SUPPLEMENTAL MATERIAL

Model Stimulation Protocol

Table S1: Model Protocol Values

Model	Species	Beats to Steady State for 1Hz pacing	Stimulus Amplitude (mA/mF)
Fox	Canine	35	-36.4
Hund	Canine	855	-32.2
Heijman	Canine	No ISO = 421; ISO @ 1mM = 388	-36.7
Shannon	Rabbit	183	-35
Livshitz	Guinea Pig	1170	-35
Devenyi	Guinea Pig	317	-30.9
TT04	Human (endo)	1	-25
TT06	Human (endo)	191	-22.6
Grandi	Human (endo)	270	-32.2
Ohara	Human (endo)	124	-20.6

Model Parameters

Canine Models

Table S2: Parameters varied in Fox Model

Fox Model is based on experimental data collected from canine midmyocardial cells.

Parameter	Definition	Baseline value
$\overline{G}_{Na}$	Maximal Na^+ conductance	12.8 mS/μF
$\overline{G}_{Nab}$	Maximal Background Na^+ conductance	0.0031 mS/μF
$\overline{P}_{Ca}$	L-type Ca^{2+} current permeability to Ca^{2+}	2.26 x 10^{-5}cm/ms
$\overline{P}_{CaK}$	L-type Ca^{2+} current permeability to K^+	5.79 x10^{-7}cm/ms
$\overline{G}_{Cab}$	Maximal background Ca^{2+} conductance	3.84 x10^{-4}mS/μF
$\overline{G}_{to}$	Maximal transient outward K^+ conductance	0.23815 mS/μF
$\overline{G}_{Kr}$	Rapid delayed rectifier K^+ current scaling factor*	0.0136 mS/μF
$\overline{G}_{Ks}$	Maximal slow delayed rectifier K^+ conductance	0.0245 mS/μF
$\overline{G}_{K1}$	Maximal inward rectifier K^+ conductance	2.8 mS/μF
$\overline{G}_{Kp}$	Maximal plateau K^+ conductance	0.002216 mS/μF
$\overline{I}_{NaK}$	Maximal Na^+-K^+ pump current	0.693 μA/μF
k_{NaCa}	Maximal Na^+-Ca^{2+} exchange current scaling factor	1500 μA/μF
$\overline{P}_{rel}$	Maximal SR Ca^{2+} release permeability scaling factor	6 ms^{-1}
$\overline{P}_{leak}$	Passive SR Ca^{2+} leak permeability scaling factor	1 x $10^{-6}ms^{-1}$
V_{up}	Maximal rate of SR Ca^{2+} uptake (SERCA)	0.1 μM/ms
$\overline{I}_{pCa}$	Maximal sarcolemmal Ca^{2+} pump current	0.05 μA/μF

Notes

*The scaling factor for I_{Kr} is not formally a maximal conductance, since this is multiplied by $\sqrt{K_o}/4$ and can therefore be greater than this value. For a constant value of extracellular $[K^+]$, changing this factor served to scale the current.

Table S3: Parameters varied in Hund Model

Hund Model is based on data from canine epicardial cells.

Parameter	Definition	Baseline value
$\overline{G}_{Na}$	Maximal Na^+ conductance	8.25 mS/μF
$\overline{G}_{Na,L}$	Maximal late Na^+ conductance	6.5×10^{-3} mS/μF
P_{Ca}	Maximal L-type Ca^{2+} current permeability to Ca^{2+}	2.43×10^{-4} cm/s
$P_{Ca,b}$	Background Ca^{2+} current permeability	1.99508×10^{-7} cm/s
$\overline{G}_{K1}$	Inward rectifier K^+ conductance scaling factor*	0.5mS/μF
$\overline{G}_{Kr}$	Rapid delayed rectifier K^+ conductance scaling factor*	0.0138542mS/μF
$\overline{G}_{Ks}$	Slow delayed rectifier K^+ conductance scaling factor†	0.02489mS/μF
$\overline{G}_{Kp}$	Maximal plateau K^+ conductance	2.76×10^{-3} mS/μF
$\overline{G}_{to\,1}$	Maximal transient outward K^+ conductance	0.19 mS/μF
$\overline{G}_{Cl,b}$	Background Cl^- conductance‡	2.25×10^{-4} mS/μF
P_{cl}	Maximal Ca^{2+}-dependent transient outward Cl^- current permeability	4×10^{-7} cm/s
$\overline{G}_{NaK}$	Maximal Na^+-K^+ pump current	0.619 μA/μF
v_{max}	Maximal Na^+-Ca^{2+} exchange current	4.5 μA/μF
$\overline{G}_{rel}$	SR Ca^{2+} release scaling factor	3000 ms^{-1}
V_{up}	Maximal sarcolemmal Ca^{2+} pump current	5.75×10^{-2} μA/μF
$\overline{I}_{up}$	Maximal rate of SR Ca^{2+} uptake (SERCA)	4.38×10^{-3} mM/ms

Notes

*The scaling factors for I_{K1} and I_{Kr} are not formally maximal conductances, since each is multiplied by $\sqrt{K_o}/5.4$ and can therefore be greater than this value. For a constant value of extracellular $[K^+]$, changing this factor served to scale the current.

†The scaling factor for I_{Ks} is not formally a maximal conductance, since it is multiplied by a function of intracellular $Ca^{2+}$and can therefore be greater than this value.

‡The units for this maximal conductance are mistakenly listed as uA/uF in the original manuscript.

Table S4: Parameters varied in Heijman Model

Parameter	Definition	Baseline value*
INaB	Fast Na^+Channel	1
INabB	Background Na^+Channel	1
INaLB	LateNa^+Channel	1
ICaLB	L-type Ca^{2+}Channel	1
ICabB	Background Ca^{2+}Channel	1
Ito1B	Transient outward K^+ Channel	1
Ito2B	Calcium-activated Cl^- Channel	1
IKrB	Rapid delayed rectifier K^+Channel	1
IKsB	Slow delayed rectifier K^+Channel	1
IK1B	Inward rectifier K^+Channel	1
IKpB	Plateau K^+Channel	1
INaKB	Na^+-K^+ pump current	1
INaCaB	Na^+-Ca^{2+} exchange current	1
IrelB	SR Ca^{2+} release	1
IleakB	Passive SR Ca^{2+} leak	1
IupB	SR Ca^{2+} uptake (SERCA)	1
IpCaB	Sarcolemmal Ca^{2+} pump current	1
IClB	Background Cl^- channel	1

Notes

*These variable names were present in the online version of the Heijman Model: http://rudylab.wustl.edu/research/cell/code/AllCodes.html. The original code had (1-IB) in front of each current equation with each baseline IB term equal to zero. We modified the code to impose variability by removing the (1-IB) with just IB and replacing its baseline value with 1.

Guinea Pig Models

TableS5: Parameters varied inLivshitzModel

Parameter	Definition	Baseline value
$\overline{G}_{Na}$	Maximal Na^+ conductance	16 mS/μF
$\overline{G}_{Na,b}$	Background Na^+ conductance	0.004 mS/μF
P_{Ca}	L-type Ca^{2+} current permeability*	$5.4x10^{-4}$ cm/s
P_{Na}	Na^+ permeability of L-type Ca^{2+} channel*	6.75×10^{-7} cm/s
P_K	K^+ permeability of L-type Ca^{2+} channel*	1.93×10^{-7} cm/s
$\overline{G}_{Ca\,(T)}$	T-type Ca^{2+} conductance	0.05 mS/μF
$\overline{G}_{Ca,b}$	Background Ca^{2+} conductance	$3.016 x10^{-3}$mS/μF
$\overline{G}_{K1}$	Inward rectifier K^+ current scaling factor†	0.75 mS/μF
$\overline{G}_{Kr}$	Rapid delayed rectifier K^+ current scaling factor[2]	0.02614 mS/μF
$\overline{G}_{Ks}$	Slow delayed rectifier K^+ current scaling factor‡	0.433
$\overline{G}_{Kp}$	Maximal plateau K^+ conductance	0.00552 mS/μF
$\overline{I}_{NaK}$	Maximal Na^+-K^+ pump current	2.25 μA/μF
c_1	Na^+-Ca^{2+} exchange current scaling factor	$2.5x10^{-4}$
α_{rel}	SR Ca^{2+} release scaling factor	0.125
$\overline{I}_{pCa}$	Maximal sarcolemmal Ca^{2+} pump current	1.15 μA/μF
$\overline{I}_{up}$	Maximal rate of SR Ca^{2+} uptake (SERCA)	$8.75x10^{-3}$mM/ms

Notes

*P_{Ca}, P_{Na}, $P_K$values were retrieved from http://rudylab.wustl.edu/research/cell/lrd2.htm and are different from the ones in the paper.

†The scaling factors for I_{K1} and I_{Kr} are not formally maximal conductances, since each is multiplied by $\sqrt{K_o}/5.4$ and can therefore be greater than this value. For a constant value of extracellular [K^+], changing this factor served to scale the current.

‡The scaling factor for I_{Ks} is not formally a maximal conductance, and is based on a function of intracellular [Ca^{2+}] and can therefore be greater than this value. $\overline{G}_{Ks} = 0.433 + \frac{0.2598}{1+(38e-\frac{6}{[Ca^{2+}]_i})^{1.4}}$

Table S6: Parameters varied in Devenyi Model

Parameter	Definition	Baseline value
$\overline{G}_{Na}$	Maximal Na^+ conductance	15.4681mS/μF
$\overline{G}_{Na,b}$	Background Na^+ conductance	0.008mS/μF
P_{Ca}	L-type Ca^{2+} current permeability	$5.4x10^{-4}$ cm/s
P_{Na}	Na^+ permeability of L-type Ca^{2+} channel	6.75×10^{-7} cm/s
P_K	K^+ permeability of L-type Ca^{2+} channel	1.93×10^{-7} cm/s
$\overline{G}_{Ca(T)}$	T-type Ca^{2+} conductance	0.0161mS/μF
$\overline{G}_{Ca,b}$	Background Ca^{2+} conductance	$4.7 x10^{-3}$mS/μF
$\overline{G}_{K1}$	Inward rectifier K^+ current scaling factor*	0.8047mS/μF
$\overline{G}_{Kr}$	Rapid delayed rectifier K^+ current scaling factor*	0.0466mS/μF
$\overline{G}_{Ks}$	Slow delayed rectifier K^+ current scaling factor†	0.0183
$\overline{G}_{Kp}$	Maximal plateau K^+ conductance	3.252×10^{-4}mS/μF
$\overline{I}_{NaK}$	Maximal Na^+-K^+ pump current	3.7004μA/μF
c_1	Na^+-Ca^{2+} exchange current scaling factor	$2.74 x10^{-4}$
α_{rel}	SR Ca^{2+} release scaling factor	0.125
$\overline{I}_{pCa}$	Maximal sarcolemmal Ca^{2+} pump current	0.3108μA/μF
$\overline{I}_{up}$	Maximal rate of SR Ca^{2+} uptake (SERCA)	0.0187mM/ms

Notes

*The scaling factors for I_{K1} and I_{Kr} are not formally maximal conductances, since each is multiplied by $\sqrt{K_o}/5.4$ and can therefore be greater than this value. For a constant value of extracellular $[K^+]$, changing this factor served to scale the current.

†The scaling factor for I_{Ks} is not formally a maximal conductance, and is based on a function of intracellular $[Ca^{2+}]$ and can therefore be greater than this value. $\overline{G}_{Ks} = 0.433 + \frac{0.2598}{1+(38e-\frac{6}{[Ca^{2+}]_i})^{1.4}}$

Rabbit Model

Table S7: Parameters varied in Shannon Model

Parameter	Definition	Baseline value
$\overline{G}_{INa}$	Maximal conductance of fast Na^+ current	16 mS/μF
$\overline{G}_{NaBk}$	Maximal conductance of background Na^+ current	0.297×10^{-3} mS/μF
P_{Ca}	Permeability of L-Type Ca^{2+} channel to Ca^{2+}	5.4×10^{-4} cm/s
$\overline{G}_{CaBk}$	Maximal conductance of background Ca^{2+} current	0.0002513 mS/μF
$G_{to,s}$	Maximal conductance of slow transient K^+ current *	0.06mS/μF
$G_{to,f}$	Maximal conductance of fast transient K^+ current *	0.02mS/μF
$\overline{G}_{IKs}$	Slow delayed rectifier K^+ current scaling factor†	0.07 mS/μF
$\overline{G}_{IKr}$	Rapid delayed rectifier K^+ current scaling factor‡	0.03 mS/μF
$\overline{G}_{K1}$	Inward rectifier K^+ current scaling factor‡	0.09 mS/μF
$\overline{G}_{Cl}$	Maximal conductance of Ca^{2+} dependent Cl^- current	0.109625 mS/μF
$\overline{G}_{ClBk}$	Maximal conductance of background Cl^- current	0.009 mS/μF
$\overline{I}_{NaK}$	Maximum current through Na-K pump	1.91 A/F
V_{max}	Maximal rate of Na^+ -Ca^{2+} exchanger	9 A/F
K_{SRleak}	Passive SR Ca^{2+} leak scaling factor	5.348×10^{-6} ms^{-1}
V_{max}	Maximal rate of SR Ca pump	286×10^{-6}mM/ms
k_s	SR Ca release rate constant	25 ms^{-1}
V_{max}	Maximal rate of SL Ca pump§	0.0673 A/F

Notes

*These values were reported incorrectly in the paper, and were taken from the source code: https://somapp.ucdmc.ucdavis.edu/Pharmacology/bers/

† The scaling factor for I_{Ks} is not formally a maximal conductance, since it is multiplied by a function of intracellular $Ca^{2+}$and can therefore be greater than this value.

‡The scaling factors for I_{K1} and I_{Kr} are not formally maximal conductances, since each is multiplied by $\sqrt{K_o}/5.4$ and can therefore be greater than this value. For a constant value of extracellular $[K^+]$, changing this factor served to scale the current.

§V_{max} is 2.2 umol/L cytosol/sec in the paper but was converted to A/F as used in the source code: https://somapp.ucdmc.ucdavis.edu/Pharmacology/bers/

Human Models

All human models are based on experimental data from endocardial cells.

Table S8: Parameters varied in TT04 Model

Parameter	Definition	Baseline value
G_{Na}	Maximal Na^+ conductance	14.838 mS/µF
G_{bNa}	Background Na^+ conductance	2.9e-4 mS/µF
G_{CaL}	Maximal L-type Ca^{2+} current permeability	1.75e-4 cm^3/µF s^{-1}
G_{bCa}	Background Ca^{2+} conductance	5.92e-4 mS/µF
G_{to}	Maximal transient outward K^+ conductance	0.073mS/µF
G_{Kr}	Rapid delayed rectifier K^+ scaling factor*	0.096 mS/µF
G_{Ks}	Maximal slow delayed rectifier K^+ conductance	0.245 mS/µF
G_{K1}	Inward rectifier K^+current scaling factor *	5.405 mS/µF
G_{pK}	Maximal plateau K^+ conductance	0.0146 mS/µF
P_{NaK}	Maximal Na^+-K^+ pump current	1.362 pA/pF
k_{NaCa}	Maximal Na^+-Ca^{2+} exchange current	1000 pA/pF
a_{rel}	SR Ca^{2+} release scaling factor	16.464 µM ms^{-1}
c_{rel}	SR Ca^{2+} release scaling factor	8.232 µM ms^{-1}
V_{leak}	Passive SR leak scaling factor	8e-5 ms^{-1}
V_{maxup}	Maximal rate of SR Ca^{2+} uptake (SERCA)	0.425µM ms^{-1}
G_{pCa}	Maximal sarcolemmal Ca^{2+} pump current	0.025 pA/pF

Notes

*The scaling factors for I_{Kr} and I_{K1} are not formally a maximal conductance, since each is multiplied by $\sqrt{K_o}/5.4$ and can therefore be greater than this value. For a constant value of extracellular [K^+], changing these factors serves to scale the current.

TableS9: Parameters varied in TT06 Model

Parameter	Definition	Baseline value
G_{Na}	Maximal Na^+ conductance	14.838 mS/µF
G_{bNa}	Background Na^+ conductance	2.9 x 10^{-4}mS/µF
G_{CaL}	Maximal L-type Ca^{2+} current permeability	3.98 x 10^{-5} cm/µF ms^{-1}
G_{bCa}	Background Ca^{2+} conductance	5.92 x 10^{-4}mS/µF
G_{to}	Maximal transient outward K^+ conductance	0.0730mS/µF
G_{Kr}	Rapid delayed rectifier K^+ current scaling factor*	0.153 mS/µF
G_{Ks}	Maximal slow delayed rectifier K^+ conductance	0.392 mS/µF
G_{K1}	Inward rectifier K^+current scaling factor *	5.405 mS/µF
G_{pK}	Maximal plateau K^+ conductance	1.46e-2 mS/µF
P_{NaK}	Maximal Na^+-K^+ pump current	2.724 pA/pF
k_{NaCa}	Maximal Na^+-Ca^{2+} exchange current	1000 pA/pF
V_{rel}	SR Ca^{2+} release scaling factor†	0.102 ms^{-1}
V_{leak}	Passive SR leak scaling factor	3.6 x 10^{-4} ms^{-1}
V_{maxup}	Maximal rate of SR Ca^{2+} uptake (SERCA)	6.375 x10^{-3}mM ms^{-1}
G_{pCa}	Maximal sarcolemmal Ca^{2+} pump current	0.1238 pA/pF

Notes

*The scaling factors for I_{Kr} and I_{K1} are not formally a maximal conductance, since each is multiplied by $\sqrt{K_o}/5.4$ and can therefore be greater than this value. For a constant value of extracellular [K^+], changing these factors serves to scale the current.

†Additionally, V_{rel} = 0.102 ms^{-1}, as per the source code available at http://www-binf.bio.uu.nl/khwjtuss/ SourceCodes/HVM2/, rather than 40.8 mM ms^{-1} as inthe manuscript.

Table S10: Parameters varied in O'Hara Model

Parameter	Definition	Baseline value
$\overline{G}_{Na,fast}$	Maximal Na^+ conductance	75 mS/μF
$\overline{G}_{Na,late}$	Maximal late Na^+ conductance	0.0075 mS/μF
$\overline{G}_{to}$	Maximal transient outward K^+ conductance	0.02 mS/μF
$\overline{G}_{Kr}$	Rapid delayed rectifier K^+ conductance scaling factor *	0.046 mS/μF
$\overline{G}_{Ks}$	Slow delayed rectifier K^+ conductance scaling factor †	0.0034 mS/μF
$\overline{G}_{K1}$	Inward rectifier K^+ conductance scaling factor *	0.1908 mS/μF
$\overline{G}_{NaCa}$	Maximal Na^+-Ca^{2+} exchange current	0.0008 μA/μF
$\overline{G}_{Kb}$	Maximal conductance of background K^+	0.003 mS/μF
P_{Ca}	L-type Ca^{2+} current permeability	0.0001 cm/s
$\overline{I}_{NaK}$	Scales the Na^+-K^+ ATPase current	30
P_{Nab}	Background Na^+ current permeability	3.75e-10 cm/s
P_{Cab}	Background Ca^{2+} current permeability	2.5e-8 cm/s
$\overline{G}_{pCa}$	Maximal sarcolemmal Ca2+ pump current	0.0005 mS/uF
$SERCA_{total}$	SR Ca^{2+} release scaling factor §	1
RyR_{total}	SR Ca^{2+} uptake(SERCA) scaling factor§	1

Notes

*The scaling factors for I_{K1} and $I_{Kr}$are not formally maximal conductance, since each is multiplied by √Ko/5.4 and can therefore be greater than this value. Changing this factor scales the current at all values of extracellular [K+] while maintaining the dependence on this variable.

†The scaling factor for I_{Ks} is multiplied by a function of intracellular [Ca2+]. This value is therefore not precisely the current's maximal conductance.

‡$\overline{I}_{NaK}$ was not labeled in the original paper and have been given these names to keep to terminology consistent.

§Parameters controlling the magnitude of SR Ca^{2+} release through the ryanodine receptor (RyR) and through SERCA are an introduced unitless multiplier with baseline value equals to 1.00.

Table S11: Parameters varied in Grandi Model

Parameter	Definition	Baseline value
G_{Na}	Maximal Na^+ conductance	23 mS/uF
$G_{Na\,B}$	Background Na^+ conductance	$0.597x10^{-3}$mS/uF
p_{Ca}	Maximal L-type Ca^{2+} current permeability*	2.7e-4cm/sec
$G_{Ca\,B}$	Background Ca^{2+} conductance	5.513e-4 uA/uF
$G_{to\,Slow}$	Maximal slow transient outward K^+ conductance	0.0376mS/uF
$G_{to\,Fast}$	Maximal fast transient outward K^+ conductance	0.0014mS/uF
g_{Kr}	Maximal rapid delayed rectifier K^+ current conductance[2]	0.035 mS/uF
$g_{ks\,sl} = g_{ks\,junc}$	Maximal slow delayed rectifier K^+ current conductance	0.0035 mS/uF
G_{K1}	Maximal inward rectifier K^+ conductance †,‡	0.35 mS/uF
g_{kp}	Maximal plateau K^+ conductance	0.002 mS/uF
$G_{Cl\,Ca}$	Maximal Ca^{2+}-activated Cl^- conductance	0.0548 mS/uF
$G_{Cl\,B}$	Background Cl^- conductance	9e-3 mS/uF
$\bar{I}_{Na\,K}$	Maximal Na^+-K^+ pump current	1.8 uA/uF
$\bar{I}_{NCX}$	Maximal Na^+-Ca^{2+} exchange current	4.5 uA/uF
k_s	SR Ca^{2+} release	25 ms^{-1}
K_{leak}	Passive SR Ca^{2+} leak scaling factor‡	5.348e-6 ms^{-1}
$V_{max\,SR\,CaP}$	Maximal rate of SR Ca^{2+} uptake (SERCA)	5.3114e-3 mM/ms
$\bar{I}_{PMCA}$	Maximal sarcolemmal Ca^{2+} pump current	0.0673 uA/uF

Notes

*p_{ca} =2.7 x 10^{-4} cm/sec, as per the source code available at https://somapp.ucdmc.ucdavis.edu/Pharmacology/bers/, rather than 1.215 x 10^{-4}cm/sec as in the manuscript.

†The scaling factors for I_{K1} and I_{Kr} are not formally maximal conductance, since each is multiplied by $\sqrt{Ko/5.4}$ and can therefore be greater than this value. Changing this factor scales the current at all values of extracellular [K+] while maintaining the dependence on this variable.

‡G_{K1} and K_{leak}were not labeled in the original paper and have been given these names to keep to terminology consistent.

Population Distributions

Table S12: Data collected during Population Runs

Model	APD Spread	# of APs Rerun
Fox	0.5252	0
Hund	0.1839	0
Heijman	0.323	10
Livshitz	0.229	0
Devenyi	0.7068	5
Shannon	0.5697	0
TT04	0.1748	0
TT06	0.1952	1
O'Hara Baseline	0.3482	0
O'Hara High I_{Ks}	0.21	0
O'Hara Low I_{Ks}	0.4122	0
Grandi	0.601	19

Table S13: Population Statistics

Model	Mean	Median	Standard Deviation
Fox	209.7	208.5	47.5
Hund	217.4	217.5	15.8
Heijman	219.3	215.1	28.8
Livshitz	154.8	155	13.8
Devenyi	171.6	162	48.9
Shannon	225.1	211.5	55.5
TT04	326.4	326	23
TT06	310.5	310	23.5
O'Hara Baseline	268.9	268.5	36.2
Grandi	321.4	302	83.3

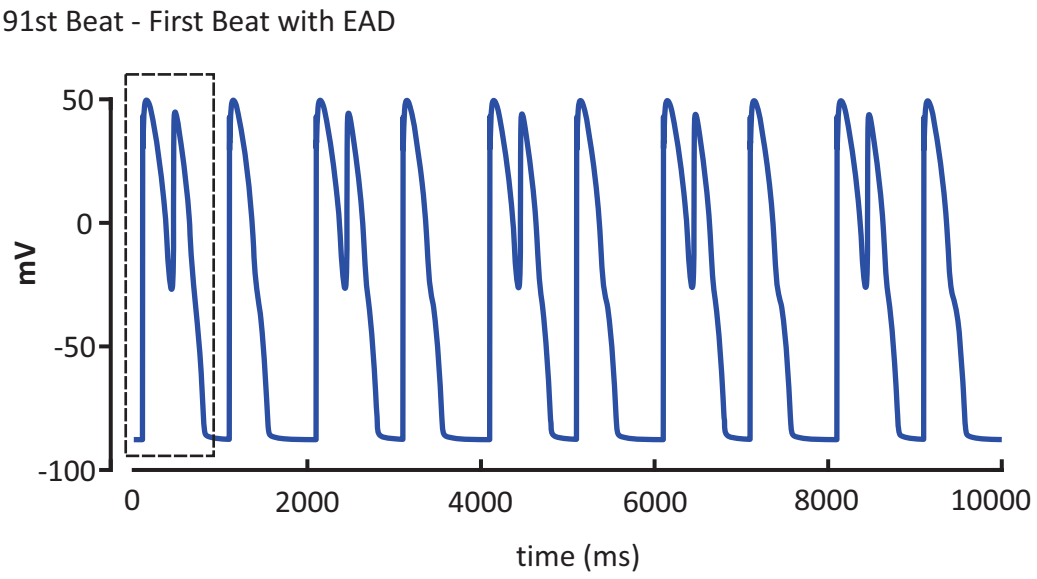


Figure S1. Procedure to determine EAD Threshold

AP waveforms of beats 91-100 of the O'Hara Human Model under calcium perturbation at 1 Hz-pacing rate. EAD appearance was not consistent at every beat. Thus, in order to address this variability, beats 91-100 were analyzed and the first I_{CaL} Factor that caused an EAD between beats 91-100 was considered the threshold for triggering EADs in the model. This procedure was repeated for each model. The O'Hara Model displayed an EAD first on the 91st beat at an I_{CaL} Factor of 15.2. This analysis was replicated in each model.

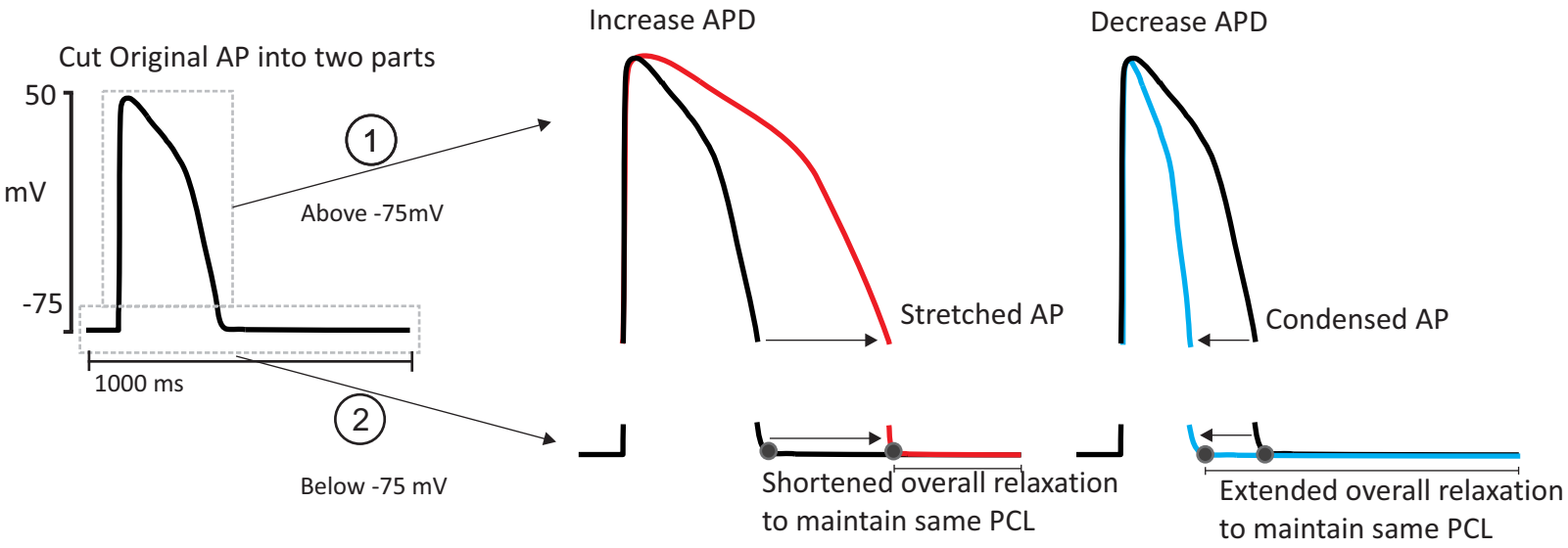


Figure S2. AP Clamp Simulation Procedure

This represents the AP Clamp procedure performed in the O'Hara Model. The baseline model's AP waveform was split into two epochs: the depolarized period when membrane potential was more positive than -75 mV and the resting period when membrane potential was more negative than -75 mV. The two epochs were either stretched or compressed using the *interp1* function in MATLAB to make the AP longer or shorter while keeping the total duration constant at 1000 ms. This procedure was replicated in the remaining nine models.

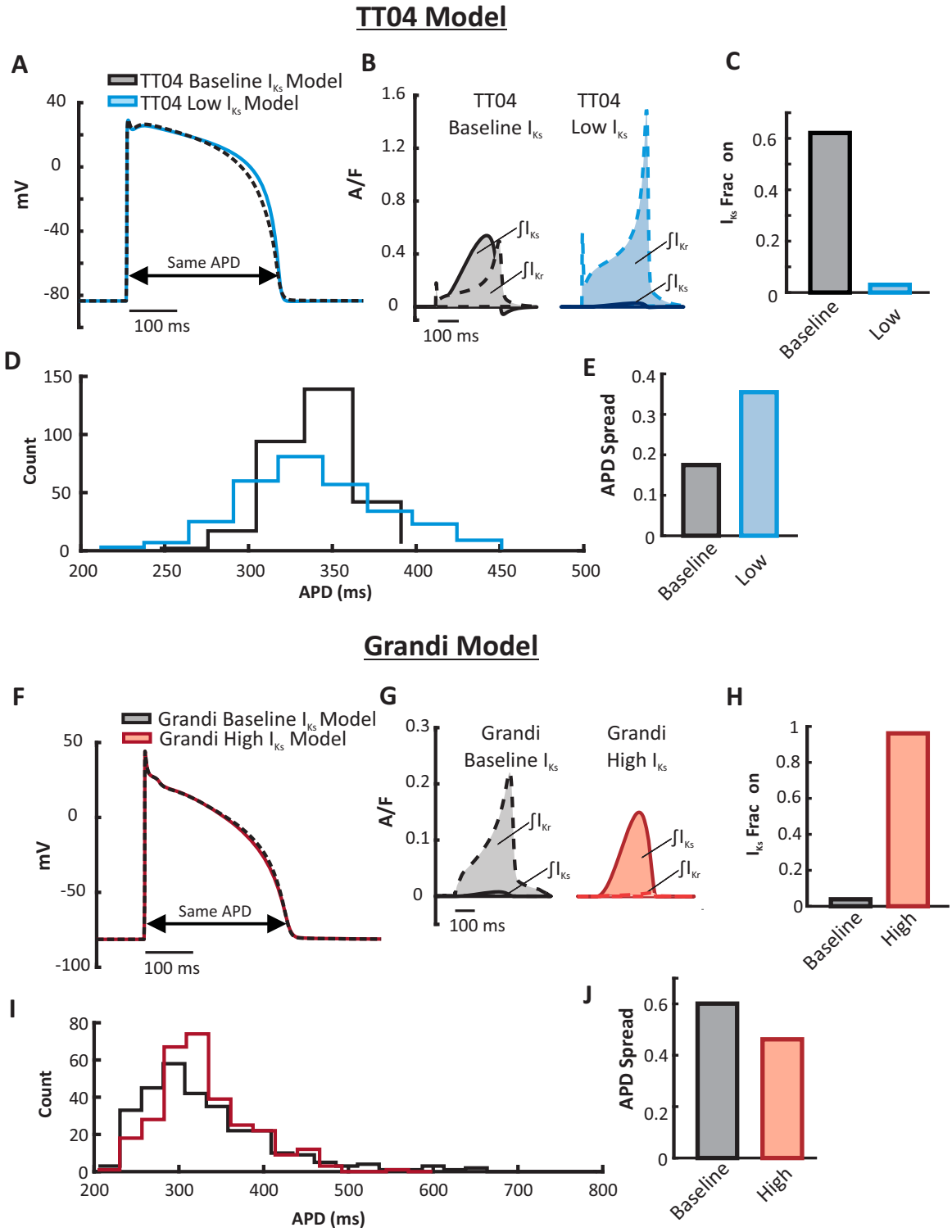
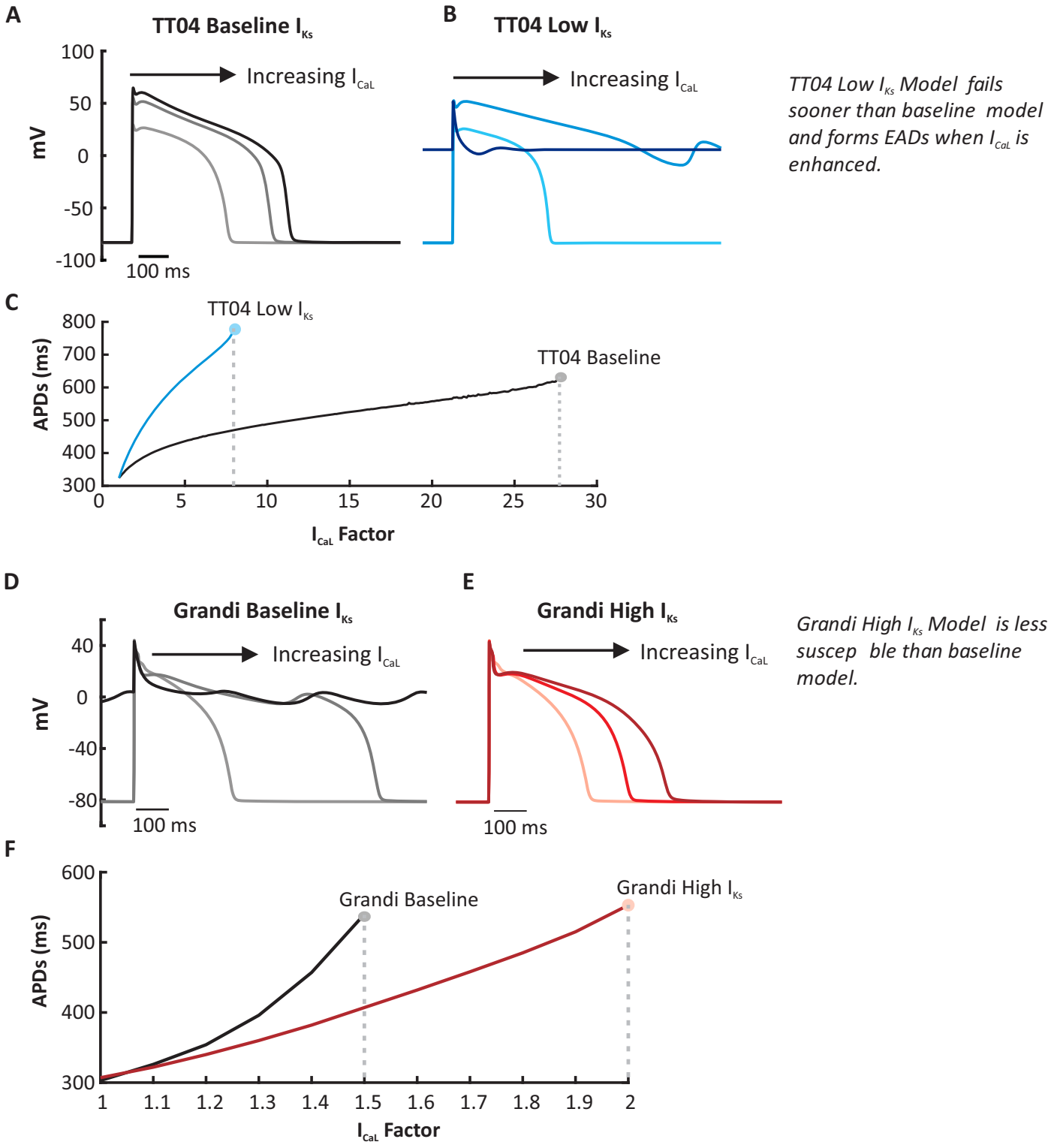


Figure S3. Altering the contribution of I_{Ks} within the same model influences population variability.
The same simulations performed in Figure 1 on the O'Hara model were replicated two additional human models (TT04 and Grandi). (A/F) Only a low I_{Ks} version for the TT04 model and a high I_{Ks} version for the Grandi model were developed because both of these models at baseline have very high and low levels of I_{Ks} at baseline, respectively. Thus, increasing the levels of I_{Ks} in the TT04 and decreasing the levels of I_{Ks} in the Grandi would not provide further information. The TT04 Low I_{Ks} version Grandi High I_{Ks} by decreasing or increasing (20 fold) IKs and adjusting IKr to produce an identical APD. (B/G) IKs and IKr waveforms of the different versions of the same model. The shaded regions represent the integrated currents (area under the curve, or AUC) during the APs. The current AUCs were used to calculate the fraction of repolarizing current contributed by (C/H) IKs (IKs Fraction) in each model. (D/I) Using each of the model variants as the baseline model, model populations (300 cells each) were generated by randomly varying parameters. Distributions of APD show that greater IKs promotes less variability within a population. (E/J) APD Spread was calculated for each of the populations to quantify the variability within the APD distributions.



TT04 Low I_{Ks} Model fails sooner than baseline model and forms EADs when I_{CaL} is enhanced.

Grandi High I_{Ks} Model is less susceptible than baseline model.

Figure S4. Altering the contribution of I_{Ks} within the same model influences arrhythmia susceptibility.
The same simulations performed in Figure 2 on the O'Hara model were replicated two additional human models (TT04 and Grandi). I_{CaL} was progressively increased in each model to induce EADs and arrhythmic behavior. I_{CaL} factor refers to the increase in channel permeability coefficient (1.0 equals control level).(A) APs simulated in the baseline version of TT04 with I_{CaL} augmentation (8.1 and 16.1 times). (B) APs simulated in the low TT04 model with the same I_{CaL} perturbations. (C) Both versions of the TT04 model were run under a wide range of I_{CaL} factors and plotted against APD. The end of each line represents the last factor before an EAD formed. (D) APs simulated in the baseline version of Grandi with I_{CaL} augmentation (1.6 and 2 times). (E) High I_{Ks} version of Grandi simulated under the same conditions. (F) Both versions of the Grandi model were run under a wide range of I_{CaL} factors and plotted against APD.

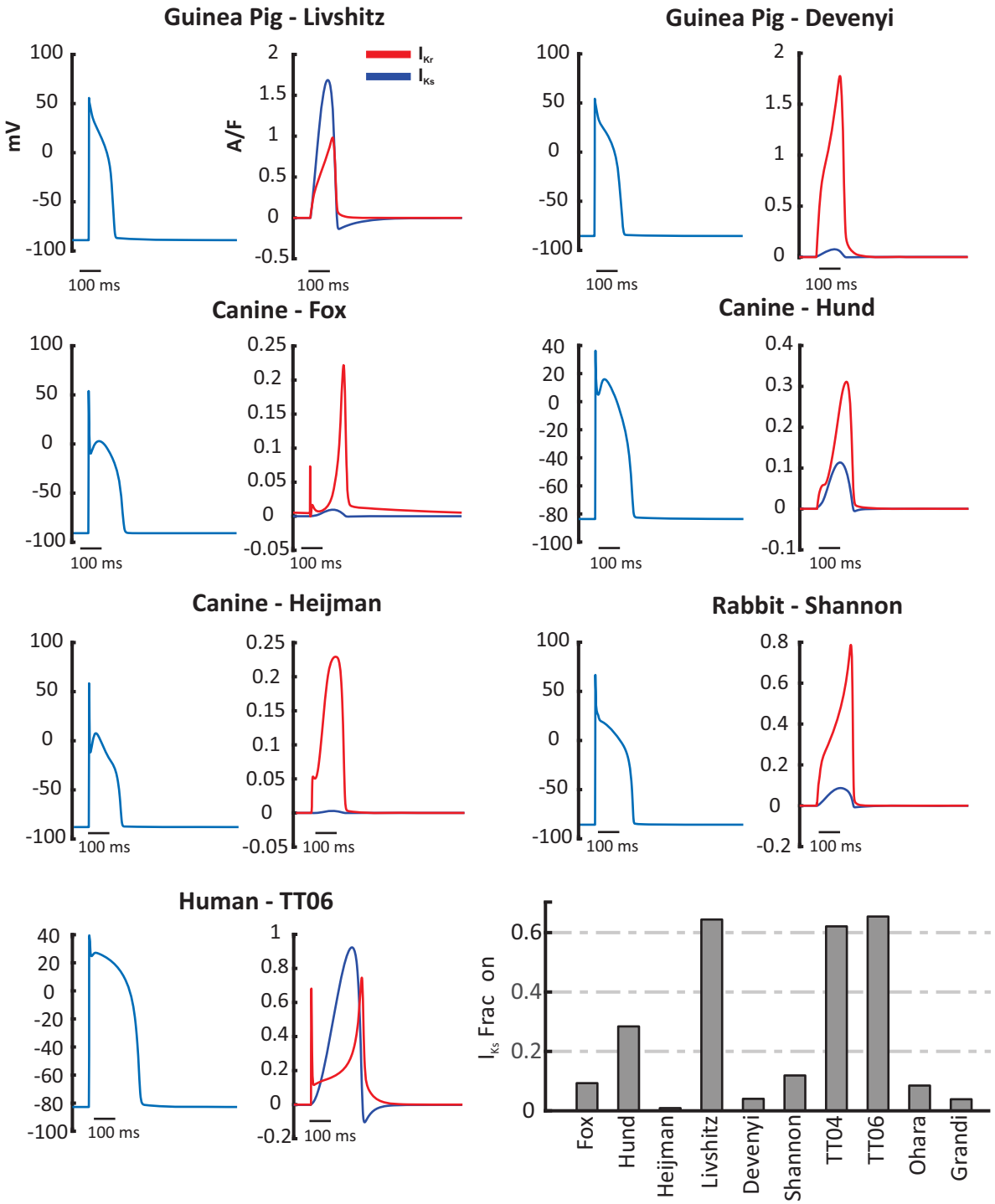


Figure S5. Baseline AP and I_{Kr}/I_{Ks} Waveforms
AP waveforms and slow & rapid delayed rectifier K^+ currents in seven additional ventricular myocyte models. Plots show the 100th beat simulated at a 1 Hz pacing rate.

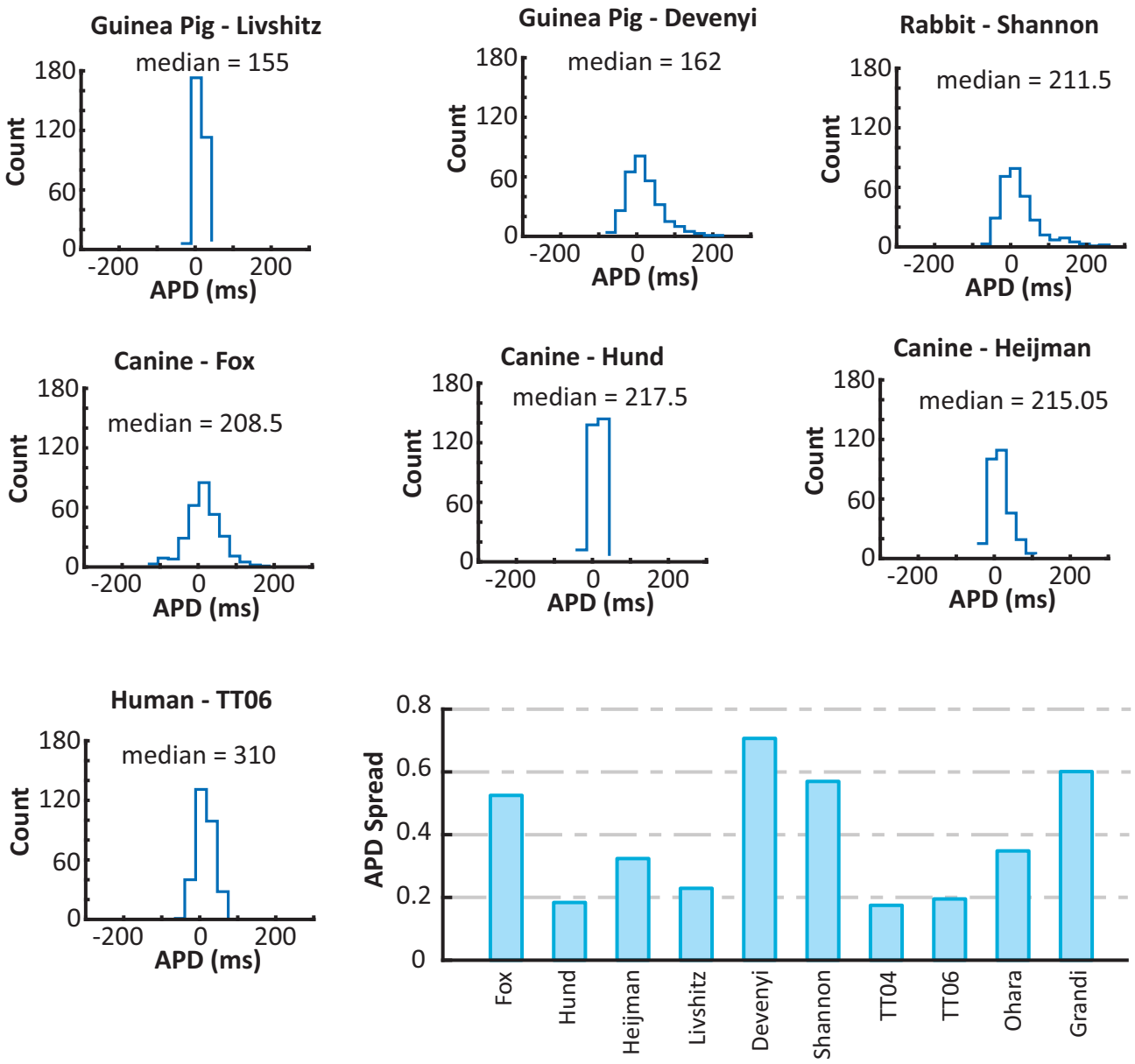


Figure S6. Population Variability across multiple species.
Histograms of AP duration of a population of 300 model variants generated by imposing random variability.

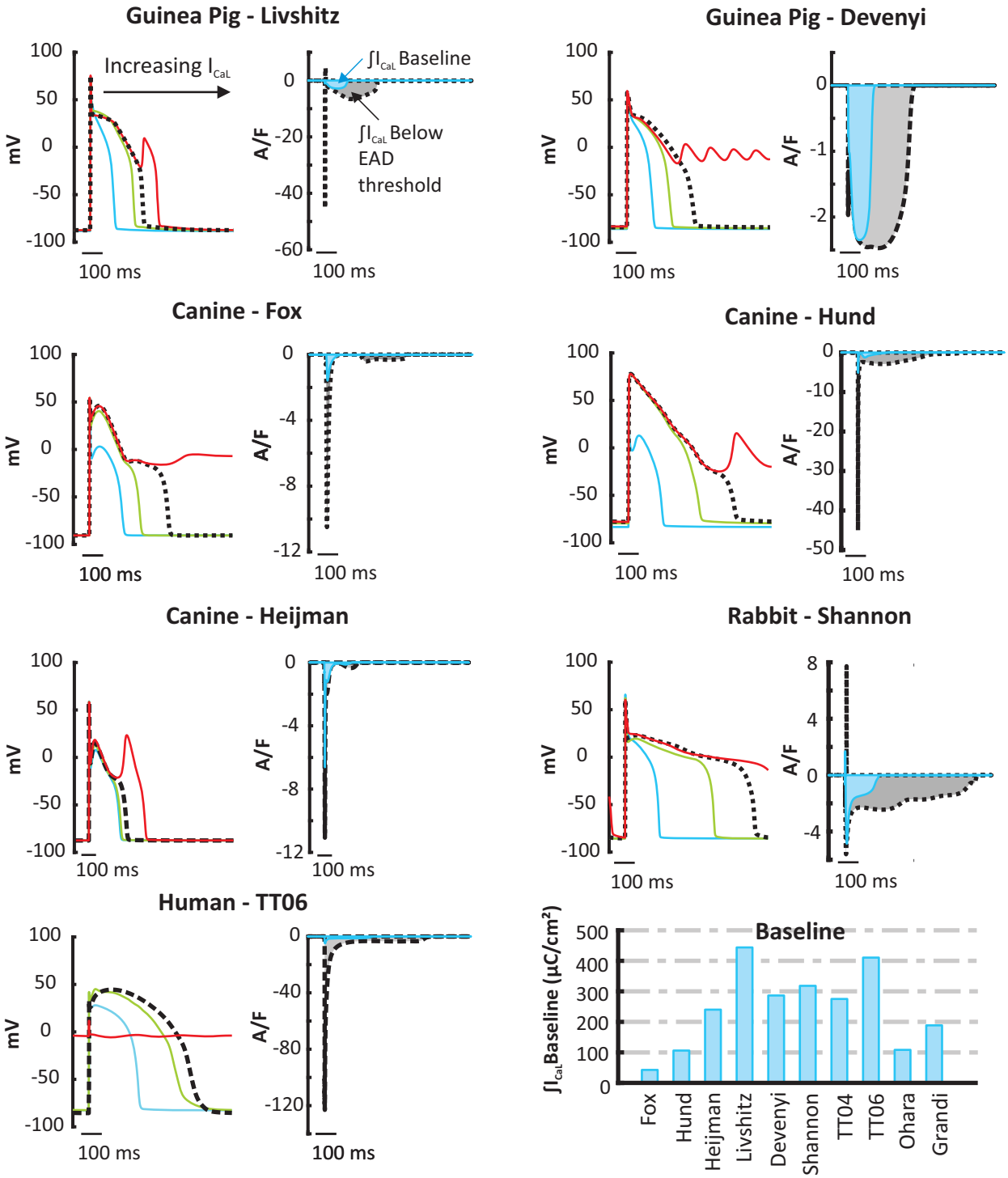


Figure S7. Susceptibility to EADs across multiple species.

Aps and ICaL waveforms of each model with increasing I_{CaL} current. IThe blue curves show the baseline I_{CaL} whereas the black dashed curves plot I_{CaL} just before the first EAD occurred. The gray shaded regions are the area under the curve (AUC). Plots of Shannon and TT06 represent the 91st beat, plot of Fox is 100th beat, plot of Hund is the 99th beat, and plots of Heijman and Devenyi are the 92nd beat, while Livshitz is the 93rd beat.

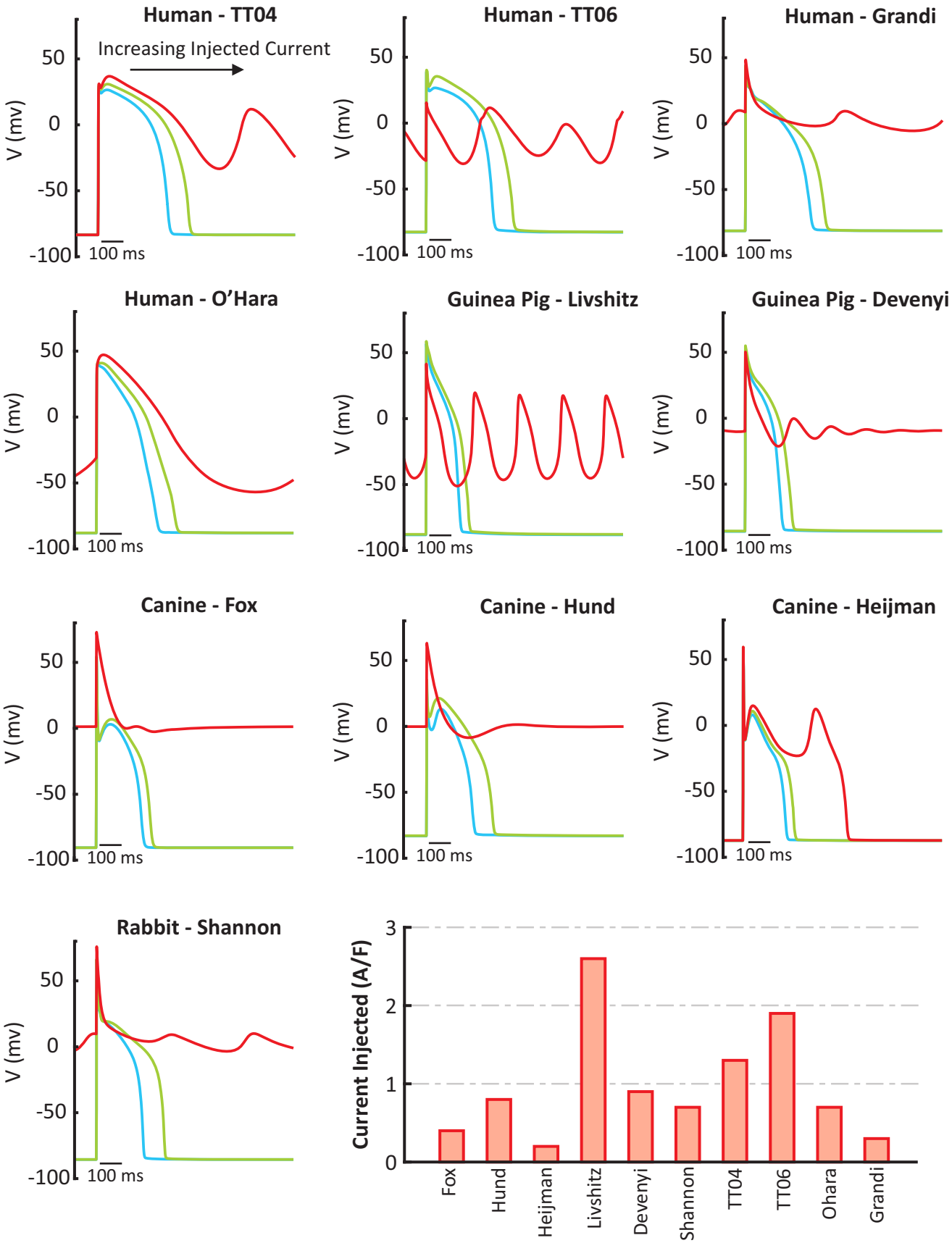


Figure S8. Inducing proarrhythmic behavior through constant inward current inject across multiple species. AP waveforms of each model with increasing constant inward current injection (from blue to red) until proarrythmic behaviors were present. The bar graph represents the level of current injected in order to produce the failed APs in red in each model.

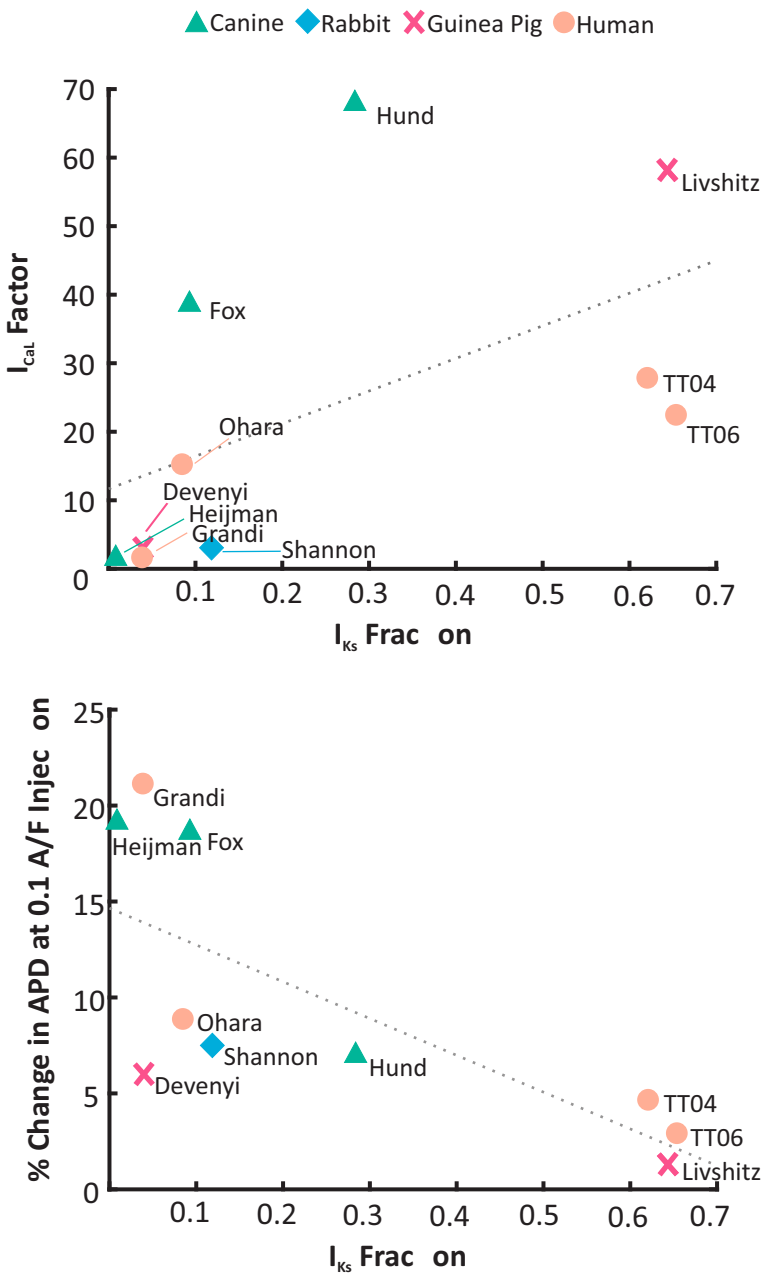


Figure S9. Addi onal correla on plots

(A) The scaling factor (I_{CaL} factor) by which the calcium current was increased does not correlate with the levels of Iks. Since the baseline I_{CaL} magnitude differed between models, the I_{CaL} factor did not provide a fair basis of comparison. To compare suscep bility to EADs, we integrated the I_{CaL} waveform at the level just under the EAD threshold as depicted in Figures 4 & 5. (B) The percent change in APD between the APD when 0.1 A/F inward current was injected into the models and the baseline APD was calculated and compared with the levels of I_{Ks}. This shows that models with low I_{Ks} are much more suscep ble to APD prolonga on when an arbitrary inward current is injected as compared to models with high I_{Ks}.

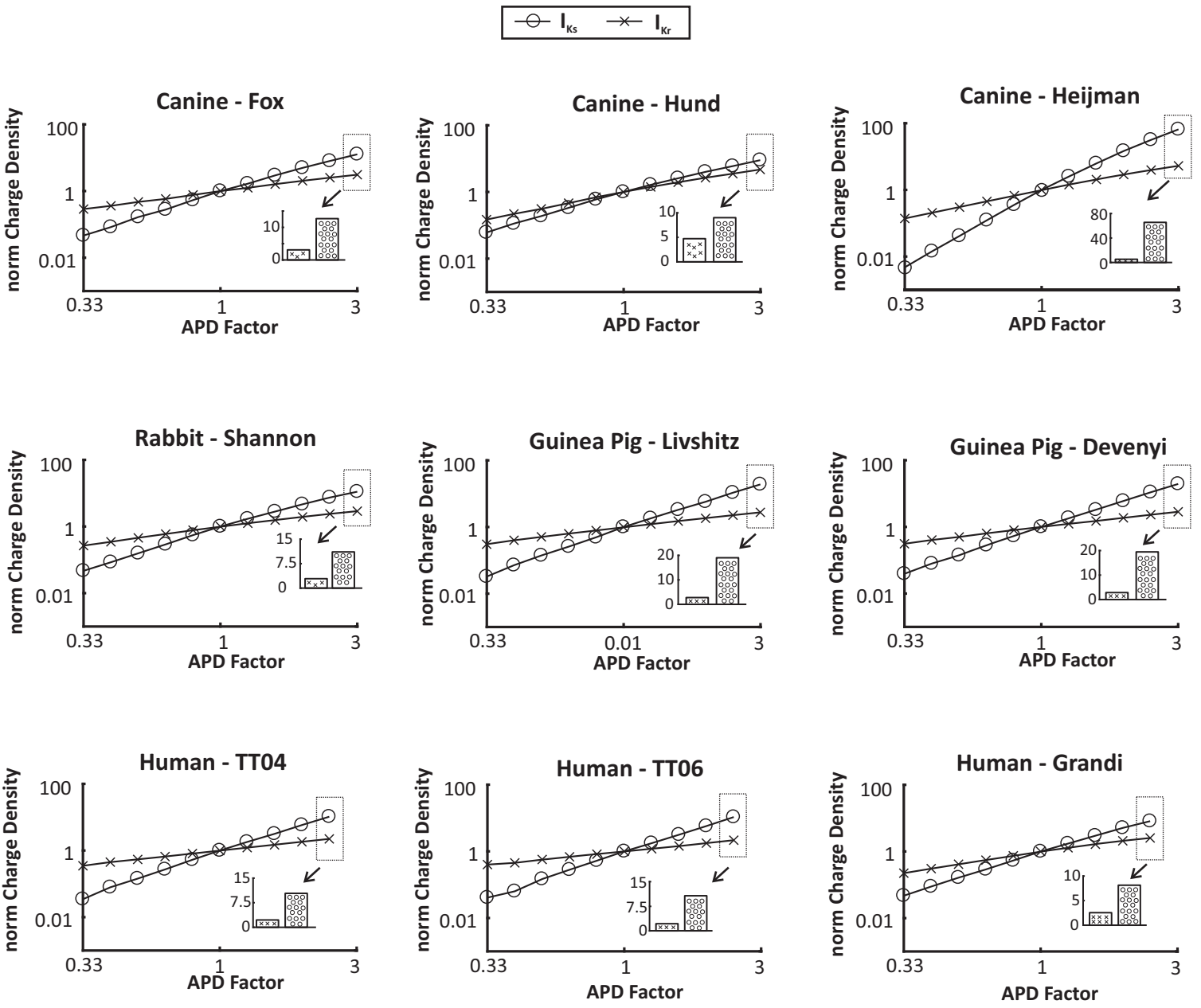


Figure S10. AP Clamp Simulations across Models

The AP Clamp simulation performed in Figure 6 was replicated in all the models. The x-axis refers to the factor by which the APD was increased. The y -axis represents the integrated currents (area under the curve, AUC) of each K^+ currents, normalized to the integrated current of the baseline AP. As APD increases, there is a much greater relative increase in I_{Ks} compared with I_{Kr} across all models. The x marked lines represent I_{Kr} and the circle marked lines represent I_{Ks}. The inset in each figure represents the normalized current at the last time point in each figure. Please note that the TT04, TT06, and the Grandi models had longer baseline APDs, thus increasing the APD by a factor of 3 was not possible.

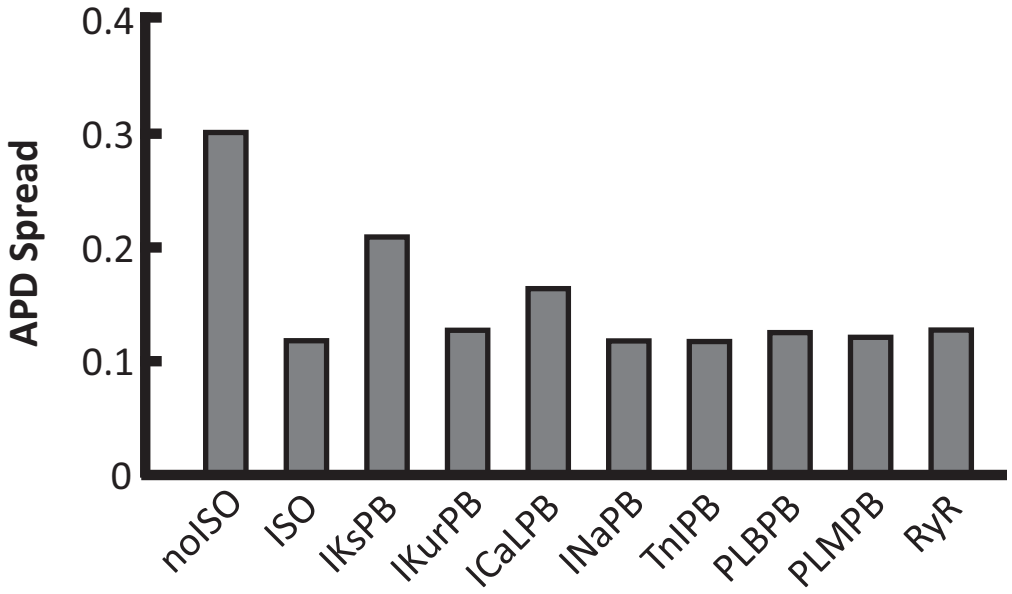


Figure S11. Contribution of individual substrates to changes in APD Spread
We individually blocked the phosphorylation of each of the eight PKA targets to see how this contributes to the change in APD Spread. We simulated the same population of 300 cells under the ten conditions. The no ISO population contained thirteen APs that formed EADs, which were removed from each population. Blocking IKs phosphorylation caused the greatest change in APD Spread.