Patterns of rapid pacing that produce action potential block at a distance and fibrillation

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Shameless self-advertisement

Other topics I am studying:

- Use of "spectral entropy" to show that the left atrium shows a higher degree of order during atrial fibrillation than the right.

- Characterization of the various phases of fibrillation using quantities based on a "predator-prey" viewpoint of wave propagation and annihilation.

- Stability of action potentials and propagating waves to alternans and other modes.

- Defibrillation using curved field lines, not heterogeneities in the tissue.

Background

In our lab (Sydney Moise), we have a population of affected German shepherds that often die suddenly, throwing often thousands of arrhythmic events per day.

- The remarkable thing about this is not they die, but that they don't die.

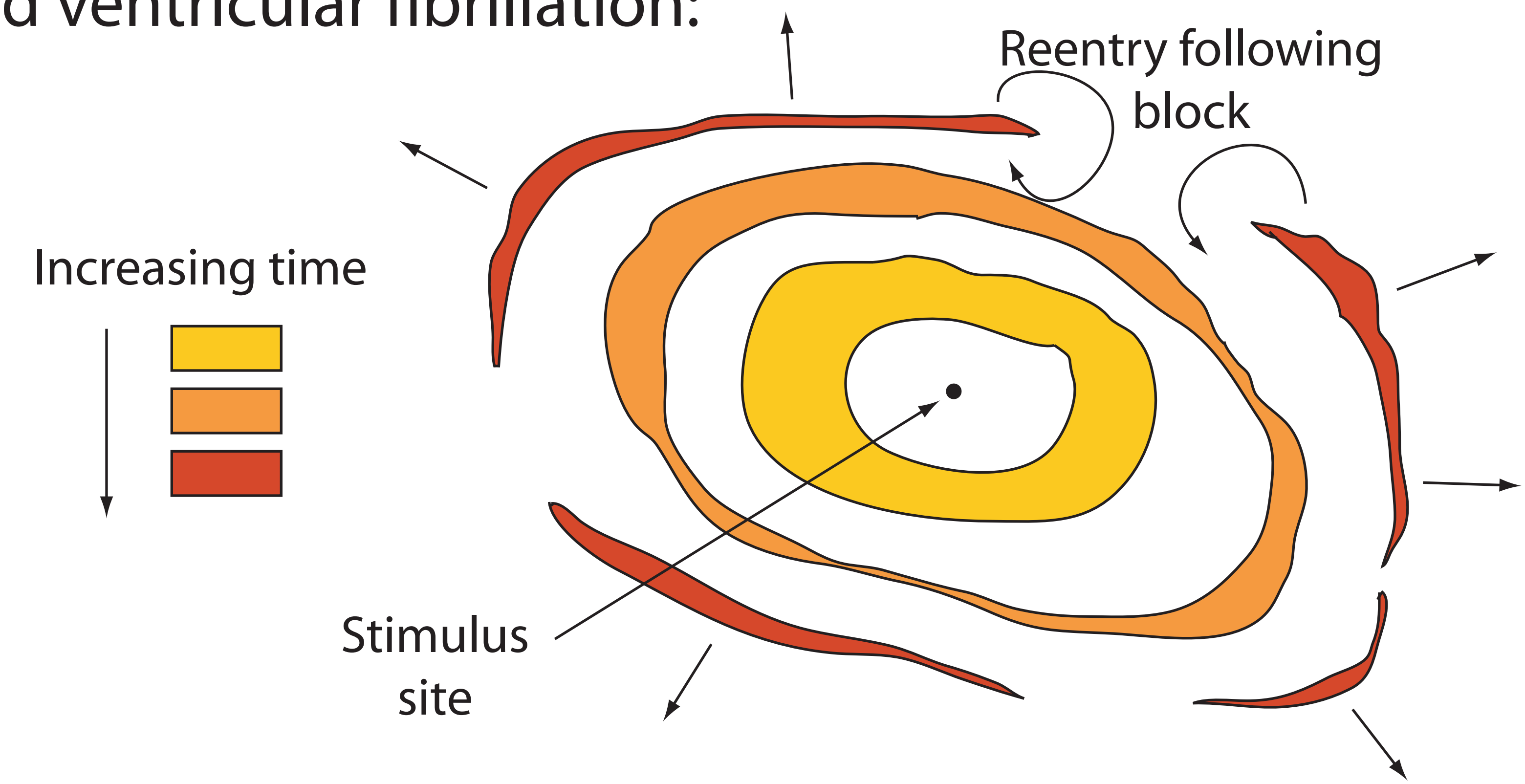
- Hypothesis: the dogs don't die because the patterns of rapid pacing the lead to VF in these dogs never (or almost never occurs).

- Question: can we determine what these patterns are?

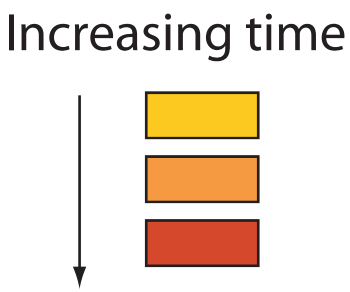
- If so, perhaps we can develop drug protocols that can dynamically prevent these patterns from occurring.

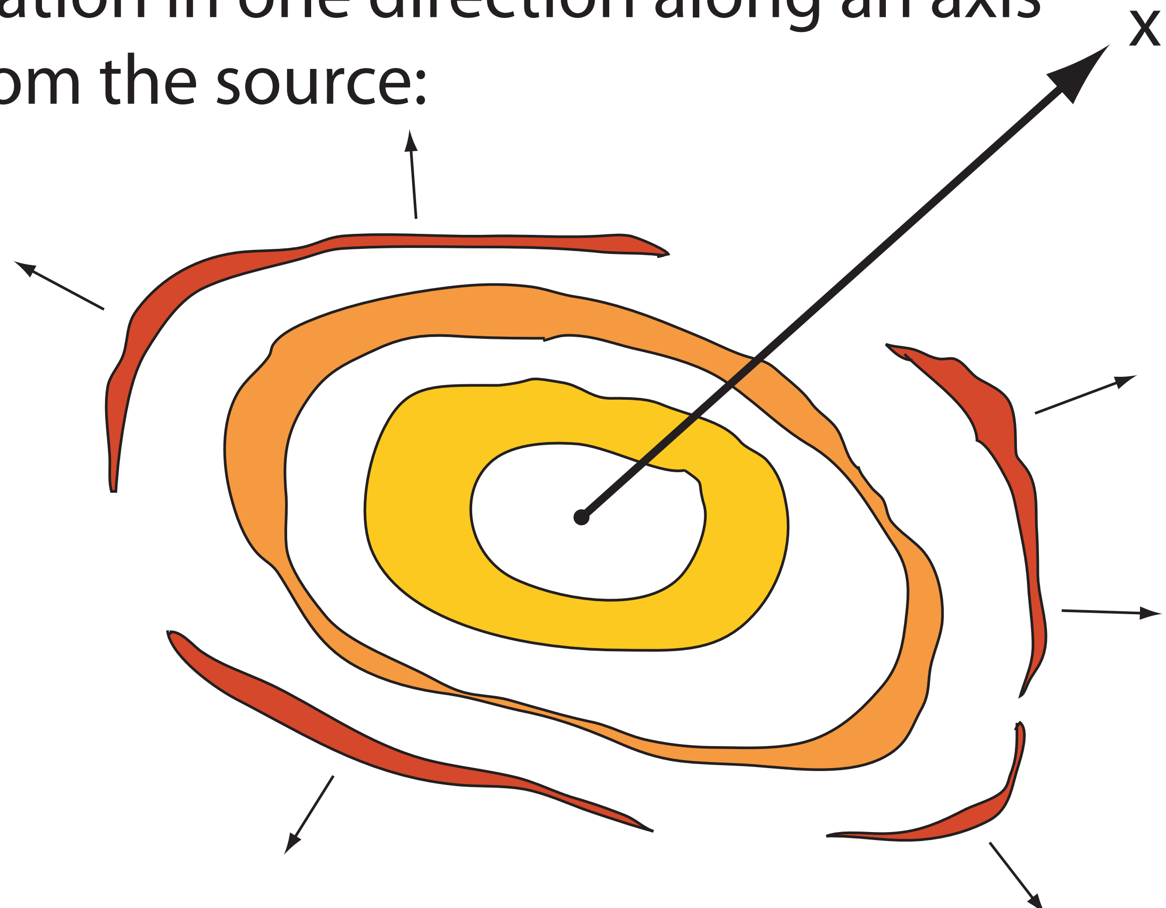
Motivation

Action potential waves that block at a finite distance from their source are important because they may lead to spiral wave reentry and subsequent onset of lethal cardiac arrhythmias such as ventricular tachycardia and ventricular fibrillation:



Consider propagation in one direction along an axis that emanates from the source:





Assume that:

- Wavefront velocity and action potential duration are functions of diastolic interval:

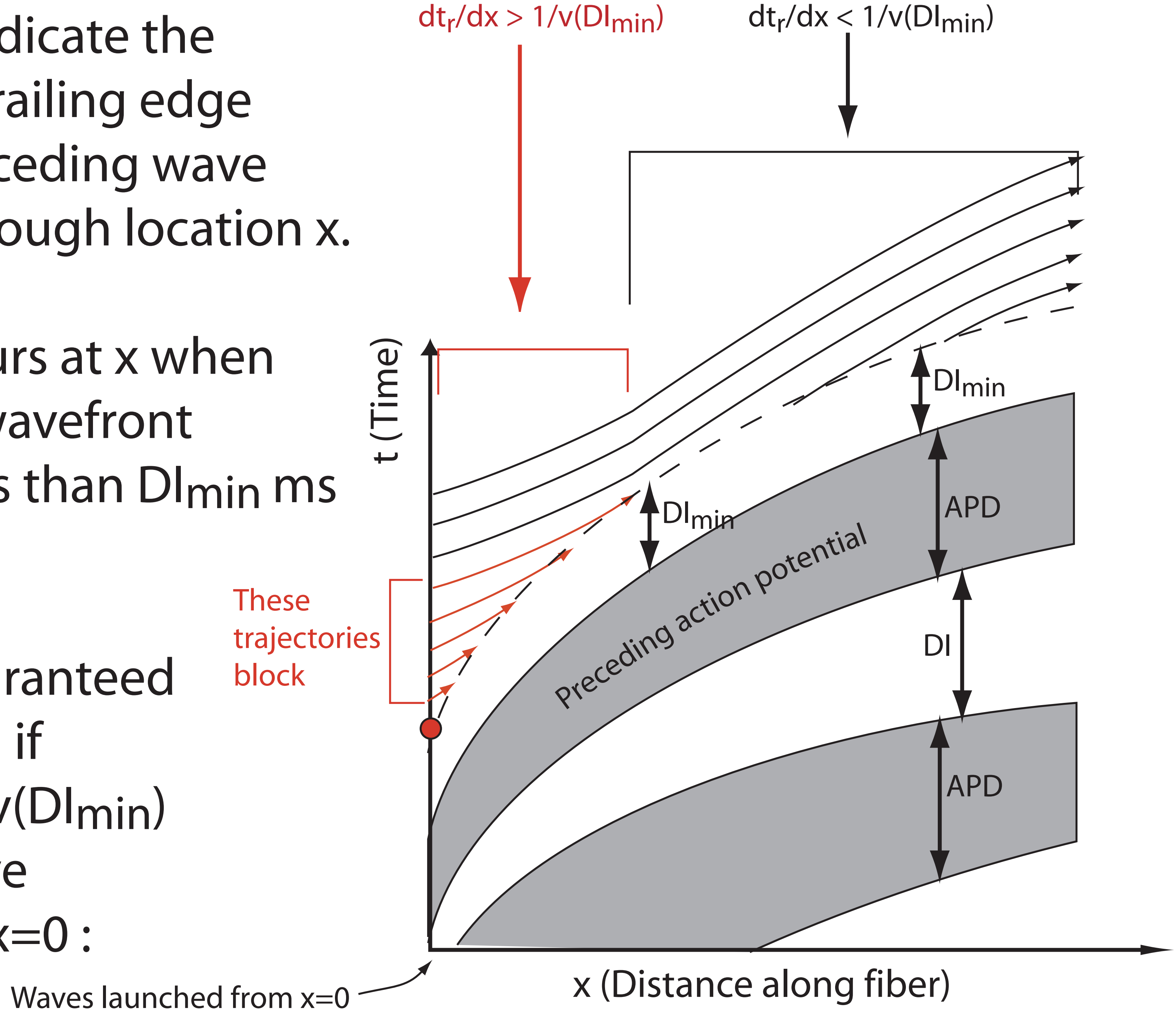
  $v(x) = v(DI(x)), \quad APD(x) = a(DI(x))$

- Block occurs when $DI(x) < DImin$ (say, 2 ms)

Let $t_r(x)$ indicate the time the trailing edge of the preceding wave passes through location x.

Block occurs at x when the next wavefront arrives less than DI_{min} ms later.

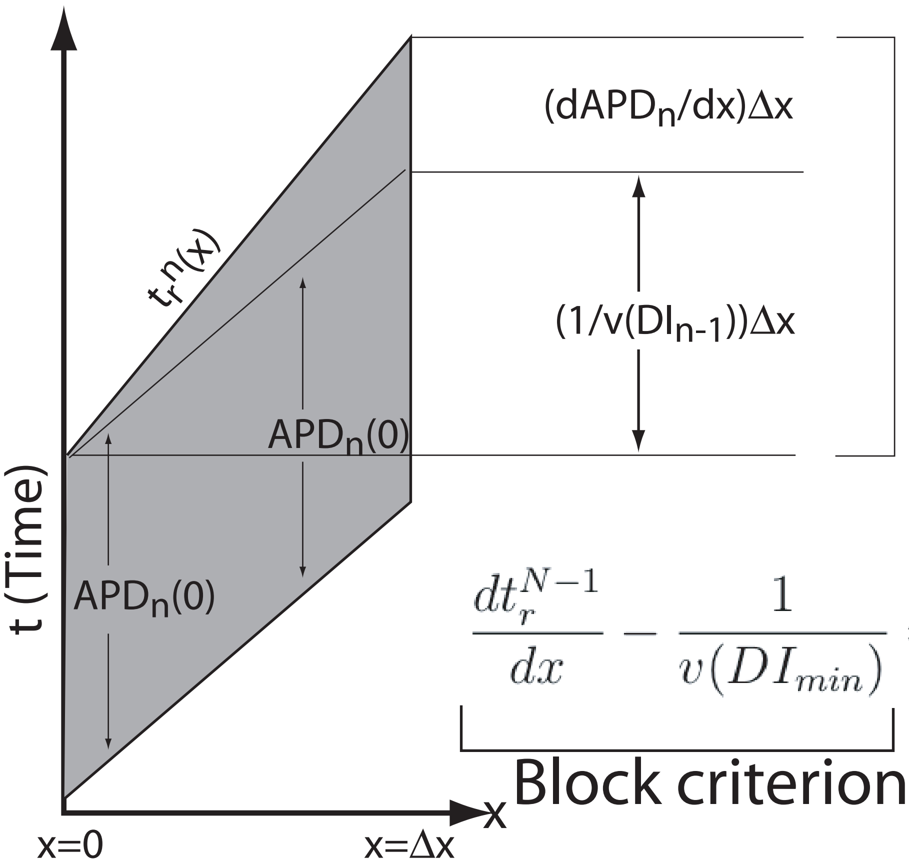
This is guaranteed to happen if $dt_r/dx > 1/v(DI_{min})$ at the wave source at x=0 :



To find evaluate the dt_r/dx, work backwards in time.

For example, the relationship,

$$\frac{dt_r^n}{dx} = \frac{1}{v(DI_{n-1})} + \frac{dAPD_n}{dx}$$



$(dt_r^n/dx)\Delta x$ ← comes from this picture.

Then subtract $1/v(DI_{min})$, use chain rule:

$$\frac{dt_r^{N-1}}{dx} - \frac{1}{v(DI_{min})} = \frac{1}{v(DI_{N-2})} - \frac{1}{v(DI_{min})} + a'(DI_{N-2})\frac{dDI_{N-2}}{dx}$$

Block criterion

Similarly:

$$\frac{dDI_n}{dx} = \frac{1}{v(DI_n)} - \frac{1}{v(DI_{n-1})} - a'(DI_{n-1})\frac{dDI_{n-1}}{dx}$$

shows that the key quantity dDI/dx is amplified when the APD restitution function is steep.

We evaluated the block criterion $dt_r^n/dx - 1/v(DI_{min}) > 0$ for the following case:

Ten S1 pacing stimuli at 500 ms pacing interval.

Then the four premature stimuli S2 through S5 were applied with relatively short diastolic intervals (labeled DI_{S2}, DI_{S3}, DI_{S4} and DI_{S5}).

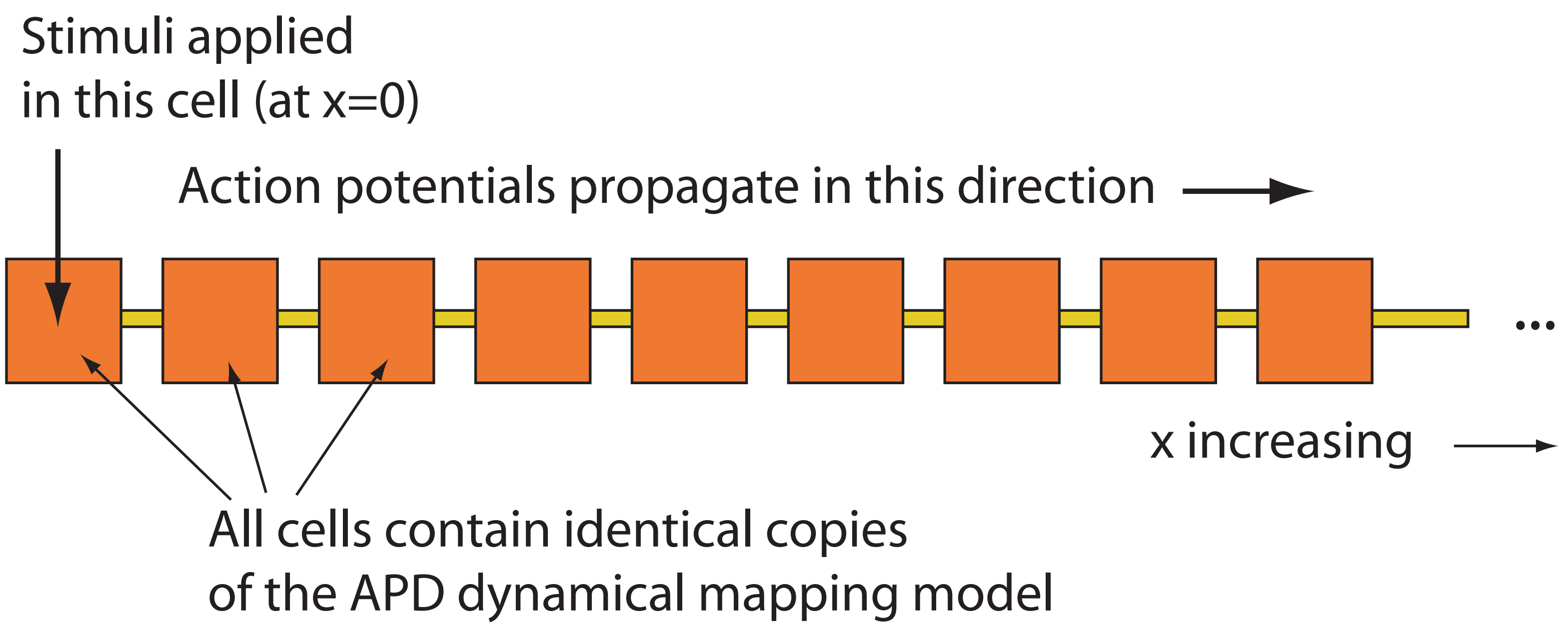
For this case, repeated substitution of the dDI/dx amplification equation yields the following block criterion for the action potential wave generated following DI_{S5}:

$$BC = \frac{dt_r^{S4}}{dx} - \frac{1}{v(DI_{min})} = \left(\frac{1}{v(DI_{S4})} - \frac{1}{v(DI_{min})}\right) - a'(DI_{S4})\left(\frac{1}{v(DI_{S3})} - \frac{1}{v(DI_{S4})}\right) + a'(DI_{S4})a'(DI_{S3})\left(\frac{1}{v(DI_{S2})} - \frac{1}{v(DI_{S3})}\right) - a'(DI_{S4})a'(DI_{S3})a'(DI_{S2})\left(\frac{1}{v(DI_{ss})} - \frac{1}{v(DI_{S2})}\right)$$

(Block criterion)

Block is predicted to occur when this quantity is positive.
Note: (1) differences in the velocities of consecutive waves contributes to block, (2) these contributions can be amplified if the slope of the APD restitution function is greater than 1.

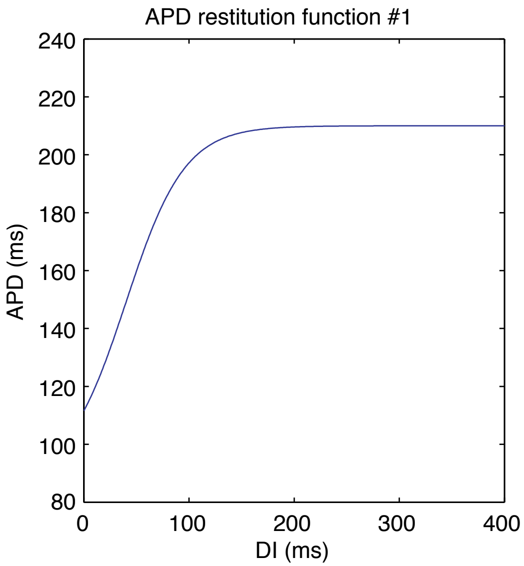
To test the block criterion theory, we used a "coupled-maps" simulation, which models action potential propagation and failure along a one-dimensional fiber:

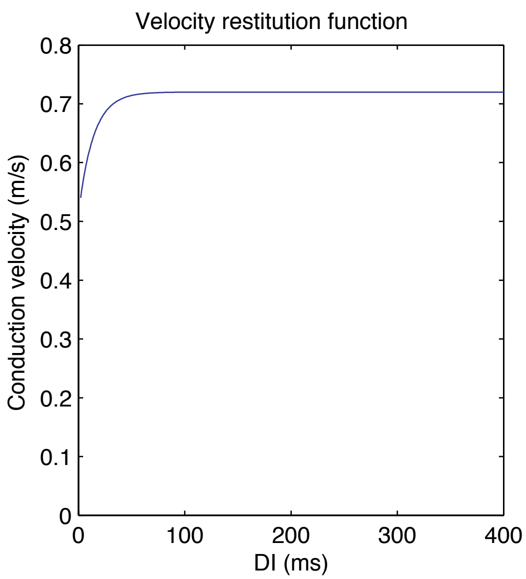


Conduction velocity determined by DI.
Propagation failure occurs when DI falls below DI_{min} = 2 ms.

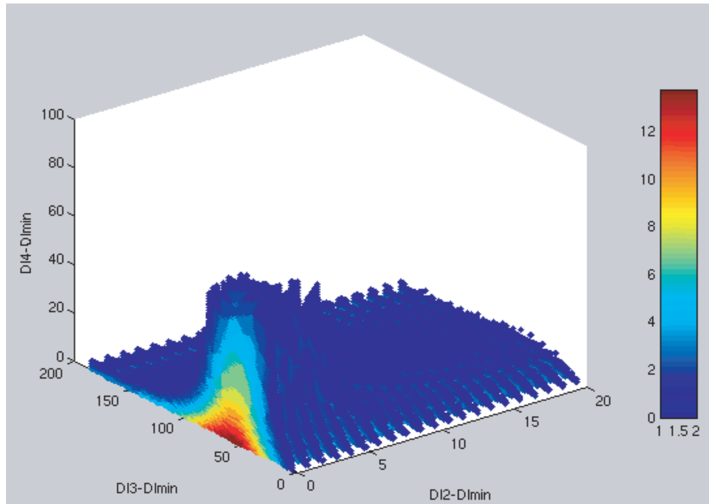
Several stimuli were applied at 500ms intervals (called S1 stimuli), followed by 4 stimuli (S2 through S5) applied with shorter intervals, BCL_{S2} through BCL_{S5}.

Model #1: a(DI) (APD restitution function) remains steep as DI -> 0

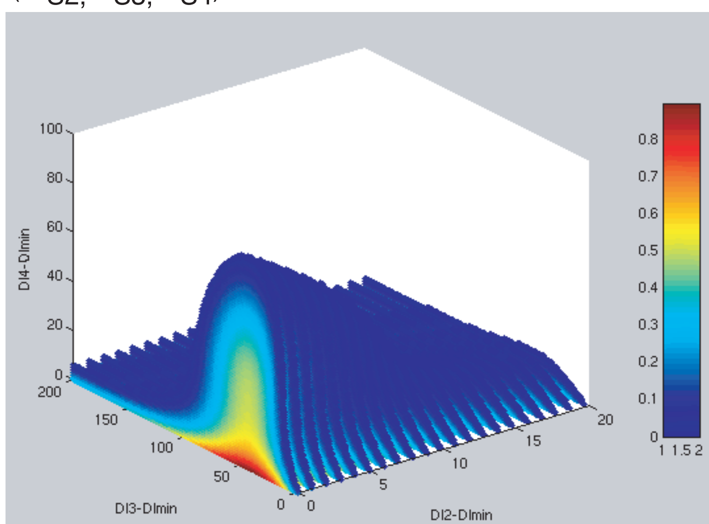




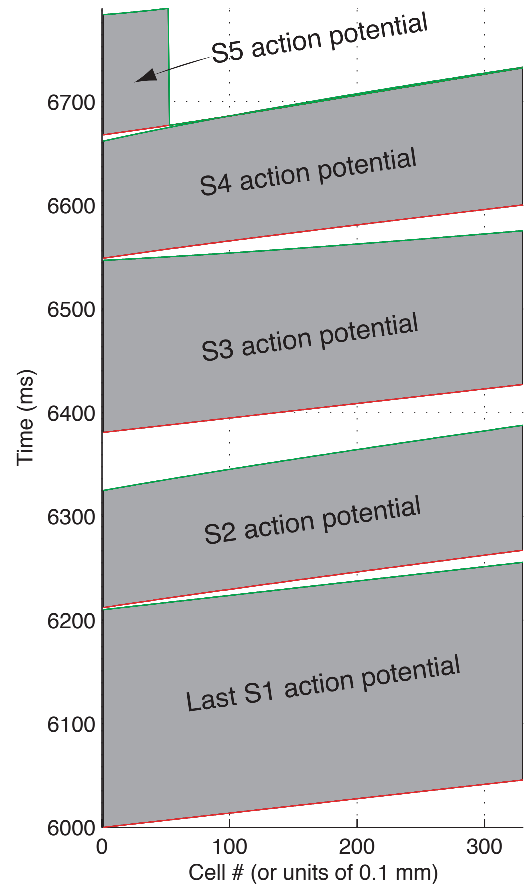
Number of DI_{S5}'s that produce block, as a function of (DI_{S2},DI_{S3},DI_{S4}) in coupled-maps simulations



Block criterion BC (when >0) calculated as a function of (DI_{S2},DI_{S3},DI_{S4})



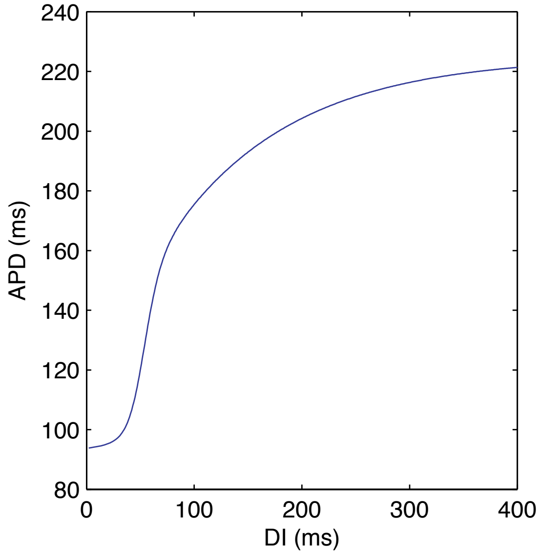
Action potential leading and trailing edge arrival times as functions of x from the coupled-map simulation:



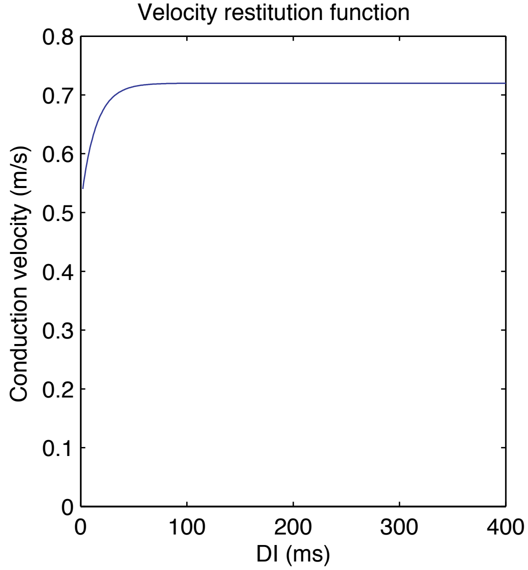
"short-long-short-short"

Model #2: a(DI) (APD restitution function) levels off as DI -> 0

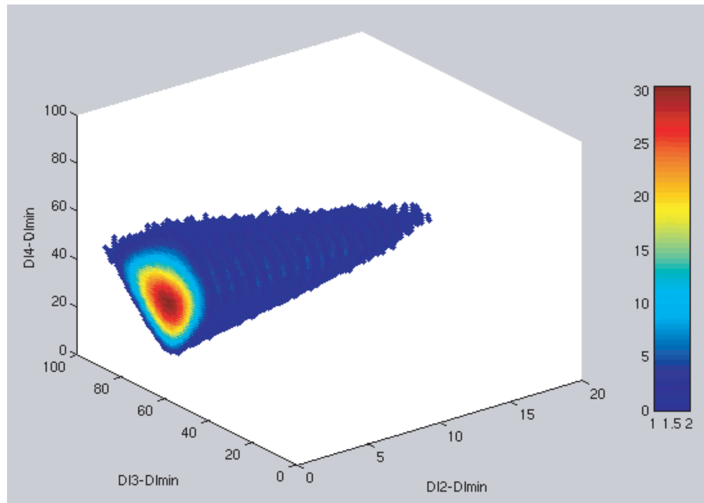
APD restitution function #2



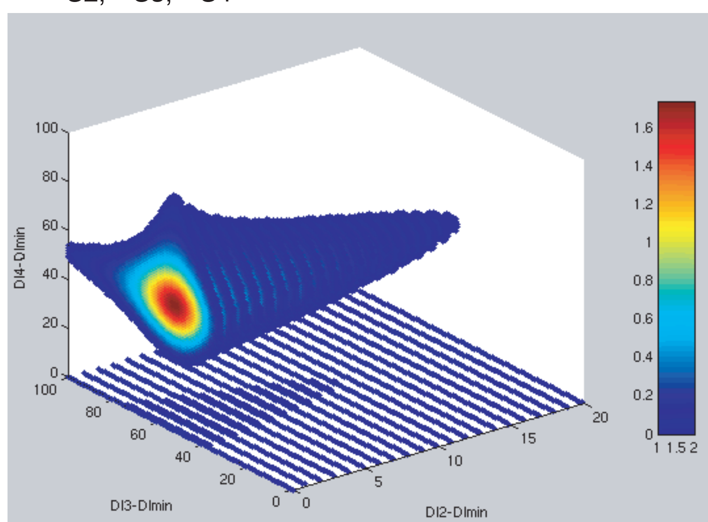
Velocity restitution function



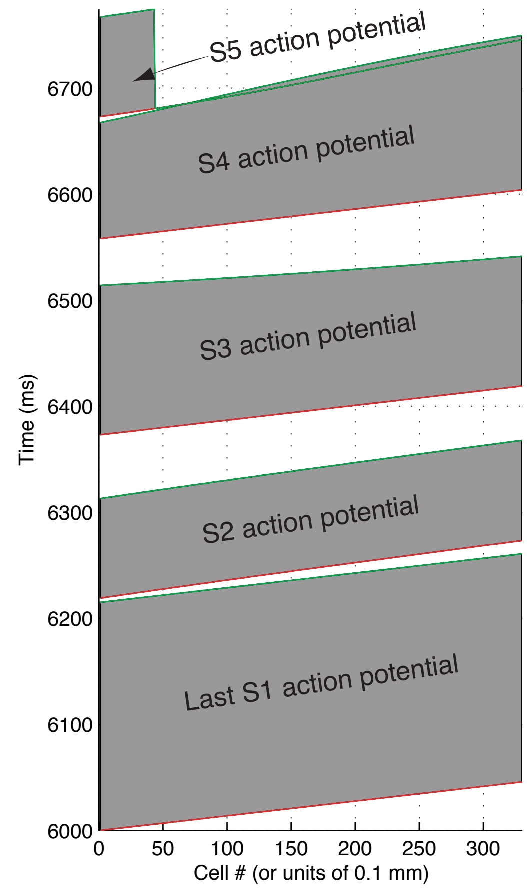
Number of DI_{S5}'s that produce block as a function of (DI_{S2},DI_{S3},DI_{S4}) in coupled-map simulations



Block criterion BC (when >0) calculated as a function of (DI_{S2},DI_{S3},DI_{S4})



Action potential leading and trailing edge arrival times as functions of x from the coupled-map simulation:



"short-long-long-short"

Effect of memory on action potential block

- Action potential duration is now also a function of memory: $APD_{n+1} = a(DI_n(x),\mathbf{M}_{n+1}(x))$
- Here, **M** is a vector of "memory" quantities, with $\mathbf{M}_{n+1}(x) = \mathbf{m}(\mathbf{M}_n,DI_n(x),APD_n)$
- Velocity is still just a function of DI: $v = v(DI(x))$.

We now find:

$$\begin{bmatrix} \frac{dDI_n}{dx} \\ \frac{d\mathbf{M}_{n+1}}{dx} \end{bmatrix} = \left(\frac{1}{v(DI_n(x))} - \frac{1}{v(DI_{n-1}(x))} \right) \begin{bmatrix} 1 \\ \frac{\partial \mathbf{m}}{\partial DI} \end{bmatrix} - A \cdot \begin{bmatrix} \frac{dDI_{n-1}}{dx} \\ \frac{d\mathbf{M}_n}{dx} \end{bmatrix}$$

The matrix A turns out to be the same linear mapping that describes stability of the APDs in single cells undergoing constant pacing. It now is the factor amplifying the difference in velocities.

Discussion

1. When the restitutions functions of beagle dogs are measured and the block condition calculated, sequences of stimuli having intervals satisfying the condition nearly always induce VF, while those that don't, generally don't! It is surprising that such a simple model can predict VF induction in live animals.

2. Block at a distance occurs when the velocity of the trailing edge of the preceding wave is slower than the velocity of the next wavefront when $DI = DI_{min}$.

3. This criterion is easiest to satisfy when S2 through S5 are chosen so that consecutive wavefront velocities are as different as possible, and the APD restitution function is as steep as possible.

Discussion/Summary

4. While APD restitution slope >1 increases the tendency for block, it is not necessary for block.

5. Blocks at a distance observed in a coupled maps simulation occur when predicted by the blocking criterion.

6. When memory is present, the role of slope of the restitution function is replaced by the eigenvalues of the same matrix used to assess the stability of the system against APD alternans.