Елена Суровяткина

Нелинейная динамика электрических процессов в сердечной клетке человека. Физические и медицинские аспекты

Институт космических исследований Российской академии наук
LOGISTIC MAP

\[ x_{n+1} = \lambda \ x_n (1 - x_n) \]

- **limit-cycle**
- **2-cycle**
- **4-cycle**
- **CHAOS**
\[ x_{n+1} = \lambda x_n (1 - x_n) \]

\[ \lambda = 3.6 \]
\[ \lambda = 3.45 \]
\[ \lambda = 3.2 \]
\[ \lambda = 2.7 \]

\[ x^* \]

limit-cycle
2-cycle

stable point of the map

\[ F(x) \]

diagramma Ламерее

\[ \lambda = 2.8 \]
\[ \lambda = 3.2 \]
\[ \lambda = 3.45 \]
\[ \lambda = 3.6 \]

control parameter \( \lambda \)
**ACTION POTENTIAL**

APD - action potential duration

DI - diastolic interval

PCL - pacing cycle length
From Pulsus to Pulseless
The Saga of Cardiac Alternans

James N. Weiss, Alain Karma, Yohannes Shiferaw, Peng-Sheng Chen, Alan Garfinkel, Zhilin Qu

\[ APD_{n+1} = F(\ PCL - APD_n) = F(DI_n) \]

\[ APD_{n+1} = F(\ APD_n) \]

**Figure 3.** Cobweb diagram of APD alternans arising from steep APD restitution slope, after Nolasco and Dahlen.\(^{15}\) Blue line shows the APD restitution curve, and red line shows the \(CL=APD+DI\) line. The top graph illustrates the effects of a perturbation, which shortens DI (asterisk), displacing the system from its unstable equilibrium point (solid black circle at the intersection of the two lines), resulting in persistent APD alternans, as shown in the bottom trace. See text for details.
Figure 2. Activation-recovery interval (ARI) restitution and slope measurement. (A) Simultaneous measurement of ARIs at three sites in the posterobasal left ventricle during S1–S2 stimulation is shown. ARIs and diastolic intervals (in parentheses) from unipolar signal-averaged electrograms—virtually 6, 8, 10—are determined using their respective first derivatives (dV/dt) from sites 7, 9, and 11 at the same sites. Maximum ARI restitution slope from a right ventricular site (B) and left ventricular site (C) are measured by 16 overlapping least-squares linear segments. LIVOT = left ventricular outflow tract, MV = mitral valve.

Figure. 2. MAP recording, reconstructed UE, and first derivative (ARI). ARI was measured by Wyatt between MAP and peak duration of ARI for negative T wave (l), positive T wave (l).

Figure. 5. Construction of restitution curves. Surface ECG shows drive train (S1) and unipolar electrogram (UE). MAP recording, reconstructed UE, and first derivative (ARI) were measured from each site and displayed simultaneously. ARI of S1 was measured by Wyatt method.

Yue et al.
Noncontact Mapping of Electrical Restitution
JACC Vol. 46, No. 6, 2005
September 20, 2005:1067–75

Figure 3. Global activation-recovery interval (ARI) restitution curves. Simultaneous restitution curves were constructed at 16 sites in a right ventricle (A) and left ventricle (B). Color codes for the 16 regional segments are illustrated in (C). Locations of the 16 segments are shown in Figure 1.
Alternans and spiral breakup in a human ventricular tissue model

K. H. W. J. ten Tusscher and A. V. Panfilov

Fig. 5. Single-cell action potential duration (APD) restitution. A–D: restitution curves obtained using a S1-S2 restitution protocol for a basic cycle length (BCL) of 600 ms measuring APD at 50% (APD$_{50}$) and 90% repolarization (APD$_{90}$) for 4 different parameter settings of our model (Table 2). APD is plotted against diastolic interval (DI). Experimental activation recovery interval (ARI) restitution curves (exp) are from Nash et al. (38–40). E–H: restitution curves obtained using a dynamic restitution protocol measuring APD$_{90}$ for the 4 same parameter settings. APD is plotted against DI. Gray shading is used to indicate the region of the restitution curve where the slope exceeds 1. I–L: same dynamic restitution curves as in E–H, but now plotting APD against stimulation period. Splitting of the restitution curve indicates the presence of 2 APDs for a single period: APD alternans.
Atrial Fibre & Ventricular Fibre Action Potentials

Propagation waves
- P-wave
- Q-wave
- S-wave
- T-wave

Normal ECG at rest

400 ms

P: Atrial distribution
Q: PQ-interval < 0.2 s
R: Ventricular depolarisation
S: ST-interval
T: Ventricular repolarisation

Why life threatening arrhythmias always suddenly start and stop?

Roughly half of the deaths caused by cardiovascular disease are sudden. The majority of those sudden deaths – an estimated 300,000 per year in US – are associated with ventricular fibrillation.
Factors known to trigger or modulate VT/VF

Goldberger J. J. at al. Risk Stratification for Sudden Death

JACC, V. 52, N. 14, 1179 –99. 2008

- changes in autonomic nervous system activity,
- metabolic disturbances,
- myocardial ischemia,
- electrolyte abnormalities,
- acute volume and/or pressure overload of the ventricles,
- ion channel abnormalities,
- proarrhythmic actions of cardiac and noncardiac drugs.


“However, these factors alone cannot explain the apparent randomness of the occurrence of fatal arrhythmias”
Multistability

- the coexistence of several stable states of a system at a fixed set of stimulation parameters;
- each of the stable states realizes from different initial conditions.
Bistability observations in vivo (animal) experiments

- Bien H. Cardiac arrhythmogenesis in urban air pollution: optical mapping in a tissue-engineered model, Doctoral thesis, Stony Brook University, 2007. (in rat)
Hodgkin-Huxley Ionic Current Model

Ohm’s Law:

\[ I_K = g_K (V_m - E_K) \]
\[ I_{Na} = g_{Na} (V_m - E_{Na}) \]
\[ I_{Cl} = g_{Cl} (V_m - E_{Cl}) \]

Nernst potentials:

\[ E_K = \frac{RT}{F} \ln \left( \frac{[K]_o}{[K]_i} \right) \]
\[ E_{Na} = \frac{RT}{F} \ln \left( \frac{[Na]_o}{[Na]_i} \right) \]
\[ E_{Cl} = \frac{RT}{F} \ln \left( \frac{[Cl]_o}{[Cl]_i} \right) \]

Conductances (1/resistance):

\[ g_K = g_K n^4 \]
\[ g_{Na} = g_{Na} m^3 h \]
\[ g_{Cl} = g_{Cl} \]

Gating variables: \( n, m, \) and \( h \)

\[ \frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n \]
\[ \frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m \]
\[ \frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h \]

Kirchhoff’s current law:

\[ I_m = I_c + I_{ion} \]
\[ = C_m \frac{dV_m}{dt} + I_{Na} + I_K + I_{Cl} \]

\[ -C_m \frac{dV_m}{dt} = g_K n^4 (V_m - E_K) + g_{Na} m^3 h (V_m - E_{Na}) + g_{Cl} (V_m - E_{Cl}) \]
The rate of change of transmembrane potential is given by

\[
dV/dt = \left( -I_{\text{ion}} + I_{\text{stim}} \right) / C
\]

- \( I_{\text{ion}} \) - the total transmembrane ionic current, determined by choice of cellular ionic model
- \( I_{\text{stim}} \) - a stimulus current,
- \( C \) - the membrane capacitance

Ionic models are increasingly detailed:

- \textbf{Noble} \(^1\) – 4 ODEs
- \textbf{Luo-Rudy} \(^2\) – 8 ODEs
- \textbf{Ten Tusscher - Panfilov} \(^3\) – 19 ODEs
- \textbf{Flaim-Giles-McCulloch} \(^4\) – 87 ODEs

\(^1\) Noble 1962; \(^2\) Luo \textit{et al.} 1991; \(^3\) Ten Tusscher & Panfilov 2006; \(^4\) Flaim \textit{et al.} 2006
**Luo-Rudy model**

\[ \frac{dV}{dt} = \frac{(-I_{ion} + I_{stim})}{C_m} \]

\[ I_{ion} = I_{Na} + I_{Ca} + I_K + I_{K_1} + I_{Kp} + I_b \]

**Ionic currents**

\[ I_{Na} = 23m^3hj(V - E_{Na}) \]

\[ I_{Ca} = G_{Ca} \cdot d \cdot f \cdot (V - E_{Ca}) \]

\[ I_K = G_K \cdot X \cdot X_i \cdot (V - E_K) \]

\[ I_{K_1} = G_{K_1} \cdot K1_\infty \cdot (V - E_{K_1}) \]

\[ I_{Kp} = 0.0183 \cdot K_p \cdot (V - E_{Kp}) \]

\[ I_b = 0.03921 \cdot (V + 59.87) \]

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C. Luo and Y. Rudy, Circ. Res. 68 (6), 1501 (1991)
\[ I_{Na} = 23 m^3 h j (V - E_{Na}) \]

\[ \frac{dy}{dt} = \frac{(y_\infty - y)}{\tau_y} = \frac{1}{\alpha_y + \beta_y} \]

\[ y_\infty = \frac{a_y}{\alpha_y + \beta_y} \]

\[ \alpha_y = f(V), \quad \beta_y = f(V) \]

\[ \alpha_y \] - rate of channel opening

\[ \beta_y \] - rate of channel closing

\[ I_{Ca} = G_{Ca} (d \cdot f) (V - E_{Ca}), \]

\[ I_k = \overline{G_k} \cdot X \cdot X_i \cdot (V - E_k), \]

\[ d([Ca]_i)/dt = -10^{-4} \cdot I_{Ca} + 0.07 (10^{-4} - [Ca]_i) \]
\[
\frac{dy}{dt} = (y_\infty - y) / \tau_y
\]

\[
y_\infty = \frac{a_y}{\alpha_y + \beta_y}
\]

\[
\tau_y = \frac{1}{\alpha_y + \beta_y}
\]

\[
I_{Na} = 23mVj(V - E_{Na})
\]

For all range of \( V \)

\[
\alpha_m = \frac{0.32(V + 47.13)}{1 - \exp[-0.1(V + 47.13)]}
\]

\[
\beta_m = 0.08 \exp(-\frac{V}{11})
\]

For \( V > -40 \) mV

\[
\alpha_h = a_j = 0
\]

\[
\beta_j = \frac{0.3 \exp(-2.535\cdot10^{-7}V)}{1 + \exp[-0.1(V + 32)]}
\]

\[
\beta_h = \frac{1}{0.13(1 + \exp[V + 10.66]/ -11.1)]}
\]

For \( V < -40 \) mV

\[
\alpha_h = 0.135 \exp[(80 + V)/ -6.8]
\]

\[
\beta_h = 3.56 \exp(0.079V) + 3.1105 \exp(0.35V)
\]

\[
\alpha_j = \frac{-1.2714 \cdot 10^5 \cdot \exp(0.2444V) - 3.474 \cdot 10^5 \cdot \exp(-0.04391V)}{1 + \exp[0.311(V + 79.23)]}
\]

\[
\beta_j = \frac{0.1212 \cdot \exp(-0.01052V)}{1 + \exp(-0.1378(V + 40.14))}
\]

\[
I_{Ca} = G_{Ca} \cdot d \cdot f \cdot (V - E_{Ca})
\]

\[
E_{Ca} = 7.7 - 13.0287 \cdot Ln([Ca]_r)
\]

\[
\alpha_d = \frac{0.095 \cdot \exp[-0.01(V - 5)]}{1 + \exp[-0.072(V - 5)]}
\]

\[
\beta_d = \frac{0.07 \cdot \exp[-0.017(V + 44)]}{1 + \exp[0.05(V + 44)]}
\]

\[
\alpha_j = \frac{0.012 \cdot \exp[-0.008(V + 28)]}{1 + \exp[0.15(V + 28)]}
\]

\[
\beta_j = \frac{0.0065 \cdot \exp[-0.02(V + 30)]}{1 + \exp[-0.2(V + 30)]}
\]

\[
d([Ca]_r)/dt = -10^{-3} \cdot I_{Ca} + 0.07(10^{-3} - [Ca]_r)
\]
ACTION POTENTIAL

\[
d\frac{V}{dt} = \left( -I_{ion} + I_{stim} \right) / C
\]

- **APD** - action potential duration
- **DI** - diastolic interval
- **PCL** - pacing cycle length
The S1-CI-S2 protocol of stimulation
(Surovyatkina et al. 2007, 2010)
Multistability in the human ventricular single cell model

Coexistence of 2:1- & 1:1- rhythms
Multistability in human myocyte

Steady-state values of APD, \( APD_\infty \) (ms)

Pacing cycle length (PCL), ms

CI=280 ms

CI=400 ms

1:1

2:1

2:2

1:1

Dynamic restitution protocol
Koeller et al. 1998

Ten Tusscher & Panfilov 2006
1. The additional mechanism of sudden change in heart rhythm based on the multistability property of the human ventricular cells is proposed.

2. The multistability mechanism may explain the apparent randomness of the occurrence of fatal arrhythmias in the human heart.
Multistability in Models of Mammalian and Human Cardiac Ventricular Cells


Listen to your heart....

Thank you!