Mathematically Simplifying PBPK Mixture Systems

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November 21, 2013

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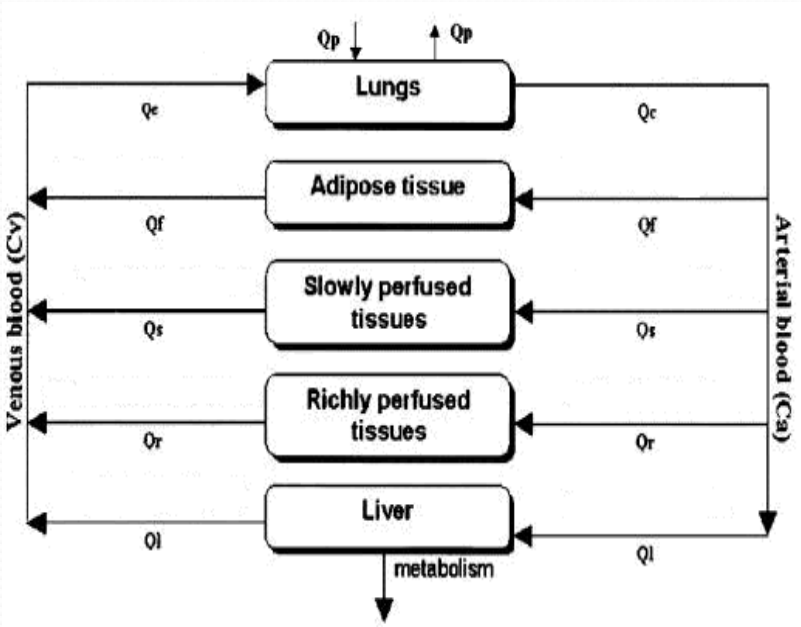
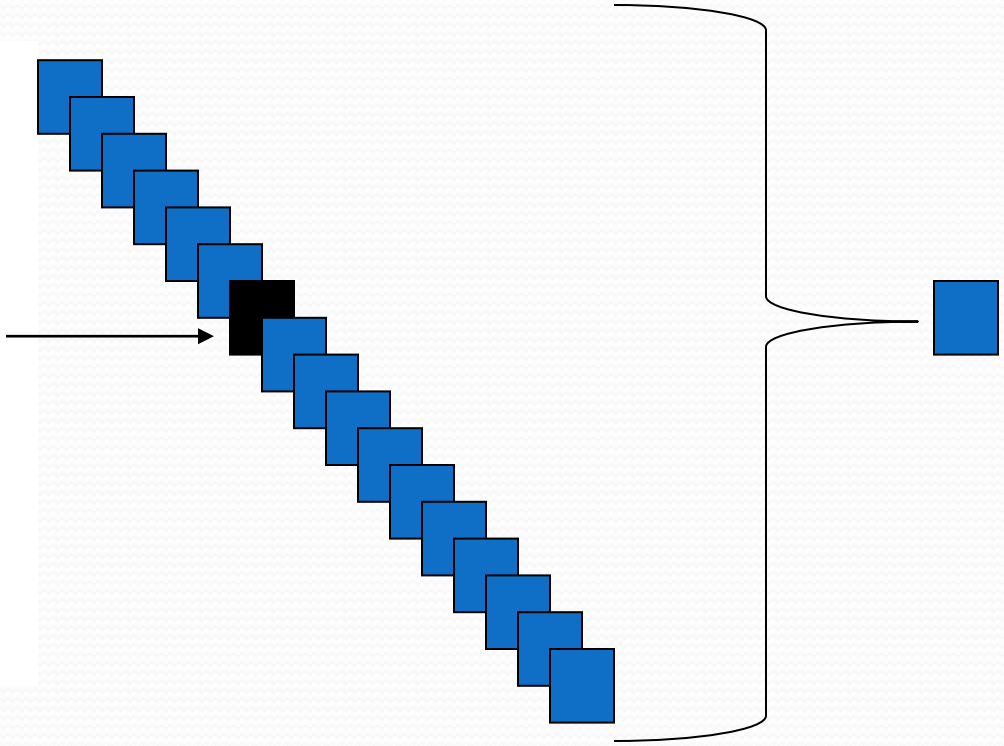
CSS Cumulative Risk 4.1.2

- **Product 2:** A computational method to utilize chemicals' similarities in kinetics and dynamic (response) determinants to optimize clustering and interactions of clusters of chemicals within complex mixtures.

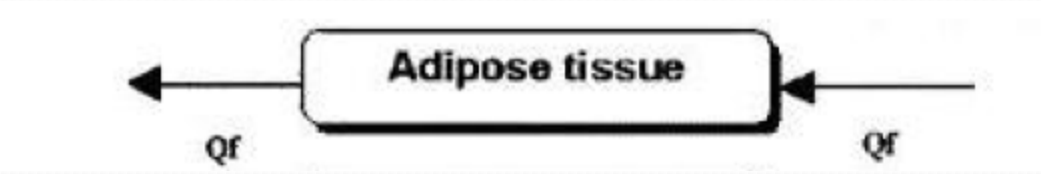




PBPK Beginnings

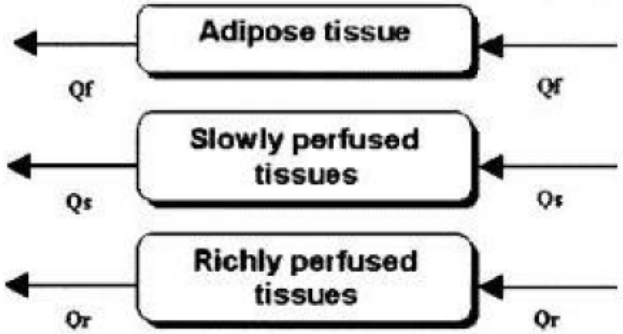
- Track the concentration of chemicals (variables) as the chemicals flow through organs (compartments)

- Ex. Fat Compartment



$$V_f \frac{dc_{f_i}}{dt} = Q_f \left(c_{a_i} - \frac{c_{f_i}}{P_{f_i}} \right) \ldots \text{Fat}$$

More compartments…



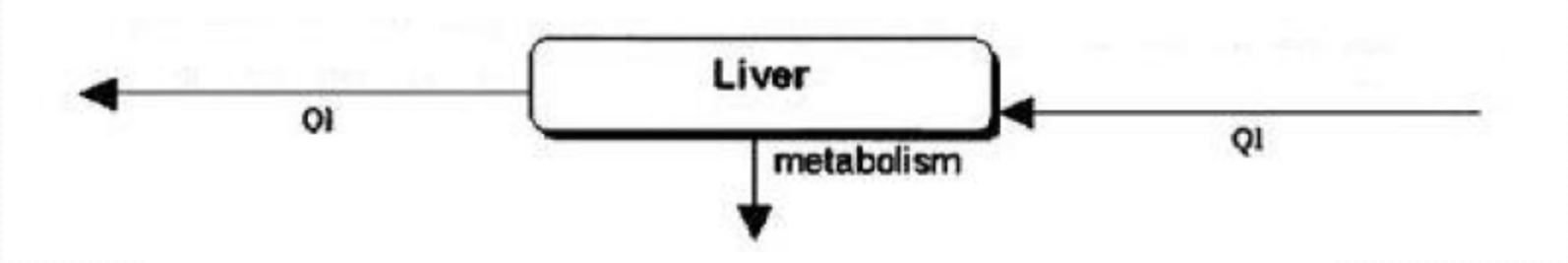
$$V_f \frac{dc_{f_i}}{dt} = Q_f \left(c_{a_i} - \frac{c_{f_i}}{P_{f_i}} \right) \text{...Fat} \quad (1)$$

$$V_r \frac{dc_{r_i}}{dt} = Q_r \left(c_{a_i} - \frac{c_{r_i}}{P_{r_i}} \right) \text{...Rapidly Perfused} \quad (2)$$

$$V_s \frac{dc_{s_i}}{dt} = Q_s \left(c_{a_i} - \frac{c_{s_i}}{P_{s_i}} \right) \text{...Slowly Perfused} \quad (3)$$

Metabolic Compartments

- In addition to flow in/out, a variety of metabolic terms are possible.



$$V_l \frac{dc_{l_i}}{dt} = Q_l \left(c_{a_i} - \frac{c_{l_i}}{P_{l_i}} \right) - \frac{V_{max_i} \frac{c_{l_i}}{P_{l_i}}}{K_{m_i} + \frac{c_{l_i}}{P_{l_i}}}$$

Interactions through Metabolism

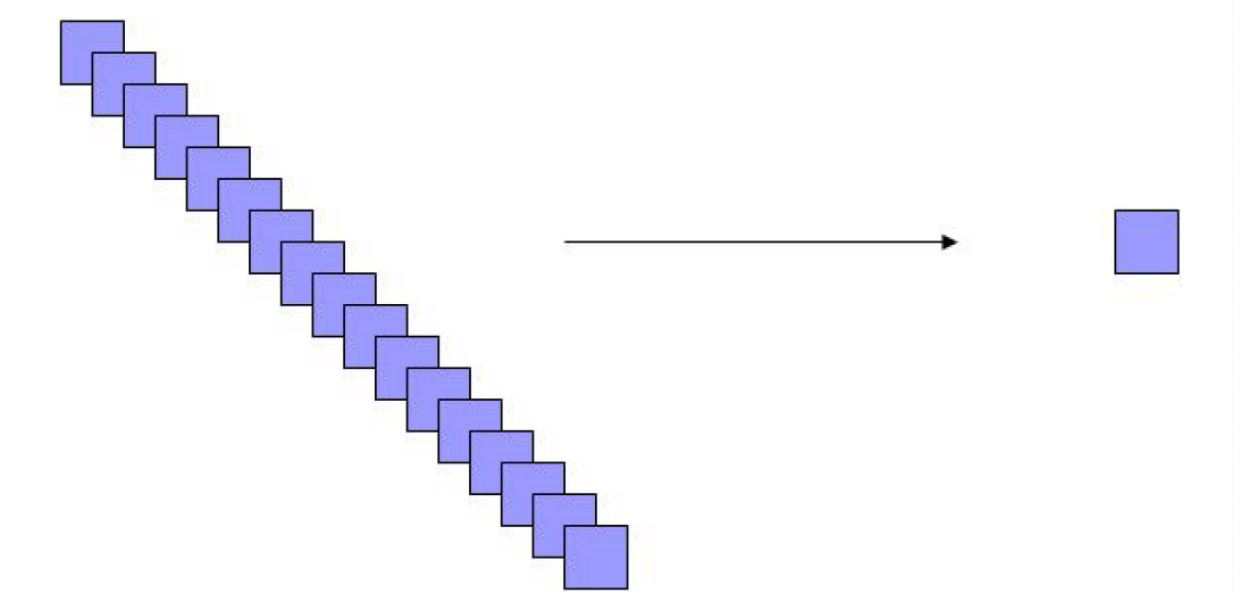
- Consider the example of competitive inhibition. Here, many chemicals have the opportunity to influence the metabolic consumption of chemical i.

$$V_l \frac{dc_{l_i}}{dt} = Q_l \left(c_{a_i} - \frac{c_l}{P} \right) - \frac{V_{max_i} \frac{c_{l_i}}{P_{l_i}}}{K_{m_i} \left(1 + \sum_{j=1, j \neq i}^{n} \frac{c_{l_j}}{P_{l_j} K_{m_j}} \right) + \frac{c_{l_i}}{P_{l_i}}}$$

Challenges with the structure of PBPK Mixture Models

- # of equations ≈ # of chemicals * # of compartments
  - Computational power
- Even more parameters may need to be specified
  - Memory storage is plentiful
- Strict experimental values for parameters in large mixtures are often unknown
  - QSAR
- Not all chemicals within a mixture may be of interest, however, for those which are interesting, all chemical interactions are of interest.
  - Lumping(?)

Lumping



Lumping reduces the number of variables in the PBPK mixture system by combining multiple chemical concentrations into a lumped concentration.

Mathematical Lumping

Consider the fat compartment. To build a lumped chemical (denoted *), sum of the concentrations of its constituents.

$$
\begin{aligned}
V_f \frac{dc_f^*}{dt} &= \sum_{i=1}^{m} V_f \frac{dc_{f_i}}{dt} \\
&= \sum_{i=1}^{m} Q_f \left(c_{a_i} - \frac{c_{f_i}}{P_{f_i}} \right) \\
&= Q_f c_a^* - \sum_{i=1}^{m} Q_f \frac{c_{f_i}}{P_{f_i}}
\end{aligned}
$$

The Simplification

In order to have an equation which is only in terms of the * chemicals, an approximation is made.

This is done through the introduction of a weighting factor.

$$w_{f_i} = \frac{c_{f_i}}{c_f^*}$$

The application of this factor gives the simplified equation:

$$\begin{aligned} V_f \frac{dc_f^*}{dt} &= Q_f c_a^* - \sum_{i=1}^{m} Q_f \frac{c_{f_i}}{P_{f_i}} \\ &= Q_f \left(c_a^* - c_f^* \sum_{i=1}^{m} \frac{w_{f_i}}{P_{f_i}} \right) \end{aligned}$$

The Approximation

Weights, by definition, should vary in time. However, we choose to approximate them as constant.

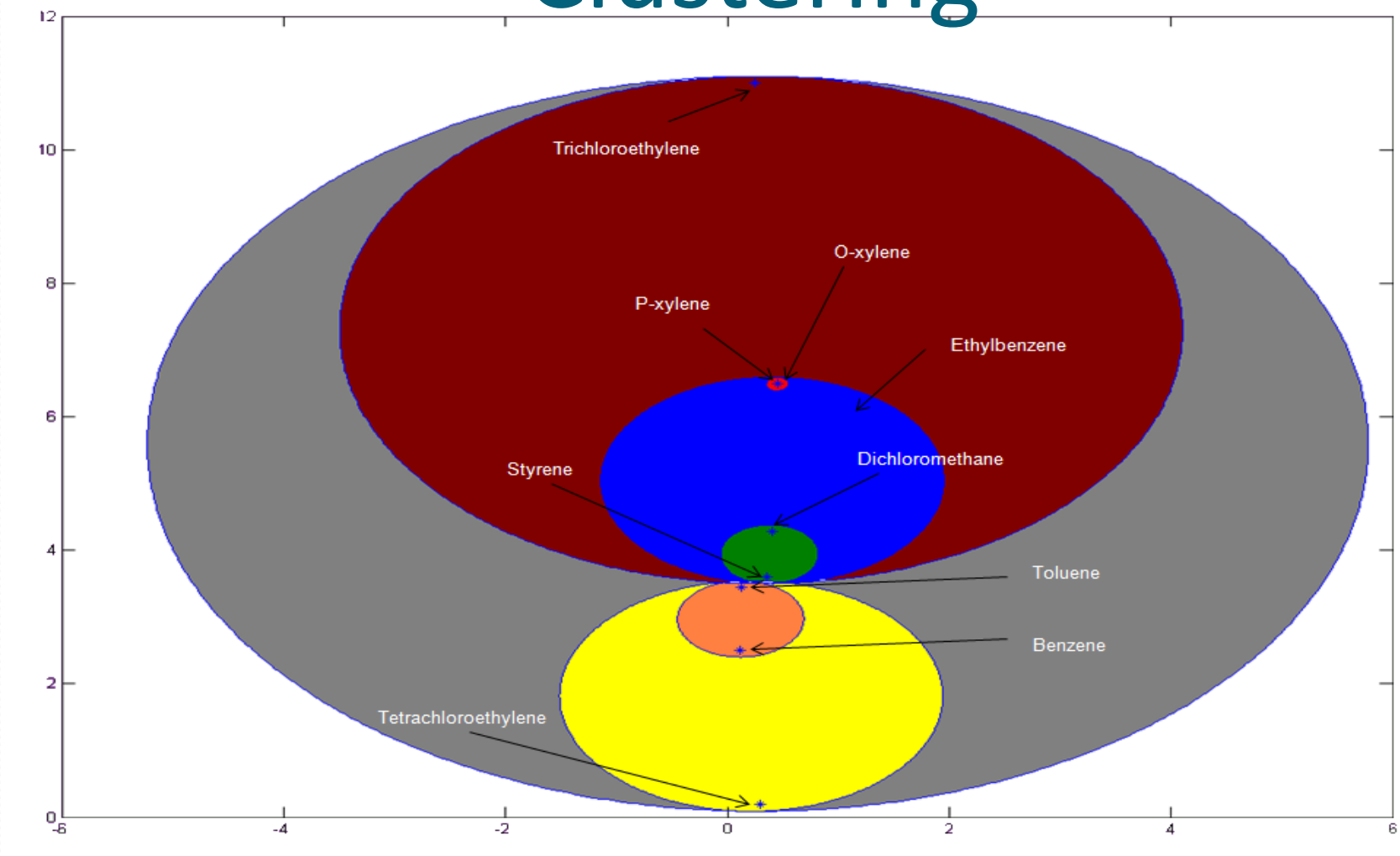
- How should their values be defined?
  - Lumping literature would suggest an evenly balanced choice (w=1/n for an n chemical lump). This is a reasonable default.
  - Additional system knowledge may refine the choice. Ex. If the system has a known (or knowable) steady state.

Biologically-base Lumping Methodology (BBLM)

Goals:

- Generate a PBPK system of criteria chemicals (those which you care about individually) and lumped chemicals (those which you do not care about individually) which replicates the behavior of the full model
- Construct/cluster lumps based on parameter (biologically-based) knowledge

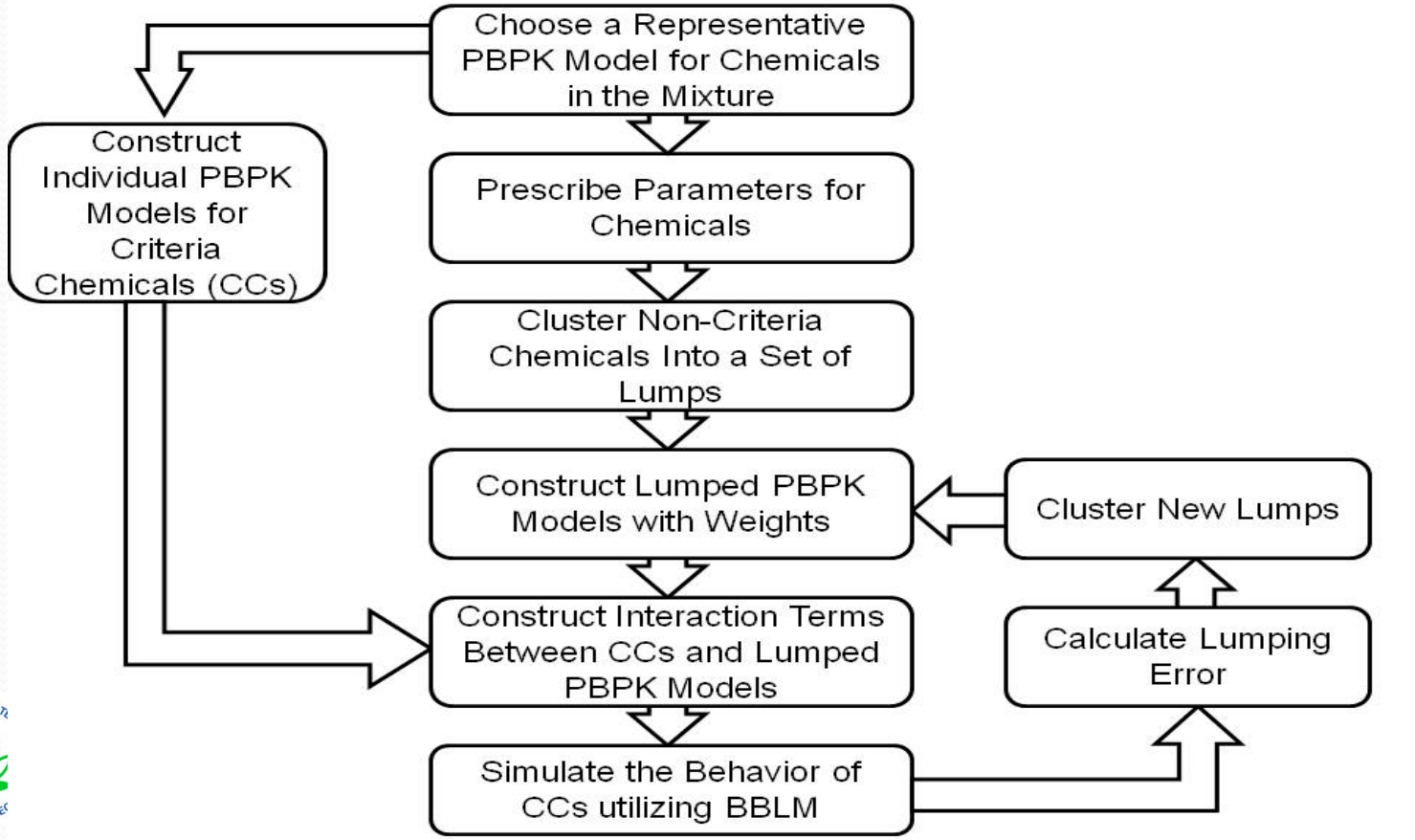
Clustering



10 VOC mixture simulation from [Haddad et al., 2000]

Biologically-based lumping methodology (BBLM)

Computational estimation of errors generated by lumping of physiologically-based pharmacokinetic (PBPK) interaction models of inhaled complex chemical mixtures. Inhalation Toxicology, 2012, 24(1):36-46.



How well does BBLM work?

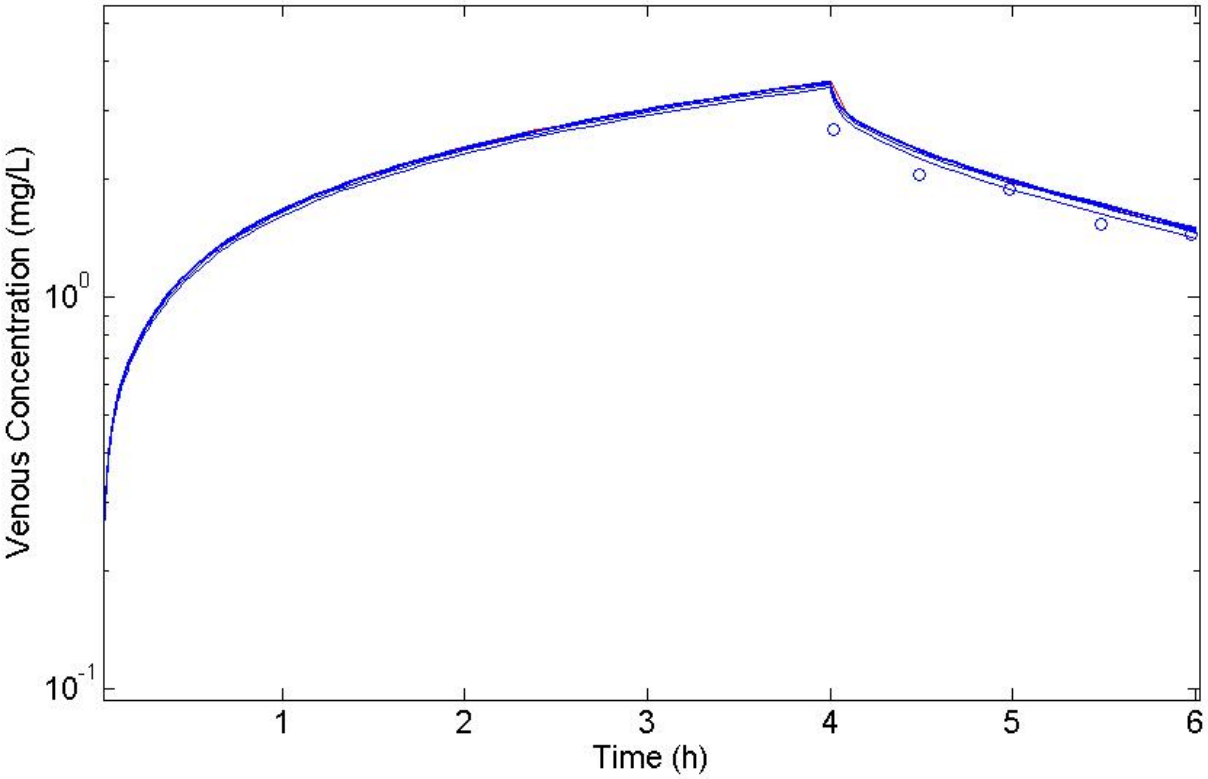
Case I:

- 10 VOC's whose binary interactions have been classified by Haddad (and others)
- 1 criteria chemical examined (m-xylene)

Case II:

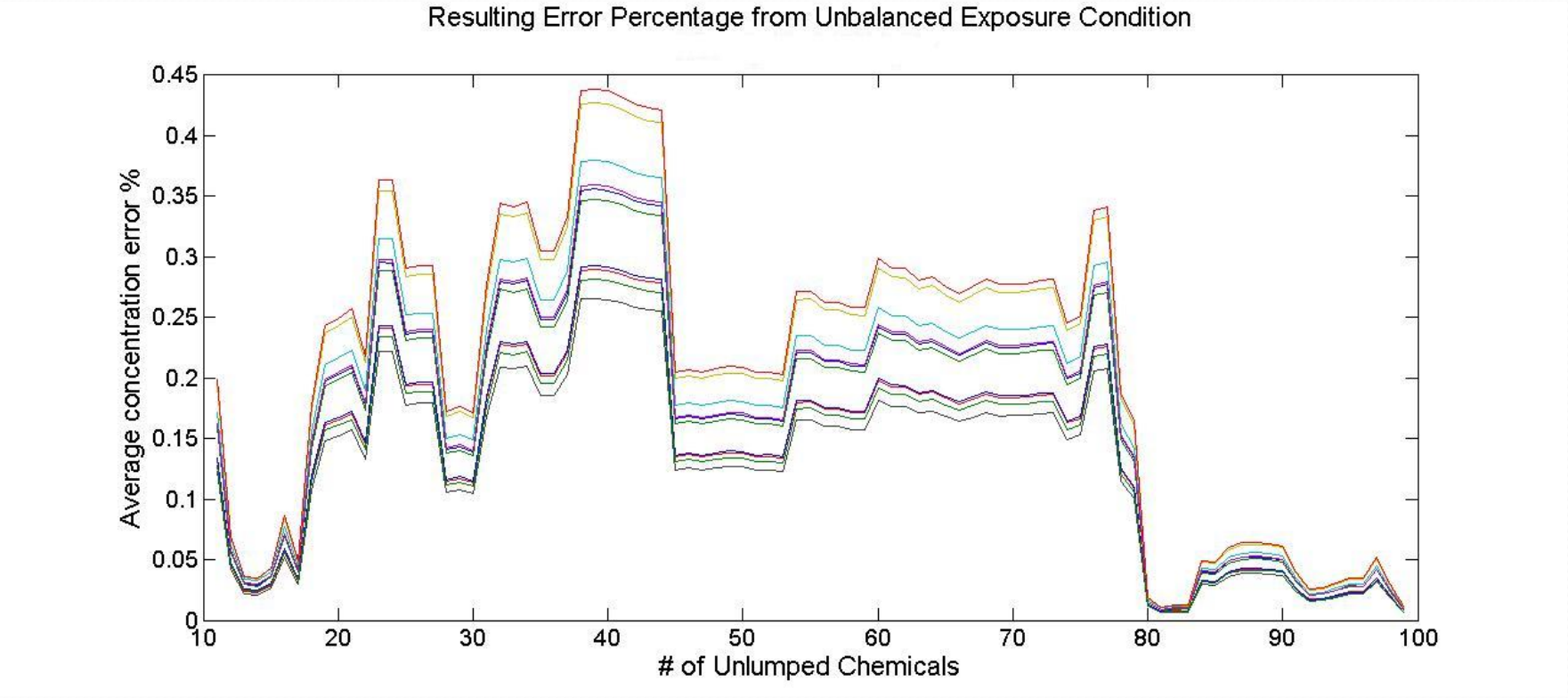
- 100 chemical mixture whose parameters are physiologically bounded by randomly generated
- 10 criteria chemicals examined simultaneously

Case I



This figure plots the venous concentration of m-xylene of the lumped simulations using BBLM (blue lines), the full PBPK simulation with Michaelis-Menten/competitive inhibition (red line, superimposed by blue lines), and experimental data (circles) against time. The experimental data are taken from (Haddad et al., 2000). The lumped simulations using BBLM are superimposed on full PBPK simulations using individual chemicals.

Case II


Resulting Error Percentage from Unbalanced Exposure Condition
Average concentration error %
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
10
20
30
40
50
60
70
80
90
100
# of Unlumped Chemicals

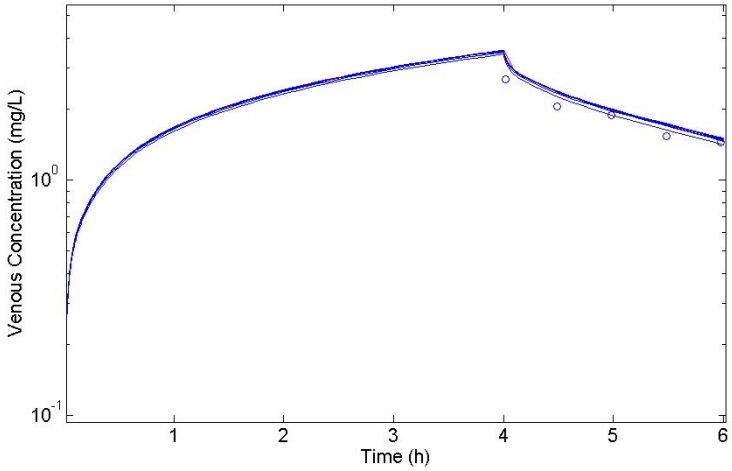
BBLM Summary

Use of BBLM to investigate the toxicological behavior of a complex mixture

- Demonstration for inhalation using 10 VOC mixture simulation
- Lumped simulations approximated both full PBPK simulation and experimental data for venous concentration
- Suggests lumping is plausible for highly complex mixtures (>> 10 components)

Developed with complex biofuel mixtures in mind (ACE), but much wider application potential.

I



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Future Work: Mixture Factor

Goal:

- Generate a PBPK mixture system which replicates the behavior of the full system, but whose variables are only the criteria chemicals. (forget about the equations for the lumps/chemicals that are not of interest)

The example of competitive inhibition will again be used. (also, consider constant exposure)

$$M(t) = \frac{V_{m_i} \frac{C_{l_i}}{P_{l_i}}}{K_{m_i}\left(1 + \sum_{j=1, i \neq j}^{n} \frac{C_{l_j}}{P_{l_j}}\right) + \frac{C_{l_i}}{P_{l_i}}}$$

Observation

Under constant exposure, the chemicals in the mixture are expected to exhibit the following mathematical properties:

- Initially zero in all compartments
- Monotonically increasing in concentration
- Approaching a steady state

Observe that when two functions of this type are summed, these characteristics are conserved.

The approximation

Based on the previous observation, consider this approximation:

$$\sum_{j=1, j\neq i}^{n} \frac{c_{l_j}}{P_{l_j}} \approx A c_{l_i}$$

Given this, the metabolic term for the ith chemical takes the form:

$$M(t) \approx \frac{V_{m_i} \frac{c_{l_i}}{P_{l_i}}}{K_{m_i}\left(1 + A c_{l_i}\right) + \frac{c_{l_i}}{P_{l_i}}}$$

(but does it work?...tbd)

Acknowledgements

Jane Ellen Simmons (Task Lead)
Kent Thomas (Project Lead)
Rory Conolly
John Wambaugh
Marina Evans
Hisham El-Masri
Sheppard Martin
Biofuels Team