Multiscale computational modeling of cardiac arrhythmogenesis

Trine Krogh-Madsen
Dept. Medicine (Cardiology) and
Institute for Computational Biology
Cardiac arrhythmias

Sudden cardiac death:
~300,000 deaths/year

Ventricular tachycardia
- Rapid activation
- May impair pumping
- May degenerate to VF

Ventricular fibrillation
- Loss of synchronous activation
- Syncope, death
• How do cardiac arrhythmias initiate?
• How are they sustained?
• What can we do to prevent their occurrence?
• How can we terminate them?
Initiation

Abnormal cellular electrical activity

Structural heterogeneity

Bill Stevenson, KITP seminar, 2006.

F. Netter, 1978
Example: how can scar tissue initiate arrhythmias?

Wave propagating in presence of dense scar

Wave propagating in presence of scar with viable, but damaged, tissue within scar
Example: how can scar tissue initiate arrhythmias?

Wave propagates around, but not into, scar

Wave propagates around, and into, scar
Example: how can scar tissue initiate arrhythmias?

Wave propagates through scar slowly because the tissue is poorly coupled.
Example: how can scar tissue initiate arrhythmias?
Example: how can scar tissue initiate arrhythmias?

Waves from either side of the scar merge and propagate beyond scar.

Waves from either side of the scar merge and propagate back into scar (excitable waves propagate into any tissue that is viable and non-refractory).
Example: how can scar tissue initiate arrhythmias?

The two intra-scar waves, flowing in opposite directions, annihilate one another. No reentrant rhythm occurs.
Example: how can scar tissue initiate arrhythmias?

Now let’s examine what can happen when an *ectopic beat* occurs at the “wrong place and wrong time”.

Example: how can scar tissue initiate arrhythmias?

Because the slow conduction zone can also lengthen refractory period, the ectopic wave can block by running into the tail of the preceding wave.
Example: how can scar tissue initiate arrhythmias?
Example: how can scar tissue initiate arrhythmias?
Example: how can scar tissue initiate arrhythmias?
Example: how can scar tissue initiate arrhythmias?
Example: how can scar tissue initiate arrhythmias?
Example: how can scar tissue initiate arrhythmias?
Example: how can scar tissue initiate arrhythmias?
Example: how can scar tissue initiate arrhythmias?
Example: how can scar tissue initiate arrhythmias?
Example: how can scar tissue initiate arrhythmias?
Maintenance

Reentry: anatomical or functional


Break-up: tachycardia to fibrillation

thevirtualheart.org
Multiscale phenomena

single channel → single cell → tissue, organ

1 Å 1 nm 10 nm 100 nm 1 μm 10 μm 100 μm 1 mm 1 cm 10 cm

10 μs 100 μs 1 ms 10 ms 100 ms 1 s 10 s 100 s
Action potential generation

Java
Cardiac action potentials

- Upstroke of ventricular AP is Na\(^+\) mediated.
- At the peak, Ca\(^{2+}\) channels open, causing an inward current that prolongs AP (plateau).
- Ca\(^{2+}\) influx triggers additional Ca\(^{2+}\) release from the sarcoplasmic reticulum.
- Cytoplasmic Ca\(^{2+}\) produces muscle contraction.
- Cardiac cells have many different types of K\(^+\) channels.
Computational modeling at the single cell level

Hodgkin-Huxley-type

\[
\frac{dV}{dt} = -\sum I_i/C_m
\]

\[I_i = g_i(V - E_i)\]

\[g_i = f(V,t)\]

CVM model of the canine ventricular myocyte
13 state variables and ~60 parameters

courtesy of R. Gilmour
Computational modeling at the single cell level

Hodgkin-Huxley-type

\[ \frac{dV}{dt} = -\sum I_i / C_m \]

\[ I_i = g_i (V - E_i) \]

\[ g_i = f(V,t) \]

\[ I_{Na} = \bar{G}_Na m^3 h j (V - E_{Na}) \]

\[ \frac{dm}{dt} = \alpha_m (1 - m) - \beta_m \]

\[ \frac{dh}{dt} = \alpha_h (1 - h) - \beta_h \]

\[ \frac{dj}{dt} = \alpha_j (1 - j) - \beta_j \]

\[ E_{Na} = \frac{RT}{F} \ln \left( \frac{[Na^+]_o}{[Na^+]_i} \right) \]

\[ \alpha_m = 0.32 \frac{V + 47.13}{1 - e^{-(V + 47.13)}} \]

\[ \beta_m = 0.08 e^{\frac{V}{11}} \]

\[ \alpha_h = 0.135 e^{-6.8} \]

\[ \beta_h = 7.5 \frac{e^{-(V + 80)}}{1 + e^{-(V + 11)}} \]

\[ \alpha_j = 0.175 e^{-23} \]

\[ \beta_j = 0.3 \frac{e^{-(V + 79)}}{1 + e^{-(V + 32)}} \]
Computational modeling at the single cell level

Activation and inactivation

\[ x \xrightarrow{\beta(V)} 1-x \]
\[ \alpha(V) \]

ODE for gating variable
\[ \frac{dx}{dt} = \alpha_x (1-x) - \beta_x x \]
\[ = -(\alpha_x + \beta_x) x + \alpha_x \]
\[ = (x_\infty - x)/\tau_x \]

where
\[ x_\infty = \frac{\alpha_x}{(\alpha_x + \beta_x)} \]
\[ \tau_x = \frac{1}{(\alpha_x + \beta_x)} \]
Computational modeling at the single cell level

Solution for constant $V$: (think voltage clamp)

$$dx / dt = (x_\infty - x) / \tau_x$$

$$1/(x_\infty - x) \frac{dr}{dt} = 1/\tau_x dt$$

$$\int_{x_0}^{x} \frac{1}{(x_\infty - x')} dx' = \int_{0}^{t} \frac{1}{\tau_x} dt'$$

$$\left[ -\ln(x_\infty - x') \right]_{x_0}^{x} = t / \tau_x$$

$$\ln \frac{x_\infty - x}{x_\infty - x_0} = -t / \tau_x$$

$$\frac{x_\infty - x}{x_\infty - x_0} = \exp(-t / \tau_x)$$

$$x = x_\infty - (x_\infty - x_0) \exp(-t / \tau_x)$$

\[+20 \text{ mV}\]
\[0 \text{ mV}\]
\[-20 \text{ mV}\]
\[-80 \text{ mV}\]
Single-channel modeling: Markov model

Beyond Hodgkin-Huxley

- May be based on channel structure
- Gates not necessarily independent
- May reproduce experimental data better than HH
Why use computational modeling for cardiac electrophysiology?

- Rodent cardiac myocytes have fundamentally different channel expression levels (especially repolarizing currents). Therefore, transgenic models are not appropriate.
- Modeling allows one to monitor each component simultaneously – not possible in experiments.
- Dynamics can be observed at resolutions that are unattainable experimentally or clinically.
- It is often faster and cheaper to do so.

Multiscale modeling example: single-channel noise

Unitary events add up to give the macroscopic current.
Multiscale modeling example: single-channel noise

Single channel noise $\rightarrow$ irregularity of beating

**Introduction**

1.1 Membrane noise

1.1.1 Single-channel noise

With the development of the patch-clamp technique it became possible to measure the current flow across tiny patches of membrane, clamped at a fixed transmembrane potential (91). An example is shown below.

![Current recordings](image)

The current varies in a step-like manner between three different levels: 0, i, and 2i. The interpretation is that the patch contains two identical ionic channels, each of which can be either closed or open. Ions can diffuse through an open channel with a fixed conductance (the single-channel conductance), but cannot go through the channel when it is in its closed configuration. Thus, when both channels in the patch are closed, no current is conducted (level 0), when one channel is open a single-channel current is conducted, and when both channels are open the current is 2i.
Multiscale modeling example: AF maintenance

Atrial fibrillation:

• 2.3 million sufferers in the U.S.
• 1/3 of all strokes over age 65
• doubled mortality rate
Multiscale modeling example: AF maintenance

Atrial fibrillation:
- 2.3 million sufferers in the U.S.
- 1/3 of all strokes over age 65
- doubled mortality rate

Clinical/exp observations:
- “AF begets AF”

Wijffels et al., Circulation, 1995.
Multiscale modeling example: AF maintenance

Atrial fibrillation:
- 2.3 million sufferers in the U.S.
- 1/3 of all strokes over age 65
- doubled mortality rate

Clinical/exp observations:
- “AF begets AF”
- electrical and structural remodeling

![Graph showing voltage vs. time for normal and AF patients with decreased currents ICa, IKur, Ito.]

Courtemanche et al., Cardiovascular Research, 1999.

Multiscale modeling example: AF maintenance

Wave length: $WL = CV \cdot APD$

$\downarrow CV \quad \downarrow APD \quad \downarrow WL \quad \rightarrow$ multiple waves can fit in the atria

Model: can separate ionic vs. structural remodeling
Sudden cardiac death: Treatment, prevention, termination

Pharmacological treatment (prevention)
- β-blockers
- ion channel blockers have increased mortality in some trials

CAST: Echt et al.
New England J. Medicine, 1991
Treatment, prevention, termination

Pharmacological treatment (prevention)
- β-blockers
- ion channel blockers have increased mortality in some trials

Ablation therapy (cure)
- doesn’t work well in ventricles
- only if a localized, abnormal region of tissue is responsible
Treatment, prevention, termination

Pharmacological treatment (prevention)
- β-blockers
- ion channel blockers have increased mortality in some trials

Ablation therapy (cure)
- doesn’t work well in ventricles
- only if a localized, abnormal region of

External defibrillation
- not always accessible
Treatment, prevention, termination

Pharmacological treatment (prevention)
- \( \beta \)-blockers
- Ion channel blockers have increased mortality in some trials

Ablation therapy (cure)
- Doesn’t work well in ventricles
- Only if a localized, abnormal region of tissue is responsible

External defibrillation
- Not always accessible

Implantable cardioverter defibrillator
- Therapy of choice for many patients
- Expensive
Alternans and its control

- repolarization alternans
- repolarization gradients
- conduction block
- tachyarrhythmias

Pastore et al., Circulation, 1999
Alternans control

Basic concept: eliminate alternans by applying (small) electrical stimuli at well-timed intervals

\[
BCL_{n+1} = \begin{cases} 
BCL^* & \text{for } \Delta BCL_{n+1} > 0, \\
BCL^* + \Delta BCL_{n+1} & \text{for } \Delta BCL_{n+1} \leq 0,
\end{cases}
\]

with

\[
\Delta BCL_{n+1} = \frac{\gamma}{2} (APD_{n+1} - APD_n),
\]
Alternans control

Basic concept: eliminate alternans by applying (small) electrical stimuli at well-timed intervals

\[
BCL_{n+1} = \begin{cases} 
BCL^* & \text{for } \Delta BCL_{n+1} > 0, \\
BCL^* + \Delta BCL_{n+1} & \text{for } \Delta BCL_{n+1} \leq 0,
\end{cases}
\]

with

\[
\Delta BCL_{n+1} = \frac{\gamma}{2} (APD_{n+1} - APD_n),
\]
Alternans control

Basic concept: eliminate alternans by applying (small) electrical stimuli at well-timed intervals

\[
BCL_{n+1} = \begin{cases} 
BCL^* & \text{for } \Delta BCL_{n+1} > 0, \\
BCL^* + \Delta BCL_{n+1} & \text{for } \Delta BCL_{n+1} \leq 0,
\end{cases}
\]

with

\[
\Delta BCL_{n+1} = \frac{\gamma}{2} (APD_{n+1} - APD_n),
\]
Alternans control

Basic concept: eliminate alternans by applying (small) electrical stimuli at well-timed intervals

\[ BCL_{n+1} = \begin{cases} 
  BCL^* & \text{for } \Delta BCL_{n+1} > 0, \\
  BCL^* + \Delta BCL_{n+1} & \text{for } \Delta BCL_{n+1} \leq 0,
\end{cases} \]

with

\[ \Delta BCL_{n+1} = \frac{\gamma}{2} (APD_{n+1} - APD_n), \]

where \( \gamma \) is the feedback gain and \( BCL^* \) is the nominal BCL.
Alternans control

Basic concept: eliminate alternans by applying (small) electrical stimuli at well-timed intervals

\[ BCL_{n+1} = \begin{cases} BCL^* & \text{for } \Delta BCL_{n+1} > 0, \\ BCL^* + \Delta BCL_{n+1} & \text{for } \Delta BCL_{n+1} \leq 0, \end{cases} \]

with

\[ \Delta BCL_{n+1} = \frac{\gamma}{2}(APD_{n+1} - APD_n), \]
Alternans control

Basic concept: eliminate alternans by applying (small) electrical stimuli at well-timed intervals

\[
BCL_{n+1} = \begin{cases} 
BCL^* & \text{for } \Delta BCL_{n+1} > 0, \\
BCL^* + \Delta BCL_{n+1} & \text{for } \Delta BCL_{n+1} \leq 0,
\end{cases}
\]

with

\[
\Delta BCL_{n+1} = \frac{\gamma}{2} (APD_{n+1} - APD_n),
\]
Alternans control works well in single cells but is only effective over ~1 cm in tissue.

CorCap Cardiac Support Device: prevent and reverse dilation; add electrode grid?
Off-site alternans control

Use data from remote site to control alternans there

Krogh-Madsen et al., Physical Review E, 2010
Use off-site control to eliminate alternans where it’s amplitude is large?
Pacing-induced termination of reentry

Implantable Cardioverter Defibrillator (ICD)

Antitachycardia pacing therapy

Defibrillation therapy
ICDs - engineering advances

- Size reduction; longevity increase.
- Arrhythmia detection improvement – reduction in false shocks, reducing pain and chronic anxiety.

ICDs - arrhythmia termination improvement

Works in 85-90% of attempted trials

Incorporation of understanding of arrhythmia nonlinear dynamics into termination strategies:

- Can we come up with better pacing algorithms for ATP?
- *Even a small improvement would positively effect tens of thousands*
Unidirectional block

Why do more stimuli work better than one?

Dynamical instability?

By exploiting such instability can we increase efficacy of pacing-induced termination?

Boersma et al., Circulation, 1993
Spatial gradient in recovery time (DI) causes unidirectional block
Spatial gradient in recovery time (DI) causes unidirectional block
Spatial gradient in recovery time (DI) causes unidirectional block.

\[ \frac{\partial DI}{\partial x} < 0 \quad \Rightarrow \quad \text{block in the anterograde direction} \]

\[ \frac{\partial DI}{\partial x} > 0 \quad \Rightarrow \quad \text{block in the retrograde direction} \]

Vulnerable window for unidirectional block (1-2 ms)
Analytical approach

Map model: APD and CV are functions of previous DI

\[ \frac{\partial DI_1}{\partial x} = -1/CV_F = -22 \text{ ms/cm} \]

\[ \frac{\partial DI_i}{\partial x} = - \frac{da(DI_{i-1})}{dDI} \frac{\partial DI_{i-1}}{\partial x} - \frac{1}{CV_{i-1}} + \frac{1}{CV_i} \]

Predictions

- the direction in which block occurs may alternate
- \( \partial DI/\partial x \) may be amplified for short coupling intervals
- the window of unidirectional block may increase for short coupling intervals

**Numerical approach**

Cable equation with periodic boundary conditions

\[
\frac{\partial V}{\partial t} = D \frac{\partial^2 V}{\partial x^2} - \frac{I_{ion}}{C_m}
\]

\(I_{ion}\) described by coupled ODEs

Aggressive ramp pacing

**FIG. 11:** Termination due to unidirectional block in aggressive ramp protocol with ∆CI = 30 ms and CI$_1$ = 255 ms. wa) Transmembrane potential and DI. wb) Successive values of DI at the stimulus site. wc) Spatial DI gradient at the stimulus site. wd) Windows of block and termination.

Unidirectional block (red diamonds). Away from the stimulus site.

In other words it sets requirements on the APD restitution curve to be sufficiently steep. However, R$_2$ block also depends on how the conduction velocity changes with DI: if CV restitution is steep, R$_2$ slows down substantially as it propagates, allowing R$_1$ more time to repolarize and thus decreasing the chance of R$_2$ block. Hence, the occurrence of R$_2$ block is increased when APD restitution is steep and CV restitution is flat.

We also derive this result in the Appendix.

Collision block and alternans amplification also both require the transient coexistence of two anterograde waves. Such double-wave reentry would effectively cut the activation time in half.

While in our simple model, we found no or very little termination when applying regular burst or ramp pacing, these protocols actually work relatively well in patients. This discrepancy may be due to intrinsic structural and ionic heterogeneity as well as anisotropy in the heart and/or the lack of a reentrant pathway in the heart as well defined as our model.

**FIG. 14:** APD restitution curves. (a) From burst protocols with three different coupling intervals. (b) From ramp protocols with two different ramp decrements. (c) From aggressive ramp protocol with two different initial step sizes.
Ramp pacing

**FIG. 8**: Dynamics due to ramp pacing with an interstimulus decrement of 30 ms. 

- **ya)** Transmembrane potential and DI.
- **yb)** Successive values of DI at the stimulus site, DI\(_{0}\).
- **yc)** Spatial DI gradient at the stimulus site.
- **yd)** Windows of block and termination. Retrograde block (open triangles), retrograde block causing termination (filled triangles), and non-local block leading to termination (gray circles).

While in our simple model we found no or very little termination when applying regular burst or ramp pacing, these protocols actually work relatively well in patients. This discrepancy may be due to intrinsic structural and ionic heterogeneity as well as anisotropy in the heart and/or the lack of a reentrant pathway in the heart as well defined as our model.
the retrograde wave on even beats, where \( \partial DI/v/ \partial x > 0 \). The termination dynamics of the two remaining anterograde waves vary with the stimulus number. Following S2 and S4 there is regular collision block \( \{ A_{1i−1} ⊣ A_{1i} ⊣ \} \), S8 and S10 lead to \( \{ A_{2i−1} ⊣ A_{2i} ⊣ \} \) termination, while small \( v > 3 \) ms windows of \( \{ A_{2i−1} ⊣ A_{2i} ⊣ \} \) and \( \{ A_{3i−1} ⊣ A_{3i} ⊣ \} \) termination exists for beats 12 and 6, respectively.

**FIG. 6:** Dynamics due to burst pacing with coupling intervals of 215 ms. Transmembrane potential and DI. Successive values of DI at the stimulus site, DIw0y. Spatial DI gradient at the stimulus site. Windows of block and termination. Retrograde block open triangles and retrograde block causing termination filled triangles.

While the type of termination dynamics is not predictable by the local DI gradient, the occurrence of block is Fig. 7. A stated above, the rapid burst protocols induce considerably large positive DI gradients, which lead to retrograde block. However, the threshold value for 14

**FIG. 14:** APD restitution curves. (a) From burst protocols with three different coupling intervals. (b) From ramp protocols with two different ramp decrements. (c) From aggressive ramp protocol with two different initial step sizes.

While in our simple model, we found no or very little termination when applying regular burst or ramp pacing, these protocols actually work relatively well in patients. This discrepancy may be due to intrinsic structural and ionic heterogeneity as well as anisotropy in the heart and/or the lack of a reentrant pathway in the heart as well defined as our 24
Take-home message

Cardiac modeling is fun and worthwhile and useful for studying many types of problems using different models ranging from very simple (e.g., threshold dynamics) to highly complex (e.g., 3D anatomical).