ELECTRONIC SUPPLEMENT

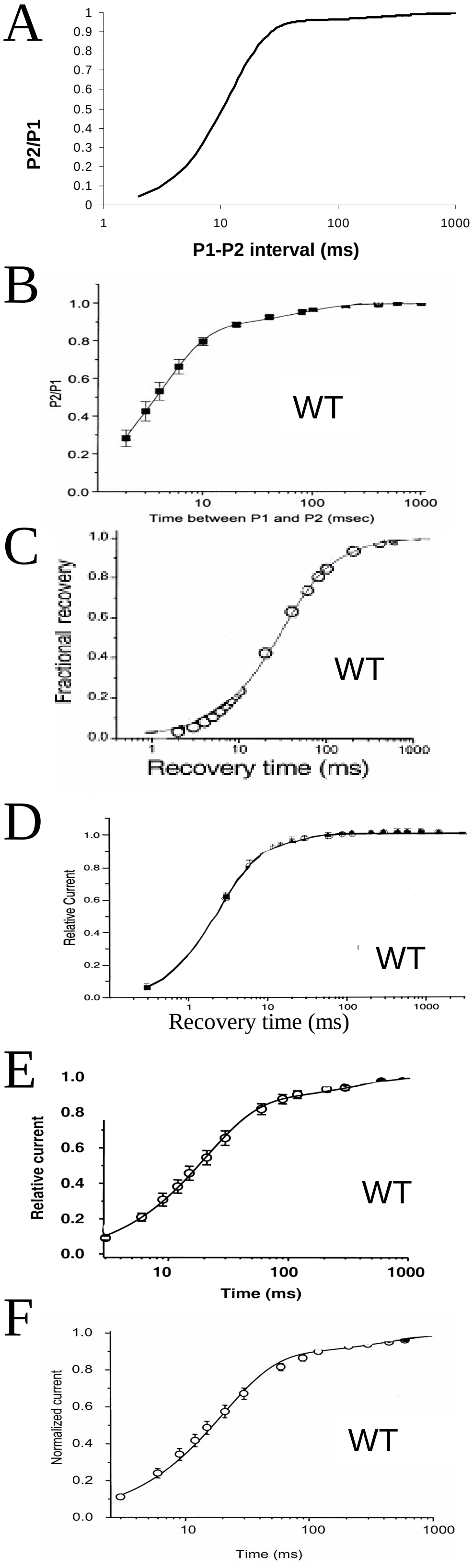
Captions for Supplemental Figures (Electronic Supplement)

Supplemental Figure 1: Comparison to experiments of simulated WT Na+ channel recovery from inactivation. The simulated recovery curve is shown in panel A, with corresponding experimental curves in panels B-F.

Supplemental Figure 2: Comparison to experiments of simulated voltage dependence of steady-state WT Na^+ channel availability and activation. The simulated curves are shown in panel A, with corresponding experimental curves in panels B-D.

Supplemental Figure 3: The voltage dependence of I_{Na} activation varies among the published experimental data, with a voltage shift for the activation curve being quite common. This figure evaluates the effect of shifting the voltage dependence of Na^+ channel activation on 1795insD mutant epicardial AP morphology at a BCL= 300ms. The activation curve (top) is shifted by –5mV (curve a) compared to the simulated curve in this study (curve b). The shift is implemented via an increase in the rate of the voltage dependent activation transitions. The corresponding (bottom, a and b) 95-99th APs are shown in the bottom panel. Even at this fast rate, where a shift in activation is most likely to affect the balance between inward and outward currents, the 1795insD induced AP morphology changes and variability are not affected by the voltage shift of activation. This establishes the robustness of the results across a range of published I_{Na} activation kinetics. Mechanistically, the low sensitivity to activation shifts stems from the fact that the mutation affects AP morphology by altering the channel recovery kinetics.

Supplemental Figure 4: Comparison to experiments of simulated WT Na^+ channel current-voltage relationships. The simulated recovery curve is shown in panel A, with corresponding experimental curves in panels B-D. Note that currents in panel A are normalized to capacitance, while in panels B-D they are not.



WT Simulation

Veldkamp et al. 2000. Circ. Res. 86:e91-97

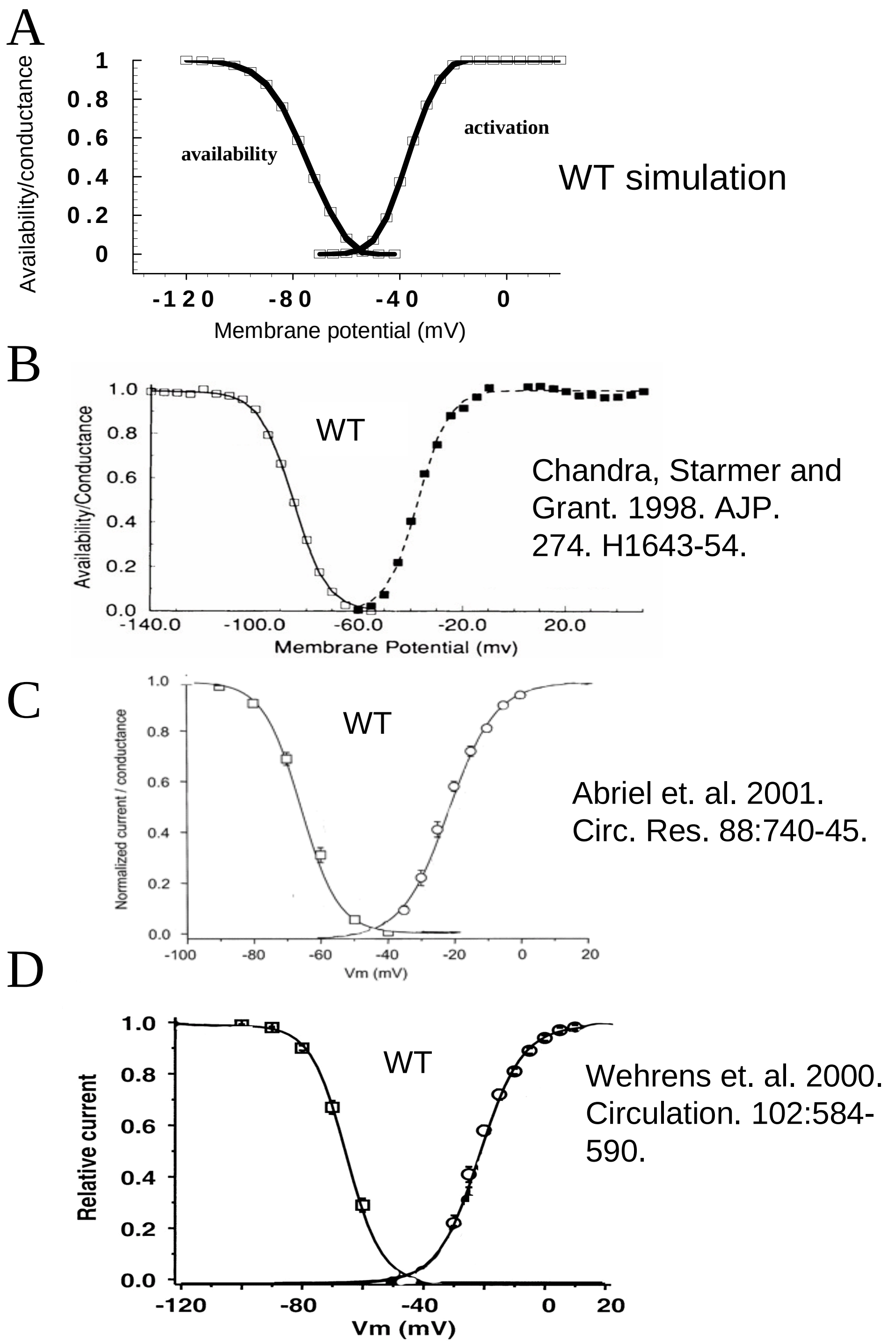
Kambouris et al. 2000. JCI. 105:1133-40

Rivolta et al. 2001. JBC. 276(33):30623-30630

Wehrens et al. 2001. Circulation. 102:584-90

Abriel et al. 2001. Circ. Res. 88:740-5

Supplemental Figure 1



WT simulation

Chandra, Starmer and Grant. 1998. AJP. 274. H1643-54.

Abriel et. al. 2001. Circ. Res. 88:740-45.

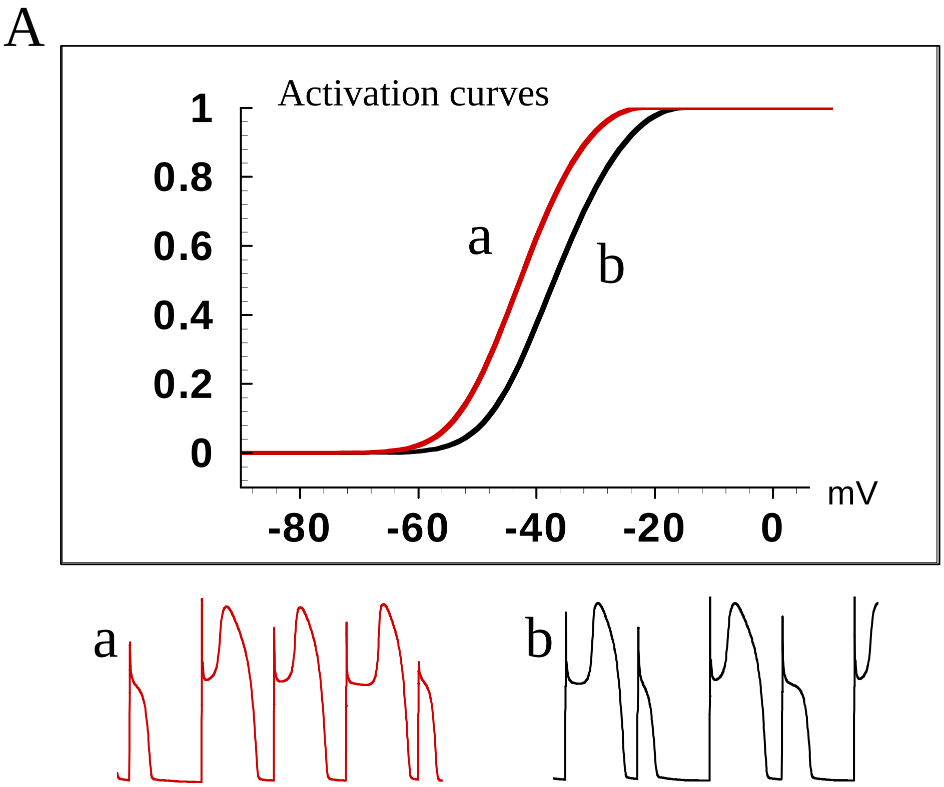
Wehrens et. al. 2000. Circulation. 102:584-590.

See also Rook et.al. 1999. Cardiovascular Res. 44. 507-17

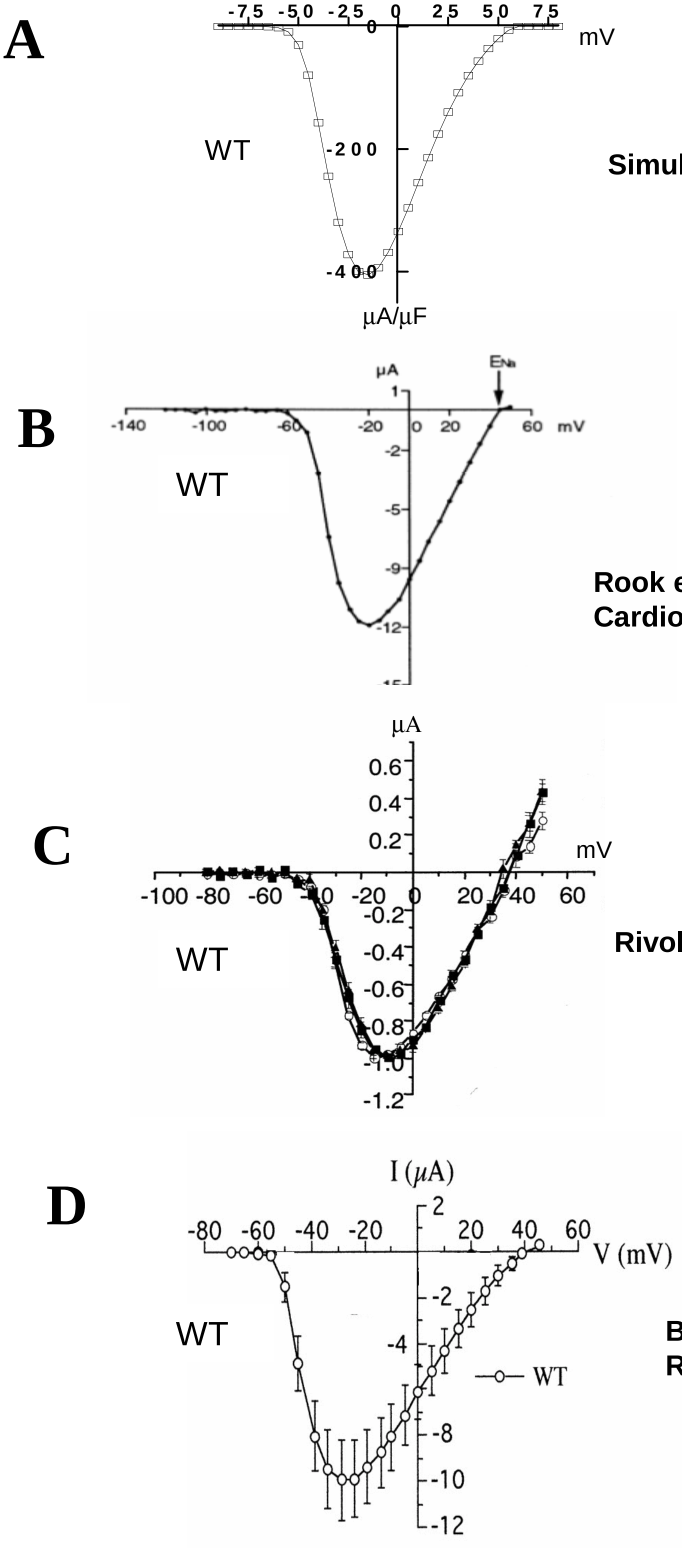
Makita et. al. 2000. Circulation. 101:54-60.

Rivolta et. al. 2001. JBC. 30623-30630.

Supplemental Figure 2



Supplemental Figure 3



Simulation

Rook et al. 1999.
Cardiovascular Res. 44:507-517

Rivolta et al. 2001. JBC. 276(33):30623-30630

Bezzina et al. 1999. Circ. Res. 85:1206-1213

Supplemental Figure 4

Data Supplement 5

Example function for General Markov Model

```
/*              C ←→ O ←→ I

                Function to compute current for simple three-state model
                Colleen Clancy
                Compile with cc (C++)
                The function should be called from Main() which contains the
                time loop and value for dt.


                C → O = a    // rate constants
                O → C = b    // can be adjusted for voltage or ion dependence
                O → I = aa
                I → O = bb

   */

/*

Global Variables (or variables passed from Main())
double C, O, I;

*/



        double Comp_current()                            // current function

{
double Eion=(r*T/F)*log(IONout/IONin);  //channel reversal potential

double Gion = 10.0;                     //maximum membrane conductance

double  a, aa, b, bb, err1, err2, y1, z1, y2, z2, dny, dnz, dny1, dnz1;
int i4;


        a= 10;
        aa= 100;                     // rate constants
```

```
          b = 10;                              // can be adjusted for voltage or ion dependence
          bb = 100;



   if (t==0)                                   // initial values
     {
          C= 1.0;
          I = 0.0;
          O = 1.0- C – I;
          }

   else

   {
     y1=C;     z1= I;

          dny= (O*b- C*a)*dt;
          dnz= (O*aa- I*bb)*dt;


     y2= C+dny;
     z2= I+dnz;


    O= 1.0-y2-z2;

err1= y2-y1;   err2= z2-z1;

          dny1= dny;
          dnz1=dnz;

i4=0;
while (((err1>1e-5)||(err1<-1e-5)||(err2>1e-5)||(err2<-1e-5))&&(i4<40))
 {
          y1=y2;                      z1=z2;

    dny= (O*b- y1*a)*dt;
    dnz= (O*aa- z1*bb)*dt;


    dny= (dny+dny1)/2;
    dnz= (dnz+dnz1)/2;


     y2= C+dny;
```

```
     z2= I+dnz;

     dny1=dny;
     dnz1=dnz;


     O= 1.0-y2-z2;

          err1=y2-y1;
          err2= z2-z1;


          i4++;

 }

 if (i4<40)
    {
   C=y2; I=z2;
    }

  else
  {
   cout<<"error_ina"<<setw(15)<<i4<<setw(15)<<t<<endl;
   exit(0);
    }
    O= 1-C -I;

    }


 Gen_current = Gion*(O)*(v-Eion);

          return Gen_current;
}
```

Data Supplement 6: Appendix:

Computer code for the LRd model can be downloaded from the RESEARCH section of http://www.cwru.edu/med/CBRTC.

I_{Na} Formulation

$I_{Na} = G_{Na} \bullet P(O) \bullet (V_m - E_{Na})$
P(O) = sum of open probabilities of I_{Na}
$G_{Na} = 23.5$ mS/μF
$E_{Na} = (R \bullet T/F) \bullet \ln([Na]_{out}/[Na]_{in})$

Transition Rates: Wild-Type (WT) channel (ms^{-1})

C3 → C2	$\alpha11 = 3.802/(0.1027\bullet\exp(-v/17.0)+0.20\bullet\exp(-v/150))$
C2 → C1	$\alpha12 = 3.802/(0.1027\bullet\exp(-v/15.0)+0.23\bullet\exp(-v/150))$
C1 → O	$\alpha13 = 3.802/(0.1027\bullet\exp(-v/12.0)+0.25\bullet\exp(-v/150))$
IC3 → IC2	$\alpha11 = 3.802/(0.1027\bullet\exp(-v/17.0)+0.20\bullet\exp(-v/150))$
IC2 → IF	$\alpha12 = 3.802/(0.1027\bullet\exp(-v/15.0)+0.23\bullet\exp(-v/150))$
C2 → C3	$\beta11 = 0.1917\bullet\exp(-v/20.3)$
C1 → C2	$\beta12 = 0.20\bullet\exp(-(v-5)/20.3)$
O → C1	$\beta13 = 0.22\bullet\exp(-(v-10)/20.3)$
IC2 → IC3	$\beta11 = 0.1917\bullet\exp(-v/20.3)$
IF → IC2	$\beta12 = 0.20\bullet\exp(-(v-5)/20.3)$
O → IF	$\alpha2 = (9.178\bullet\exp(v/29.68))$
IF → O	$\beta2 = (\alpha13\bullet\alpha2\bullet\alpha3)/(\beta13\bullet\beta3)$
IF → C1	$\alpha3 = 3.7933\bullet10^{-7}\bullet\exp(-v/7.7)$
IC2 → C2	$\alpha3 = 3.7933\bullet10^{-7}\bullet\exp(-v/7.7)$
IC3 → C3	$\alpha3 = 3.7933\bullet10^{-7}\bullet\exp(-v/7.7)$
C1 → IF	$\beta3 = (0.0084+0.00002\bullet v)$
C2 → IC2	$\beta3 = (0.0084+0.00002\bullet v)$
C3 → IC3	$\beta3 = (0.0084+0.00002\bullet v)$

IF → IM1	$\alpha4= \alpha2/100$
IM1 → IF	$\beta4 = \alpha3$
IM1 → IM2	$\alpha5 = \alpha2/(9.5\bullet10^4)$
IM2 → IM1	$\beta5 = \alpha3/50$

Transition rates: 1795insD mutant channel * (ms^{-1})

xC3 → xC2	$\alpha11= 3.802/(0.1027\bullet\exp(-v/17.0)+0.20\bullet\exp(-v/150))$
xC2 → xC1	$\alpha12= 3.802/(0.1027\bullet\exp(-v/15.0)+0.23\bullet\exp(-v/150))$
xC1 → xO	$\alpha13= 3.802/(0.1027\bullet\exp(-v/12.0)+0.25\bullet\exp(-v/150))$
UIC2 → UIF	$\alpha12= 3.802/(0.1027\bullet\exp(-v/15.0)+0.23\bullet\exp(-v/150))$
UIF → UIC2	$\beta12= 0.20\bullet\exp(-(v-5)/20.3)$
xC2 → xC3	$\beta11= 0.1917\bullet\exp(-v/20.3)$
xC1 → xC2	$\beta12= 0.20\bullet\exp(-(v-5)/20.3)$
xO → xC1	$\beta13= 0.22\bullet\exp(-(v-10)/20.3)$
UO → UIF	$\alpha2= (9.178\bullet\exp(v/29.68))$
UIF → UO	$\beta2= (\alpha13\bullet\alpha2\bullet\alpha3)/(\beta13\bullet\beta3)$
UIF → UC1	$\alpha3= (3.7933\bullet10^{-7}\bullet\exp(-v/7.7))/2.5$
UIC2 → UC2	$\alpha3= (3.7933\bullet10^{-7}\bullet\exp(-v/7.7))/2.5$
UIC3 → UC3	$\alpha3= (3.7933\bullet10^{-7}\bullet\exp(-v/7.7))/2.5$
UC1 → UIF	$\beta3= (0.0084+0.00002\bullet v)$
UC2 → UIC2	$\beta3= (0.0084+0.00002\bullet v)$
UC3 → UIC3	$\beta3= (0.0084+0.00002\bullet v)$
UIF → UIM1	$\alpha4= \alpha2/100$
UIM1 → UIF	$\beta4 = \alpha3$
UIM1 → UIM2	$\alpha5= \alpha2/(3.5\bullet10^4)$
UIM2 → UIM1	$\beta5= \alpha3/20$

$\exp(n) = e^n$

* x represents U or L since transition rates within Background or Burst modes are the same. Transition rates between modes are:

background to burst (U→L) = $1\bullet10^{-7}$ ms^{-1} burst to background (L→U) = $9.5\bullet10^{-4}ms^{-1}$