2011 NSF-CMACS Workshop on Atrial Fibrillation (4th day)

Flavio H. Fenton

Department of Biomedical Sciences
College of Veterinary Medicine,
Cornell University, NY
and
Max Planck Institute for Dynamics and
Self-organization, Goettingen, Germany

Lehman College,
Bronx, NY. Jan 3-7, 2011
Mathematical Model

All cardiac cell models in tissue are reaction-diffusion equations.

\[
C_m \frac{\partial V(t, x)}{\partial t} = \nabla \cdot (D(x) \nabla V) - I_{ion}(V, m) - I_{stim}(t, x)
\]

\[
\frac{\partial m(t, x)}{\partial t} = f(V, m)
\]
Cell Modeling (Continuum Mathematical Model)

Nonlinear parabolic reaction-diffusion equations:

\[
C_m \frac{\partial_t V}{\partial t} = \nabla \cdot (D(x) \nabla V) - I_{\text{ion}}(V, m) - I_{\text{stim}}(t, x)
\]

\[
\frac{\partial_t m}{\partial t} = f(V, m)
\]

- \(V(t,x)\) membrane potential
- \(m(t,x)\) gating variables, ionic concentrations
- \(C_m\) membrane capacitance
- \(D(x)\) conductivity tensor
- \(I_{\text{ion}}\) total ionic current across the membrane of the cell
- \(I_{\text{stim}}\) external stimulus current

Neumann boundary conditions on potential \(V\):

\[n \cdot \nabla V = 0\]
Continuum Mathematical Model

Nonlinear parabolic reaction-diffusion equations:

\[ C_m \partial_t V(t, x) = \nabla \cdot (D(x) \nabla V) - I_{\text{ion}}(V, m) - I_{\text{stim}}(t, x) \]
\[ \partial_t m(t, x) = f(V, m) \]
Continuum Mathematical Model

Nonlinear parabolic reaction-diffusion equations:

\[
C_m \partial_t V(t, x) = \nabla \cdot (D(x) \nabla V) - I_{\text{ion}}(V, m) - I_{\text{stim}}(t, x)
\]
\[
\partial_t m(t, x) = f(V, m)
\]

Examples:

Ventricular:
- Luo-Rudy 1 (LR1) 8v
- Luo-Rudy d (LRd) 20v
- Fox et al. 13v

Atrial:
- Courtemanche. 19v
- Nygren. 29v
Many Models for Different Cell Types

- FitzHugh-Nagumo Generic
- Beeler-Reuter Generic ventricular
- Noble Generic Purkinje
- Fenton-Karma (3V) Generic ventricular
- Luo-Rudy 1 Guinea pig ventricular
- Luo-Rudy dynamic Guinea pig ventricular
- Priebe-Beuckelmann Human ventricular
- Ten Tusscher et al. Human ventricular
- Iyer et al. Human ventricular
- Bueno-Orovio et al. Human ventricular
- Fox et al. Canine ventricular
- Hund-Rudy Canine ventricular
- Shannon et al. Rabbit ventricular
- Mazhari et al. Rabbit ventricular
- Pandit et al. Rat ventricular
- Bondarenko et al. Mouse ventricular
- Nygren et al. Human atrial
- Courtemanche et al. Human atrial
- Cherry et al. Canine atrial
- Cherry et al. Canine pulmonary vein

Many Models for Different Cell Types

Different mammalian hearts have different AP morphology and duration. Because they are different in size (various orders of magnitude).
Many Models for Different Cell Types
Many Models for Different Cell Types
Many Models for Different Cell Types

Implemented most (~40) of the published models in single cells and in tissue.
Many Models for Different Cell Types

Implemented most (~40) of the published models in single cells and in tissue.

Many Models for Different Cell Types

Implemented most (~40) of the published models in single cells and in tissue.
Many Models for Different Cell Types

Implemented most (~40) of the published models in single cells and in tissue.

- FitzHugh-Nagumo Generic
- Beeler-Reuter Generic ventricular
- Noble Generic Purkinje
- Fenton-Karma (3V) Generic ventricular
- Luo-Rudy 1 Guinea pig ventricular
- Luo-Rudy dynamic Guinea pig ventricular
- Priebe-Beuckelmann Human ventricular
- Ten Tusscher et al. Human ventricular
- Iyer et al. Human ventricular
- Bueno-Orovio et al. Human ventricular
- Fox et al. Canine ventricular
- Hund-Rudy Canine ventricular
- Shannon et al. Rabbit ventricular
- Mazhari et al. Rabbit ventricular
- Pandit et al. Rat ventricular
- Bondarenko et al. Mouse ventricular
- Nygren et al. Human atrial
- Courtemanche et al. Human atrial
- Cherry et al. Canine atrial
- Cherry et al. Canine pulmonary vein

Many Models for Different Cell Types

Implemented most (~40) of the published models in single cells and in tissue.

Many Models for Different Cell Types

Implemented most (~40) of the published models in single cells and in tissue.
Many Models for Different Cell Types

Implemented most (~40) of the published models in single cells and in tissue.

Remember this and the next atrial models.
Many Models for Different Cell Types

Implemented most (~40) of the published models in single cells and in tissue.

<table>
<thead>
<tr>
<th>Model</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>FitzHugh-Nagumo</td>
<td>Generic</td>
</tr>
<tr>
<td>Beeler-Reuter</td>
<td>Generic ventricular</td>
</tr>
<tr>
<td>Noble</td>
<td>Generic Purkinje</td>
</tr>
<tr>
<td>Fenton-Karma (3V)</td>
<td>Generic ventricular</td>
</tr>
<tr>
<td>Luo-Rudy 1</td>
<td>Guinea pig ventricular</td>
</tr>
<tr>
<td>Luo-Rudy dynamic</td>
<td>Guinea pig ventricular</td>
</tr>
<tr>
<td>Priebe-Beuckelmann</td>
<td>Human ventricular</td>
</tr>
<tr>
<td>Ten Tusscher et al.</td>
<td>Human ventricular</td>
</tr>
<tr>
<td>Iyer et al.</td>
<td>Human ventricular</td>
</tr>
<tr>
<td>Bueno-Orovio et al.</td>
<td>Human ventricular</td>
</tr>
<tr>
<td>Fox et al.</td>
<td>Canine ventricular</td>
</tr>
<tr>
<td>Hund-Rudy</td>
<td>Canine ventricular</td>
</tr>
<tr>
<td>Shannon et al.</td>
<td>Rabbit ventricular</td>
</tr>
<tr>
<td>Mazhari et al.</td>
<td>Rabbit ventricular</td>
</tr>
<tr>
<td>Pandit et al.</td>
<td>Rat ventricular</td>
</tr>
<tr>
<td>Bondarenko et al.</td>
<td>Mouse ventricular</td>
</tr>
<tr>
<td>Nygren et al.</td>
<td>Human atrial</td>
</tr>
<tr>
<td>Courtemanche et al.</td>
<td>Human atrial</td>
</tr>
<tr>
<td>Cherry et al.</td>
<td>Canine atrial</td>
</tr>
<tr>
<td>Cherry et al.</td>
<td>Canine pulmonary vein</td>
</tr>
</tbody>
</table>

Remember This and the Previous atrial models

Many Models for Different Cell Types

Implemented most (~40) of the published models in single cells and in tissue.

67 variables
2D (200x200x67 = 2,680,000)
Imagine in 3D!
Number of equations to solve each iteration in time

Dimensions:
3cm x 3cm x 3cm
~500,000 nodes

1s = 1X10^{14} equations
100 trillion operations

This is a rabbit

Human ventricles at least 3 times bigger
13,500,000 nodes
13,500,000*67 = 904,500,000
Almost a billion operations every time step (.01 ms)
Many Models for Different Cell Types

Implemented most (~40) of the published models in single cells and in tissue.
Many Models for Different Cell Types

Implemented most (~40) of the published models in single cells and in tissue.
Examples of differences in cardiac cell models of same type

Three comparisons
Comparing two canine cell models

Two ionic models of canine ventricular myocytes:

- Fox et al., 2002:
  - 13 variables.
  - 13 transmembrane currents.
  - Intracellular calcium handling includes single-compartment SR, buffering.
  - No other intracellular concentrations.
- Hund-Rudy, 2004:
  - 30 variables.
  - 14 transmembrane currents.
  - Intracellular calcium handling includes two-compartment SR, buffering, subspace, CaMKII autophosphorylation.
  - Intracellular Na+, K+, Cl- concentrations.

Fox et al.: larger amplitude (145 vs. 107mV), with smaller RMP (-95 vs. -87mV) and larger peak voltage (50 vs. 30mV).

Hund-Rudy: more pronounced notch, longer AP.
Increased $I_{Kr}$ suppresses alternans.

Fox et al. Hund-Rudy

Increased $I_{Kr}$ suppresses alternans.

Fox et al. Hund-Rudy Fox 2g$_{Kr}$
AP Morphology Changes in Tissue

- Action potentials in the Hund-Rudy model decrease in amplitude and substantially change morphology in tissue.
AP Morphology Changes in Tissue

- Action potentials in the Hund-Rudy model decrease in amplitude and substantially change morphology in tissue.

L-type Ca\(^{2+}\) current may be responsible!
• Hund-Rudy tissue model (HRt) restores L-type calcium current by increasing AP amplitude.
Spiral Waves in 2D

- Stable spirals.
- Similar tip trajectories.
- Hund-Rudy meanders more strongly.

Fox et al.

Hund-Rudy

18x18cm
Period: ~169 ms

15x15cm
Period: ~120 ms
Spiral Waves in 2D

- Stable spirals.
- Similar tip trajectories.
- Hund-Rudy meanders more strongly.

Fox et al.

18x18cm
Period: ~169 ms

15x15cm
Period: ~120 ms
Summary

• **Good news:**
  - Both models have similar CV restitution and max CV.
  - Both models have similar linear spiral trajectories in 2D.
  - Similar $D_I_{\text{min}}$.

• **Bad news: two different beasts!**
  - Different alternans CL ranges, onset CLs.
  - Different values of $dv/dt_{\text{max}}$.
  - Different spiral periods.
  - Both CV restitutions are unrealistically flat.
  - Pronounced differences in AP morphology in tissue for Hund-Rudy model.
  - Spiral stability can depend on initial conditions.
Models of same type with even larger difference in dynamics

- Human Atrial models
Anatomically Realistic Model of Human Atria

Dimensions:
7.5cm x 7cm x 5.5cm
2.5 million nodes

Harrild and Henriquez, 2000 + coronary sinus

Bachmann's Bundle
Superior Vena Cava
Left Atrial Appendage
Left Atrium
Right Atrium
Coronary Sinus
Pulmonary Veins
Bundle Conductivities

*Healthy atria*
- Fast CV: 150 cm/s
- Bulk CV: 60 cm/s
- Slow CV: 35 cm/s

- Intercaval Bundle
- Superior Vena Cava
- Right Atrium
- Pectinate Muscles
- Crista Terminalis
- Fossa Ovalis
- Left Atrium
Example of Simulated AT and AF Reentry in the Atrial Model

Nygren et al model Atrial Tachycardia

Courtemanche et al Atrial Fibrillation
Models of same type with even larger difference in dynamics

- Human Atrial models
- Human Ventricular models
Computational models for human ventricular APs

- **Priebe L, Beuckelmann DJ (PB):**
  - “Simulation study of cellular properties in heart failure.”  
  - 22 variables.
  - Epicardial cells only.

- **Ten Tusscher KHWJ, Noble D, Noble PJ, Panfilov AV (TNNP):**
  - “A model for human ventricular tissue.”  
  - 17 variables.
  - Epicardial, endocardial and midmyocardial cells.

- **Iyer V, Mazhari R, Winslow RL (IMW):**
  - “A computational model of the human left-ventricular epicardial myocyte.”  
  - **67 variables.**
  - Epicardial cells only.
Minimal model for human ventricular action potentials in tissue

(3V-SIM) makes use of the minimum number of equations (3 variables) capable of reproducing published physiological data:
+ thresholds for excitation.
+ $dv/dt|_{\text{max}}$ in tissue.
+ APD$_{\text{min}}$ and DI$_{\text{min}}$.
+ APD and CV restitution curves.
+ AP morphology.
Minimal model for human ventricular action potentials in tissue

Why?

3V — 4V

(3V-SIM) makes use of the minimum number of equations (3 variables) capable of reproducing published physiological data:

+ thresholds for excitation.
+ $\frac{dv}{dt}_{\text{max}}$ in tissue.
+ $\text{APD}_{\text{min}}$ and $\text{DI}_{\text{min}}$.
+ APD and CV restitution curves.
+ AP morphology.

JCE Vol 15 1357-1363 Dic. 2004
AP morphology (epicardial single cell)

- AP shapes are qualitatively and quantitatively different depending on the ionic model.

**Experimental** epicardial AP.
(M. Nåbauer *et al.*, Circulation 1996, 93: 168-177.)

**Simulated** epicardial APs for the different ionic models.
AP morphology (epicardial single cell)

- AP shapes are qualitatively and quantitatively different depending on the ionic model.

**Experimental epicardial AP.**
(M. Näbauer et al., Circulation 1996, 93: 168-177.)

**Simulated epicardial APs for the different ionic models.**

<table>
<thead>
<tr>
<th>Model</th>
<th>Time to simulate 10 s</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNNP</td>
<td>4.1 s</td>
</tr>
<tr>
<td>PB</td>
<td>9.2 s</td>
</tr>
<tr>
<td>IMW</td>
<td>17 min</td>
</tr>
<tr>
<td>4V</td>
<td>0.13 s</td>
</tr>
</tbody>
</table>

Ratio of IMW : PB : TNNP : 4V = 8084 : 70 : 31 : 1
AP morphology (epicardial 1D tissue)

- PB, TNNP and IMW model APs lose a considerable fraction of the phase 0 amplitude when coupled into tissue.

Simulated epicardial AP (single cell).

Simulated epicardial AP (tissue).
APD and CV restitutions in 1D tissue (epicardium)

- APD restitution: APD larger for PB and Iyer *et al.* models.
- CV restitution: using published data, the diffusion coefficient for the human ventricular myocyte is estimated to be $D=1.16 \text{cm}^2/\text{s}$. For this value, the detailed ionic models fail to reach experimental $CV_{\text{max}}$.

Dynamics in homogeneous 2D-tissue (epicardium)
Simplified model fitted to experiments
Why not to other models?
Mathematical Model

All cardiac cell models in tissue are reaction-diffusion equations.

\[ C_m \frac{\partial V(t, x)}{\partial t} = \nabla \cdot (D(x) \nabla V) - I_{\text{ion}}(V, m) - I_{\text{stim}}(t, x) \]

\[ \frac{\partial m(t, x)}{\partial t} = f(V, m) \]

\( V(t, x) \) membrane potential
\( m(t, x) \) gating, concentrations
\( C_m \) membrane capacitance
\( D(x) \) conductivity tensor
\( I_{\text{ion}} \) total ionic current \( (I_{\text{Na}} + I_{\text{K}} + I_{\text{Ca}}) \)
\( I_{\text{ion}} \) external stimulus current

We will describe now the 3V and 4V models (FK-models)
The model consists of 3 variables: the membrane voltage $V$, a fast ionic gate $v$, and a slow ionic gate $w$.

The variables are used to produce 3 independent phenomenological ionic currents.

$$I_{fi}(V; v) = -v \frac{p(V - V_c)(V - V_m)}{\tau_d}$$

$$I_{so}(V) = \frac{(V - V_o)(1 - p)}{\tau_o} + \frac{p}{\tau_r}$$

$$I_{si}(V; w) = -w \left(1 + \tanh \left[k(V - V_{c,si})\right]\right) / (2\tau_{si})$$
The equations for the 3 variables are:

\[ \partial_t V(\vec{x}, t) = \nabla \cdot (\tilde{D} \nabla V) - I_{\text{ion}} \]
\[ \partial_t v(t) = (1 - p) (1 - v)/\tau_v^{-}(V) - p v/\tau_v^+ \]
\[ \partial_t w(t) = (1 - p) (1 - w)/\tau_w^{-} - p w/\tau_w^+ \]

where
\[ \tau_v^{-}(V) = (1 - q) \tau_v^{-1} + q \tau_w^{-2} \]
\[ p = \begin{cases} 1 & \text{if } V \geq V_c \\ 0 & \text{if } V < V_c \end{cases} \quad \text{and} \quad q = \begin{cases} 1 & \text{if } V \geq V_v \\ 0 & \text{if } V < V_v \end{cases} \]
Comparison with Other Models

The equations for the 3 variables are:

\[
\begin{align*}
\frac{\partial_t}{\partial_t} V(\vec{x}, t) &= \nabla \cdot (\tilde{D} \nabla V) - I_{\text{ion}} \\
\frac{\partial_t}{\partial_t} v(t) &= (1 - p) (1 - v)/\tau_v^-(V) - p v / \tau_v^+ \\
\frac{\partial_t}{\partial_t} w(t) &= (1 - p) (1 - w)/\tau_w^- - p w / \tau_w^+
\end{align*}
\]

where

\[
\tau_v^-(V) = (1 - q) \tau_{v1}^- + q \tau_{v2}^-
\]

\[
p = \begin{cases} 
1 & \text{if } V \geq V_c \\
0 & \text{if } V < V_c
\end{cases}
\quad \text{and} \quad q = \begin{cases} 
1 & \text{if } V \geq V_v \\
0 & \text{if } V < V_v
\end{cases}
\]

Beeler-Reuter  Courtemanche  Rabbit experiment
4V Cell Model Equations

\begin{align*}
\partial_t u &= \nabla(\tilde{D}\nabla u) - (J_{fi} + J_{so} + J_{st}) \quad (1) \\
\partial_t v &= (1 - m)(v_\infty - v)/\tau_v^- - mw/\tau_v^+ \quad (2) \\
\partial_t w &= (1 - p)(w_\infty - w)/\tau_w^- - pw/\tau_w^+ \quad (3) \\
\partial_t s &= ((1 + \tanh(k_s(u - u_s)))/2 - s)/\tau_s \quad (4) \\
J_{fi} &= -vm(u - u_m)(u - u)/\tau_{fi} \quad (5) \\
J_{so} &= (u - u_o)(1 - p)/\tau_o + p/\tau_{so} \quad (6) \\
J_{st} &= -pws/\tau_{st} \quad (7) \\
\tau_v^- &= (1 - q)\tau_{v1} + q\tau_{v2} \quad (8) \\
\tau_w^- &= \tau_{w1} + (\tau_{w2} - \tau_{w1})(1 + \tanh(k_w(u - u_w)))/2 \quad (9) \\
\tau_{so} &= \tau_{so1} + (\tau_{so2} - \tau_{so1})(1 + \tanh(k_{so}(u - u_{so}))/2 \quad (10) \\
\tau_s &= (1 - p)\tau_{s1} + p\tau_{s2} \quad (11) \\
\tau_o &= (1 - r)\tau_{o1} + r\tau_{o2} \quad (12) \\
v_\infty &= \begin{cases} 
1 & u < u_q \\
0 & u \geq u_q
\end{cases} \quad (13) \\
w_\infty &= (1 - r)(1 - u/\tau_{w_\infty}) + rw_{\infty}^* \quad (14) \\
m &= \begin{cases} 
0 & u < u_m \\
1 & u \geq u_m
\end{cases} \quad (15) \\
p &= \begin{cases} 
0 & u < u_p \\
1 & u \geq u_p
\end{cases} \\
q &= \begin{cases} 
0 & u < u_q \\
1 & u \geq u_q
\end{cases} \quad (16) \\
r &= \begin{cases} 
0 & u < u_r \\
1 & u \geq u_r
\end{cases}
\end{align*}
Mathematical Model

All cardiac cell models in tissue are reaction-diffusion equations.

\[ C_m \frac{\partial V(t, x)}{\partial t} = \nabla \cdot (D(x) \nabla V) - I_{\text{ion}}(V, m) - I_{\text{stim}}(t, x) \]

\[ \frac{\partial m(t, x)}{\partial t} = f(V, m) \]
Cardiac tissue modeling

Nonlinear parabolic reaction-diffusion equations:

\[ C_m \partial_t V(t, x) = \nabla \cdot (D(x) \nabla V) - I_{ion}(V, m) - I_{stim}(t, x) \]
\[ \partial_t m(t, x) = f(V, m) \]

- \( V(t,x) \) membrane potential
- \( m(t,x) \) gating variables, ionic concentrations
- \( C_m \) membrane capacitance
- \( D(x) \) conductivity tensor
- \( I_{ion} \) total ionic current across the membrane of the cell
- \( I_{stim} \) external stimulus current

Neumann boundary conditions on potential \( V \):

\[ n \cdot \nabla V = 0 \]
How to couple cardiac cells to represent tissue?

The Cable Equation

The flow of current along the cable is proportional to the voltage gradient (Ohm’s law).

\[ I_{\text{membrane}} = I_{\text{axial}} \]

Any change on the axial current, produces a change on the membrane current.

\[ I_m 2\pi rl = [I_a(x + l) - I_a(x)]\pi r^2 \approx -\left(\frac{\partial i_a}{\partial x}\right)\pi lr^2 \quad (1) \]

\[ \left(\frac{\partial V_m}{\partial x}\right) = -\rho i_a \quad (2) \]

\[ Q = CV; \quad \frac{dQ_m}{dt} = I_m = C \frac{dV_m}{dt} \quad \text{and} \quad I_m = I_c + I_{\text{ion}} \]

Combinando Eq 1,2 y 3 obtenemos:

\[ \left(\frac{\partial V_m}{\partial t}\right) = r\left(\frac{\partial^2 V_m}{\partial x^2}\right) - \frac{I_{\text{ion}}}{C_m} = D\left(\frac{\partial^2 V_m}{\partial x^2}\right) - \frac{I_{\text{ion}}}{C_m} \quad (4) \]
Cardiac tissue modeling

Nonlinear parabolic reaction-diffusion equations:

\[
C_m \partial_t V(t, x) = \nabla \cdot (D(x) \nabla V) - I_{ion}(V, m) - I_{stim}(t, x)
\]

\[
\partial_t m(t, x) = f(V, m)
\]

\[
\left( \frac{\partial V_m}{\partial t} \right) = r \left( \frac{\partial^2 V_m}{\partial x^2} \right) - \frac{I_{ion}}{C_m} = D \left( \frac{\partial^2 V_m}{\partial x^2} \right) - \frac{I_{ion}}{C_m}
\]

(4)
Como resolver estas ecuaciones Numericamente?

\[ \frac{\partial V}{\partial t} = \frac{\partial^2 V}{\partial x^2} + (a - V)(V - 1)V - v \]

\[ \frac{\partial v}{\partial t} = \epsilon(\beta V - \gamma v - \delta) \]

\[ \left( \frac{\partial V_m}{\partial t} \right) = r \left( \frac{\partial^2 V_m/\partial x^2}{2\rho C_m} \right) - \frac{I_{ion}}{C_m} = D \left( \frac{\partial^2 V_m}{\partial x^2} \right) - \frac{I_{ion}}{C_m} \]

(4)
Integration

Given an ODE, \( \frac{dV}{dt} = f(V) \), we can develop an integration method to evolve the solution in time using Taylor series:

\[
V(t + \Delta t) = V(t) + \Delta t \frac{dV(t)}{dt} + \frac{\Delta t^2}{2} \frac{d^2V(t)}{dt^2} + O(\Delta t^3)
\]

A first-order approximation of the derivative can be obtained as:

\[
\frac{V(t + \Delta t) - V(t)}{\Delta t} = \frac{dV(t)}{dt} + O(\Delta t)
\]
Integration

• Thus, for simplicity, we can approximate the derivative to first order as

\[
\frac{V(t + \Delta t) - V(t)}{\Delta t} = \frac{dV}{dt} = f(V)
\]

\[
V(t + \Delta t) = V(t) + \Delta t \cdot f(V)
\]

• We can represent \( V(t) \) as \( V^i \) and \( V(t+\Delta t) \) as \( V^{i+1} \). Then

\[
V^{i+1} = V^i + \Delta t \cdot f(V)
\]

• Note that we need to begin with an initial condition \( V^0 \) (usually resting membrane potential).
Integration in Tissue

• In tissue, the equation of interest includes a spatial derivative:

\[
\frac{dV(x,t)}{dt} = f(V(x,t)) + D \frac{\partial^2 V(x,t)}{\partial x^2}
\]

• In this case we also need an approximation for the spatial derivative.
Integration in Tissue

• In this case we combine the following:

\begin{align*}
V(x + \Delta x, t) &= V(x, t) + \Delta x \frac{\partial V(x, t)}{\partial x} + \frac{\Delta x^2}{2} \frac{\partial^2 V(x, t)}{\partial x^2} + O(\Delta x^3) \\
V(x - \Delta x, t) &= V(x, t) - \Delta x \frac{\partial V(x, t)}{\partial x} + \frac{\Delta x^2}{2} \frac{\partial^2 V(x, t)}{\partial x^2} - O(\Delta x^3)
\end{align*}

• Summing, we get the following:

\begin{align*}
V(x + \Delta x, t) + V(x - \Delta x, t) &= 2V(x, t) + \Delta x^2 \frac{\partial^2 V(x, t)}{\partial x^2} - O(\Delta x^4)
\end{align*}

• and to second order

\[
\frac{\partial^2 V(x, t)}{\partial x^2} = \frac{V(x + \Delta x, t) - 2V(x, t) + V(x - \Delta x, t)}{\Delta x^2}
\]
Integration in Tissue

• We can use the following approximation to advance the solution in time (first order in time, second order in space):

\[ V_{i}^{n+1} = V_{i}^{n} + \Delta t \cdot f(V_{i}^{n}) + \frac{\Delta t}{\Delta x^2} \left( V_{i+1}^{n} - 2V_{i}^{n} + V_{i-1}^{n} \right) \]

where \( V_{i}^{n} \) represents the \( i^{\text{th}} \) point in space and the \( n^{\text{th}} \) time step.

• Note that now we need both an initial condition \( V(x,0) \) and boundary conditions \( V(0,t) \), e.g.

\[ \frac{\partial V(0,t)}{\partial x} = 0, \quad \frac{\partial V(L_x,t)}{\partial x} = 0 \]
Simulations in 1D (FHN-model)

http://thevirtualheart.org/java/fhn1d.html
Simulations in 2D (FHN-model)

http://thevirtualheart.org/java/2dfhn.html
3V Cell Model Equations

The model consists of 3 variables: the membrane voltage \( V \), a fast ionic gate \( v \), and a slow ionic gate \( w \).

\[
I_{fi}(V; v) = -v p (V - V_c)(V - V_m)/\tau_d \\
I_{so}(V) = (V - V_o) (1 - p)/\tau_o + p/\tau_r \\
I_{si}(V; w) = -w (1 + \tanh [k (V - V_c^{si})])/(2\tau_{si})
\]

The equations for the 3 variables are:

\[
\frac{\partial V}{\partial t} = \frac{\partial^2 V}{\partial x^2} + (a - V)(V - 1)V - v \\
\frac{\partial v}{\partial t} = \epsilon(\beta V - \gamma v - \delta) \\
\frac{\partial t}{\partial t} V(\vec{x}, t) = \nabla \cdot (\bar{D} \nabla V) - I_{ion} \\
\frac{\partial t}{\partial t} v(t) = (1 - p) (1 - v)/\tau_v^-(V) - p v/\tau_v^+ \\
\frac{\partial t}{\partial t} w(t) = (1 - p) (1 - w)/\tau_w^- - p w/\tau_w^+
\]

where

\[
\tau_v^-(V) = (1 - q) \tau_v^{v1} + q \tau_v^{v2}
\]

\[
p = \begin{cases} 
1 & \text{if } V \geq V_c \\
0 & \text{if } V < V_c
\end{cases}
\]

and

\[
q = \begin{cases} 
1 & \text{if } V \geq V_v \\
0 & \text{if } V < V_v
\end{cases}
\]
3V Cell Model Equations