Short-term memory induced complex APD dynamics in cardiac myocytes

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- **Introduction**
    1. What is short-term cardiac memory?
    2. What has been known about memory on APD dynamics?
- **Memory unmasked or exacerbated by diseases**
    1. Early repolarization syndrome: Short-QT, Brugada, & J-wave syndrome
    2. Reduced repolarization reserve: Long QT syndrome
- **Memory induced complex APD dynamics**
    1. Memory from ion channel recovery
    2. Memory from ion accumulation
- **Constant-DI pacing control of voltage-driven instabilities**
- **Future work**

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Memory-Induced Chaos in Cardiac Excitation

Julian Landaw,[1,2] Alan Garfinkel,[1,3] James N. Weiss,[1,4] and Zhilin Qu[1,2,*]

PHYSICAL REVIEW E 97, 042414 (2018)

Memory-induced nonlinear dynamics of excitation in cardiac diseases

Julian Landaw and Zhilin Qu[*]

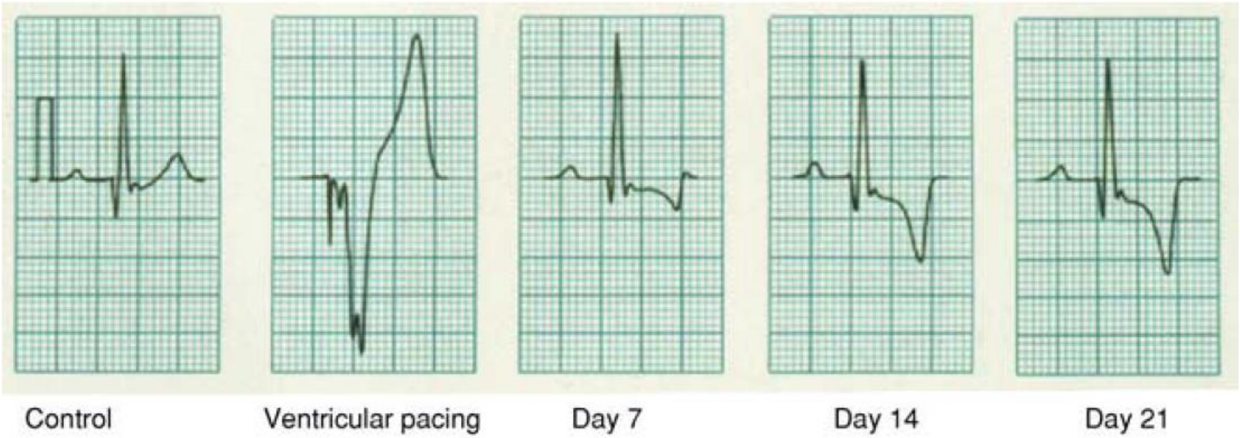
Failure of constant-diastolic-interval-pacing control of voltage-driven instabilities in cardiac myocytes with memory

Julian Landaw[1,2] and Zhilin Qu[1,2,a)]

(under review)

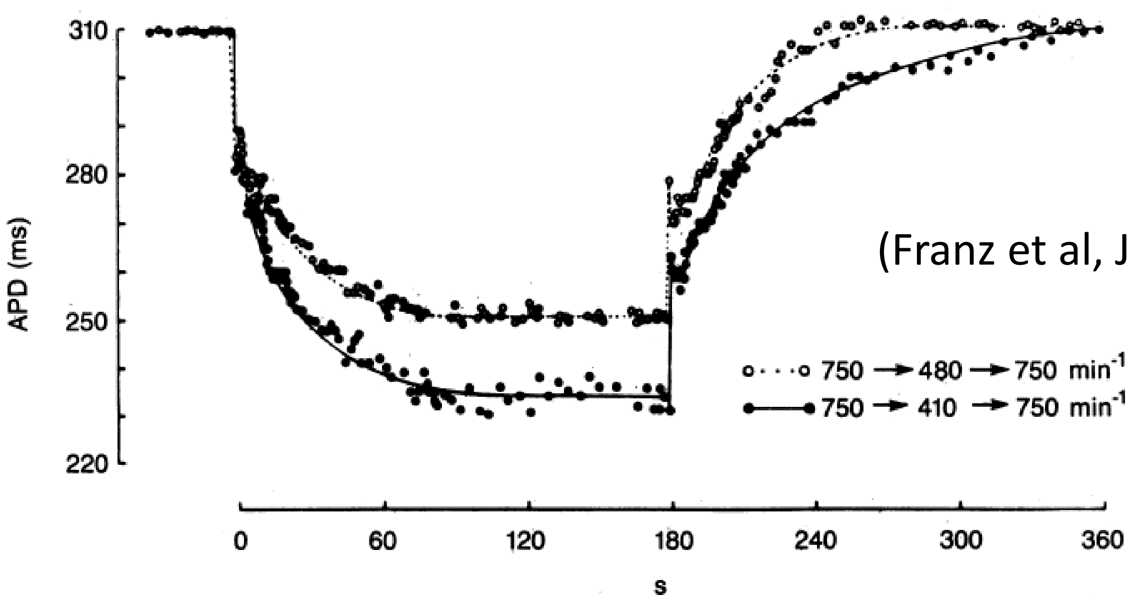
Cardiac memory

Long-term memory



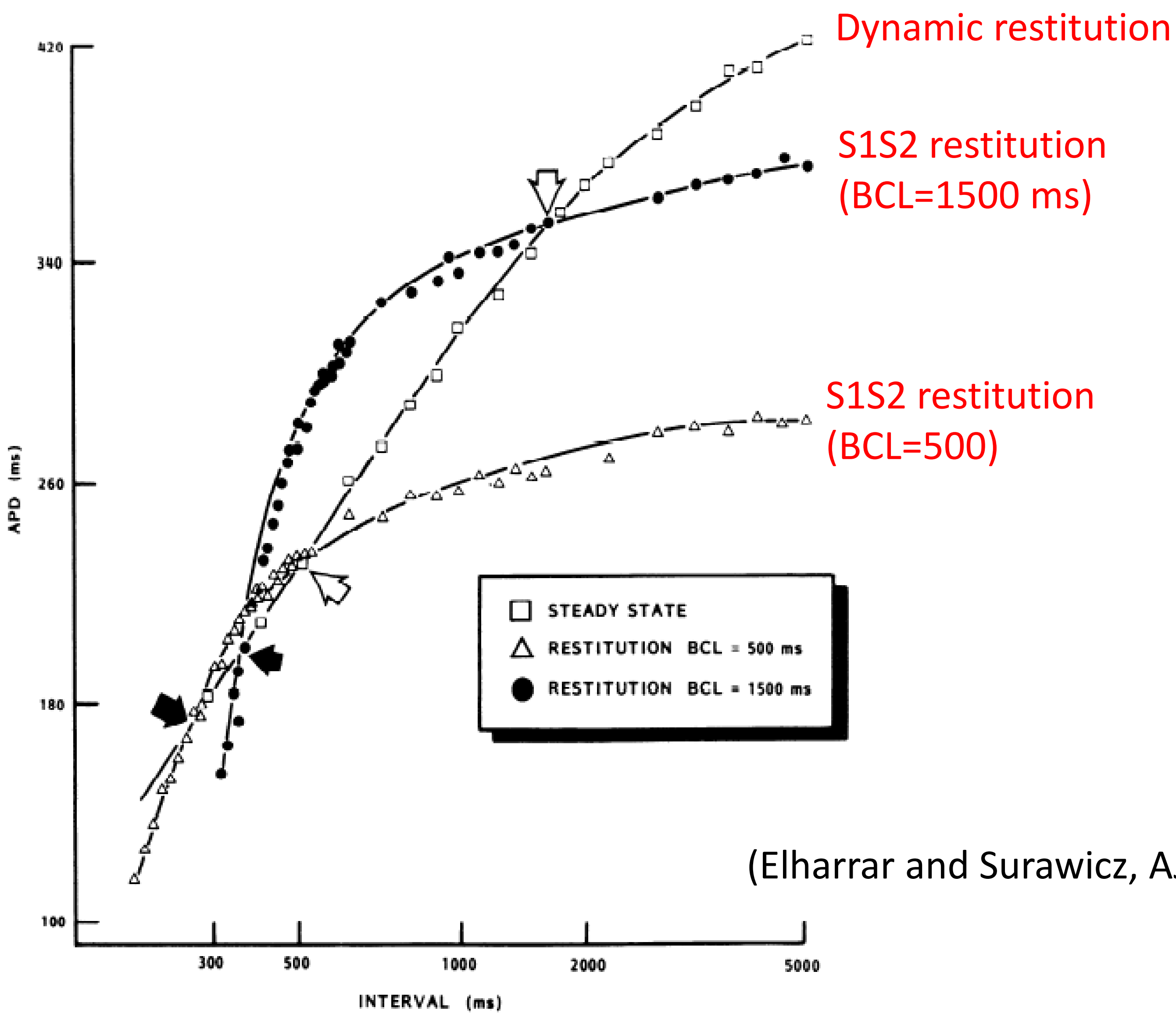
(Rosen and Cohen, JP 2006)

Short-term memory



(Franz et al, JCI 1988)

S1S2 and dynamic APD restitution curves

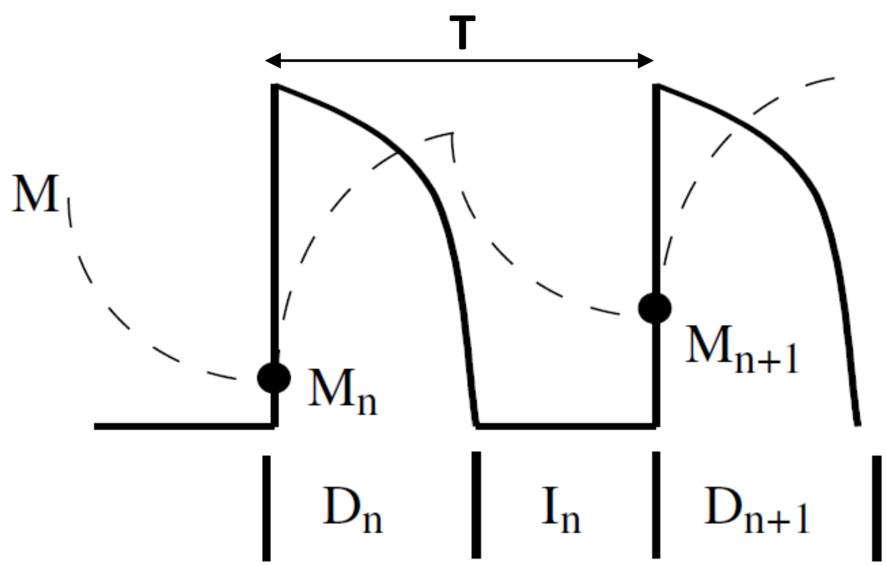


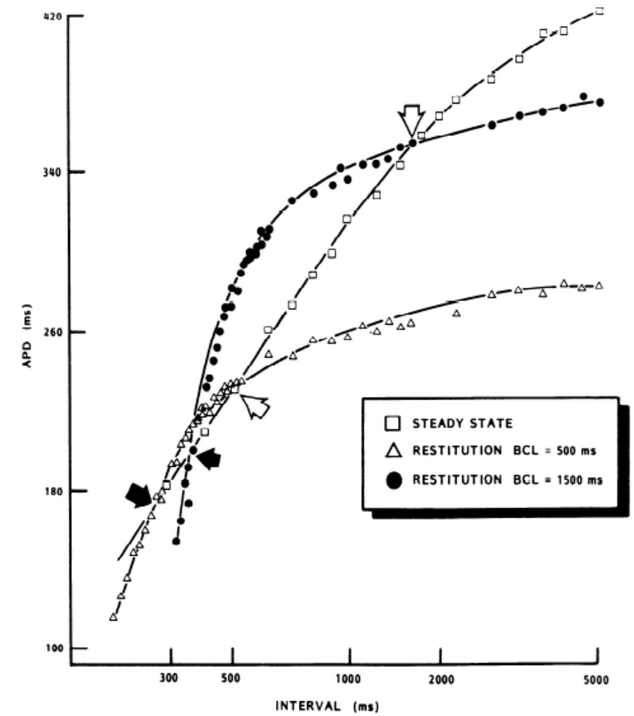
(Elharrar and Surawicz, AJP 1983)

An iterated map model without memory

$$APD_{n+1}=f(DI_n)=f(mT\text{-}APD_n)$$

An iterated map model with memory





$$M_{n+1} = g(M_n, I_n, D_n) = e^{-I_n/\tau}[1 + (M_n - 1)e^{-D_n/\tau}]$$

$$D_{n+1} = f(M_{n+1}, I_n) = (1 - \alpha M_{n+1})\left(A + \frac{B}{1 + e^{-(I_n - C)/D}}\right)$$

$$I_{n+1} = T - D_{n+1}$$

$APD_{n+1} = (1-\alpha M_{n+1})f(DI_n)$

(Fox et al, PRL 2002)

Sources of memory

- **Long-term memory:** protein synthesis, posttranslational regulation

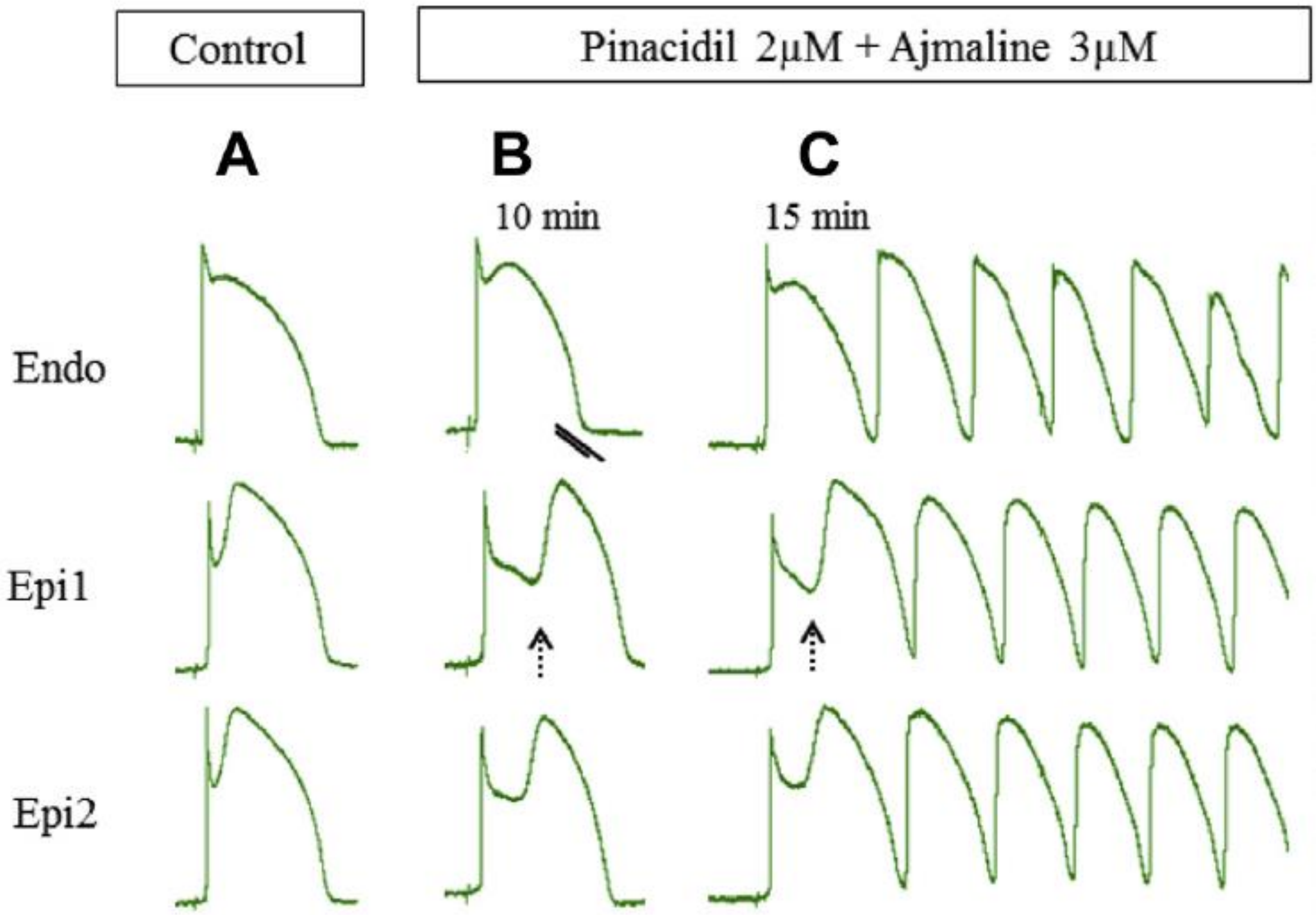
- **Short-term memory:**

1. Slow ion channel recovery: I_{ks}
Time scale: 1-2 sec

2. Slow intracellular ion concentration accumulation: [Ca], [Na]
Time scale: many secs to minutes

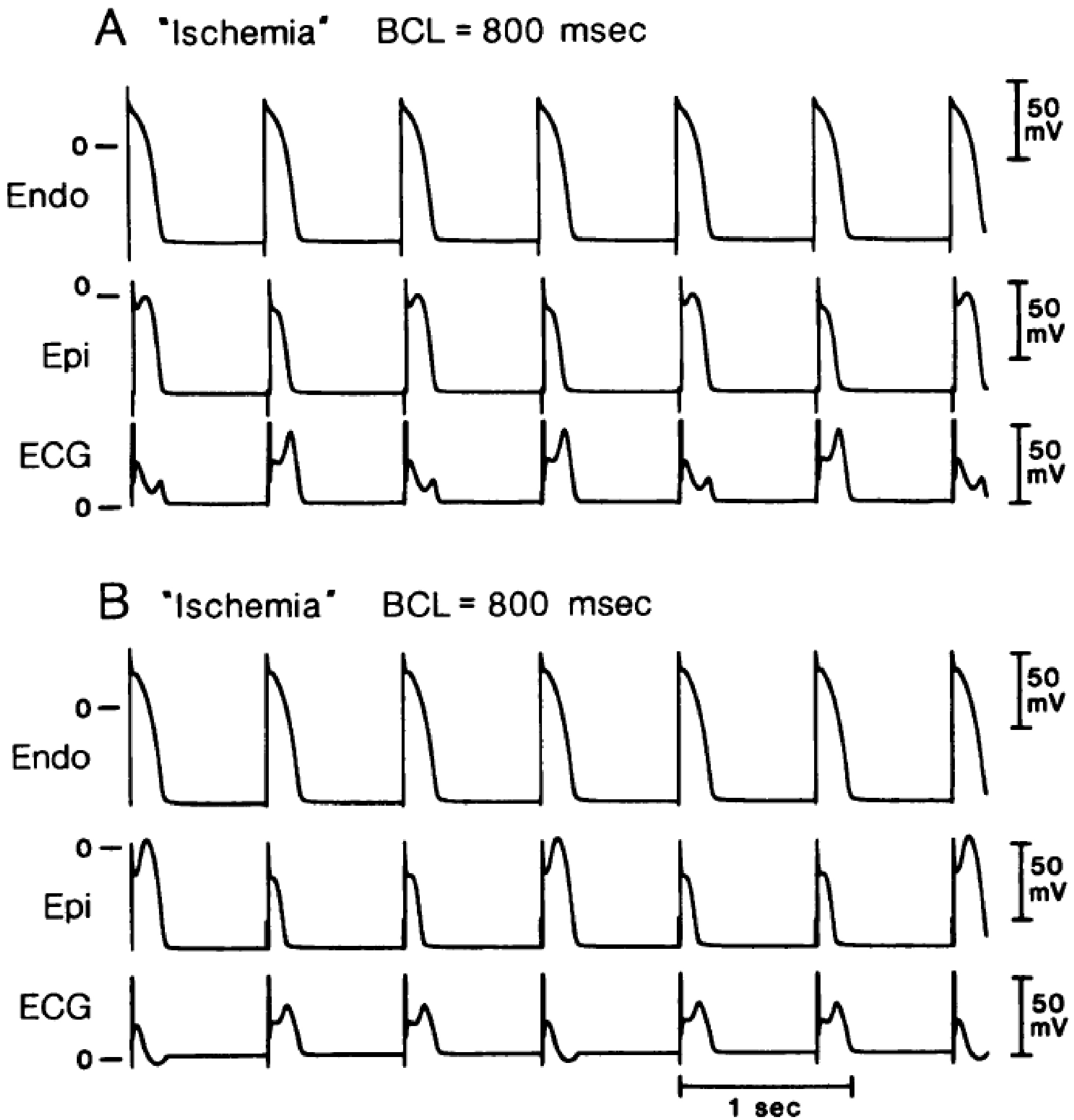
Memory from ion channel recovery

Early repolarization syndrome: Brugada syndrome



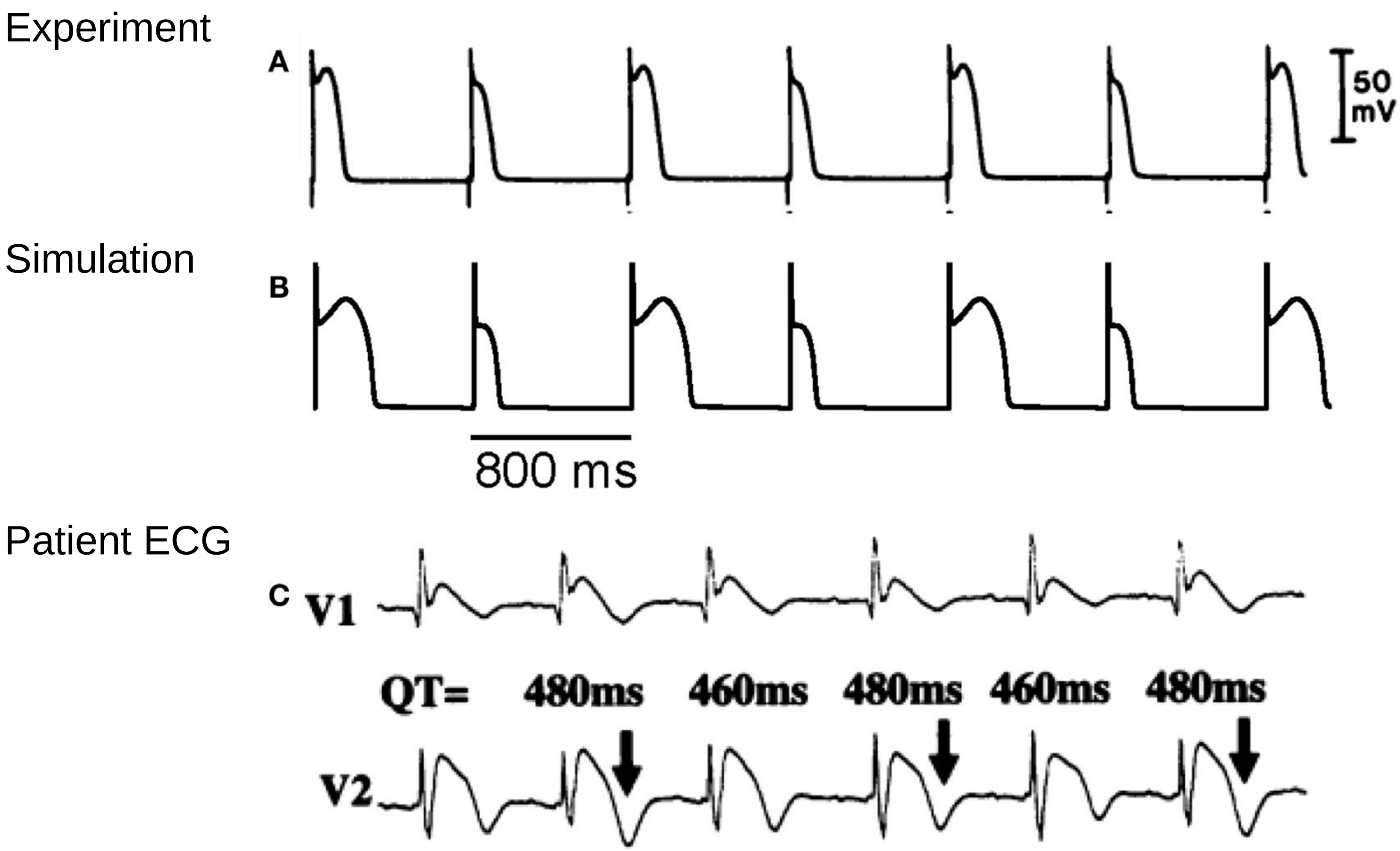
(Patocskai et al, JACC-CE 2017)

Complex APD dynamics in Brugada syndrome



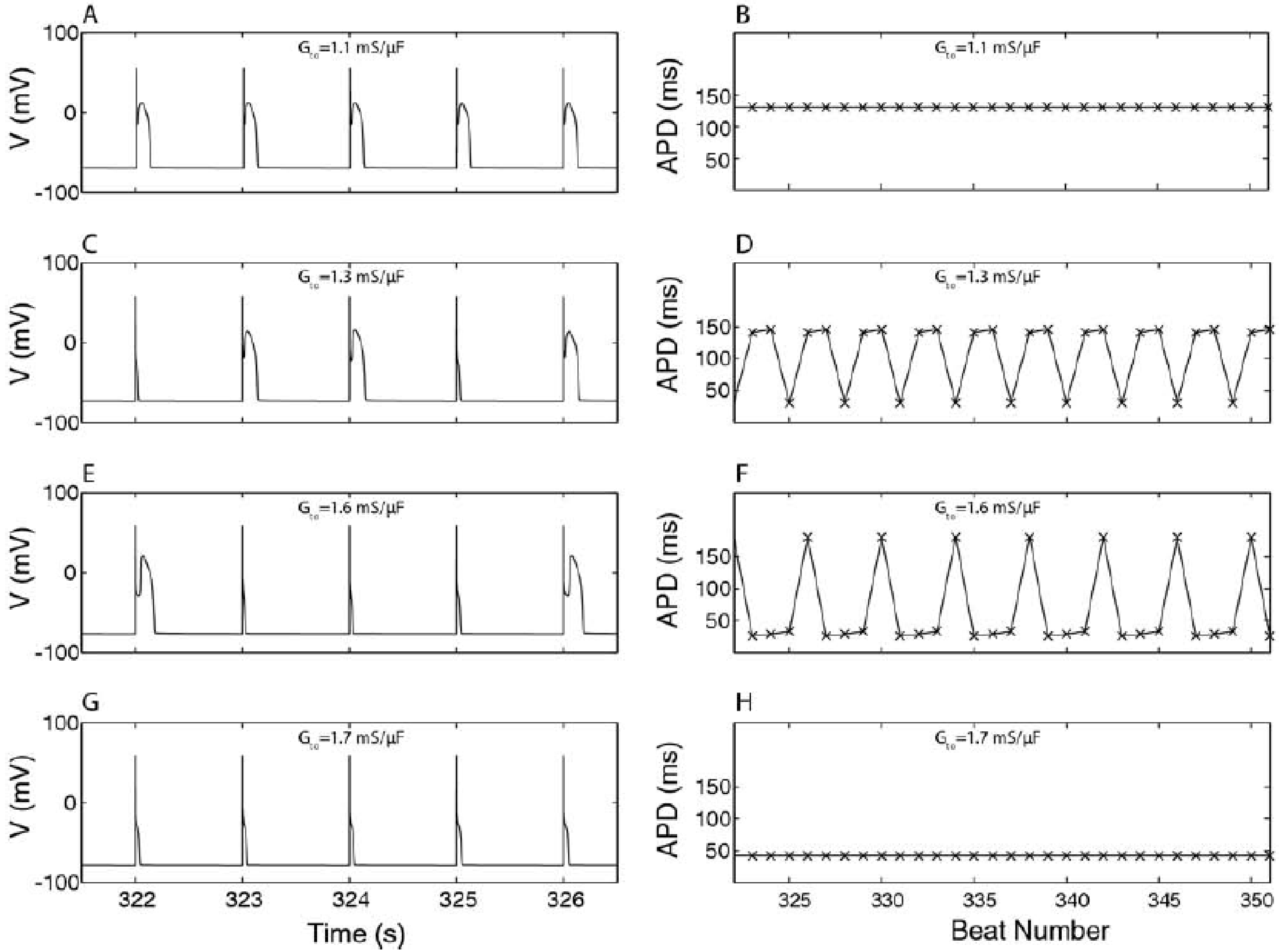
(Lukas & Antzelevitch, Circulation 1993)

T-wave alternans in Brugada syndrome



(Qu et al, Front Physiol, 2010)

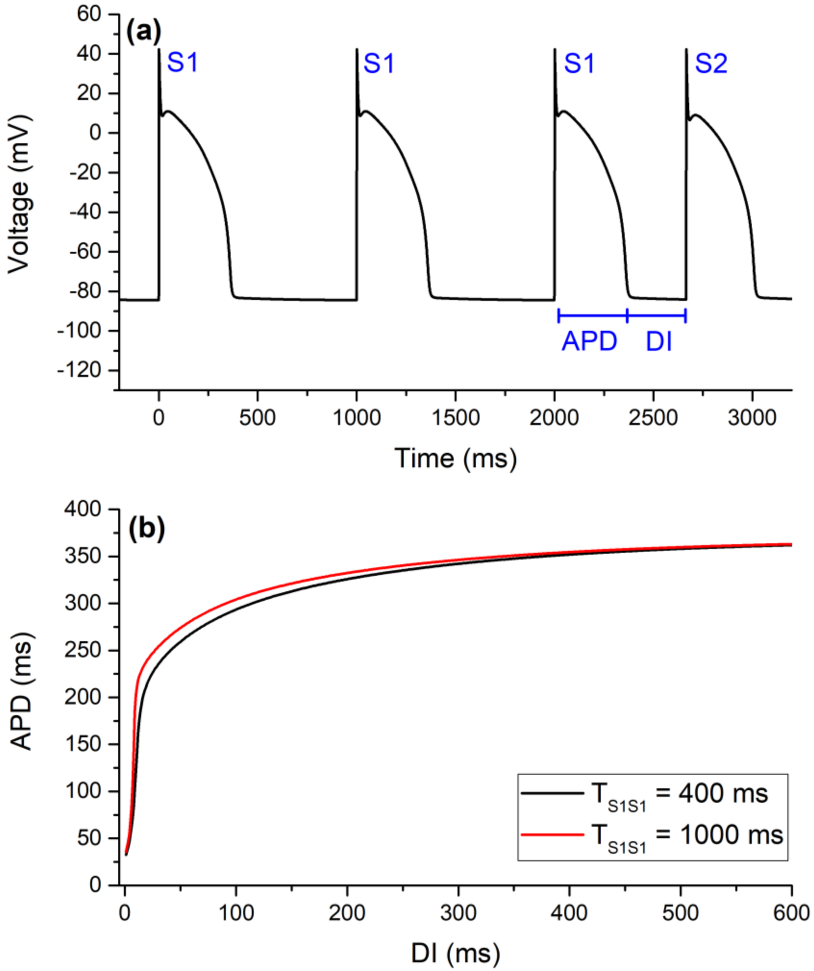
Complex APD dynamics in the presence of Ito

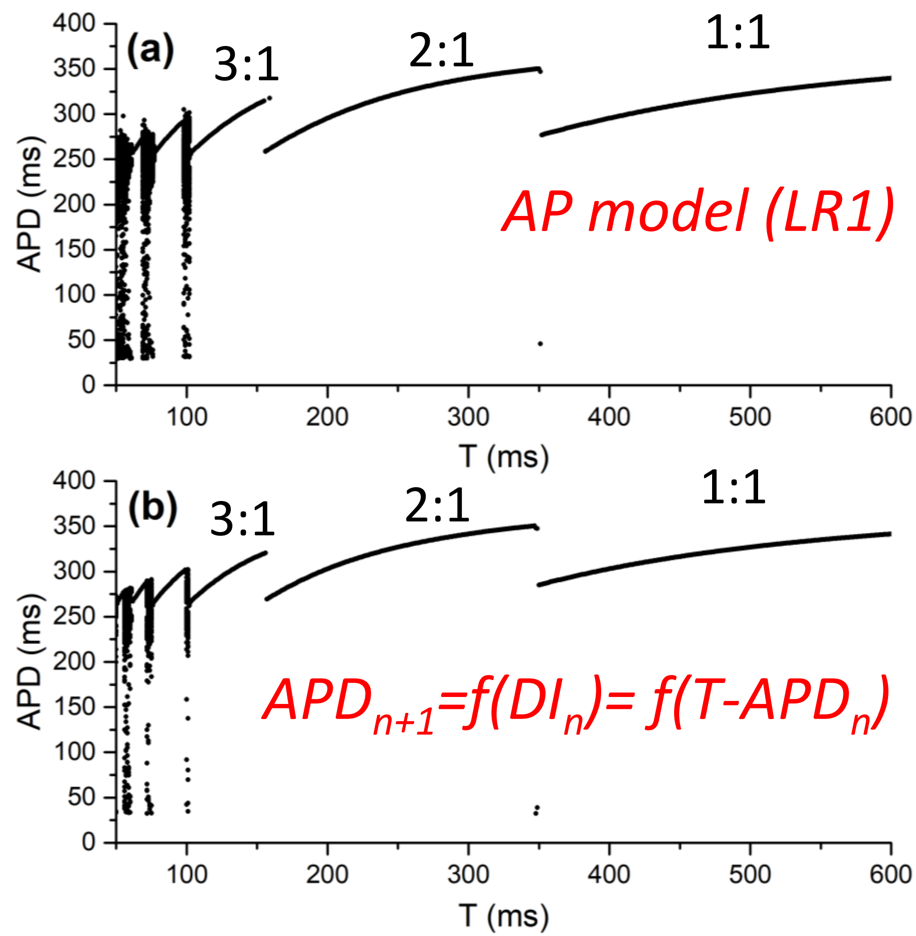


(Maoz et al, Heart Rhythm, 2009)

Unmask/exacerbation of memory by Ito

1991 Luo and Rudy (LR1)





Adding Ito to the LR1 model

LR1

$$I_{\text{ion}} = I_{\text{Na}} + I_{si} + I_K + I_{K1} + I_{Kp} + I_b + I_{to,f},$$

$$I_{\text{to,f}} = g_{\text{to,f}} X_{\text{to,f}} Y_{\text{to,f}} (V - E_{\text{K}})$$

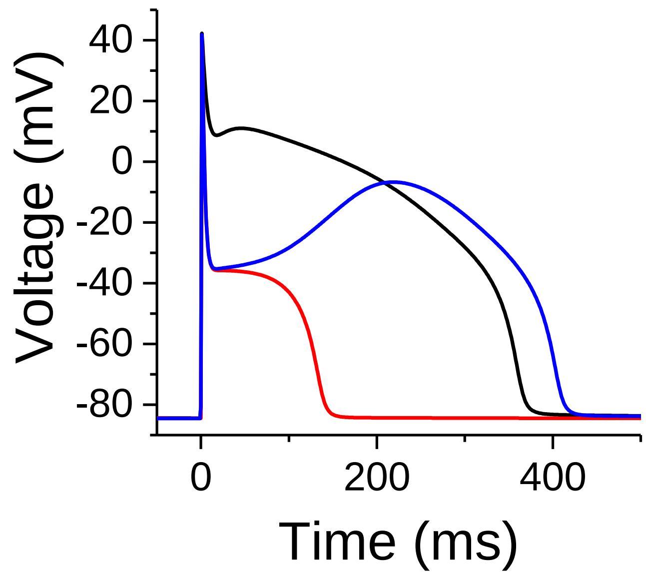
$$X_{\text{to,f}}^{\infty} = \frac{1}{1 + e^{-(\text{V}+3)/15}}$$

$$Y_{\text{to,f}}^{\infty} = \frac{1}{1 + e^{(\text{V}+33.5)/10}}$$

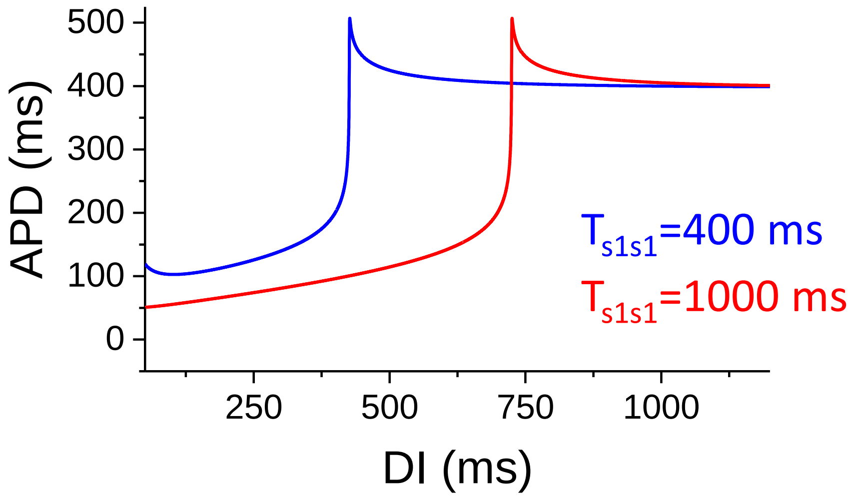
$$\tau_{\text{Xto,f}} = 3.5 e^{-(\text{V}/30)(\text{V}/30)} + 1.5$$ <5 ms

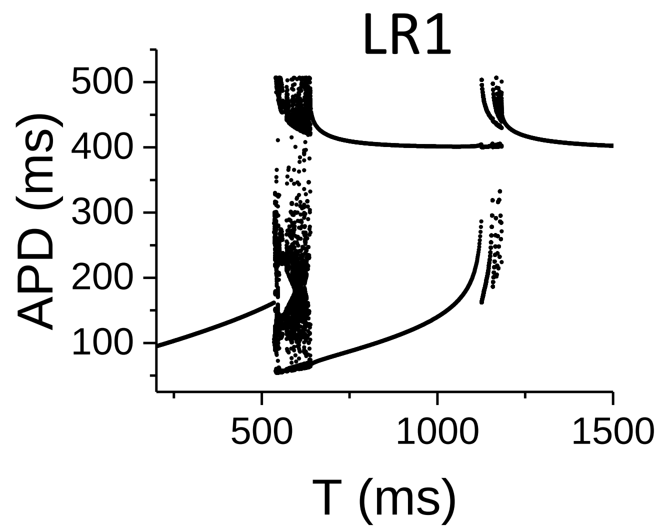
$$\tau_{\text{Yto,f}} = \frac{20}{1 + e^{(\text{V}+33.5)/10}} + 20$$ <40 ms

(Mahajan et al, Biophys J, 2008)

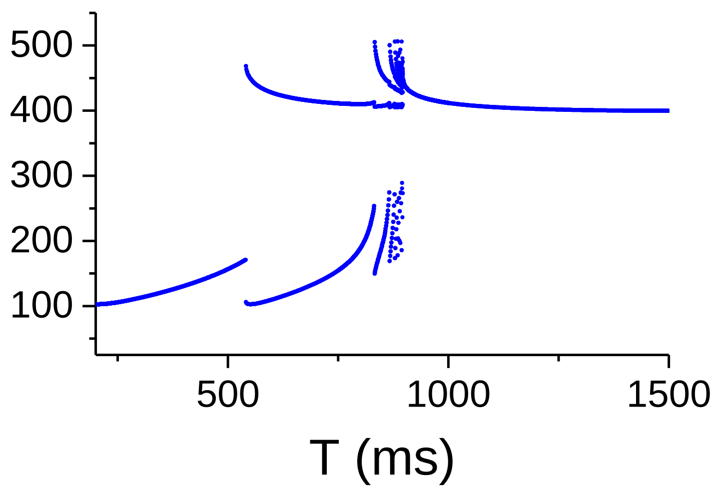


Ito induced memory and chaos





$APD_{n+1}=f(DI_n)= f(T-APD_n)$



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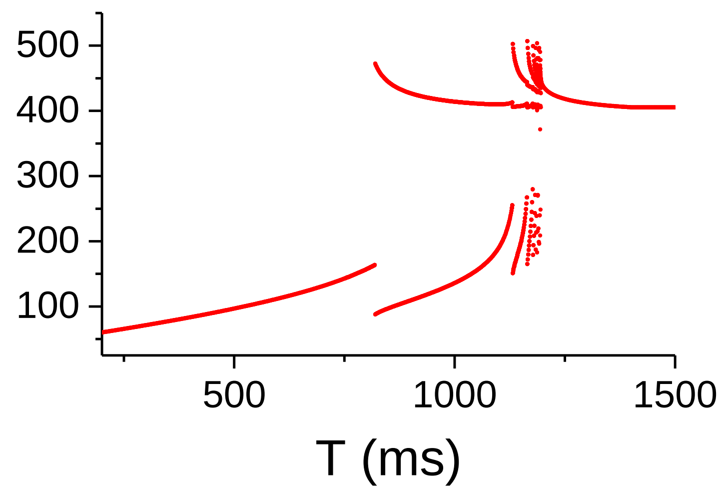

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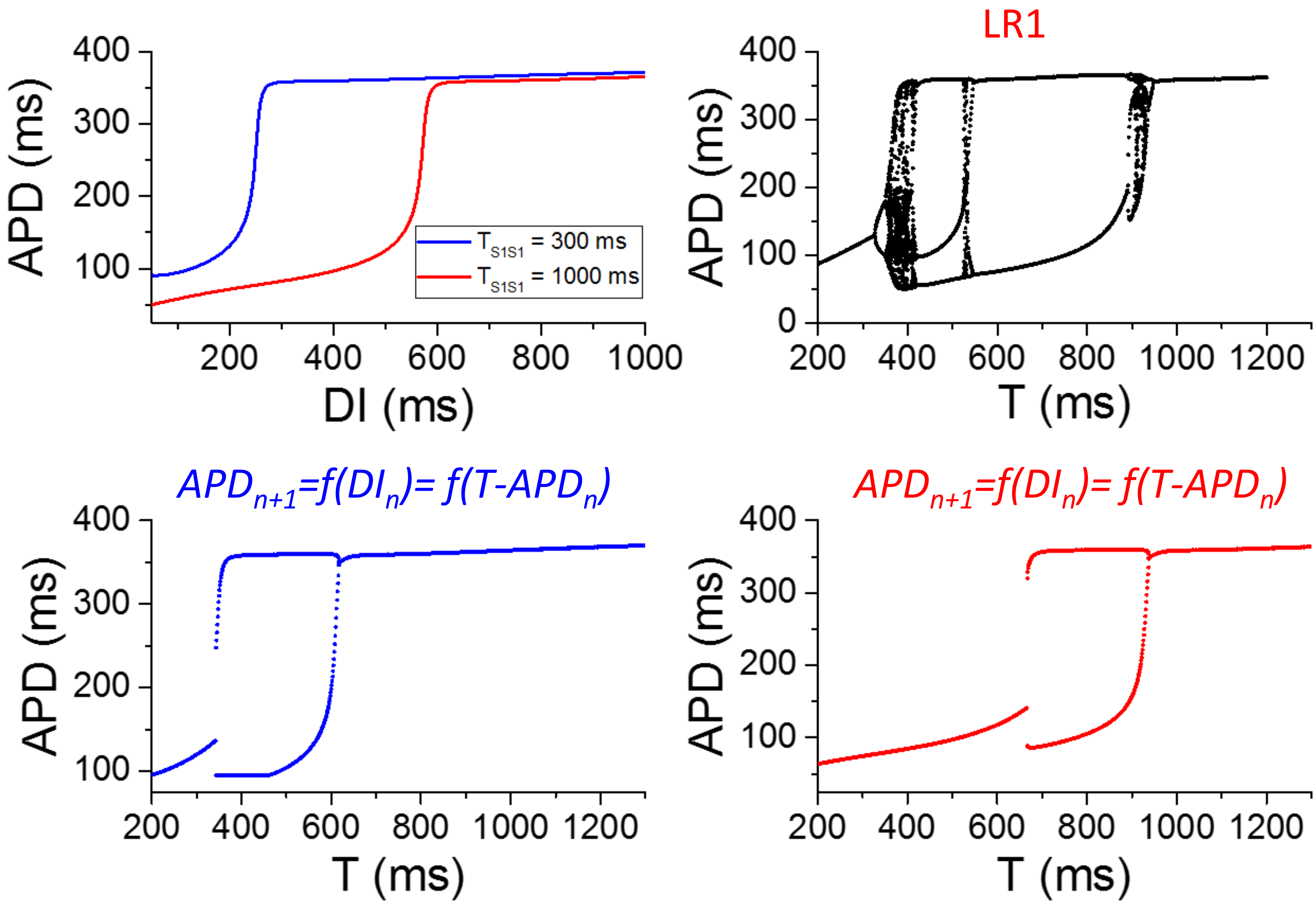
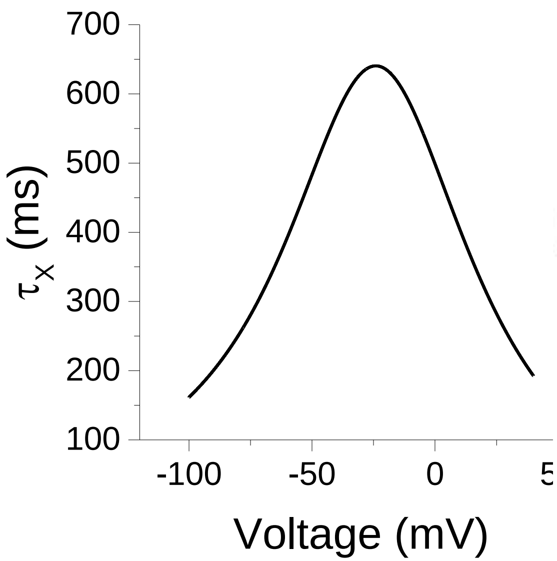
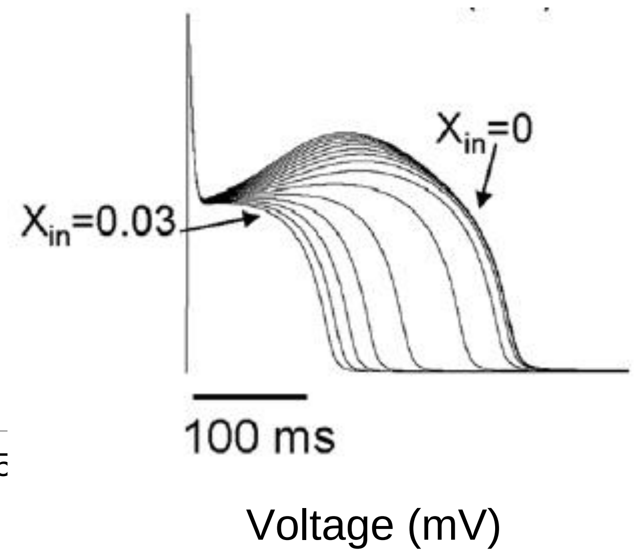
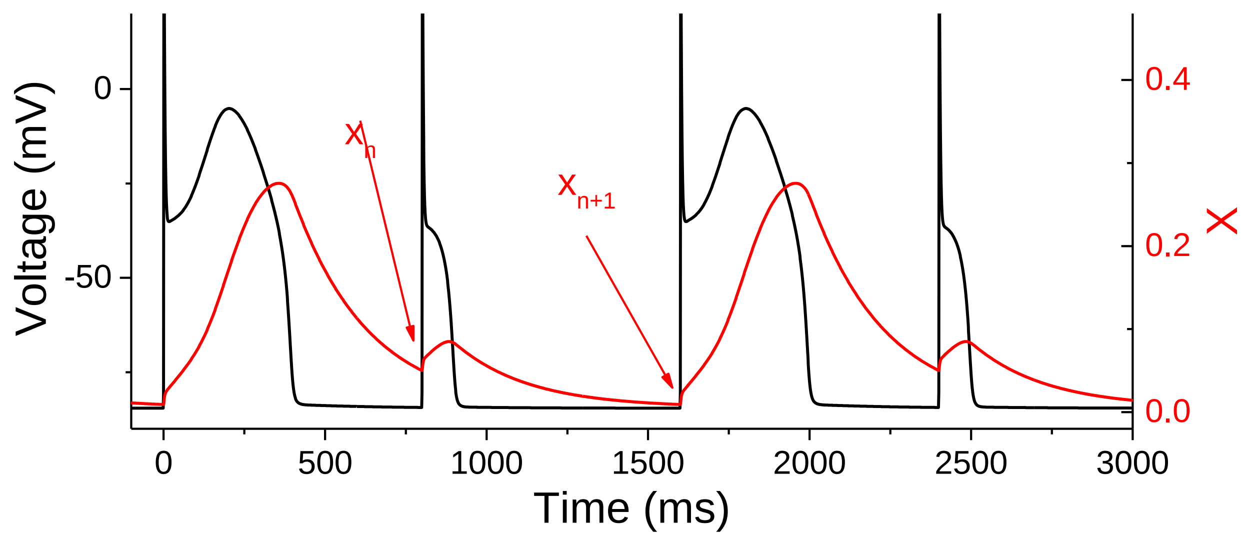


Slow recovery of X-gate is responsible for the memory effect

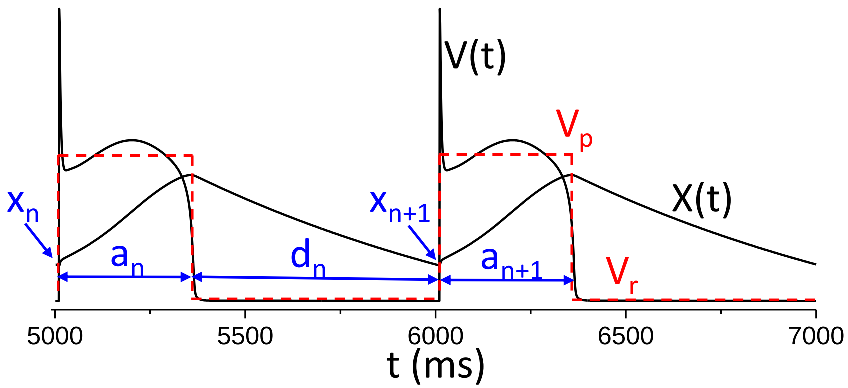




$$\frac{dX}{dt} = \frac{X_\infty - X}{\tau_X}$$



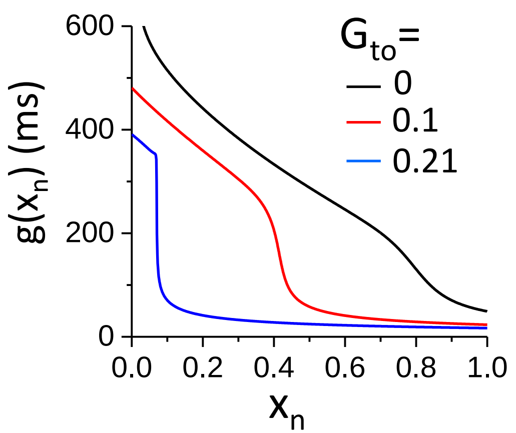
A new iterated map model incorporating memory

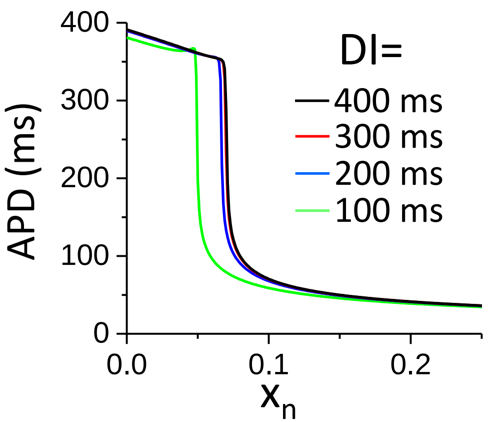


$$\frac{dX}{dt} = \frac{X_\infty - X}{\tau_X}$$

$$x_{n+1} = \left[x_a - (x_a - x_n)e^{-(a_n/\tau_a)}\right]e^{-(d_n/\tau_d)} = w(x_n, a_n)$$

$$a_{n+1} = g(x_{n+1}, d_n) \longrightarrow a_{n+1} = g(x_{n+1})$$

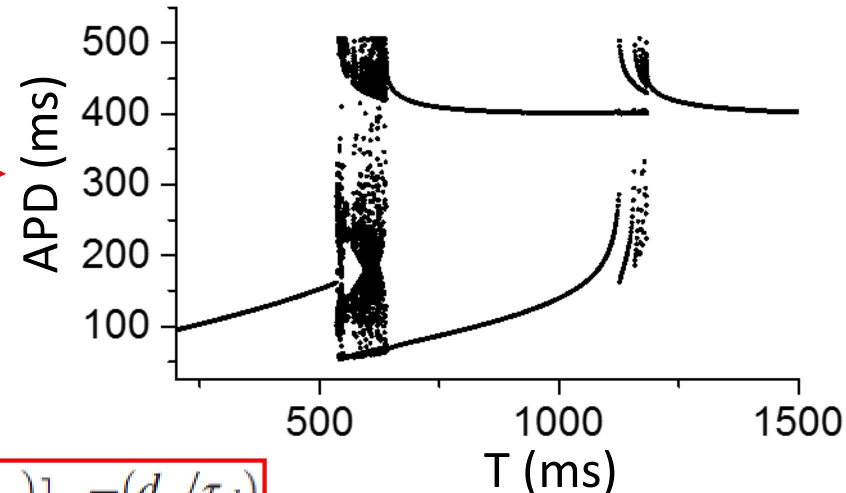




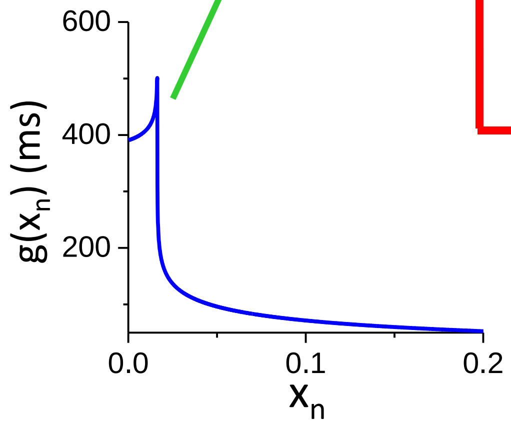
Recapitulate the bifurcations by the new iterated map model

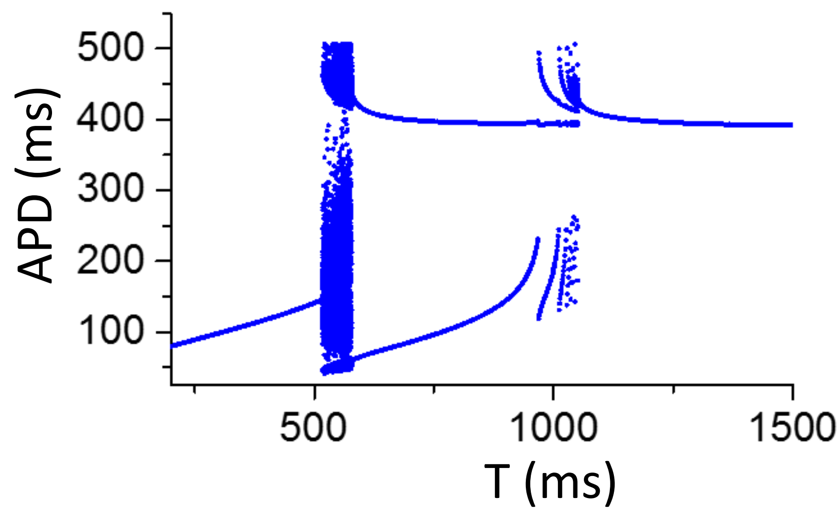
$$C_m \frac{dV}{dt} = -I_{\text{ion}} + I_{\text{sti}}$$

$LR1+I_{to}$



$$x_{n+1} = [x_a - (x_a - x_n)e^{-(a_n/\tau_a)}]e^{-(d_n/\tau_d)}$$
$$a_{n+1} = g(x_{n+1})$$

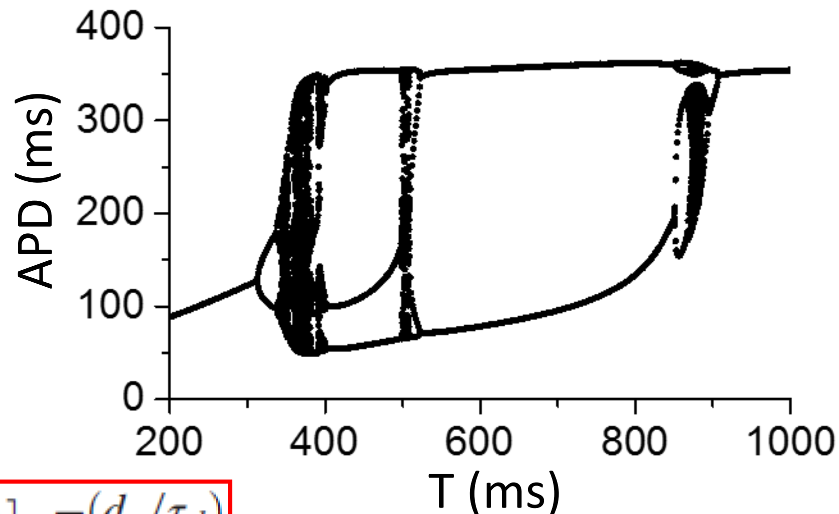




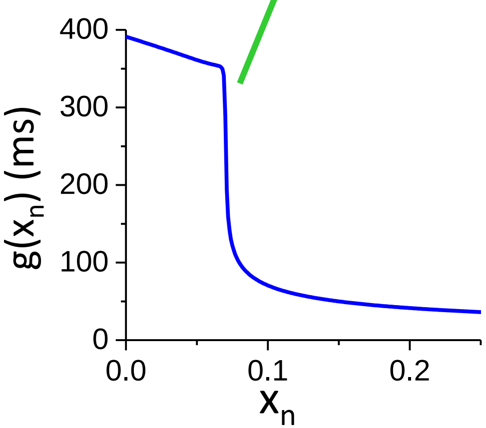
Recapitulate the bifurcations by the new iterated map model

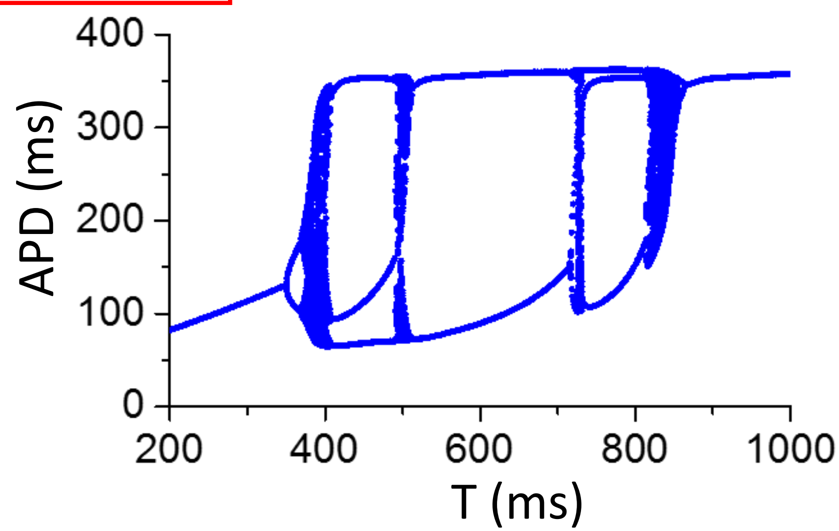
$$C_m \frac{dV}{dt} = -I_{\text{ion}} + I_{\text{sti}}$$

$LR1_m + I_{to}$



$$x_{n+1} = [x_a - (x_a - x_n)e^{-(a_n/\tau_a)}]e^{-(d_n/\tau_d)}$$
$$a_{n+1} = g(x_{n+1})$$





Mechanistic insights from the new iterated map model

$$x_{n+1} = [x_a - (x_a - x_n)e^{-(a_n/\tau_a)}]e^{-(d_n/\tau_d)} = w(x_n, a_n)$$

$$a_{n+1} = g(x_{n+1}, d_n)$$

$$a_{n+1} = g(x_{n+1}) \longrightarrow x_n = g^{-1}(a_n)$$

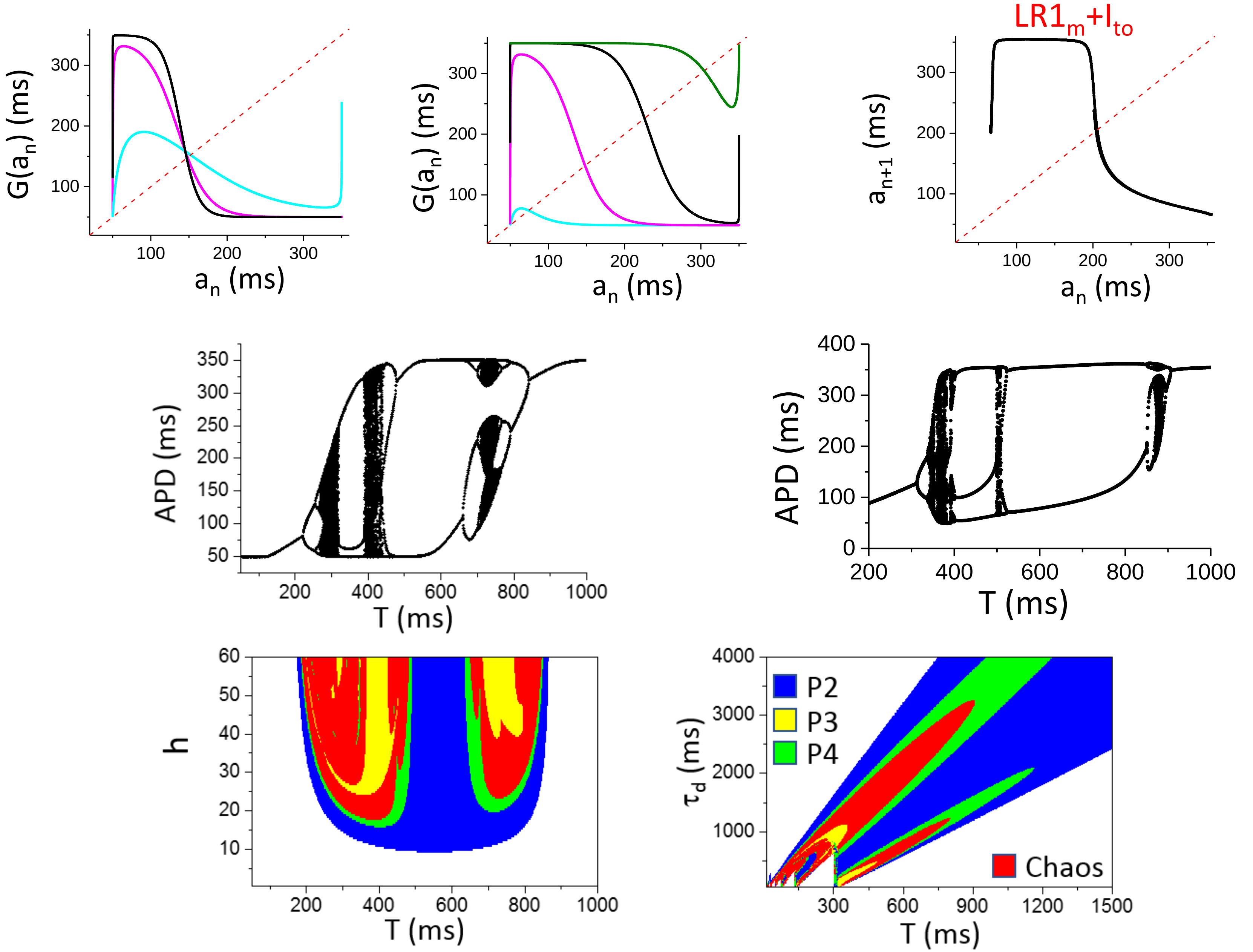
$$x_{n+1} = w[g^{-1}(a_n), a_n]$$

$$a_{n+1} = g\{w[g^{-1}(a_n), a_n]\} = G(a_n)$$

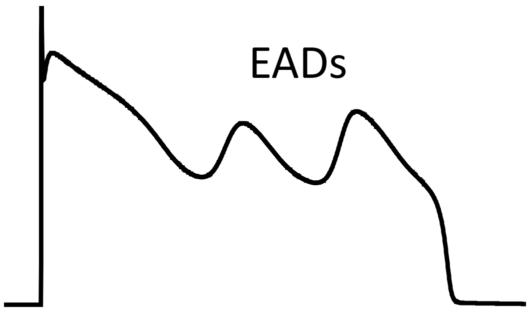
$$a_n = g(x_n) = a_{\min} + \frac{a_{\max} - a_{\min}}{1 + \left(\frac{x_n}{k_x}\right)^h}$$

$$x_n = g^{-1}(a_n) = k_x \left[\frac{a_{\max} - a_n}{a_n - a_{\min}}\right]^{1/h}$$

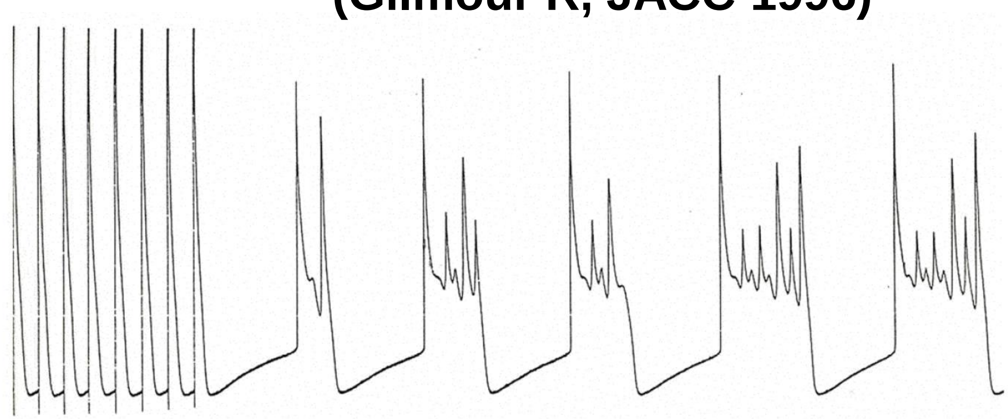
Mechanistic insights from the new iterated map model



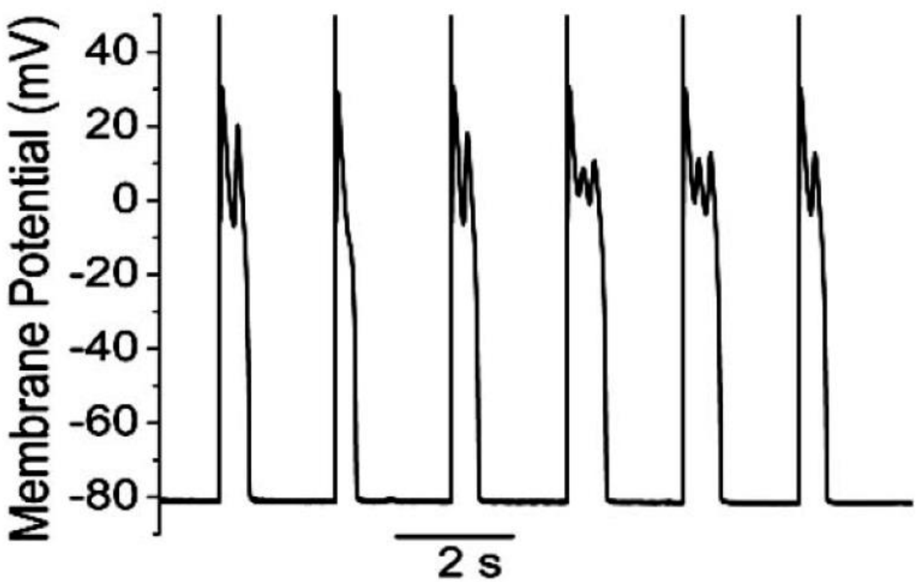
Reduced repolarization reserve: long QT syndrome

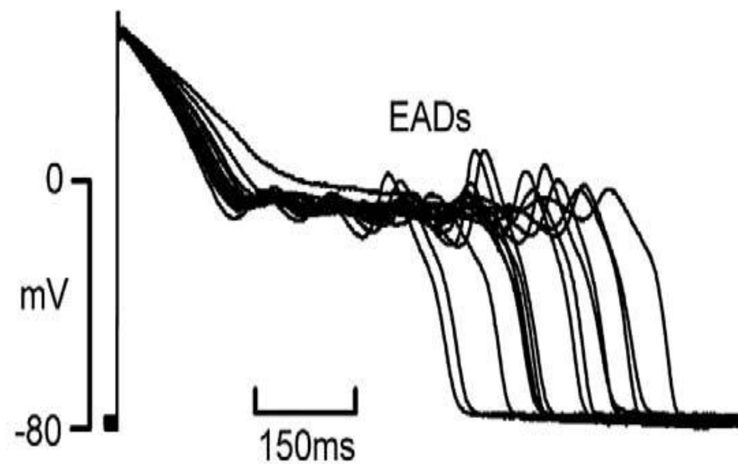


(Gilmour R, JACC 1996)



(Sridhar A, Am J Physiol 2008)

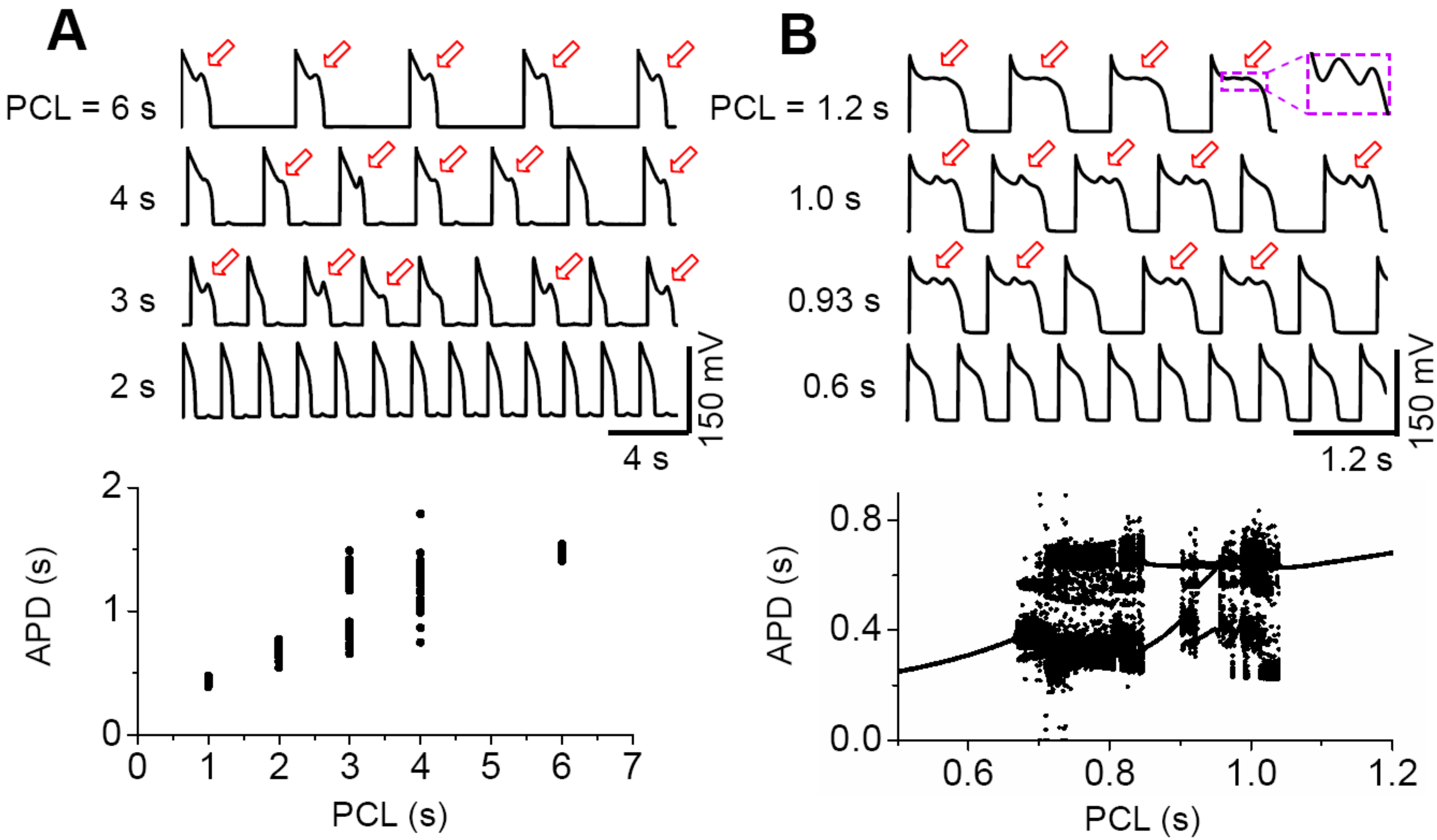




Chaotic EADs in ventricular myocytes

Isolated rabbit ventricular myocyte exposed to 1 mM H_2O_2.

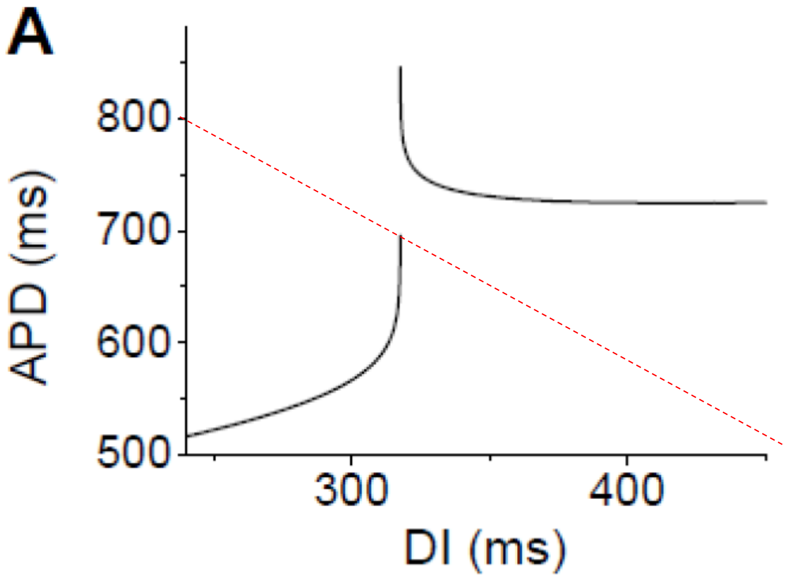
Computational model
(UCLA rabbit ventricular model with modifications)

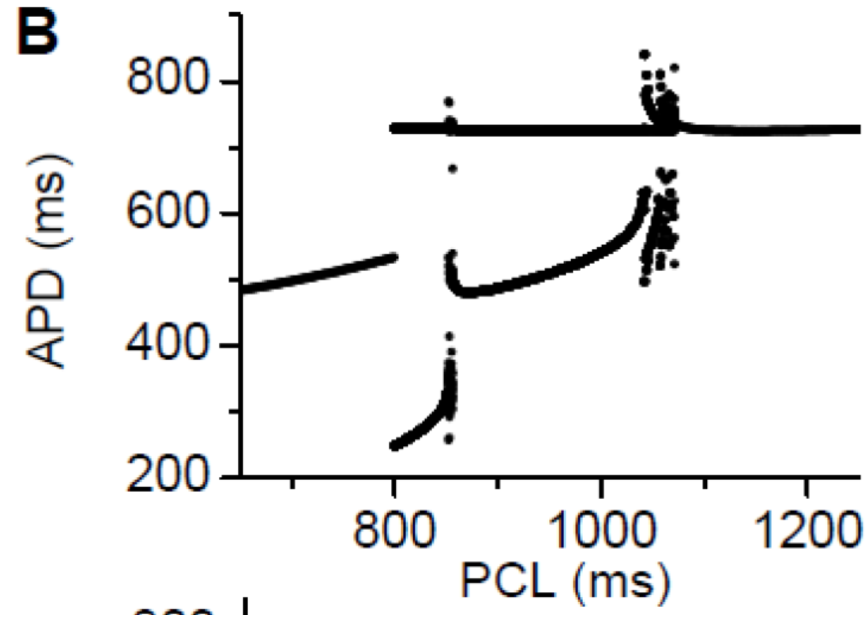


(Sato, et al., PNAS 2009)

What is the dynamical mechanism of EAD chaos?

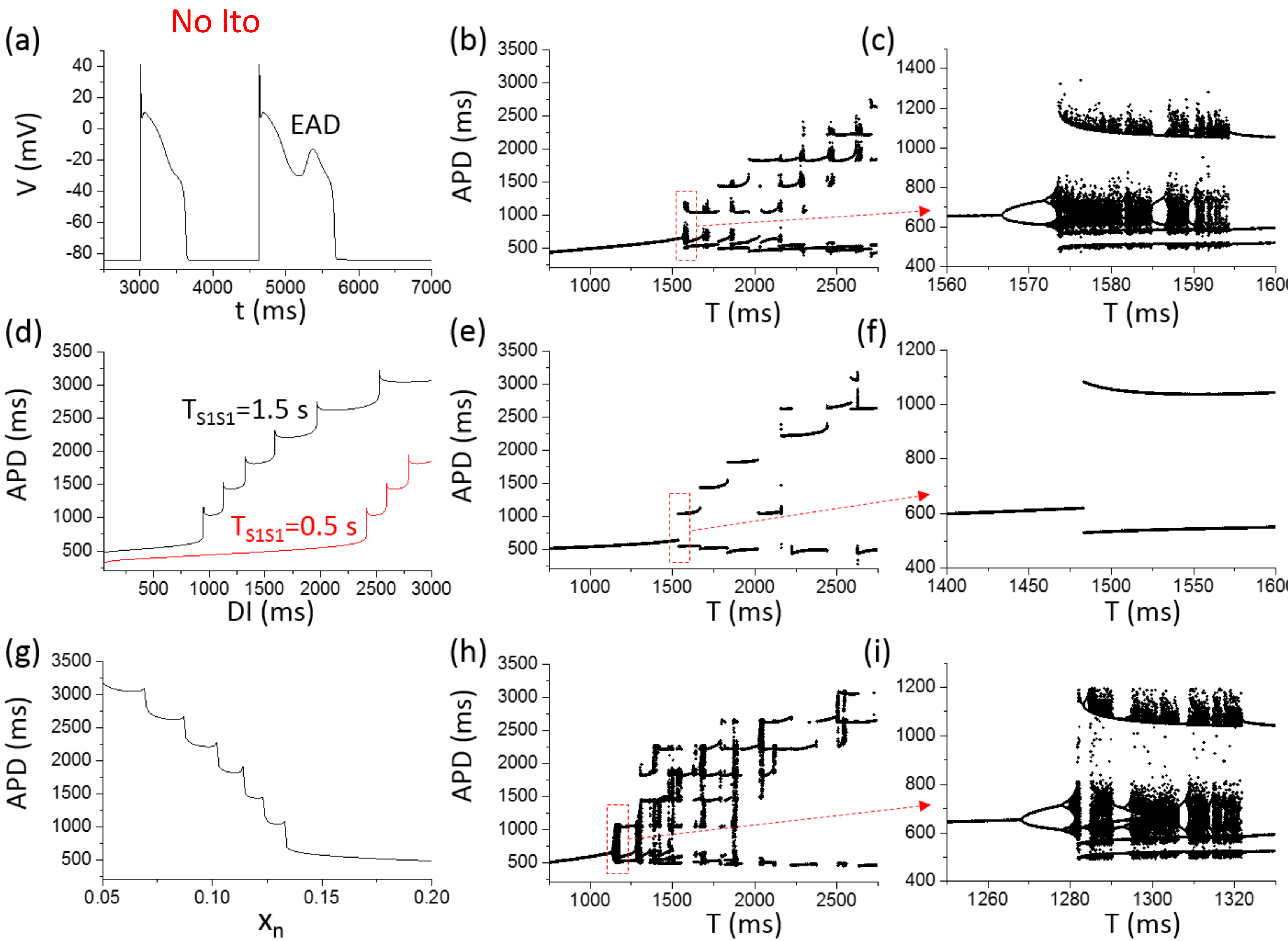
$$APD_{n+1}=f(DI_n)= f(T\text{-}APD_n)$$





(Sato et al, Biophys J 2010)

Memory under reduced repolarization reserve



Summary

Memory due to slow ion channel recovery (namely IKs) plays important roles in inducing complex APD dynamics (high periodicity and chaos) in either early repolarization syndrome (BrS) or reduced repolarization reserve (LQTS and HF). Memory promotes instabilities instead of suppressing instabilities.

Memory from intracellular ion accumulation

TP04 (Ten Tusscher et al, AJP Heart 2004)

Memory caused by intracellular Ca accumulation

$$I_{\text{ion}} = I_{\text{Na}} + I_{\text{K1}} + I_{\text{to}} + I_{\text{Kr}} + I_{\text{Ks}} + I_{\text{CaL}} + I_{\text{NaCa}} + I_{\text{NaK}} + I_{\text{pCa}} + I_{\text{pK}} + I_{\text{bCa}} + I_{\text{bNa}}$$

$$I_{\text{to,f}} = g_{\text{to,f}} X_{\text{to,f}} Y_{\text{to,f}} (V - E_{\text{K}})$$

$$X_{\text{to,f}}^{\infty} = \frac{1}{1 + e^{-(\text{V}+3)/15}}$$

$$Y_{\text{to,f}}^{\infty} = \frac{1}{1 + e^{(\text{V}+33.5)/10}}$$

$$\tau_{\text{Xto,f}} = 3.5 e^{-(\text{V}/30)(\text{V}/30)} + 1.5$$ <5 ms

$$\tau_{\text{Yto,f}} = \frac{20}{1 + e^{(\text{V}+33.5)/10}} + 20$$ <40 ms

(Mahajan et al, Biophys J, 2008)

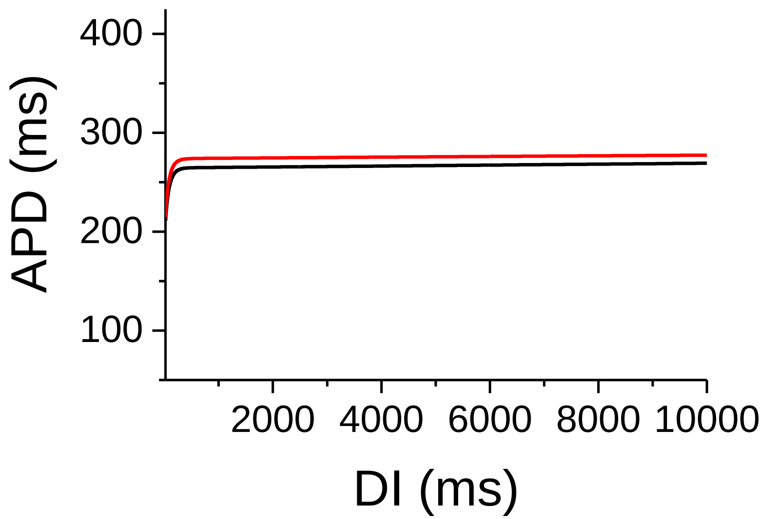
Recover quickly, no contribution to memory.

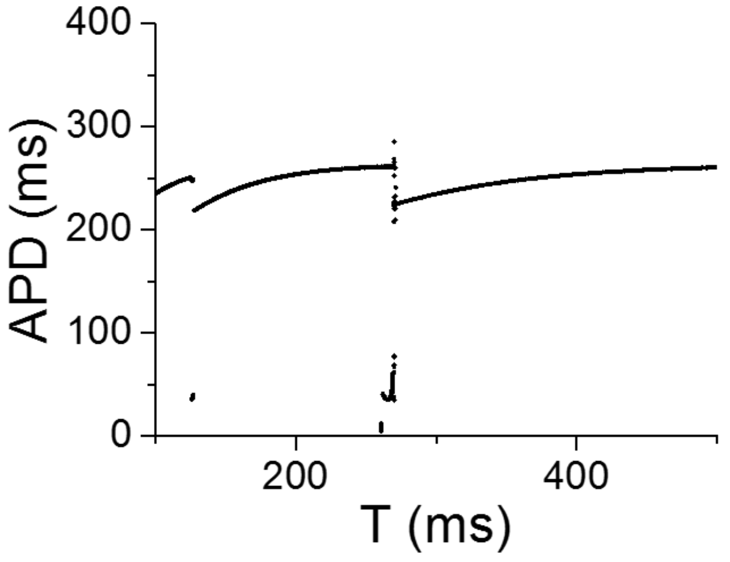
$[\text{Na}]_i$=constant

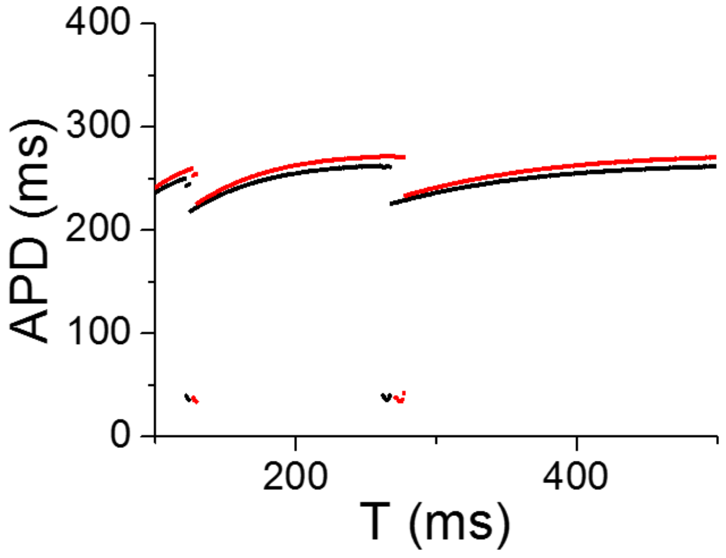
Source of Memory:

$[\text{Ca}]_i$

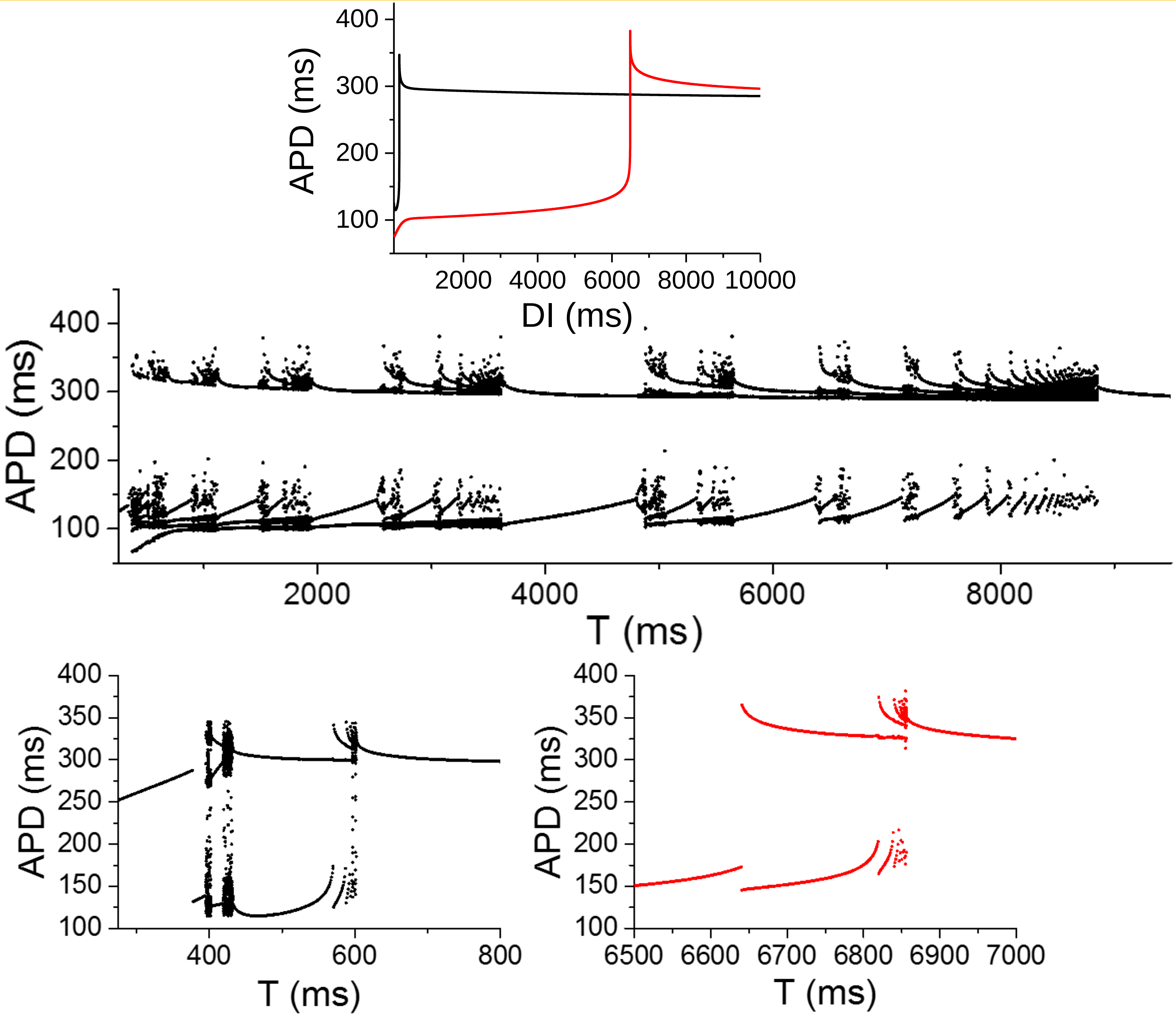
TP04 without Ito



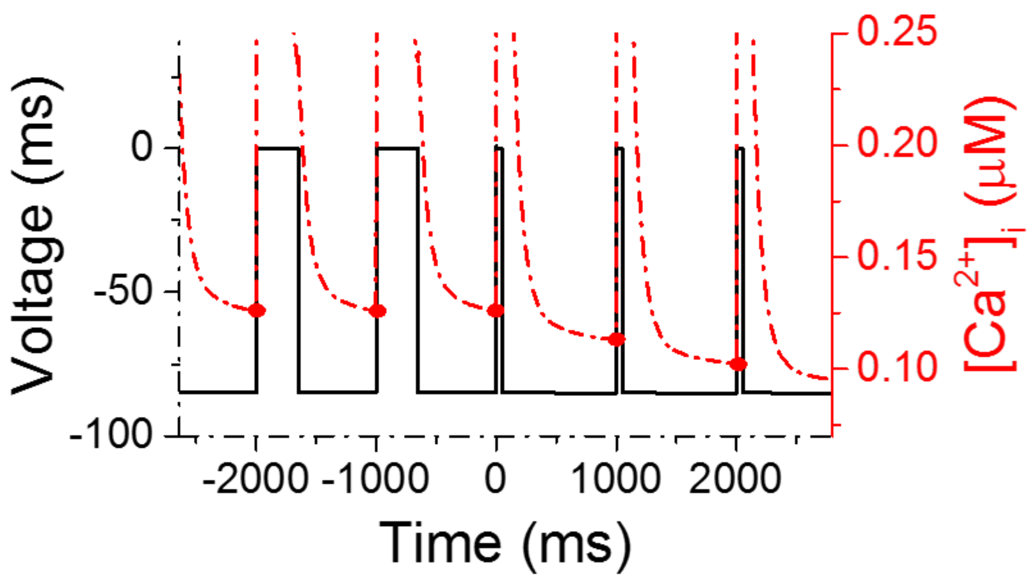


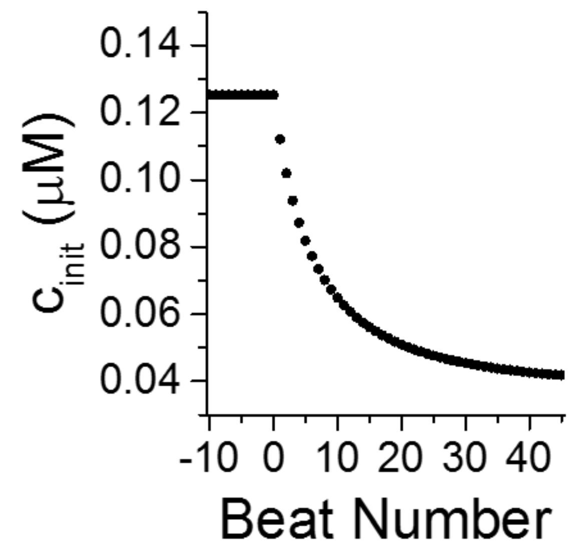


TP04 with Ito



An iterated map model with Ca^{2+} accumulation memory



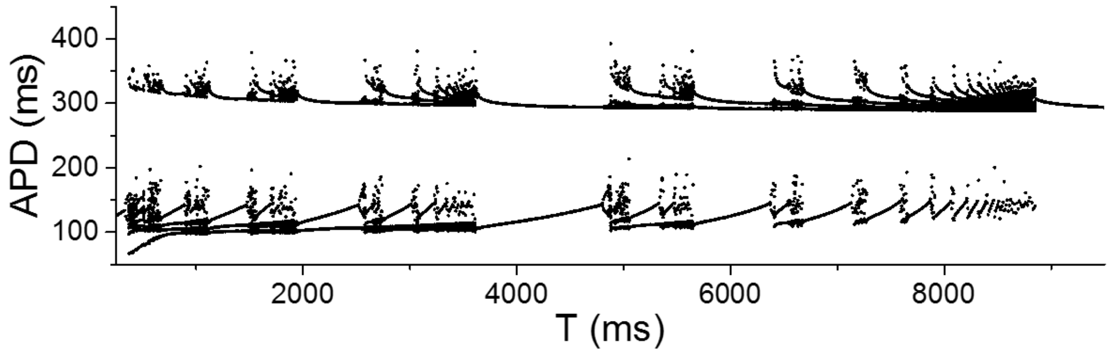


$$c_{n+1} - c^* = (c_n - c^*)\exp[f(a_n)],$$

$$c_{n+1} = c_n \exp[f(a_n)] + c^*\{1 - \exp[f(a_n)]\},$$

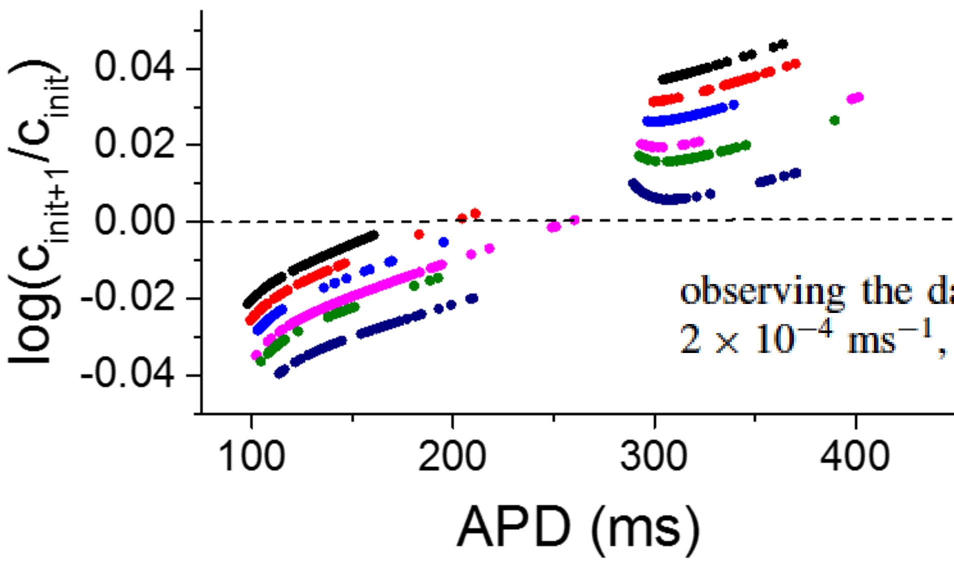
$$c_{n+1} = c_n \exp[f(a_n)]$$

An iterated map model with Ca^{2+} accumulation memory



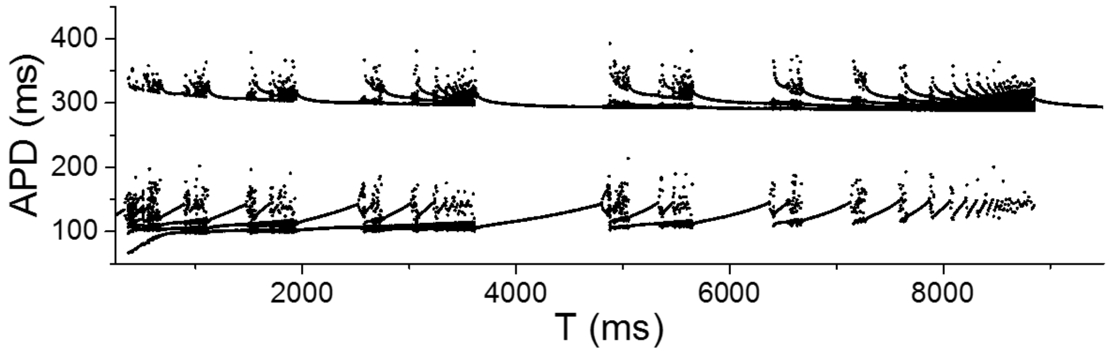
$$\ln\left(\frac{c_{\text{init}+1}}{c_{\text{init}}}\right) = f(\text{APD}) \approx \gamma_a \text{APD} - \gamma_T T + \delta,$$

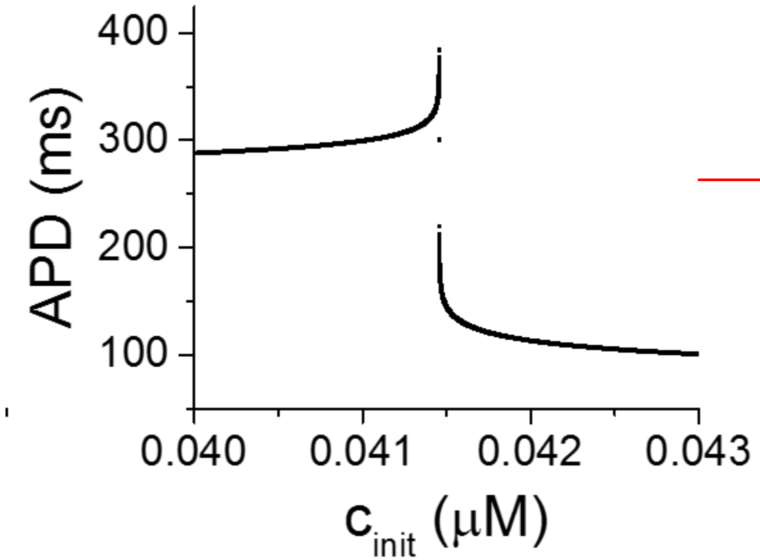
$$c_{n+1} = c_n \exp[f(a_n)] = c_n \exp[\gamma_a a_n - \gamma_T T + \delta].$$



observing the data in Fig. 18(c). We obtain the values $\gamma_a = 2 \times 10^{-4}$ ms^{-1}, $\gamma_T = 3.625 \times 10^{-6}$ ms^{-1}, and $\delta = -0.0275$.

A new map with Ca^{2+} accumulation memory



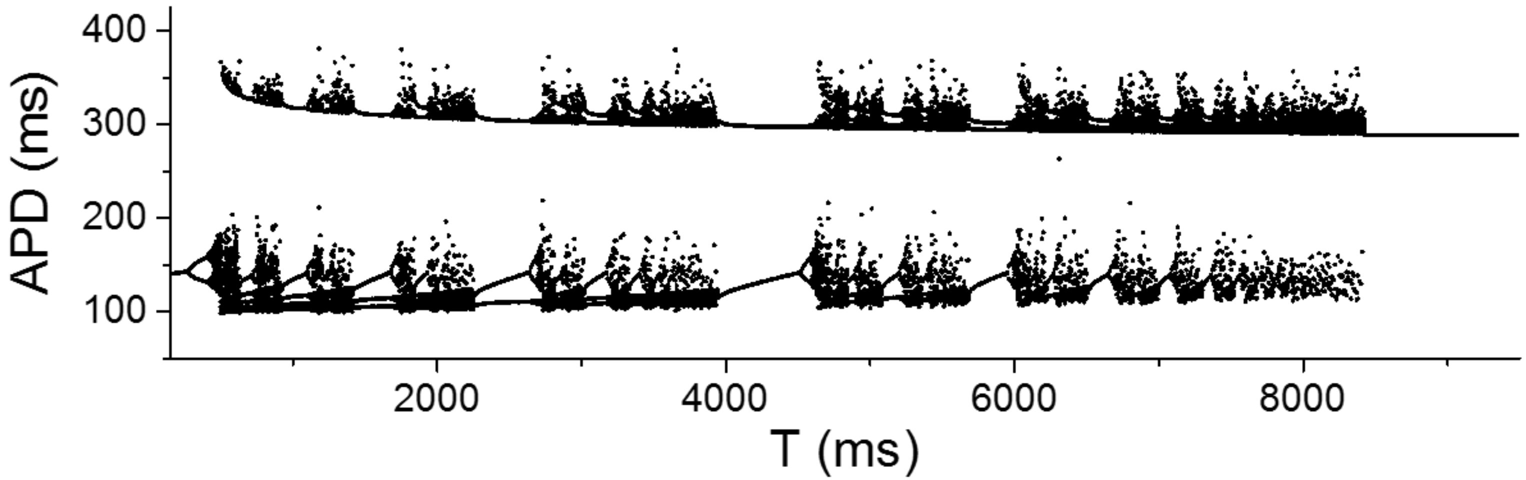


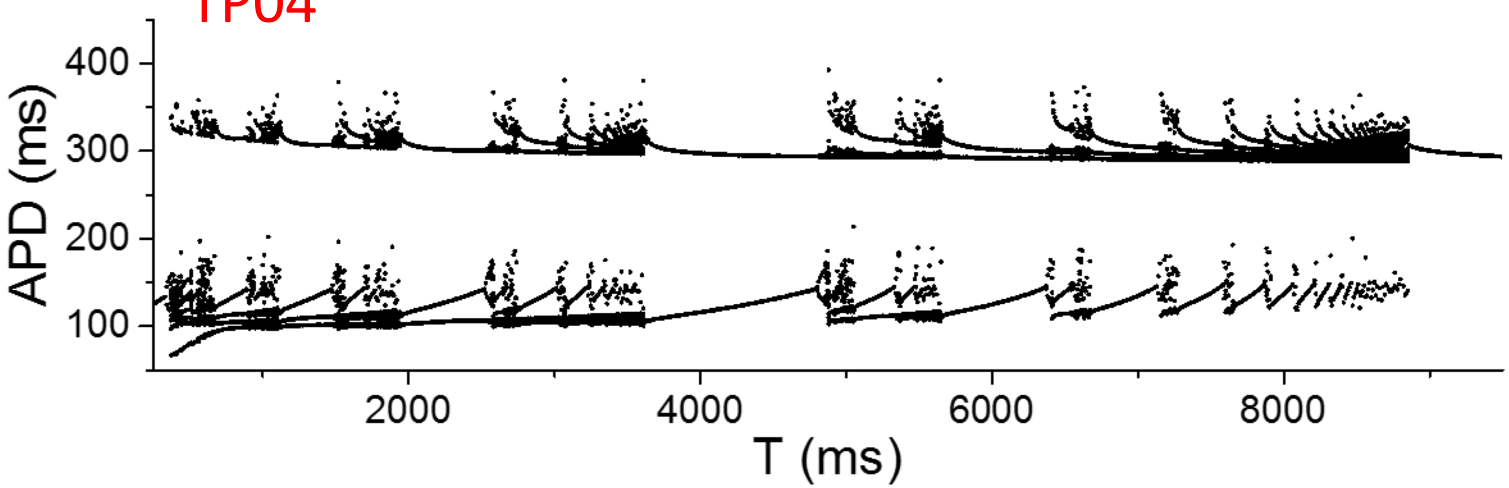
$$a_n = g(c_n).$$

An iterated map model with Ca^{2+} accumulation memory

$$c_{n+1} = c_n \exp[f(a_n)] = c_n \exp[\gamma_a a_n - \gamma_T T + \delta]$$

$$a_n = g(c_n)$$



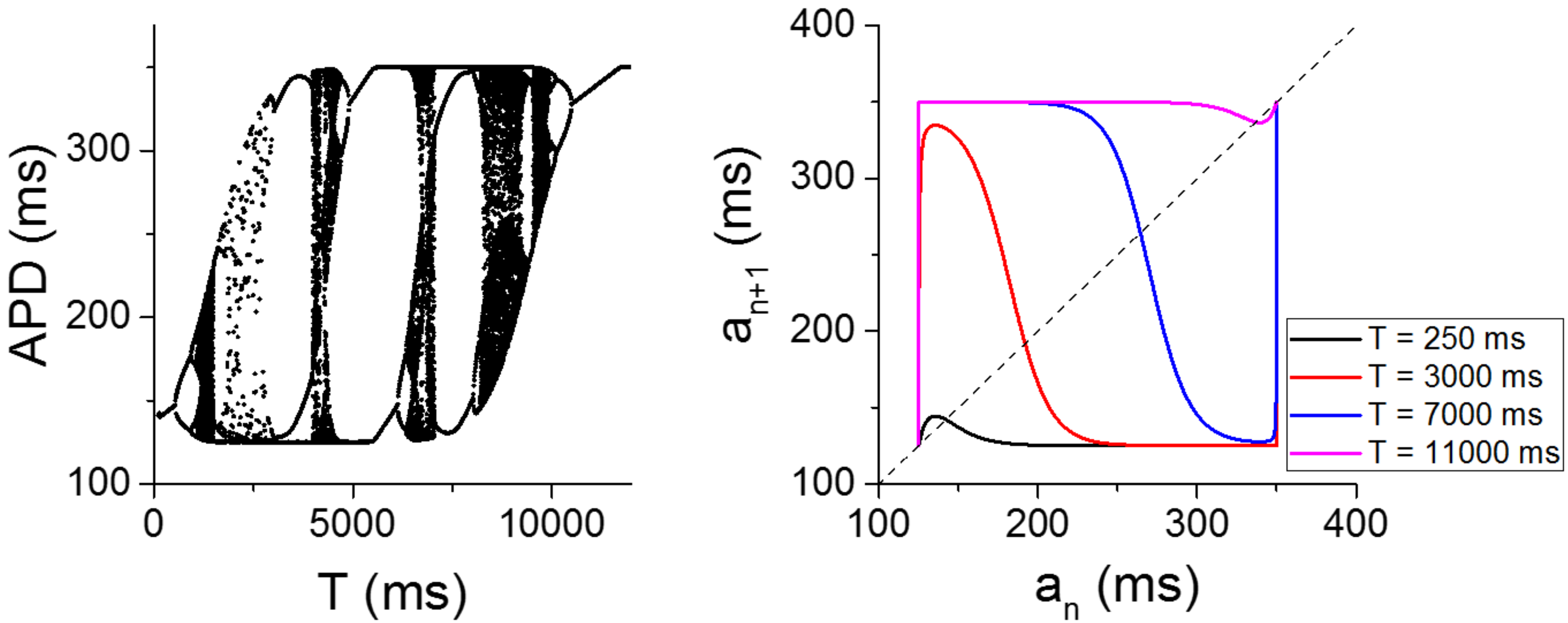


Theoretical prediction of the iterated map model

$$c_{n+1} = c_n \exp[f(a_n)] = c_n \exp[\gamma_a a_n - \gamma_T T + \delta]$$

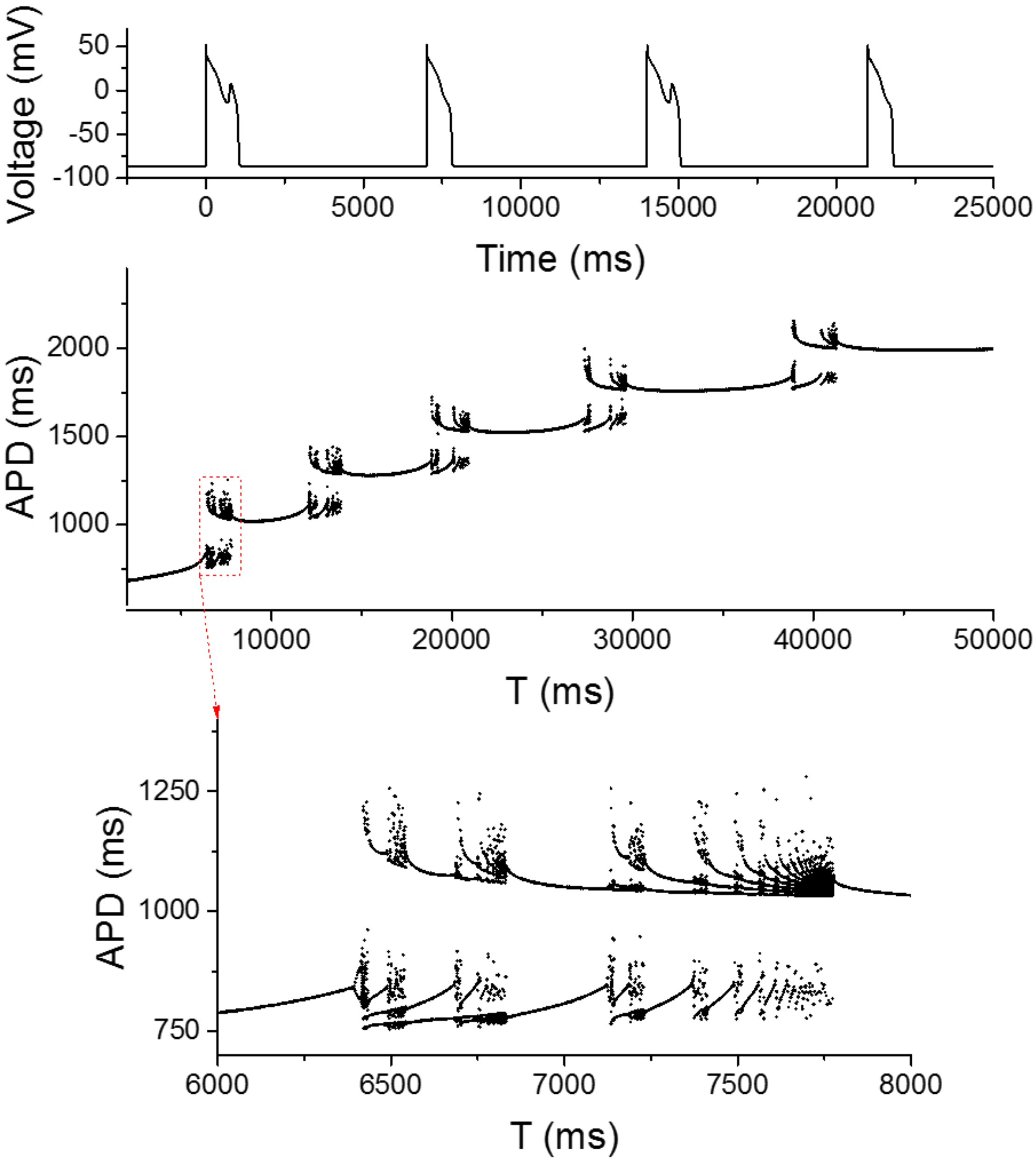
$$a_n = g(c_n) = a_{\min} + \frac{a_{\max} - a_{\min}}{1 + \left(\frac{c_n}{k_c}\right)^h}$$

$$x_{n+1} = [x_a - (x_a - x_n)e^{-(a_n/\tau_a)}]e^{-(d_n/\tau_d)} = w(x_n, a_n)$$

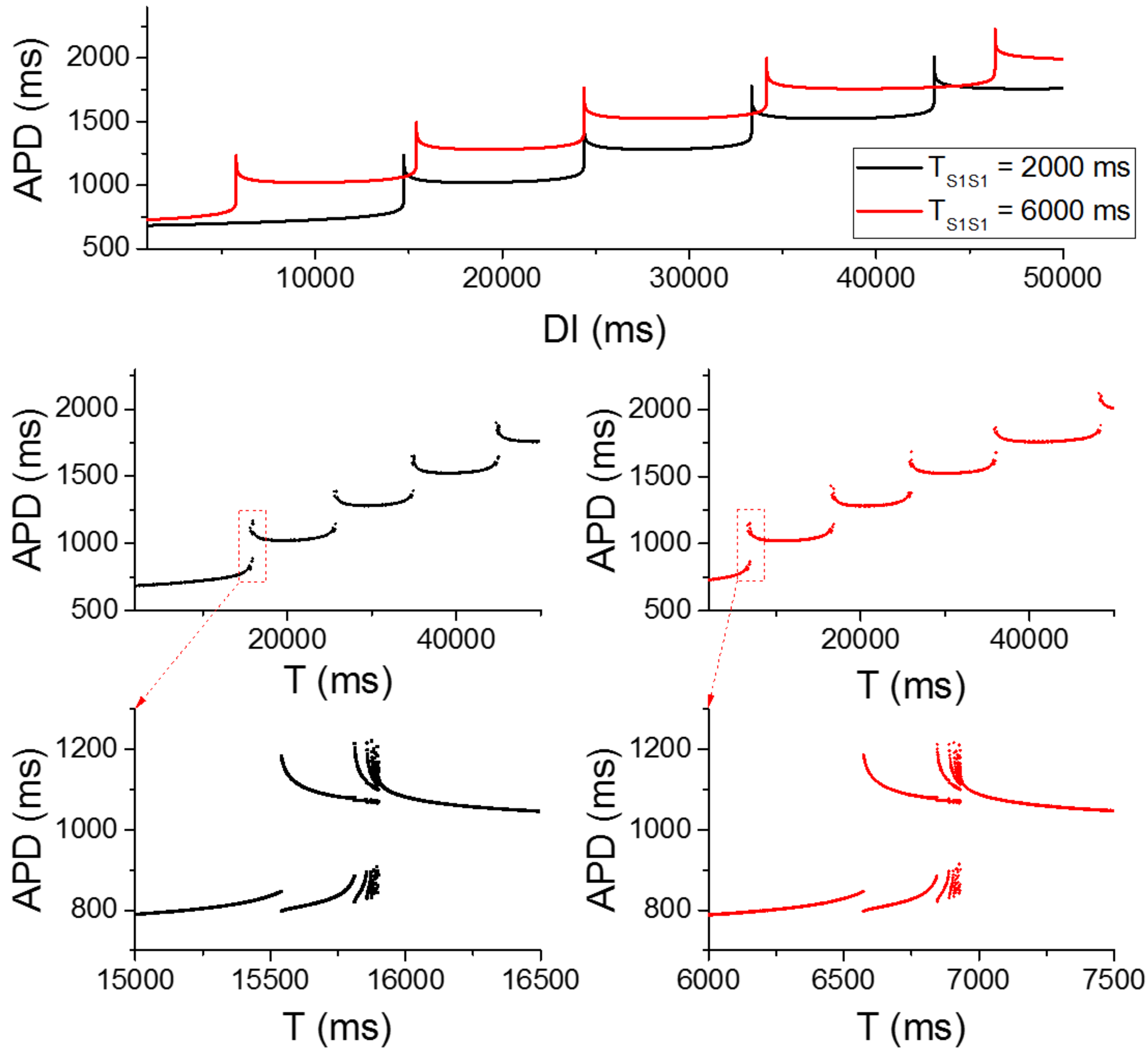


EAD and chaos in the TP04 model

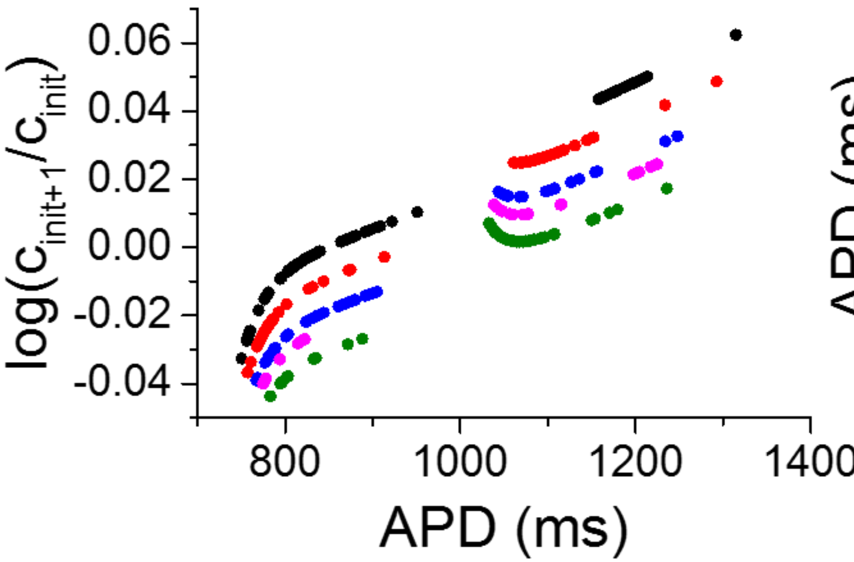
No Ito

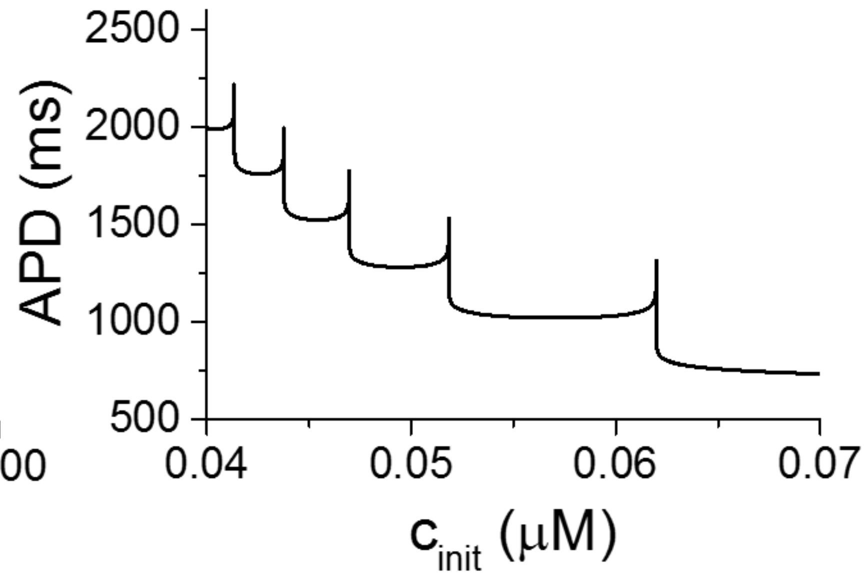


Bifurcations using APD=f(DI)



Bifurcation of the new iterated map model

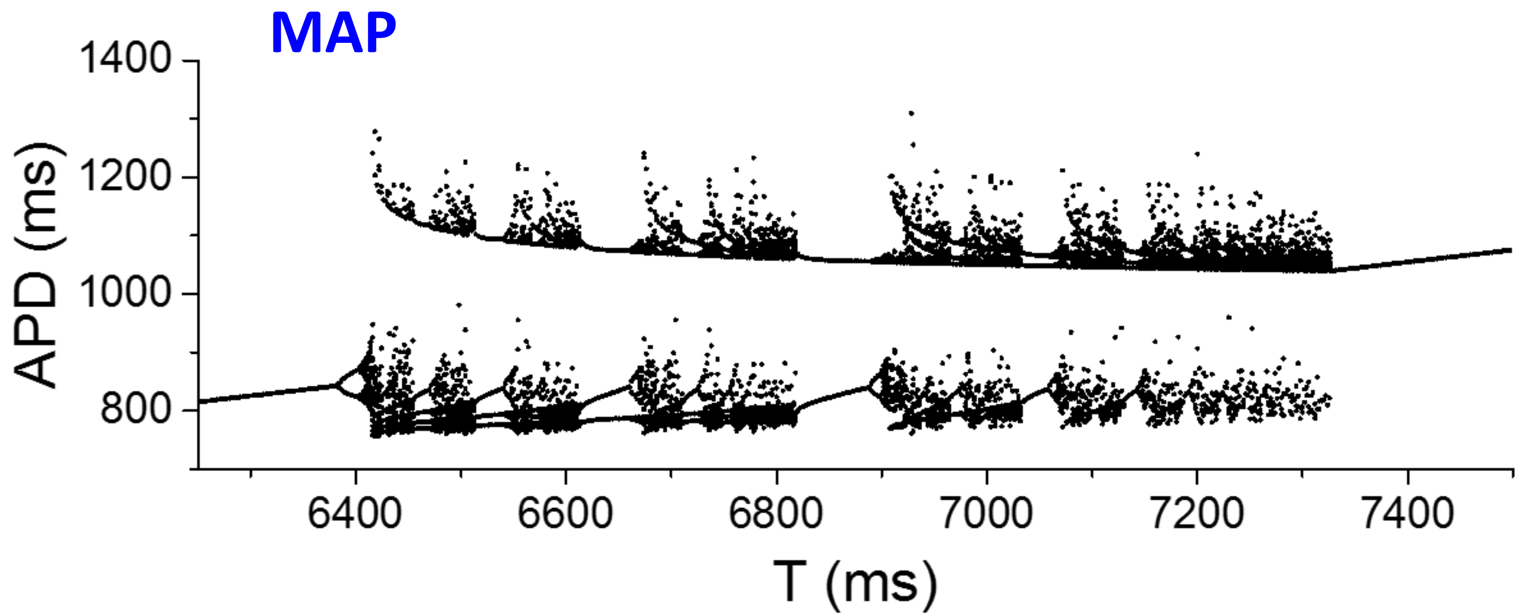


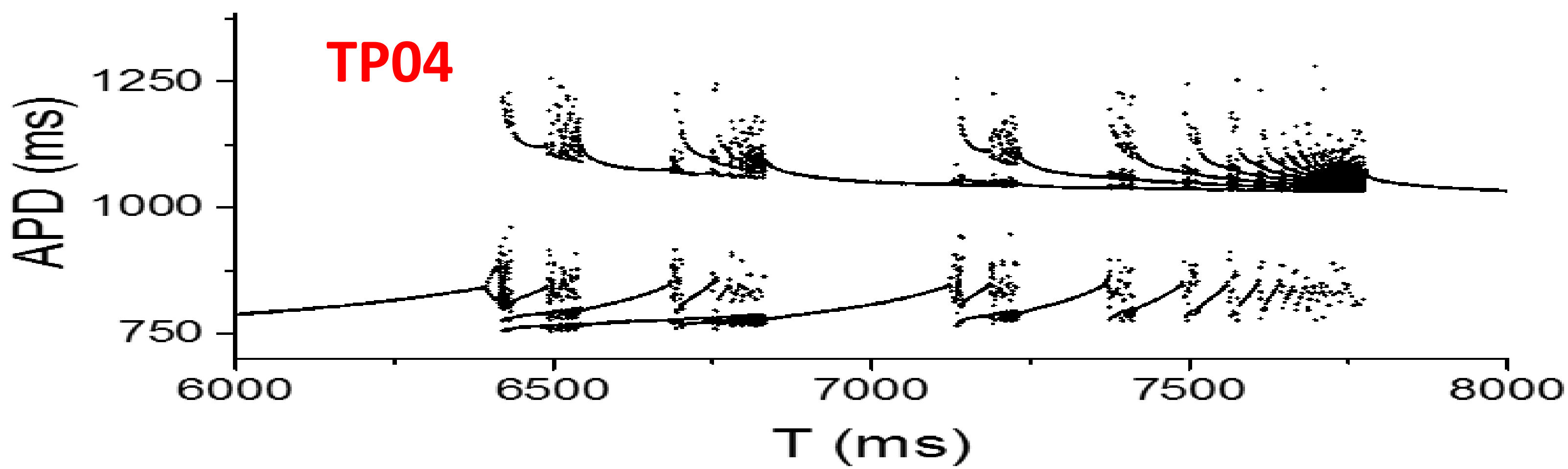


$$c_{n+1} = c_n \exp[f(a_n)] = c_n \exp[\gamma_a a_n - \gamma_T T + \delta]$$

$$a_n = g(c_n)$$

Bifurcation of the new iterated map model





Summary

Memory due to slow intracellular Ca accumulation plays some roles as slow ion channel recovery in inducing complex APD dynamics, i.e., instead of suppressing instabilities, it promote APD instabilities.

Constant-DI pacing control

$$APD_{n+1}=f(DI_n)$$

Jordan and Christini, JCE 2004

Chaos focus issue (2017)

Zilochiver et al: Model-dependent or V-Ca coupling strength

Cherry: can be used for inferring the source of instability-V-driven or Ca-driven.

Otani: General map analysis

A general iterated map analysis by Otani

$$A_{n+1} = f(D_n, M_{n+1}),$$
$$M_{n+1} = g(M_n, D_n, A_n),$$
$$D_n = T_n - A_n.$$

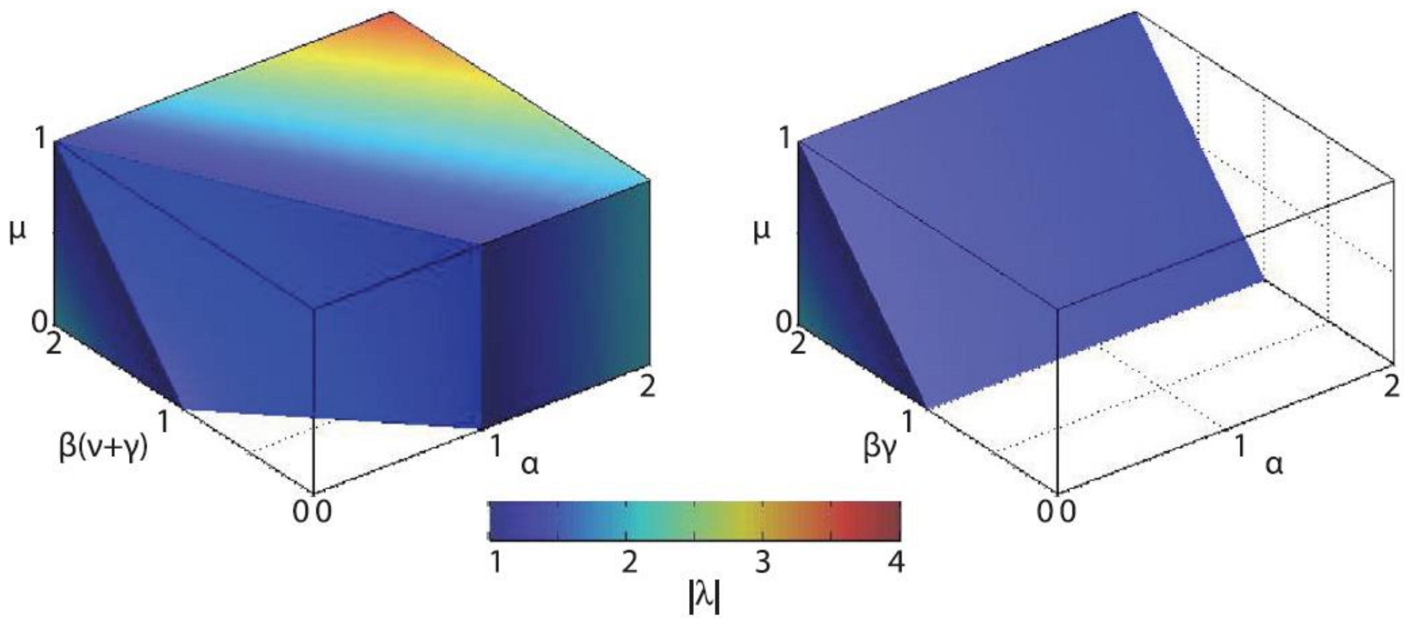
$$\delta A_{n+1} = \alpha \delta D_n - \beta \delta M_{n+1},$$
$$\delta M_{n+1} = \mu \delta M_n - \nu \delta D_n + \gamma \delta A_n,$$
$$\delta D_n = \delta T_n - \delta A_n,$$

Constant-T pacing

$$\alpha > 1 - \beta(\nu + \gamma)/(1 + \mu)$$

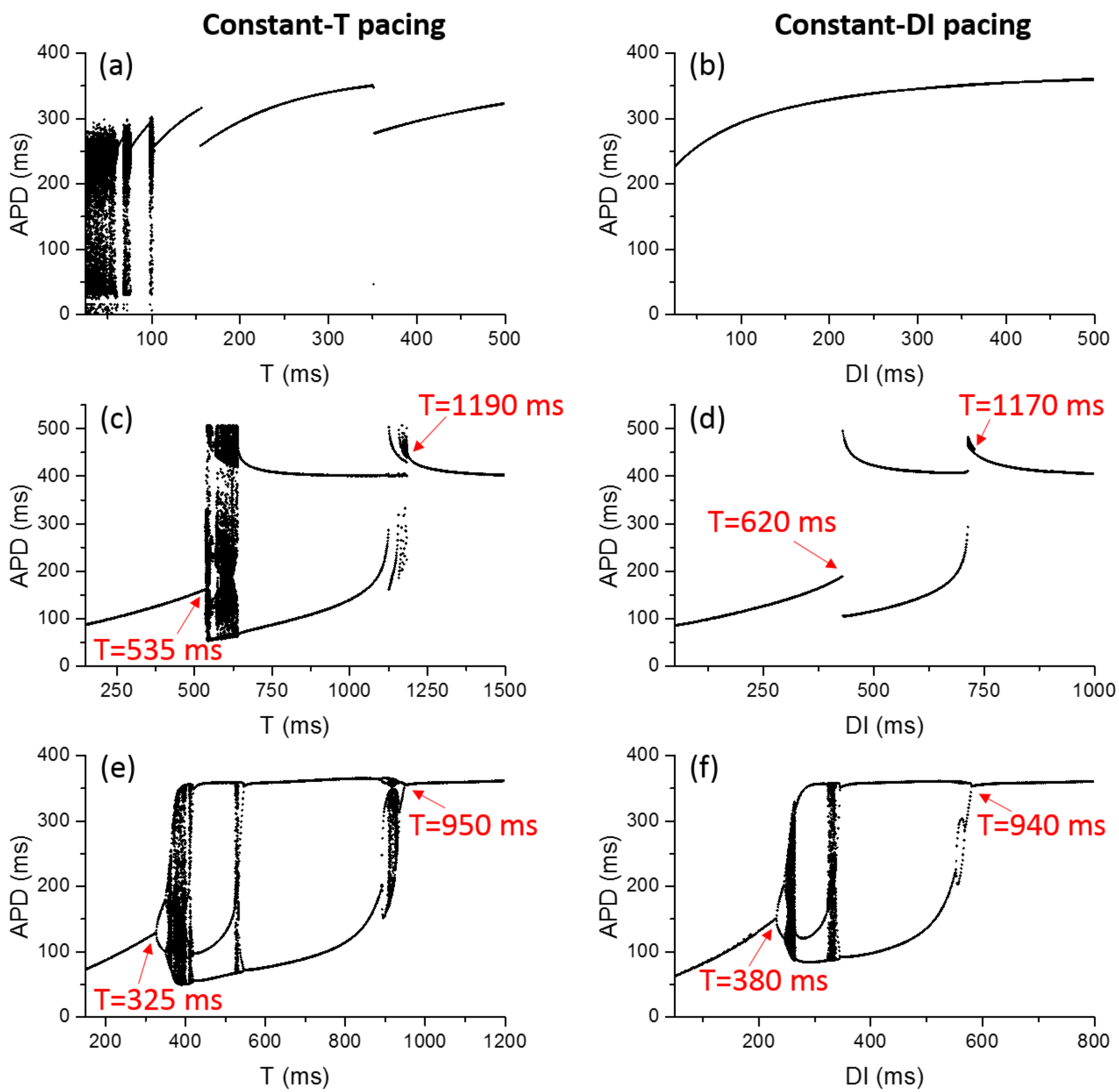
Constant-DI pacing

$$\beta\gamma > 1 + \mu > 1$$

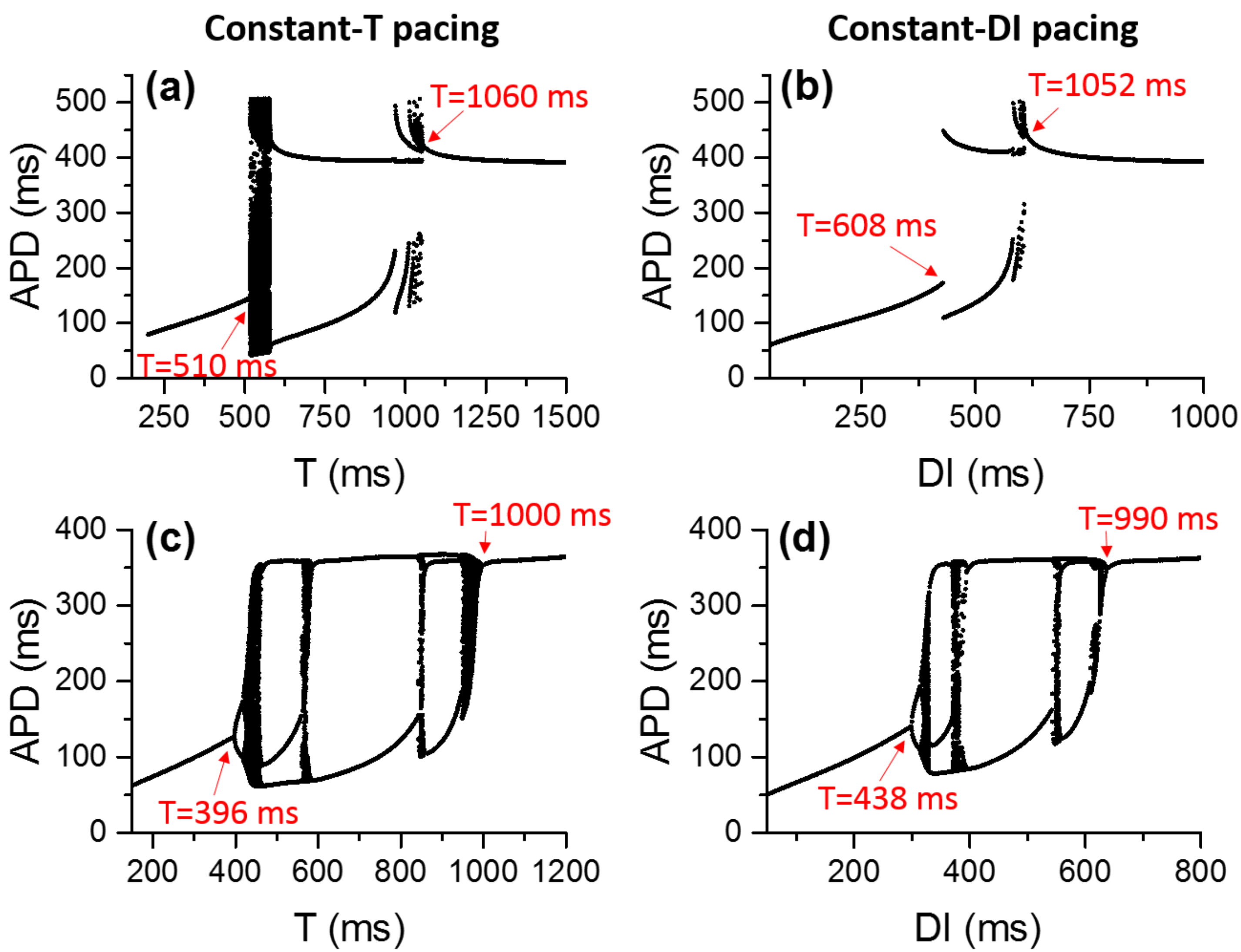


(Otani, Chaos 2017)

Constant-T and constant-DI pacing in the LR1 model



Constant-T and constant-DI pacing in the iterated maps



Conclusions

1. Memory can be unmasked/exacerbated by Ito (early repolarization syndrome) or by reduced repolarization reserve (long QT syndrome)

2. Memory, instead of suppressing complex APD dynamics, can induce complex APD dynamics, namely high periodicity and chaos, by converting monotonic map functions into nonmonotonic map functions.

3. Constant-DI pacing may fail to control voltage-driven instabilities.

Future works

$$x_{n+1} = [x_a - (x_a - x_n)e^{-(a_n/\tau_a)}]e^{-(d_n/\tau_d)} = w(x_n, a_n)$$

$$c_{n+1} = c_n \exp[f(a_n)] = c_n \exp[\gamma_a a_n - \gamma_T T + \delta]$$

$$a_{n+1}=g(d_n, x_{n+1}, c_{n+1})$$

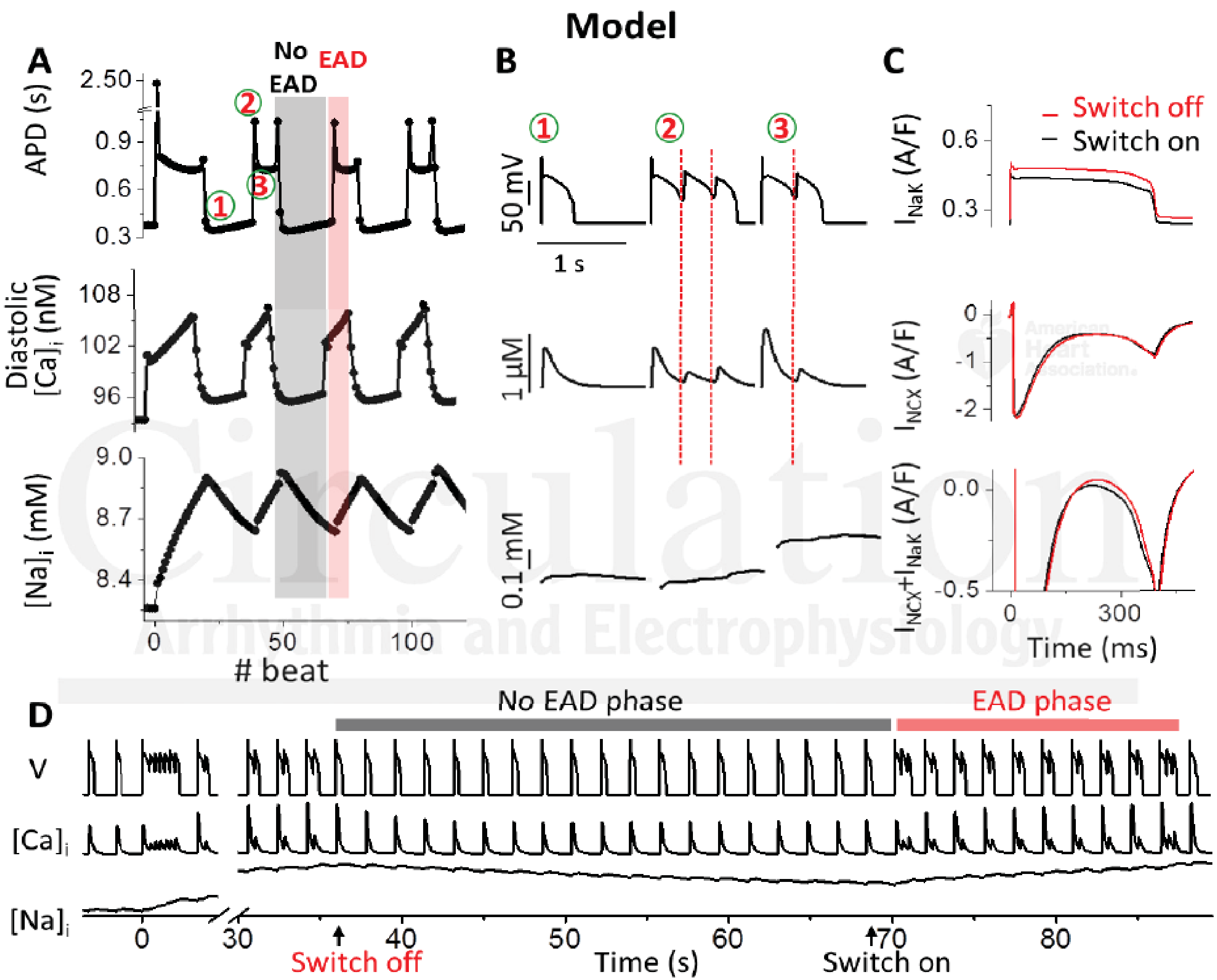
Memory due to slow recovery of other ion channels, such LCCs or slow Ito

An equation describing the intracellular Na accumulation is needed to investigate the effects caused by [Na] accumulation memory.

$$s_{n+1}=h(a_n, T, c_n)$$

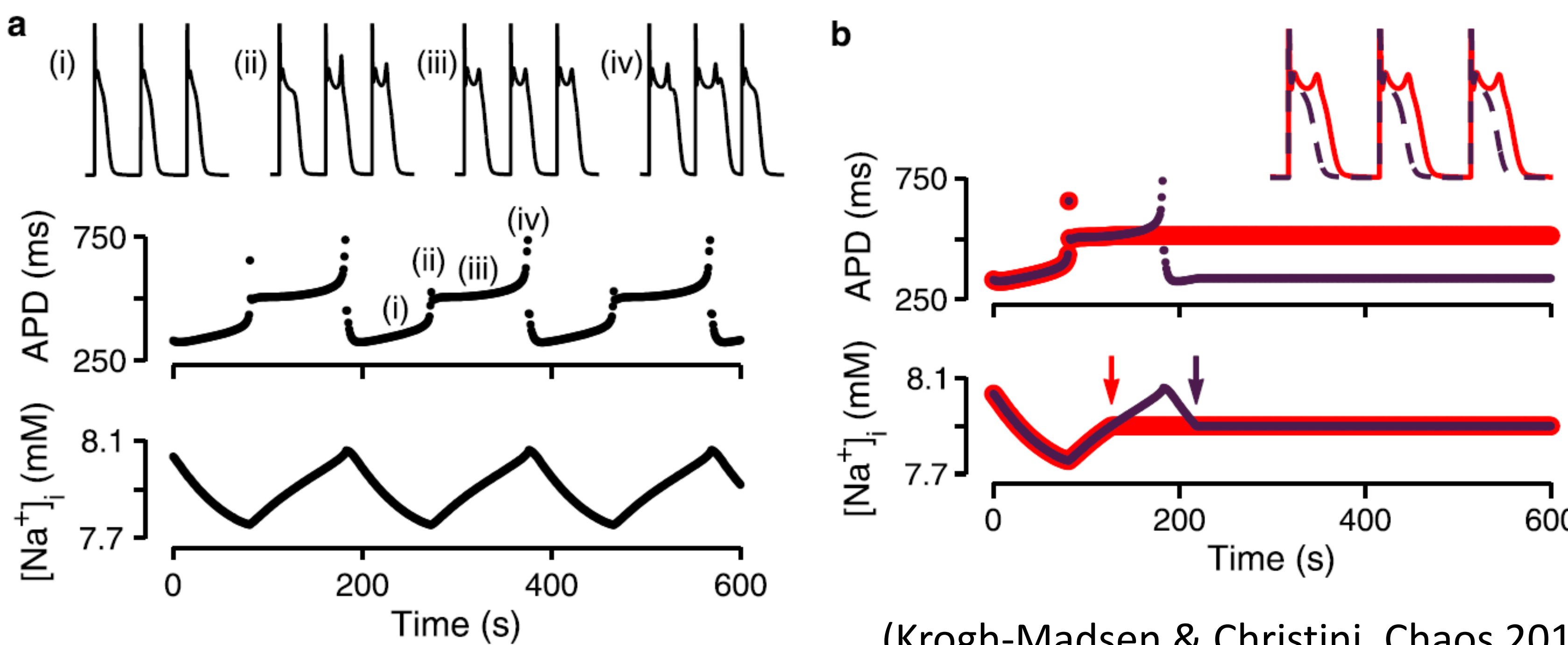
$$a_{n+1}=g(d_n, x_{n+1}, c_{n+1}, s_{n+1})$$

Future works

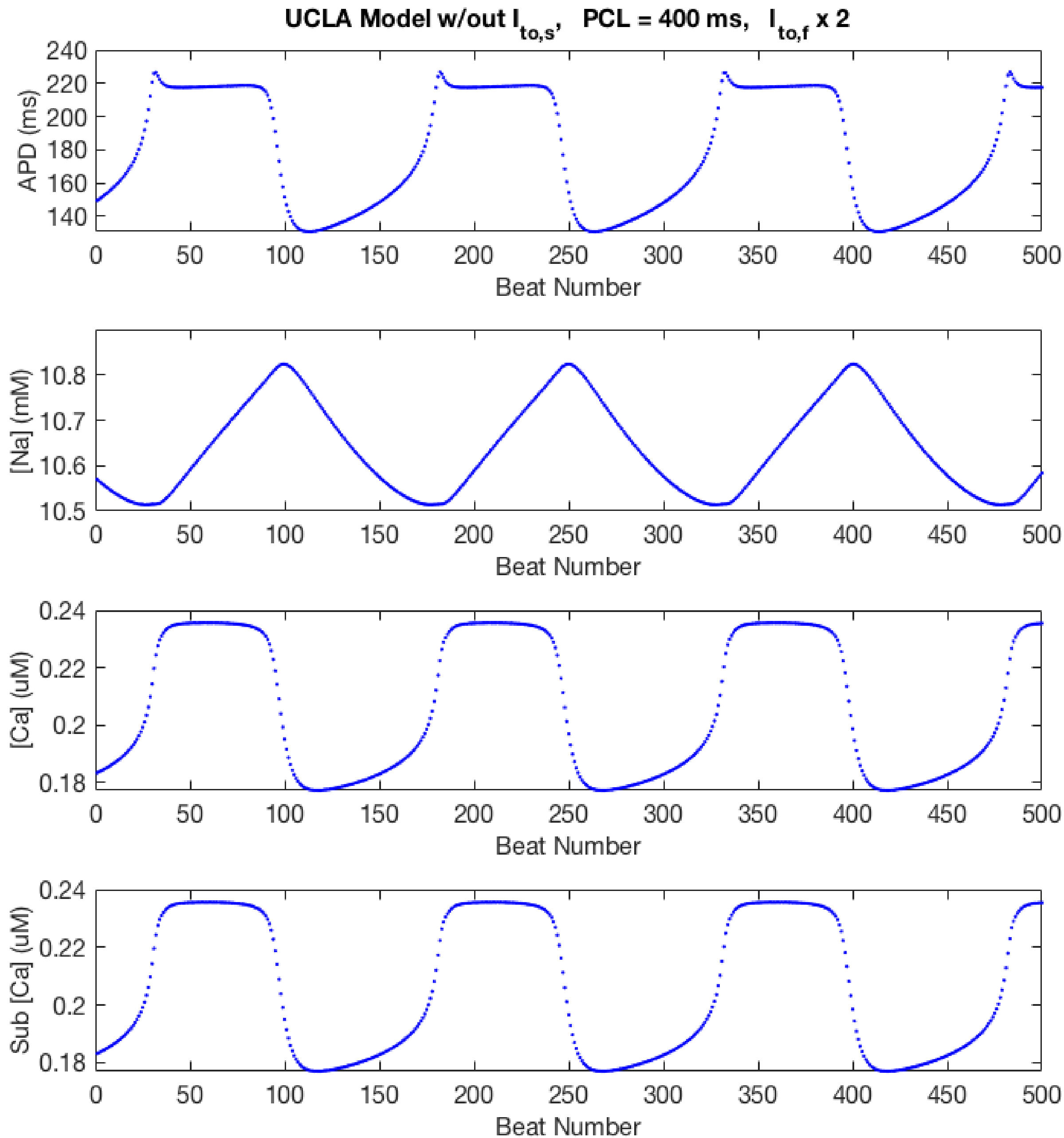


(Xie et al, Circulation AE 2015)

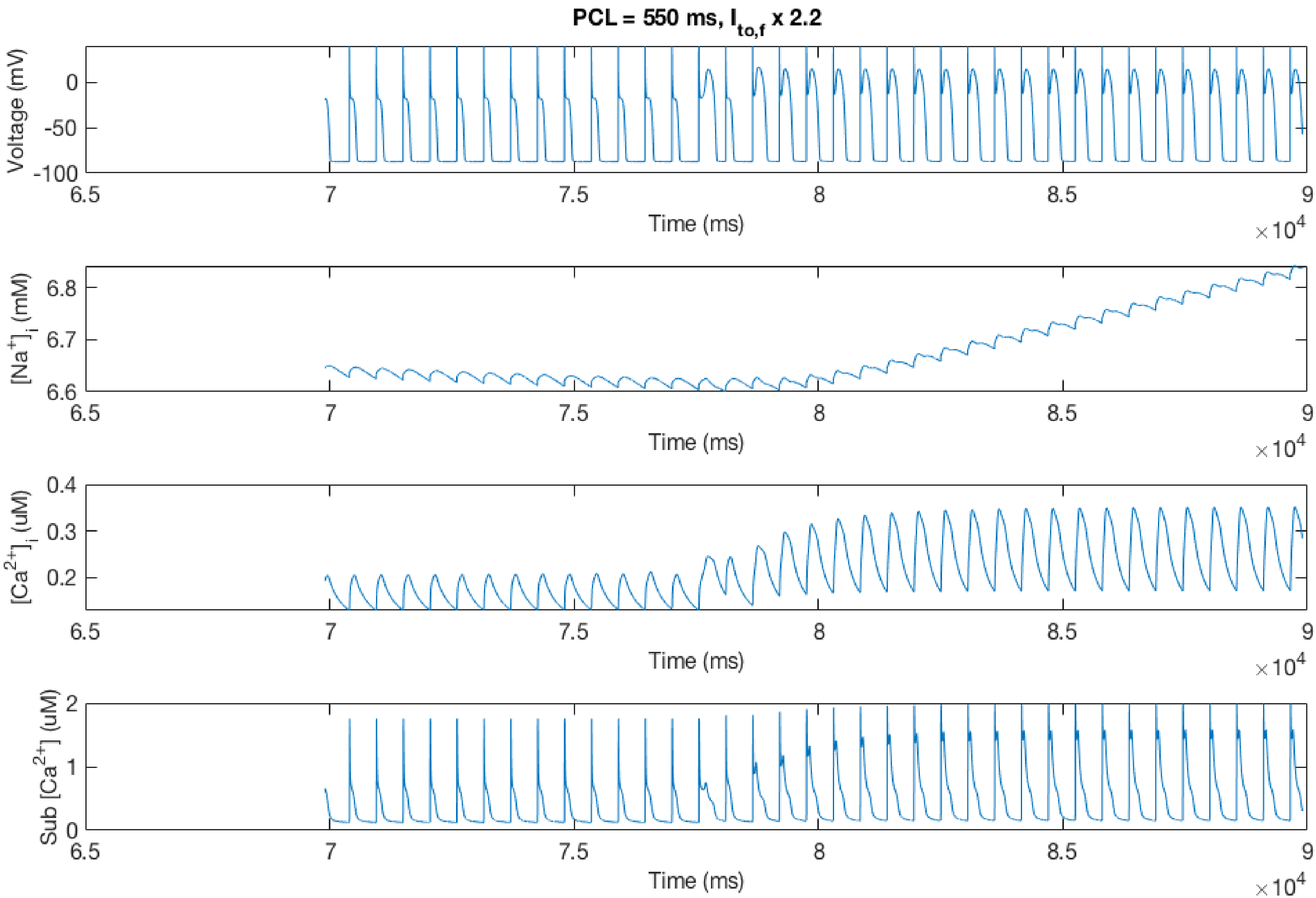
Future works



(Krogh-Madsen & Christini, Chaos 2017)



UCLA Model w/out $I_{to,s}$, PCL = 400 ms, $I_{to,f}$ x 2
APD (ms)
240
220
200
180
160
140
[Na] (mM)
10.8
10.7
10.6
10.5
[Ca] (uM)
Sub [Ca] (uM)
0.24
0.22
0.2
0.18
0
50
100
150
200
250
300
350
400
450
500
Beat Number


PCL = 550 ms, $I_{to,f}$ x 2.2
Voltage (mV)
0
-50
-100
[Na+]i (mM)
6.8
6.7
6.6
[Ca2+]i (uM)
0.4
0.3
0.2
Sub [Ca2+] (uM)
2
1
0
6.5
7
7.5
8
8.5
9
Time (ms)
×10^4

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