Description of August 24-30, 2008 T15 Course
Modeling Transport and Metabolism in the Respiratory and Cardiovascular Systems: Modeling for Experimental Data Analysis and for Experiment Design
Hosted by
the University of Washington Physiome Project and Simulation Resource Facility, Departments of Bioengineering, Applied Mathematics, Medicine and Radiology

SYLLABUS AND SCHEDULE

Sunday, 24 August 2008:

Afternoon → Early attendee arrival for those desiring to format their data for analysis. Arrive at Foege Bldg Rm N141 Bioengineering (North Wing, south entrance) and go to Rm N141.
2 to 4 PM: Meet to Discuss and to transfer data files, if needed. (Bassingthwaighte, Raymond)

Monday, 25 August 2008:

Morning → Transport and reaction in biological systems
8:30 AM System modeling process: Forming hypothesis; Model construction; Hypothesis testing and analysis; Iterative process (Bassingthwaighte)
(Example situation: handgrip response, Science 2008
Imaging: PET time-activity curve for NH3 uptake in heart)
9:40 AM Introduction to JSim modeling: The JSim environment and how to get started (Gary Raymond)
10:00 AM Hands on modeling with JSim: Single compartment convective transport model. Input functions. (Model = Comp1Flow) (Raymond)
10:45 AM Break
11:00 AM Revising an existing model to make a new one. (Transforming the one compartment flow model into: reaction chamber, two compartments in series, passive exchange with a stagnant chamber.) (Jim Bassingthwaighte)
11:30 AM: Overview of the compartmental tutorial (Tutorial: Compartments). Run the first 8 models.
12:30 Lunch:

Afternoon →1:30 PM. System modeling concepts: Conservation principles; Example program = BTEX10; (Transport Text Bassingthwaighte Ch 14) , input/output relationships and transport functions. units; introduce ODEs versus PDEs; reproduce the results in the figures in the Chapter.

2:30 PM Introducing blood-tissue exchange. Review Crone (1963) and Rankin (1959): two region axially distributed capillary-tissue exchange. Equations for PS, permeability-surface area product. Equivalence to a clearance. Clearance-Flow diagram. Transorgan extraction E(t). Influence of cellular uptake on E(t) using 3 region distributed model composed from a 2-region model.

3:15 Tea time.

3:30 PM Fitting model solutions to data using manual and automated optimization. Purposes of Model fitting to data: Discussion.

A. Generate a model solution. (BTEX30 with McCormack solver. Save it and add noise to it.

Optimize fits of model solutions (same model) to estimate parameters of the model fitting noisy curves.

(i) Use manual parameter adjustment.

(ii) Use loop mechanism to help explore.

(iii) Calculate sensitivity functions. Use knowledge of sensitivity function shape to fit model to data.

(iv) Meanings of confidence limits, Covariance.

(Bassingthwaighte, Raymond)

Discussion: Advantages and disadvantages of automated optimization. Why should modeling be used in experiment design.

Supper: (On one's own. See list of local cafes and restaurants)

Evening → 7:00 – 9:00 PM: Guided and self paced computational session

Tuesday, 26 August 2008:

Morning → 8:30 AM: Multiscale integrative modeling: definitions, approaches (Bassingthwaighte)

9:00 AM: Discussion on integrative modeling. Robustness in systems. Why study all the underlying processes, mechanisms, anatomy, physical chemistry, etc.

9:30: Modeling Diffusion: Fick's laws; Diffusion through an isotropic media. 1-D diffusion model: (Raymond) (Reference handout: Diffusion chapter)

10:30: Coffee

10:40: Diffusion across a thick membrane: Barrer time lag problem (Barrer, 1953; DiffSlab.proj)

11:30: Diffusion in the presence of binding sites. Facilitated diffusion. Mobile versus immobile sites (Bassingthwaighte: handout: Barta, Bassingthwaighte, Sideman 2002)

12:15: Lunch

Afternoon →1:15 PM Concentration-dependent volumes of distribution: the corollary to solute binding. (Bassingthwaighte; handout: Anderson Chapter)

2:00 PM Osmotic pressure. Osmosis; Osmotic water fluxes. Cell volume. General expressions for coupled water and solute transport. Modeling Kedem and Katchalsky equations for coupled exchanges of water and solutes across a membrane

3:15 PM: Coffee

3:30 PM: Metabolic Reactions: Michaelis-Menten kinetics; Modeling a simple enzymatic reaction with the full reaction equations. Progress curves.

4:15 PM: Specialized membrane transport processes: Passive carrier-mediated transporter modeling. (Raymond).

Supper: (On one's own. See list of local cafes and restaurants)

Evening → 7:00 – 9:00 PM: Guided and self paced computational session

Wednesday, 27 August 2008:

Morning →8:30 AM: Capillary tissue exchange: Indicator dilution experiments; Convection and diffusion problem formulation; Single-capillary, single-barrier BTEX Model sensitivity analysis. Use in experiment design. (Bassingthwaighte)

9:00 AM Modeling K and Rb uptake in heart. Estimation of regional flows. Fitting the data and analysis: Optimization methods and their pitfalls; Sensitivity analysis to find out critical parameters; Residual analysis; Parameter estimation)

10:00 AM Coffee

10:15 AM. Active transport (pumps and exchangers); The NaKATPase. (Chapman, Kootsey, Johnson model).

11:15 AM Modeling uptake and washout of ions from the heart. (K+, Tl+, and Rb+. Combined binding, large volumes of distribution, and permeation. Reference papers KTl paper with Winkler. (Bassingthwaighte)

12:15 PM LUNCH

Afternoon →1:00 PM Cardiac Electrophysiology: Nernst potential and Ionic fluxes; Transmembrane potentials; Boltzmann equation; GoldmanHodgkinKatz expression for the resting potential. Influence of pump currents (Bassingthwaighte)

2:00 PM: The Nerve Action Potential: Hodgkin-Huxley equations; Boltzmann version (Raymond and Bassingthwaighte).

3:00 PM: Cardiac Action Potential Models. Beeler-Reuter 1977; Luo-Rudy 1994; Noble 1998; Michailova-McCulloch 2001.

4:00 PM: Excitation-contraction coupling. Two sarcomere model for force generation and ATP utilization.

Supper: (On one's own. See list of local cafes and restaurants)

Evening → 7:00 – 9:00 PM: Guided and self paced computational session

Thursday, 28 August 2008:

Morning → 8:30 AM: Blood Flows: Mechanics of the Circulations – Pulmonary and Systemic. Laplace relation. Network structures and scaling properties. . Cardiac Output and Pulmonary vascular network pressures and flows.

9:30 AM: Vascular Mechanics Modeling. Pressures and flows in steady states. Poiseuille Flow. Pressure-volume-flow relationships in blood vessels. Dynamics of pulsatile flow. Womersley equation. Pulse wave forms. Pulse pressure amplification. (Veress)

10:15 AM: COFFEE

10:30 AM: Cardiac muscle sarcomere mechanics, Cardiac elastance model for single ventricle, two chambers and then four chamber model as part of whole circulation modeling. (Veress)

11:30 AM: Linking pressure-flow models and solute transport models (Bassingthwaighte)

12:15 LUNCH

Afternoon →1:00 Mechanics of Respiratory Minute Volume. (Anderson)

2:00 Modeling of Ventilation and Gas Exchange. Airflow and solute carriage. Modeling pressure-volume relationships. Distinguishing solutes in air from bulk flow. Positive pressure versus normal ventilation. (Anderson)

3:00 Tea Time

3:15 PM. Capillary-alveolar exchange. Linking spatially distributed region to mixing chambers. Intracapillary gradients. Alveolar arterial O2 differences. Hemoglobin binding of O2/CO2. (Anderson, Bassingthwaighte)

4:00 PM. Capillary endothelial uptake of vasoactive solutes. The bolus sweep techniques. Endothelial membrane transport and reaction. Graded doses of serotonin. (from Linehan and Dawson's work) (Jardine/Bassingthwaighte)

Supper: (On one's own. See list of local cafes and restaurants)

Evening → 7:00 – 9:00 PM: Guided and self paced computational session

Friday, 29 August 2008:

Morning → Linking Genome to Physiome.

8:30 AM. Herbert Sauro: Genetic and Protein Network Regulation. Deriving rate laws for gene expression kinetics. Simulating basic genetic circuits, protein networks and understanding their function.

9:30 AM: Modeling protein networks with Jarnac and JSim (Sauro)

10:15 AM. COFFEE

10:30 AM: Protein Network Dynamics. Hyperbolic and sigmoidal Responses.

11:15 AM: Modeling simple bistable switches and oscillatory networks, using genetic networks. (Sauro)

12:15 LUNCH

Cardiac Imaging, Flow Imaging and Finite Element Modeling:

Afternoon → 1:00 PM Image Analysis, PET and MRI: Quantification in Image interpretation of non-invasive methods for evaluating the (patho) physiology. Modeling NH3 uptake in the heart for estimating regional blood flows. Axially distributed capillary-tissue exchange with metabolism. (James Caldwell).

3:00 Tea Time

3:15 PM: Finite Element Modeling Cardiac Images. (Alex Veress)

4:00 PM: Modeling Cardiac regional flows and metabolism in cardiac dyssynchrony. (Alex Veress and James Caldwell)

Evening → Final Dinner (hosted)

Saturday, 30 August 2008:

Morning → 8:30 AM Finite Element Analysis and Continuity (FE computational package from UCSD. Veress and Gao)

9:45 AM Illustration: Applications to cardiac contraction with regional ischemia. With bundle branch block. (Veress)

11:00 Further analysis of data brought by participants

12:00 PM Course Review and Discussion

12:30 PM End