Supplementary Data

Models of HERG Gating

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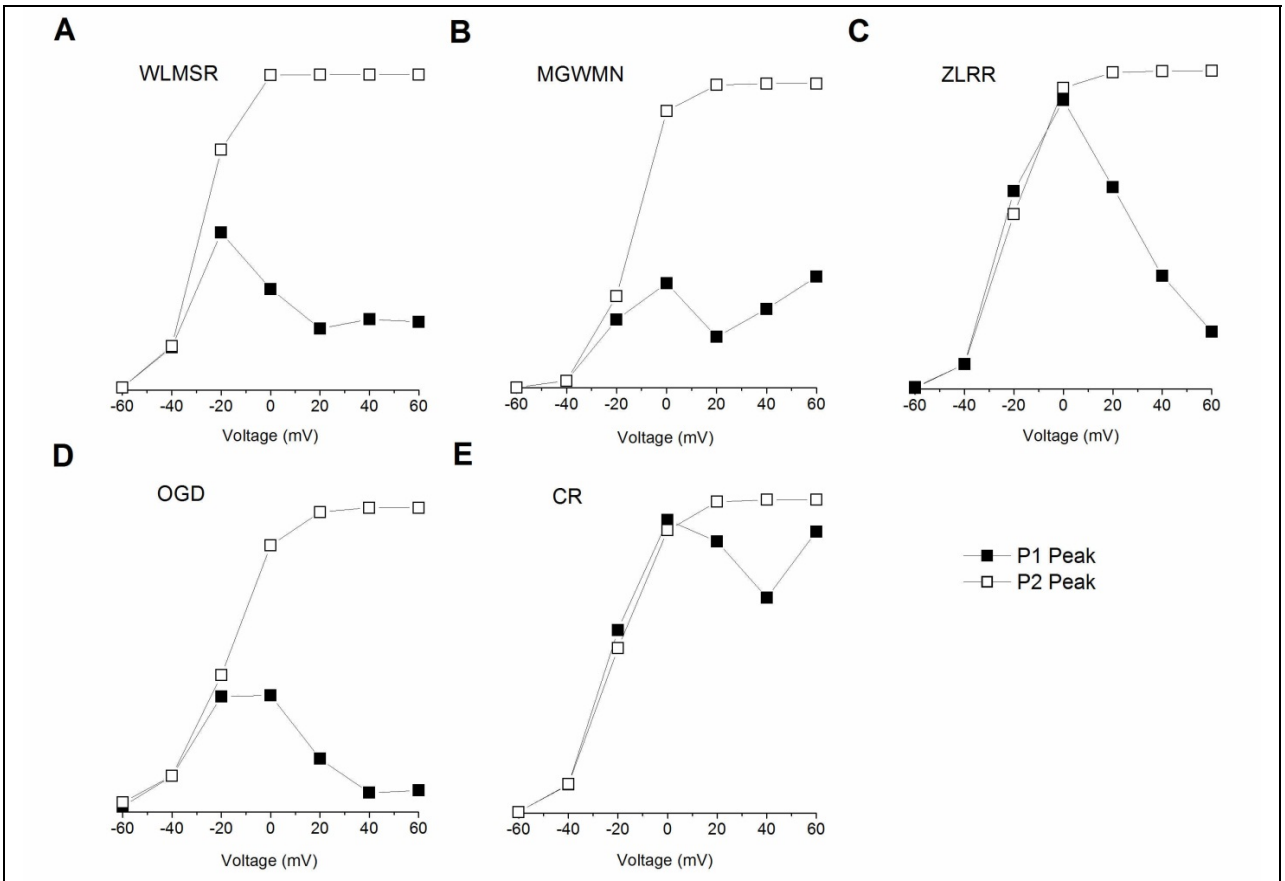
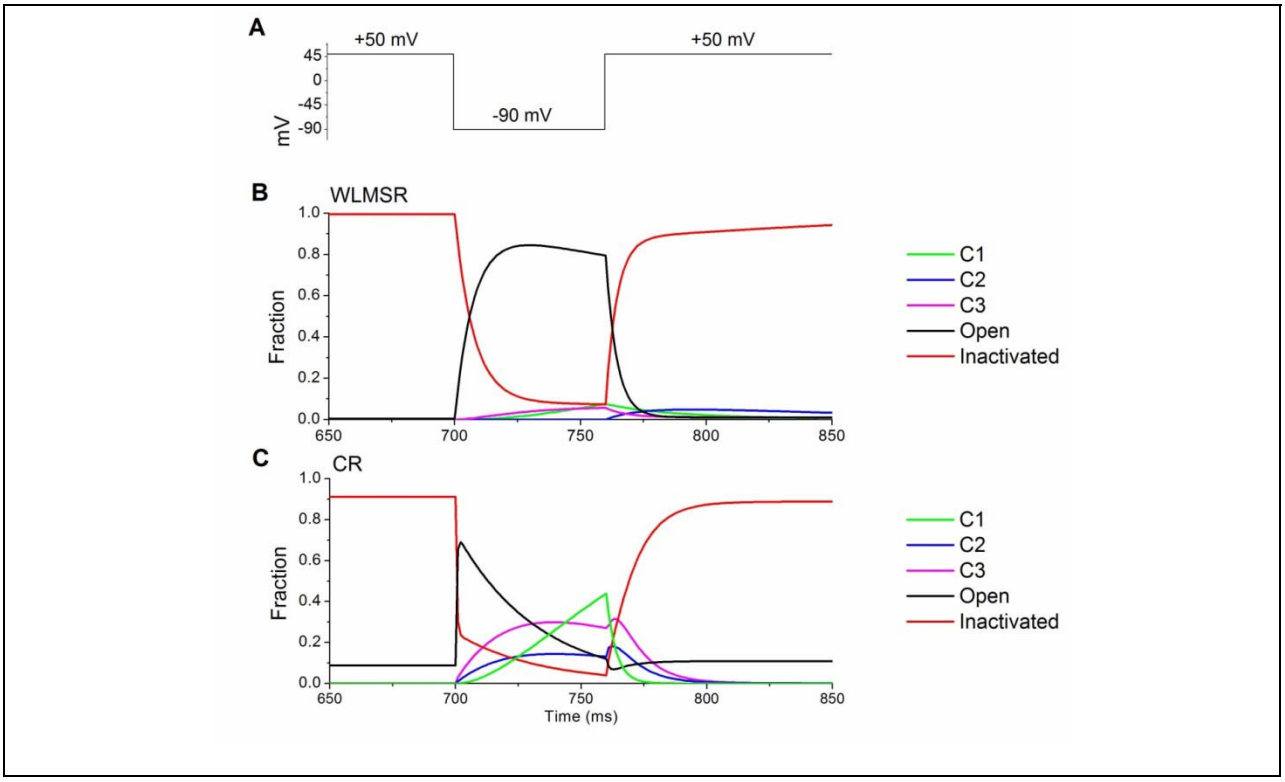
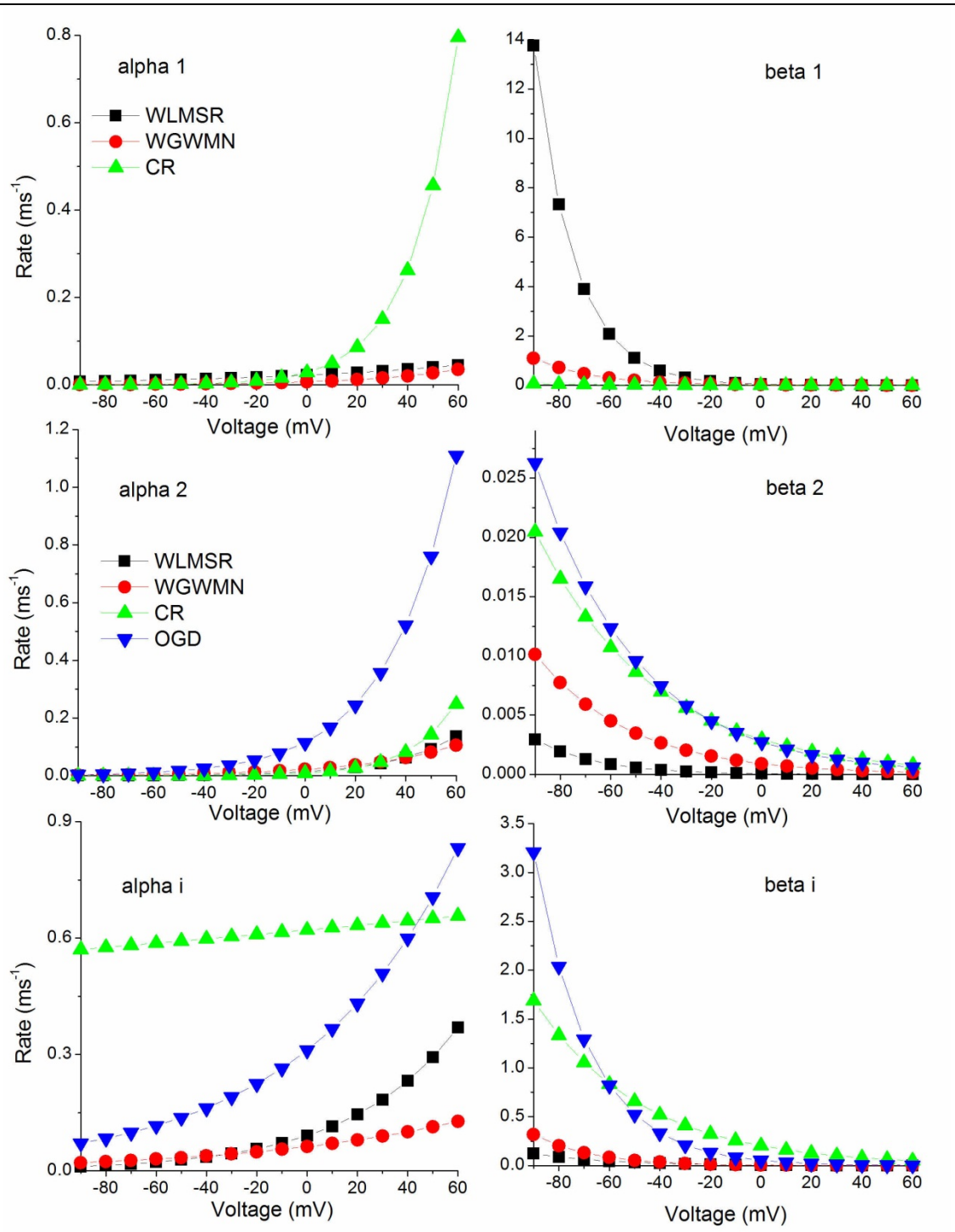


Supplementary Figure 1. Rectification of HERG is a defining characteristic of HERG gating. The maximum current elicited by the P1and P2 pulses in the protocol used in **Figure 1** is plotted against the P1 voltage. WLMSR, MGWMN and OGD models exhibit the expected rectification. The ZLRR has modest rectification only at higher voltages. The CR model has minimal rectification. The ZLRR and CR models have greater P1 than P2 current at voltages within the physiological range.


A
+50 mV
+50 mV
45
0
-45
-90
mV
-90 mV
B
WLMSR
Fraction
1.0
0.8
0.6
0.4
0.2
0.0
650
700
750
800
850
C1
C2
C3
Open
Inactivated
C
CR
Fraction
Time (ms)

Supplementary Figure 2. State Occupancy of WLMSR and CR models during the inactivation protocol (cf. figure 6 in the main paper). **A:** Voltage. **B:** In the WLMSR model repolarization results in the channels transitioning to the open state. On depolarization, the channels transition from the open to the inactivated state, and the whole cell current is a good reflection of inactivation. **C:** In the CR Model repolarization results in channels transitioning to the open state, but then quickly to the closed states. Subsequent depolarization results in brief inactivation of the remaining open states, but is dominated by the activation of the now closed channels.



Supplementary Figure 3 rate constants plotted against voltage for all models. OGD has no alpha 1 and beta 1. CR has only modest voltage dependence of alphai

Transition	Voltage (mV)	WLMSR	MGWMN	CR	OGR
Alpha1	-90	77.5×10^{-4}	5.97×10^{-4}	1.94×10^{-4}	-
	-60	11.0×10^{-3}	1.3×10^{-3}	1.0×10^{-3}	-
	-30	15.7×10^{-3}	3.1×10^{-3}	5.4×10^{-3}	-
	0	22.3×10^{-3}	6.9×10^{-3}	28.5×10^{-3}	-
	30	0.0318	0.0156	0.1506	-
	60	0.0453	0.0353	0.7955	-
Beta 1	**-90**	**13.755**	**1.098**	**0.0635**	-
	-60	**2.0718**	**0.3014**	**0.02117**	-
	-30	0.3121	0.0827	0.0071	-
	0	0.0470	0.0227	0.0024	-
	30	70.79×10^{-4}	62.30×10^{-4}	7.86×10^{-4}	-
	60	10.66×10^{-4}	17.10×10^{-4}	2.62×10^{-4}	-
	-90	4.41×10^{-4}	20.63×10^{-4}	2.29×10^{-4}	-
Alpha 2	-90	4.41×10^{-4}	20.63×10^{-4}	60.36×10^{-4}	38.25×10^{-4}
	-60	13.88×10^{-4}	45.26×10^{-4}	3.19×10^{-4}	118.89×10^{-4}
	-30	4.37×10^{-3}	9.93×10^{-3}	1.68×10^{-3}	36.95×10^{-3}
	0	0.0137	0.0218	0.0089	0.1149
	30	0.0432	0.0478	0.0470	0.3570
	60	0.1359	0.1050	0.2480	1.1095
Beta 2	-90	0.0030	0.0101	0.0205	0.0263
	-60	0.0013	0.0059	0.0133	0.0159
	-30	3.66×10^{-4}	26.4×10^{-4}	69.6×10^{-4}	74.54×10^{-4}
	0	1.05×10^{-4}	11.78×10^{-4}	36.43×10^{-4}	35.00×10^{-4}
	30	$\mathbf{2.99 \times 10^{-5}}$	$\mathbf{52.6 \times 10^{-5}}$	$\mathbf{190.7 \times 10^{-5}}$	$\mathbf{164.3 \times 10^{-5}}$
	60	$\mathbf{8.53 \times 10^{-6}}$	$\mathbf{234.00 \times 10^{-6}}$	$\mathbf{998.00 \times 10^{-6}}$	$\mathbf{772. \times 10^{-6}}$
Alpha i	-90	0.0111	0.0211	0.5707	0.0711
	-60	0.0223	0.0303	0.5870	0.1163
	-30	0.0450	0.0434	0.6038	0.1902
	0	0.0908	0.0622	0.6211	0.3110
	30	0.1832	0.0892	0.6388	0.5087
	60	0.3696	0.1278	0.6571	0.8321
Beta i	-90	0.1230	0.3180	1.6875	3.2082
	-60	0.0462	0.0842	0.8333	0.8218
	-30	0.0173	0.0223	0.4115	0.2105
	0	6.50×10^{-3}	5.9×10^{-3}	203.20×10^{-3}	53.9×10^{-3}
	30	$\mathbf{2.44 \times 10^{-3}}$	$\mathbf{1.56 \times 10^{-3}}$	$\mathbf{100.34 \times 10^{-3}}$	$\mathbf{13.8 \times 10^{-3}}$
	60	$\mathbf{9.14 \times 10^{-4}}$	$\mathbf{4.14 \times 10^{-4}}$	$\mathbf{495.5 \times 10^{-4}}$	$\mathbf{35.38 \times 10^{-4}}$
Alpha i2	-90	-	1.29×10^{-5}	6.04×10^{-5}	-
	-60	-	1.29×10^{-5}	32×10^{-5}	-
	-30	-	1.29×10^{-5}	168×10^{-5}	-
	0	-	1.29×10^{-5}	889×10^{-5}	-
	30	-	1.29×10^{-5}	4695×10^{-5}	-
	60	-	1.29×10^{-5}	24798×10^{-5}	-

Table S1. Transition rates for all models at various potentials. Rows highlighted have disparities of ~100-fold between model rates.

Voltage	MGWMN $\alpha_2 : \alpha_{i2}$
-40	593
-30	770
-20	1001
-10	1300
0	1690
10	2196
20	2854
30	3708
40	4819
50	6262

Table S2: Ratio of the magnitude of the transition of the closed to open state vs. closed to inactivated state for various voltages in the MGWMN model.