[simula . research laboratory]

Using mathematical models to test physiological hypotheses

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Outline

- Mathematical models in physiology
  - Phenomenological models
  - Multiscale/integrative models
- Model examples
  - Circulatory models (demo)
  - ECG/ischemia model
  - Coupling heart models to circulatory models
- Concluding remarks

“All models are wrong, some models are useful”

George Box (statistician)

The most detailed models are not necessarily the most useful

Flow through a vessel with resistance *R:*

$$Q = \Delta p / R$$

Volume of a vessel with pressure *p:*

$$V = V_0 + Cp$$

Cauchy´s equation of motion:

$$\rho \frac{\partial v}{\partial t} = \nabla \cdot \sigma + \rho g$$

Which one is better?

- Equation of motion:
  - Well established physical principle (Newtons 2nd law)
  - High resolution information
  - Difficult to solve
  - (Very) difficult to determine material properties

- Simpler models:
  - Narrow regime of applicability
  - Less information output
  - Few parameters to determine
  - Easy to solve

Adding (simple) material properties to the equation of motion

Fluid; the Navier-Stokes equations

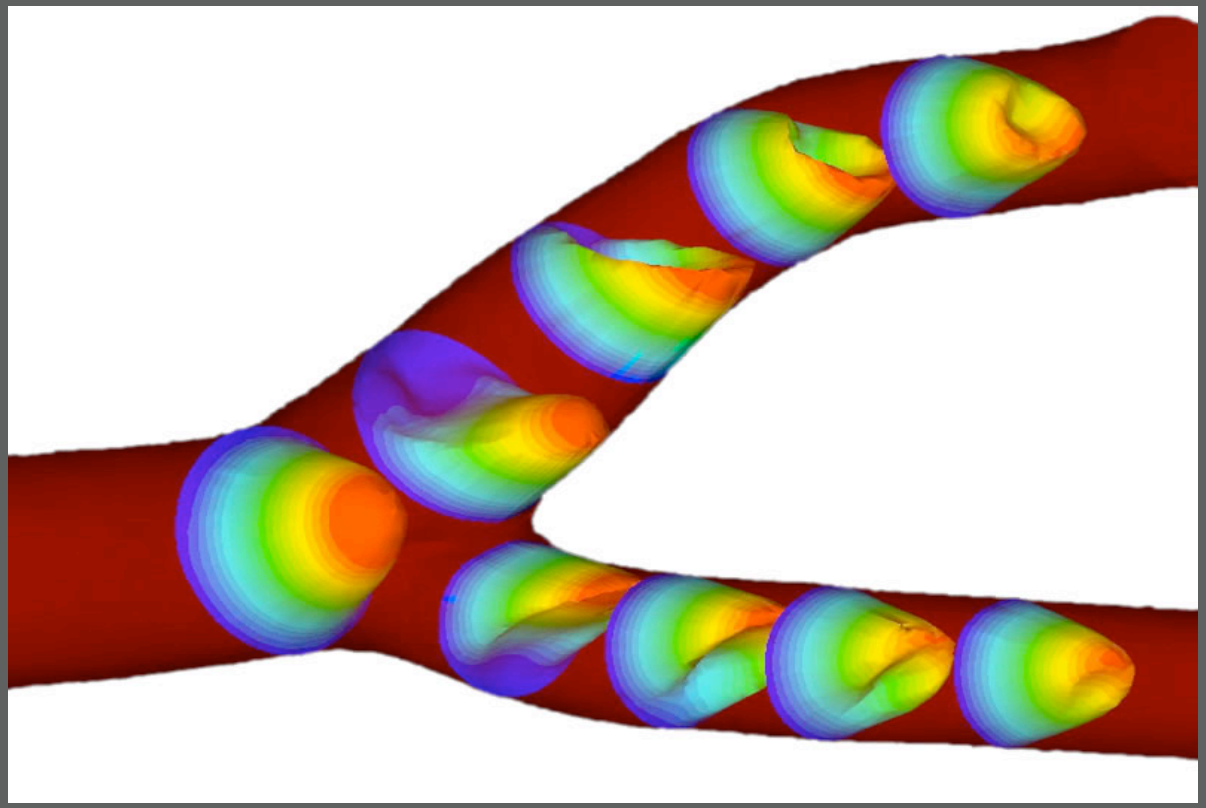
$$\rho\left(\frac{\partial v}{dt} + v \cdot \nabla v\right) = -\nabla p + \mu \nabla^2 v + \rho g$$

$$\nabla \cdot v = 0$$

Elastic materials (linear)

$$\nabla\left[(\lambda + \mu)\nabla \cdot u\right] + \nabla \cdot \left[\mu \nabla u\right] = -\rho b$$

The detailed models can only view a small part of the system



Phenomenological models can describe the complete circulation

Networks of smaller vessels are seen as linear resistance vessels

$$Q = \Delta p / R$$

Larger vessels are approximated as linear compliance vessels

$$V = V_0 + Cp$$

The heart can be described as a compliance vessel with time varying parameters

$$V_h = V_0(t) + C(t)p$$

Models made from these simple components have been tuned to fit experimental data

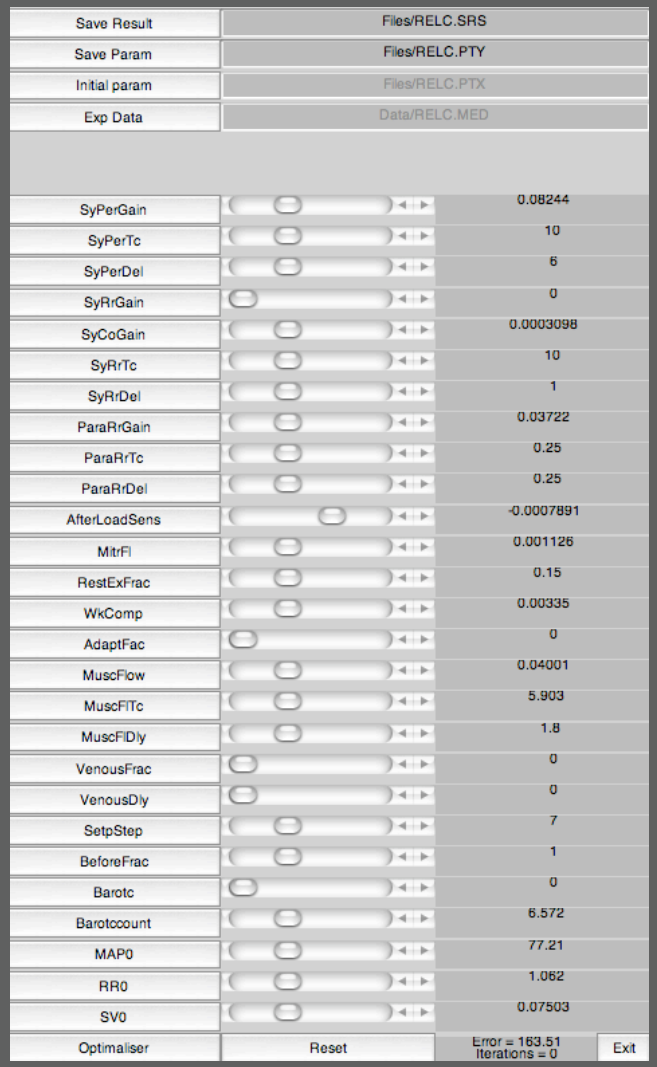
Toska, Eriksen, Walløe. Short-term control of cardiovascular function: estimation of control parameters in healthy humans. Am J Physiol. Heart Circ Physiol, 1996.

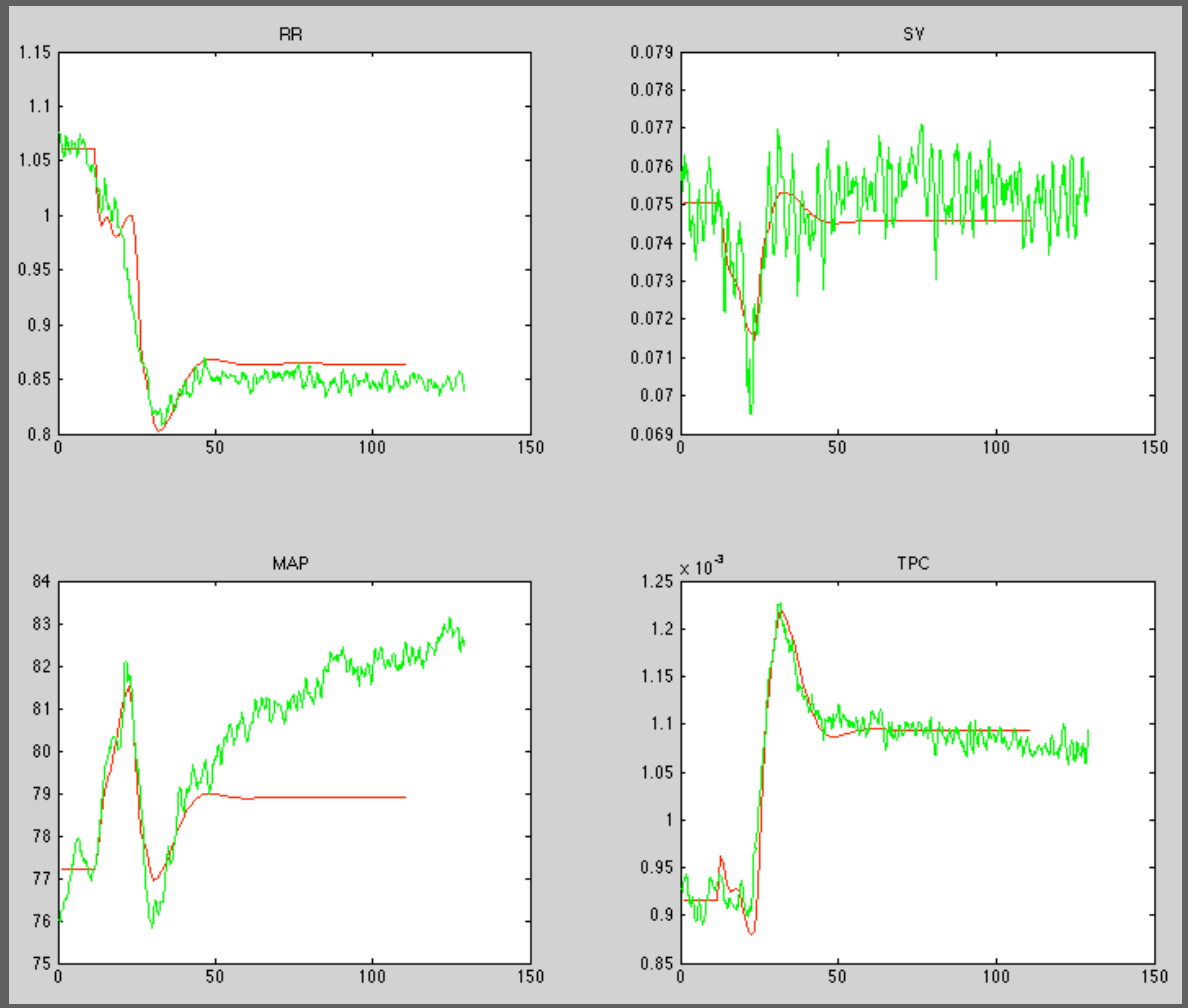
Elstad, Toska, Walløe. Model simulation of cardiovascular changes at the onset of moderate exercise in humans. J Physiol, 2002.

Hoppensteadt, Peskin. Modeling and simulation in medicine and the life sciences, Springer-Verlag, 2002.

Lu et al, A human cardiopulmonary system model applied to the analysis of the Valsalva maneuver. Am J Physiol. Heart Circ Physiol, 2001.

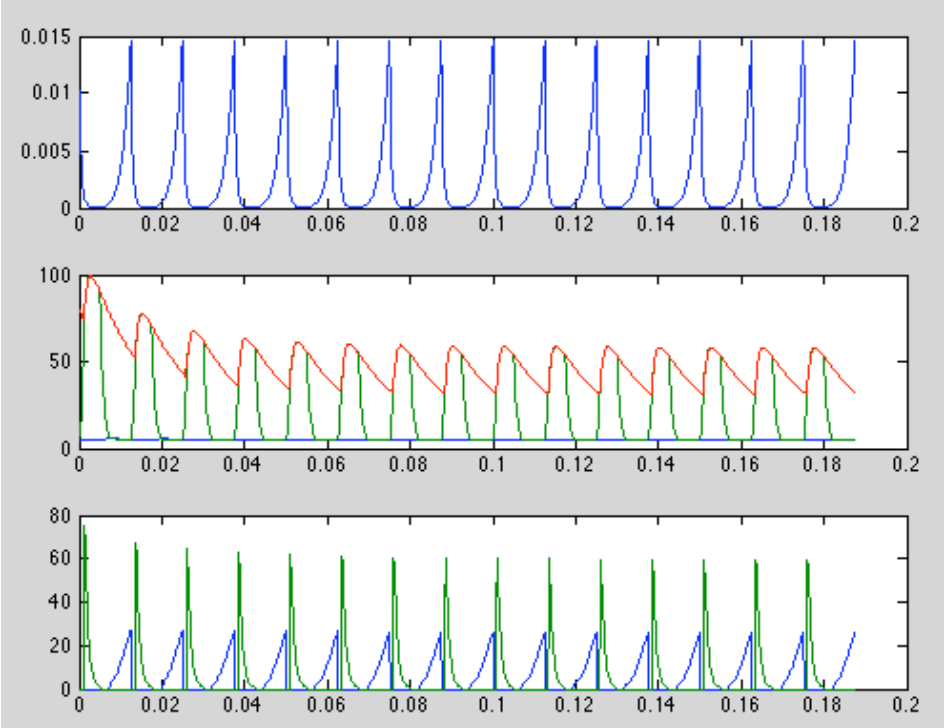
Example 1; simple hemodynamics, advanced feedback loop

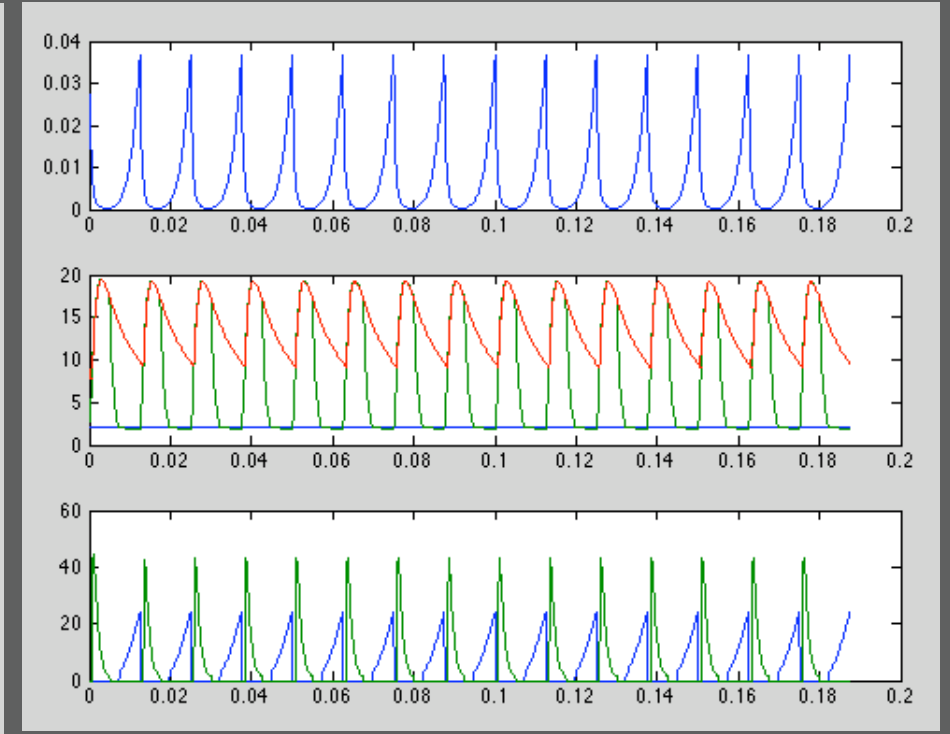




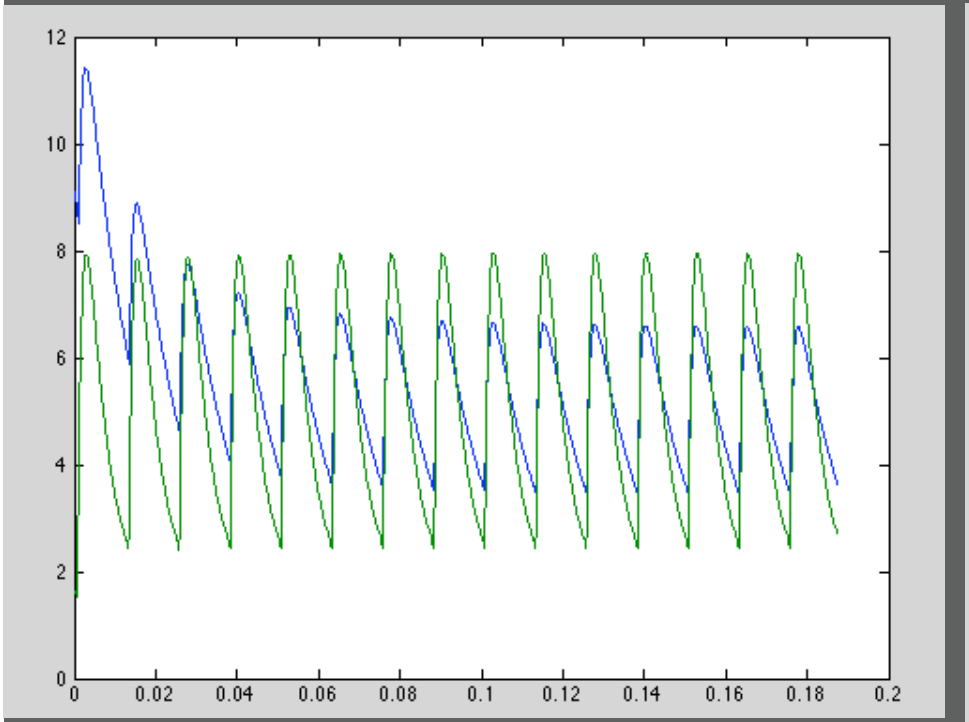
Toska, Eriksen, Walløe, 1996
Elstad, Toska, Walløe, 2002

Example 2; more advanced hemodynamics model, unregulated circulation





Hoppensteadt, Peskin, 2002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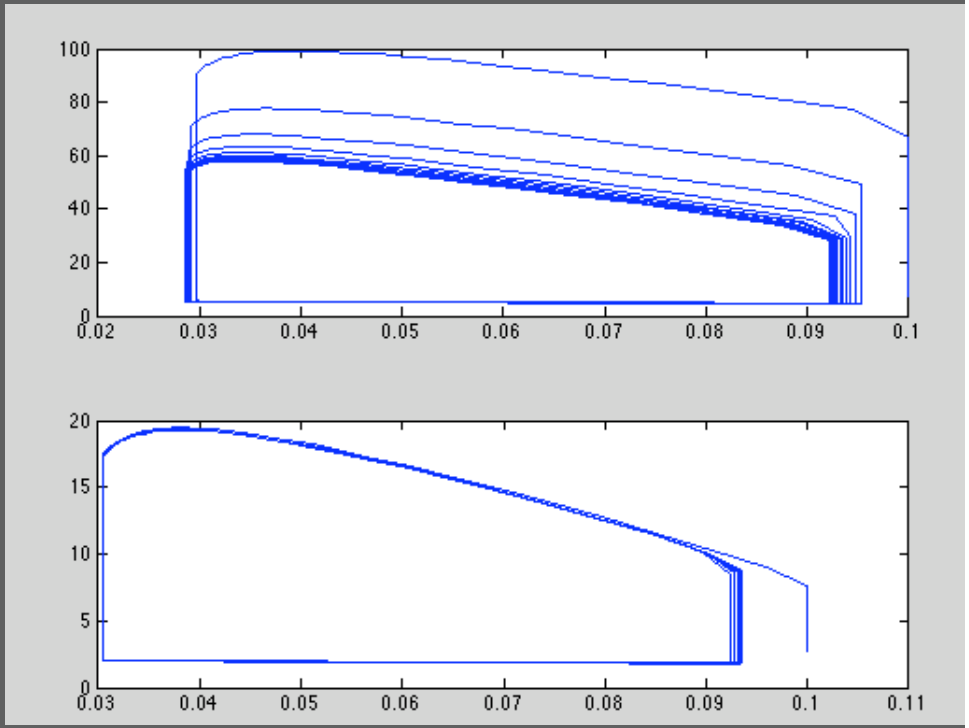
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Although useful, the lumped parameter models have severe limitations

- Made from coarse scale data
  - Ex; the heart is a simple mathematical function, hard to modify for pathologies etc
- Little or no link to the smaller scale biophysical processes

Multiscale models of physiological systems

Build models for organs and organ systems based on smaller building blocks such as cells and sub-cellular units.

Huge potential, but similarly huge challenges

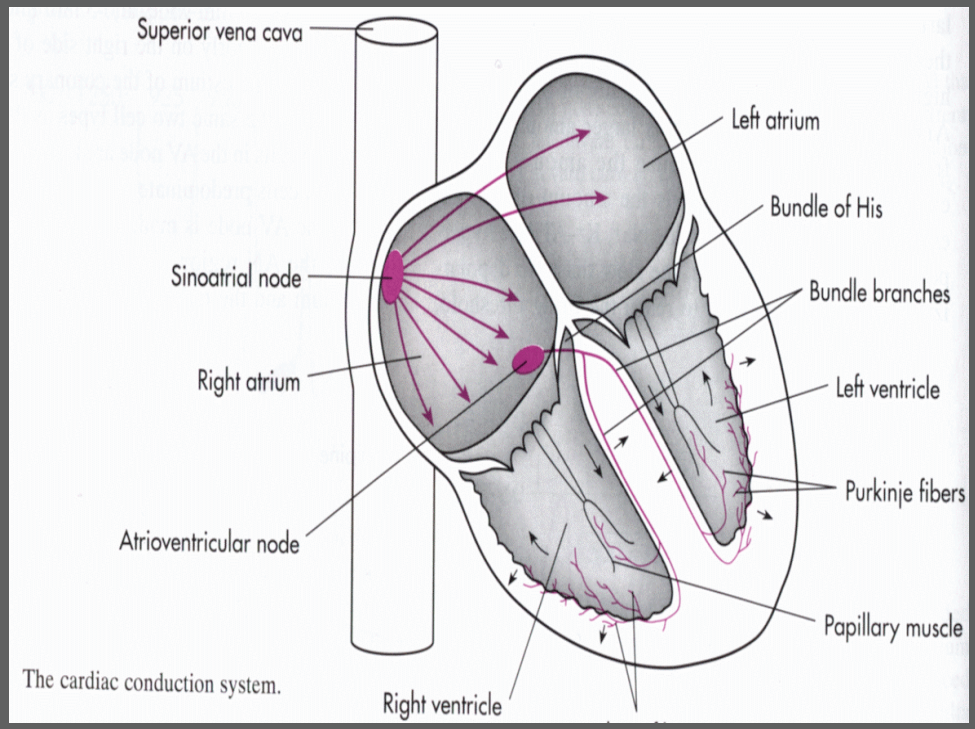
- Potential to provide a direct link from sub-cellular processes to the function of organs and organ systems
- High-profiled initiatives:
  - IUPS Physiome project
  - Virtual Physiological Human
- Substantial challenges related to data collection, modeling, and solving the resulting equations

Multiscale model of heart electrophysiology

-Well established mathematical models

- Difficult to access input data; fiber directions, cell types etc

- Huge computational load



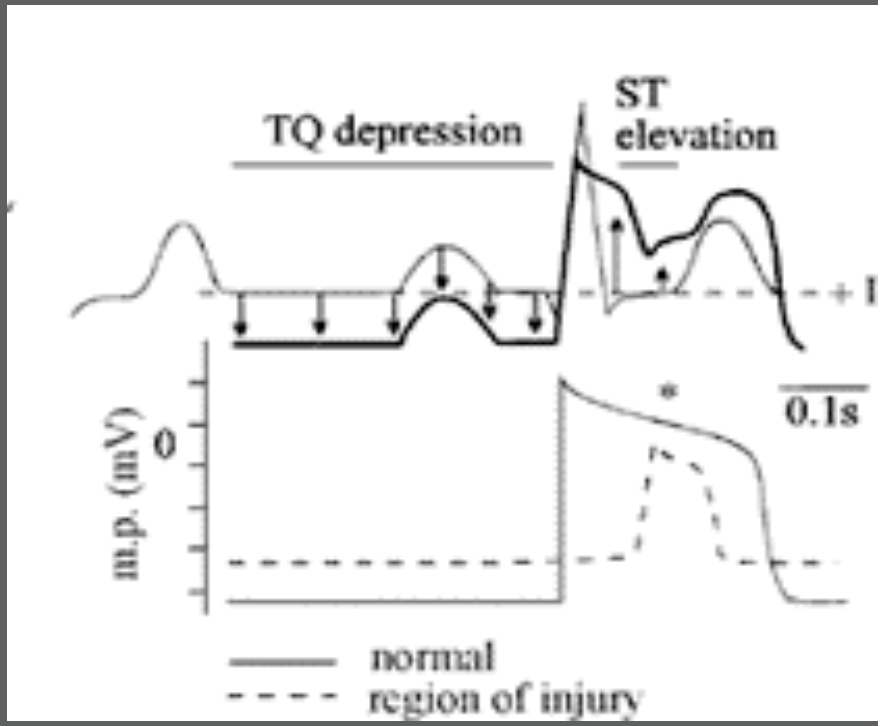
$$f\left(\frac{\partial s}{\partial t}, s, v, \lambda_{n-1}, \left\{\frac{\partial \lambda}{\partial t}\right\}_{n-1}\right) = 0$$

$$\frac{\partial v}{\partial t} + I_{\text{ion}}\left(v, s, \lambda_{n-1}\right) = \nabla \cdot \left(M_i \nabla v\right) + \nabla \cdot \left(M_i \nabla u_e\right)$$

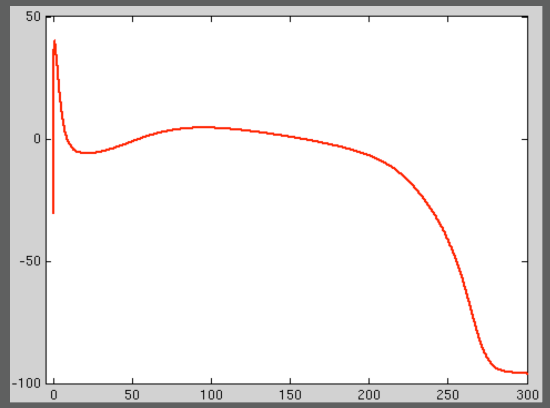
$$0 = \nabla \cdot \left(M_i \nabla v\right) + \nabla \cdot \left(\left(M_i + M_e\right) \nabla u_e\right)$$

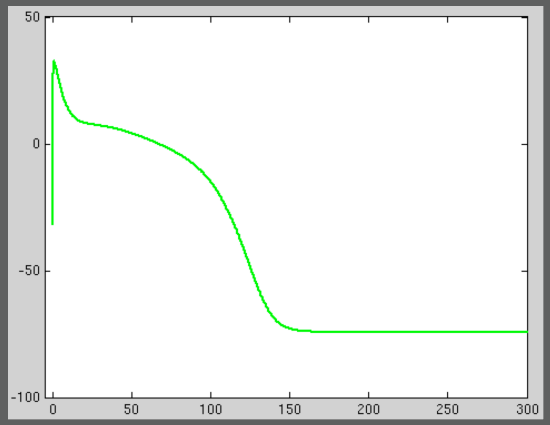
Example; diagnosis of myocardial ischemia

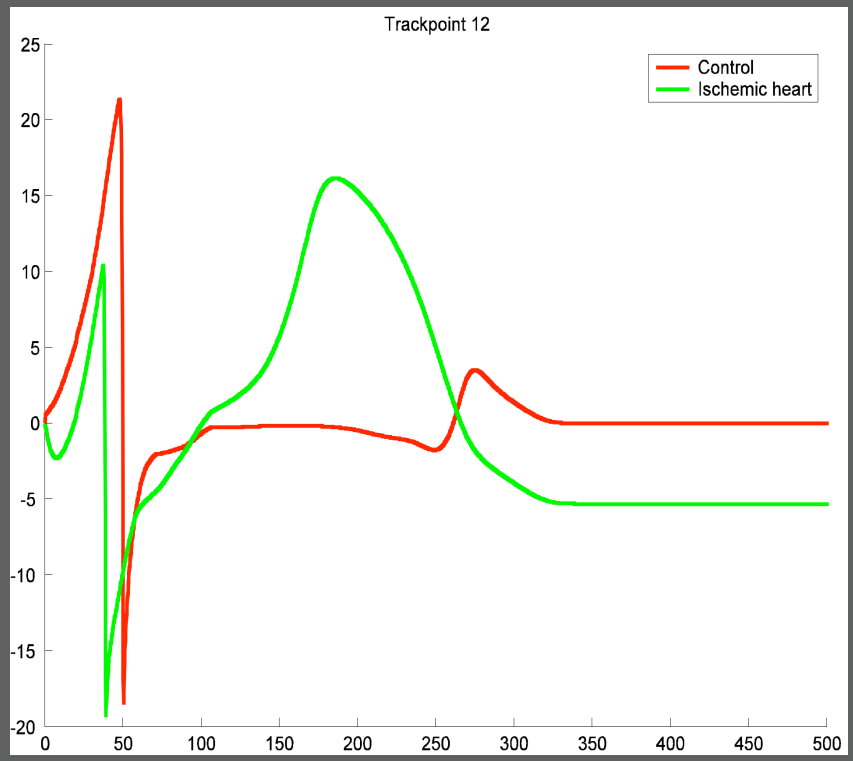
- ST segment shift is a key indicator
  - Depression or elevation
- Origins from changes in cell action potential
  - Elevated resting potential
  - Lowered plateau potential



Full bidomain model can only give qualitatively correct results

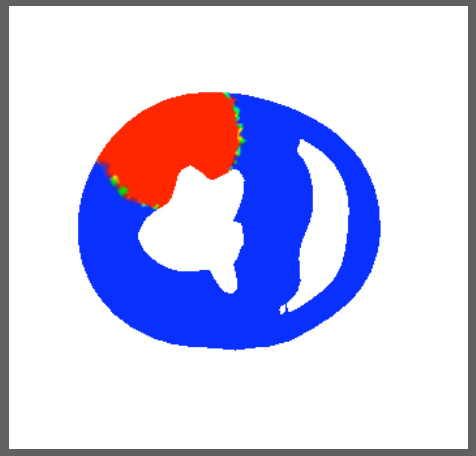


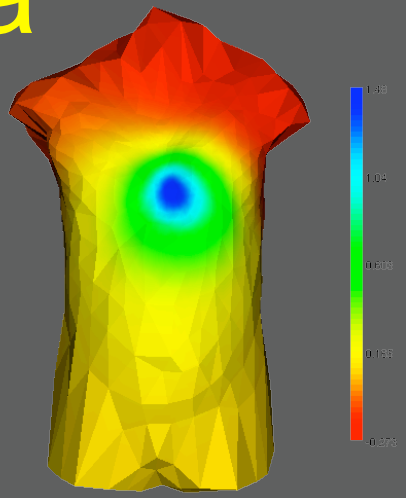


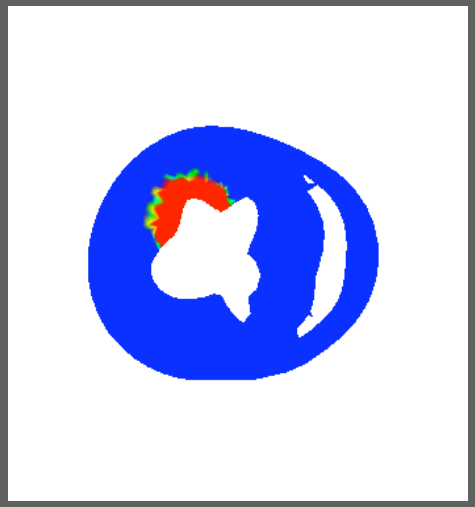


Due to the computational load of the full model, we need to derive a simpler model that only models the ST shift

Two distinct cases; transmural and sub-endocardial ischemia



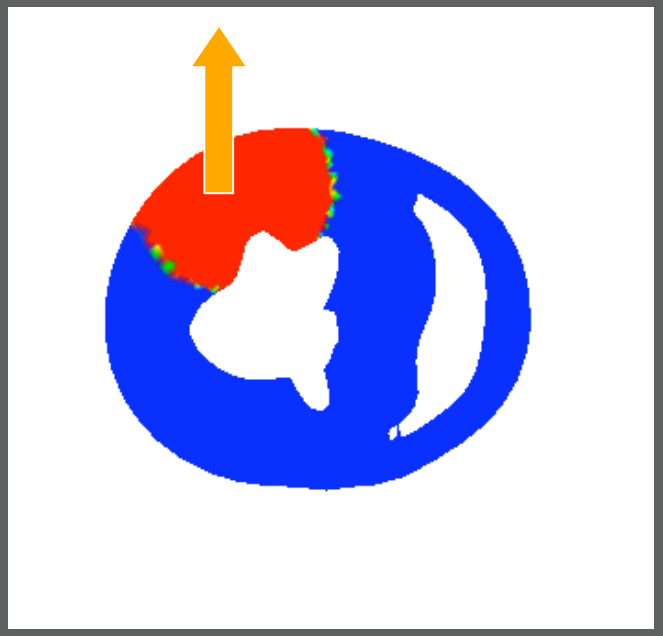


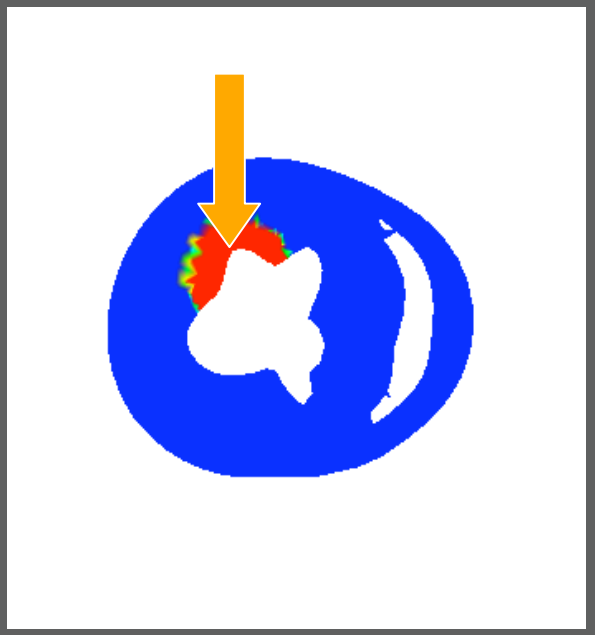


“Text book explanation”

- Transmural ischemia is locatable by ST elevation, subendocardial ischemia by ST depression

- ST shift caused by injury current across the ischemic border



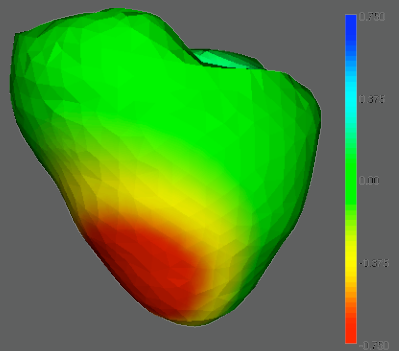


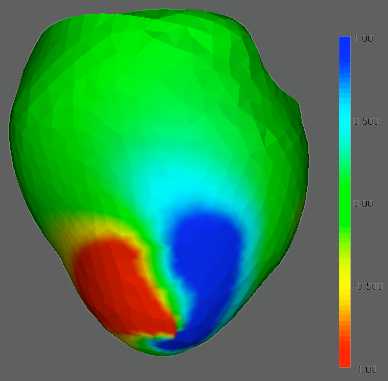
Experiments and model results

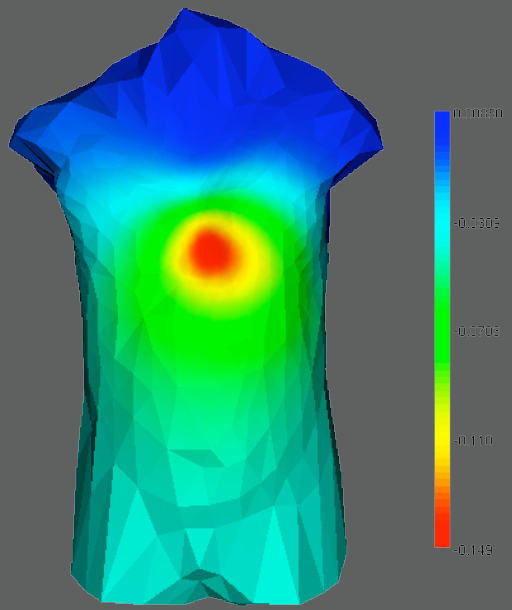
Li, Li, Yong, Kilpatrick. Source of electrocardiographic changes in subendocardial ischemia. Circ Res 1998.

- Experiments on sheep hearts suggest that subendocardial ischemia is impossible to locate from the ST depression
- This contradicts model simulations done with isotropic conductivity parameters, which supports the “textbook version”

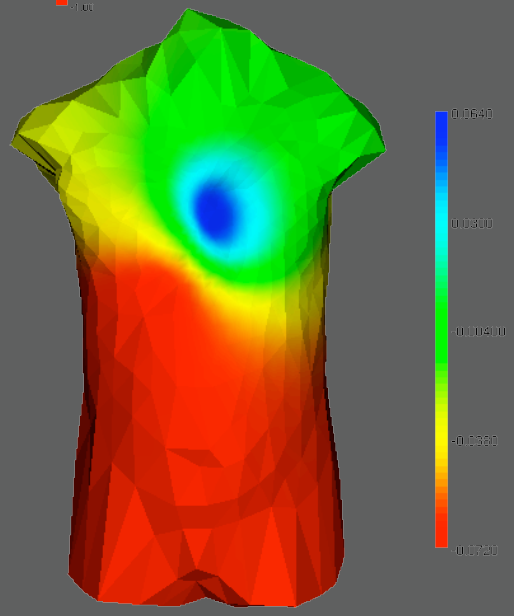
Detailed modeling of muscle fibres gives better agreement with experiments





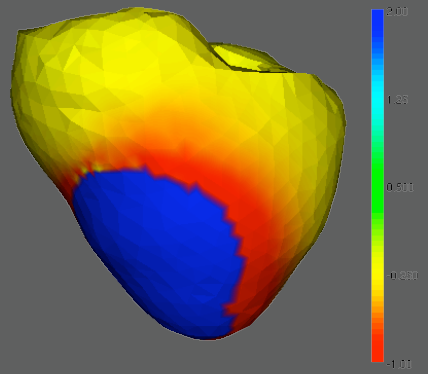


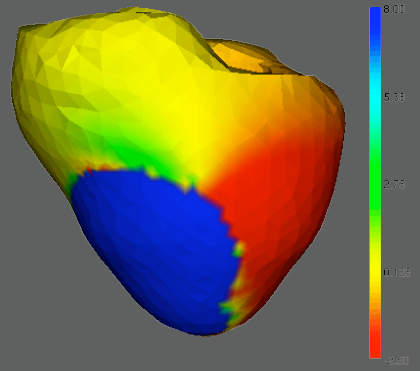
Isotropic conductivities

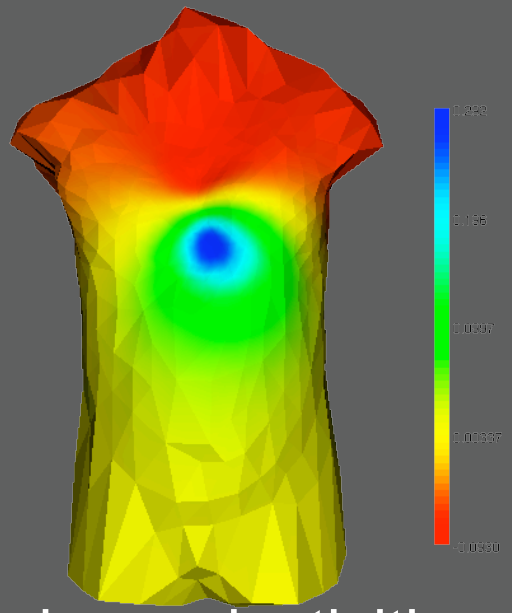


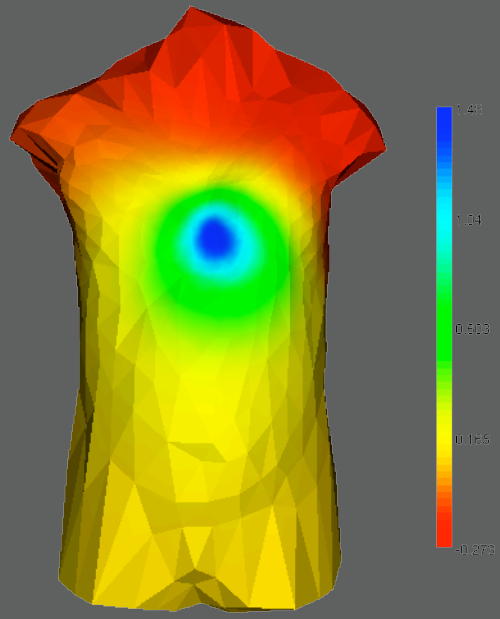
Realistic conductivities

For the simpler case of transmural ischemia, the models are indifferent









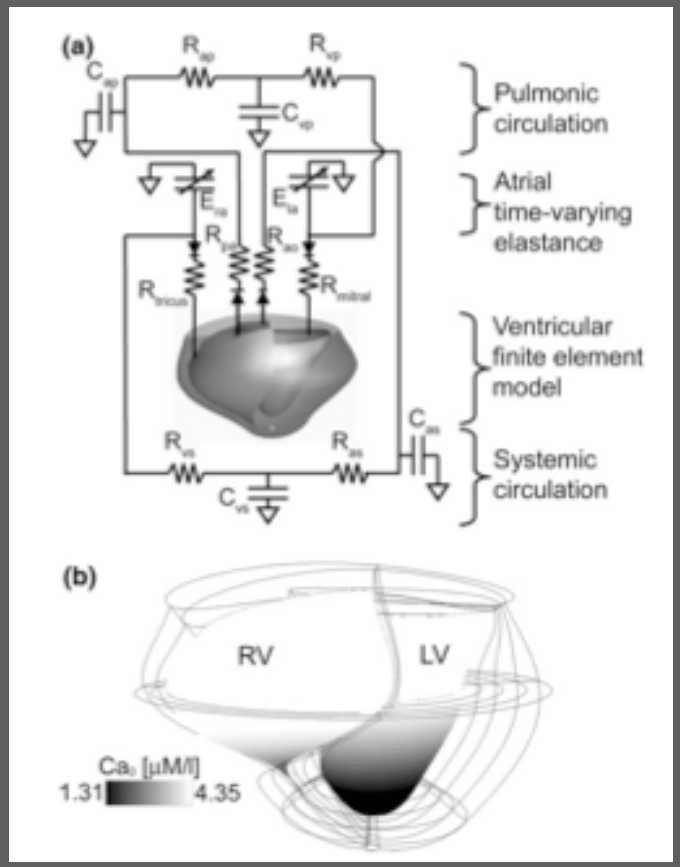
Isotropic conductivities

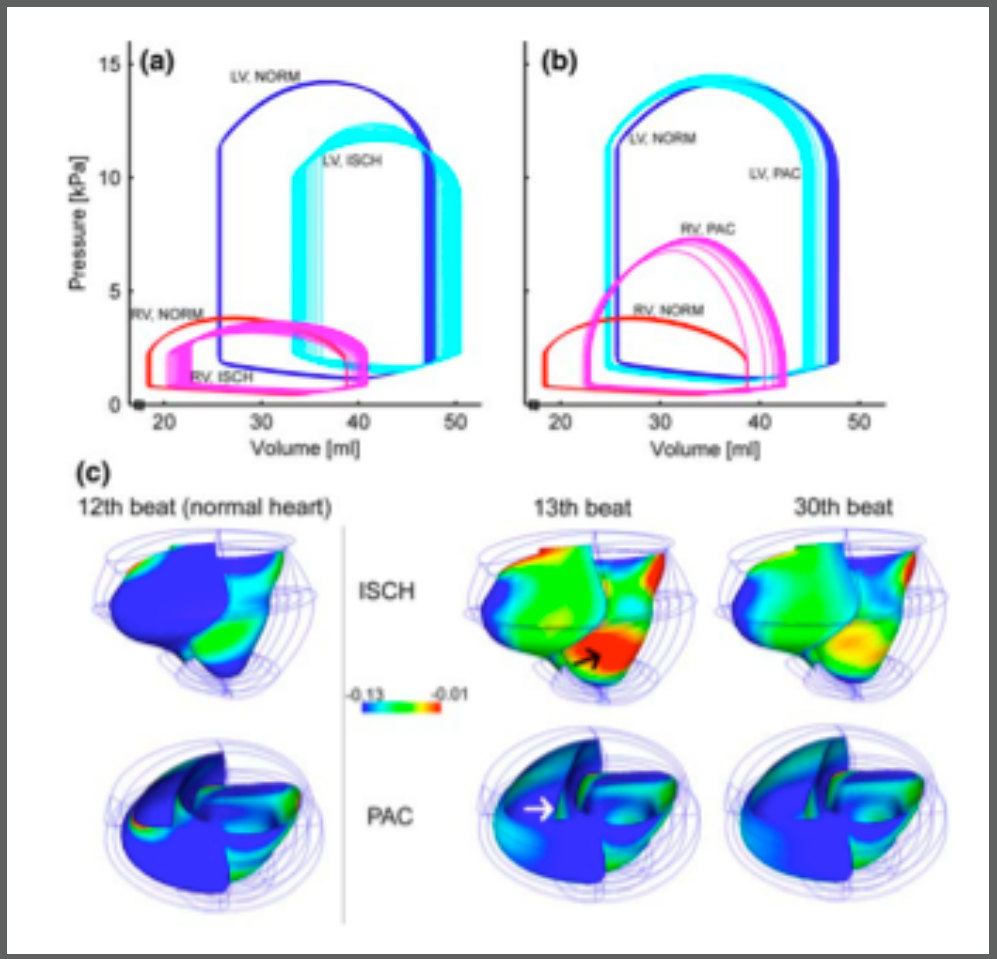
Realistic conductivities

True multiscale; coupling lumped parameter models to fine-scaled physical models

- Kerckhoffs et al. Coupling of a 3D finite element model of cardiac ventricular mechanics to lumped systems models of the systemic and pulmonary circulation. Ann Biomed Eng, 2006.
- Replace the simple elastance model of the heart with an electromechanics finite element model.
- Enables studying cellular changes, regional differences in the heart etc, and their impact on the circulation

Model output is circulatory parameters and regional stresses and strains in the heart





Summary and conclusions

- Mathematical modeling has a long history in physiological research
- Over the last decade we have seen a dramatic improvement in computational tools, data acquisition and imaging technology
- The potential of applying multiscale models for physiological research and clinical investigations is increasing rapidly
- There are still substantial challenges, related to computational load, data acquisition, individual variations etc

- Multiscale models of physiological systems are still in their infancy
- A detailed model is useless without good data
- Significant progress requires close collaboration between physiologists, bioengineers, mathematicians, computer scientists etc

Norwegian Center of Excellence

Center for Biomedical Computing

2007 - 2017

```
M = G.compute_mass_matrix(velocity_element)
A = G.compute_stiffness_matrix(velocity_element)
B = G.compute_div_matrix(velocity_element, pressure_element)
D = G.compute_stiffness_matrix(pressure_element)

T = 1; dt = 0.1
while t < T:
  t = t + dt;
  f = G.compute_source_vector(rhs)
  C = G.compute_convection_matrix(velocity_element, v_prev)

  A1 = M + dt*A + dt*C
  prec1 = MLPrec(A1)
  v, iter = precondBiCGStab(prec1, A1, v, f , 1.0e-9)

  g = (1.0/dt)*B.t*v
  phi, iter = precondConjGrad(MLPrec(D), D, phi, g , 1.0e-9)
  v = v - dt*B.t*phi
  p = (Mp + dt*Ap)phi
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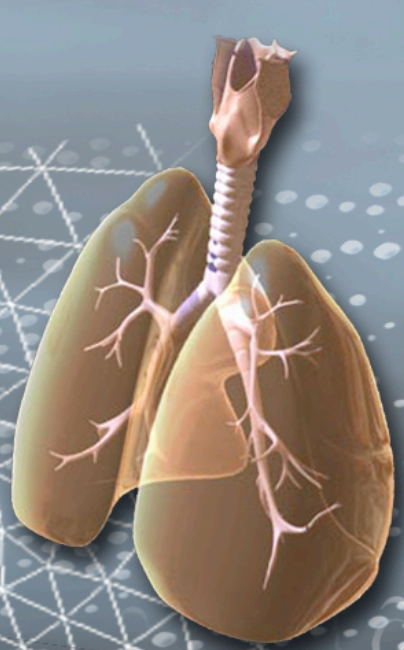

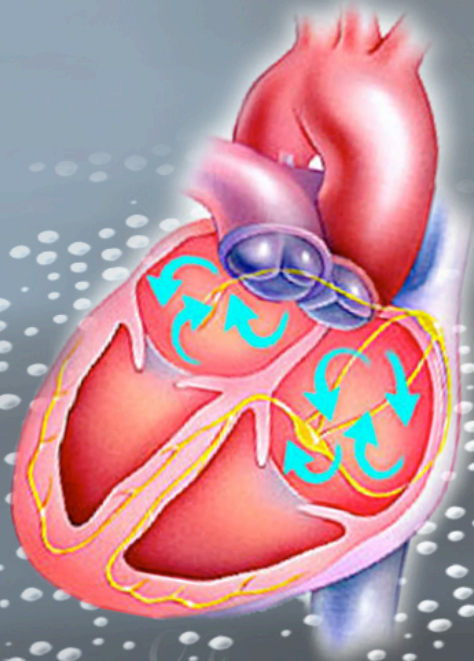

$$\rho\left(\frac{\partial u}{\partial t} + V \cdot \nabla u\right) = -\frac{\partial p}{\partial x} + \frac{\partial \tau_{xx}}{\partial x} + \frac{\partial \tau_{yx}}{\partial y} + \frac{\partial \tau_{zx}}{\partial z} + \rho f_x$$