Restitution Curve Splitting as a Mechanism for the Bifurcation to Alternans

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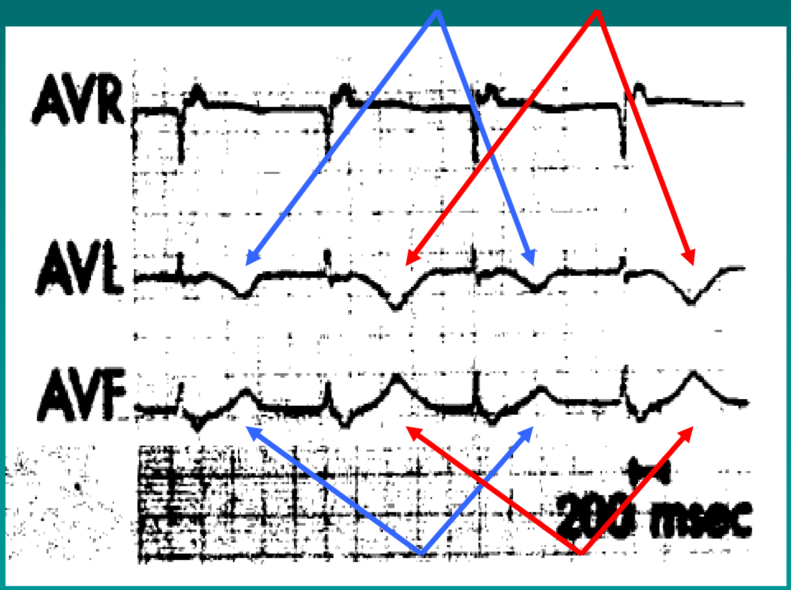
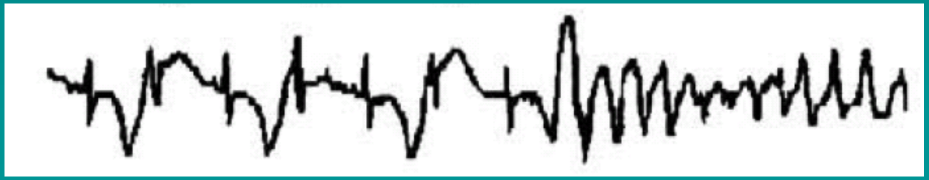
Alternans

- Alternans is a beat-to-beat alternation in cellular action potential shape and duration that leads to alternans in the T-wave of the ECG.
- Alternans can be electrical and/or mechanical; here we focus on electrical.



Alternans often precedes more dangerous arrhythmias like ventricular fibrillation.

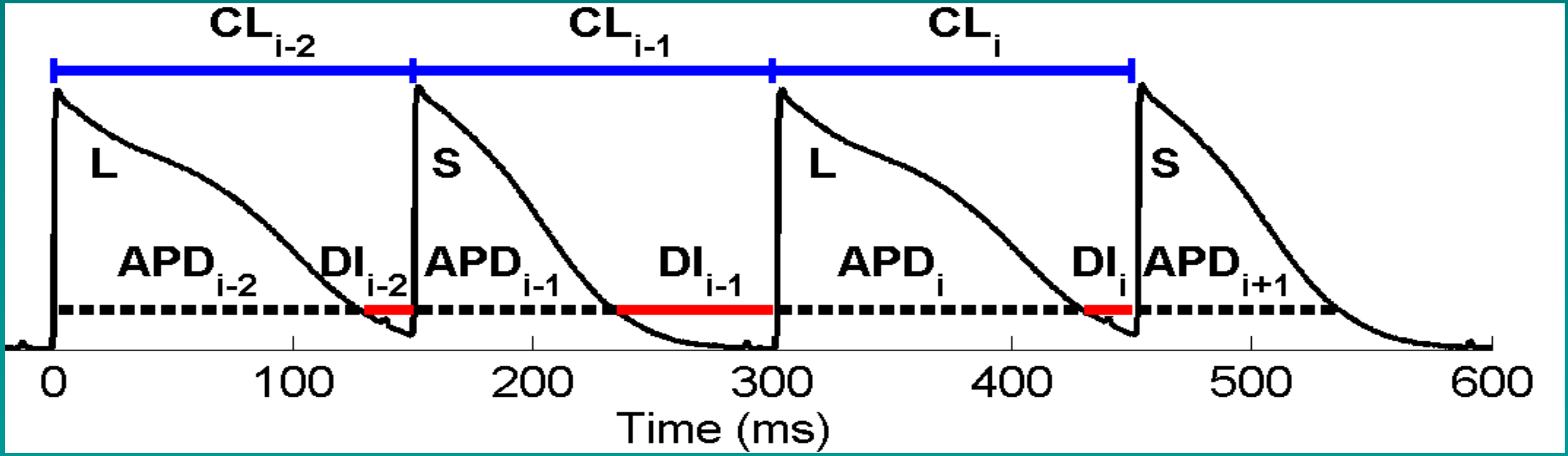


Wellens HJ. 1972. Chest 62, 319.

Raeder RA, et al. 1992. N Engl J Med 326, 271.

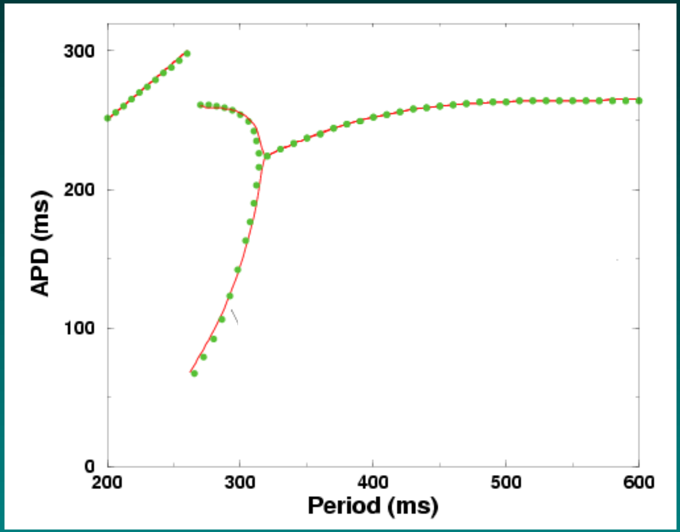
Alternans

- At the cellular level, alternans appears as a beat-to-beat long (L)-short (S) alternation despite a constant pacing period (cycle length CL).
- Action potential duration (APD) and/or amplitude may alternate.



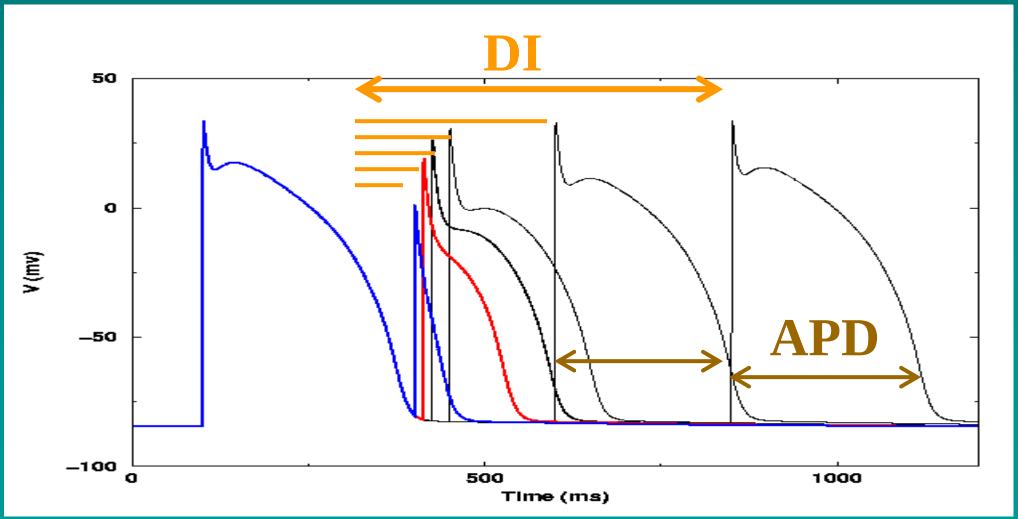
Alternans Bifurcation

- Plotting APD as a function of cycle length (period) shows a period-doubling bifurcation.
- At short cycle lengths, the curve usually terminates when every other beat is blocked.

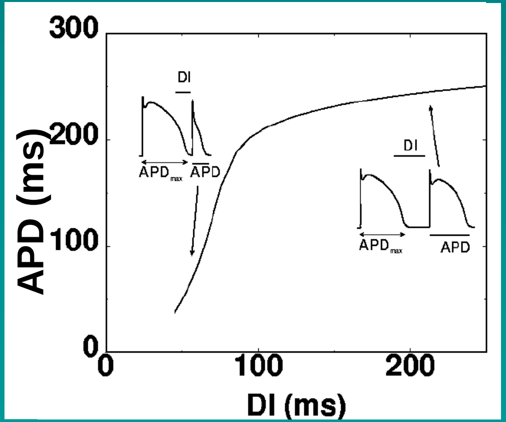


Restitution Curve

- Plotting APD as a function of preceding DI gives the restitution curve, which provides a first approximation of the system's dynamics.
- Defining $APD_{i+1}=f(DI_i)=f(CL-APD_i)$ gives an iterative map (for a fixed period $CL=APD_i+DI_i$).
- Linearizing around the fixed point $APD^*=f(DI^*)$ by letting $APD_i=APD^* + \delta APD_i$ gives $\delta APD_{i+1}=-f'(DI)\ \delta APD_i$, which has a bifurcation when $|f'(DI)| = 1$.



APD Restitution

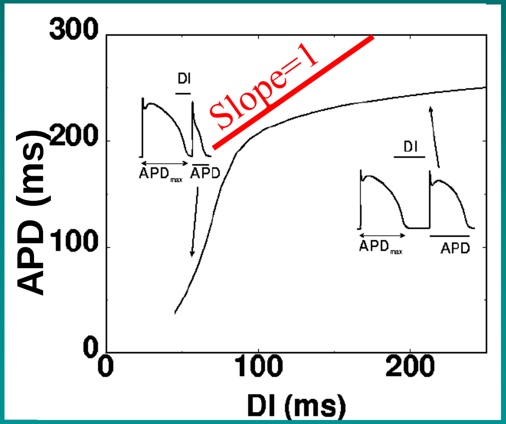


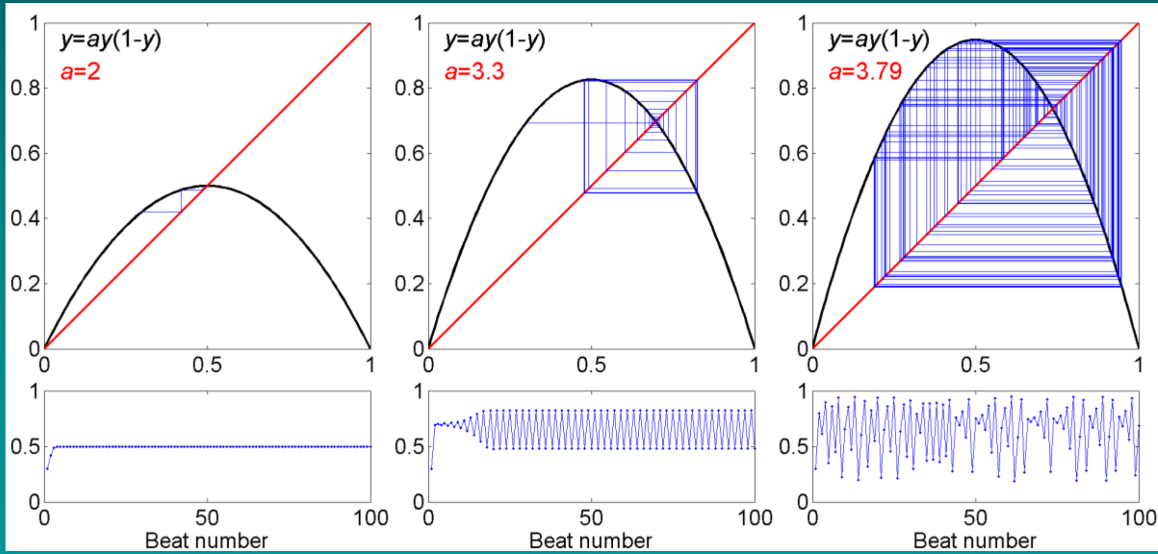
Restitution Curve

- $APD_{i+1}=f(DI_i)$ is stable when $|f'(DI_i)|<1$.
- Alternans is predicted for $|f'(DI_i)|<1$.

Cobwebbing technique useful for visualization of the iterative map. (Similar to logistic map.)

APD Restitution





JB Nolasco, RW Dahlen. 1968. J Appl Physiol 25, 191.
MR Guevara et al. 1984. Comput Cardiol, 167.
A Karma. 1993. Phys Rev Lett 71, 1103.

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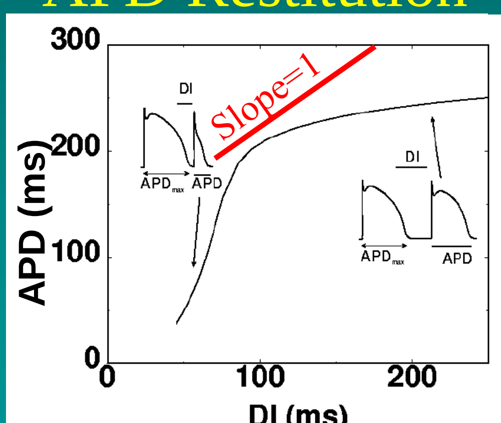
APD Restitution

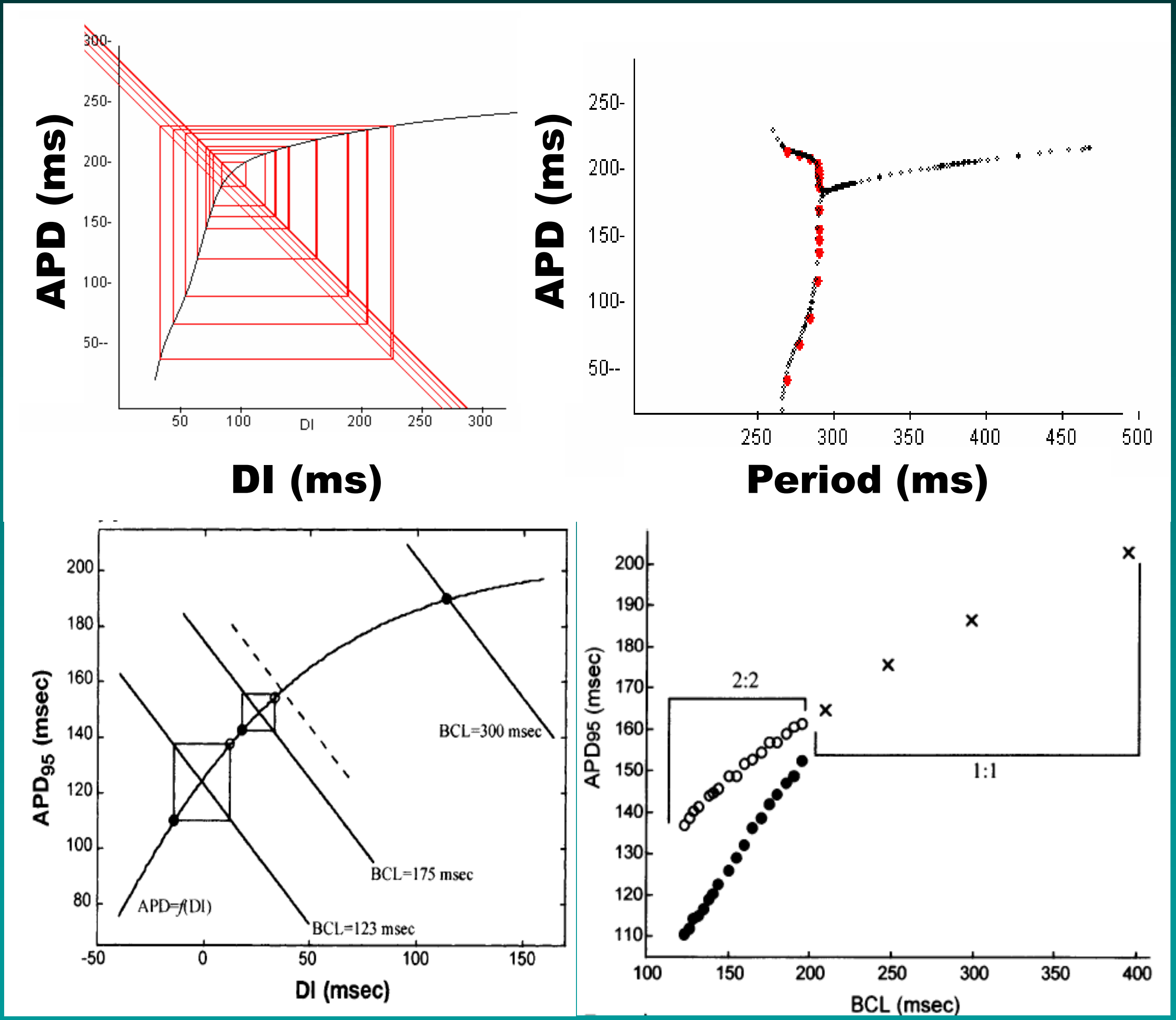


JB Nolasco, RW Dahlen. 1968. J Appl Physiol 25, 19
MR Guevara et al. 1984. Comput Cardiol, 167.
A Karma. 1993. Phys Rev Lett 71, 1103.

Alternans Characteristics

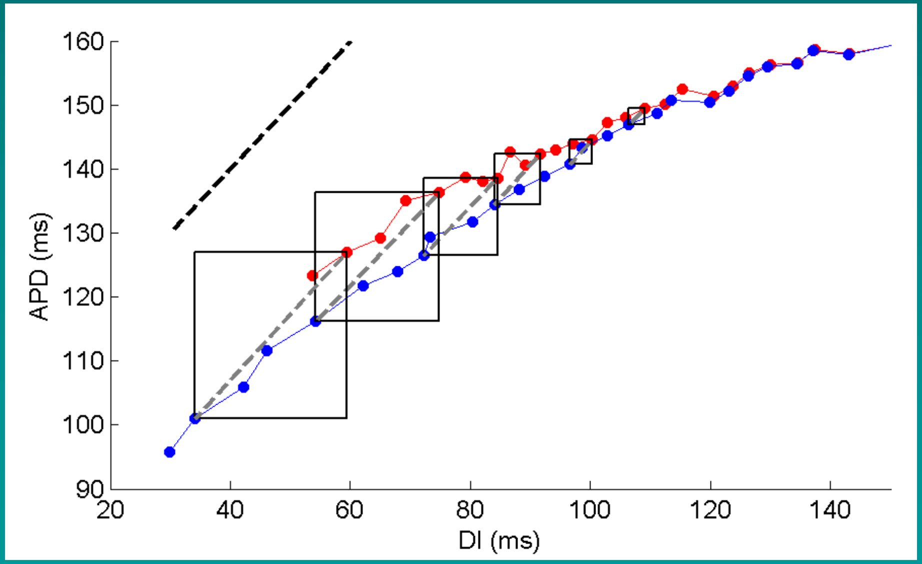
In models and one-dimensional maps, alternans is characterized by nested “boxes” and large magnitude.

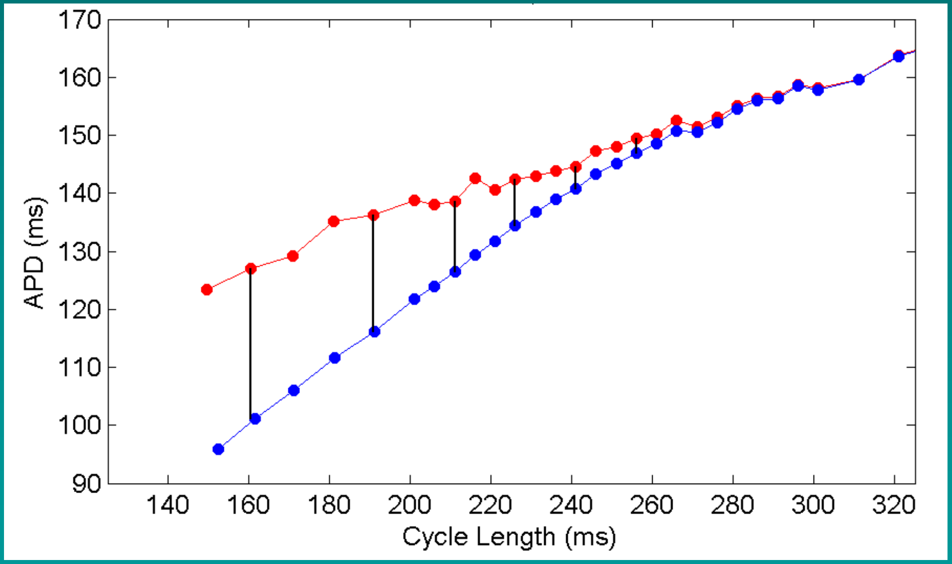
But in experiments, alternans boxes slide down and the magnitude of alternans is smaller.



Restitution Curve Splitting

- Sliding boxes can be explained if the restitution curve splits into two branches.
- Each DI,APD pair then involves one point from each branch.
- Branches can have any slope, steep or flat.

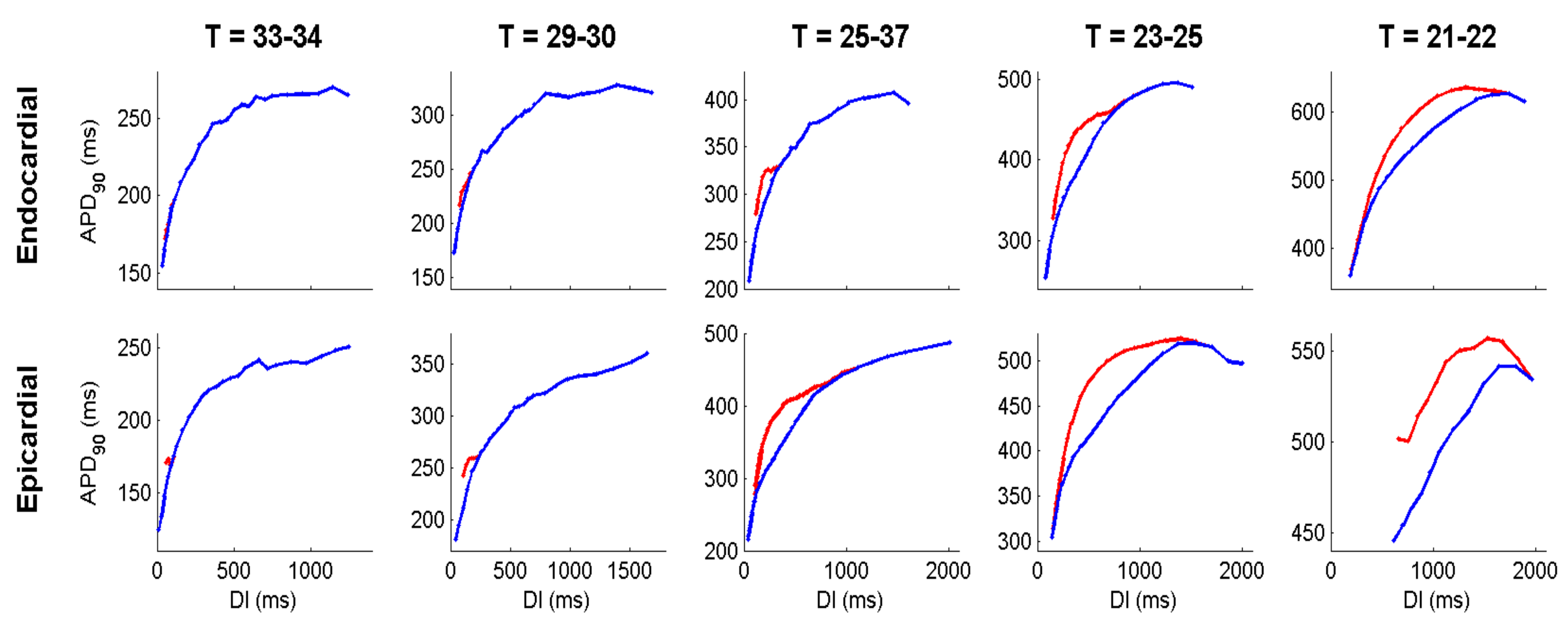




Canine Purkinje fiber

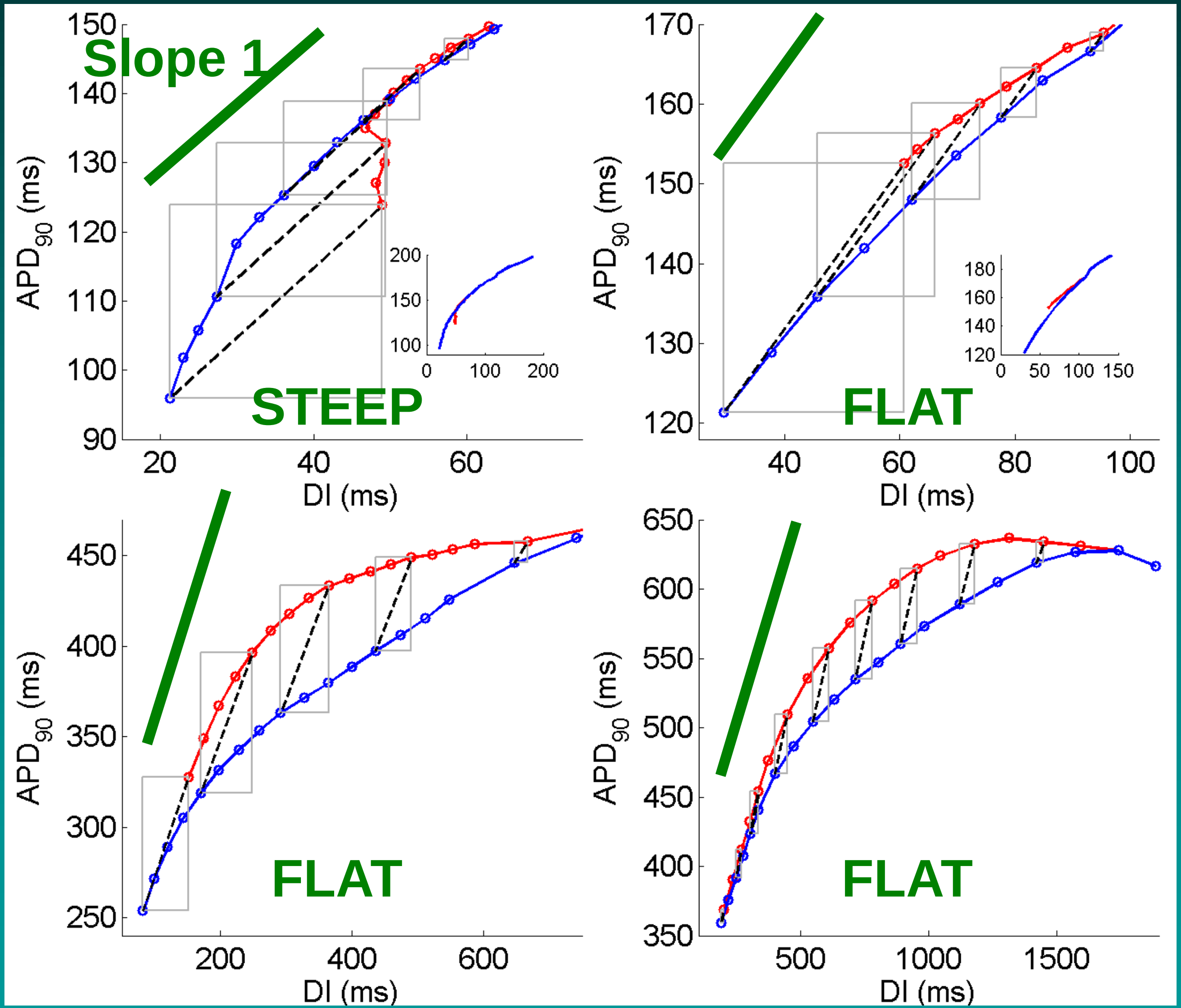
Restitution Splitting in Experiments

- Microelectrode recordings are used.
- Decreasing temperature can increase alternans and splitting.



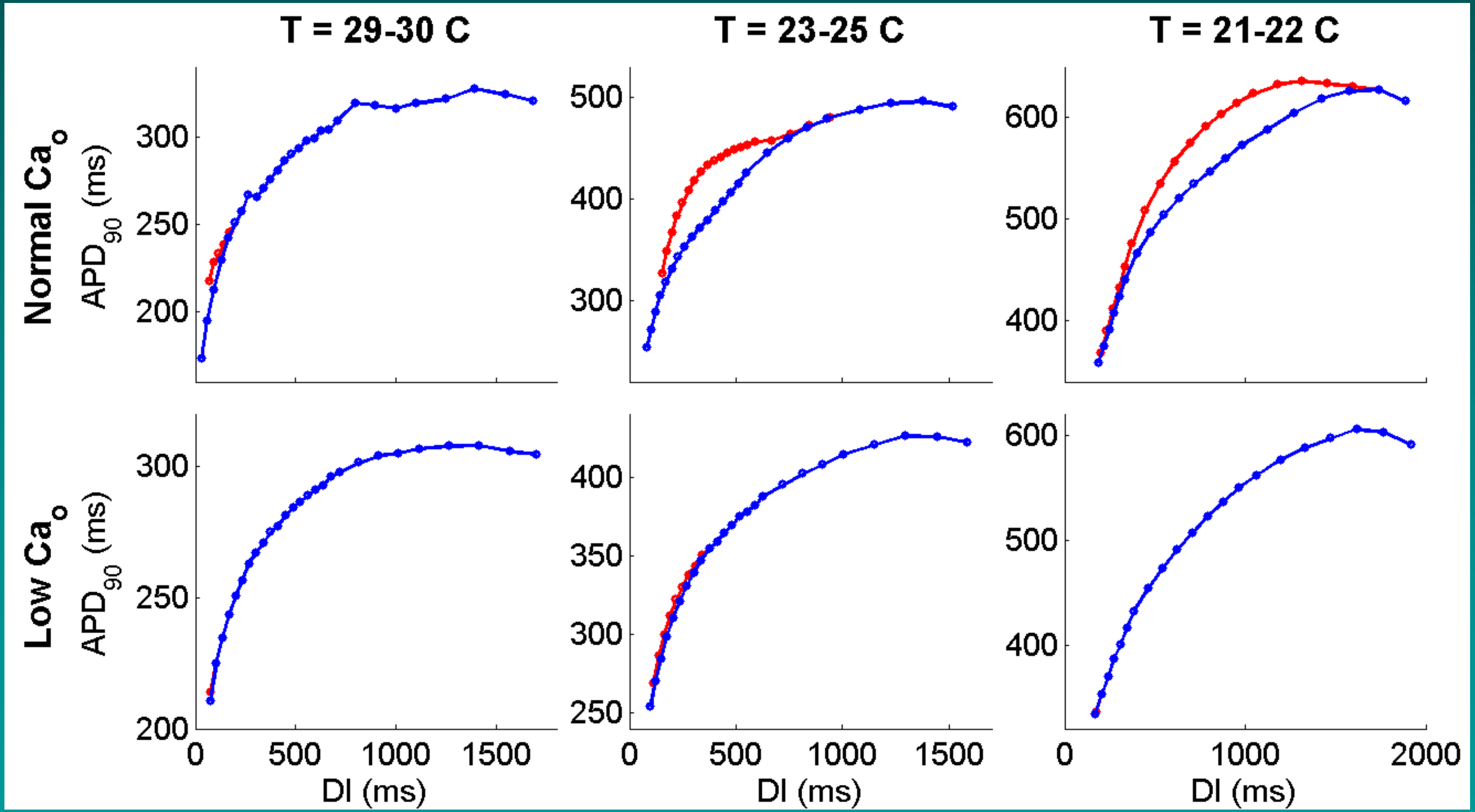
Restitution Splitting in Experiments

- During alternans, lines with slope one connect DI,APD pairs.
- Branch slopes can be steep or flat.
- Purkinje fibers more likely to be steep; epicardium and endocardium more likely to be flat.
- “Long” branch can be above or below “short” branch.



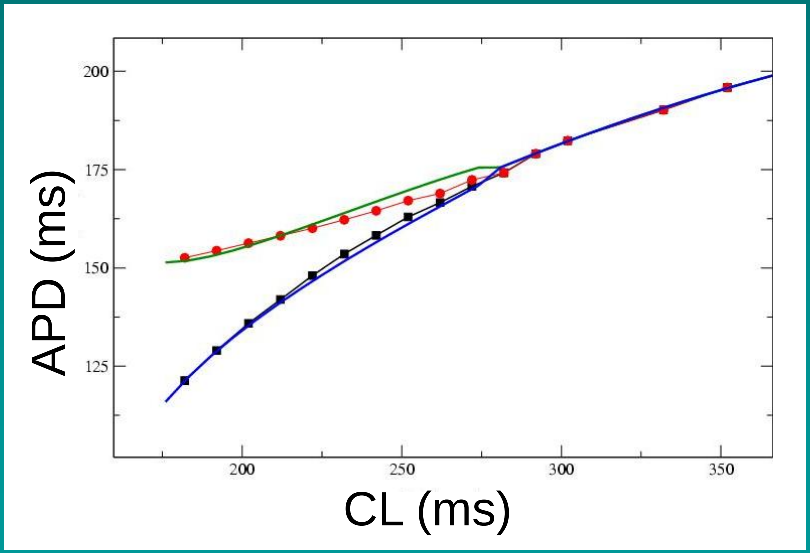
Calcium in Experimental Alternans

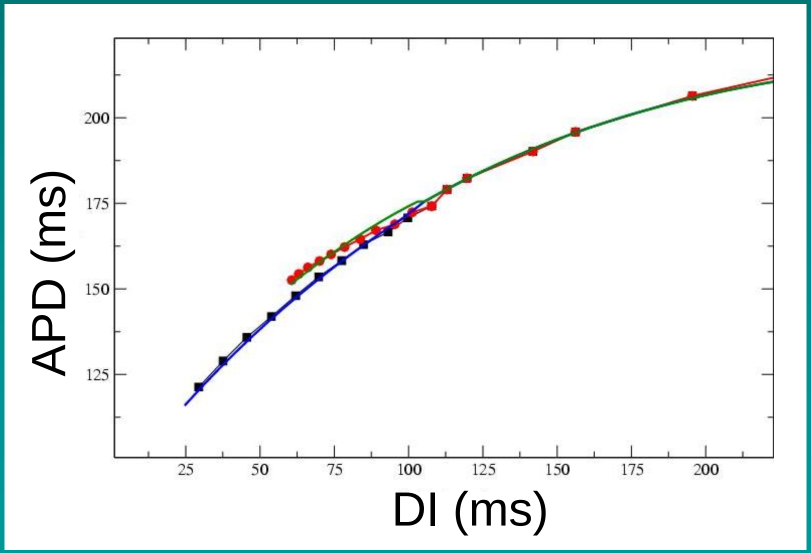
- Reducing extracellular Ca^{2+} (from ~2 mM to 62.5 μM) removes splitting but also eliminates alternans.



2-Dimensional Map Model

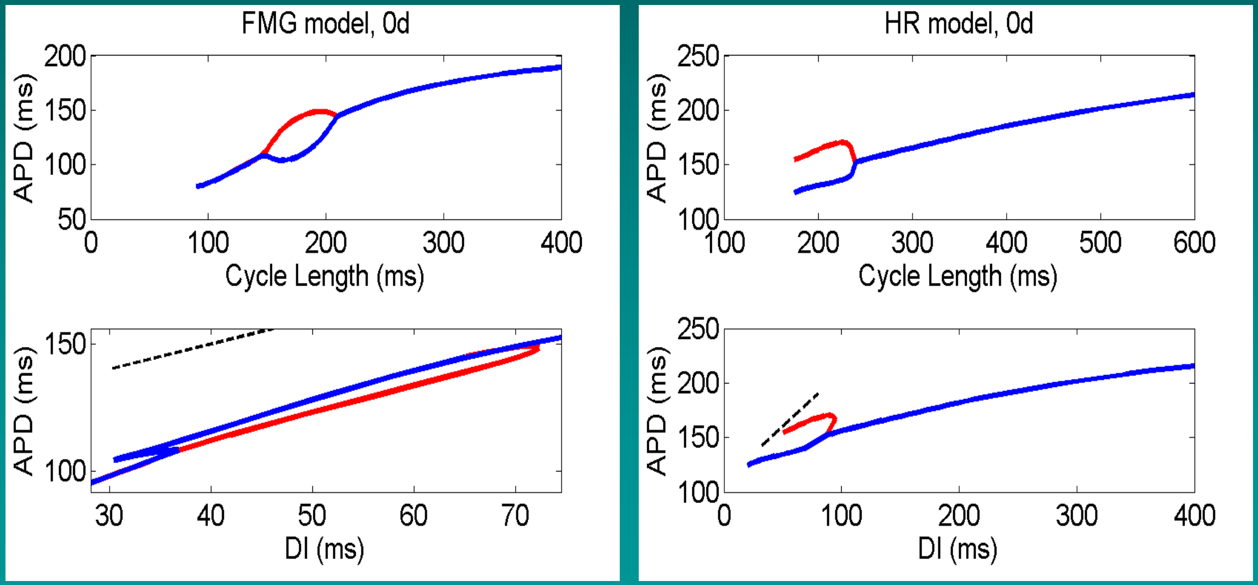
- A 2-dimensional map model using both DI and peak calcium to predict APD can reproduce splitting: $APD_{n+1} = f\,(DI_n, Ca_{n+1})$.
- Purkinje splitting data are well-matched.





Restitution Splitting in Models

- Some models also exhibit restitution curve splitting.
- Branches for FMG model have slope > 1, for HR model have slope < 0.5.

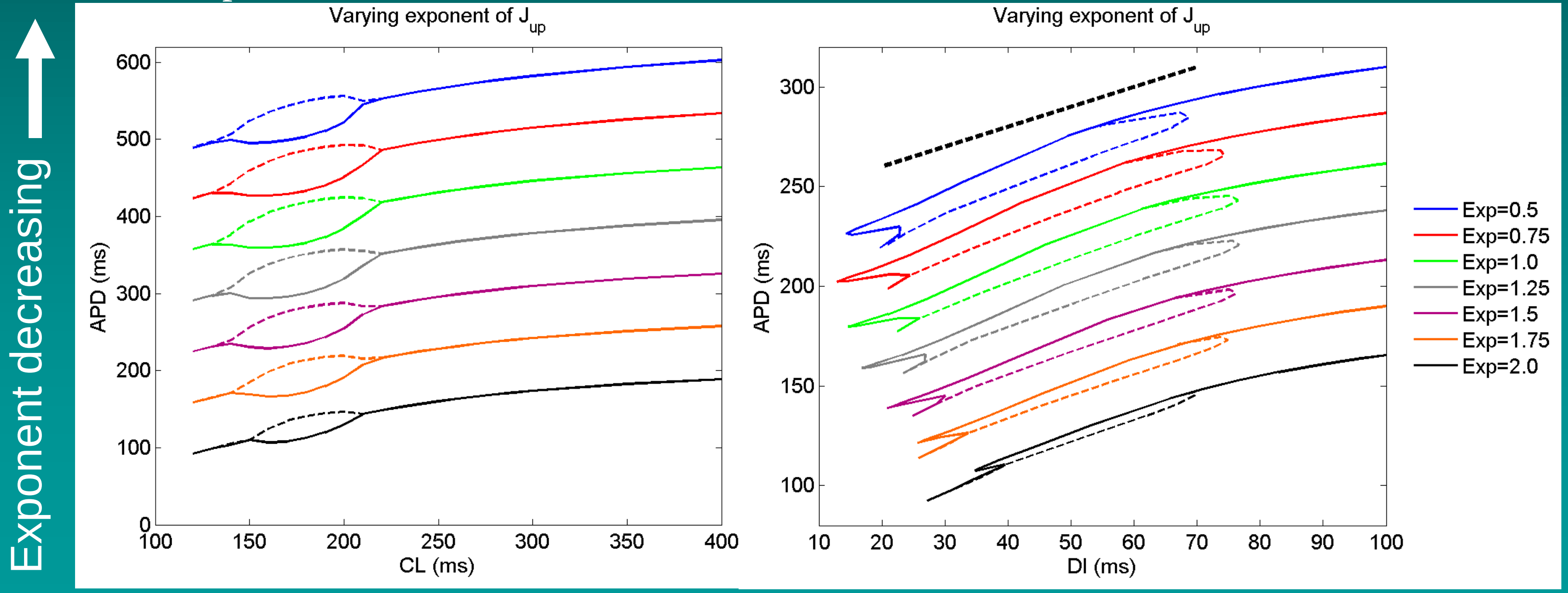


Fox JJ et al. 2002. Am J Physiol 282, H516. Hund T, Rudy Y. 2004. Circulation 110, 3168. Cherry EM and Fenton FH. 2007. Am J Physiol 292, H43.

Enhancing Restitution Splitting

- In the FMG model, restitution splitting can be enhanced by decreasing the exponent in the J_{up} term (0.5-2.0).

$$J_{\mathrm{up}} = \frac{V_{\mathrm{up}}}{1 + \left(\frac{K_{m_{\mathrm{up}}}}{[\mathrm{Ca}^{2+}]_{\mathrm{i}}} \right)^{2}}$$



Summary

- Restitution splitting occurs experimentally in normal canine Purkinje fibers and ventricular tissue.
- Slope of restitution curve branches can be steep or flat; no slope > 1 criterion for alternans.
- Models, 2-d map also can exhibit splitting.

Acknowledgements: Robert F. Gilmour, Jr., NSF, NIH

Web site: http://thevirtualheart.org