Noontime Seminar Series:
Computational Biology & Bioinformatics
Physiologically Based System Modeling
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Outline

- Empirical models
- Physiologically based pharmacokinetic models
- Pharmacodynamic models
- Next generation of physiologically based models
  - Development
  - Neurological
  - Cardiovascular
  - Respiratory
Evolution of Quantitative Toxicology
Drive Toward Biological Realism in Dosimetry Modeling

Descriptive (empirical)

Predictive (biologically based)

Compartmental PK

Physiologically Based Pharmacokinetic Model

Metabolism & Pharmacokinetics

Peripheral Compartment

Central Compartment

Input

Clearance

Inhalation Exposure

Exhaled Air

IV Infusion

Dermal Exposure

Oral Exposure

IP Injection

Alveolar Air

Lung Blood

Richly Perf.

Slowly Perf.

Skin

Fat

Liver

Kidney

Metabolites

Feces

Metabolites

Urine
Dose-Response Question

Increasing Dose or Exposure

Observable Range

Increasing Response
Illumination of Pharmacological/Toxicological Black Box

Exposure → ? → Response

Exposure → Tissue Dose → ? → Response

Exposure → Tissue Dose → Mech. Action → Response
Animal-To-Human Extrapolation
Traditional Approach for Non-Carcinogens
Based on Exposure Concentration or Applied Dose

Human is Considered a Large Rat

Equivalent Applied Dose = Equivalent Effect
Control Level = Safe Level in Animals / Uncertainty Factor
(10, 100 or 1000)
Advantages/Disadvantages of PBPK Models

Allow extrapolations:
- From high-to-low dose
- Between dose routes
- Between species

You need a LOT of data for PBPK modeling
- Not always available
Information Required in PBPK Models

• **Species-specific information**
  - Organ sizes
  - Ventilation rates
  - Cardiac output/perfusion rates

• **Chemical-specific information**
  - Solubility of material in blood/tissues
  - Metabolic pathways/rates
  - Elimination pathways/rates

• Most useful when something is known about potential modes of action.
Sources of Model Parameters

Physiological parameters:
- Medical/toxicology literature

Tissue solubility (partition coefficients):
- Vial equilibration (volatiles)
- Equilibrium dialysis
- Ultrafiltration
- IV infusion

Biochemical constants:
- Gas uptake
- *In vivo/In vitro* metabolism
- Cell replication
- Quantitative histopathology
- Other mechanism-specific studies
Process for Model Development

1. Problem Identification
2. Literature Evaluation
   - Mode of Action
   - Biochemical Constants
   - Physiological Constants
3. Model Formulation
4. Simulation
   - Refine Model
   - Compare to Kinetic Data
   - Sensitivity Analysis
   - Critical Experiments
5. Validated Model
   - Extrapolations
Evolution of Quantitative Toxicology
Incorporate Response to Target Tissue Dose

Predictive
(changing biology
growth, development, aging,...)

Predictive
(dynamic response)

Predictive
(spatial orientation)

PBPK

PBPK/PD or
BBDR or
MBDR

3-D Virtual Body

Inhalation
Lung
Mammary
Poorly Perf.
Richly Perf.
Liver
Metab
Gut
Placenta
Liver
Brain
Body

Inhalation
Lung
Mammary
Poorly Perf.
Richly Perf.
Liver
Metab
Gut
Placenta
Liver
Brain
Body

B’

A
B
C

Mechanism Model

Pacific Northwest National Laboratory
U.S. Department of Energy
Linkage of PBPK/PD With Risk Models

PBPK Model

Risk Assessment Model

Bioassay
Dose
Regimen

Biological (PD) Model
Future Developments

ENVIRONMENT
Air, Water, Food, Soil

PHARMACOKINETIC MODEL

BLOOD
LIVER
GUT
KIDNEY
TARGET

BIOLOGICAL MODEL
A → B → ... → C
A' → B' → ...

RISK ASSESSMENT MODEL

RESPONSE
EFFECTIVE DOSE, C

Pacific Northwest National Laboratory
U.S. Department of Energy
Application of PK & PD Models to Assess Neurotoxicity

Cholinesterase Inhibiting Insecticides
Acetylcholine & Acetylcholinesterase Function
Neuromuscular Junction

Acetylcholine → Acetylcholinesterase
Acetate + Choline

(Ach receptors
(Nicotinic))
AChE binding & Inhibition

Oxon
Enzyme Inhibitor

\[
\begin{align*}
&\text{C}_2\text{H}_5\text{O} \\
&\text{C}_2\text{H}_5\text{O} \\
\end{align*}
\]

ACh
agonist

AChE
Enzyme

SOURCE: Adapted from AD Little (1988, Ch. 5).
Metabolism of Chlorpyrifos (CPF)

Toxicity
AChE Inhibition

Chlorpyrifos

3,5,6-trichloro-2-pyridinol (TCP)

Conjugates - O

Sulfate or glucuronides of TCP

Diethylphosphate

Diethylthiophosphate

P450

Oxon

PON1 (CPF-oxonase) & B-esterase

C2H5O
C2H5O
C2H5O
C2H5O
C2H5O
C2H5O
Organophosphate ChE Inhibition
PBPK/PD Model Structure (Timchalk et al., 2002)

**Dermal Exposure**
- CPF (Qe) absorbed by skin (Qsk) and blood (Qb)
- CPF-Oxon (Qe) absorbed by skin (Qsk) and blood (Qb)

**Arterial Blood**
- CPF (Qh) and CPF-Oxon (Qh) to rapidly perfused compartments
- CPF (Qd) and CPF-Oxon (Qd) to slowly perfused compartments

**Venous Blood**
- CPF (Qv) and CPF-Oxon (Qv) to blood
- CPF (Qs) and CPF-Oxon (Qs) to slowly perfused compartments

**Compartment Model**
- Ke (B-EST inhibition rate)
- Km1, Vmax1 for CPF
- Km2, Vmax2 for CPF-Oxon

**B-Esterase (B-EST) Inhibition (shaded compartments)**
- CPF-Oxon (Qe) to CPF (Qe)
- CPF-Oxon (Qe) to CPF-Oxon (Qe)

**Dietary Exposure**
- Gavage Exposure
- Stomach (Ks) to intestine (Ks)
- Skin (Kp) to venous blood

**Synthesis of New Esterase**
- "Free" CPF-Oxon + CPF
  - Free Esterase
  - Oxon-Esterase
  - Aged Complex

**Inhibition**
- Inhibition of B-Esterase
- hr\(^{-1}\)

**Degradation of Esterase**
- Degradation of Free Esterase
- Degradation of Oxon-Esterase

**Regeneration**
- HR\(^{-1}\) for regeneration of Free Esterase

**Released TCP Metabolite**
- Released TCP Metabolite from degradation of Esterase

*Liver and blood only.*
CPF Time-Course in Serum of Poison Victim
(Drevenkar et al., 1993)

Estimated CPF Dose = ~ 180 mg/kg
Adult Human Plasma ChE Inhibition (Timchalk et al., 2002; Nolan et al., 1984)

Dermal 5 mg/kg
Oral 0.5 mg/kg

% of Control

Time (hrs)
Children’s Sensitivity

Numerous studies have shown that neonatal rats are more sensitive than adults:

- MTD- PND17 20 mg/kg ; adult 100 mg/kg – ratio 5

Increased sensitivity may be related to age-dependent differences in metabolism (activation/detoxification)

Are human children also more susceptible?

To address this question we are modifying the PBPK/PD model to incorporate age-dependent changes (allometric scaling) in metabolism and enzyme levels.
Rodent Age-dependent Metabolism of CPF
(adapted from Atterberry et al., 1997; Karanth and Pope, 2000).

**CYP450**
- Dearylation (detoxification)
- Desulfation (Activation)

**Liver CaE**

**PON1**
- Blood
- Liver
Brain AChE Inhibition, Oral 15 mg/kg

% of Control

0  20  40  60  80  100

0  10  20  30

Time (hrs)

Adult Rat

PND17 Neonate Rat

~4x
Advanced Models

Environmental Health Perspectives • VOLUME 109 | NUMBER 4 | April 2001

The Virtual Body Workshop: Current and Future Application of Human Biology Models in Environmental Health Research

Charles Timchalk,¹ Nigel Walker,² Reinhold C. Mann,³ and F. Blaine Metting ¹

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Gestational/Developmental Modeling
Organ Weight vs. Age in Humans
(Gompertz eq & allometric scaling)

Adapted from Corley et al. (2003)
Imaging Gestational Development

I. GD 6 → GD 7 → GD 9.5
   → GD 11.5 → GD 13.5 → GD 15.5

II.

S. Ruffins & R. Jacobs,
Caltech µMRI Mouse Development Atlas
(http://atlasserv.caltech.edu/~johnc/index_content.html)
Image Co-registration

Combined PET/MRI Imaging - BNL


From Womb to Recovery

11C-Cocaine

PET

MRI
Dynamics of AChE Inhibition

A.

Peripheral Binding Site
Preferred at High Concentrations

K_2

K_1

Oxon 

Oxon~AChE_{PBS}

Oxon

K_{12}

Metab

[Oxon~AChE_{PBS}~Oxon]

AChE_{PBSphos}

DEP

AChE_{PBS}

B.

Active Binding Site
Preferred at Low Concentrations

AChE~Oxon

[Oxon~AChE_{PBS}~Oxon]

K_i

Metab

AChE_{Phos}

DEP

AChE

10^0

10^{-1}

10^{-2}

10^{-3}

10^{-4}

10^{-5}

PO (pM)

10^0

10^{-1}

10^{-2}

10^{-3}

10^{-4}

10^{-5}

Ki (pM^{-1} h^{-1})

1.E+00

1.E-01

1.E-02

1.E-03

1.E-04

1.E-05

0.1

1

10

100

1000

10000

100000
• P. Taylor et al UC San Diego have now solved the structure of mouse AChE, which is being used to investigate candidate AChE inhibiting drugs used in treating Alzheimer's.

• Simulations use of a scalable parallel molecular dynamics code, nwARGOS, part of the NWChem suite of programs developed by Tjerk Straatsma et al PNNL.
MRI Imaging Rat Neuronal Development

Coronal View PND 5


Brain regions readily identifiable
Functional Imaging Animals to Humans

Instrumentation - detectors

GOAL

Awake child imaging

PET imaging (Brookhaven National Lab)
Brain 3-D Imaging and Computational Modeling

Data Intensive Computing

Medical Imaging  
Data Visualization

Pacific Northwest National Laboratory  
U.S. Department of Energy
The long-range goal of the Physiome Project is to understand and describe the human organism, its physiology and pathophysiology quantitatively, and to use this understanding to improve human health. Insight will be gained from the physiomes of other organisms, from bacteria to mammals.

The Physiome Project is more than science: it is education, exploration, archiving, dissemination, and databases. Inherent to the Project are the notions of effective collaboration and the free exchange of information: the data, concepts, and descriptions of biological elements, processes, and models will be accessible publicly via the Internet.
Investigation of mechano-electrical feedback in the heart

F. Vedder, Cardiac Mechanics Research Group, UCSD

Finite element model of the rabbit heart ventricular geometry (552 degrees of freedom) and fiber angles (184 DOF). Yellow: endocardial fibers. Blue: epicardial fibers.
Cardiac Mechanics - Wave Propagation

Green- fully excited  Red- refractory

Time = 0 msec  14 msec  28 msec

F. Vedder, Cardiac Mechanics Research Group, UCSD

Computation time: 733 seconds on a SGI Indigo2 195 MHz R10000 running IRIX 6.2 with 192 Mb main RAM.

http://cmrg.ucsd.edu/modelling/gallery/vetter/vetter_gallery.html
Cardiac Mechanics
Left ventricular finite element model

End Diastole

End Systolic

K. Costa, Bioengineering, UCSD
Coupled model: Myocardial Mechanics Coronary Blood Flow

Model can simulate temporal compression & deformation of vessel segments.

Model used to quantify impact of myocardial contraction on coronary blood flow.

P. Hunter, University of Auckland, Bioengineering Institute
3-D Imaging & Computer Modeling of the Respiratory Tract
NIHLB (Program Director: R. Corley)
But the Lung is Complex!
(LBNL Image Library http://imglib.lbl.gov)
3-D Imaging & Computer Modeling of the Respiratory Tract: Objectives

Focus on Airborne Particulate Matter

- Develop full respiratory tract 3D/CFD models for animals and humans
  - Build upon current models and databases
  - Incorporate visco-elasticity, inhalation/exhalation, particle physics
- Develop NMR for structure, airflow dynamics & particle deposition
- Groundwork for integrating models across scales of information
  - Macro-scale: connections to cardiovascular system and whole body
  - Micro-scale: cellular systems supporting respiratory function
- Adapt model for simulations of pulmonary disease states
- EMSL national user facility
  - Models, software & computers available to research community
Software
PNNL (H. Trease et al)

- **Mesh generation (NWGrid)**
  - Semi-automated process using recursive, hierarchical parallel Adaptive Mesh Refinement (AMR) algorithms
  - Input for simulation code

- **Problem execution (NWPhys)**
  - Parallel, unstructured, hybrid multi-dimensional adaptive code
  - Simulation of fluid dynamics, continuum mechanics, diffusion, particle transport, etc.

NWGrid and NWPhys
NorthWest Grid Generation and Physics Codes

http://www.emsl.pnl.gov:2080/nwgrid
http://www.emsl.pnl.gov:2080/nwphys
NMR Image of Male F344 Rat URT
(K. Minard)

(a) (b)

Old Method  New Method

Airways
NMR Image Stack of Male F344 Rat URT
256 x 100 µm slices
Reconstruction of Rat URT Geometry for CFD Modeling

DDV Airway Segmentation

NMR Images

NWPhys CFD Airflow Simulation

NWGrid Mesh Generation

DDV Isosurface Extraction

Viewer isosurface
Reconstructed Rat URT Geometry
Rats 5 & 7 December, 2001
Acquisition of Geometry Data from Casts
Lovelace Lung Cast Database (Raabe et al., 1976)

Lung Cast

Idealized Geometry

3D Mesh Reconstruction

CFD Model
Acquisition of Geometry Data from Casts
Imaging Lung Cast (with Jack Harkema, MSU)

Lung Cast
Validation of Gas Exchange Models
Xenon CT Imaging of Sheep
Collaboration with E. Hoffman, Iowa

Plethysmography

CFD Modeling

Xenon Gas Exchange
In vivo NMR Lung Imaging
A. Johnson (Duke); B. Saam (Utah)

$^3$He images Guinea Pig  $^3$He images overlaying $^1$H-NMR of Rat

Diffusion Map of Human With emphysema
Potential Impacts of 3-D Imaging & Biological Modeling in Human Health Research

- Quantitative repository of knowledge that can be interrogated
- Simulate impact on susceptible subpopulations (personalized models)
- Rapid construction of database of models for testing variability
- Spatially distributed linkage between dosimetry & cellular or molecular responses
- Drug delivery

Stepping stone to the Virtual Human
Be determined in achieving your goals...