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Title: Cardiac Energy Grid

Abstract:

MSM Challenges being addressed: These selected [PAR-15-085](https://grants.nih.gov/grants/guide/pa-files/par-15-085.html) bullets are targets of our research efforts in this U01, the Cardiac Energy Grid:

9)    Model predictions that drive a community of experimentalists towards systematic testing and validation.

10)  Predictive multiscale models that strongly incorporate uncertainty quantification

6)    Multiscale models strongly coupled with standardized protocols for model-driven data collection

5)    Reproducible and reusable multiscale models that will be integrated and adopted into model-poor fields (e.g.  tissue engineering, regenerative medicine, drug and gene delivery, preventive interventions)

18)  Predictive multiscale models to improve clinical workflow, standard operating procedures, patient-specific modeling for diagnosis and therapy planning (e.g. image analysis on-line)

**Are you using machine learning or causal inference methods, and how?**

Our methods are basically biophysical, biochemical, and deterministic, with thermodynamic constraints so far. We are exploring how to use machine learning re alternative pathway fluxes, e.g. where does optimal control play a role in defining cell usage of glucose versus fatty acid for energy production.

**Describe significant MSM achievements:**

**Experiments iterated with modeling analysis:**

Efforts have focused on the central aspects of cardiac energy production and utilization with the long term objective being to define the varied routes to cardiac failure. To do this we perform experimental studies in order to define the models for the processes required for to deliver substrates from the blood to the sites of metabolic reactions: the PATHWAYS for glucose, fatty acid, oxygen, nucleosides and ATP.

Putting these together into biologically relevant cardiac model systems characterizes the links among mechanical, electrical, and metabolic models. This allows us to formulate compatible, multi-regional correlated models of the whole heart with the tradeoffs in substrate use versus contractile and electrical activity during differing states of rest and exercise up to maximum exercise in normal activation, as well as with abnormalities of conduction and excitation. Control of substrate choice, of vasomotor state locally, and of force development locally are all dependent on patterns of excitation.

The overall aims are two: (1) To provide a set of reproducible models of central aspects of cardiac metabolism to the research and clinical investigative communities, and (2) To provide a modeling framework for investigations into the conditions for and causes of cardiac failure. The details are expressed as a set of projects categorized by PATHWAYS related to requirements for, and utilization of ATP generation in the heart.

**Pathway for Substrate Delivery by Coronary Blood Flow:**

Models for blood-tissue exchange, convection, diffusion, permeation, reaction;

Flow-limited exchange for O2, H2O; barrier-limited for most solutes;

Flow heterogeneity: fractal correlation structure; fractal vascular system;

Correlation structure in flows and effects of vasodilators;

Models of vaso-regulatory processes in normoxia and hypoxia;

Pressure-flow autoregulation in the heart;

Role of ATP and Ado in hypoxia and SM response via A2 receptors;

Adenosine vasodilation differs depends on the source: blood versus cardiac cell.

**Pathway for Glucose**:

Multicapillary transport across endothelium, interstitium and cardiac cell membrane.

Modeling Glut4 regulation (+/- insulin and insulin receptor activation).

Glycolysis, hexokinase, glycogen cycle, to lactate and pyruvate. FDG kinetics for PET studies.

Kinetic models with thermodynamic constraints.

Osmotic responses in strenuous exercise dynamics.

Pentose shunt.

**Pathway for Fatty Acid**:

Albumin binding affinities and release kinetics.

Endothelial and sarcolemmal transporters; interstitial radial diffusion modeling;

Formation of acyl CoA, DAG, TAG, into vacuoles or lipid droplets; re-acylation from droplet;

Acyl CoA transferase into mitochondria; beta oxidation.

**Pathway to CHO and fat oxidation, the TCA cycle**:

TCA cycle w/wo aspartate/glutamate shuttle;

Tracer versions of TCA for 13C - glutamate isotopomer analysis;versions for C1 or C2 labeling.

**Pathway for Oxygen**:

Oxygen inflow/ CO2 excretion: Ventilatory mechanics and alveolar gas exchange

Hb(O2)4 binding models: Effects of pO2, pCO2, pH.

Temperature and density affects on Hb-oxygen binding. Determination of Kd.

Competition: Hb binding with CO, NO

Tutorials for HbO sequence in JSim, later for Matlab, SBML, CellML libraries

Hyperbaric Rx for CO poisoning.

Hypoxia, NO and NO release

Capillary-tissue Exchange of O2, H2O, CO2

Diffusion of H20 and O2 inside RBC, cell binding sites (muscle Mb)

Binding and reaction at cytochrome oxidase (Dash)

Oxidative Phosphorylation models, a sequence of them: (Beard05, Beard07, Dash,)

**Pathway for Nucleosides and Nucleotides:** Experiments and modeling analysis:

Exchange and reactions of adenosine, inosine hypoxanthine, xanthine, uric acid in the heart.

Cardiac purine release in hypoxia.

Modeling PCr-ATP shuttle (myokinase, Cr kinase, mito membrane)

Low flow perfusion causes 5’nucleosidase down regulation and IMP accumulation

Purine salvage: definition, mechanisms, models

**ATP use for Excitation-Contraction Coupling and Ionic Balance:**

Cardiac action potential and EC-coupling models

Cross-bridge models with accounting for increased axial cooperativity with deoxyATP

Reduced forms for for excitatory spread and arrhythmia susceptibility (long QT)

Applications linking LBBB and metabolic shifts

Heart failure: diminished deltaG is only part of the story!

NOTE (January 2018): At this halfway point in the grant period we have the data for over 80% of the projects listed, about 2/3 of the models are developed fully operational status, about 40% being completed to validation and available for distribution (free) on the model repository at [www.physiome.org](http://www.phsyiome.org/). Only about 10% have used uncertainty quantitation so far. Tutorials are developed and on this website for the more elementary topics such respiratory mechanics and gas exchange, compartmental analysis, and blood-tissue exchange. There is, for example, a 100-page operators manual for GENTEX, a convection-diffusion-permeation-reaction multipath model for metabolic reaction sequences that in fully-expanded form uses 110,000 differential equations, but can be reduced to one compartment. In the next 2.5 years we expect to have all of the models, and thus a firm base on which to characterize heart failure.

**New MSM challenges**:

A next challenge in cardiac metabolism/energetics is *protein metabolism.* Protein fluxes are large; the balance between proteolysis and protein synthesis fluctuates with activity. Athletic stresses require long recoveries. The pathway to protein synthesis begins with the signaling and control of mRNA production to supply the recipe for transcription. The influences of environment, organism activities, humoral and neural signals, and cellular state come together drive many cells simultaneously to transcription in a coordinated fashion: the nuclear (or mitochondrial) DNA response to these drivers are guided by the composite set of input signals from all of these levels. Defining these signals and their origins and connections throughout the body's systems is a hugely complex problem.

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