Multiscale Modeling:

Providing Underpinnings for Guyton-style Cardiorespiratory System Modeling through Cardiac Cellular-level Submodels

Jim Bassingthwaighte, Maxwell Neal, Howard Chizeck, and Les Atlas

National Simulation Resource

Department of Bioengineering

University of Washington

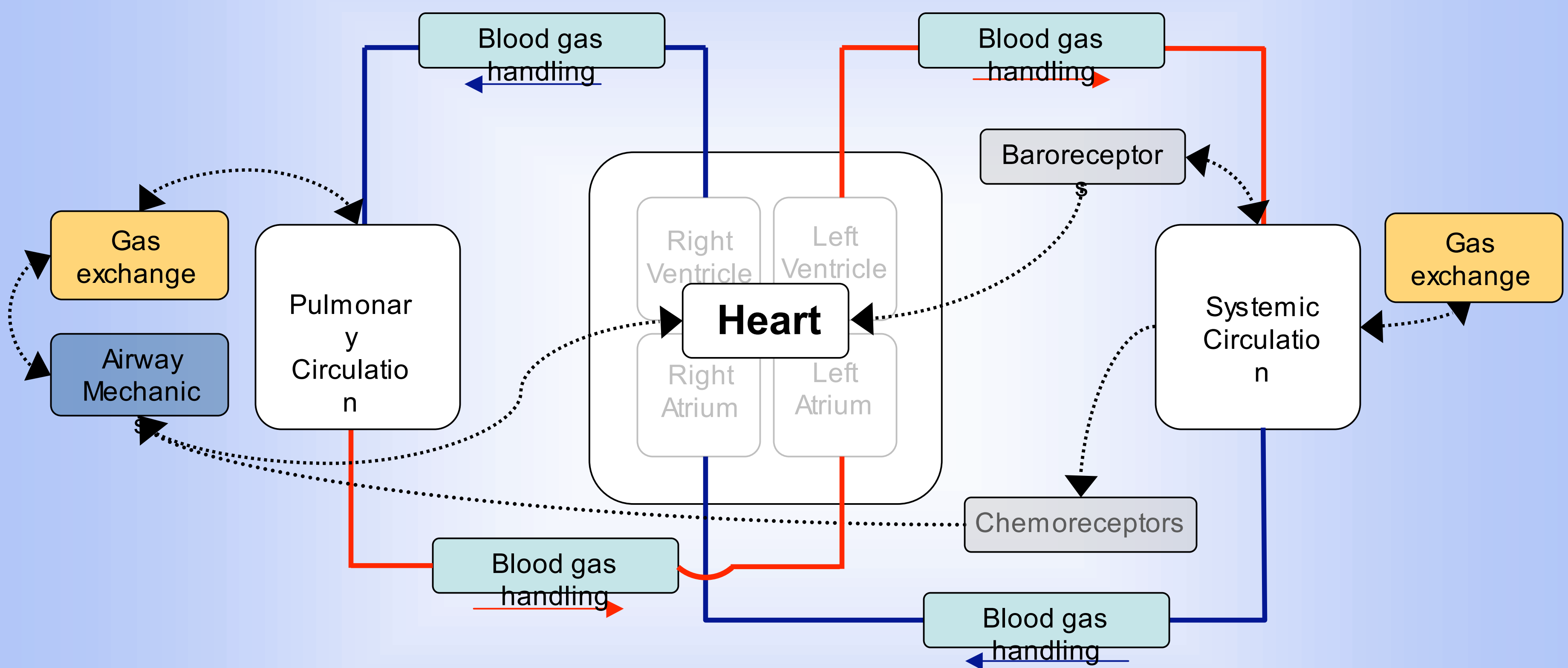
Speedy Model Computation

- Modeling Analysis of Data:
  - optimization requires iteration
  - heterogeneous systems require multiple parameterizations
  - clinical data analysis turns into supercomputing
- Large Scale Modeling --> Emergent behavior
  - exploring: compute at the speed of thought
  - semi-automate explorations
    - iterative looping on parameters
    - behavioral analysis with 2D and 3D displays

Working from Top Down

- Cardiorespiratory System Models without cells, but needing them
- Constraints on Integrated Systems
  - mass and volume for blood and gasses
  - optimizing behavior of closed multiparameter systems
  - lack of adaptability of single or dual level systems
- Cellular metabolic and signaling systems are needed for extending adaptability to extreme changes in conditions
- Reducing cellular models for computation - an optimization process for each of several levels of complexity
- Detection and control of adaptive computation by substitution for reduced-form modules

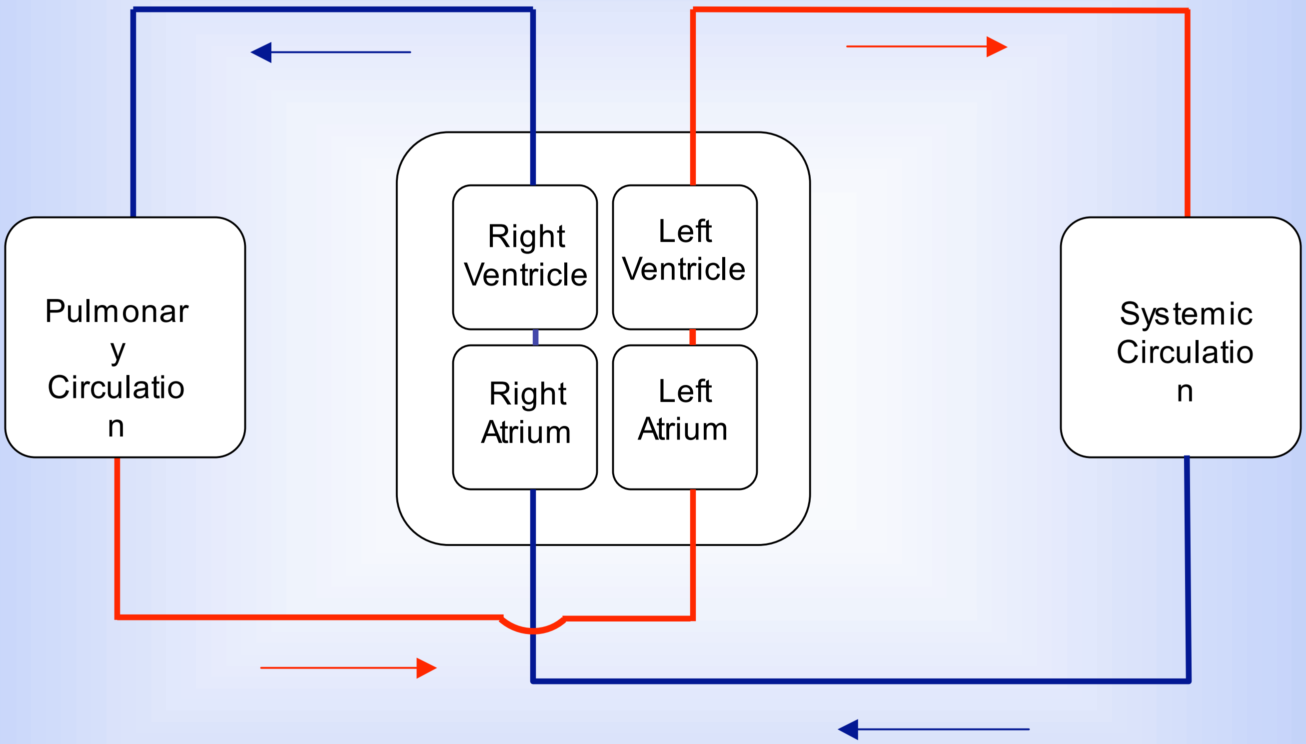
Highly Integrated Physiology (HIP) model structure

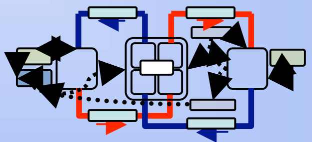


Models available at http://nsr.bioeng.washington.edu

Circulatory model

(Lu 2001, Rideout 1991, Zinemanas 1994)

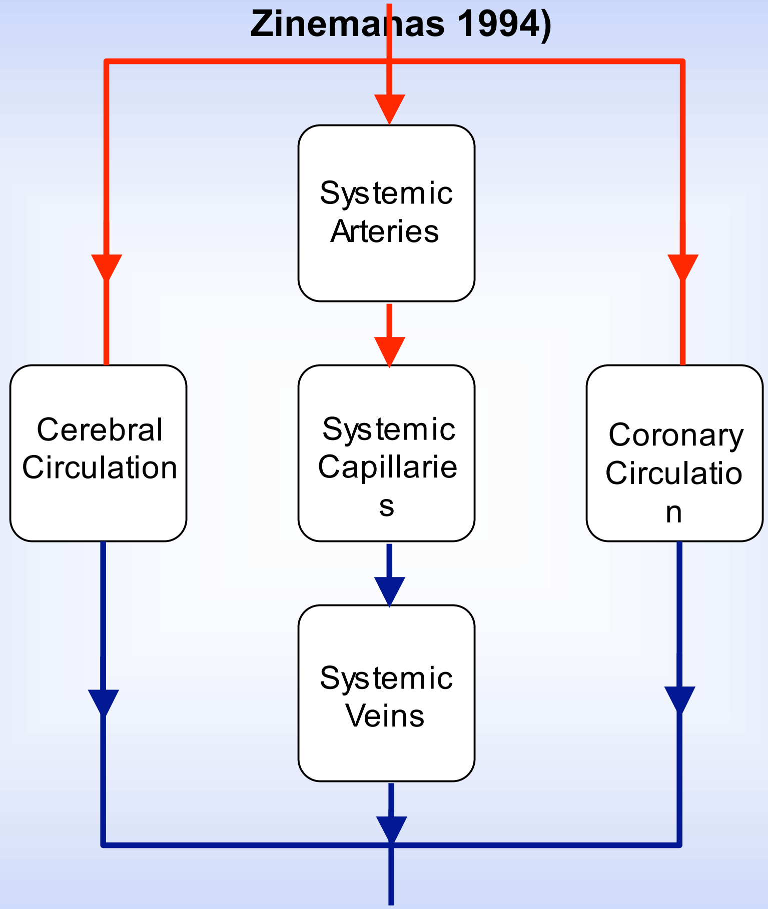


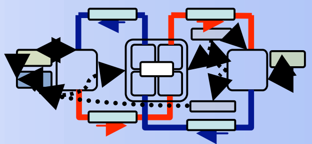


HIP model

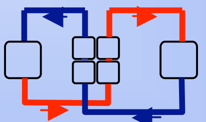
Models available at http://nsr.bioeng.washington.edu

Systemic circulation (Lu 2001, Zinemanas 1994)





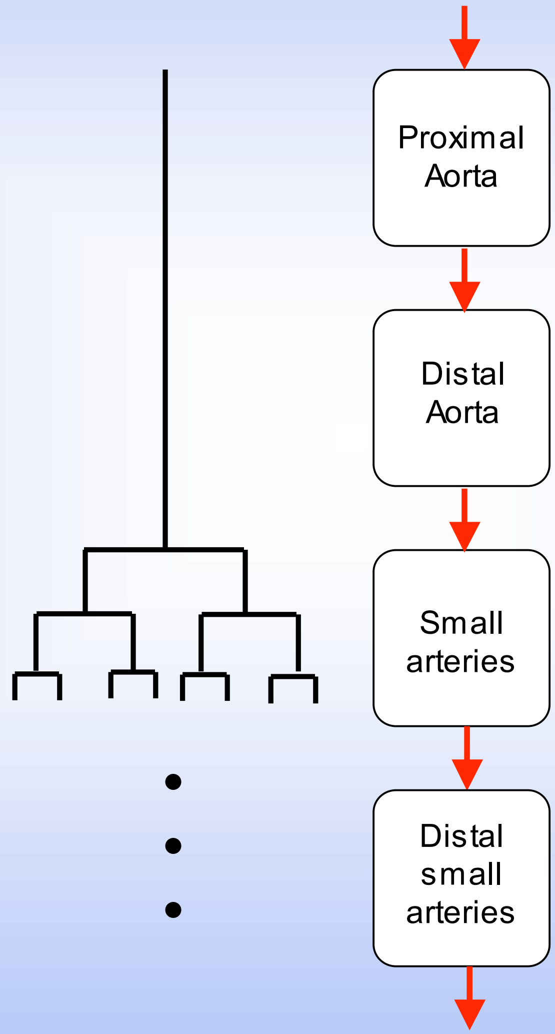
HIP model

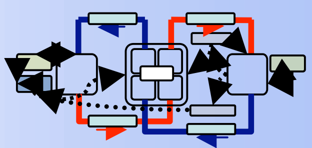


Circulatory model

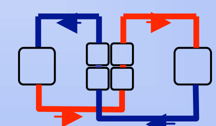
Models available at http://nsr.bioeng.washington.edu

Systemic Arteries
(Lu 2001)





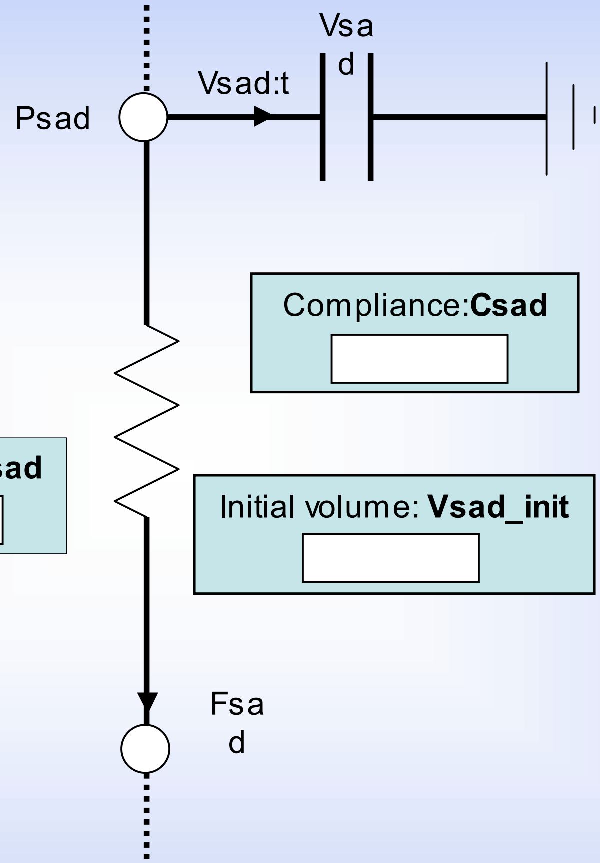
HIP model



Circulatory model

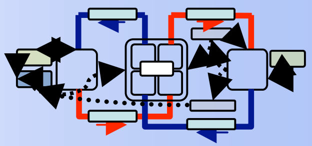
Models available at http://nsr.bioeng.washington.edu

Small Arteries

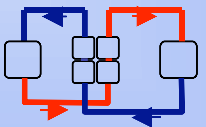


Psad = Vsad/Csad

Change in vessel volume = Flow in – Flow out

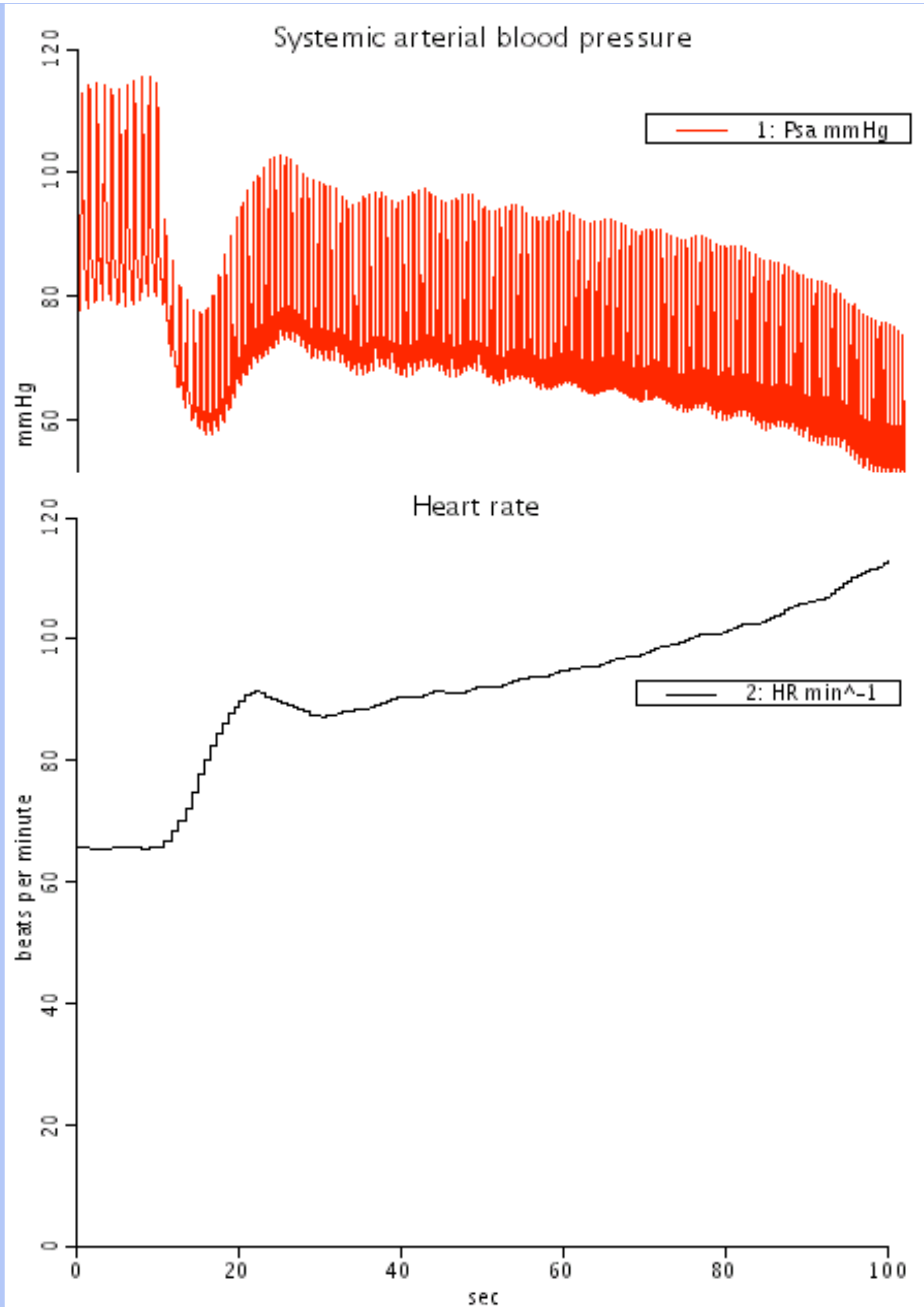


HIP model



Circulatory model

Models available at http://nsr.bioeng.washington.edu



Response to 4 mm diameter wound in LV free wall
with
40% reduction in contractility,
both at t = 10 sec

(1300 ml blood lost from an initial blood volume of 5100 ml. The Initial loss from 10 to 60 seconds is into pleura spacel, then pericardium clots so that tamponade develops from 60 to 100 seconds)

JSim Demo of a Cardiorespiratory model

Working from Top Down

- Cardiorespiratory System Models without cells
- Constraints on Integrated Systems
  - conservation: mass and volume for blood and gasses
  - optimizing behavior of closed multiparameter systems
  - lack of adaptability of single or dual level systems
- Cellular metabolic and signaling systems are needed for extending adaptability to extreme changes in conditions
- Reducing cellular models for computation - an optimization process for each of several levels of complexity
- Detection and control of adaptive computation by substitution for reduced-form modules

What to do next:

- Match multiple data sets for validation
- Improve lung mechanics and blood gas handling
- Use separate systemic circuits for gut, kidney,muscle
- Replace electrical with mechanical models for pressure-volume-flow in blood vessels.
- Incorporate blood-tissue water exchanges due to Starling forces; account for Hct and osmolarity reduction with hemorrhage and intravenous infusion.
- Numerical improvements, better solvers and optimizers.

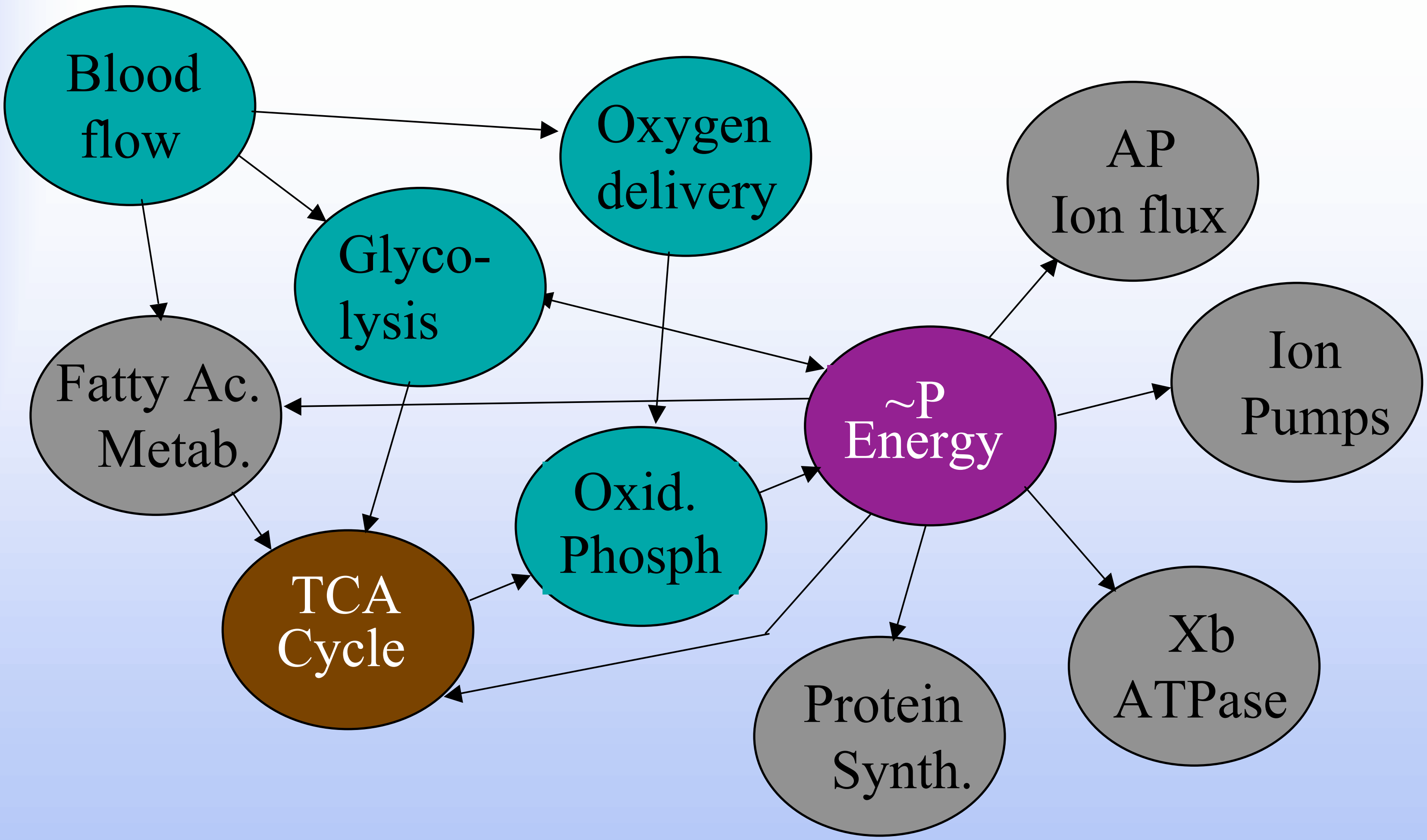
Working from Top Down

- Cardiorespiratory System Models without cells
- Constraints on Integrated Systems
  - mass and volume for blood and gasses
  - optimizing behavior of closed multiparameter systems
  - lack of adaptability of single or dual level systems
- Cellular metabolic and signaling systems are needed for extending adaptability to extreme changes in conditions
- Reducing cellular models for computation - an optimization process for each of several levels of complexity
- Detection and control of adaptive computation by substitution for reduced-form modules

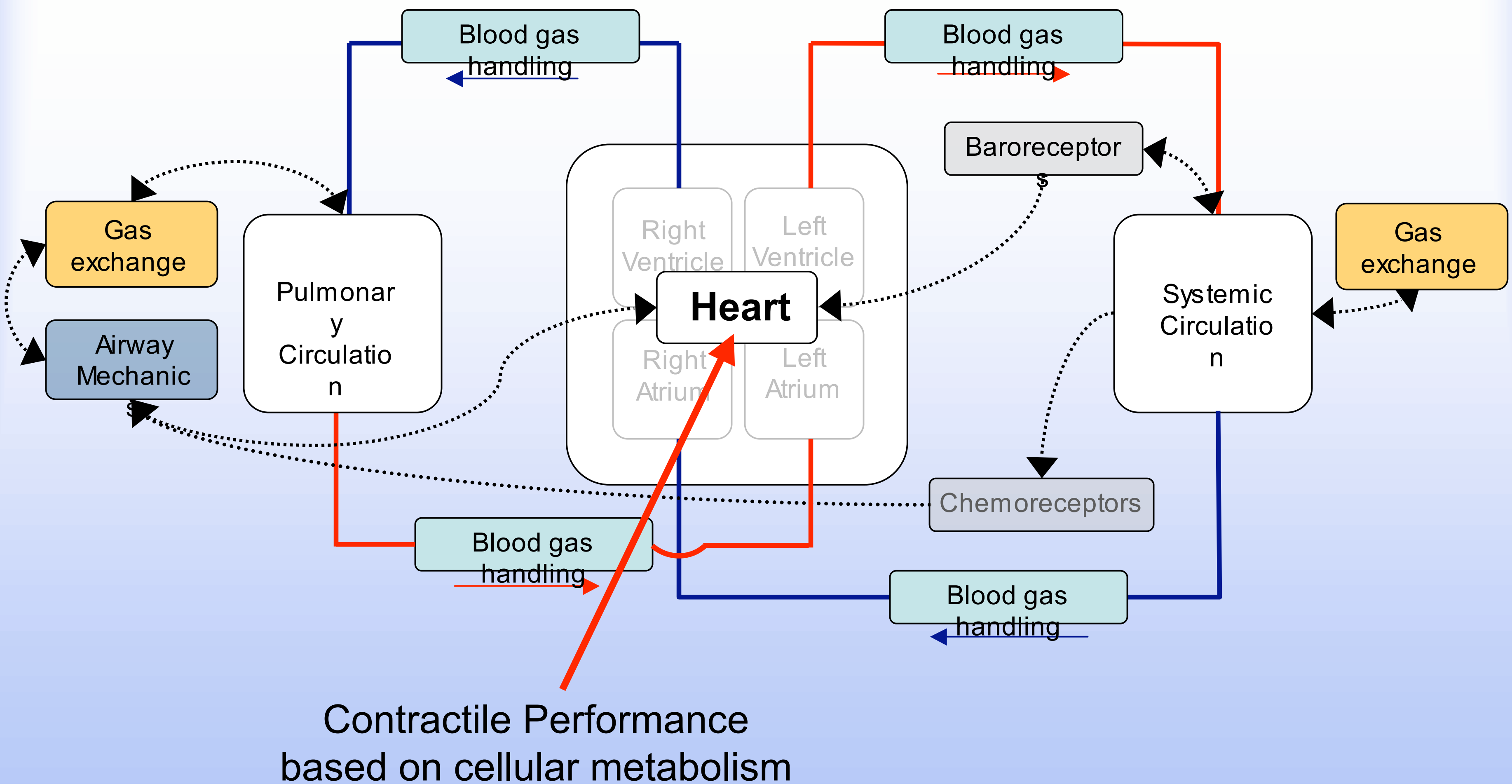
Working from Top Down

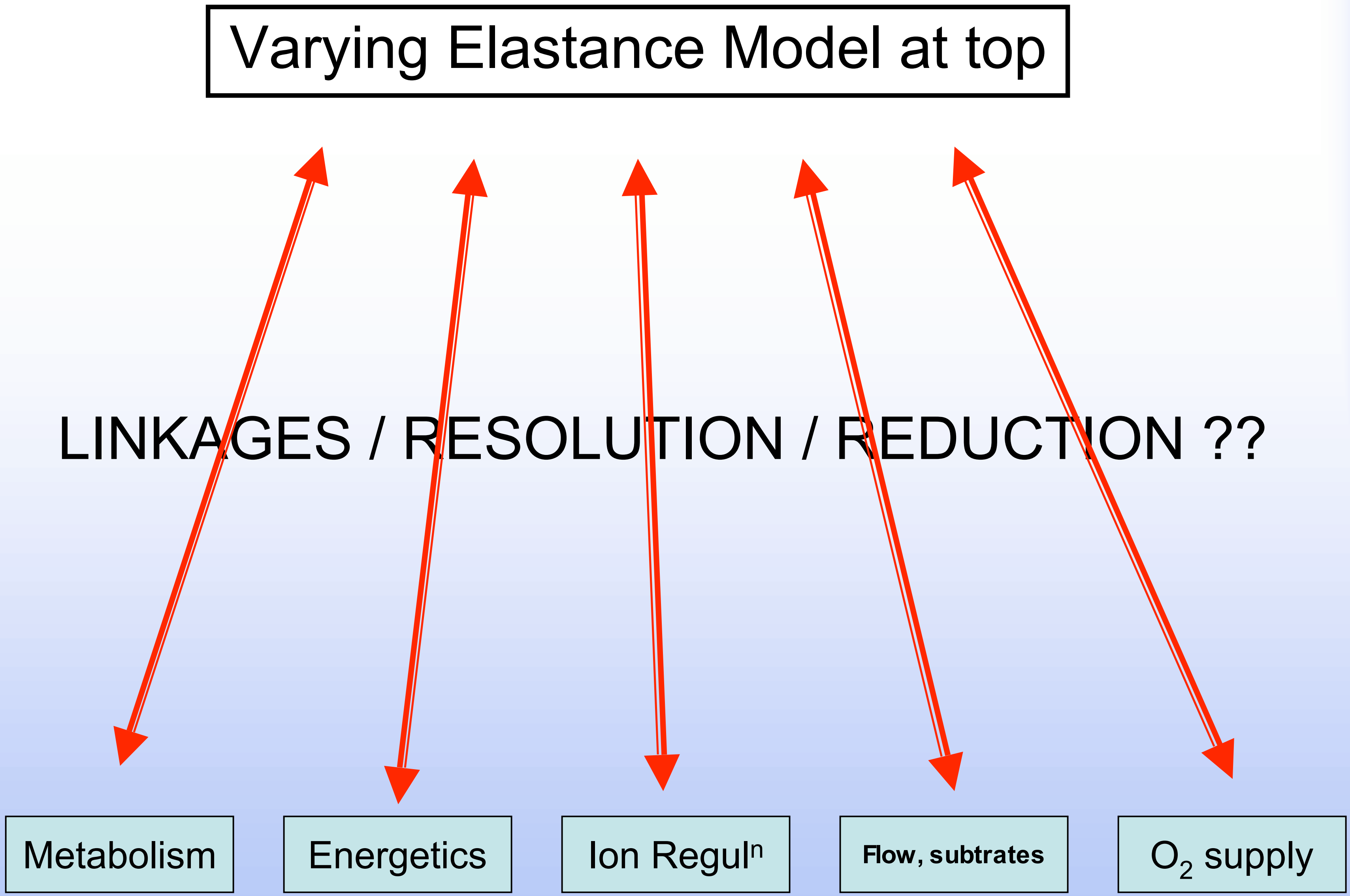
- Cardiorespiratory System Models without cells
- Constraints on Integrated Systems
  - mass and volume for blood and gasses
  - optimizing behavior of closed multiparameter systems
  - lack of adaptability of single or dual level systems
- Cellular metabolic and signaling systems are needed for extending adaptability to extreme changes in conditions
- Reducing cellular models for computation - an optimization process for each of several levels of complexity
- Detection and control of adaptive computation by substitution for reduced-form modules

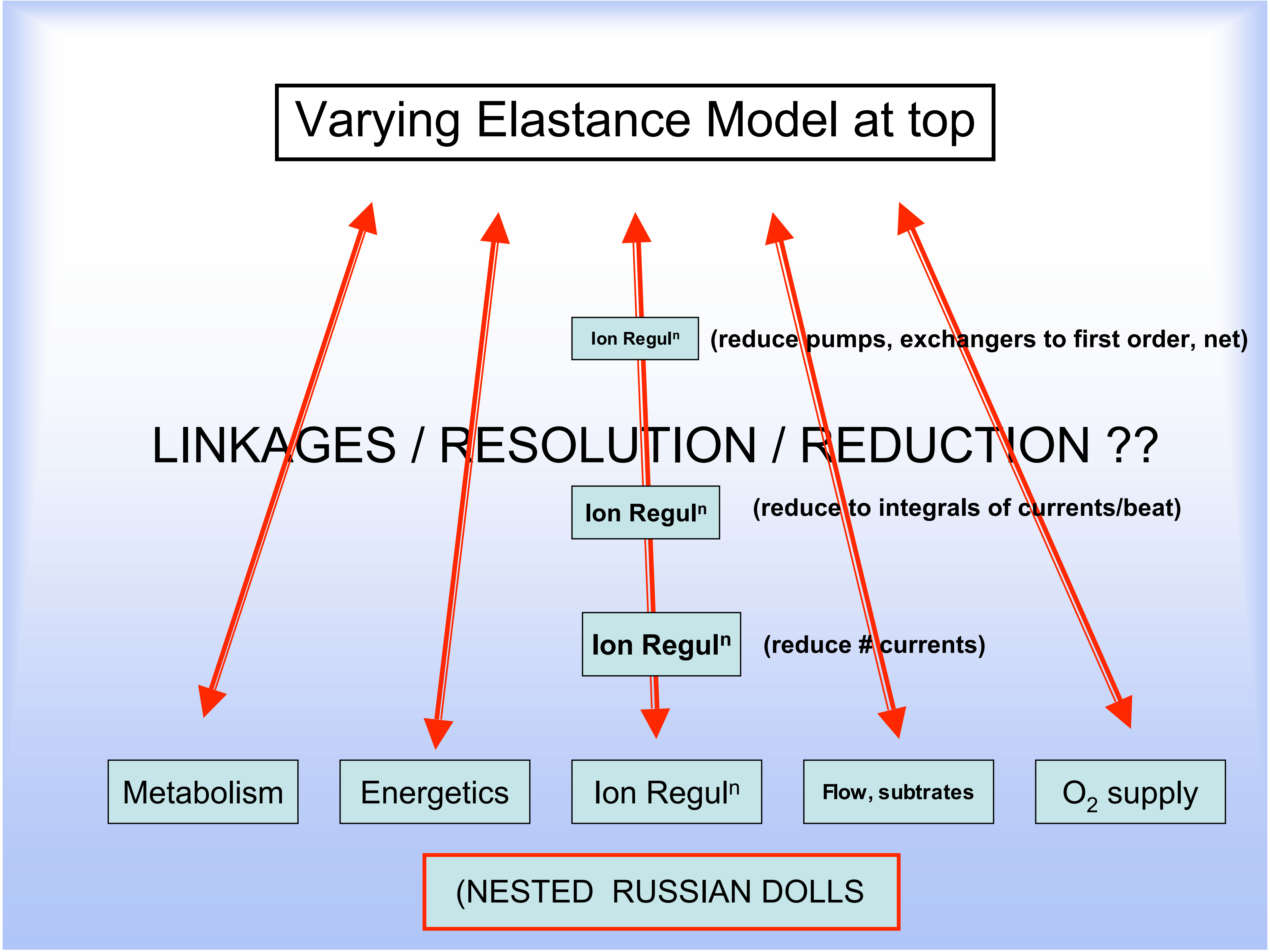
Multicomponent models of cardiac intermediary metabolism

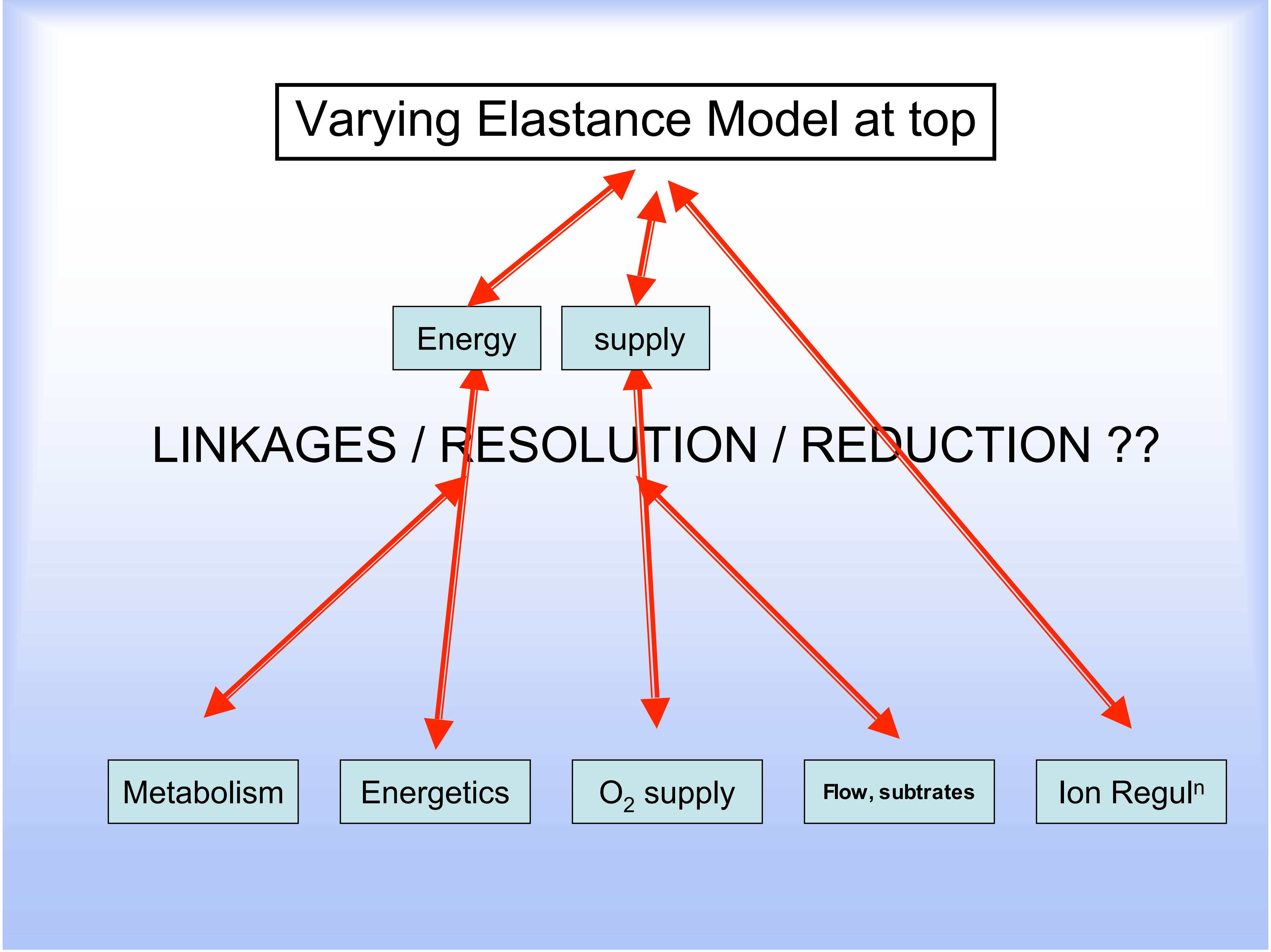


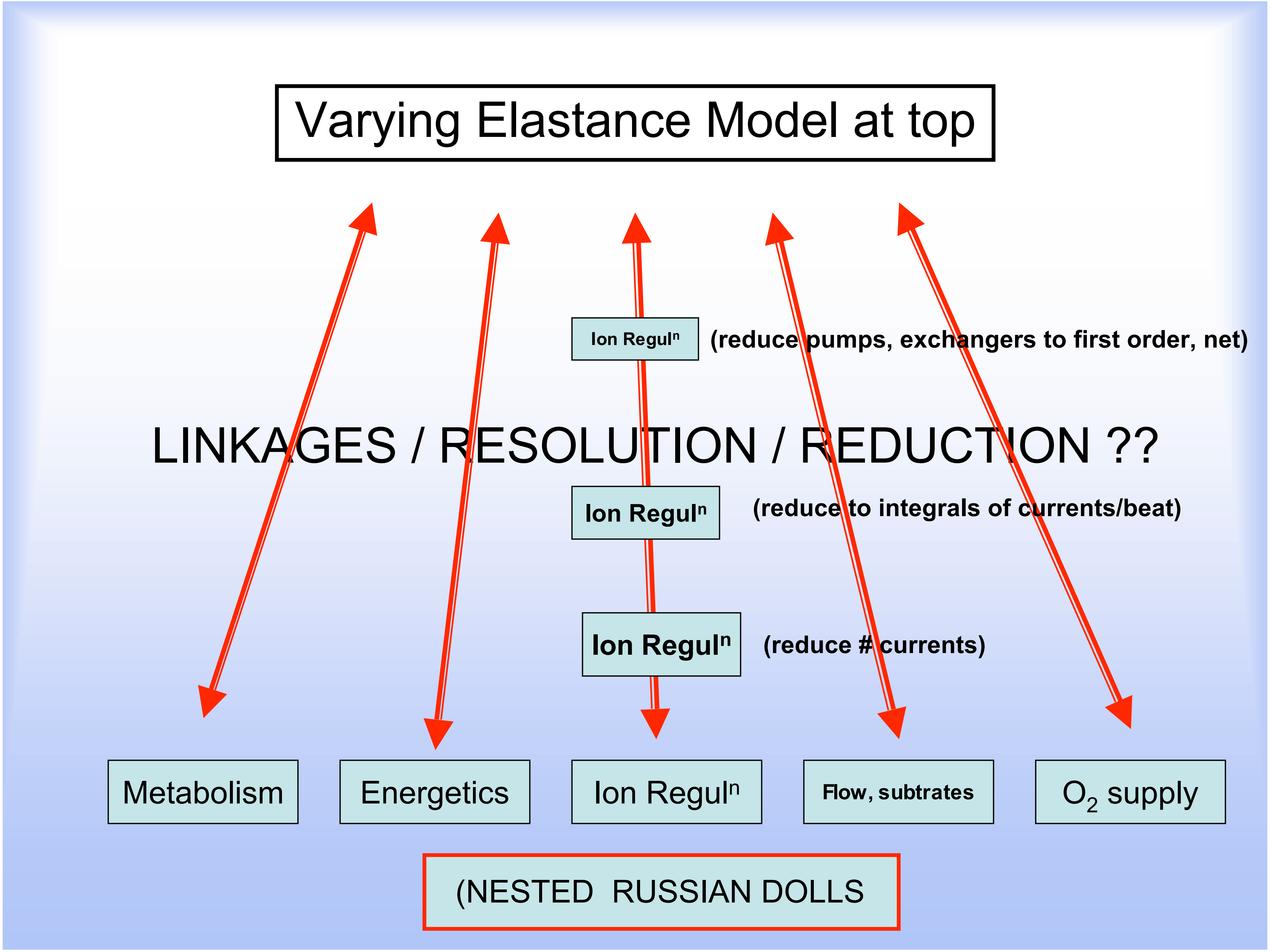
Keeping the biophysics available to allow adaptations at the top level




Varying Elastance Model at top
LINKAGES / RESOLUTION / REDUCTION ??
Metabolism
Energetics
Ion Reguln
Flow, subtrates
O2 supply


Varying Elastance Model at top
Ion Reguln
(reduce pumps, exchangers to first order, net)
LINKAGES / RESOLUTION / REDUCTION ??
Ion Reguln
(reduce to integrals of currents/beat)
Ion Reguln
(reduce # currents)
Metabolism
Energetics
Ion Reguln
Flow, subtrates
O2 supply
(NESTED RUSSIAN DOLLS


Varying Elastance Model at top
Energy
supply
LINKAGES / RESOLUTION / REDUCTION ??
Metabolism
Energetics
O_2 supply
Flow, subtrates
Ion Regul^n


Varying Elastance Model at top
Ion Regul^n
(reduce pumps, exchangers to first order, net)
LINKAGES / RESOLUTION / REDUCTION ??
Ion Regul^n
(reduce to integrals of currents/beat)
Ion Regul^n
(reduce # currents)
Metabolism
Energetics
Ion Regul^n
Flow, subtrates
O_2 supply
(NESTED RUSSIAN DOLLS

Working from Top Down

- Cardiorespiratory System Models without cells
- Constraints on Integrated Systems
  - mass and volume for blood and gasses
  - optimizing behavior of closed multiparameter systems
  - lack of adaptability of single or dual level systems
- Cellular metabolic and signaling systems are needed for extending adaptability to extreme changes in conditions
- Reducing cellular models for computation - an optimization process for each of several levels of complexity
- Detection and control of adaptive computation by substitution for reduced-form modules

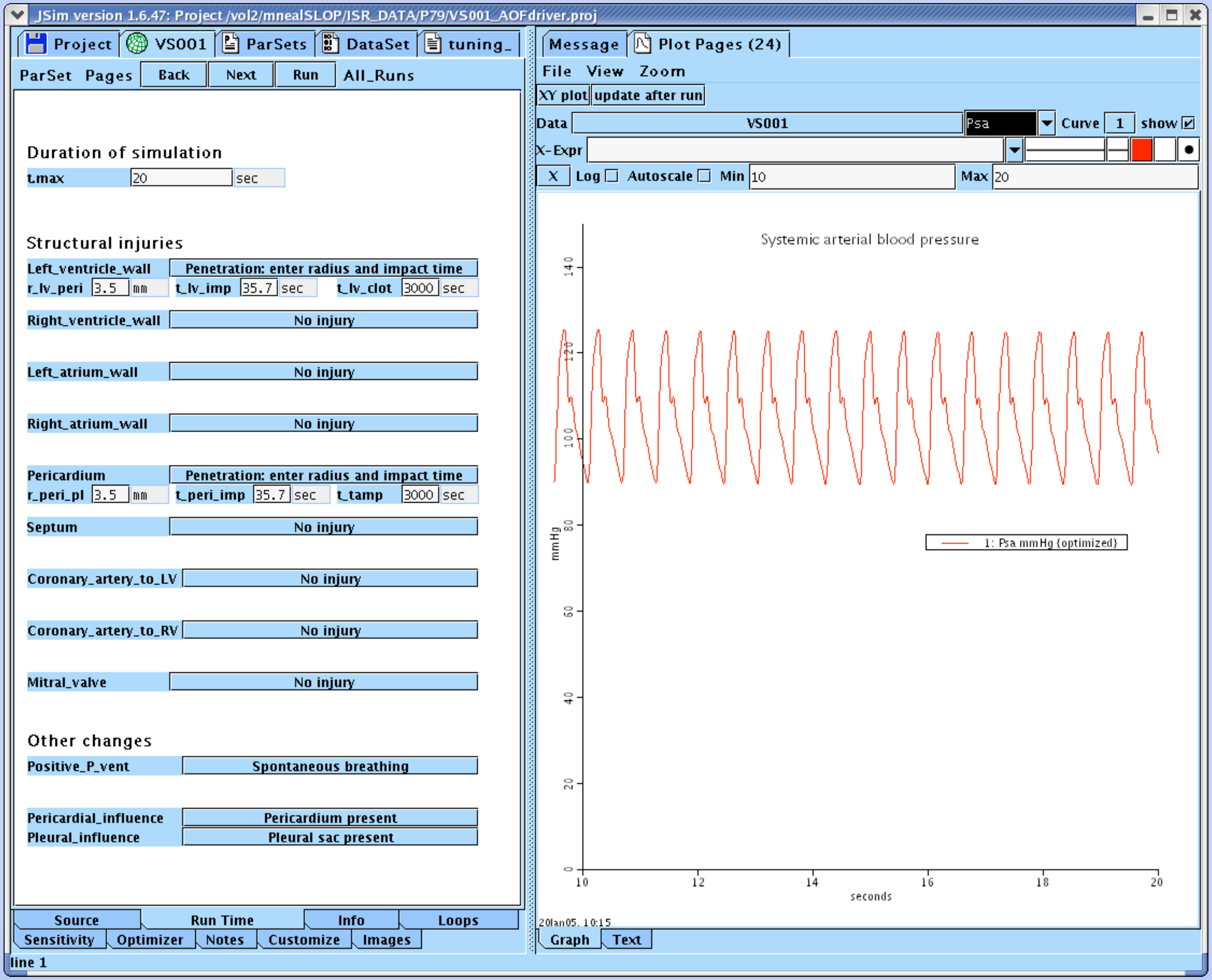
Working back down to the more basic models that control the adaptive responses

- Detection and control of adaptive computation by substitution for reduced-form modules
  - a little artificial intelligence:
    - Decision making based on observation that model conditions are outside of prescribed limits.
    - the observation points to the modules to go back down the tree to put into operation.
    - having a menagerie of reduced model forms covering different ranges of conditions can avoid some antireductionist trips to the root modules
  - automated deviation detection:
    - Detection by continuously running signal analysis programs that identify when a signal changes character (frequency content, Lyapunov exponent, correlation structure, etc.)
    - No so easy to identify the most relevant route to model re-expansion
    - combine this with some AI to choose simplest route

SUMMARY

- Compute at the speed of thought.
- Model reduction, multiscale, is essential.
- Multiscaling is difficult and fraught with compromise.
- Successive reductions cause successive constraints AND successive losses in adaptability to changing conditions.
- Going back up the down staircase should be automated while running large scale reduced-form models.
- It’s a tricky art form, but turning into science.

Simulation environment: JSim



Models available at http://nsr.bioeng.washington.edu