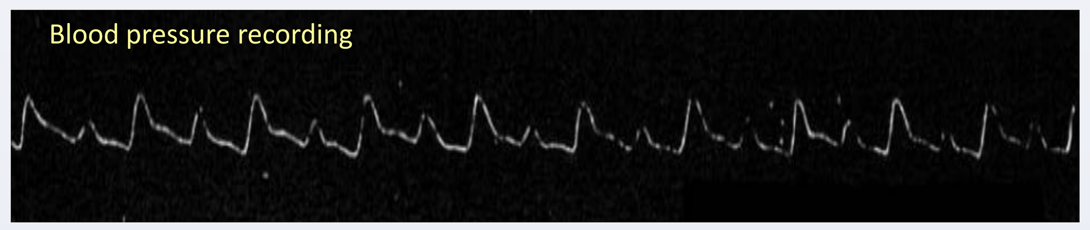
Alternans: The Effects of Alternating Pacing on Cardiac Activity

UCDAVIS UNIVERSITY OF CALIFORNIA

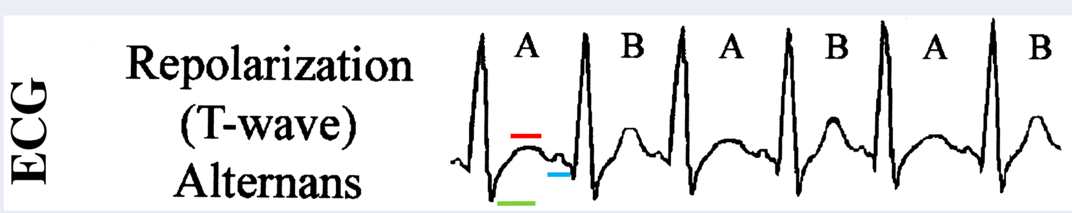
Michael Smolkin, Zana A Coulibaly, Leighton T Izu, Daisuke Sato
Department of Pharmacology, University of California, Davis

Introduction

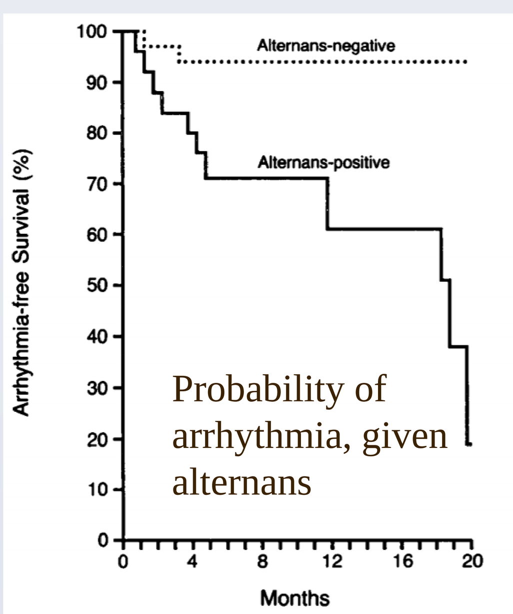
Cardiac Alternans



Ein Fall von Pulsus bigeminus nebst Bemerkungen über die Leberschwellungen bei Klappenfehlern und über acute Leberatrophie. Berliner Klinische Wochenschrift, 1872, 9: 185–188, 221–224

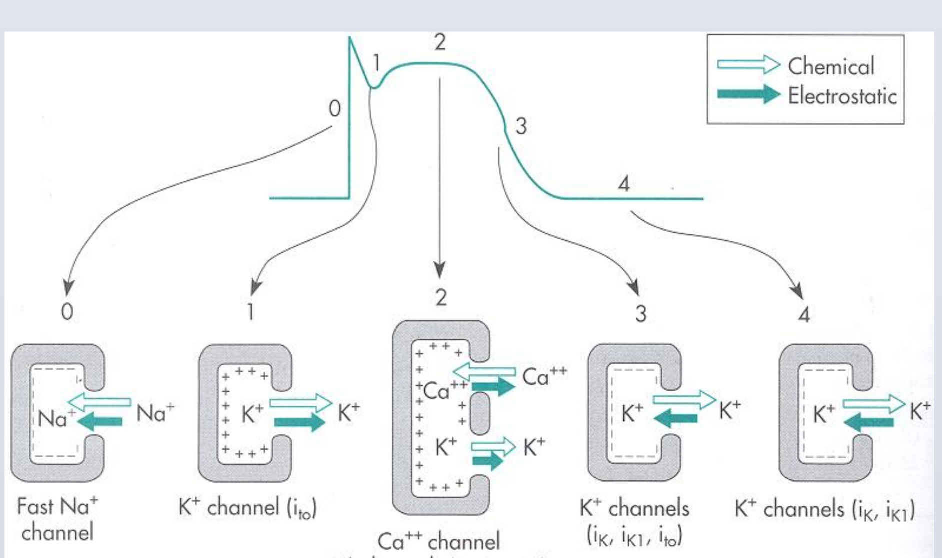


J Am Coll Cardiol. 2006 Jan 17;47(2):269-81.



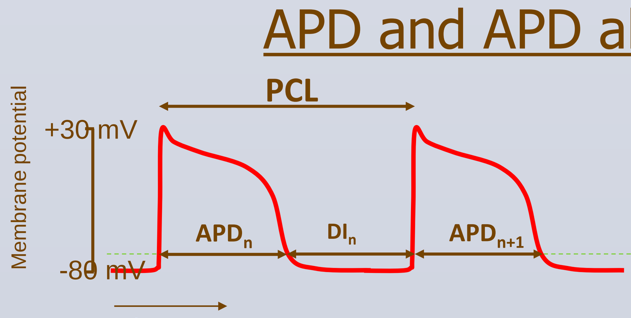
T-wave alternans refers to fluctuations in the ST-segment (green) or T-wave (red) or U-wave (blue) of an electrocardiogram. Prior research has identified TWA as a major biomarker for sudden cardiac death (SCD), the leading cause of death in the United States and throughout the world. TWA is observed as a result of APD alternans.

Cardiac Action Potential

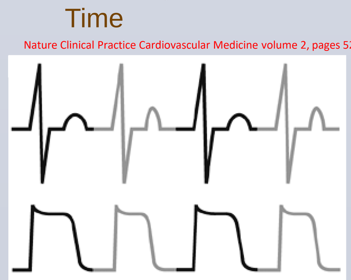


Cardiac myocytes are excitable. When cells are electrically stimulated, an action potential occurs. The action potential is mainly caused by sodium, potassium, and calcium ion flow through ion channels.

APD and APD alternans



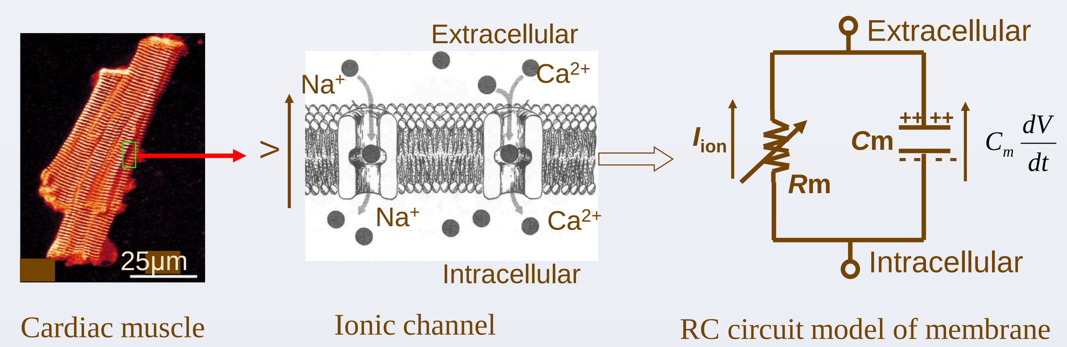
Nature Clinical Practice Cardiovascular Medicine volume 2, pages 521–528 (2005)



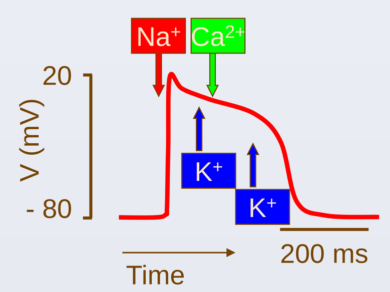
APD refers to the duration of an action potential. In human ventricular cells, this is usually between 200 and 400 ms. Electrical alternans is defined as a beat-to-beat change in the APD, and it is a known precursor of SCD

Methods

Mathematical model of cardiac cell



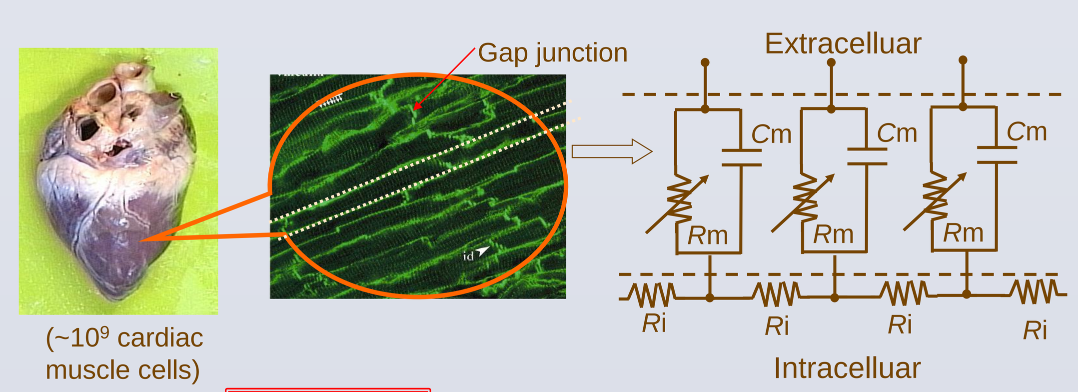
Cardiac muscle Ionic channel RC circuit model of membrane



$$\frac{dV}{dt} = -I_{ion}/C_m$$

The cell membrane can be modeled as a capacitor. The ion channels can be modeled as nonlinear resistors. In this study, the electrical activity of the heart was modeled by the Hodgkin-Huxley type equations. We use a physiologically detailed action potential model by Echebarra and Karma. This model has three currents : $I_{Na} + I_K + I_{Ca} (= I_{ion})$.

Mathematical Model of Cardiac Tissue



(~10⁹ cardiac muscle cells)

$$\frac{\partial V}{\partial x} = -\frac{I_{ion}}{C_m} + D\frac{\partial^2 V}{\partial x^2}$$

$$D = \frac{l}{2\pi R_i}$$

l: Length of cardiac muscle cell

R_i: Radius of cardiac muscle cell

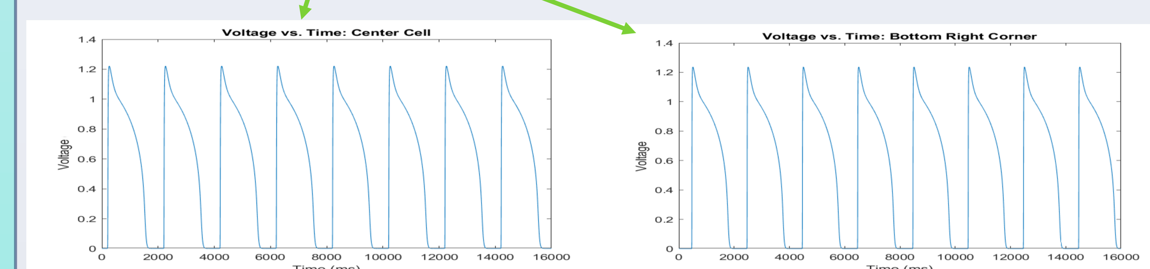
When multiple cells are connected by gap junctions, the action potential can propagate as a nonlinear wave. In this study, cardiac tissue is modeled using a cable equation. The diffusion constant depends on the physiological conditions. In our simulations, D is 0.001 cm²/ms. Using this model, we investigated effects of alternating pacing.

Computer simulation

Using C++, we were able to simulate a two-dimensional cardiac tissue within a practical time. Each cell was paced 300 times to ensure it reached the steady state, and then tissue was paced one hundred times. We then recorded the APDs with respect to cell position and pacing factors. At every point, an APD map was also generated and colorized based on APD amplitude.

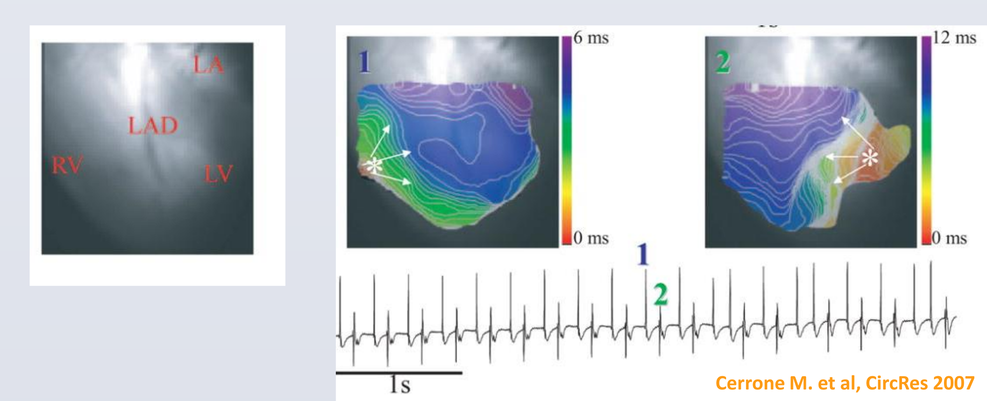
Results

Pacing Protocol I (control)

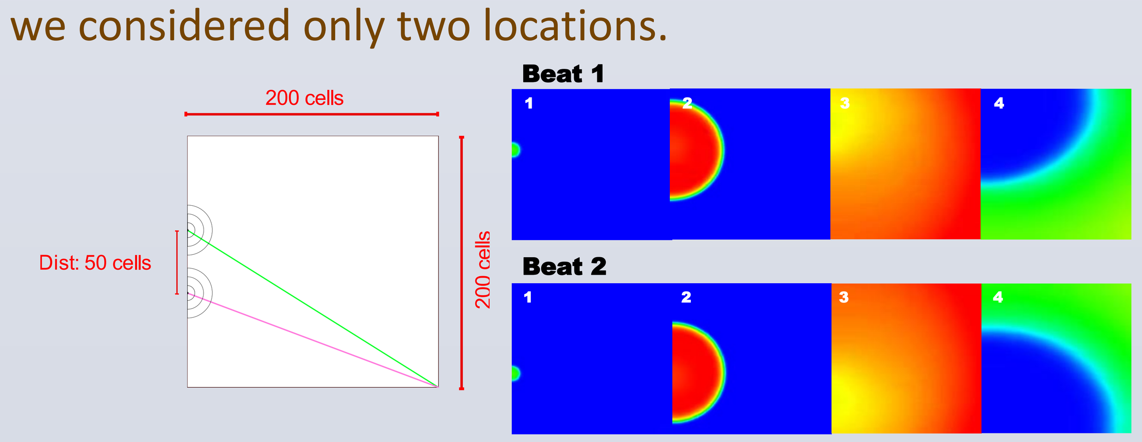


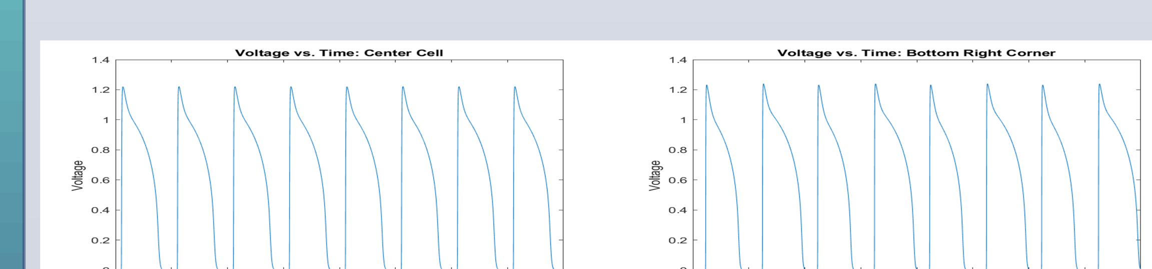
When tissue is paced from a single point, the action potential waves propagate concentrically. The action potentials are also periodic everywhere.

Pacing Protocol II (alternating pacing)



Experimental observations show that the action potential wave can be initiated from multiple points. In this study, we considered only two locations.

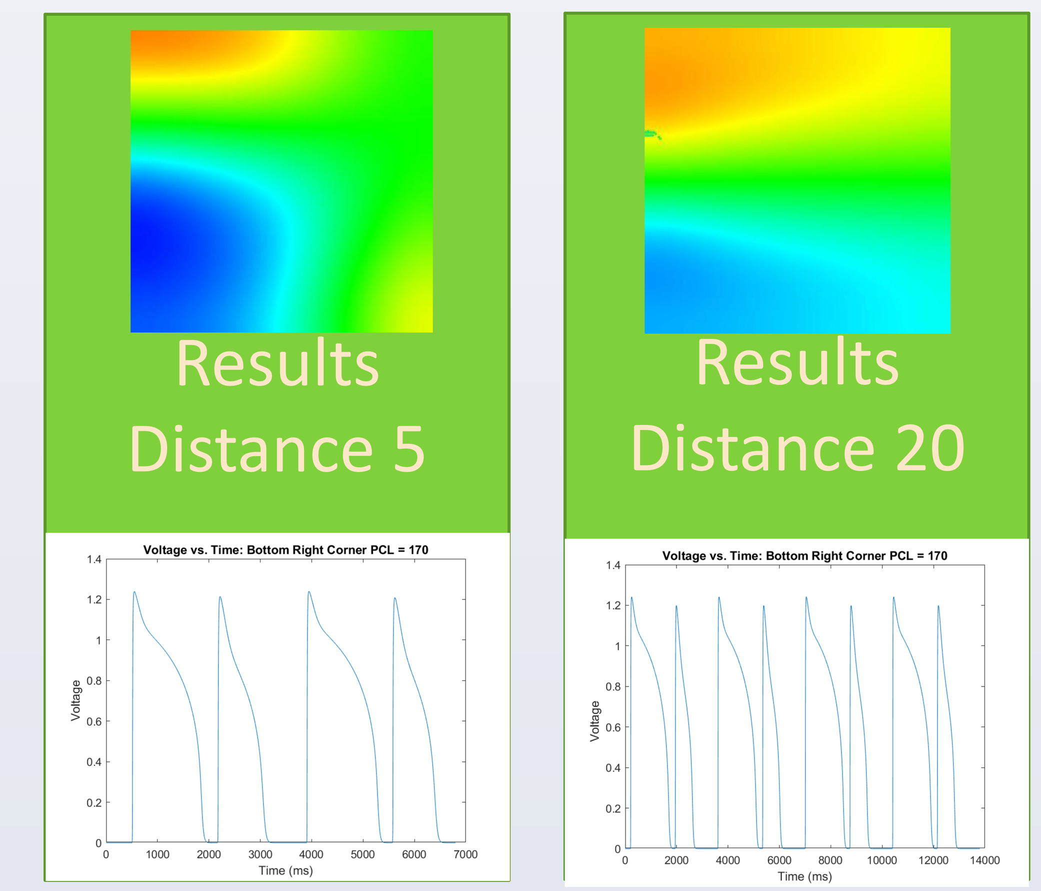




When tissue is paced from two points, the action potential waves propagate nonuniformly. In this simulation, the distance between two pacing cites is 50 cells (=7.5 mm) The action potentials are periodic at the center. However, large APD alternans is observed at the bottom-right corner.

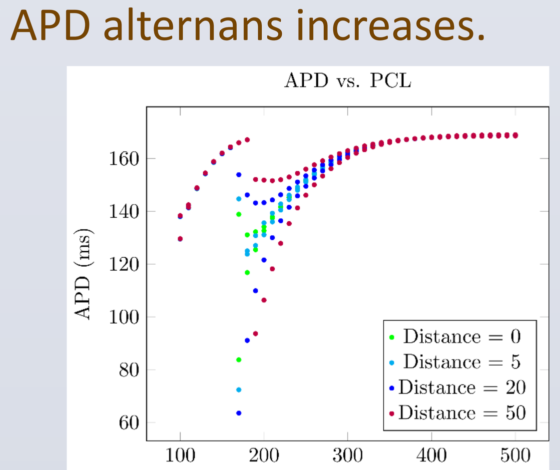
Results *(continued)*

Effects of Distance Between Two Pacing Sites



V vs. time

As the distance between two pacing sites increases, the amplitude of APD alternans increases.



Alternans occurs earlier as the distance between two pacing sites increases.

In this study we found

- When pacing from a single point (the control), as the action potentials always follow the same propagation path through the tissue, alternans is not present at physiological PCLs.
- However, when multiple points are stimulated, as happens when Purkinje fibers take over the pacing, alternating pacing leads to large alternans.

References

[1]Weiss et al. *Circ Res.*, **2006**, *98*, 1244-1253.
[2]Echebarria and Karma. *Eur. Phys. J. Special Topics*, **2007**, *146*, 217-231.