Modeling K,ATP-Dependent Excitability in Pancreatic Islets

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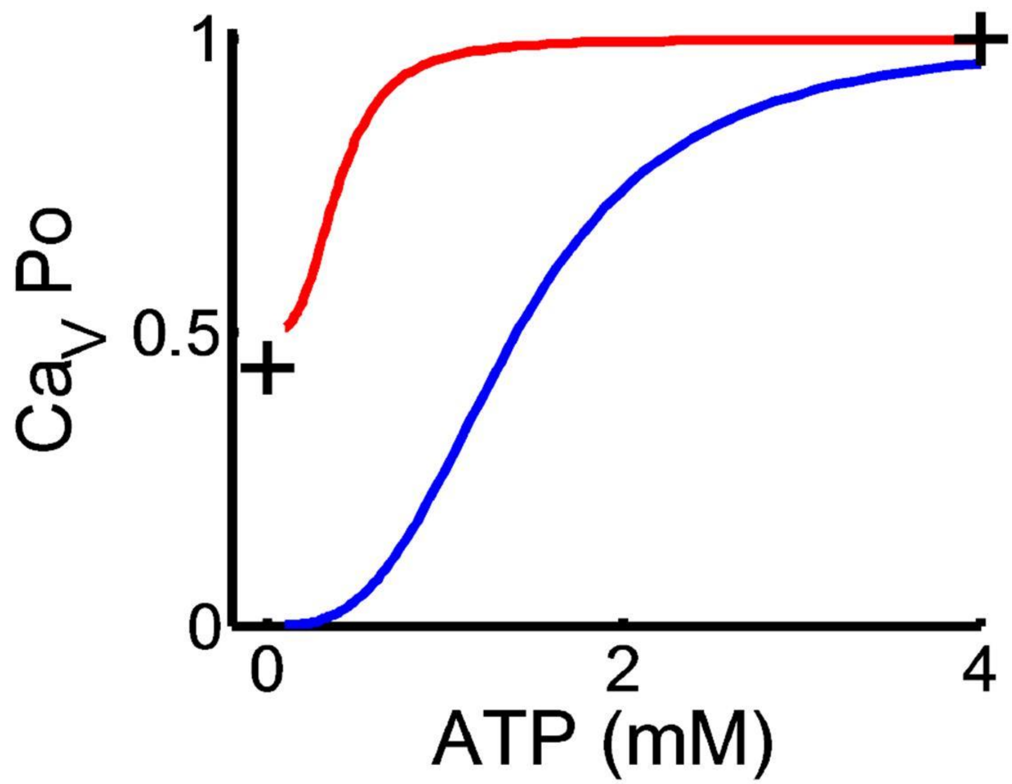

Figure S1. ATP-Dependence of Ca_V

Channels and pumps whose current is linked to ATP levels were investigated to address the lack of bursting at low glucose with zero K,ATP conductance. I_{CaV} from the Cha et al model (24) showed an over-dependence on glucose. Blue lines represent original model and red is the updated model with reduced ATP-dependence of $I_{Ca,V}$ compared to data from Hiriart and Matteson (30) (crosses).

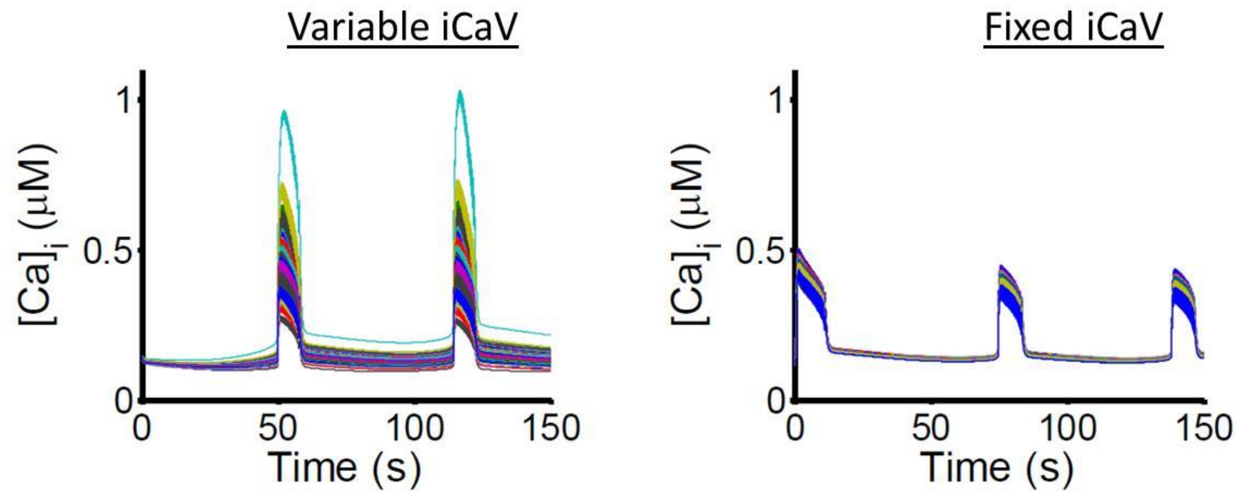

Figure S2. Effect of variability of iCaV on intracellular [Ca^{2+}]

Two 4x4x4 islets are shown with (left) and without (right) ICa¬V permeability variability as described in the Methods. As can be seen by comparing the two figures, the islet with ICaV variability shows many cells with different amplitudes of [Ca2+]i, which will significantly affect insulin release.

MATLAB implementation of the Cha-Noma Model by J. Silva & C. Nichols.

```
% MATLAB implementation of the Cha-Noma Model by J. Silva & C. Nichols
% Changes were made to allow bursting at 0 gK,ATP
% See code for comments regarding implementation

function r=betacell

% Time to run
totaltime=1e6;     % ms

%Initial  Values
%Vm=x(1); Nai=x(2); Ki=x(3); Cai=x(4); CaER=x(5); ATP=x(6); MgADP=x(7);
%Re=x(8); dCaV=x(9); UCaV=x(10); fus=x(11); rKDr=x(12); qKDr=x(13);
%mKto=x(14); hKto=x(15); Eitot=x(16); I1=x(17); I2=x(18);
xinit=[ -48.9045 5.80400 126.776 0.000306139 0.0234849 2.64667 0.127093
0.641950 ...
        0.101898 0.635696 0.827114 0.00105694 0.970421 0.0170783 0.301612
0.354892 ...
        0.151253 0.48958];

% Glucose in mM
G=[2 4 6];

% Run simulation for each G
for i=1:length(G)
    tic  % Keep track of simulation time
    [t,y]=ode15s(@derivs,[0 totaltime],xinit,[],0,G(i)); % Solve Diff
Eqs.
    toc  % Write time
    figure; plot(t,y(:,1))  % Plot Voltage
    clear currents
    % Calculate currents
    for j=1:length(t)
        currents(:,j)=derivs(0,y(j,:),1,G(i));
    end
    figure; plot(t,currents)  % Plot Currents
end

function y=derivs(t,x,a,G)

% Inputs
Iinject=0;

% Constants
R=8.314;       % mV C mmol-1 K-1
T=310;    % K
F=96.485;      % C mmol-1

Nao=140;        % mM
Ko=5.4;         % mM
Cao=2.6;        % mM

Cm=6.158;       % pF
```

```
voli=764;        % fl
volER=280;       % fl
fi=0.01;
fER=0.025;

Vm=x(1); Nai=x(2); Ki=x(3); Cai=x(4); CaER=x(5); ATP=x(6); MgADP=x(7);
Re=x(8); dCaV=x(9); UCaV=x(10); fus=x(11); rKDr=x(12); qKDr=x(13);
mKto=x(14); hKto=x(15); Eitot=x(16); I1=x(17); I2=x(18);

% Constant Field & Nernst Eqs.
zna=1; zk=1; zca=2;
CFNa=zna*F*Vm/(R*T)*(Nai-Nao*exp(-(zna*F*Vm)/(R*T)))/(1-exp(-
(zna*F*Vm)/(R*T)));
CFK=zk*F*Vm/(R*T)*(Ki-Ko*exp(-(zk*F*Vm)/(R*T)))/(1-exp(-
(zk*F*Vm)/(R*T)));
CFCa=zca*F*Vm/(R*T)*(Cai-Cao*exp(-(zca*F*Vm)/(R*T)))/(1-exp(-
(zca*F*Vm)/(R*T)));
EK=R*T/(zk*F)*log(Ko/Ki);

% INaK
PNaK=350;
%Fglc=0.4+0.6*exp(-G/5.84);  Original Eq. from Cha Noma
Fglc=0.3+0.7*exp(-G/2);
Pi=1.9;  H=0.0001;

DNao=0.44; DNai=-0.14; DKo=0.23; DKi=-0.14;
KdNao0=26.8; KdKo0=0.8;  KdNai0=5.0; KdKi0=18.8;
KdNao=KdNao0*exp(DNao*F*Vm/(R*T)); KdNai=KdNai0*exp(DNai*F*Vm/(R*T));
KdKo=KdKo0*exp(DKo*F*Vm/(R*T)); KdKi=KdKi0*exp(DKi*F*Vm/(R*T));
KdMgATP=0.6;

MgATP=ATP;  % ???? not specified
Naibar=Nai/KdNai;  Naobar=Nao/KdNao;
Kibar=Ki/KdKi; Kobar=Ko/KdKo;
MgATPbar=MgATP/KdMgATP;

k1p=1.2528; k2p=0.1392; k3p=6.96; k4p=0.522;
k1m=0.139; k2m=0.0139; k3m=13900; k4m=0.348;

a1p=k1p*Naibar^3/((1+Naibar)^3+(1+Kibar)^2-1);
a2p=k2p;
a3p=k3p*Kobar^2/((1+Naobar)^3+(1+Kobar)^2-1);
a4p=k4p*MgATPbar/(1+MgATPbar);

a1m=k1m*MgADP;
a2m=k2m*Naobar^3/((1+Naobar)^3+(1+Kobar)^2-1);
a3m=k3m*Pi*H/(1+MgATPbar);
a4m=k4m*Kibar^2/((1+Naibar)^3+(1+Kibar)^2-1);

sigma=a1m*a2m*a3m+a1p*a2m*a3m+a1p*a2p*a3m+a1p*a2p*a3p ...
     +a2m*a3m*a4m+a2p*a3m*a4m+a2p*a3p*a4m+a2p*a3p*a4p ...
     +a3m*a4m*a1m+a3p*a4m*a1m+a3p*a4p*a1m+a3p*a4p*a1p ...
     +a4m*a1m*a2m+a4p*a1m*a2m+a4p*a1p*a2m+a4p*a1p*a2p;
Veye=(a1p*a2p*a3p*a4p-a1m*a2m*a3m*a4m)/sigma;
```

```
INaK=PNaK*Veye*Fglc;

% INaCa
PNaCa=204;  % pA
k1=exp(0.32*Vm*F/(R*T));
k2=exp((0.32-1)*Vm*F/(R*T));
k3=1; k4=1;

KdNai=20.75; KdCai=0.0184; KdNao=87.5; KdCao=1.38;
pEiNa=1/(1+(KdNai/Nai)^3*(1+Cai/KdCai));
pEoNa=1/(1+(KdNao/Nao)^3*(1+Cao/KdCao));
pEiCa=1/(1+KdCai/Cai*(1+(Nai/KdNai)^3));
pEoCa=1/(1+KdCao/Cao*(1+(Nao/KdNao)^3));

fca=Cai/(Cai+0.004);
a1=(0.002*fca+0.0015*(1-fca));
b1=0.0012*fca+5e-7*(1-fca);
a2=3e-5*fca+0.01*(1-fca);
b2=0.09*fca+1e-4*(1-fca);

Eotot=1-(Eitot+I1+I2);
INaCa=PNaCa*(k1*pEiNa*Eitot-k2*pEoNa*Eotot);
dI1dt=a1*pEiNa*Eitot-b1*I1;
dI2dt=a2*Eitot-b2*I2;
kf=k2*pEoNa+k4*pEoCa;
kb=k1*pEiNa+k3*pEiCa;
dEitotdt=kf*Eotot+b1*I1+b2*I2-(kb+a1*pEiNa+a2)*Eitot;

% IPMCA
PPMCA=1.56;
%IPMCA=PPMCA/(1+(0.00014/Cai)^2); Original Eq. from Cha Noma
IPMCA=PPMCA/(1+(0.00018/Cai)^2);

% JSERCA
PSERCA=0.096;
JSERCA=PSERCA/(1+(0.0005/Cai)^2);

% Jrel
Prel=0.46;  Jrel=Prel*(CaER-Cai);

% Glycolysis- ATP and Glucose
hgl=2.5;  KG=13;
fglc=1/(1+0.5/ATP)*1/(1+(KG/G)^hgl);

% NADH production
kglc=0.000126;  kbox=0.0000063;
Retot=10;  % mM
Jglc=kglc*fglc*(Retot-Re);
Jbox=kbox*(Retot-Re);

% ATP from oxidative phosphorylation
Pop=0.0005; N=2.5; Rvol=2.5;
Jop=Pop*Re/(1+(0.02/MgADP)^2);
dRedt=Jglc+Jbox-Rvol/N*Jop;
```

```
% Ca2+ dependent ATP consumption
ATPtot=4;
kATP=0.000062; kATPCa=0.187; kADPf=0.0002; kADPb=0.00002;
JcATP=(kATP+kATPCa*Cai)*ATP;
ADPf=MgADP/0.55;

ADPb=-ADPf+ATPtot-ATP;
dMgADPdt = -0.55*(Jop-((INaK+ IPMCA)/F+JSERCA/2)/voli-
(kATP+kATPCa*Cai)*ATP) ...
           +0.55*kADPb*ADPb-kADPf*MgADP;

dATPdt=Jop-JcATP-((INaK+IPMCA)/F+JSERCA/2)/voli;

% ICaV
PCaV=48.9;  %pA mM-1

shift=3;
ad=1/(0.88*exp(-(Vm-shift)/50)+0.09*exp(-(Vm-shift)/600));
bd=1/(5.48*exp((Vm-shift)/12)+1.245*exp((Vm-shift)/30));
ddCaVdt=ad*(1-dCaV)-bd*dCaV;

iCa=0.0676*CFCa;
au=0.0084; bu=0.2318*(-1.15*iCa*dCaV^2+Cai);
dUCaVdt=au*(1-UCaV)-bu*UCaV;

afus=1/(75000*exp(Vm/34));
bfus=1/(5000*exp(-Vm/19)+500*exp(-Vm/100));
dfusdt=afus*(1-fus)-bfus*fus;

% ATP sensitivity
%ATPs=1/(1+(1.4/ATP)^3);   Original Eq. from Cha Noma
ATPs=0.5+0.5/(1+(0.4/ATP)^3);
poCaV=dCaV^2*UCaV*(0.4+0.6*fus)*ATPs;

ICaVCa=PCaV*poCaV*CFCa;
ICaVNa=0.0000185*PCaV*poCaV*CFNa;
ICaVK=0.000367*PCaV*poCaV*CFK;
ICaV=ICaVCa+ICaVNa+ICaVK;

% IKDr
PKDr=2.1;
ar=1/(33.0682*exp(Vm/-8)+0.9368*exp(Vm/-100));
br=1/(22.7273*exp(Vm/100));
drKDrdt=ar*(1-rKDr)-br*rKDr;

aq=1/800;  bq=1/(1000*exp(-Vm/8)+100*exp(-Vm/100));
dqKDrdt=aq*(1-qKDr)-bq*qKDr;
poKDr=rKDr*(0.6*qKDr+0.4);
IKDr=PKDr*poKDr*CFK;

% IKto
GKto=2.13;    % pA mV-1
```

```
am=1/(13.65*exp(-Vm/20));
bm=1/(6.2*exp(Vm/60));
dmKtodt=am*(1-mKto)-bm*mKto;

ah=1/(570*exp(Vm/500));
bh=1/(7.765*exp(-Vm/9)+4.076*exp(-Vm/1000));
dhKtodt=ah*(1-hKto)-bh*hKto;

poKto=mKto*hKto;
IKto=GKto*poKto*(Vm-EK);

% IKSK
PKSK=0.2;  % pA mM-1
poKSK=1/(1+(0.00074/Cai)^2.2);
IKSK=PKSK*poKSK*CFK;

% IbNSC
%PbNSC=0.00396;  Original Eq. from Cha Noma
PbNSC=0.003; % pA mM-1
IbNSCNa=PbNSC*CFNa;
%IbNSCK=2.525*PbNSC*CFK; Original Eq. from Cha Noma
IbNSCK=6*PbNSC*CFK;
IbNSC=IbNSCNa+IbNSCK;

% ISOC
PSOC=0.00764;   % pA mM-1
K05ER=0.003;    % mM
poSOC=1/(1+exp((CaER-K05ER)/0.003));
ISOCNa=0.8*PSOC*poSOC*CFNa;
ISOCK=PSOC*poSOC*CFK;
ISOCCa=20*PSOC*poSOC*CFCa;

ISOC=ISOCNa+ISOCK+ISOCCa;

% ITRPM
PTRPM=0.0234;
poTRPM=1/(1+(0.00076/Cai)^1.7);
ITRPMNa=0.8*PTRPM*poTRPM*CFNa;
ITRPMK=PTRPM*poTRPM*CFK;
ITRPM=ITRPMNa+ITRPMK;

% IKATP
GKATP=2.31;
KAf1=1;
KAf2=1;
poKATP=(KAf2*0.08*(1+KAf1*2*MgADP/0.01)+KAf1*0.89*(MgADP/0.01)^2)...
        /((1+MgADP/0.01)^2*(1+0.45*MgADP/0.026+ATP/0.05));
IKATP=GKATP*poKATP*(Vm-EK);

% Ions
dNaidt=(-ICaVNa-ITRPMNa-ISOCNa-IbNSCNa-3*INaK-3*INaCa+IPMCA)/(voli*F);
dKidt=(-IKDr-IKto-IKSK-IKATP-ICaVK-ITRPMK-ISOCK-IbNSCK+2*INaK-
Iinject)/(voli*F);
dCaidt=fi/voli*((-ICaVCa-ISOCCa+2*INaCa-2*IPMCA)/(2*F)-JSERCA+Jrel);
```

```
dCaERdt=fER/volER*(JSERCA-Jrel);

% Vm
Itot=ICaV+ITRPM+ISOC+IbNSC+IKDr+IKto+IKSK+IKATP+INaK+INaCa+IPMCA;
dVmdt=-(Itot+Iinject)/Cm;

y(1)=dVmdt; y(2)=dNaidt; y(3)=dKidt; y(4)=dCaidt; y(5)=dCaERdt;
y(6)=dATPdt; y(7)=dMgADPdt;
y(8)=dRedt; y(9)=ddCaVdt; y(10)=dUCaVdt; y(11)=dfusdt; y(12)=drKDrdt;
y(13)=dqKDrdt;
y(14)=dmKtodt; y(15)=dhKtodt; y(16)=dEitotdt; y(17)=dI1dt; y(18)=dI2dt;
y=y';

if a  % if calculating currents
    y=[IbNSC IKDr IKto IKATP ITRPM ICaV INaK INaCa IPMCA IKSK ISOC];
end
```