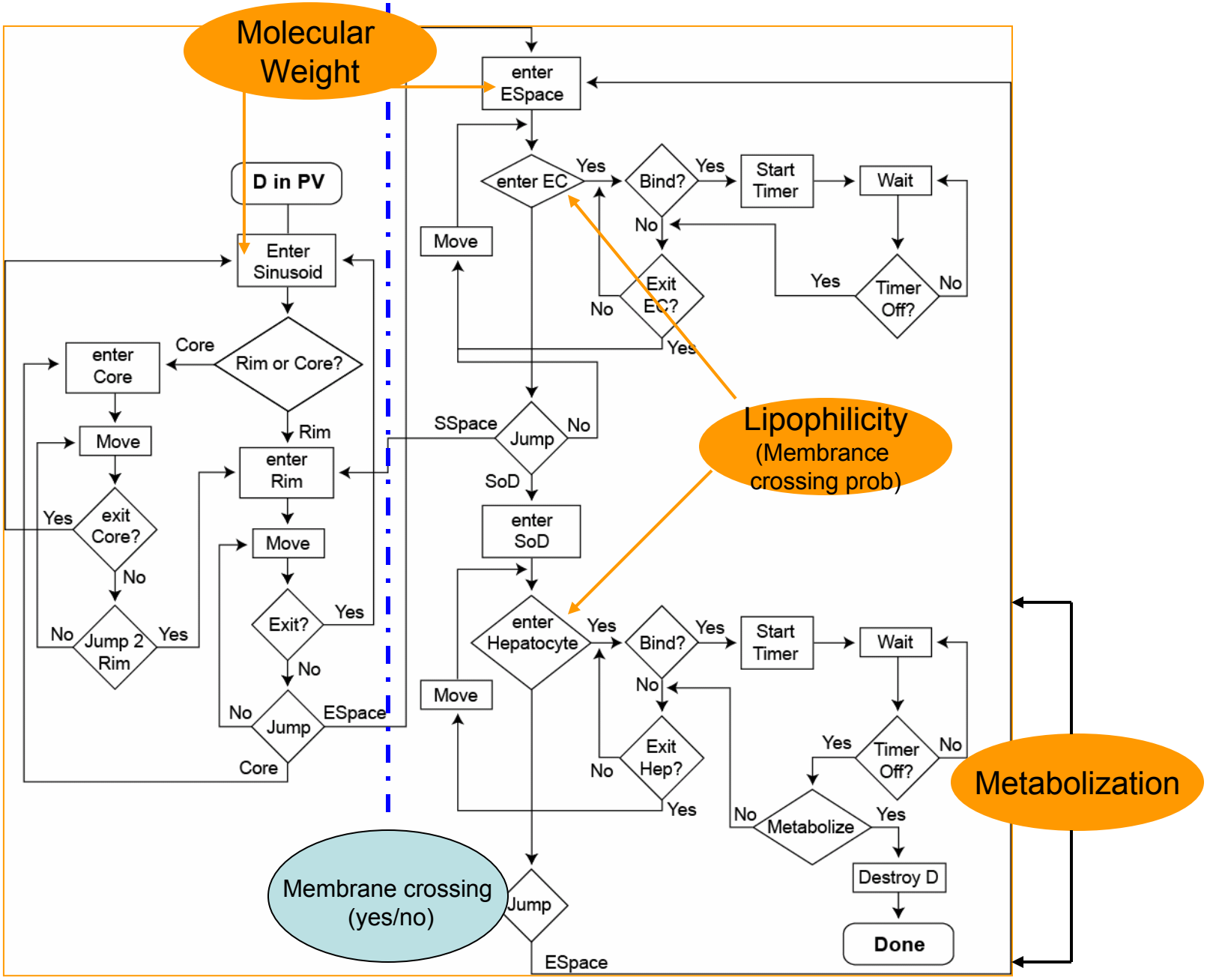
## 6 cationic drugs' physicochemical properties

| Derivative | Empirical Formular | Mol. Wt. | Log $P_{app}$[a] | $f_{uB}$[b] | p$K_a$[c] |
|---|---|---|---|---|---|
| Atenolol | $C_{14}H_{22}N_2O_3$ | 266.34 | 0.14 | 0.74 | 9.60 |
| Antipyrine | $C_{11}H_{12}N_2O$ | 188.22 | 0.33 | 0.60 | 1.45 |
| Prazosin | $C_{19}H_{21}N_5O_4$ | 383.41 | 1.88 | 0.54 | 6.50 |
| Labetalol | $C_{19}H_{24}N_2O_3$ | 328.41 | 2.69 | 0.52 | 7.40 |
| Propranolol | $C_{16}H_{21}NO_2$ | 259.34 | 3.10 | 0.45 | 9.45 |
| Diltiazem | $C_{22}H_{26}N_2O_4S$ | 414.52 | 3.53 | 0.28 | 7.70 |

Log $P_{app}$[a]: octanol/eater partition coefficient at pH 7.4

$f_{uB}$[b]: Unbound fraction in 2% BSA MOPA buffer (pH 7.4)

p$K_a$[c]: the negative logarithm of the ionisation constant.




Solute options within a sinusoidal segment

# Acknowledgement

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