Multiscale computational modeling of cardiac action potentials

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### **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



**F. Netter, 1978** 

### Cardiac arrhythmia mechanisms

### Ventricular tachycardia



# Ventricular fibrillation



### Defibrillation



thevirtualheart.org

### **Multiscale phenomena**









Nernst potential (equilibrium potential for electrodiffusion):

$$E_{\mathsf{K}} = \frac{RT}{zF} \ln \frac{[\mathsf{K}^+]_o}{[\mathsf{K}^+]_i} \approx -85 \,\mathrm{mV}$$

#### **Cardiac action potentials** Ca<sup>2+</sup> K<sup>+</sup> Na<sup>+</sup> Injection of a Ca Na stimulus current initiates depolarization, which cause Na<sup>+</sup> $K^+$ ● Na+ Ca<sup>2+</sup> and Ca<sup>+</sup> channels to open and further depolarize the membrane, V≈+20mV

 $(E_{\text{Na}}\approx+50\,\text{mV}, E_{\text{Ca}}\approx+30\,\text{mV})$ 

#### **Cardiac action potentials** Ca<sup>2+</sup> K<sup>+</sup> Na<sup>+</sup> Ca Na Na<sup>+</sup> and Ca<sup>+</sup> channels inactivate (close) with K<sup>+</sup> ●Na+ Ca<sup>2+</sup> prolonged depolarization. K<sup>+</sup> channels open and cause repolarization

to  $V \approx -85 \,\text{mV}$ .

### **Cardiac action potentials**

- Upstroke of ventricular AP is Na<sup>+</sup> mediated.
- A prolonged inward Ca<sup>2+</sup> current prolongs the AP (plateau).
- Ca<sup>2+</sup> influx triggers additional Ca<sup>2+</sup> release from the sarcoplasmic reticulum.
- Cytoplasmic Ca<sup>2+</sup> produces muscle contraction.
- Cardiac cells have many different types of K<sup>+</sup> channels.



### The membrane as an electrical circuit



Equation for capacitor:  $Q = C_m V$ Current across capacitor:  $I_c = dQ/dt = C_m dV/dt$ Charge conservation:  $I = I_c + I_{ion} = 0$ Hence,  $dV/dt = -I_{ion}/C_m$ , where  $I_{ion} = I_{Na} + I_K + I_{Ca}$ 





*x*: fraction of gates that are open 1-x: fraction of gates that are closed  $\alpha_x(V)$ : opening rate  $\beta_x(V)$ : closing rate

ODE for gating variable:

$$dx/dt = \alpha_x(1-x) - \beta_x x$$
  
=  $-(\alpha_x + \beta_x)x + \alpha_x$   
=  $(x_{\infty} - x)/\tau_x$ 

where  $x_{\infty} = \alpha_x / (\alpha_x + \beta_x)$  $\tau_x = 1 / (\alpha_x + \beta_x)$  Solution for constant *V*:

$$dx/dt = (x_{\infty} - x)/\tau_{x}$$

$$1/(x_{\infty} - x) dx = 1/\tau_{x} dt$$

$$\int_{x_{0}}^{x} 1/(x_{\infty} - x') dx' = \int_{0}^{t} 1/\tau_{x} dt'$$

$$[-\ln(x_{\infty} - x')]_{x_{0}}^{x} = t/\tau_{x}$$

$$\ln \frac{x_{\infty} - x}{x_{\infty} - x_{0}} = -t/\tau_{x}$$

$$\frac{x_{\infty} - x}{x_{\infty} - x_{0}} = \exp(-t/\tau_{x})$$

$$x = x_{\infty} - (x_{\infty} - x_{0}) \exp(-t/\tau_{x})$$

Solution for constant *V*:

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

### Voltage clamp experiments:



### The Hodgkin-Huxley model of the squid giant axon



The axon is giant, not the squid







Action potential recordings from squid giant axon

#### **Full Hodgkin-Huxley model**



$$\begin{aligned} \alpha_m &= 0.1(V+35)/(1-\exp(-(V+35)/10)), \\ \beta_m &= 4\exp(-(V+60)/18), \\ \alpha_h &= 0.07\exp(-(V+60)/20), \\ \beta_h &= 1/(\exp(-(V+30)/10)+1), \\ \alpha_n &= 0.01(V+50)/(1-\exp(-(V+50)/10)), \\ \beta_n &= 0.125\exp(-(V+60)/80). \end{aligned}$$

### Single cardiac myocyte model example



courtesy of R. Gilmour

### Single cardiac myocyte model example



#### **Cell model evolution: Noble, 1962**

The sodium current

$$\begin{split} I_{\mathrm{Nn}} &= (400m^3\hbar + 0.14)(E_{\mathrm{m}} - 40), \\ \alpha_h &= 0.17\,\exp{[(-E_{\mathrm{m}} - 90)/20]}, \\ \beta_h &= \left[\exp{\left(\frac{-E_{\mathrm{m}} - 42}{10}\right)} + 1\right]^{-1}, \\ \alpha_m &= \frac{0.1(-E_{\mathrm{m}} - 48)}{\exp{[(-E_{\mathrm{m}} - 48)/15]} - 1}, \\ \beta_m &= \frac{0.12(E_{\mathrm{m}} + 8)}{\exp{[(E_{\mathrm{m}} + 8)/5]} - 1}. \end{split}$$

$$\begin{split} The \ potassium \ current \\ I_{K} &= (g_{K_{1}} + g_{K_{2}})(E_{m} + 100), \\ g_{K_{1}} &= 1\cdot 2 \ \exp\left[(-E_{m} - 90)/50\right] + 0\cdot 015 \ \exp\left[(E_{m} + 90)/60\right], \\ g_{K_{3}} &= 1\cdot 2n^{4}, \\ \alpha_{n} &= \frac{0\cdot 0001(-E_{m} - 50)}{\exp\left[(-E_{m} - 50)/10\right] - 1}, \\ \beta_{n} &= 0\cdot 002 \ \exp\left[(-E_{m} - 90)/80\right]. \end{split}$$

the anion conductance,  $g_{An}$ 

$$g_{An} = I_{An}/(E_m - E_{An}),$$

Noble, J Physiol, 1962.

### Cell model evolution: Luo & Rudy, 1991

TABLE L. Formulations of Ionic Currents

```
benand currents
Fast sodium current
  L_n = 23 \cdot m^2 \cdot 3 \cdot j \cdot (V - L_m)
  For Vit −40 mV
  a,=a=0.0, B,=1/00.13(1+mp)/V+10.664/-11.1284
  B=0.3 · esp(-2.535 · 10-7 V)(1+esp(-0.3(V+32)))
  For V<-40 mV
  a,=0.135+exp(0.00+V)/-6.8[, j],=3.56+exp(0.079V)+3.1+107-exp(0.35V)
  n=[-1.2714-10<sup>2</sup> - mp(0.2444V)-3.474 - 10<sup>-5</sup> - exp(-0.04091V)] - (V+37.78)(1+exp[0.311-(V+29.23)))
  fl=0.1212-exp(-0.00052V)/[1+exp[-0.1376(V+40.14)]]
  For all range of V
  na=0.32(V+47.13)(1-exp[-0.1(V+47.13)]), fa=0.08 cop(-V/11)
Slow inward current
  L=0.09-d-I-(V-E_), E_=7.7-13.0387-lo([Ca]).
  m_c = 0.095 \cdot exp[-0.03(V-5)]/[1 + exp[-0.072(V-5)]]
  fl,=0.07 - exp[-0:017(V+44)]/(1+exp[0.05(V+44)])
  n/=0.012 - exp[--0.008/V+28)//(1+exp]0.15/V+28)]]
  fi=0.0063 · exp[-0.02(V+30)]/2+exp[-0.2(V+30)])
  Calcium uptake: d()Call/idt=-10<sup>-4</sup>-L+6.07(10<sup>-4</sup>-0Call)
Outward currents
Time-dependent potassium ourrent
  I_K = \overline{G}_K - X - X + (V - E_K), \overline{G}_K = 0.282 + \sqrt{|K|} / 5.4
  X,=2.837 · [exp[0.06(V+77)]-150(V+77) · exp[0.06(V+35)]) for V>-100 mV and X,=1 for Vu-100 mV
  a<sub>1</sub>=0.0005 · exp[0.083/V+50][(1+exp[0.057]V+50]]]
  \beta_1 = 0.0013 - exp[-0.06(V + 20)]/[1 + exp[-0.04(V + 20)]]
Time-independent potassium current
  I_{C} = \overline{G}_{C} \cdot K1, (V - E_{C}), \overline{G}_{C} = 0.6947 \cdot \sqrt{|K|} \cdot 5.4
  ng.=1.02(1+mp[0.2385-(V-Eg)-59.215)[]
  \beta_{01} = [0.49124 \cdot exp[0.08032 \cdot (V - E_{01} + 5.476)] + exp[0.06175 \cdot (V - E_{01} - 594.31)]/
    {1+mp[-0.5]43 · {V-En+4.753}]}
Platnau potassiem current
  Ing=0.0183 · Kp · (V - Eng). Eng=En-
  Kp+1/0+expb/7.488-V)/5.985
Background current
  L=0.03921 - (V+59.87)
Total time-independent potassium current
  have the + have he
```

Luo & Rudy, Circ Res, 1991.

### Cell model evolution: lyer et al. 2004

lyer et al.

3100 1.600 g 100 1.500 g 100

For fine tuning of the optimal parameter set, the output of the annealing	TABLE 2 Cell geometr	y constants		TABLE 4 Initial conditions
downhill moves are accepted). This approach has been shown to be superior	Constant	Symbol	Vahae	State
inding the absolute minimum of functions of several variables (Goffe,	Cell capacitance	Ausp	153.4 pF	Membrane potential, mV
294).	Myoplasm volume	Varya	25.84 E <sup>-6</sup> µL	Intracellular sodium, mM
	Junctional SR volume	VIN	0.16 E L	Intracellular potassium, mM
adel equations and nerometers	Network SR volume	VNE	2.1 E - µL	Intracellular calcium, mM
iouer equations and parameters	Subspace voturne	¥ <sub>m</sub>	1.2.2 µL	NSR calcium, mM
Il rate constants are expressed in units of ms <sup>-1</sup> unless otherwise noted.	10			SS calcian, mM
milarly, all concentrations are expressed in mM unless otherwise noted.	$\frac{dO_{2Na}}{dO_{2Na}} = -(\omega + \nu)$	$(O_{m_{1}}) + (\epsilon)(O_{m_{2}}) +$	$(n)(C_{\infty})$ , (9)	JSR carcian, mM
	dr	- 2847 - 1717 - 1847	Correlation of the second s	ByR state ().
opetante	dClma .			RyR state C <sub>1</sub>
onstants	$dt = -(c_t$	$+ 4\alpha a)(C_{3N_4}) + (\beta/4)$	$T(CI_{1Na})$	RyR state O2
e Tables 1-4.	+ (c)	(C)	(10)	L-type state C <sub>0</sub>
	$+ (\varepsilon_n$	(Conia)-	(10)	L-type state C <sub>1</sub>
and an an an and a	dCIm.			L-type state C2
embrane currents	$dt = -(\beta/a + 3\alpha)$	$a + c_t/a)(CI_{1Na}) + (4)$	$laa)(CI_{tNa})$	L-type state C <sub>3</sub>
e Table 5		116-200	(11)	L-type state C.
	+ (2p/a)(CI	$_{2Na}$ ) $+ (c_a a) (c_{1Na}).$	(11)	Longe state C -
	dCIm.			L-type state C-1
adium current Ina	$\frac{da}{dt} = -(2\beta/a + 2)$	$\alpha a + c_t/a^{-})(CI_{2Na}) +$	(3au)(CI <sub>1Na</sub> )	L-type state Card
		1		L-type state C <sub>en1</sub>
$I_{Na} = \bar{G}_{Na}(O_{1Na} + O_{2Na})(V - E_{Na}).$ (1)	$+ (3\beta/a)(C)$	$_{Na}$ ) + ( $c_{a}a$ )( $C_{2Na}$ ).	(12)	L-type state Coul
	dCIm.			L-type inactivation variable
$F_{-} = \frac{RT}{10} \left( \frac{ Na^{+} _{*}}{2} \right) \qquad (2)$	$= -(3\beta/a + \alpha)$	$a + c_t/a')(CI_{3Na}) + ($	$(2\alpha a)(CI_{2Na})$	High affinity troponin bound fra
$L_{N_{h}} = \frac{1}{F} m \left( \frac{ N_{h}^{+} }{ N_{h}^{+} } \right)^{-1} (2)$		and here a		Low affinity troponin bound frac
	$+ (4\beta/a)(C)$	$c_{Na}$ ) + ( $c_{a}a$ )( $C_{Na}$ ).	(13)	K14.3 state C1
$\frac{dC_{W_{\alpha}}}{dC_{W_{\alpha}}} = -(4\alpha + c_{\alpha})(C_{W_{\alpha}}) + (\beta)(C_{W_{\alpha}}) + (c_{\alpha})(CL_{W_{\alpha}}),$ (3)	dC1			Kr43 state C:
dr ( dr	$\frac{1}{4t} = -(4\beta/a + \gamma)$	$\gamma + c_l/a^*)(CI_{4Na}) + ($	$(\alpha a)(CI_{3Na})$	Kr4.3 state C,
dC				Kv4.3 state O
$\frac{i\alpha}{ds} = -(\beta + c_a \cdot a + 3\alpha)(C_{1Na}) + (4\alpha)(C_{0Na})$	$+ (\delta\delta)(I_{Na}) +$	$(c_n a^*)(C_{4Na}).$	(14)	Kr4.3 state CI <sub>1</sub>
(20)(C ) + (- (-)(CL ) (4)	dl.			Kr4.3 state CI <sub>2</sub>
$+ (2p)(C_{2Nk}) + (c_1/a)(CI_{1Nk}).$ (4)	$\frac{m_{Ab}}{ds} = -(\delta\delta + o_t)(I_t)$	$_{i_{\alpha}}$ ) + $(\gamma\gamma)(CI_{av_{\alpha}})$ + $($	$o_n)(O_{1N_n})$ . (15)	Kv4.3 state CI <sub>3</sub>
dC	cu -			Kr4.3 state CI <sub>4</sub>
$\frac{du}{dt} = -(2\beta + c_n \cdot a^2 + 2\alpha)(C_{2Nn}) + (3\alpha)(C_{2Nn})$	See Table 6.			Ket A state C
$+(20)(C_{-}) + (-(-2)(C_{-}))$ (6)				Kr1 A state C.
$+ (3p)(C_{3Ni}) + (c_f/a_j)(CI_{2Ni}).$ (3)				Ky1.4 state C <sub>1</sub>
dCm.	Rapidly-activating	delayed rectifier I	C*	Kv1.4 state C4
$\frac{1}{dt} = -(3\beta + c_n \cdot a^r + \alpha)(C_{Nin}) + (2\alpha)(C_{Nin})$	current I <sub>Kr</sub>			Kv1.4 state O
	L = G	$f([K^{+}])(Q_{-})(V = E$	(16)	Kv1.4 state CI <sub>1</sub>
$+ (4\beta)(C_{Big}) + (c_l/a_l)(CI_{Big}).$ (6)	·6 ·6	/(H 1_/(H K)(C H	k). (11)	Kv1.4 state CI <sub>2</sub>
dC <sub>m</sub>		$RT_{i_{n}}([K^{+}]_{o})$	(17)	KVL4 state CI <sub>3</sub>
$\frac{ds}{ds} = -(4\beta + c_s \cdot a^s + \gamma + \eta)(C_{sh})$	E <sub>K</sub>	$= \frac{1}{F} \ln \left( \frac{1}{ K^+ } \right)$	(17)	AVL4 state C.24
		100 11/		In state C.
$+ (a)(c_{3Na}) + (b)(O_{1Na}) + (b)(O_{2Na})$		( <b>K</b> *1)		In state C
$+ (c_l/a^4)(CI_{0N_d}).$ (7)	f([K	$(1) = \sqrt{\frac{1}{1} + \frac{1}{1}}$	(18)	Ine state C1
		- ((4)		Ike state O
$\frac{dO_{1Na}}{dO_{2Na}} = -(\delta + \varepsilon + \alpha)(O_{2Na}) + (\gamma)(C_{2Na})$	dC.m.			Ike state I
dr (a construction) (a) (a construction)		$(\alpha_{a})(C_{1Ke}) + (\beta_{0})(C_{1Ke})$	ac). (19)	I <sub>Kn</sub> state C <sub>0</sub>
$+ (\omega)(O_{2Na}) + (o_Y)(I_{Na}).$ (8)	dr			IKa state C1
	$dC_{2k} = -(\theta_{1} + b)/\theta_{2k}$	$(-) + (\alpha)(C_{-}) +$	(E)(C) (20)	Fig. state O <sub>1</sub>
ARIE 1 Discussional connectancie	$dr = -(p_0 + x_f)(t)$	$(u_0)(C_{3G}) +$	(Ab)(4-36c). (20)	In state Ca
AUCC 1 PHYSICAL CONSIGNAL				In state C.
Constant Symbol Value	TABLE 3 Standard ion	ic concentrations		INe state C2
raday's constant F 96.5°C/mmol	Bernard int	Freehol	Value	INe state C3
imperature T 310 K	PUTTICARE INS	sympol	Vallac	I <sub>Na</sub> state C <sub>4</sub>
as constant R 8.315 J/mol -K	Sodium	[Na <sup>+</sup> ].	138 mM	INe state O1
	Potassiam	[K <sup>+</sup> ],	4 mM	I <sub>Na</sub> state O <sub>2</sub>
foltzmann's constant K 1.381 E <sup>-21</sup> J/K		and Take		

ate constant Kr4.3 current, ms <sup>-1</sup> Kr1.4 current, r	ns <sup>-1</sup>	Parameter	Value
$\begin{array}{rcl} a_{\kappa} & 0.678, 425 & \exp(0.0285 \ V) & 1.3 & 0024 & \exp(0.0285 \ V) \\ \beta_{\kappa} & 0.080239 & \exp(-0.0833 \ V) & 0.010137 & \exp(-0.030298 \ \beta_{\kappa} & 3.030398 \ \beta_{\kappa} & 3.030398 \ \beta_{\kappa} & 3.030398 \ \beta_{\kappa} & 1.030398 \ \beta_{\kappa} & 1.$	177 V) 1779 V)	$\begin{array}{c} G_{0, \pm} & & 0.01 \\ K_{a, \pm 0} & & 0.01 \\ K_{a, \pm 0} & & 0.02 \\ \lambda_{a} & & 0.2 \\ \eta & & 0.3 \\ \lambda_{b, a} & & 0.2 \\ \lambda_{b, a} & & 0.2 \\ K_{b, a} & & 0.3 \\ \lambda_{a, b} $	i mSjµF i mM i mM i mM i i i i i i i i i i i i i i i i i i mM i i mM i i mM i i mM i i mM i i mM i i mM i i mM i i mM i i mM i i i mM i i mM i i mM i i i mM i i i mM i i i mM i i i mM i i i mM i i i mM i i i mM i i i mM i i i mM i i i mM i i i mM i i i mM i i i mM i i i i
b <sub>2</sub> 0.47656 1.17100 b <sub>3</sub> 7.77537 0.63902		Coloise bondling maskening	
b <sub>4</sub> 318.252 2.12035		Sarcolemmal Ca <sup>2+</sup> pump current L <sub>2020</sub>	
$K_i^{\pm}(V) = \frac{1}{0.94 + \exp(\frac{1.26}{RT/F}(V - EK))}$ .	(56)	$I_{\mu(\Omega)} = \overline{I}_{\mu(\Omega)} \frac{[Ca^{2+}]_{i}}{K_{a\mu(\Omega)} + [Ca^{2+}]_{i}}$	(64
the start a		Ca <sup>2+</sup> background current I <sub>Ca,b</sub>	
$E_{\mathbf{K}} = \frac{H}{F} \ln \left( \frac{ \mathbf{K} _{\mu}}{ \mathbf{K}^{+} _{i}} \right).$	(57)	$I_{Cab} = \overline{G}_{Cab}(V - E_{Ca}).$	(65)
$\ddot{G}_{K1} = 0.125 \frac{mS}{\mu F \cdot mM^{1/2}}$ .	(58)	$E_{\text{cs}} = \frac{RT}{2F} \ln \left( \frac{ \text{Ca}^{2+} _s}{ \text{Ca}^{2+} _s} \right).$	(66)
		See Table 11.	
odium handling mechanisms		L-type Ca <sup>2+</sup> current I <sub>Ca</sub>	
ICX current I <sub>NACe</sub>		$\alpha = 1.997e^{0.02(V-15)}$ .	(67
$s_{Ca} = k_{SC} \frac{1}{m^2} + \frac{1}{m^2} \frac{1}{m$	102	$\beta = 0.0882e^{-0.065(V-22)}$ .	(68)
$K_{mNa} + [Na]_{a}K_{mNa} + [Ca]_{b} I + k_{ab}e^{-i}$ $\times \left(e^{\frac{i\pi}{24}}[Na^{+1}][Ca^{2+1}] - e^{\frac{i\pi}{24}}[Na^{+1}]^{2}[Ca^{2+1}]\right)$	(59)	$\alpha' = \alpha a.$	(69)
······································	(0.7)	$\beta' = \frac{\beta}{b}$ .	(70
a background current I <sub>NK,b</sub>		$\gamma = 0.0554[Ca^{2+}]_{m}$ .	(71
$I_{\text{Nab}} = \tilde{G}_{\text{Nab}}(V - E_{\text{Na}}).$	(60)	$\frac{dC_{0L}}{dr} = -(4\alpha + \gamma)C_{0L} + \beta C_{1L} + \omega C_{CalL}.$	(72
h <sup>+</sup> M <sup>+</sup> array array 1		dCa ca	c
а чк ратр сатит г <sub>лак</sub>		$\frac{dt}{dt} = -(3\alpha + \beta + \gamma a)C_{1L} + 4\alpha C_{0L} + 2\beta C_{1L} + \frac{1}{b}$	COR-
$I_{NaK} = k_{NaK} f_{NaK} \frac{1}{1 + \left(\frac{K_{max}}{(N_{m})}\right)^{1.5}} \frac{[K^{+}]_{s}}{[K^{+}]_{s} + K_{m,Ko}},$	(61)	$\frac{dC_{\pm}}{dt} = -(3\alpha + \beta + \gamma a)C_{\pm} + 4\alpha C_{\pm} + 2\beta C_{\pm} + \frac{b}{b}$ $\frac{dC_{\pm}}{dt} = -(2\alpha + 2\beta + \gamma a^2)C_{\pm} + 3\alpha C_{\pm} + 3\beta C_{\pm} + \frac{b}{b}$	(73)
$\begin{split} & = & \gamma_{\rm back} = k_{\rm back} f_{\rm back} \frac{1}{1 + \left(\frac{g_{\rm back}}{g_{\rm back}}\right)^{1/2}} \frac{ \mathbf{K}^* _{\perp}}{ \mathbf{K}^* _{\perp} + K_{\rm m,Ko}} \\ & f_{\rm back} = \frac{1}{1 + 0.1245e^{-1\frac{2K}{4}} + 0.0365\sigma e^{-10\frac{2K}{4}}}. \end{split}$	(61)	$\begin{split} \frac{dC_{\infty}}{dr} &= -(s\alpha+\beta+\gamma u)C_{\infty}+4aC_{\infty}+2\beta C_{\infty}+\frac{1}{b}\\ \frac{dC_{\infty}}{dr} &= -(2\alpha+2\beta+\gamma u^2)C_{\infty}+3\alpha C_{11}+3\beta C_{\infty}+\frac{1}{b}\\ \frac{dC_{\infty}}{dr} &= -(\alpha+3\beta+\gamma u^2)C_{\infty}+2\alpha C_{\infty}+4\beta C_{\alpha}+\frac{1}{b} \end{split}$	(73)
$\begin{split} & = \mathbf{K} \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \$	(61) (62) (63)	$\begin{split} \frac{dc_m}{dr} &= -(3\alpha + \beta + \gamma a)(c_m + 4ac_m + 2\beta c_m + \frac{2}{2}\beta_m +$	(73) (73) (74) (74) (74) (75) (75)

TABLE 11 Membrane calciu	n exchangers, backgrou	nd	TABLE 12 Ica parameters	
current			Parameter	Value
Parameter	1	abae	1	0.3 ms <sup>-1</sup>
L <sub>p(Ca)</sub>	0.08 p.	A/pP mM	1	4 ms *
Gco	7.684	f <sup>-1</sup> ms/µF	b	2
			20 P-	2.5 d <sup>-3</sup> ms <sup>-1</sup> m 1 2283 d <sup>-3</sup> cm/s
			PK	3.2018 d <sup>-6</sup> cm/s
dO <sub>L</sub>	$a0 \pm 6^{\circ}$	(77)	ICabult	-0.265 pA/pF
dr	Sof i left.	(00)		
$\frac{dC_{cast.}}{dt} = -(4\alpha' + \omega)C$	$C_{\text{CML}} + \beta' C_{\text{CML}} + \gamma C_{\text{HL}}$	(78)	$\frac{dP_{CI}}{d_4} = k_a^+ [Ca^{2+}]_a^n P_{CI} =$	$k_a^- P_{01} - k_b^+ [Ca^{2+}]_a^n P_{01}$
$\frac{dC_{call}}{dC_{call}} = -(3\alpha' + l)$	$S' + \frac{\omega}{\omega} C_{Cos} + 4\alpha' C_{Cos}$		$dI + k_{b}^{-}P_{02} - k_{c}^{+}P$	$b_{01} + k_{\mu}^{-}P_{C2}$ . (6)
dr + 28'C	+ yaC.	(79)	$\frac{dP_{01}}{dP_{01}} = k^+  C $	$a^{2+} ^{n}P_{m} = k^{-}P_{m}$ (6)
dCoat (	w) -		dr	- 12
$dr = -(2\alpha' + 2\beta')$	$+\frac{1}{b^2}C_{Call} + 3\alpha'C_{Call}$		$\frac{dr}{dr} = k_i$	$^{+}P_{01} - k_{v}^{-}P_{02}$ . (6)
$+ 3\beta^{\circ}C_{CML} +$	μa <sup>*</sup> C <sub>π.</sub> .	(80)	$J_{ee} = v_1(P_{01} + P_{02})$	$([Ca^{2+}]_{38} - [Ca^{2+}]_{38}).$ (6)
$\frac{dC_{CAL}}{dt} = -\left(\alpha' + 3\mu\right)$	$V + \frac{\omega}{b^2} C_{ColL} + 2\alpha' C_{Col}$	a.		
$+ 4\beta' C_{\text{Cell.}}$	$+ \gamma a^3 C_{3L}$ .	(81)	SERCA2a pump	
$\frac{dC_{Call.}}{dt} = -\left(4\beta' + \frac{\omega}{b^*}\right)C$	$C_{colL} + \alpha' C_{colL} + \gamma a^4 C_4$	L. (82)	f (	$\frac{[Ca^{2+}]_i}{K_{th}}$ (6)
$\frac{dy_{Cs}}{dt}$	$\frac{y_n - y}{\tau_y}$	(83)	$r_b = \left(\frac{\left[t\right]}{t}\right)$	$\frac{\operatorname{Ca}^{2+}]_{NNR}}{K_{th}}^{N_{th}}$ (6)
$y_{+} = \frac{0}{1+}$	$\frac{82}{e^{2}+\frac{21}{12}}$ + 0.18.	(84)	$J_{sp} = K_{SR} \left(\frac{1}{2}\right)$	$\frac{v_{max}f_h - v_{max}r_h}{1 + f_h + r_h}$ . (6)
$\tau_{1} = -0.00053$	1	(85)	See Table 13.	
$0.5 \pm e^{-V/}$	$\frac{1}{1}$ + 0.00512 $e^{-V/393}$		Intracellular Co <sup>2+</sup> fluxe	
$\bar{P}_{C} 4VF^2 0.001c$	$r_{VF/RT} = 0.341[Ca^{2+}]$ .		intracellular Ca tiuxe	5
$I_{C_{\alpha}} = \frac{C_{\alpha}}{C_{\alpha}} RT$	e <sup>2vp/RT</sup> - 1	(86)	$J_{+} = \frac{[Ca^{2+}]}{[Ca^{2+}]}$	$ _{NSR} - [Ca^{2+}]_{ISR}$ (5)
le s	L xO.	(87)		η
	et av et 🖉 – av et 🔪		TABLE 13 SR parameters	
$I_{Ca,K} = \frac{P_K}{C} O_L \left( \frac{V}{T} \right)$	$\frac{F^{*}}{T} \frac{ \mathbf{K}^{*} _{\mathbf{c}}^{*} \mathbf{c}^{*} -  \mathbf{K}^{*} _{\mathbf{c}}}{2t}$	(88)	Parameter	Value
Cac (1	<i>I</i> e <sup>a</sup> <sup>t</sup> − 1 )		$K_{a}^{+}$	0.01215 µM <sup>-4</sup> m
PC	Ρ <sub>K</sub>	(80)	K. K'	0.576 ms <sup>-1</sup> 0.00405 µM <sup>-1</sup> m
P K =	1 + <u>I</u> <sub>Ca</sub>	(89)	K.	1.93 ms <sup>-1</sup>
	I <sub>Co,MI</sub>		K' K-	0.3 ms <sup>-1</sup>
See Table 12			n, 1	1.8 ms <sup>-1</sup>
			Ka	0.000168 mM
			Na. Ka	1.2 3.29 mM
RvR channel			N <sub>a</sub>	1
40			Tmand	0.0748 d <sup>-1</sup> mM/m
$\frac{dP_{Ci}}{dr} = -k_i^+ [0]$	$a^{2*} P_{c1} + k^{-} P_{cn}$	(90)	T <sub>mate</sub>	0.03748 d ~ mM

	ued						
State	Symbol	0.25 Hz		1 Hz		2 Hz	
I <sub>Na</sub> state CI <sub>1</sub>	CI <sub>INs</sub>	2.625 E	0	2.707 E <sup>-01</sup>	2	979 E-91	
Ju, state CI:	Cl <sub>2Na</sub>	4.768 E <sup>-4</sup>		5.496 E <sup>-43</sup>		880 E <sup>-43</sup>	
INa state CI4	Class	$1.606 E^{-6}$	4	$1.958 E^{-0.1}$	3	833 E <sup>-04</sup>	
I <sub>Na</sub> state I	INA	3.097 E <sup>-6</sup>	6	4.177 E <sup>-01</sup>	1	271 E <sup>-41</sup>	
$\label{eq:delta_state} \begin{split} \frac{dO_{\rm kc}}{dt} &= -(\beta_t \\ \frac{dO_{\rm kc}}{dt} &= -(\beta_t \\ \frac{dI_{\rm kc}}{dt} &= -(\psi + \delta_t ) \\ \\ & \text{See Table 7.} \end{split}$	$+ \alpha_i)(O_{ici}) + (\alpha_1)(O_{ici}) + (\alpha_$	$\hat{\gamma}_{SL}$ ) + $(\beta_i)(I_{Lc})$ $\hat{\gamma}_{SL}$ ) + $(\beta_i)(I_{Lc})$ $\hat{\gamma}_{SL}$ ) + $(\alpha_i)(O_{Lc})$ . $\hat{\gamma}_{SL}$ ) + $(\alpha_i)(O_{Lc})$ . i) ifier K <sup>+</sup> currer $(V - E_K)$ .	(21) (22) (23) (24) nt I <sub>Ks</sub> (25)	$\frac{dC_{SKet}}{dt} = -(4)$ $\frac{dC_{SKet}}{dt} = -(\beta)$ $+ (2)$ $\frac{dC_{2Ket}}{dt} = -(2)$ $+ (3)$ $\frac{dC_{SKet}}{dt} = -(3)$ $+ (4)$ $\frac{dC_{Ket}}{dt} = -(3)$	$(\alpha_s + \beta_i)(C_{oxet})$ $(\alpha_s + \beta_i)(C_{oxet}) + (c_{oxet})$ $(\alpha_s)(C_{oxet}) + (c_{oxet}) + $	$(C_{36ct}) + (\beta_s)(C_{36ct}) + (4\alpha_s)(C_{16ct}) + (4\alpha_s)(C_{16ct}) + (4\alpha_s)(C_{16ct}).$ $(i_1(b_1)(CI_{36ct}).$ $(i_1(b_2)(CI_{36ct}).$ $((C_{36ct}) + (2\alpha_s)(CI_{36ct}).$ $(C_{36ct}) + (2\alpha_s)(CI_{36ct}).$ $(C_{36ct}) + (\alpha_s)(CI_{36ct}).$	(ai) Kel
dC.	$E_{K} = \frac{RT}{F} \ln \left( \frac{ \mathbf{K}^{*} }{ \mathbf{K}^{*} } \right)$	<u>.</u> ).	(26)	dr	$= -(4\beta_s + f_s) + (\alpha_i/b_s)(e_i)$	$\beta_i)(O_{Kel}) + (\alpha_s)(O_{Kel})$ .	36-1
dC <sub>1Ks</sub> (0	$\frac{\mathbf{x}_{\alpha}}{t} = -(\alpha)(C_{0K_{\alpha}}) + (\alpha)(C_{0K_{\alpha}}) + (\alpha)(C_{0K_$	$(\beta)(C_{1K_{1}}).$	(27)	$\frac{dCI_{0Kef}}{dt} = -$	$-(b_1 4 \alpha_s + a_i)($	$CI_{iKvl}$ + $(\beta_s/f_1)(0)$	T <sub>IK</sub>
$\frac{dO_{3Ks}}{dr} = -(\delta - \frac{dO_{3Ks}}{dr})$	$+\varepsilon (O_{3Ks}) + (\gamma)(C_3)$ $\frac{\gamma_{Ks}}{t} = -(\omega)(O_{3Ks}) + (\gamma)(C_3)$	$_{K_{5}}$ + ( $\omega$ )( $O_{2K_{5}}$ ) ( $\epsilon$ )( $O_{1K_{5}}$ ).	(29)		(pr)(*skn).		
See Table 8.				TABLE 6 ALL	$\lambda = Q \frac{kT}{k} exp$	$\left(\frac{-\Delta H_{\pm}}{RT} + \frac{\Delta S_{\pm}}{R} + \frac{z_{\pm}FV}{RT}\right)$	) pa
Transient out	ward K <sup>+</sup> current	lao1		Reto constant	All Hand	AF Band W	-
Fast recovering	component Kv43			Police Constraint	114.007	234.114	
				β	272,470	708.146	
	$c_{v4.3} = G_{Kv4.3}(O_{Kvf})(V$	$(-E_{\kappa}).$	(31)	γ	196,337	529.952	
1.	mm (mr <sup>+</sup> )	13		8	133,690	229.205	
1	- KL / K	1.1				1.610	
,	$E_{K} = \frac{KI}{F} \ln \left( \frac{ K }{ K } \right)$	<del>†</del> ).	(32)	0.	97.658		
4	$E_{K} = \frac{KI}{F} ln \left( \frac{ K }{ K } \right)$	<del>[</del> )·	(32)	01 77	97,658 -116,431	-578.317	
	$E_{K} = \frac{KI}{F} \ln \left( \frac{ \mathbf{K} }{ \mathbf{K} } \right)$	<u>.</u> ).	(32)	0, 0, 77 88	97,658 -116,431 55,701	-578.317 -130.639	
TABLE 5 Time-c	$E_{K} = \frac{KI}{F} \ln \left( \frac{ K }{ K } \right)$ lependent current der	veities	(32)	0, 0; 77 88 E	97,658 -116,431 55,701 85,800 121,955	-578.317 -130.639 70.078 225.175	
TABLE 5 Time-C	$E_{K} = \frac{KI}{F} ln \left( \frac{ K }{ K } \right)$ Rependent current der rent	ia). vaities Symbol Di	(32) maity	0, 0, 77 88 2 2 8 7	97,658 -116,431 55,701 85,800 121,955 147,814	-578.317 -130.639 70.078 225.175 338.915	
TABLE 5 Time-o	$E_{K} = \frac{KI}{F} ln \left( \frac{ K }{ K } \right)$ lependent current der	nii). vaities Symbol Di G <sub>Na</sub> 56.32	(32) msity mS/µF	0, 0, 77 88 2 4 7 7	97,688 -116,431 55,701 85,800 121,955 147,814 121,322	-578.317 -130.639 70.078 225.175 338.915 193.265	
TABLE 5 Time-C Cur Sodium current Debayed rectifier, m	$E_K = \frac{KI}{F} ln \left( \frac{K}{[K]} \right)$ dependent current der ront	nsities Symbol Da G <sub>Na</sub> 56.32 G <sub>Re</sub> 0.010 G <sub>Re</sub> 0.0100	(32) mity mS/µF inS/µF inS/µF	0, 0; 77 88 г и 7 г С.	97,658 -116,431 55,701 85,800 121,955 147,814 121,322 287,913 49,964	-578,317 -130,639 70,078 225,175 338,915 103,265 786,217 0,0071*	
TABLE 5 Time-C Cur Sofium current Delayed rectifier, ng Delayed rectifier, ag	$E_{K} = \frac{KI}{F} ln \left( \frac{ K }{ K } \right)$ dependent current der rent sid component <i>m</i> component immet, fant recovery	maities Symbol Da G <sub>554</sub> 56.32 G <sub>554</sub> 0.0388 G <sub>554</sub> 0.0398 G <sub>554</sub> 0.0398	(32) msity mS/µF i mS/µF i mS/µF i mS/µF	0, 0, 77 88 z 4 7 7 6 , 6 , 6 , 7 7 8 , 7 7 8 , 8 , 7 7 , 7 7 , 88 , 77 , 88 , 77 , 88 , 77 , 88 , 77 , 88 , 77 , 88 , 77 , 88 , 77 , 88 , 77 , 88 , 77 , 88 , 77 , 88 , 77 , 88 , 87 , 77 , 88 , 87 , 77 , 88 , 87 , 77 , 88 , 87 , 8 8 , 87 , 87 , 87 , 8 8 8 , 8 8 8 8 8 8 8 8 8	97,658 -116,431 55,701 85,800 121,955 147,514 121,322 267,913 59,565 1,4004	-578,317 -130,639 70,078 225,175 338,915 193,265 786,217 0,00711	
TABLE 5 Time-c Cur Sofium current Delayed rectifier, sig Transient extrand of Transient entrand	$E_{K} = \frac{KI}{F} ln \left( \frac{ K }{ K } \right)$ dependent current der rent vid component w component ment, fast recovery	milies Symbol Da G <sub>300</sub> 56.32 G <sub>400</sub> 0.0100 G <sub>400</sub> 0.0000 G <sub>400</sub> 0.0000 G <sub>400</sub> 0.0000	(32)	0, 0, 77 88 2 9 7 7 7 6 7 7 6 7 7 6 7 7 8 7 8 7 7 7 8 7 7 7 8 8 8 8	97,658 -116,431 55,701 85,900 121,955 147,814 121,522 287,913 59,565 1,4004 1,280	-578.317 -130.639 70.078 225.175 338.915 103.265 786.217 0.00711	
TABLE 5 Time-c Cur Softuns current Delayed recifice, rg Delayed recifice, rg Transient outward of Transient outward of	$E_{\mathbf{k}} = \frac{KI}{F} \ln \left( \frac{ \mathbf{k} }{ \mathbf{k} ^{*}} \right)$ dependent current der reur pid component arrest, has recovery ment, doe recovery	$\begin{array}{c c} \hline \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ $	(32) msity $mS/\mu F$ $mS/\mu F$ $mS/\mu F$ $mS/\mu F$ $mS/\mu F$	0, 0, 77 88 e 4 7 7 6, 6, 6, 6, 6, 6, 6, 9 9 8 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9	97,658 97,058 -116,431 35,500 122,955 147,514 122,522 287,913 99,565 1,4004 1,389 Bi	-578.337 -130.639 70.078 225.175 338.915 103.265 766.217 0.00711	(3) :
TABLE 5 Time-C Car Sodians current Dolayed rectifier, ng Dolayed rectifier, de Transient outward co Transient outward co	$E_{\rm K} = \frac{K_{\rm H}}{F} \ln \left( \frac{ {\rm K} }{ {\rm K}^* } \right)^2$ Aspendent current der rot pid component arrest, har rocovery arrest, slow recovery arrest, slow recovery	$\begin{array}{c} \\ \hline \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ $	(32) mity mS/µP i mS/µP i mS/µP i mS/µP d <sup>-x</sup> cm/s	0, , 77 28 28 2 2 3 2 3 2 5 3 2 5 4 5 4 5 3 2 10 8 2 5 2 5 2 5 2 5 2 5 2 5 2 5 2 5 2 5 2	97,683 97,683 -116,451 38,500 121,055 147,314 123,512 287,013 95,555 1,4004 1,389 Bi	- 773.317 - 130.639 - 70.078 225.175 333.915 191.265 786.217 0.00711	(3) 1

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TABLE	7 4 <sub>6</sub> , rate constants			dC-m-	
Rate con	tant	Value	_	$\frac{d\sigma_{\text{GKm}}}{dt} = -(4\alpha_s + \beta_i)(C_{\text{GKm}}) + (\beta_s)(C_{\text{IKm}})$	
α,		0.0171 · exp(0.0330 V) n	sx <sup>-1</sup>	$+ (\alpha_i)(CI_{0Kee}).$	(45)
β.		0.0397 · exp(-0.0431 V) 0.0206 · exp(0.0262 V) n	ms 1		
β.		0.0013 · exp(-0.0269 V)	ms <sup>-1</sup>	$\frac{dC_{1Krs}}{ds} = -(\beta_s + 3\alpha_s + f_1\beta_i)(C_{1Krs}) + (4\alpha_s)(C_{0Krs})$	
α, β.		0.1067 - exp(0.0057 V) n 0.0065 - exp(-0.0454 V)	ms <sup>-1</sup>	$(28)(C_{m}) + (\alpha/h)(C_{m})$	(46)
<i>a</i> <sub>0</sub>		8.04 E-3 - exp(6.98 E-7 )	i) ms <sup>-1</sup>	· (dpa)(cana) · (ca)=1)(cana).	(10)
- A		0.0251 ms 0.1483 ms <sup>-1</sup>		$\frac{dC_{3Km}}{dC_{2Km}} = -(2\theta + 2\alpha + f(\theta))(C_{2m})$	
				$dr = -(ap_a + aa_a + j_2p_i)(c_{2Km})$	
dCl	$\frac{16\pi t}{t} = -(\beta_s/f_1 + b_2)^2$	$(x_s/b_1 + \alpha_i/b_1)(CI_{1Eel})$		+ $(3\alpha_s)(C_{16m})$ + $(3\beta_s)(C_{36m})$ + $(\alpha_i/b_2)(CI_2)$	кч.). (47
	$+ (b_1 4 \alpha_s) (CI_m$	$(f_1 2\beta_a/f_2)(CI_{2Kel})$			
	$+ (f_i\beta_i)(C_{iKel})$		(39)	$\frac{dC_{3Km}}{dt} = -(3\beta_s + \alpha_s + f_1\beta_i)(C_{3Km}) + (2\alpha_s)(C_{2Km})$	
dCI <sub>2Kot</sub>	$= -(f_1 2\beta_s)/f_2 + b_s 2d$	$a_{a}/b_{2} + a_{i}/b_{2})(CI_{2Kel})$		$+ (4\beta_s)(C_{46m}) + (\alpha_i/b_j)(CI_{56m}).$	(48)
-	$+ (b_2 3 \alpha_s / b_1) (CI_{1K})$	$_{st}$ ) + $(f_2 3\beta_s/f_3)(CI_{3Ket})$		$\frac{dO_{Km}}{ds} = -(4\beta_s + f_t\beta_i)(O_{Km}) + (\alpha_s)(C_{3Km})$	
	$+ (f_2\beta_i)(C_{2Kvt}).$		(40)	$+ (a_i/b_i)(OI_{Km}).$	(49)
dCI <sub>3Kot</sub>	$= -(f_2 3\beta_s/f_3 + b_s \alpha_s)$	$(b_3 + \alpha_i/b_3)(CI_{3Eed})$		dCl-	
	$+ (b_1 2 \alpha_1 / b_2) (CI_{20})$	$(f_14\beta_1/f_2)(OI_{k+1})$		$\frac{derogan}{dt} = -(b_1 4\alpha_s + a_i)(CI_{1Ken}) + (\beta_s/f_1)(CI_{1Ken})$	
	$+ (f_{2}\beta_{i})(C_{3Kel}).$		(41)	$+ (\beta_i)(C_{mes}).$	(50)
				101	
dOI <sub>1</sub> dr	$\frac{d}{dt} = -(f_1 4\beta_s/f_1 + \alpha_s)$	$(b_4)(OI_{Kel}) + (b_4\alpha_s/b_3)$		$\frac{\mathrm{d}CI_{\mathrm{Res}}}{\mathrm{d}t} = -(\beta_s)/f_1 + b_2 3\alpha_s/b_1 + \alpha_s/b_1)(CI_{\mathrm{Res}})$	
	$\times (CI_{3Kel}) + (f_i\beta$	$(O_{Kel})$ .	(42)	+ $(b_1 4 \alpha_s)(CI_{16Km})$ + $(f_1 2 \beta_s/f_2)(CI_{2Km})$ + $(f, \beta_s)(C_{})$	en e
Slowly	recovering componen	t, Kv1.4		$((ip_i)) (\in \operatorname{Kin})$ .	(51)
	$4VF^{2}[K^{+}]/$	$exp\left(\frac{VF}{PT}\right) - [K^+]_a$		$\frac{dCI_{2Km}}{dt} = -(f_1 2\beta_s/f_2 + b_1 2\alpha_s/b_2 + \alpha_i/b_2)(CI_{2Km})$	
$I_{K+1.4} =$	PKs14OKes RT	(VF) + I <sub>Kv1</sub>	4.Na-	$+ (b_2 3 \alpha_s / b_1) (CI_{1Km}) + (f_2 3 \beta_s / f_3) (CI_{3Km})$	
	4	$\exp\left(\frac{RT}{RT}\right) = 1$		$+ (f_2\beta_i)(C_{2Km}).$	(52)
			(43)		
		$Ni_{r+1} = (VF)$	au*1	$\frac{dCI_{3Km}}{ds} = -(f_2 3\beta_s/f_3 + b_1\alpha_s/b_3 + \alpha_i/b_3)(CI_{3Km})$	
1	$= 0.02 \cdot P_{-} \cdot Q_{-} \frac{41}{4}$	$T^2 \left[ rea \right] \exp \left( \frac{1}{RT} \right)^{-1} r$	va je	$+(b_12\alpha_r/b_2)(CI_{Wer}) + (f_14\beta_r/f_2)(OI_{Wer})$	
	the set of	$T = \exp\left(\frac{VF}{mr}\right) - 1$		$+ (f_3\beta_i)(C_{3Km}).$	(53)
		· (RI )	(44)		
			(44)	$\frac{dOI_{Km}}{dt} = -(f_2 4\beta_s/f_t + \alpha_i/b_t)(OI_{Km}) + (b_t\alpha_s/b_t)(CI_{III})$	6m)
TABLE	8 4 <sub>cs</sub> rate constants			$+ (f_i \beta_i)(O_{Em}).$	(54)
Rate con	tant	Value		See Table 9.	
a		7.956 E <sup>-3</sup> ms <sup>-1</sup>			
β		2.10 E · · · exp (-0.00002 * 3.97 E <sup>-2</sup> ms <sup>-1</sup>	() IIK."	Time-independent K <sup>+</sup> current I <sub>K1</sub>	
â		7 E <sup>-3</sup> · exp(-0.15 V) ms <sup>-</sup>			
2 40		3.80 E <sup>-1</sup> · exp(-0.014 V)		$I_{K1} = \tilde{\mathbf{G}}_{K1} K_1^{\times}(V) \left( \sqrt{[\mathbf{K}^*]_o} \right) (V - E_K).$	(55)

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Human Ventricular Myccyte Model	1523
$J_{sile} = \frac{[Ca^{2+}]_{sile} - [Ca^{2+}]_{s}}{\tau_{silee}}$ (99)	$\beta_{ISK} = \left(1 + \frac{ CSQN _{in}K_m^{(SQN)}}{(K_m^{(SQN)} +  Ca^{2+} _{ISK})^2}\right)^{-1}.$ (108)
$J_{iqu} = \frac{d[HTRPN_{Ci}]}{dt} + \frac{d[LTRPN_{Ci}]}{dt}$ (100) $d[HTRPN_{Ci}]$	$\frac{d[Ca^{2+}]_{u}}{dt} = \beta_{u} \left( J_{ub} \frac{V_{BR}}{V_{u}} - J_{ub} \frac{V_{upo}}{V_{u}} - (I_{Ca}) \frac{A_{up}C_{u}}{2V_{u}F} \right). (109)$
$\frac{dt}{dt} = k_{hingel}^{+}[Ca^{2+}]_{i}([HTRPN]_{ist} - [HTRPN_{Ca}]) - k_{hingel}^{-}[HTRPN_{Ca}].  (101)$	$\frac{d[Ca^{2+}]_{BR}}{dt} = \beta_{BR}(J_{\nu} - J_{et}).  (110)$
$\frac{d[LTRPN_{Ca}]}{dt} = k_{topa}^{+}[Ca^{2+}]_{*}([LTRPN]_{tot}$	$\frac{d[Ca^{2+}]_{NSR}}{dt} = J_{sp} \frac{V_{sys}}{V_{NSR}} - J_{sr} \frac{V_{RR}}{V_{NSR}}.$ (111)
$- [LTRPN_{Ce}]) - k_{hepe}^{*} [LTRPN_{Ce}].  (102)$	$\frac{dV}{dr} = -(I_{Na} + I_{Ca} + I_{CaK} + I_{Ke} + I_{Ke} + I_{Ke} + I_{Ne} + I_{NeKe} + I_{NeKe}$
See Table 14.	$+ I_{k_{11,4}} + I_{k_{24,3}} + I_{p(Ca)} + I_{Ca,b} + I_{Na,b} + I_{sim}$ (112)
Intracellular ion concentrations and membrane potential	$I_{sim} = -100 \text{ pA/pF.}$ (113)
$\frac{d[Na^{+}]_{i}}{dt} = -(I_{Na} + I_{Nab} + 3I_{Nab} + 3I_{Nab} + I_{K14,Na})\frac{A_{up}C_{u}}{V_{upp}F},$ (103)	This work is supported by grants from the National Institutes of Health (RO1 HL-61711, RO1 HL-60133, RO1 HL-73488, P50 HL-52307, and NO1 HV-23108). The Falk Medical Trust, The Whinker Foundation, and IBM Corporation.
$\frac{d[K^+]}{dt} = -(I_{K*} + I_{K*} + I_{K*1.4,K} + I_{K*1.4,K} + I_{K1} + I_{C*,K}$	REFERENCES
$-2I_{NK} + I_{dim}\frac{A_{eq}C_{w}}{V_{eqs}F}.$ (104) $d[Ca^{2+}] = \sqrt{-1}$	Armoundas, A. A., I. A. Hobai, G. F. Tornaselli, R. L. Winslow, and B. O'Rourke. 2003. Role of sedium-calcium exchanger in modulating the action potential of ventricular myocytes from normal and failing hearts. <i>Circ. Rev.</i> 93:946–93.
$\frac{\cdot}{dt} = \beta_i \left( J_{abs} - J_{ag} - J_{bga} - (I_{Cab} - 2I_{SaCa} + I_{\mu(Ca)}) \right)$ $\times \frac{A_{iap}C_{ia}}{2V_{iap}F} \left( 105 \right)$	Bailly, P., M. Mouchoniere, J. P. Benitah, L. Camilleri, G. Vasseri, and P. Lerente. 1998. Extracellular K <sup>+</sup> dependence of investd rectification kinetics in human left ventricular cardiomyscytes. <i>Circulation</i> , 98:2753–2759.
$\beta_i = \left(1 + \frac{[CMDN]_{in}K_m^{CMDN}}{(K_m^{CMDN} + [\mathbf{Cn}^{2+}]_i)^2} + \frac{[EGTA]_{in}K_m^{SUTx}}{(K_m^{SUTx} + [\mathbf{Cn}^{2+}]_i)^2}\right).$	Bernus, O., R. Wilders, C. W. Zemlin, H. Verschelde, and A. V. Patrilov. 2002. A computationally efficient electrophysiological model of harman ventricular cells. Am. J. Physiol. Heart Circ. Physiol. 282:H2296– H3308.
(106)	Bers, D. M. 2001. Excitation-Contraction Coupling and Cardiac Contractile Force. Klawer Academic Publishers, Dordrecht, The Netherlands.
$\beta_n = \left(1 + \frac{\left[CMDN\right]_{in}K_m^{CMDN}}{\left(K_m^{CMDN} + \left[Cn^{2+}\right]_m\right)^2} + \frac{\left[EGTA\right]_{in}K_m^{MOTA}}{\left(K_m^{MOTA} + \left[Cn^{2+}\right]_m\right)^2}\right).$	Beuckelmann, D. J., and E. Erdmann. 1992. Ca <sup>2+</sup> -currents and intracellular [Ca <sup>2+</sup> ]_transients in single ventricular myocytes isolated from terminally failing human myocardiam. <i>Basic Res. Caroliol.</i> 87:5235–5243.
(107)	Beuckelmann, D. J., M. Nabuser, and E. Erdmann. 1992. Intracellular calcium handling in isolated ventricular myocytes from patients with terminal heart failure. <i>Circulation</i> , 85:1046–1085.
TABLE 14 Calcium buffering and diffusion Patameter Value	Bruckelmann, D. J., M. Nabaser, C. Kruger, and E. Erdmann. 1998. Altered diastolic [Cs <sup>2+</sup> ], handling in human ventricular myocytes from restients with seminal beam follow: An Houry 1 120 08LAMD
τ <sub>o</sub> 0.5747 ms τ <sub>obs</sub> 26.7 ms	Chancy, C. E., and Y. Rudy. 1999. Linking a genetic defect to its cellular physicisms in a cardiac software also 566,560
HTRPN <sub>ini</sub> 140 $d^{-3}$ mM           LTRPN <sub>ini</sub> 70 $d^{-3}$ mM           K <sup>+</sup> <sub>ETRPN</sub> 20 mM <sup>-1</sup> ms <sup>-1</sup> $m = 1$ $m = 1$	Corana, M. 1987. Minimizing multimodal functions of continuous variables with the simulated annealing algorithm. ACM Trans. Mech. Software. 13:262–280.
$\kappa_{1700}$ 0006 d <sup>-1</sup> ms <sup>-1</sup> $K_{1700}$ 40 m <sup>1-1</sup> ms <sup>-1</sup> $K_{1700}$ 40 d <sup>-1</sup> ms <sup>-1</sup> $K_{1700}$ 2.58 d <sup>-1</sup> mM	Desga, S., M. A. Islam, C. R. Weher, S. M. Pogwizd, and D. M. Bers. 2002. Intracellular Na <sup>+*</sup> concentration is elevated in heart failure but Na/K pump function is unchanged. <i>Circulation</i> . 105:2543–2548.
$K_{max}^{(0)}$ 0.8 mM $K_{max}^{(0)}$ 1.5 d <sup>-1</sup> mM EGTA <sub>est</sub> 0 mM	Dixon, J. E., W. Shi, H. S. Wang, C. McDonald, H. Yu, R. S. Wymere, I. S. Cohen, and D. McKinnen. 1996. Role of the K+4.3 K <sup>+</sup> channel in ventrichter marche. A medicular constate for the transient outward current. Circ. Res. 79:659–668.

lyer	et a	١.,		
Bior	hvs	J.	2004.	

vsical Journal 87(3) 1507-1525

### Markov model example: I<sub>Na</sub>

$$I_{Na} = g_{Na}(O+BO)(V-E_{Na})$$



 $\begin{array}{ll} \mathrm{dO}/\mathrm{d}t = \kappa \mathrm{BO} - \lambda \mathrm{O} + \mu \mathrm{C1} - v \mathrm{O} + \xi \mathrm{IF} - \rho \mathrm{O} & 13 \ \mathrm{ODEs} \\ \mathrm{dBO}/\mathrm{d}t = \dots & (\mathrm{vs} \ \mathrm{4} \ \mathrm{for} \ \mathrm{HH}) \\ \vdots \end{array}$ 

- May reproduce experimental data better than HH
- Integration time step usually small
- Many parameters

### **Multiscale phenomena**



### **Three-dimensional virtual cardiac tissue**

Virtual cells coupled by Ohmic resistances (gap junctions)





# Why use computational modeling for cardiac electrophysiology?

- Rodent cardiac myocytes have fundamentally different channel expression levels (especially repolarizing currents). Therefore, transgenic models are not always 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.



### **Cardiac ionic model surge**

- Surge in development of cell models
- 66 in total (at CellML)
- Different species, regions, pathologies
- Multiple models for the same species/ region/condition





### Five different rabbit SAN models



Different models, different action potential shapes and duration

Kurata et al. (2002) AJP 283, H2074-2101.

### Four different human ventricular cell models



## Why do different models of the same species and regions disagree?

- Some models are simply better than others:
  - Uses better data
  - Uses more data from particular species/region
- The models are equally good/bad:
  - Differences reflect electrophysiological heterogeneity
  - Differences reflect different age, sex, etc.

### Model component heritage



**Figure 1.** Phylogenetic schematic for the ten Tusscher *et al.* (2004; *A*) and the lyer *et al.* (2004; *B*) cell **models (***B***), showing the links between modelling (trapeziums) and experimental studies (ellipses)** Modelling studies are broken up into components (boxes), with connections (arrows) between components and published studies. \* Luo & Rudy (1994) model; and + Jafri *et al.* (1998) model.

Niederer et al., Exp Physiol, 2009.

### **Other modeling considerations**

- Models are validated for specific conditions. They may not be valid for your numerical experiments (fast rates, temperature, concentrations, drugs, age, sex).
- A model can give a "right" result for the wrong reason.
- The more complicated the model (more variables and parameters), the more realistically it may behave. However,
- the more complicated the model, the harder it is to pinpoint cause-and-effect relationships and the more components may be wrong.
- *Math instead of mice vs. insights from math/physics*

$$\frac{d\mathbf{x}}{dt} = f(\mathbf{x}, t)$$



### Multiscale modeling example: single-channel noise Beat-to-beat variability in cardiac action potentials

GP ventricular myocytes

25 mV A 100 msec 0 mV301 msec 326 msec В APD<sub>90</sub>(msec) 330 315 300 20 5 15 0 10 beat number

Zaniboni et al., Am J Physiol, 2000

Rabbit SAN myocytes



Wilders & Jongsma, Biophys J, 1993

### Multiscale modeling example: single-channel noise



**Excised patch** 







Unitary events add up to give the macroscopic current.



### Multiscale modeling example: single-channel noise



## One current stochastic at a time



IKs: few channels, slow gating

### Multiscale modeling example: atrial fibrillation maintenance Atrial fibrillation:

- Rapid, irregular activation of the atria
- Loss of synchronized atrial contraction
- Rapid, irregular ventricular rate
- The most common sustained arrhythmia: more than 10% of population over the age of 80
- Associated with significant mortality and morbidity



- In patients with chronic AF, fibrillatory episodes are of increased duration and frequency of occurrence
- This is due to ionic, structural, and contractile remodeling processes.



Schotten et al., Physiol Rev, 2011





### **Ionic and structural remodeling**



Courtemanche et al., Cardiovascular Research, 1999.





J. American College of Cardiology, 2005.



### Effects of remodeling on wavelength



Wavelength: WL = CV · APD



### **Anatomical structure**



### ~2,000,000 virtual cells.

Computationally demanding, but easily parallelized.



### No remodeling



### Ionic and structural remodeling



### **Alternans and alternans control**

Repolarization alternans: a beat-to-beat alternation in action potential duration



### **Alternans and arrhythmogenesis**



Alternans can induce large repolarization gradients across the heart, ultimately causing unidirectional block.

This may cause lifethreatening ventricular tachyarrhythmias.

Fox et al. Circ Res 2002











### **Alternans control**

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

$$BCL_{n+1} = \begin{cases} BCL^{\star} & \text{for } \Delta BCL_{n+1} > 0, \\ BCL^{\star} + \Delta BCL_{n+1} & \text{for } \Delta BCL_{n+1} \le 0, \end{cases}$$

with

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





microelectrode: 65432

Alternans control works well in single cells but is only effective over ~1 cm in tissue.

Christini et al., Physical Review Letters, 2006



### Summary

- The cardiac action potential is generated by diffusion of ions through specific ion channels in the cell membrane
- Voltage-gated channel dynamics may be described quantitatively by HH-type equations or by Markov models
- Computational models can be used to explain mechanisms of experimentally or clinically observed phenomena