National Simulation Resource

NSR

University of Washington

Circulatory Transport and Exchange

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Recent Progress and New Directions at NSR

The National Simulation Resource for Circulatory Transport, Exchange and Metabolism is a collaborative effort involving faculty and students at the University of Washington and other universities. The effort is focused on the development and distribution of analytical methods for the interpretation of data.

Now, in its 22nd year of funding from the NIH Center for Research Resources, NSR is developing new tools and strategies to support the coupling of information on flow and transport with information on large biochemical systems.

NSR's model developments in blood flow, transcapillary and transmembrane transport and cellular reaction have been applied to cardiac imaging and metabolism. The scope has broadened, however, and NSR models and methods are now used not only in whole organ representations, but also in large-system representations such as linked biochemical systems, cellular systems, and integrated organ systems for gas transport and exchange and blood pressure regulation. In the heart, for example, the applications include nucleotide energetics, the spread of electrical activation, the regulation of ionic pumps, calcium cycling and force development by actin-myosin interactions, ATP utilization for ion pumping and force generation and metabolic function, oxygen transfer from circulating RBC through myoglobin buffering to the mitochondria, ATP generation by oxidative phosphorylation, and energy supply through fatty acid and glucose metabolism.

New computational methods that allow the rapid linking of individual programs are the key to putting comprehensive programs together. They are also the key to maintaining the code as explicit complete modules for public distribution and interuniversity cooperative efforts. The NSR modeling system, JSim, which effects a translation from the equation-based Mathematical Modeling Language into code for numerical solutions, is a Java-based user interface for developing models and for using them in data analysis. JSim, in accord with the general NSR policy of free software distribution, has been made publicly available.

JSim's features and stability make it good for student usage. In courses using it, students program differential equation models to solve problems—within 2 to 4 hours of starting the course! All they need to create a functioning model are the raw algebraic or differential equations (ODEs or PDEs). The JSim system automatically parses, chooses solvers and compiles, then presents the control and graphical interface for running the model solutions, fitting data, etc. We have used JSim as the basis of two graduate courses, Bioengineering Physiology and Transport Phenomena in Biological Systems.

JSimStudio Version 1.5

JSim is a software environment for scientific modeling that provides tools for development of models, for their run-time control, and for analysis of their outputs. NSR will release a major upgrade of JSim (new version 1.5) this month. New features and changes are listed below.

1. A larger class of PDE boundary conditions and state equations can be handled. The previous version was limited to problems solvable by the LSFEA PDE solver.
2. Recirculating PDE models are supported.
3. Linear and nonlinear implicit equations are supported.
4. Symbolic differentiation is more robust.
5. A variable may contain any number of domains. ODE and PDE problems for variables with extra domains are supported.
6. The requirement that a model must have at least one domain has been removed. The special nature of the first domain (e.g., relationship to ODE and PDE problems) has been removed.

Contents

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7. Variable query syntax is partially supported. This is especially useful for delay lines and external function interpolation.
8. The unit system has been revamped, allowing Moles to become a fundamental unit, and improved diagnostics are provided for unit correction error diagnosis;
9. A numerical error in the LSFEA PDE solver has been fixed.

The BTEX Biological Component Library (BCL) has been revised and expanded to include fast-equilibration chemical reactions and flux-based reactions. BTEX BCL now supports the use of physical units and using units is recommended. BTEX BCL models from the previous version of JSim will run with minor modifications to the Reaction statements.

Two new BCLs have been added, that present alternative views for the chemical networks analyzable using the BTEX BCL. The Markov BCL provides a stochastic simulation of the system. The FBA BCL provides flux-balance analysis, which is useful in complex systems with limited information on rate constants.

A new command-line based text interface to JSim, jsbatch, has been added. This interface is especially useful for batch computation and debugging. JSimStudio remains the main program for interactive modeling.

The JSim documentation has been completely rewritten and several extensive tutorials have been added.

The JSim source code has been dramatically restructured in the 1.5 release with the goal of

- making addition of new planning features easier and more robust;
- making model verification and debugging more robust;
- improving the isolating interface and back-end code bases to increase developer effectiveness.

These changes may be noticeable to JSim users indirectly via a more stable and full-featured product.

by Erik Butterworth

ModelBuilder: Code Modularity for JSIM

NSR recently produced a demonstration program, ModelBuilder, which automates the building of JSIM models by using code from existing models as subroutines.

The subroutines are stand-alone JSIM programs written in JSIM's Mathematical Modeling Language (MML). Directives in the form of comments are included in the model to identify the arguments and pieces of code that will be used. The directives in a subroutine are SUBROUTINE, which gives a list of local variables, and START and END directives, which surround the block of code that will be used.

The main model contains its own code (MML) along with the following directives: EXTERNAL, which gives a list of the name of the subroutine and subroutine file; CALL, which lists the template name followed by a list of global variables to replace the local variables; START and END, which include a code block from the main model in the ModelBuilder; and PROCESS, which directs the assembly process.

As each CALL statement is encountered, the appropriate model is accessed, the block of code inside its START and END directives is extracted, and the template's variables are replaced with the main model variable names. The modified lines of code are added to a holding buffer. This is done for each CALL statement.

Code from the main model between its own START and END directives is also added to the holding buffer. When the PROCESS directive is encountered, the code in the holding buffer replaces the CALL directives in the main model. If a calculation is for a differential equation, the holding buffer is scanned for additional equations for the same variable, and when found, combined. For example, if the code buffer contained:

```
S:t = J1; ... S:t = -J2;
```

the generated code would be:

```
S:t = J1+(-J2);
```

The final model contains all the code originally in the main model plus the code generated by the PROCESS directive.

At present, ModelBuilder is restricted to one level of templates or subroutines; all derivatives must be given by a single line of code (continuation lines are not supported); total code produced is limited to 512 lines of no more than 256 characters each; and only one START and END directive can be used in each template.

For additional details and documentation contact Gary Raymond at garyr@bioeng.washington.edu.

by Gary Raymond

NSR and the Multiple Indicator Dilution Technique

The founding of the National Simulation Resource (NSR) in 1981 was closely tied to the development of the Multiple Indicator Dilution (MID) experimental technique in the 1960's and 1970's. MMID4, MSID4 and GENTEX, models developed at NSR, address the need inherent in MID studies for modeling microvascular exchange and tissue metabolic processes. These models can be run by NSR's backbone simulation software interfaces, XSIM and JSIM (and NSR's legacy program, SIMCON).

MID studies measure the movement of solutes across the capillary wall of an organ, and thus evaluate the permeability properties of vascular endothelium. The MID technique uses a whole organ preparation which has a single vascular inflow and a single vascular outflow. To measure the permeability of the organ's endothelium, a single bolus injection of solutes is made into the inflow; outflow is then collected continuously as small fractions in order to chart the pattern of solute emergence from the organ.

An injected bolus for a MID study typically contains three solutes, radiolabeled so that they can be followed easily in the organ outflow over a wide range of concentrations. One of the radiolabeled solutes is a molecule that is confined to the vascular space within the organ and is not metabolized in the organ. This tracer molecule, usually albumin, measures the transit time of fluid through the vascular system. Another of the injected solutes is a molecule that has access to both the vascular space and the interstitium and is also not metabolized in the organ. This molecule, usually L-glucose or sucrose, measures the transit time of tracer

that enters the interstitium but is not taken up or metabolized by the parenchymal cells of the organ. The third solute in a typical MID bolus is a molecule that has access to the parenchymal cells of the organ as well as the vascular space and the interstitium. The goal of a MID study is to measure the rate of uptake and intracellular transformation of this molecule in the organ studied.

The outflow pattern of the solutes injected for a MID study is determined by which tissue compartments the solutes enter and what metabolic transformations occur in those compartments. MID experimentally measures what goes into and what comes out of the organ studied. The technique then infers what happened to the solutes within the organ to produce the observed outflow, by mathematically modeling the physiology of the organ. Mathematical models used to make the inference incorporate current scientific understanding of the organ structure, including the organ's vascular geometry, interstitial structure and cellular anatomy. Current understanding of transvascular exchange, cellular uptake and intracellular biochemical transformation is also incorporated. Optimization of model parameters is used to maximize the fit between the model output and the experimentally observed solute outflow pattern. The goodness of fit between the optimized model and the experimental outputs provides investigators with a quantitative measure of the validity of the model, and thus provides a measure of the understanding of the biology involved.

Models developed at NSR (MMID4, MSID4, and GENTEX) assist in the inference of the physiology of solute exchange and metabolism for MID studies. The models are supported by simulation interface systems also developed at NSR: XSIM, JSIM, and the legacy program, SIMCON. The XSIM, JSIM and, formerly, SIMCON interface systems facilitate the construction and optimization of models as well as the fitting of model parameters to experimental data. These systems became progressively easier to use as they developed, from the command line interface of SIMCON, to XSIM's graphical user interface, to today's JSIM, a java-based simulation interface system. This current system, JSIM, is available for free download at NSR's website (http://nsr.bioeng.washington.edu), along with the earlier system, XSIM.

JSIM provides an excellent environment for rapid construction and testing of relatively small models. When it is fully developed, JSIM will allow the construction of models with larger systems of ODEs and biochemical networks. As currently planned, however, JSIM will not replace the workhorse analytical capability of GENTEX, run under XSIM, for blood–tissue exchange studies.

Models useful for MID studies and, generally, blood–tissue exchange studies, along with the backbone simulation interface systems that support those models, are not the only software developed and distributed by NSR. In addition, NSR supports and distributes the locally developed I4 functional imaging system, as well as mathematical and modeling software libraries, and fractal analysis programs. Visit our website at http://nsr.bioeng.washington.edu and click the Software link to learn more.

by John Bassett

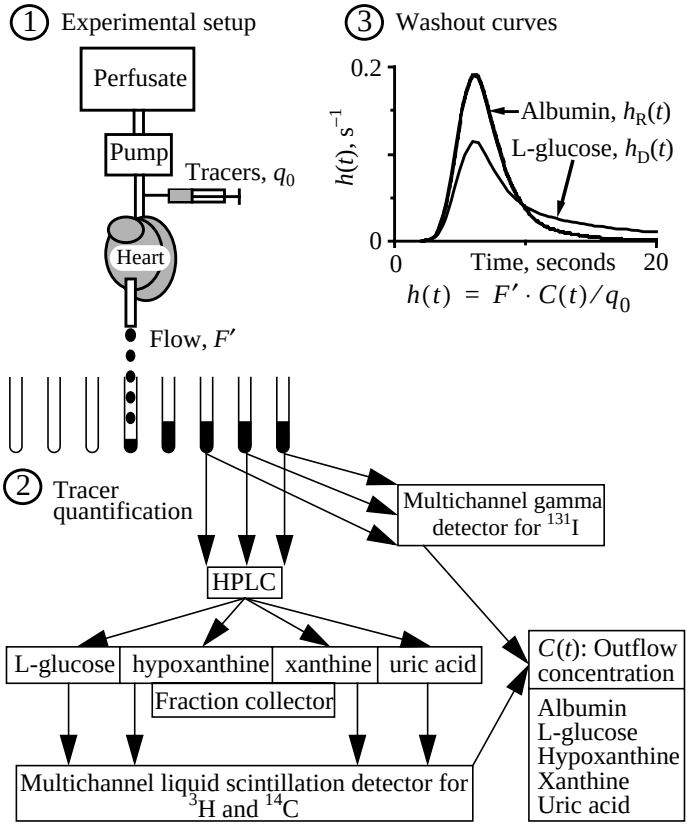

Figure 1. Schematic overview of procedures underlying the application of the multiple-indicator dilution technique to investigation of multiple metabolites. HPLC is high pressure liquid chromatography.

New Model Equations for O_2 and CO_2 Saturations of Hemoglobin

Transport and exchange of oxygen (O_2) and carbon dioxide (CO_2) in the circulatory system is highly influenced by the competitive binding of O_2 and CO_2 with hemoglobin (nonlinear O_2-CO_2 interactions) in red blood cells (RBCs). Other influences include the level of pH, the concentration of 2,3-DPG (diphosphoglycerate), and the blood temperature. So, to mathematically model the simultaneous transport and exchange of O_2 and CO_2 in the circulating blood, it is important to incorporate all these influences into the modeling. Suitable model equations for O_2 and CO_2 saturations of hemoglobin (S_{HbO_2} and S_{HbCO_2}) should be coupled and linked to each other through the kinetics of O_2 and CO_2 binding to hemoglobin. See Hill et al. (1977) and Singh et al. (1989) for the detailed reactions of O_2 and CO_2 with hemoglobin in RBCs.

In view of this, new mathematical model equations for S_{HbO_2} and S_{HbCO_2} have been developed by considering the detailed reactions of O_2 and CO_2 with hemoglobin. These new model equations are in the form of the well-known Hill's equation, which has the advantage of being invertible, allowing the O_2 and CO_2 concentrations ($[O_2]$ and $[CO_2]$) or their partial pressures (P_{O_2} and P_{CO_2}) to be calculated from their saturations (S_{HbO_2} and S_{HbCO_2}) and vice-versa. These equations are

$$S_{HbO_2} = \frac{[HbO_2]}{[Hb]} = \frac{K_{HbO_2}[O_2]^n}{1 + K_{HbO_2}[O_2]^n}, \qquad \text{Eq. 1.a}$$

$$S_{HbCO_2} = \frac{[HbCO_2]}{[Hb]} = \frac{K_{HbCO_2}[CO_2]}{1 + K_{HbCO_2}[CO_2]}, \qquad \text{Eq. 1.b}$$

where the modified Hill's coefficients K_{HbO_2} and K_{HbCO_2} account for the influences of nonlinear O_2-CO_2 interactions and the effects of pH, 2,3-DPG concentration and temperature on binding of O_2 and CO_2 with hemoglobin in RBCs. The expressions for K_{HbO_2} and K_{HbCO_2} are given by

$$K_{HbO_2} = \frac{K'_4 \left(K'_3 [CO_2] \left\{ 1 + \frac{K''_3}{[H^+]} \right\} + \left\{ 1 + \frac{[H^+]}{K''_6} \right\} \right)}{\left(K'_2 [CO_2] \left\{ 1 + \frac{K''_2}{[H^+]} \right\} + \left\{ 1 + \frac{[H^+]}{K''_5} \right\} \right)}, \qquad \text{Eq. 2.a}$$

$$K_{HbCO_2} = \frac{\left(K'_2 \left\{ 1 + \frac{K''_2}{[H^+]} \right\} + K'_3 K'_4 \left\{ 1 + \frac{K''_3}{[H^+]} \right\} [O_2]^n \right)}{\left(\left\{ 1 + \frac{[H^+]}{K''_5} \right\} + K'_4 \left\{ 1 + \frac{[H^+]}{K''_6} \right\} [O_2]^n \right)}, \qquad \text{Eq. 2.b}$$

where the equilibrium constant K'_4 (in units of M^{-n}) for oxygenation of hemoglobin is obtained as a function of $[H^+]$, $[CO_2]$, [DPG], and temperature (T), written as in Eq. (3).

$$\begin{aligned} K'_4 &= K''_4 \left\{ \frac{[H^+]_S}{[H^+]} \right\}^{n_1} \left\{ \frac{[CO_2]_S}{[CO_2]} \right\}^{n_2} \left\{ \frac{[DPG]_S}{[DPG]} \right\}^{n_3} \left\{ \frac{T_S}{T} \right\}^{n_4} \qquad \text{Eq. 3} \\ &= K''_4 \left\{ \frac{57.5 \text{ nM}}{[H^+]} \right\}^{n_1} \left\{ \frac{0.85 \text{ mM}}{[CO_2]} \right\}^{n_2} \left\{ \frac{4.65 \text{ mM}}{[DPG]} \right\}^{n_3} \left\{ \frac{37^\circ \text{ C}}{T} \right\}^{n_4}. \end{aligned}$$

The subscript "S" in Eq. (3) refers to the values under standard physiological conditions, that is, $[H^+]_S = 57.5$ nM (or $pH_S = 7.24$), $[CO_2]_S = 0.85$ mM (or $P_{CO_{2S}} = 40$ mmHg), $[DPG]_S = 4.65$ mM and $T_S = 37°$ C in RBCs. The proportionality equilibrium constant K''_4 and the empirical indices n_1, n_2, n_3 and n_4 are to be determined suitably. In Eqs. (2.a) and (2.b), K'_2 and K'_3 are the equilibrium constants (in units of M^{-1}) for the reactions of CO_2 with the reduced and oxygenated hemoglobin ($HbNH_2$ and O_2HbNH_2), whereas K''_2, K''_3, K''_5 and K''_6 are the ionization constants (in units of M) of HbNHCOOH, O_2HbNHCOOH, $HbNH_3^+$ and $O_2HbNH_3^+$; HbO_2 (oxyhemoglobin) refers to the sum of O_2HbNH_2, $O_2HbNH_3^+$, O_2HbNHCOOH and $O_2HbNHCOO^-$, whereas $HbCO_2$ (carbomino hemoglobin) refers to sum of HbNHCOOH, $HbNHCOO^-$, O_2HbNHCOOH and $O_2HbNHCOO^-$; n is the order of the overall reaction of O_2 uptake by hemoglobin in one-step kinetics and is well- known as the Hill's exponent.

The equations for saturations (S_{HbO_2} and S_{HbCO_2}) and modified Hill's coefficients (K_{HbO_2} and K_{HbCO_2}) can be expressed in terms of O_2 and CO_2 partial pressures (P_{O_2} and P_{CO_2}) by expressing the concentrations $[O_2]$ and $[CO_2]$ in terms of P_{O_2} and P_{CO_2} by Henry's law: $[O_2] = W_{rbc}\, \alpha_{O_2}\, P_{O_2}$ and $[CO_2] = W_{rbc}\, \alpha_{CO_2}\, P_{CO_2}$, where W_{rbc} is the fractional water space in RBCs and α_{O_2} and α_{CO_2} are the solubility coefficients of O_2 and CO_2 in water; $W_{rbc} = 0.65$ and at normal body temperature ($T = 37°$ C), $\alpha_{O_2} = 1.46\times10^{-6}$ M mmHg^{-1} and $\alpha_{CO_2} = 3.27\times10^{-5}$ M mmHg^{-1}. Variation of the solubility coefficients α_{O_2} and α_{CO_2} with the temperature T can be expressed through the following quadratic curve-fit equations, corrected for the plasma fractional water content ($W_{pl} = 0.94$):

$$\begin{aligned} \alpha_{O_2} &= [1.37 - 0.0137(T - 37) + 0.00058(T - 37)^2] \\ &\quad \times [10^{-6} / W_{pl}] \quad \text{M/mmHg}, \\ \alpha_{CO_2} &= [3.07 - 0.057(T - 37) + 0.002(T - 37)^2] \\ &\quad \times [10^{-5} / W_{pl}] \quad \text{M/mmHg}, \end{aligned} \qquad \text{Eq. 4}$$

Now, to compute the HbO_2 and $HbCO_2$ dissociation curves, we use values from the data used by Hill et al. (1977): $K_2 = K'_2 K''_2 = 2.4\times10^{-5}$, $K''_2 = 1\times10^{-6}$ M, $K_3 = K'_3 K''_3 = 2.4\times10^{-5}$, $K''_3 = 5\times10^{-6}$ M, $K''_5 = 7.2\times10^{-8}$ M, and $K''_6 = 8.4\times10^{-9}$ M. We also fix the value of Hill's exponent n at 2.7. We then estimate the values of the proportionality equilibrium constant K''_4 and empirical indices n_1, n_2, n_3 and n_4, in order to get appropriate shifts in the HbO_2 dissociation curves with respect to the levels of pH, P_{CO_2}, [DPG] and T in RBCs as reported in the literature. For this purpose, we actually use the values of P_{50} as a function of pH, P_{CO_2}, [DPG] and T from the model equation of nonstandard HbO_2 dissociation curves obtained by Buerk and Bridges (1986), which agree well with those obtained theoretically by Kelman (1966) and experimentally by Winslow et al. (1983). Here P_{50} is referred to as the level of P_{O_2} at which the hemoglobin is 50% saturated by O_2 (i.e., $S_{HbO_2} = 0.5$); P_{50} is conventionally used as the measure of O_2 affinity for hemoglobin. We fit our model equations [Eqs. (1.a) and (2.a)] to these P_{50} data to estimate the value of K''_4 and the functional forms of n_1, n_2, n_3 and n_4. This way, we get $K''_4 = 6.77\times10^{11}$ M^{-n} and the following quadratic polynomial curve fit equations for n_1 as a function of pH, n_2 as a function of P_{CO_2}, n_3 as a function of [DPG], and n_4 as a function of T:

$$\begin{aligned} n_1 &= -6.775 + 2.0372\ \text{pH} - 0.1235\ \text{pH}^2, \\ n_2 &= -0.008765 + 0.00086\ P_{CO_2} + 6.3\times10^{-7} P_{CO_2}^2, \\ n_3 &= 0.2583 + 28.6978\ [\text{DPG}] - 917.69\ [\text{DPG}]^2, \\ n_4 &= 1.6914 + 0.06186\ T + 0.00048\ T^2. \end{aligned} \qquad \text{Eq. 5}$$

Thus, Eqs. (1) – (5) completely determine the O_2 and CO_2 saturations of hemoglobin (S_{HbO_2} and S_{HbCO_2}), and hence these equations can be used to quantitatively describe the nonstandard HbO_2 and $HbCO_2$ dissociation curves as well as the Bohr and Haldane effects. The mathematical simplicity and invertibility allows these formulas for S_{HbO_2} and S_{HbCO_2} to be more conveniently used in the modeling of simultaneous O_2 and CO_2 transport and exchange in the alveoli–blood and blood–tissue exchange systems.

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by Ranjan Dash

NSR Summer Course on Kinetic Modeling: Biochemical, Biophysical and Physiological Systems

23-25 September 2002, Academic Computer Center
3737 Brooklyn Avenue NE, Room 120,
Seattle, Washington 98195-7962

September 23, Monday morning: Session I. Introduction to modeling and JSIM

07:50-08:00 *Arrive at Harris Hydraulics Laboratory*

08:00-08:15 *Welcome and introductions* (Jim Bassingthwaighte)

08:15-09:15 *Jumping into modeling* (Gary Raymond)

09:15-10:00 ***Problem 1:*** *Writing a new model, S+E↔SE↔P+E* (Gary Raymond)

10:00-10:15 *Morning Break*

10:15-10:45 *Writing a new model, S+E↔SE↔P+E* (continued)

10:45-12:00 *The Michaelis-Menten Kinetics Derived* (Jim Bassingthwaighte). ***Problem 2:*** *Writing the Michaelis-Menten model and running it*

12:00-01:15 Lunch

September 23, Monday afternoon: Session II. Transport modeling

01:15-02:15 *The one- and two-compartment ODE models* (Gary Raymond). ***Problem 3:*** *The three-compartment ODE model*

02:15-03:15 ***Problem 4:*** *The two-compartment ODE model* (Gary Raymond)

03:15-03:30 Afternoon Break

03:30-04:15 ***Problem 5:*** *Serial stirred tanks* (Gary Raymond)

04:15-04:50 *A two-region BTEX model: Looking at the code* (Jim Bassingthwaighte)

04:50-05:00 Evaluation and discussion

September 24, Tuesday morning: Session III. Transport and Metabolic Modeling

08:15-09:00 *Introduction to transport modeling* (Jim Bassingthwaighte)

09:00-09:30 *Convection and diffusion* (Dan Beard)

09:30-10:00 ***Problem 6:*** *Transport in a pipe* (Dan Beard)

10:00-10:15 Morning break

10:15-10:45 *Blood-tissue exchange with a Sangren-Sheppard Model* (Dan Beard)

10:45-11:30 ***Problem 7:*** *Running BTEX20* (Gary Raymond)

11:30-12:00 *BTEX30: Three-region blood–tissue exchange* (Gary Raymond)

12:00-01:15 Lunch

September 24, Tuesday afternoon: Session IV. Transport and model building

01:00-02:00 *BTEX models and nonlinear transporters* (Dan Beard)

02:00-03:00 *Whole-organ transport and flow heterogeneity* (Jim Bassingthwaighte)

03:00-03:15 Afternoon break

03:15-05:00 ***Problem 8:*** *Model building* (Gary Raymond)

19:00-22:00 Hors d'oeuvres & dinner, Waterfront Activities Center

September 25, Wednesday morning: Session V. Parameter Estimation, Advanced Modeling

08:00-09:00 *Kinetics and parameter estimation* (Paolo Vicini)

09:00-10:00 ***Problem 9:*** *Fitting data with Jsim Studio using a three-region BTEX model and Monte Carlo simulation* (Gary Raymond)

10:00-10:15 Morning break

10:30-11:30 *Complex cell metabolic model: The RBC* (Dan Beard)

11:30-12:30 *Ion Channel Modeling and Electrophysiology* (Hong Qian)

12:30-01:30 Lunch

September 25, Wednesday Afternoon: Session VI: Metabolic Modeling Systems

01:30-02:00 *Biochemical kinetics and thermodynamics of living cells* (Hong Qian)

02:00-03:15 *Flux balance analysis and constraint-based metabolic modeling* (Dan Beard, Hong Qian)

03:15-03:30 Afternoon break

03:45-04:30 *Future of JSIM* (Eric Butterworth)

04:30-05:00 Discussion and evaluation