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Supporting Material

Irregularly-Appearing Early Afterdepolarizations in Cardiac Myocytes: Random Fluctuations or Dynamical Chaos?

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Online Supplemental Materials

1. A minimal model demonstrating EAD chaos

We developed a 3-variable model which can generate EADs. The equations are:

$$\frac{dV}{dt} = -[g_{Ca} \cdot d_\infty \cdot f(V - E_{Ca}) + g_K \cdot x(V - E_K)] + I_{sti}$$

$$\frac{df}{dt} = \frac{f_\infty - f}{\tau_f}$$

$$\frac{dx}{dt} = \frac{x_\infty - x}{\tau_x}$$

where V is voltage, f is the inactivation gating variable of the L-type Ca channel, and x is the gating variable of the time-dependent K channel. $d_\infty = \frac{1}{1+\exp(-(V+35)/6.24)}$, $f_\infty = \frac{1}{1+\exp((V+20)/8.6)}$, $x_\infty = \frac{1}{1+\exp(-(V+40)/5)}$, and $\tau_f = 80$, $\tau_x = 300$, $E_{Ca} = 100$, $E_K = -80$, $g_{Ca} = 0.025$, $g_K = 0.04$. $I_{sti} = V_0\delta(t - nT)$ in which the δ-function satisfies $\int_{(n-1/2)T}^{(n+1/2)T} \delta(t - nT)dt = 1$. The results are summarized in Figs.S2-4.

2. Supplemental Figures

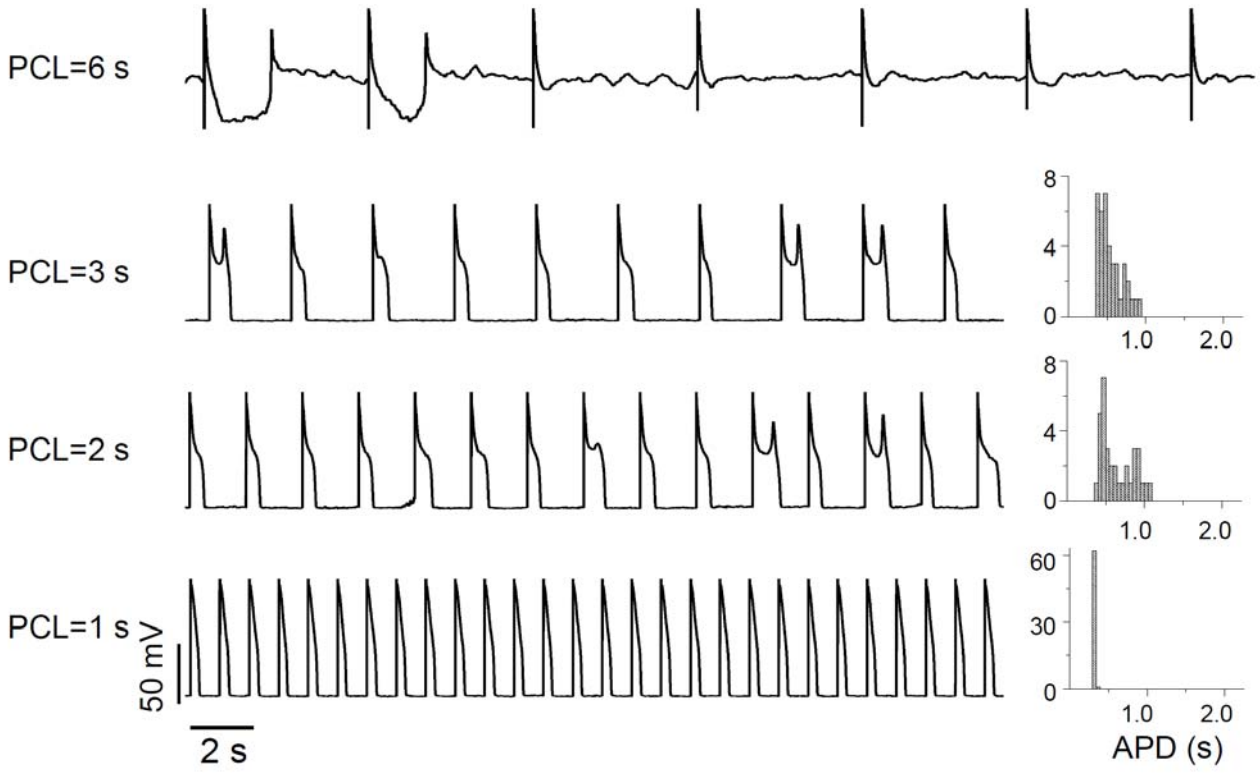

Fig.S1. Voltage (left) and APD histograms from a rabbit ventricular myocyte under the condition of hypokalemia ($[K]_o$=2.7 mM), showing EADs and their variations. The top panel shows that at PCL=6 s, the myocyte failed to repolarize.

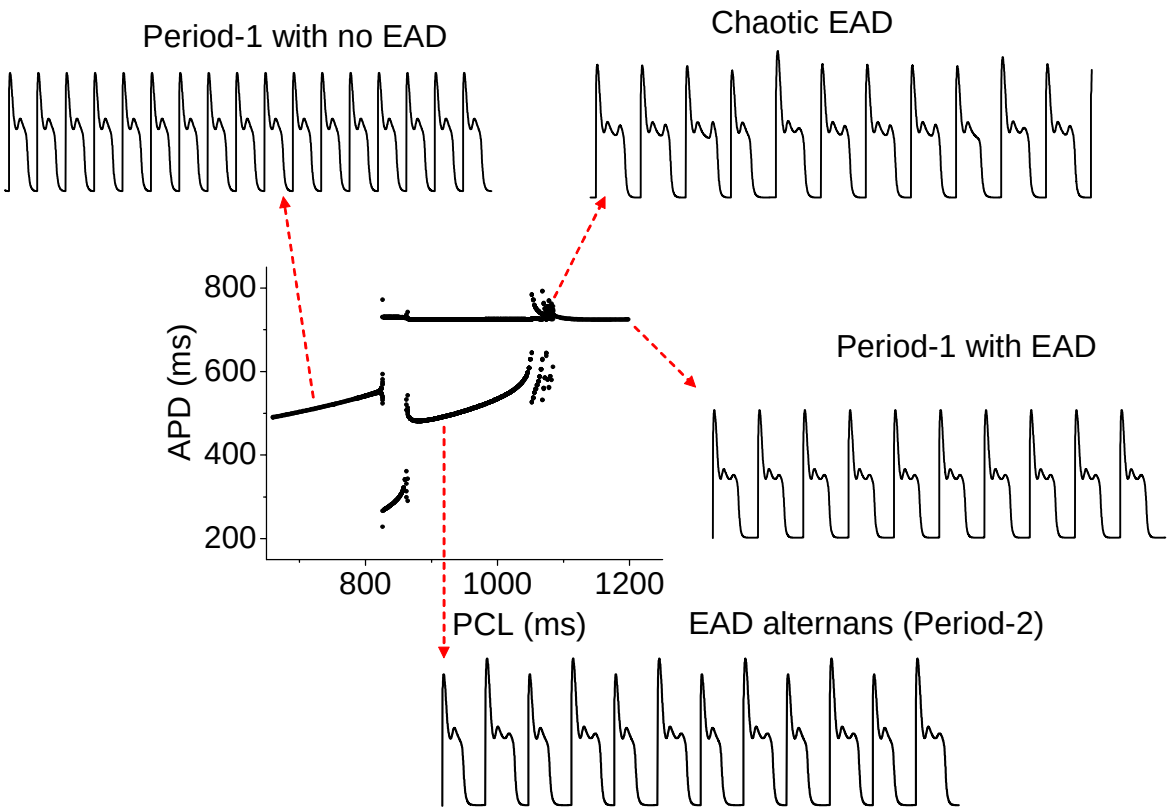

Fig.S2. Bifurcation diagram and voltage traces from different PCLs (indicated by arrows) of the 3-variable model.

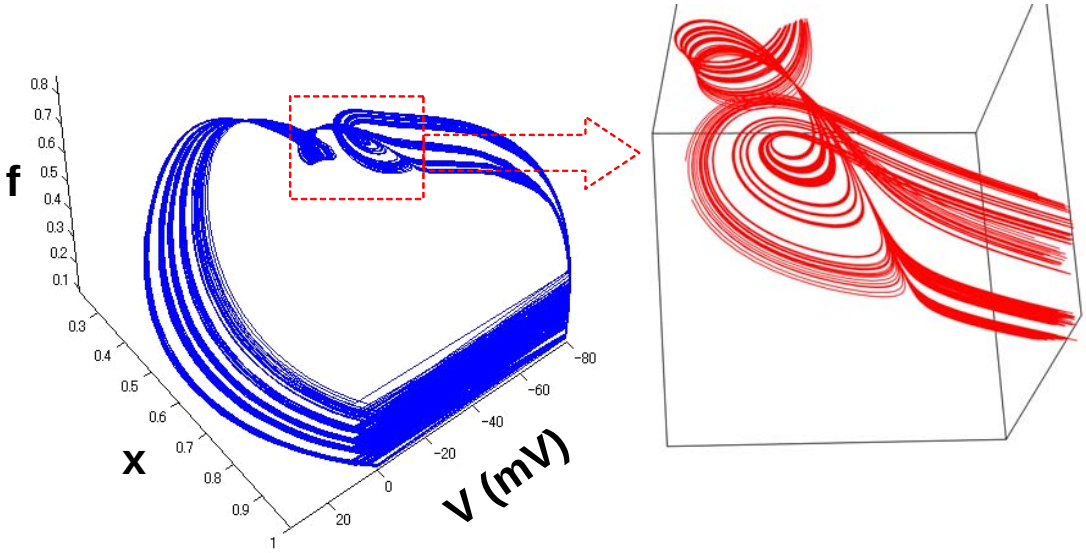

Fig.S3. EAD chaotic attractor of the 3-variable model shown in x-f-V space for PCL=1078 ms.

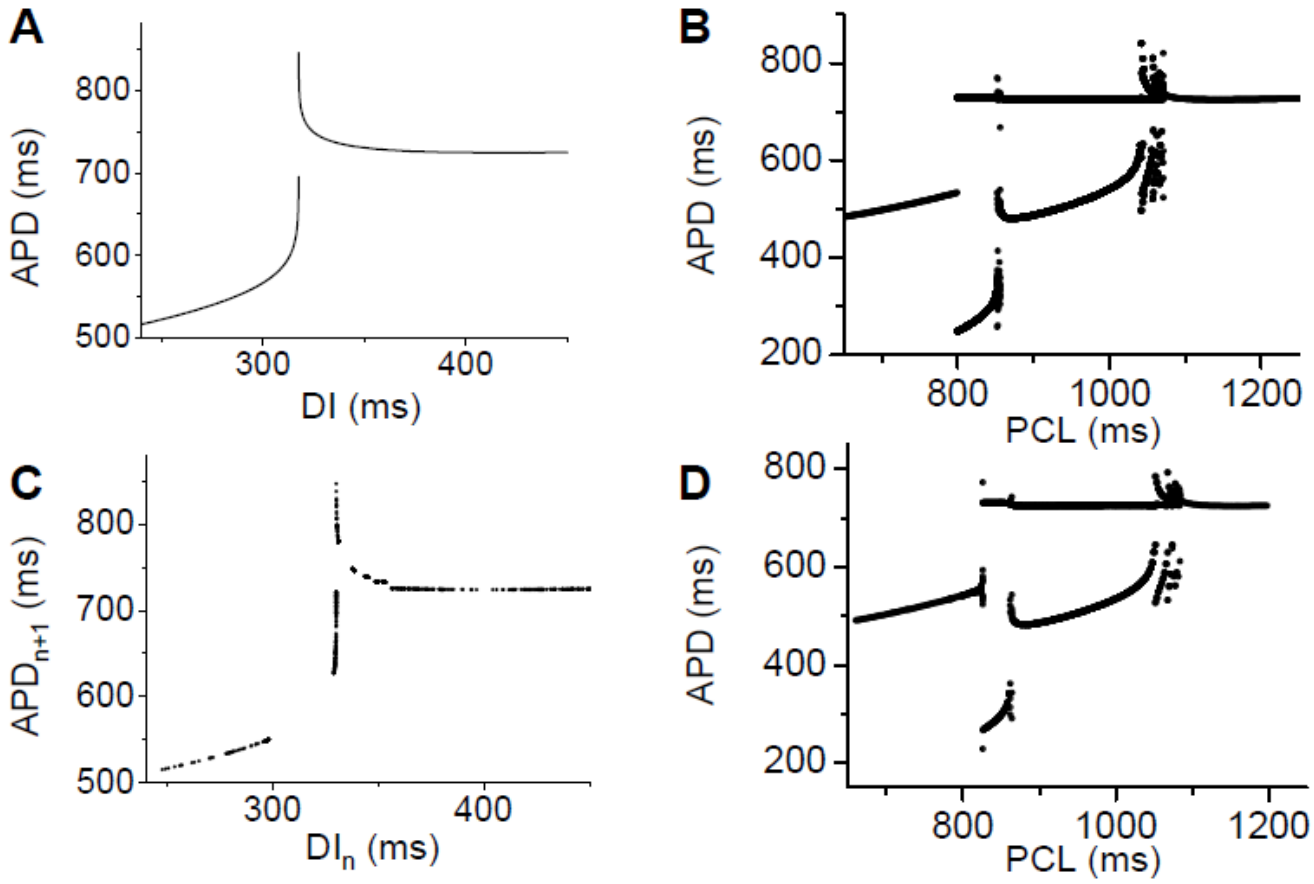

Fig.S4. **A**. S1S2 APD restitution curve obtained from the 3-variable model. **B**. Bifurcation diagram showing APD vs. PCL obtained by iterating Eq.5 in main text using the restitution curve shown in A. **C**. APD_{n+1} vs DI_n from the chaotic attractor of the 3-varaible model at PCL=1078 ms, which is very similar to the APD restitution curve shown in A. **D**. Replot of the bifurcation diagram shown in Fig.S2 for comparison with the result of iterated map shown in B. Note that panel B and panel D are almost the same, demonstrating that the iterated map is very accurate since there is little memory in the 3-varaible model. However, in the physiologically detailed AP model, there is a large memory effect, the iterated map model using the S1S2w restitution curve can be only qualitative.

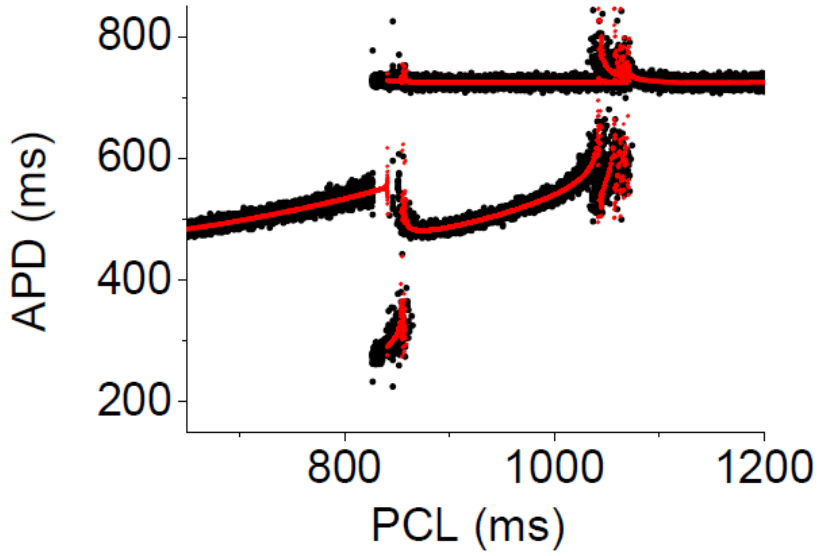

Fig.S5. Bifurcation diagrams showing APD vs PCL from the 1D map of the 3-variable model without (red) and with (black) 10% noise added to the APD.

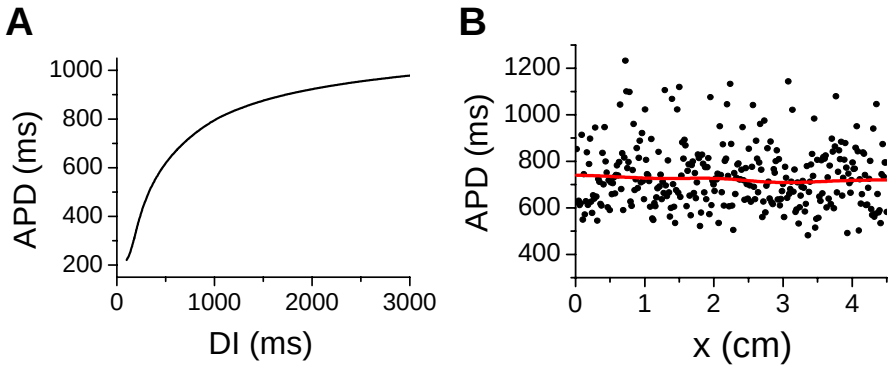

Fig.S6. **A.** APD restitution curve when the AP model does not exhibit EADs, which is a continuous function of DI. The model was modified from the original Mahajan et al model by reducing both I_{Ks} and I_{Kr} maximum conductance to 25%. Note that when EAD occurs, the APD restitution curve is discontinuous. **B.** APD distribution at PCL=1500 ms in a 1D cable when the myocytes are not coupled (black dots) and when they are coupled (red line). The stochastic fluctuations were simulated using Eqs.3 and 4. We chose the total channel number of I_{Ks} to be 100 to result in large APD fluctuations. In this case, gap junction coupling smoothes the large random APD variations.

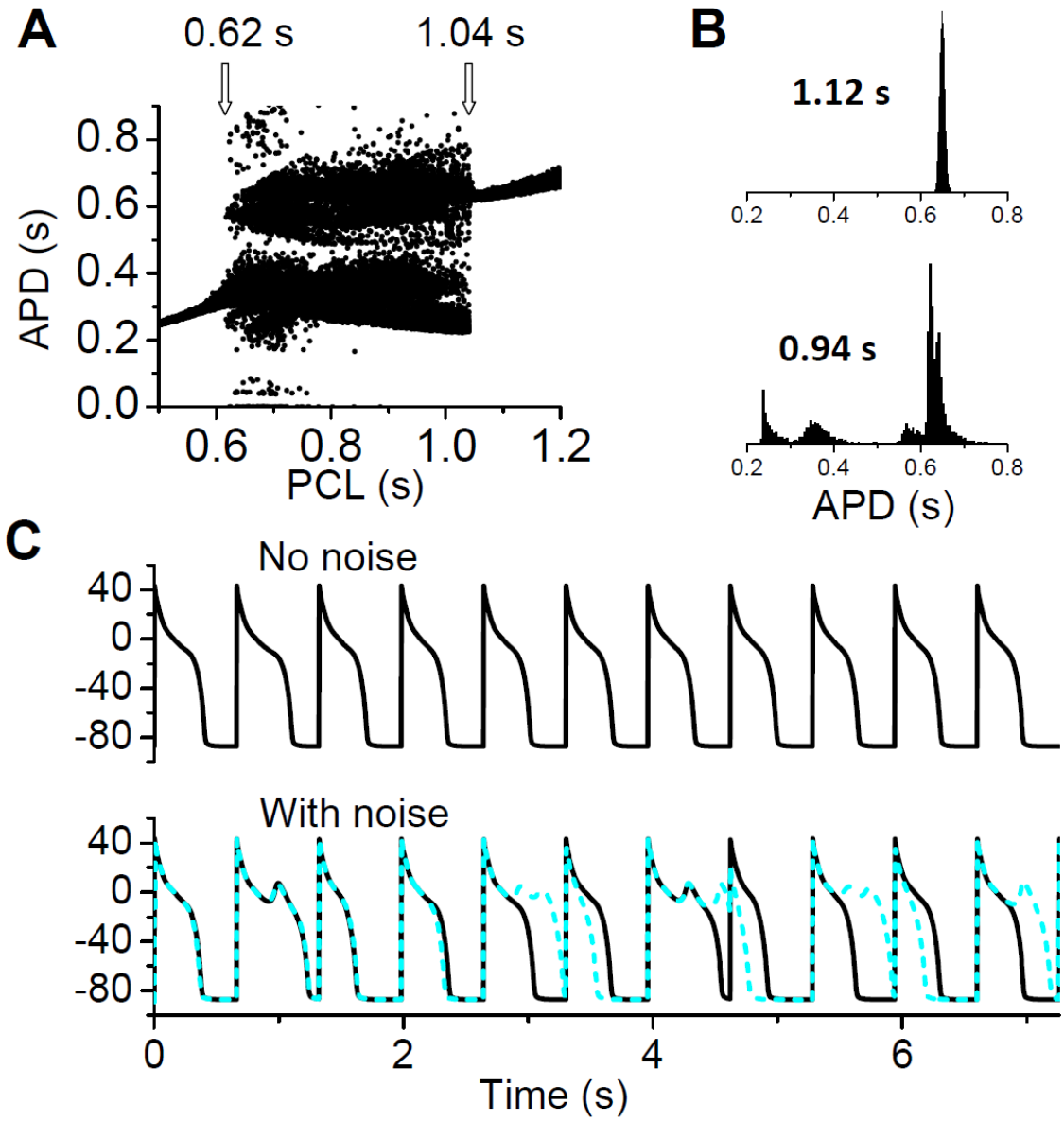

Fig.S7. **APD dynamics when random noise was added to I_{Na} (N=22000); I_{Ks} (N=22000), I_{Kr} (N=22000); I_{tos} (N=22000), and I_{tof} (N=22000)**. **A**. APD versus PCL. **B**. APD histograms for PCL=1.12 s and PCL=0.94 s. **C**. Upper panel: Voltage versus time when no noise was added for PCL=660 ms. Lower panel: voltage versus time when the same noise as in A was present. The same random sequence was used for the two traces but simulations were started with two slightly different initial values of voltage (1% difference).

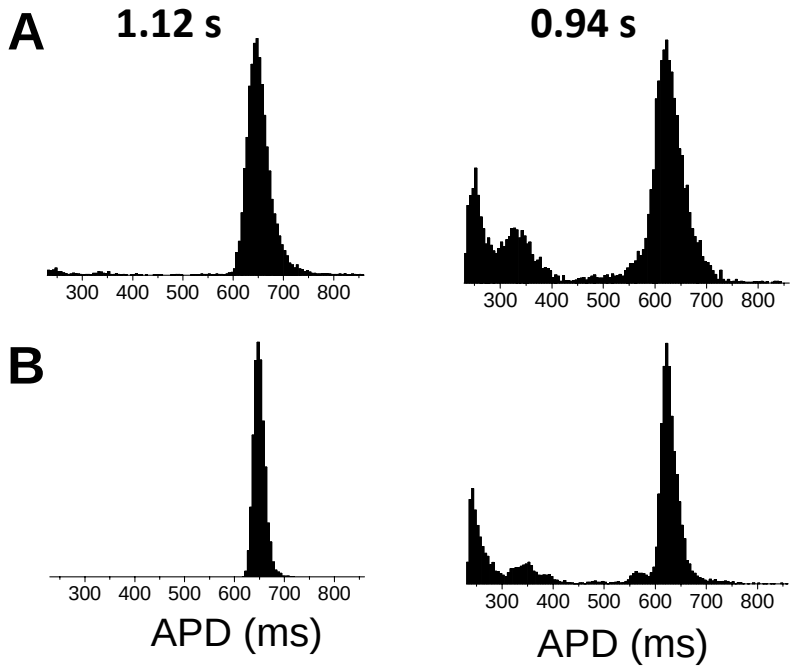

Fig.S8. **APD histograms when random noise was added to I_{Na} (**N=22000**); I_{Ks} (**N=22000**), I_{Kr} (**N=22000**); I_{tos} (**N=22000**), I_{tof} (**N=22000**), and $I_{Ca,L}$**. The number of $I_{Ca,L}$ channel was N=2000 (**A**) and N=80000 (**B**).

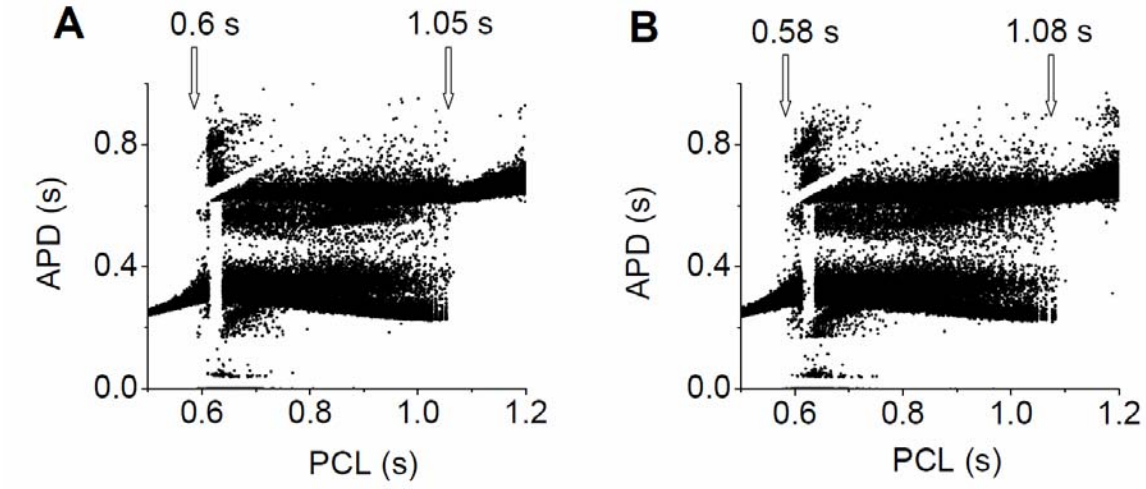

Fig.S9. APD versus PCL when random noise was added to I_{Ks} only with N=5000 (**A**) and N=2500 (**B**).