18.10.01 NIH/NHLBI U01-122199 Mid-year progress report to IMAG
co PIs: Bassingthwaighte, Beard, Dash, McCulloch (U.Washington, U.Michigan, Medical College Wisconsin, UC San Diego)

THE PATHWAY FOR OXYGEN: DASH PROGRAM

1. Several of the mathematical models of oxygen and carbon dioxide saturations of hemoglobin accounting for variations of other physiological state variables (e.g. pH, 2,3-DPG, temperature) from the literature and that of Dash et al. (2004, 2006, 2010, 2015) were coded in Matlab and/or JSim and published on the Physiome website.

a.Hemoglobin binding for O2, CO2, 2,3-DPG at varied temperatures and pH levels (The 2004/2010 model: Dash RK and Bassingthwaighte JB. Erratum to: Blood HbO2 and HbCO2 dissociation curves at varied O2, CO2, pH, 2,3-DPG and Temperature Levels. Ann Biomed Eng 38(4): 1683-1701, 2010.
This model is available for download (open Source) or can be run as a web applet at:
https://www.physiome.org/jsim/models/webmodel/NSR/TUTORIAL/Hemoglobin_Oxy/HbCO2/ (Model 37)
https://www.physiome.org/jsim/models/webmodel/NSR/HbO2_HbCO2_diss/ (model 149)
b. The 2006 model:
Dash RK, Li Z, and Bassingthwaighte JB. Simultaneous blood-tissue exchange of oxygen, carbon dioxide, bicarbonate, and hydrogen ion. Ann Biomed Eng 34: 1129-1148, 2006.
https://www.physiome.org/jsim/models/webmodel/NSR/Exchange_O2_CO2_HCO3_and_H/ (model 134)

c. The 2016 model:
Dash RK, Korman B, and Bassingthwaighte J. Simple accurate mathematical models of blood HbO2 and HbCO2 dissociation curves at varied physiological conditions: evaluation and comparison with other models. Eur J Appl Physiol 116(1): 97-113, DOI: 10.1007/s00421-015-3228-3, 2016.
https://www.physiome.org/jsim/models/webmodel/NSR/SHbO2CO2_Dash2016/ (Model 399)

2. Dr. Dash has provided the MATLAB codes for his previous computational models of skeletal muscle cellular metabolism and energetics that can simulate metabolic dynamics in skeletal muscle during ischemia and exercise. This model is being converted to JSim and will the model will be run on the web through JSim applet.
Carlson BE, Anderson JC, Raymond GR, Dash RK, and Bassingthwaighte JB. Modeling oxygen and carbon dioxide transport and exchange using a closed loop circulatory system. In: Oxygen Transport to Tissue XXIX, edited by Kang KA, Harrison DK, and Bruley DF. New York, NY: Springer, 2008, pp 353-360.
The current MATLAB code is available in the Physiome website
https://www.physiome.org/jsim/models/webmodel/NSR/Dash2008/ (Model 403)
https://www.physiome.org/jsim/models/webmodel/NSR/Li2012/ (Model 404)

3. Dr. Dash is in the process of documenting and disseminating codes for his models of mitochondrial reactive oxygen species (ROS) production and scavenging, including superoxide production through the plasma membrane NADPH oxidase. These codes will be published in the Physiome website.

BASSINGTHWAIGHTE (with others) PROGRAM:

1. Pathway for Fatty Acid.
   a. Equilibrium binding of fatty acids to albumin in the plasma.(done but writing)
   b. Kinetics of Albumin binding and release of fatty acids. (done but writing)
   c. Radial diffusion and membrane permeation of albumin-bound fatty acid (published, needs more)
   d. Receptor enhanced release of fatty acid from albumin. (done but writing)
   e. AcylCoA formation to DAG, TAG, and lipid vacuole formation (Nathan Barr) (in process)
   f. Lipid vacuoles to Acyl CoA (Nathan) (modeling in process)
   g. Acyl CoA -> acyl-carnitine (future)
   h. Acylcarnitine transferase (future)
2. Pathway for Glucose (Kevin Christmas)
   a. Glucose to Lactate and Pyruvate (in process, 10 modules with 4 levels of each)
   b. Glyogenolyis and glycogen synthesis (writing)
   c. Pyruvate dehydrogenase: Pyruvate to acylCoA (done, but writing)
3. Beta oxidation: from Long or Short Chain FA to AcCoA (derived from Bakker) (future)
4. Tricarboxylic Acid Cycle (have MM versions only):
5. Pathway for Nucleo-sides and –tides: The phosphocreatine shuttle:
   a. PCr shuttle: mito intermembrane space to cytosolic PCr and ATP (done?)
   b. PCr shuttle: cycling the Alpe de Huez (van Beek model, on web)
   c. Endothelial nucleoside metabolism, Ado → Ino → Hx → Xa → UA (writing)
   d. Central Purine Nucleotide balance, ATP, ADP, AMP, IMP + nucleosides (model)
6. Mitochondrial Oxidative Phosphorylation (Beard 2005, 2007) (published and on website)
7. Pathway for Oxygen:
   a. Recirc O2CO2 model: [Bart Jardine] A four region, recirculating model describing the transport, exchange, and metabolism of oxygen and carbon dioxide is nearly finished: https://www.physiome.org/jsim/models/webmodel/NSR/RecircO2CO2BTEX_3CompLung/ Model (components and overall) being tested currently for validation against data. The full JSim model is built from seven model modules, three of which are based on published models. The modules are put together by the Modular Program Constructor (MPC) [https://f1000research.com/articles/4-1461/v3] using directives embedded in each module. (www.physiome.org/Models/ model #405)
   b. Haldane and Bohr reciprocity in exercise. Blood temperature and density effects.
   c. Oxygen and CO2 solubilities: Temperature and density dependence (published)
8. Capacitance in Biochemical Networks: Responses in Transients. (starting)
9. Regional Myocardial Blood Flow: Coronary Reserve Capacity by MRI with Ado stress.

This is a clinical assessment using BTEX modeling for determining regional reserve by comparing the whole heart flow distribution during control state and then with Ado infusion to maximally dilate the coronary vessels. Dr. Peter Kellman's analytical method, using the blood-tissue exchange model as a component of the MRI reconstruction algorithm, provides the report within two minutes after the second injection of Gd contrast agent. **Fifteen thousand cases** have been done in the past two years.

Kellman P, Hansen MS, Nielles-Vallespinm S, Nickander J, Ugander M, and Xue H. Myocardial perfusion cardiovascular magnetic resonance: optimized dual sequence and

reconstruction for quantification. Journal of Cardiovascular Magnetic Resonance 19: 43 (14pp), 2017.

NEW TOOLS: MPC, Modular Program Constructor.

BEARD PROGRAM (U. Michigan):

We are assembling a new Metabolic Modeling Resource [1] to disseminate models of components/pathways of mammalian central metabolism for potential combination into large-scale models. The emphasis of this collection is in energy metabolism in muscle, including models of glycolysis/glycogenolysis, beta-oxidation, the tricarboxylic acid cycle, mitochondrial transporters, and oxidative phosphorylation. Many of the models and model components are built for use with the MATLAB-based Biochemical Simulation Environment (BISEN) for modular construction of metabolic systems models [2].

A page, http://www.virtualrat.org/computer-modeling-metabolic-kinetics, is being developed for distribution of model code. This page collects and disseminates models of components/pathways of mammalian central metabolism for potential combination into large-scale models. The emphasis of this collection is in energy metabolism in muscle, including models of glycolysis/glycogenolysis, beta-oxidation, the tricarboxylic acid cycle, mitochondrial transporters, and oxidative phosphorylation. It provides specific information on **Biochemical Thermodynamics:** A Database of biochemical thermodynamic quantities that can be used to obtain formation properties and dissociation constants (provided as pK's) for reference species associated with biochemical reactants at specified temperature and ionic strength; and to obtain reaction properties (including free energies and enthalpies) for associated reactions of glycolysis, the tricarboxylic Acid Cycle & the pentose phosphate pathway. This uses BISEN. A collection, **Models of Enzymes and Transporters,** provides a set of mechanistic models of functional components of metabolism to use as building blocks to construct computational models of biological systems.

**Another collection**, Integrated Systems Models is:

**Oxidative phosphorylation:**The Bazil et al. 2016 model (PMID: 26910433) includes the components of the respiratory chain (Complex I, III, & IV) the F1F0 ATPase, ANT, and phosphate transporter, as well as K+/H+ exchange. The model also accounts for ROS production at Complexes I and III. The model is parameterized against data from rat cardiac mitochondria.

**Tricarboxylic acid cycle:** The Dasika et al. model includes pyruvate dehydrogenase and the enzymes of the TCA cycle, as well as the mono-, di-, and tricarboxylate exchangers. (The model is integrated with the Bazil et al. model of oxidative phosphorylation.)

**Glycolysis/glycogenolysis:** The Vinnakota et al. (PMID:16617075) model includes the oxidation of glycogen to pyruvate and lactate. It also includes ATP hydrolysis, as well as the adenylate and creatine kinase reactions. (The model works well for resting conditions for skeletal muscle, but requires some structure changes to effectively simulate exercise conditions.)Tricarboxylic acid cycle: The Dasika et al. model includes pyruvate dehydrogenase and the enzymes of the TCA cycle, as well as the mono-, di-, and tricarboxylate exchangers. (The model is integrated with the Bazil et al. model of oxidative phosphorylation.)

1. http://virtualrat.org/news/metabolic-modeling-resources

2. http://virtualrat.org/software/bisen
3. Vanlier, J, F Wu, F Qi, K C Vinnakota, Y Han, RK Dash, and DA Beard. BISEN: Biochemical simulation environment (link is external). *Bioinformatics* 25:836-837, 2009.
4. Bazil JN, KC Vinnakota, DA Beard. Catalytic Coupling of Oxidative Phosphorylation, ATP Demand, and Mitochondrial Reactive Oxygen Species Generation (link is external). *Biophys J.* 110:962-71, 2016.
5. Li, X, and DA Beard. A database of thermodynamic properties of the reactions of glycolysis, the tricarboxylic acid cycle, and the pentose phosphate pathway(link is external). *Database* (Oxford) 2011:bar005

MCCULLOCH / REGNIER PROGRAM (UCSD / UW):

Our major effort at the moment is to link atomistic molecular models of contractile proteins (actin, myosin, troponins and tropomyosin) to filament scale Markov models of dynamic calcium dependent cross-bridge cycling, tension development and energetics. New coarse-graining approaches using Brownian dynamics, and Langevin dynamics are enabling us to bridge these scales to understand the mechanisms by which 2-deoxy-ATP can improve cardiac contractile function and may be a promising therapeutic for heart failure. We have also been developing workflows and JuPyter notebooks to facilitate model sharing though these are large scale simulations that require some expertise in the methods.