Multi-scale modeling of the cardiovascular system

Roy Kerckhoffs, PhD
Cardiac Mechanics Research Group
University of California San Diego
La Jolla, CA
Outline

• Model Development for Cardiac Electromechanics
  – Electrophysiology
    » Cellular
    » Tissue
  – Biomechanics
    » Cellular
    » Tissue
    » Organ to system
    » System to cell

• Two applications to heart failure:
  – Interaction between scar tissue and pacing therapy
  – Sensitivity analysis of regional cardiac function
Background
Cardiac Resynchronization Therapy

- Heart failure: 250,000 deaths/year in US alone
- Conduction abnormalities such as bundle branch block are common complications of HF
- Cardiac resynchronization therapy (CRT)
  - improves timing between LV and RV contraction
  - improves quality of life*
  - reduces mortality*
- ~30% of patients do not respond to CRT, especially those with myocardial infarcts
- Lack of experimental *in-vivo* data on regional electrical activation and mechanical function
- No objective protocols to optimize pacing

*Cleland, 2005*
So why multiscale modeling of heart failure?

- Cell: dysregulation of excitation-contraction coupling
- Tissue: fibrosis and conduction abnormalities
- Organ: dilation or hypertrophy
- Circulation system: increased blood volume and resistance
- Person: shortness of breath and fatigue
Overall objective

To develop multi-scale models of the cardiovascular system
to ultimately apply these models in the clinic to predict interventions
Modeling from cell to system...

...and back again
Electrophysiology at the cellular level: Congestive Heart Failure

β₁-AR: -75%

SERCA: -30%

NCX: +55%

Congestive Heart Failure

Holt, ET et al. (1998) J Mol Cell Cardiol 30(8): 1581-93
### Cell-to-Tissue Models

![Diagram of cell-to-tissue models](image)

**Currents Densities (mS/µF)**

<table>
<thead>
<tr>
<th></th>
<th>Epi</th>
<th>Endo</th>
<th>Mid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient outward K⁺, Gto</td>
<td>0.045</td>
<td>0.025</td>
<td>0.025</td>
</tr>
<tr>
<td>Rapid delayed rectifier K⁺, GKr</td>
<td>0.040</td>
<td>0.030</td>
<td>0.015</td>
</tr>
<tr>
<td>Slow delayed rectifier K⁺, GKh</td>
<td>75%</td>
<td>30%</td>
<td>25%</td>
</tr>
<tr>
<td>Plateau K⁺, GKh</td>
<td>0.008</td>
<td>0.004</td>
<td>0.004</td>
</tr>
<tr>
<td>Sodium, GNa</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

\[
\frac{\partial V_m}{\partial t} = -\frac{1}{C_m} I_{\text{ion}} + \frac{1}{S C_m} \nabla \cdot D \nabla V_m
\]

Purkinje System

Auckland Canine Heart

Purkinje Fibers

LV Endocardial Model

Activation Times

(Usyk et al, 2002, CVS)
Biomechanics Models

- filament
- crossbridge
- regulatory unit
- ventricles
- myocardial tissue
- myofilament lattice
Cellular level
Myocyte Excitation-Contraction Coupling Model

Flaim et al, 2006

Rice et al, 2008

STIMULUS

ELECTROPHYSIOLOGY MODEL

MYOFILAMENT MODEL

UNLOADED CELL SHORTENING

(Ca²⁺ RELEASE, REUPTAKE, BUFFERING, ETC)

(Ca²⁺ BUFFERING BY TnC)

MODEL

EXPERIMENT

ACTION POTENTIAL

Ca²⁺ TRANSIENT
Mid- and Endo- Cells Display Similar Ca\textsuperscript{2+}-Shortening Dynamics

(Campbell et al. 2008)
Ventricular Wall Mechanics

- Conservation of mass, momentum and energy
- Pressure boundary conditions from hemodynamic model
- Myofiber angle and sheet distributions
- 3-D mechanical properties
Stress-strain relations for myocardium

- Fiber stress
- Stress normal to sheet
- Cross-fiber stress

Passive Stress (kPa)

Stress vs. Strain

Fiber stress, Stress normal to sheet, Cross-fiber stress

Normal vs. Failing

Stress vs. Time (ms)
Going back from system to cell: The cardiovascular baro-reflex
Baro-reflex controls blood pressure

Lu et al (AJP 2001)
FE model in circulation, modified for dog

Circulation model by Lu et al (AJP 2001)
System to cell:
Test of baro-reflex model with ischemia

3 normal beats
40 beats with left ventricular anterior ischemia
Hemodynamics

Systemic Pressures [mmHg]

Pulmonary Pressures [mmHg]

Left ventricular Volume [ml]

Right ventricular Volume [ml]

Aorta

Left Ventricle

Right Ventricle

Pulmonary Artery

Right Atrium

normal

ischemia

Time [sec]
Hemodynamics

dP/dt_{max} (mmHg/sec)

Stroke Volume (ml)

Beat number

Baroreflex response

Firing freqs [Hz]

Heart rate [bpm]

Contractility [-]

Time [sec]
beta-AR is distributed heterogeneously transmurally in heart failure

$\beta_1$ and $\beta_2$ density

subepicardium subendocardium
Applications: Multi-scale models of heart failure

- Heart failure (HF) is the result of a disease
- Heart failure big problem, especially in combination with asynchronous activation
- Cardiac Resynchronization Therapy (CRT) popular treatment of HF patients with asynchronous activation
Application 1: Interaction between scar and CRT

- About 30% of HF patients undergoing CRT classified as non-responders
- Most of these had a prior myocardial infarct
- Investigate relation between myocardial scar and CRT using a computational model
Hypothesis

• The relative improvement in cardiac function, going from an asynchronous contraction (LBBB) to a more synchronous one (CRT), decreases as the scar increases.
Effects of Myocardial Scars

- Inferior infarct
  - 0%
  - 40%

- Anterior infarct
  - 0%
  - 60%
Beating hearts

Non-failing

Failing, inferior infarct

LBBB
LVpace

fiber strain
-0.15 0.10
Relative improvement in *global function* with LV pacing was independent of scar size.

*Helm et al. Circulation 115:953, 2007*
Relative improvement in *regional function* with LV pacing decreased with increasing scar size.
Therefore, the hypothesis was confirmed for regional function but rejected for global function.

However....
Anterior scar of increasing size
Models of dilated dyssynchronous HF with scar

Kerckhoffs et al, Medical Image Analysis, 2008, in press
Regional function independent of scar size

![Graph showing variance of isovolumetric strain (C) and CURE index (E) as a function of scar size.](image)
Application 2: Sensitivity analysis of regional cardiac function

- To increase the number of CRT responders, investigators have designed clinical indices like CURE, ISF and dyssynchrony of contraction (DOC) to quantify regional cardiac function.

- ISF has been shown to be a good predictor of reverse remodeling (=CRT response).

- Four major abnormalities in dyssynchronous HF: dilation, reduced inotropy, prolonged relaxation and asynchronous activation
Objectives

• What is the impact of individual variations of
  – dilation
  – asynchronous activation
  – decreased inotropy
  – prolonged relaxation

on the dispersion of regional function and clinical indices of this dispersion?

• How sensitive is dispersion of regional function and clinical measures to interactions between these four abnormalities?
Methods

• In the numerical models, there are four alterations from normal to failing:
  – geometry
    • normal vs. dilated
  – inotropy
    • normal vs. reduced
  – twitch duration
    • normal vs. longer
  – impulse conduction
    • Normal vs LBBB
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\[ \text{myofiber stress [kPa]} \]

\[ +17\% \]
Methods

• In the numerical models, there are four alterations from normal to failing:
  – geometry
    • normal vs. dilated
  – inotropy
    • normal vs. reduced
  – twitch duration
    • normal vs. longer
  – impulse conduction
    • Normal vs LBBB
Bunch of simulations for all possible combinations

<table>
<thead>
<tr>
<th>Simulation name</th>
<th>Geometry</th>
<th>Inotropy</th>
<th>Twitch duration</th>
<th>Impulse conduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>a</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>LBBB</td>
</tr>
<tr>
<td>l</td>
<td>Normal</td>
<td>Normal</td>
<td>Prolonged</td>
<td>Normal</td>
</tr>
<tr>
<td>la</td>
<td>Normal</td>
<td>Normal</td>
<td>Prolonged</td>
<td>LBBB</td>
</tr>
<tr>
<td>r</td>
<td>Normal</td>
<td>Reduced</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>ar</td>
<td>Normal</td>
<td>Reduced</td>
<td>Normal</td>
<td>LBBB</td>
</tr>
<tr>
<td>rl</td>
<td>Normal</td>
<td>Reduced</td>
<td>Prolonged</td>
<td>Normal</td>
</tr>
<tr>
<td>rla</td>
<td>Normal</td>
<td>Reduced</td>
<td>Prolonged</td>
<td>LBBB</td>
</tr>
<tr>
<td>d</td>
<td>Dilated</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>da</td>
<td>Dilated</td>
<td>Normal</td>
<td>Normal</td>
<td>LBBB</td>
</tr>
<tr>
<td>dl</td>
<td>Dilated</td>
<td>Normal</td>
<td>Prolonged</td>
<td>Normal</td>
</tr>
<tr>
<td>dla</td>
<td>Dilated</td>
<td>Normal</td>
<td>Prolonged</td>
<td>LBBB</td>
</tr>
<tr>
<td>dr</td>
<td>Dilated</td>
<td>Reduced</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>dra</td>
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<tr>
<td>drl</td>
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<td>Reduced</td>
<td>Prolonged</td>
<td>Normal</td>
</tr>
<tr>
<td>drla*</td>
<td>Dilated</td>
<td>Reduced</td>
<td>Prolonged</td>
<td>LBBB</td>
</tr>
</tbody>
</table>
Definition of Dispersion of regional function: Non-uniformity of work density

Calculated as coefficient of variation of work density, throughout the cardiac cycle:

\[
W = \int_0^{\text{cardiac cycle}} \sigma_f d\varepsilon_f + \int_0^{\text{cardiac cycle}} \sigma_c d\varepsilon_c + \int_0^{\text{cardiac cycle}} \sigma_s d\varepsilon_s
\]

- Fiber stress [kPa]
- Fiber strain

Graph showing work (W) versus fiber strain, with early and late activated states.
Clinical indices of dispersion of regional function

<table>
<thead>
<tr>
<th>Dispersion of regional function [unit]</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOC [ms]</td>
<td>Dyssynchrony of contraction: standard deviation of time to peak shortening, with respect to pacing stimulus</td>
</tr>
<tr>
<td>mCURE [-]</td>
<td>Modified Circumferential Uniformity Ratio Estimate, calculated for midwall circumferential ejection strain in the LV; 1 is a non-uniform contraction, and 0 is completely uniform</td>
</tr>
<tr>
<td>ISF [-]</td>
<td>Internal Stretch Fraction, defined as the ratio of LV fiber stretching to shortening during ejection, calculated for midwall circumferential strain in the LV</td>
</tr>
</tbody>
</table>
Internal Stretch Fraction: ISF

- Measure of discoordinate contraction during ejection

\[
\varepsilon_p = \int_{T_1}^{T_2} \tilde{e}_p(t) dt, \quad \varepsilon_n = \int_{T_1}^{T_2} \tilde{e}_n(t) dt
\]

\[
\text{ISF} = -\frac{\varepsilon_p}{\varepsilon_n}
\]
CURE index of non-uniform contraction

- Fourier decomposition of strain in a short axis slice
- Relating $S_0$ to $S_1$ through:
  - $CURE = 0$: non-uniform
  - $CURE = 1$: uniform

$$CURE = \sqrt{\frac{\sum_t S_0}{\sum_t S_0 + \sum_t S_1}}$$

Helm, 2005
mCURE index of mechanical dyssynchrony

- Redefined CURE such that:
  - mCURE = 1 – CURE
  - mCURE = 0: uniform
  - mCURE = 1: non-uniform

- Now an increase in all measures of regional function represents a detrimental change
Dyssynchrony of contraction (DOC): Standard deviation of time to peak shortening

Fiber strain

Time [ms]

208 ms

0 500
Write index of regional function as function of abnormality parameter

\[ ISF(d,r,l,a) = c_0 + c_1 d + c_2 r + c_3 l + c_4 a + c_5 d \cdot r + \ldots + c_{15} d a r l \]

- ISF for normal heart
- Change in ISF for change in geometry
- Change in ISF due to interaction between geometry and reduced force
- Third order interactions
- Fourth order interaction

Results in 16 coefficients
Treat abnormality parameters nominally

- $d=0$ represents a normal geometry and $d=1$ dilation
- $r=0$ represents normal inotropy and $r=1$ reduced
- $l=0$ represents normal relaxation and $l=1$ prolonged
- $a=0$ represents normal activation sequence and $a=1$ left bundle branch block sequence
Calculate sensitivity

• Next, calculate the relative contribution of altered properties to the change in dispersion of regional function:

\[ c_{x,rel} = \frac{c_x}{(\text{ISF}_{\text{failing}} - \text{ISF}_{\text{non-failing}})} \cdot 100\% \]

• For example, \( c_{da,rel} = 92\% \) for ISF means that 92% of the increase in ISF in the failing heart is due to the interaction between dilation and asynchronous activation
Procedure

• Simulate cardiac cycles for every model (16 of them) until steady-state reached
• Compute displacements, strain, stress
• Quantify:
  – Regional function (e.g. dyssynchrony of contraction)
  – Global function (e.g. $dp/dt_{max}$, ejection fraction)
Results
Validity of the models
<table>
<thead>
<tr>
<th>Global or regional output</th>
<th>Non-failing heart</th>
<th>Non-failing heart + LBBB</th>
<th>Failing heart + normal activation</th>
<th>Failing heart + LBBB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Simulation (baseline)</td>
<td>Experiment and reference</td>
<td>Simulation and reference</td>
<td>Simulation and reference</td>
</tr>
<tr>
<td>dP/dt&lt;sub&gt;max&lt;/sub&gt; [mmHg/sec]</td>
<td>1590</td>
<td>1627 ± 644&lt;sup&gt;31&lt;/sup&gt;</td>
<td>1335</td>
<td>1212 ±</td>
</tr>
<tr>
<td>P&lt;sub&gt;max&lt;/sub&gt; [mmHg]</td>
<td>102</td>
<td>98.8 ±</td>
<td>98</td>
<td>92.2 ±</td>
</tr>
<tr>
<td>Ejection fraction [%]</td>
<td>43.7</td>
<td>38.0&lt;sup&gt;11&lt;/sup&gt;</td>
<td>42.7</td>
<td>28&lt;sup&gt;31&lt;/sup&gt;</td>
</tr>
<tr>
<td>Long axis shortening during ejection [%]**</td>
<td>89</td>
<td>85 ± 3&lt;sup&gt;6&lt;/sup&gt;</td>
<td>60</td>
<td>66</td>
</tr>
<tr>
<td>DOC [ms]</td>
<td>11.1</td>
<td>34.3</td>
<td>42.7</td>
<td>66.1</td>
</tr>
<tr>
<td>CURE [-]</td>
<td>0.95</td>
<td>0.79</td>
<td>0.92</td>
<td>0.70</td>
</tr>
<tr>
<td>ISF [-]</td>
<td>0.004</td>
<td>0.04 ± 0.03</td>
<td>0.04</td>
<td>0.02</td>
</tr>
</tbody>
</table>
“raw” regional results

- non-uniformity of work density [kJ/m³]
- DOC [ms]
- mCURE [-]
- ISF [-]
Non-uniformity of fiber stress depends strongly on geometry and pattern of activation
In fact, non-uniformity of fiber stress at end-isovolumic contraction correlates strongly with log(ISF) and log(mCURE), but less for dyssynchrony.

\[ R^2 = 0.84 \]

\[ R^2 = 0.84 \]

\[ R^2 = 0.65 \]
ISF is still very sensitive - and DOC insensitive - to dilation and asynchronous activation for different magnitudes of abnormalities:
Conclusions (1)

• The distribution of fiber shortening during ejection is more sensitive to a changing pattern of activation in a dilated heart than in a normal-sized heart
Conclusions (2)

• As a result, clinical measures of regional function such as CURE and ISF – but not dyssynchrony of contraction – are sensitive to an interaction between an activation pattern such as LBBB and dilation and are therefore better measures of dispersion of regional function.
Clinical relevance

• These results might explain the good reflection of ISF with contractile capacity that can be recruited by CRT as only a dilated heart has the best potential to remodel reversely significantly.
Workflow for design of patient-specific model to predict the outcome of CRT

1. IRB approval
2. Patient selection
3. CT scan
4. Lead implant
5. Cardiac ED geometry
6. Activation map LBBB
7. EP model LBBB
8. CRT model
9. Pacing same site as in patient
10. LBBB:
    - EA mapping pressures
    - Activation map LBBB
11. Pacing ON
12. LBBB:
    - Activation times
    - Pressures
    - Volumes
    - Stress/Strains
    - Calculate improvement in regional function
    - Predict responder/nonresponder
13. CRT:
    - Activation times
    - Pressures
    - Volumes
    - Predict responder/nonresponder
14. Echo LBBB:
    - Activation map LBBB
15. Echo CRT:
    - Activation map CRT
16. Echo 3 month follow up
17. Confirm prediction
Study Design

- Two patient groups with dilated cardiomyopathy at San Diego VAMC indicated for CRT
- First group is considered probable responders without infarcts
- Second group has an infarct or other indication of less probable response rate
- Multi-slice CT imaging prior to implantation
- LV and RV electroanatomic mapping (NavX) and right and left heart cardiac catheterization during implantation procedure with and without pacing
- Echo two weeks after implantation with pacing on and off
- Retrospective model building and analysis
- 3-month clinical follow-up
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Collaborators:
Sanjiv Narayan, UCSD VAMC
David Krummen, UCSD VAMC
Don Bers, Loyola University Chicago
Jose Puglisi, Loyola University Chicago
Wayne Giles, University of Calgary
Chae Hun Leem, University of Ulsan
Larry Frank, UCSD Radiology
Paul Stark, UCSD VAMC Radiology