A Second Course on Exposure Modeling:
Exposure Biology and Exposure Reconstruction Methods
Using the MENTOR and DORIAN Systems

PART II

Panos G. Georgopoulous

Computational Chemodynamics Laboratory

Environmental and Occupational Health Sciences Institute (EOHSI) - Exposure Science Division
EOHSI is an institute of Rutgers University

Rutgers University
There is a critical need for "multicontaminant" analyses ("cumulative exposures") : these require mechanistic consistency which is not offered in "traditional" PBTK models.

Existing PBTK models for metals have different mechanistic structures due to differences in dominant transport processes. The "multi-component" nature of exposures to metals and their compounds, and the presence of potentially significant metal-metal interactions, highlight the need for simultaneous and consistent toxicokinetic modeling of these chemicals.
MENTOR-3P combined with DORIAN/ SPARTA provides a unique multicontaminant modular “whole body” platform for consistent characterization of toxicokinetic and toxicodynamic processes in individuals and populations; it provides links with physiology databases to account for intra- and interindividual variation and variability.

Modules of different levels of complexity for specific organs/tissues and alternative formulations for different types of contaminants are available in the MENTOR system.
Individual and population human biology (physiology and biochemistry) is interlinked with exposure and changes non-uniformly with development, aging, disease, drug treatment, diet, environmental exposures, etc.

Weights of water, fat, protein, and other components as a function of age, from birth to one year of age. [Figure reproduced from Fomon (1966) with permission from W.B. Saunders Co.]

Hepatic cytochrome CYP1A2 and CYP2E1 in children of various age groups as a percentage of adult weights (from Cresteil, 1998).

MENTOR-3P offers a “whole organism” modular platform for incorporating computational “virtual organs”

- Data from Jaques & Kim (2000) and Daigle, et al. (2003) studies at rest and during moderate exercise
- Experimental data compared to model predictions using MPPD2, ICRP, and (HUMTRN-derived) module of MENTOR-3P; experimental conditions used as model inputs

- Incorporation of “virtual organs” (under development in the DORIAN library) in MENTOR-3P supports the evolution from Physiologically Based Pharmacokinetic models to integrative Physiologically Based Pharmacokinetic/Pharmacodynamic models

---

**Graph:**
- Particle Number Deposition Fraction at Rest
- Particle Size (nm)

---

**Graph:**
- Particle Number Deposition Fraction during moderate exercise
- Particle Size (nm)
Example demonstrations of the “Generalized” Mixture PBPKM of MENTOR-3P:
(a) simultaneous exposure to multiple metals
(b) exposure of pregnant female and fetus to MeHg

Simulated concentration profile of chemicals and metabolites in the liver of a standard reference male ingesting a mixture of metals.

Simulated concentration profile of methylmercury for a pregnant woman and fetus. The physiological parameters of both the maternal and fetal systems are changing over time.
Example: Spatial variability of factors affecting metabolism in the liver

Mixing: different liver models

- Well Stirred (CSTR)
- CSTRs in series
- Plug flow (PFR)
- Dispersion flow

Variation in metabolic activity

- Variability in a large number of micro-compartments (acinar structure) approximated by discrete macro-compartments
- This variability can also be represented using probability distributions
Variation of CYP induction across liver sub-compartments

Results from a distribution-based formulation

Currently available liver modules within MENTOR-3P can account efficiently for biochemical heterogeneity through the use of either subcompartment or distribution-based approaches.

Discrete versus distribution-based representation of spatial variation

Variation of CYP induction across liver sub-compartments

Results from a distribution-based model formulation
MENTOR-4M provides a unified multimedia/multiscale/multipathway modeling approach to support aggregate/cumulative exposure assessments.
Geographical and Spatiotemporal Information Systems (GIS/STIS) link geodatabases of contamination and receptor attributes;

Multimedia environmental modules link processes at the regional, field, meso, pore, and molecular scales

Constitutive equations are generally available to “translate” physicochemical attributes at one scale to fate/transport properties of the scale “above”

(Source of figure materials: ESRI and PNNL)
The Bayesian approach offers a powerful framework for the analysis of “uncertain” environmental and biological information in conjunction with process (“mechanistic”) models and optimization algorithms. Assimilates prior information and information contained in data:

- prior information on parameters are specified by probability distribution functions
- Convenient for mechanistic, biological and environmental process models
- However – it presents serious challenges for the non-expert

Parameters characterized by probability pdfs:

- in contrast to classical parameter estimation, no single “true” value

“in this new century ... a significant part of the everyday practice of Statistics ... will consist of applying Bayes' formula via MCMC ...”

Markov Chain convergence (left) and probability density (right) of chlorpyrifos dose and metabolic parameters.

The red bar indicates the “burn-in”; the black lines indicate a span of samples; the green bars indicate accepted samples after convergence.
MENTOR-DOT in conjunction with MENTOR-1A/4M/3P provide a general framework for systematic exposure reconstruction from biomarker data.

Tools for Sensitivity and Uncertainty Analysis (MENTOR-DOT)

Environmental & Microenvironmental Models (MENTOR-4M & 1A)

Mechanistic Models for Forward Modeling (PBTK and BBDR Models of MENTOR-3P & DORIAN)

Auxiliary Databases
- Environmental Concentrations
- Intake Rates
- Demographics/Housing
- Population Genetic Variability (from USEPA, USGS, CDC, etc.)

Biological Data
- Tissue Concentrations
- Metabolite Levels
- Proteomic Biomarkers

Numerical Optimization and Inversion Techniques

Estimates of Doses, Exposures, and Environmental Concentrations
Contribution of prior exposures to observed biomarker levels as a function of biochemical properties: Case of idealized linear single-compartment biokinetics

- Pyrethroids (6-12 h)
- Organophosphates/BTEX (~1 d)
- As (2-3 d)
- MeHg (2-3 mo)
- Cd (2-3 mo in blood; 10-40 y in body)
Contribution of prior exposures to observed biomarker levels as a function of intake frequency, sampling time, and biochemical properties: Case of idealized linear single-compartment biokinetics

The rows represent the time period of exposure (e.g. every 12 h, every 2 days, etc), the columns represent the time of sampling after the last exposure. For cases when sampling time is unknown, the mean values of the contributions are shown, assuming a uniformly random sampling time.
“Brute-force” approach for exposure reconstruction from inversion of biomarker data
## Examples of available population biomarker databases

<table>
<thead>
<tr>
<th>Program/Study</th>
<th>OP</th>
<th>VOCs</th>
<th>Metals</th>
<th>Location; Number of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAMACOS (1999-2000)</td>
<td>bd</td>
<td>bd</td>
<td></td>
<td>CA; 600 pregnant women</td>
</tr>
<tr>
<td>[Castorina et al., 2003]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTEPP (2000-01)</td>
<td>ac</td>
<td></td>
<td></td>
<td>NC, OH; 257 children (1.5-5 yrs)</td>
</tr>
<tr>
<td>[Wilson et al., 2004]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MNC-PES (1997)</td>
<td>ac</td>
<td>ac</td>
<td>ac</td>
<td>MN; 102 children (3-12 yrs)</td>
</tr>
<tr>
<td>[Quackenboss et al., 2000]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHANES-III (1988-94)</td>
<td>c</td>
<td>c</td>
<td>c</td>
<td>US; 1000 adults (20-59 yrs)</td>
</tr>
<tr>
<td>[Hill et al., 1995]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHANES (1999-2000)</td>
<td>cd</td>
<td>cd</td>
<td>bc</td>
<td>US; 9,282 subjects (all ages)</td>
</tr>
<tr>
<td>[CDC, 2005b] (*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHANES 2001-02</td>
<td>cd</td>
<td>cd</td>
<td></td>
<td>US; 10,477 subjects (all ages)</td>
</tr>
<tr>
<td>[CDC, 2005b] (*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHANES 2003-04 (*)</td>
<td>cd</td>
<td>cd</td>
<td>c</td>
<td>US; 9,643 subjects (all ages)</td>
</tr>
<tr>
<td>NHEXAS-AZ (1995-97)</td>
<td>ac</td>
<td>ac</td>
<td>ac</td>
<td>AZ; 179 subjects (all ages)</td>
</tr>
<tr>
<td>[Robertson et al., 1999]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHEXAS-MD (1995-96)</td>
<td>ac</td>
<td></td>
<td>ac</td>
<td>MD; 80 subjects (above 10 yrs)</td>
</tr>
<tr>
<td>NHEXAS-V (1995-97)</td>
<td></td>
<td>ac</td>
<td>ac</td>
<td>EPA Region V; 251 subj. (all ages)</td>
</tr>
<tr>
<td>[Whitmore et al., 1999]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key: a: Measurements of multimedia concentrations (indoor, outdoor, and personal air; drinking water; duplicate diet; dust; and soil). b: Partial measurements of environmental concentrations (e.g. outdoor air concentrations; pesticide use; etc.). c: Specific metabolites. d: Non-specific metabolites. OP: Organophosphates
Inversion approaches used for CPF exposure reconstruction

Preliminary evaluation included three techniques for inversion:

- **Steady-state** assumption (Rigas et al., 2001; Mage et al., 2004)

- **Deconvolution** of marginal densities from **linear forward model** (Tan et al., 2006)
  - Estimation of the probability distribution function of the biomarker resulting from a “unit dose,” and development of a distribution for dose/biomarker “exposure conversion factor” (ECF)
  - Use of the conversion factor to convert biomarker data into distributions of potential doses

- **Simplified Bayesian approach for posterior estimation** (Sohn et al., 2004; Tan et al., 2007)
  - Application of a discrete approximation of Bayes’ Theorem to obtain the probabilities of doses given measured biomarker data
  - Computation of posterior probabilities of exposures/doses using biomarker data and forward model results at regularly spaced samples (“bins”) spanning prior probabilities
NHEXAS Maryland (NHEXAS-MD) data for chlorpyrifos (CPF)

- Longitudinal; multiple biomarkers
- Environmental measurements at homes
- CPF data
  - urinary TCPy measurements
  - first void of the day
- Concentrations of CPF chlorpyrifos in food, air (at home), dust, etc.,
- Corresponding TCPy concentrations in food, however, were not measured
- Food intake through 4-day duplicate plate
  - actual amount not available easily
- Also not available
  - Urinary void volume
  - Time of earlier urination
  - Last food intake time
Assumptions regarding unknown exposure factors (e.g. frequency of exposures) affect substantially the outcomes of reconstruction ("inversion"): Demonstration case study with NHEXAS-MD data.
Comparison of different methods for exposure reconstruction ("inversion") and Bayesian "caveats:" Demonstration of a "computational" case study with synthetic data consistent with the NHEXAS-MD data (incorporating lower but reasonable levels of uncertainty)
In progress: Optimization-aided Bayesian approach for exposure reconstruction from inversion of biomarker data

Novel methods have been developed that allow the systematic construction of Fast Equivalent Operational Models (FEOMs); these include the Stochastic Response Surface Method (SRSM) and the High Dimensional Model Representation (HDMR).

Potential Exposures Distribution

Improved Sampling

Optimization Algorithms

Distribution of Exposures Consistent with Biomarker data

Potential Exposures (Samples)

Efficient Samples

PBPK Model or FEOM run with E*N input

PBPK Model or FEOM run with E*1 input

Biomarker data (NHEXAS, NHANES, etc)

Comparison with Biomarker Data

Small proportion of rejected samples

Screening Level Model

Supplemental Data (“Exposure Related”)