The dynamics of action potential propagation—implications for initiating and terminating tachyarrhythmias

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Overview

- Introduction: Nonlinear dynamics: what is it; why is it needed?
- Electrical restitution theory
- Eigenmode analysis
- Perturbation analysis
- “Magic numbers”
- Conclusions

1. Introduction

- Opinion: There are at least two required components in the 3-D Modeling of the heart
  - Effects due to the anatomy and geometry of the heart
  - Effects due to nonlinear dynamics
- This talk will concentrate on nonlinear dynamical effects.

Nonlinear dynamics

- What is it?
  - Nonlinear dynamical systems are systems whose behavior is governed by rules that specify how future states of the system depend on previous states.
  - Simple cases:

$$d\mathbf{x}/dt = f(\mathbf{x}(t))$$

or

$$\mathbf{x}_{n+1} = \mathbf{f}(\mathbf{x}_n)$$

Nonlinear dynamics

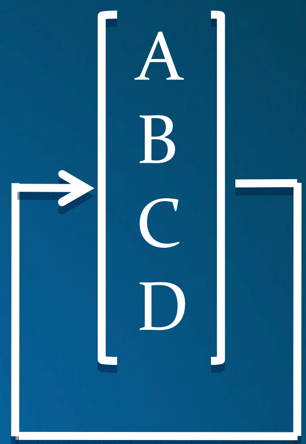
- You can often understand a system like the following without using nonlinear dynamics:

$$A \longrightarrow B \longrightarrow C \longrightarrow D$$

- Nonlinear dynamics helps us to understand this kind of system:

$$\begin{tikzcd} A \arrow[r] & B \arrow[r] & C \arrow[r] & D \arrow[lll, bend left] \end{tikzcd}$$

- And is even more useful for understanding this kind of system:



Nonlinear dynamics

- Examples from cardiac action potential propagation:
  - Nonlinear dynamics not so important for wave propagation during sinus rhythm:

Sinus node → Atria → AV node → Purkinje system → Ventricles

  - Nonlinear dynamics is often important for reentrant waves:

Spatial pattern of wavefronts → Spatial pattern of repolarization

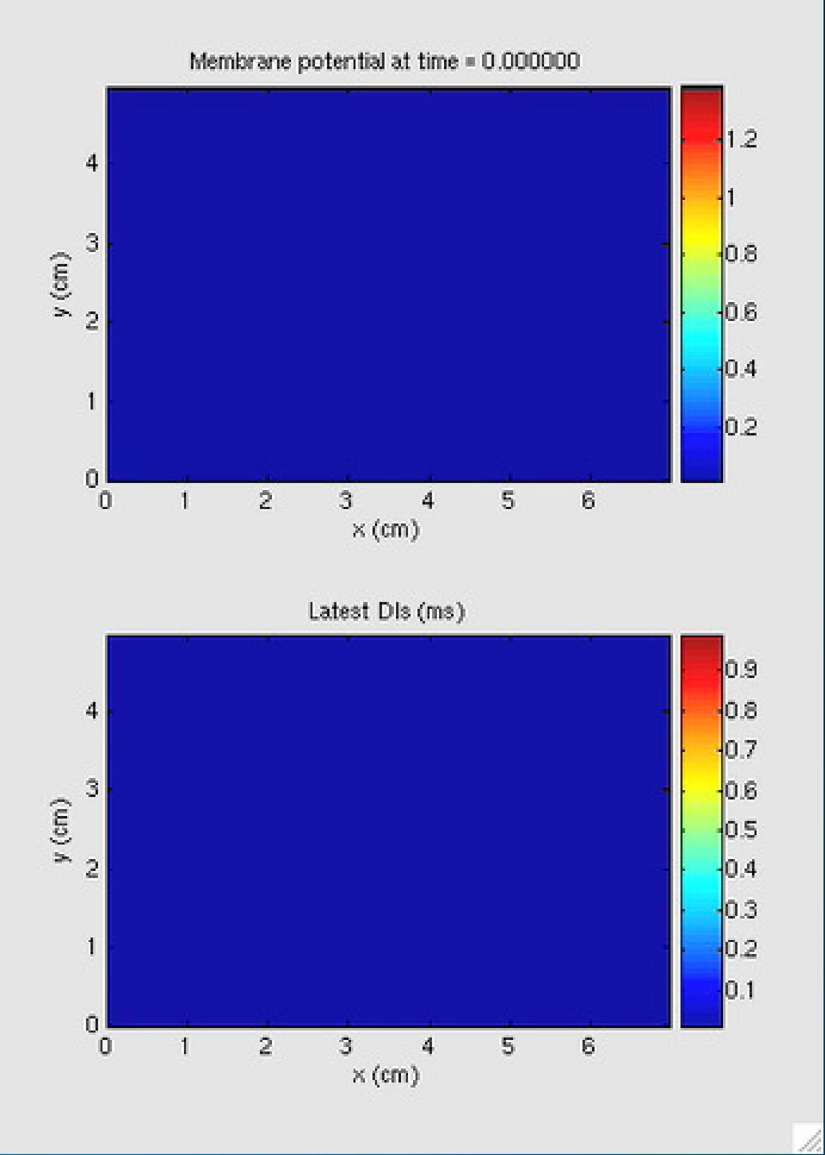
Nonlinear dynamics

- For example consider the following simulation:

Top: membrane potential

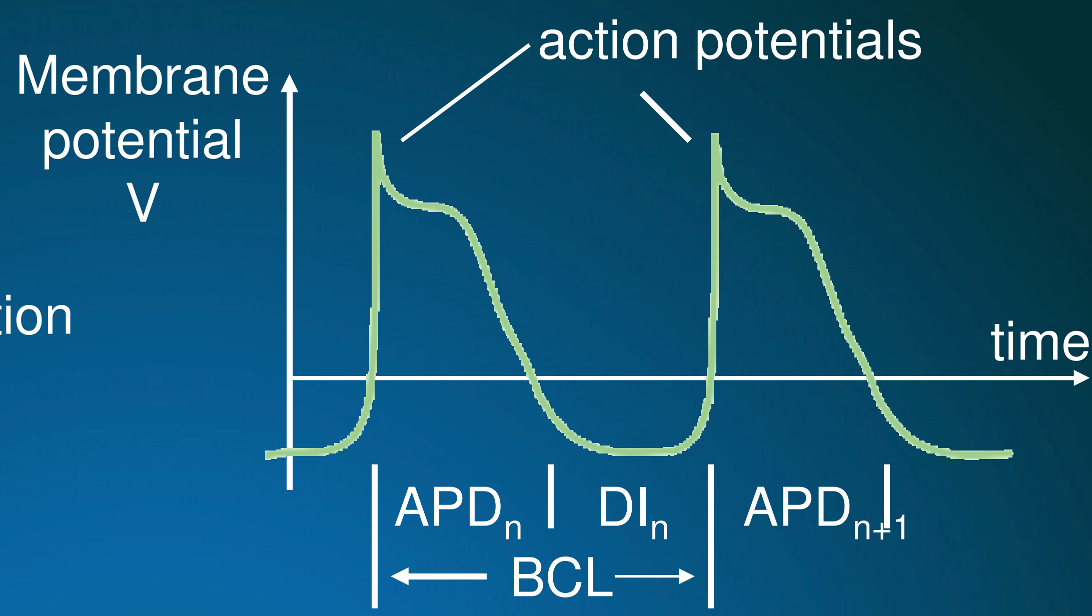
Bottom: Last diastolic interval

Compare the left half of the simulation to the right half.



2. Electrical restitution theory

- Nonlinear dynamics of constant pacing provides some clues.
- Theory of electrical restitution relates APD (action potential duration) and DI (diastolic interval):

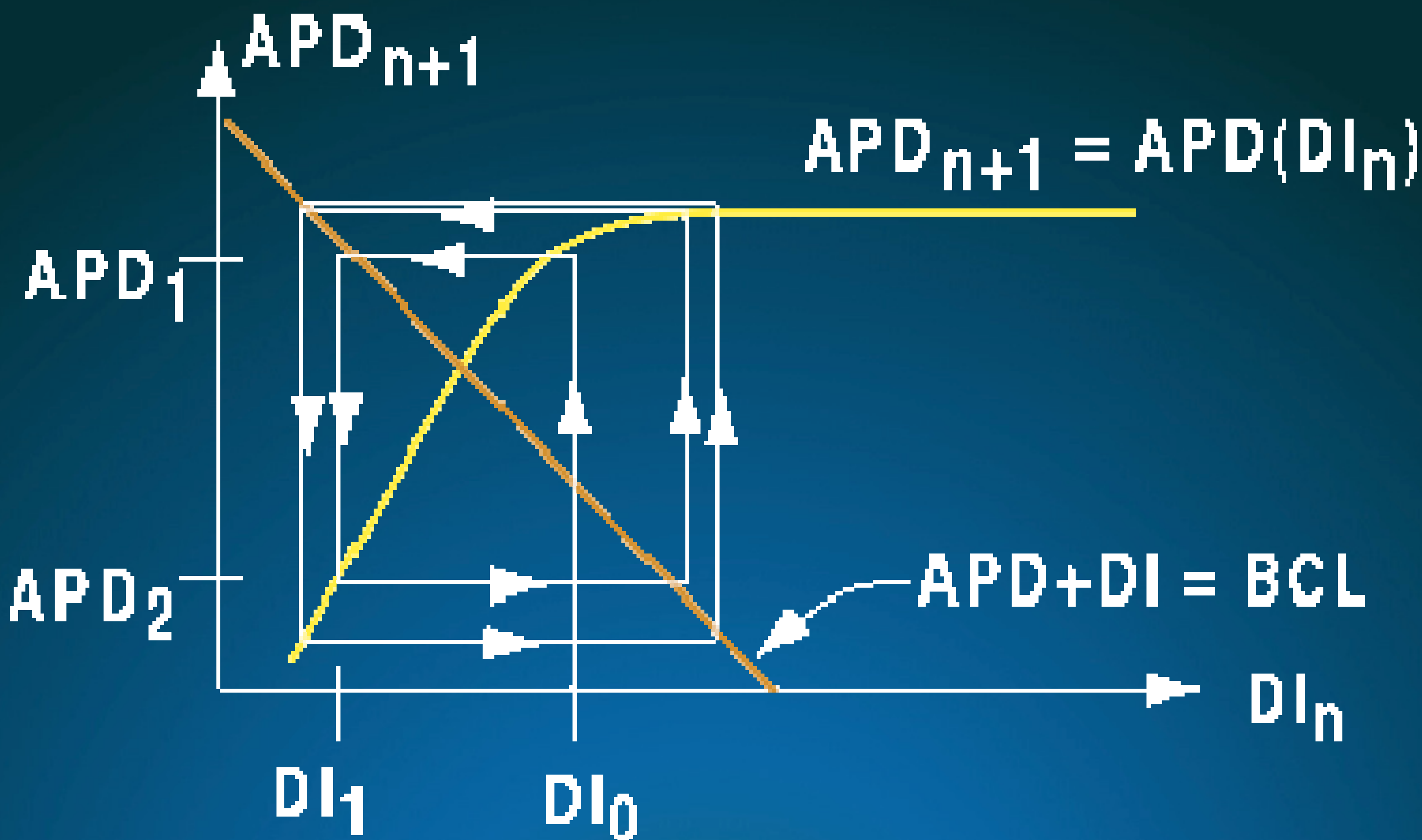


APD = action potential duration
DI = diastolic interval
BCL = basic cycle length

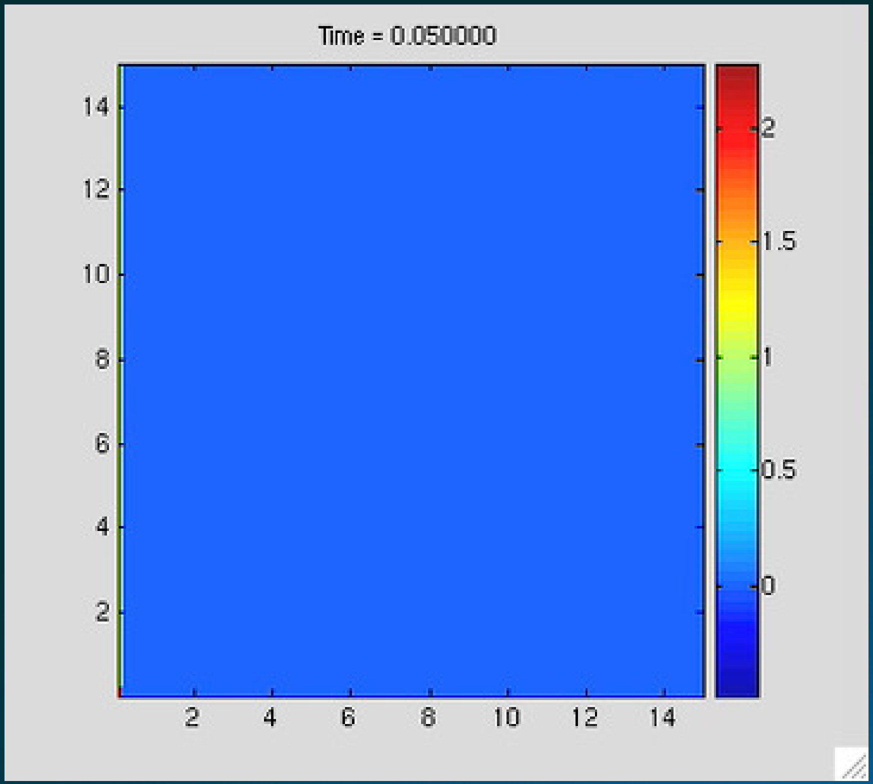
Simple model, valid to zero order:

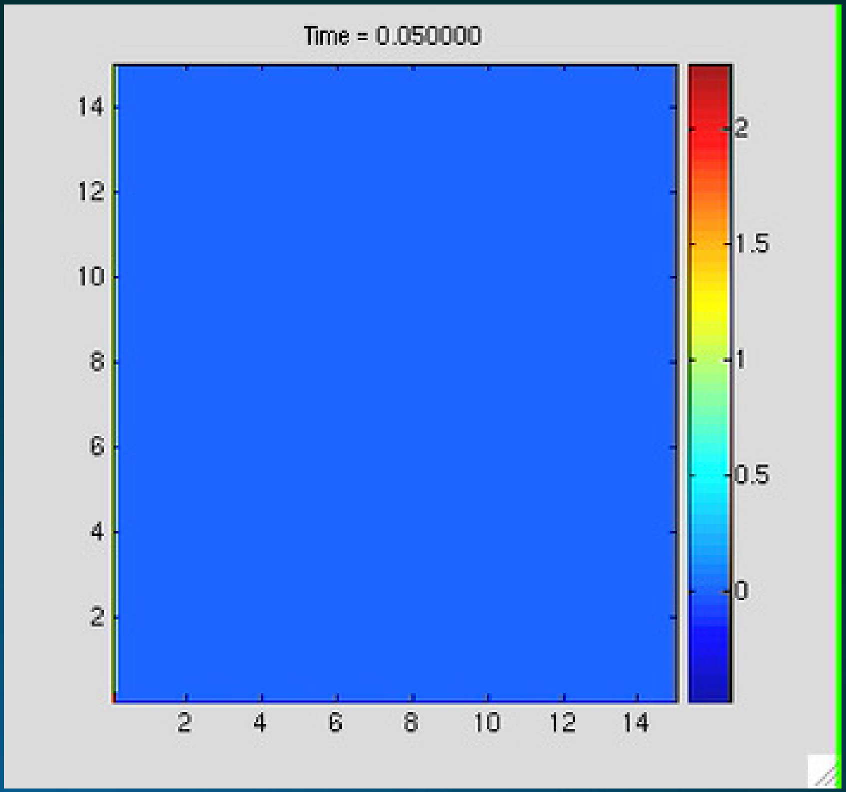
$APD_{n+1} = APD(DI_n)$ -> "Restitution function"
$DI_{n+1} = BCL - APD_{n+1}$

Nonlinear dynamical system



Not all reentrant wave patterns are the same:





- Different types of patterns will likely require different therapies to stop or prevent.
- What causes these differences?

Electrical restitution

- Electrical restitution dynamics suggests one mechanism by which wave breakup can occur:

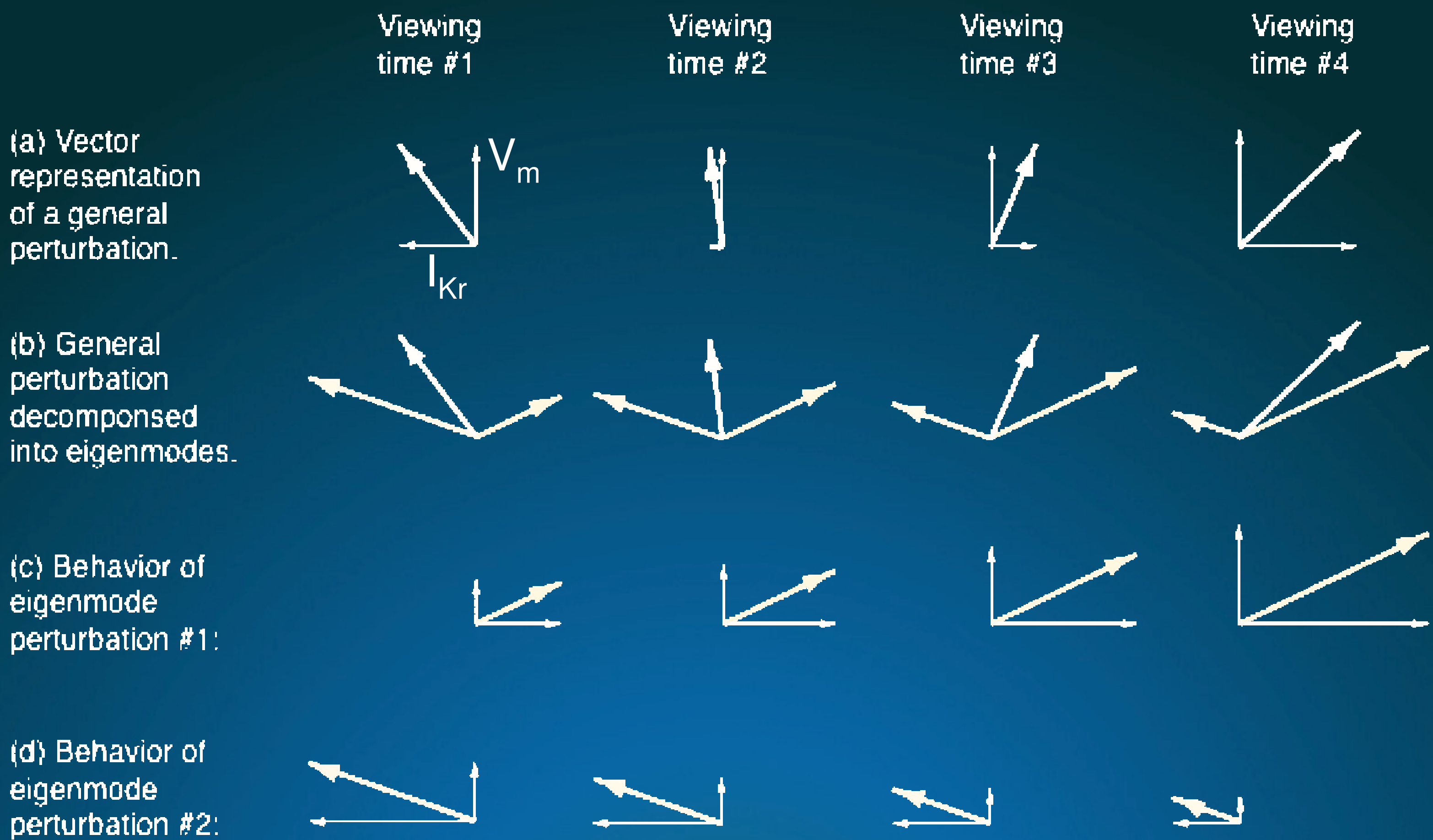
Head-tail interaction → Decrease in APD following short DIs → Positively sloped APD vs. DI restitution function

Steep slope in the restitution function → Alternation in successive APDs (called "alternans")

Large enough alternations → NO action potential → Wave breakup

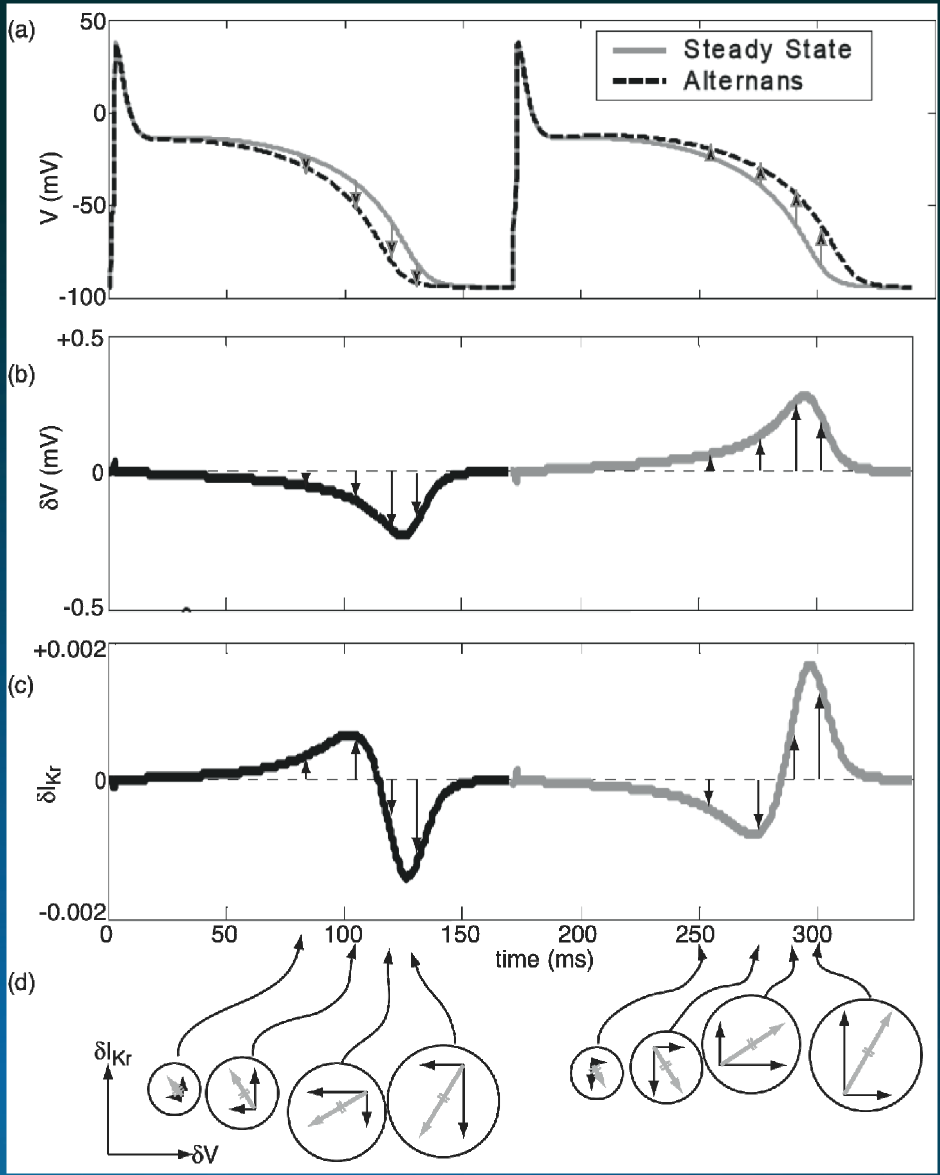
3. Eigenmode analysis

- Actually, APD is not a strict function of DI. When this is taken into account, behavior other than alternans is simultaneously present. What to do?



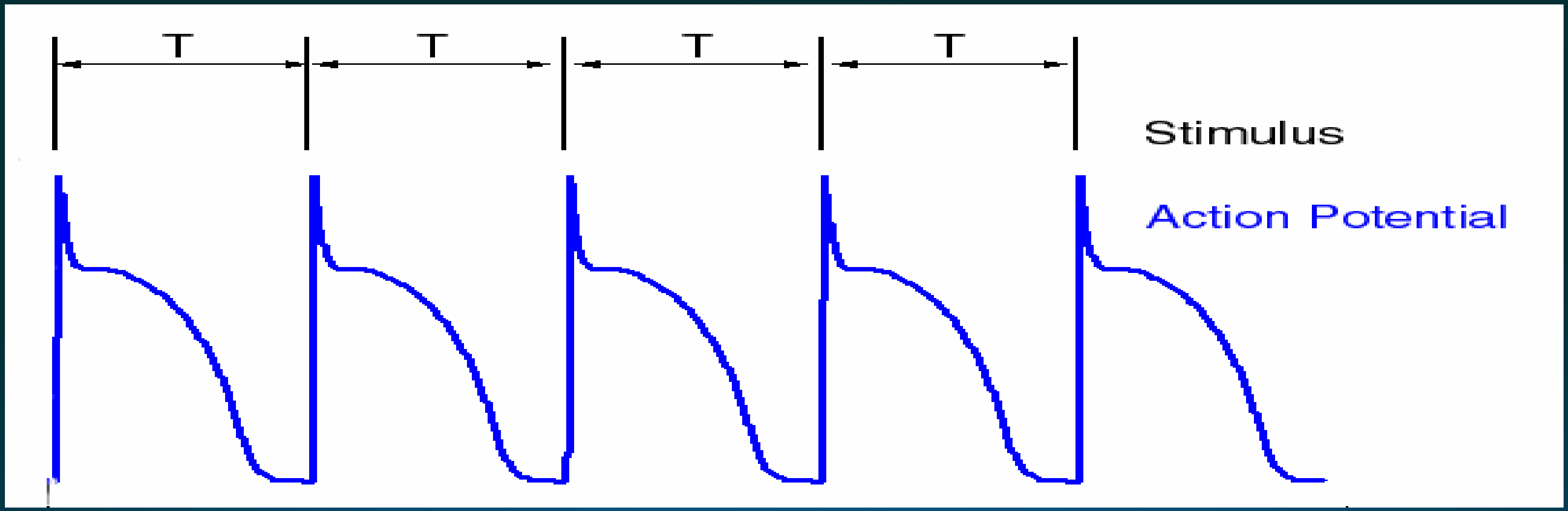
Eigenmode analysis

Anatomy of the alternans eigenmode in a single cell:



The eigenmode method

- Step #1: Determine the steady state



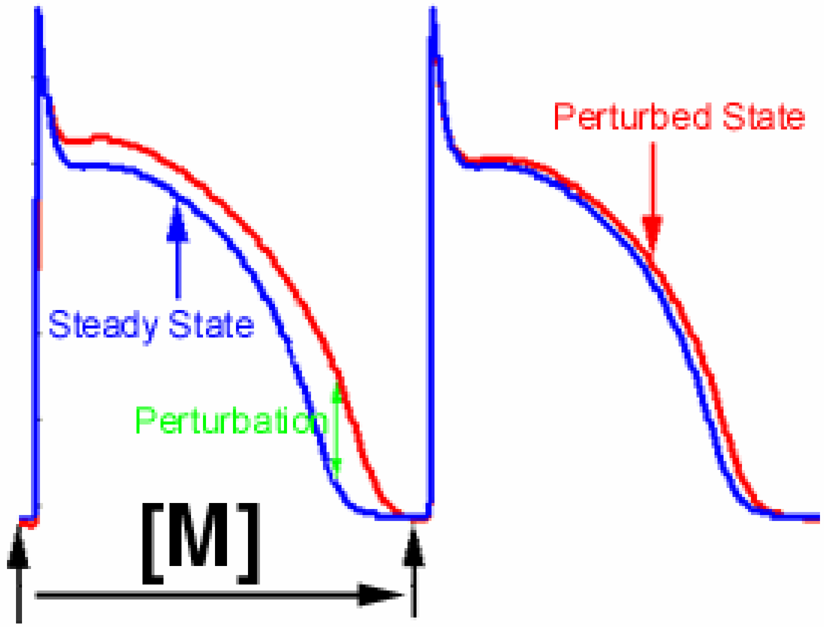
- Let the system settle down to steady state behavior, or use a secant method to solve the steady state equations.

Method

- Step #2: Construct a linear map M relating the perturbations of successive cycles:

$$\delta\mathbf{x}(T) = \mathbf{M} \cdot \delta\mathbf{x}(0)$$

where T is pacing period.



$$\begin{bmatrix} \Delta V(T) \\ \Delta m(T) \\ \Delta h(T) \\ \Delta j(T) \\ \Delta d(T) \\ \Delta f(T) \\ \Delta x1(T) \\ \Delta[Ca^{2+}]_i(T) \end{bmatrix} = [M] \cdot \begin{bmatrix} \Delta V(0) \\ \Delta m(0) \\ \Delta h(0) \\ \Delta j(0) \\ \Delta d(0) \\ \Delta f(0) \\ \Delta x1(0) \\ \Delta[Ca^{2+}]_i(0) \end{bmatrix}$$

Perturbation after a cycle

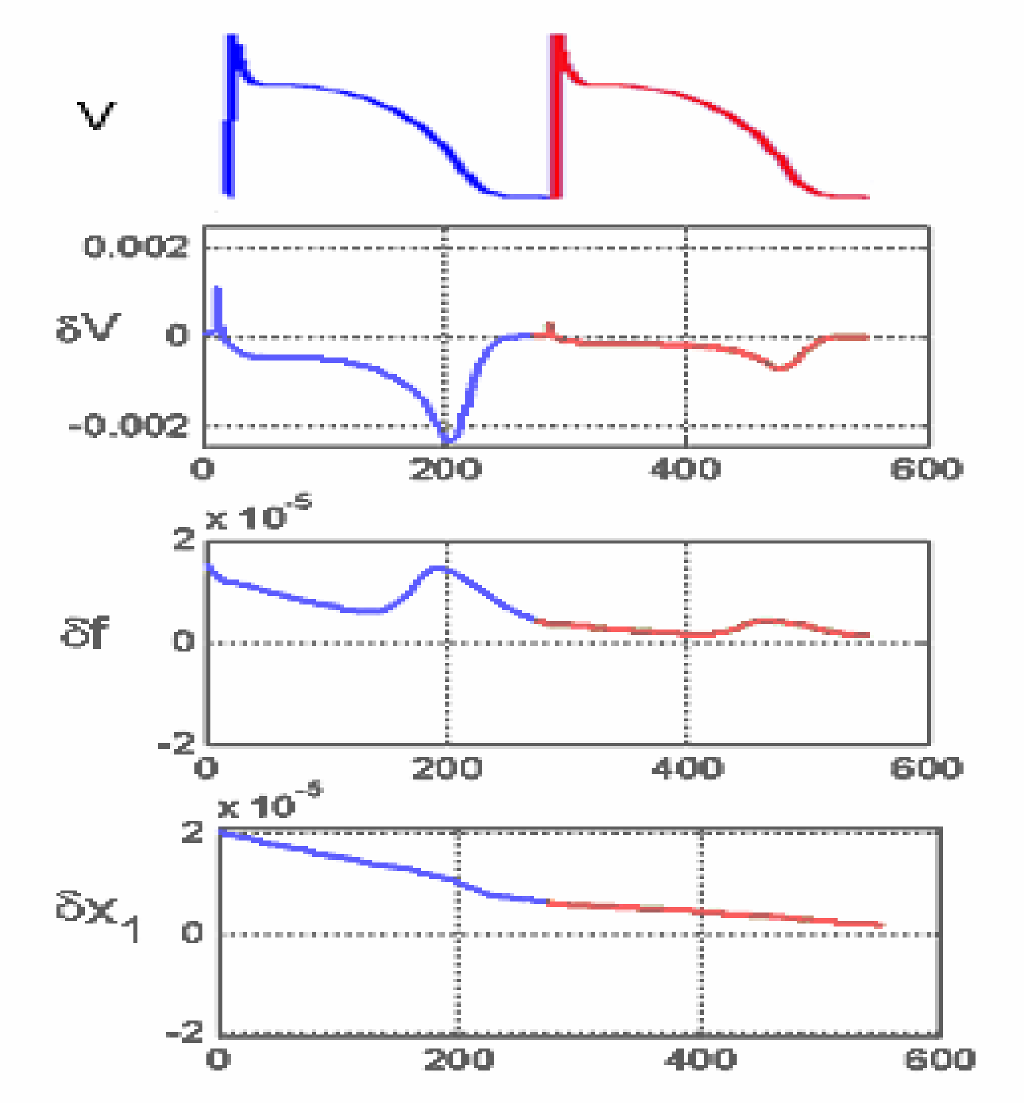
Initial Perturbation

Method

- Step #3: Find the eigenmodes of the mapping as functions of time, i.e., find vectors **v** such that,

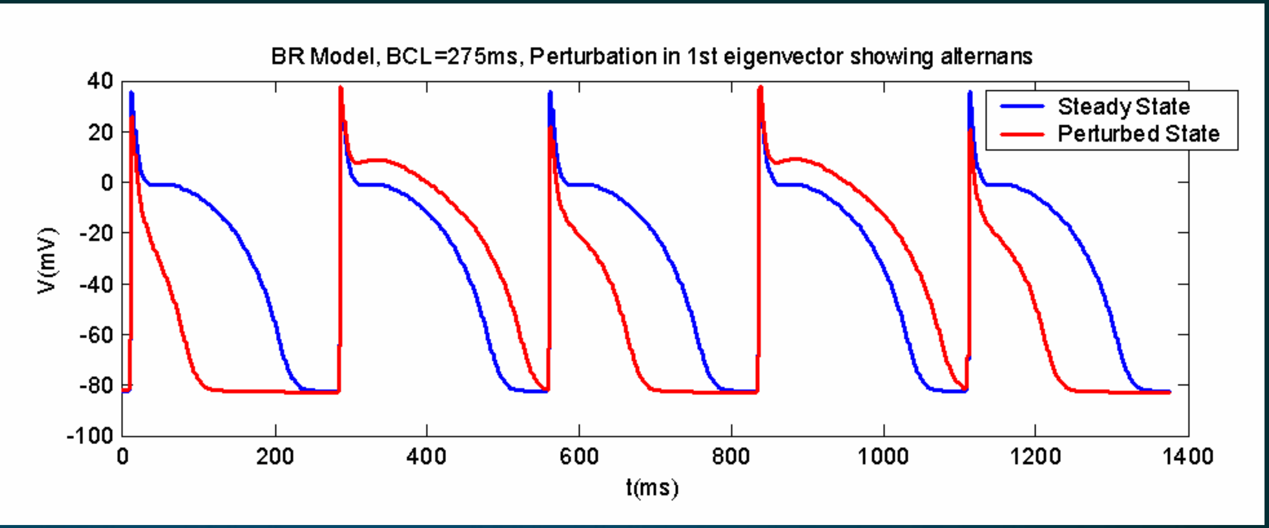
$$\mathbf{M} \cdot \mathbf{v} = \lambda \mathbf{v}$$

for some constant λ .

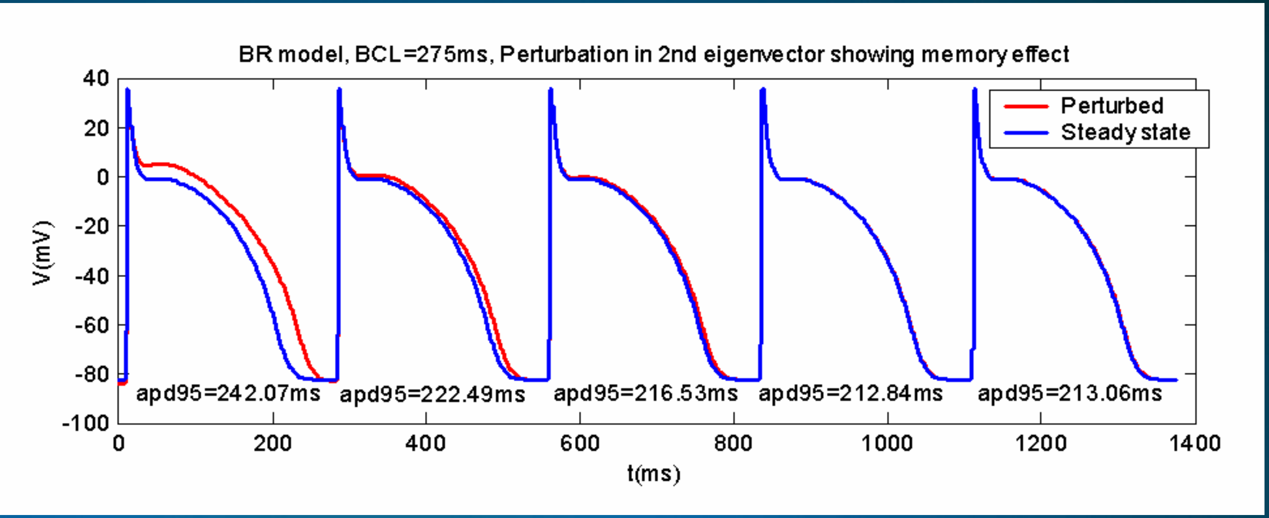


- Two types of eigenmodes are common: model: (1) an alternans mode, and (2) a “memory” mode:

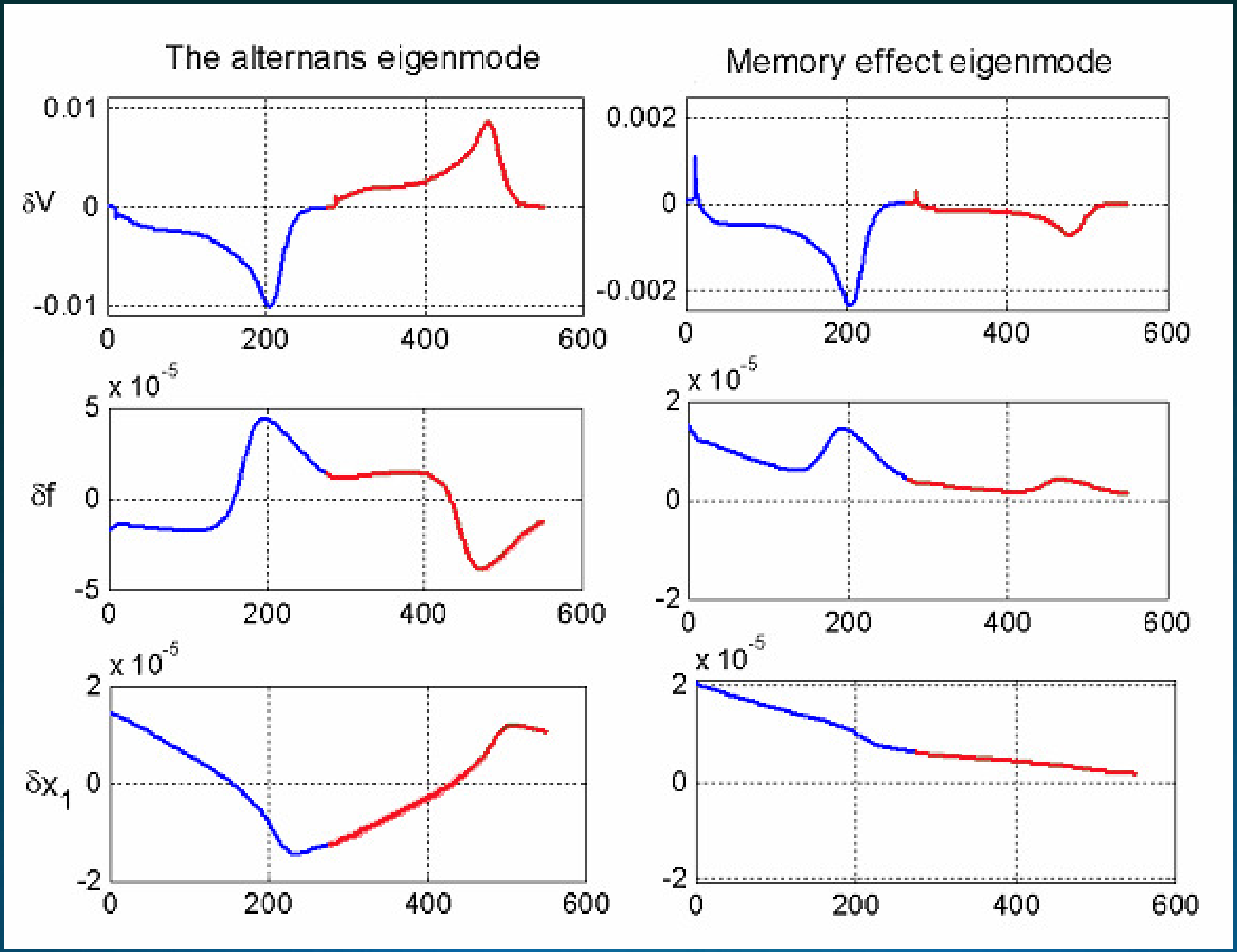
Alternans eigenmode:



Memory eigenmode:

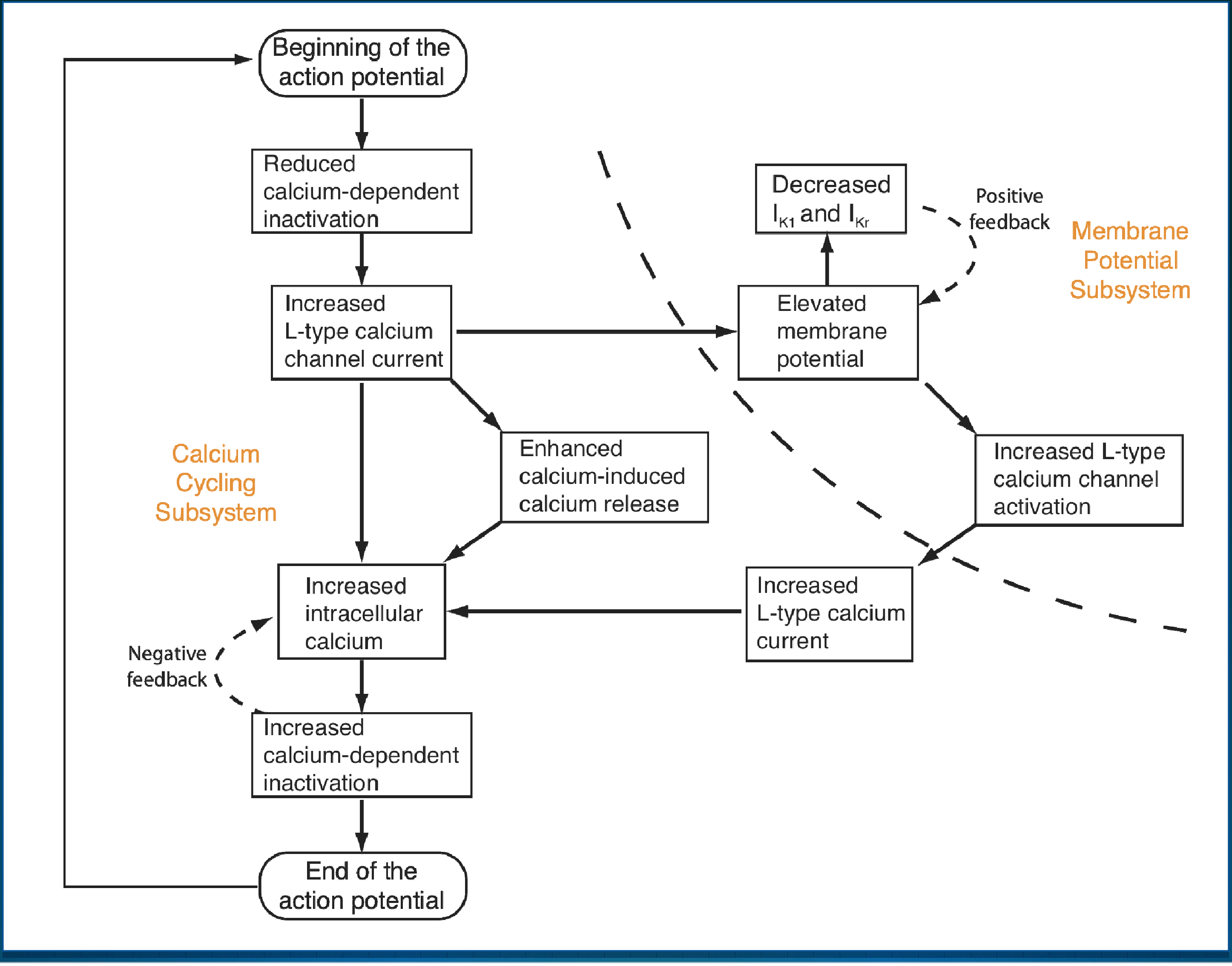


The eigenmodes reveal the underlying mechanisms



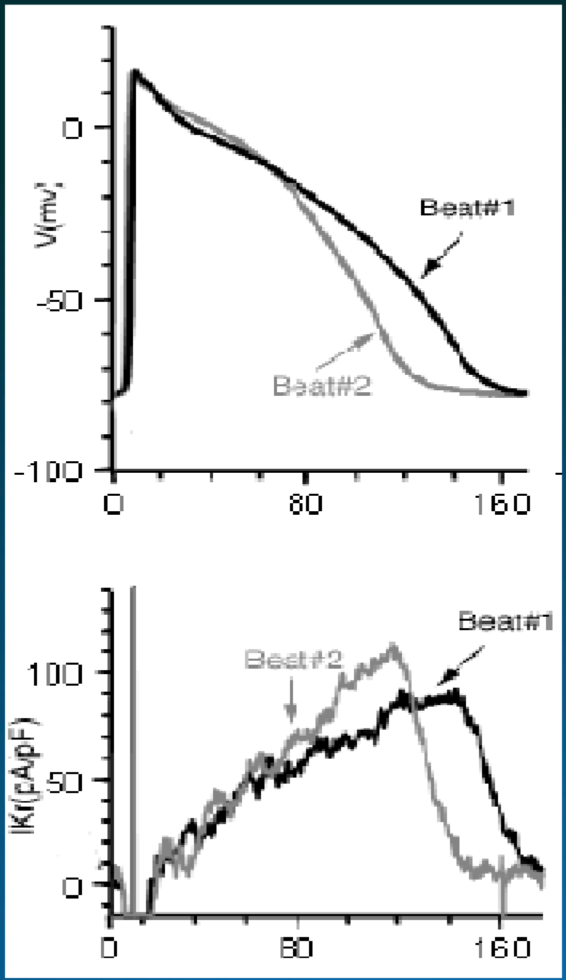
Eigenmode analysis

- For the Fox et al. ion channel model of canine ventricular myocyte:

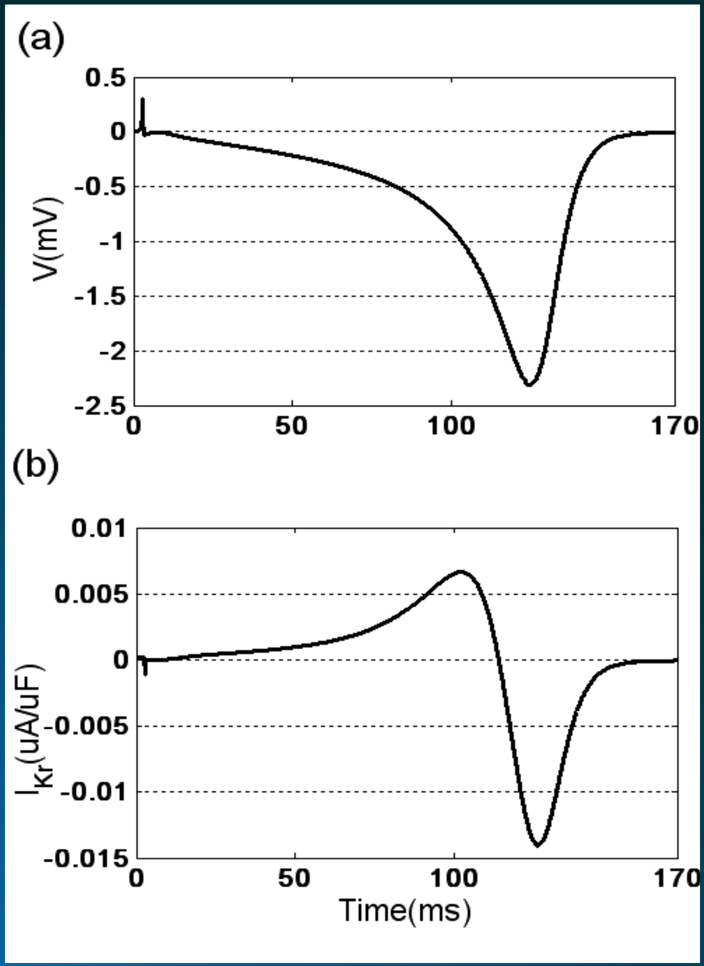


Experimental observation of an eigenmode (R. Gilmour, Jr.)

- Patch clamp experiment (action potential clamp)
- I_{Kr} current component of the alternans eigenmode



Experiment



Eigenmode analysis

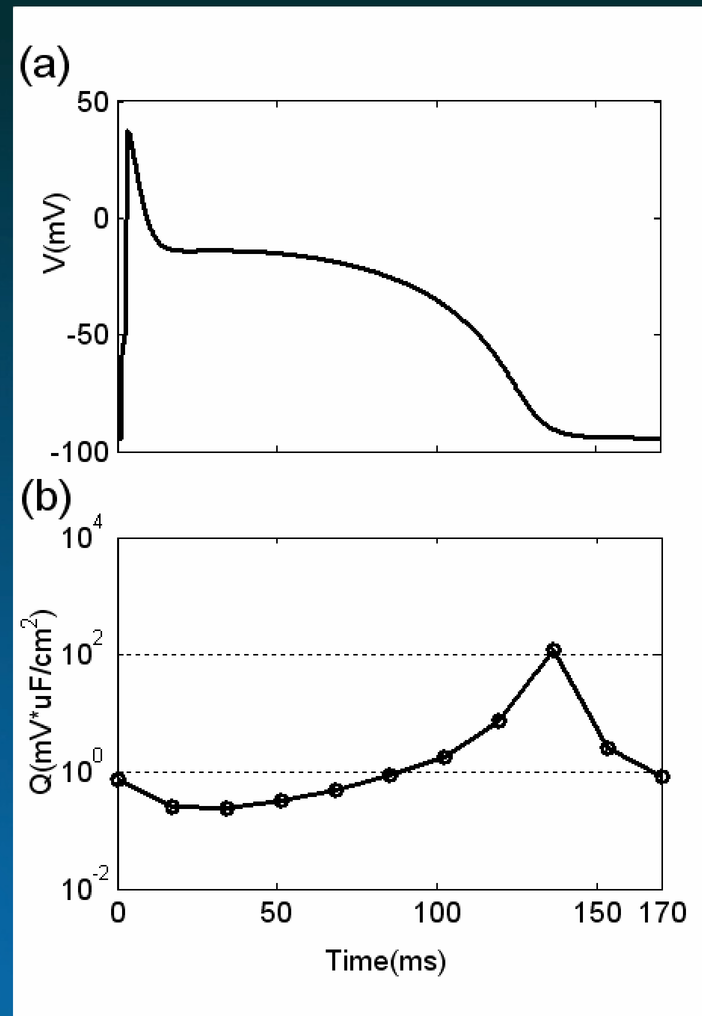
Left eigenmodes used to develop alternans control algorithms

- Eigenmode theory also yields so-called "left eigenmodes" **w**:

$$\boxed{\mathbf{w} \cdot \mathbf{M} = \lambda \mathbf{w}}$$

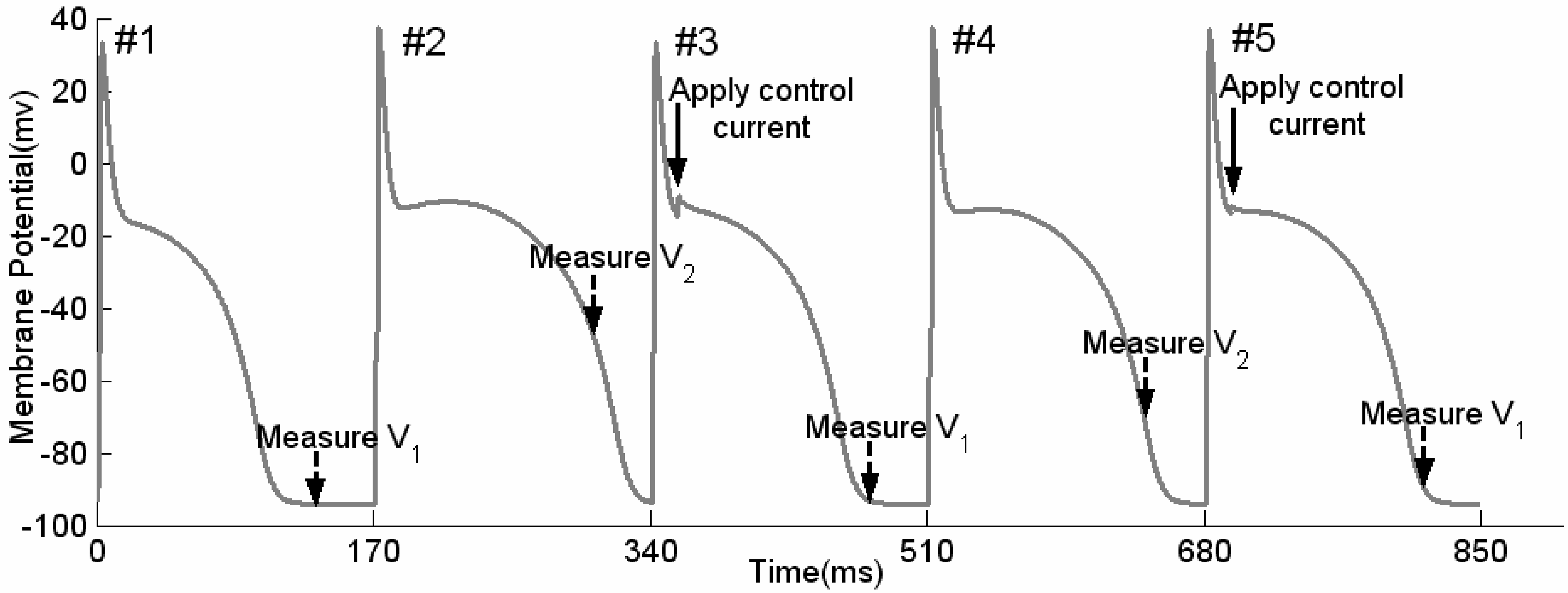
- Left eigenmodes helped determine: (1) the best time to apply the stimulus, (2) the stimulus amplitude required.

- Charge required to neutralize the alternans mode when applied at different times during the action potential:

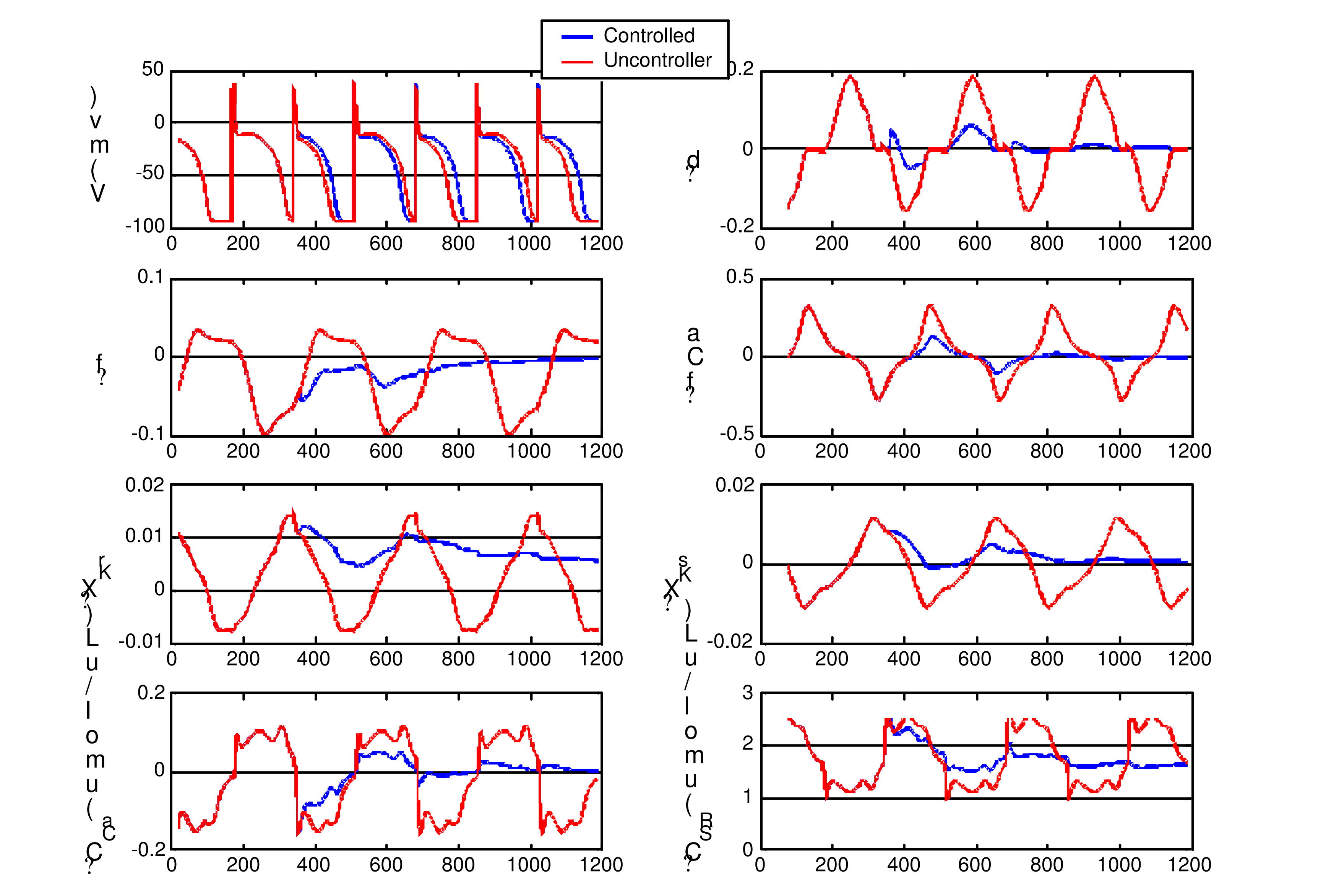


Control algorithm

- Left eigenmode theory can be used to design alternans control algorithms.
- Control current applied is proportional to the previously measured value of (V_1-V_2):

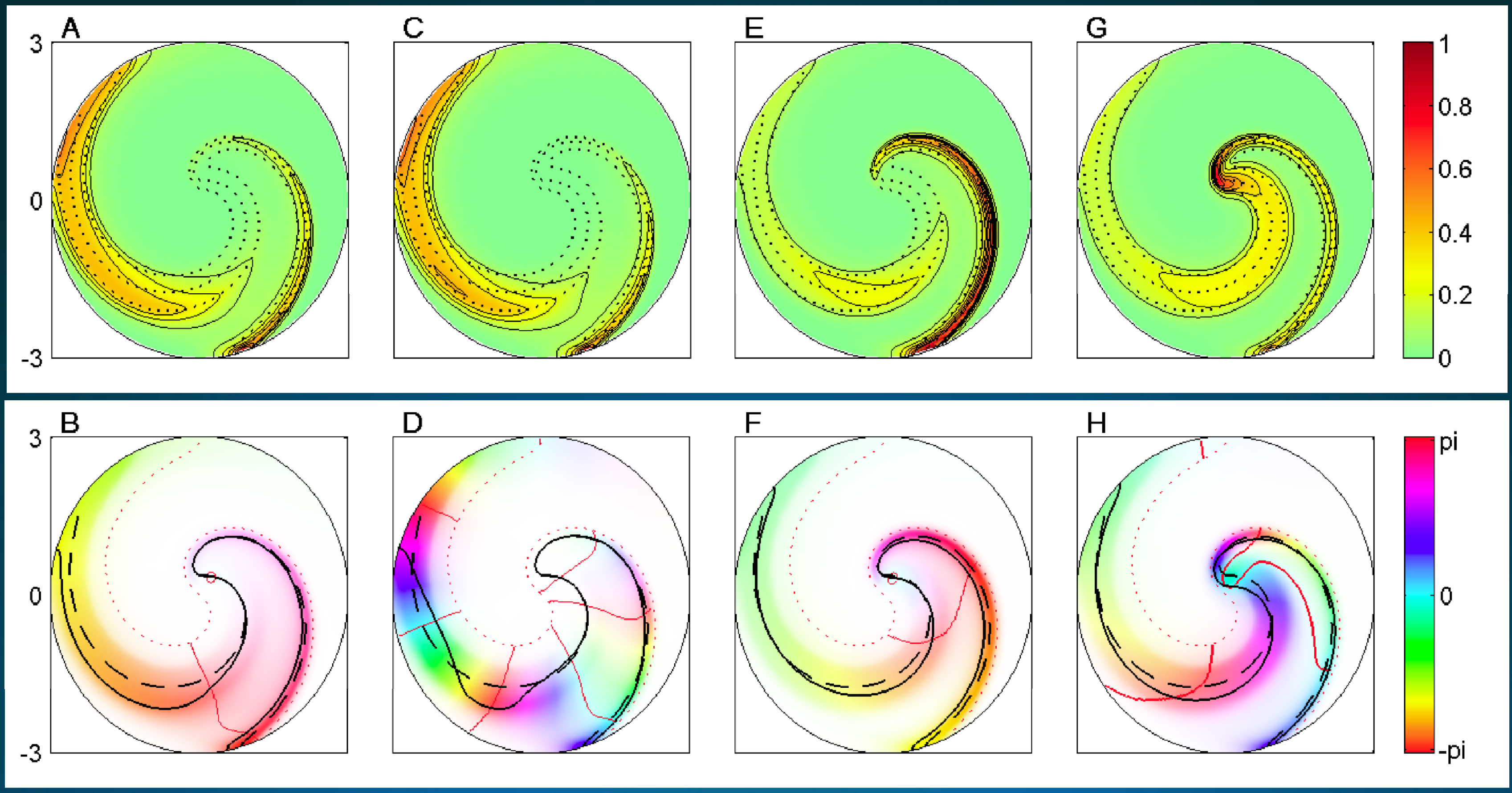


Effect of the control algorithm



Eigenmode analysis of spiral waves

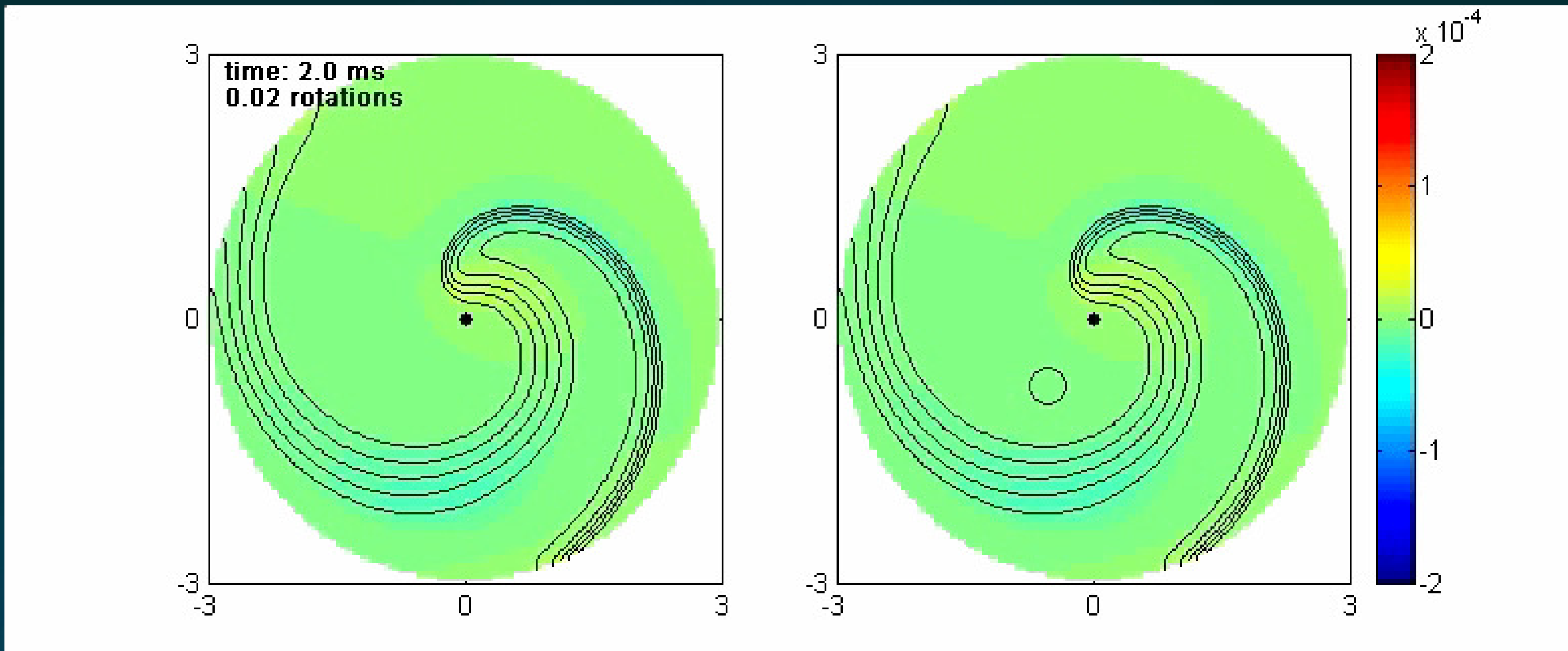
- Eigenmode analysis is also applicable to finite-sized systems containing waves:
  - Membrane potential amplitudes (top) and phases (bottom) for 4 different eigenmodes:



Eigenmode analysis

- Again, control of alternans on a spiral wave can be effected using left eigenmode theory:

No control | Control using a single stimulus



Note how the action potential itself propagates the effect of single point stimulus to the entire system.

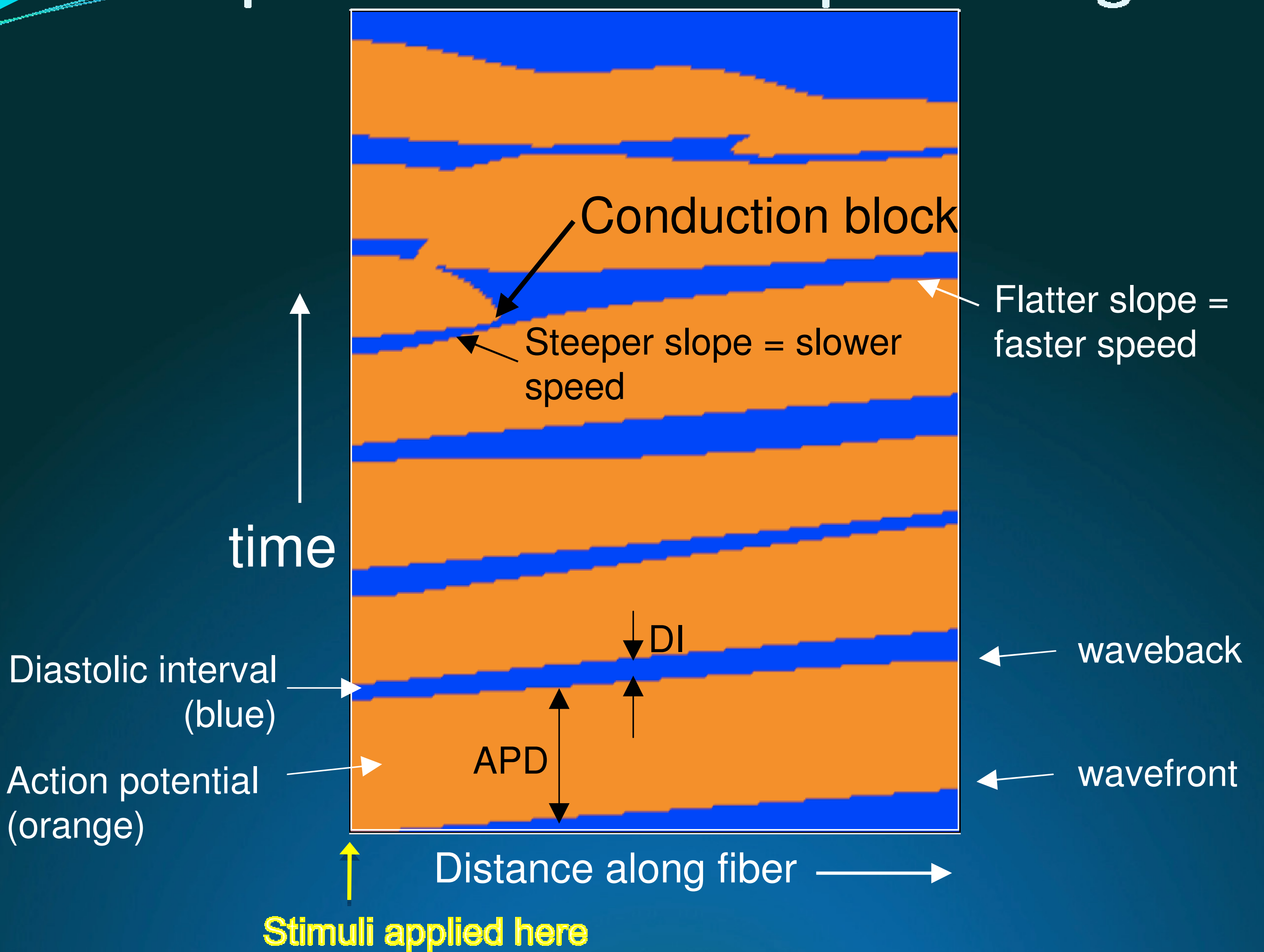
Eigenmodes: Summary

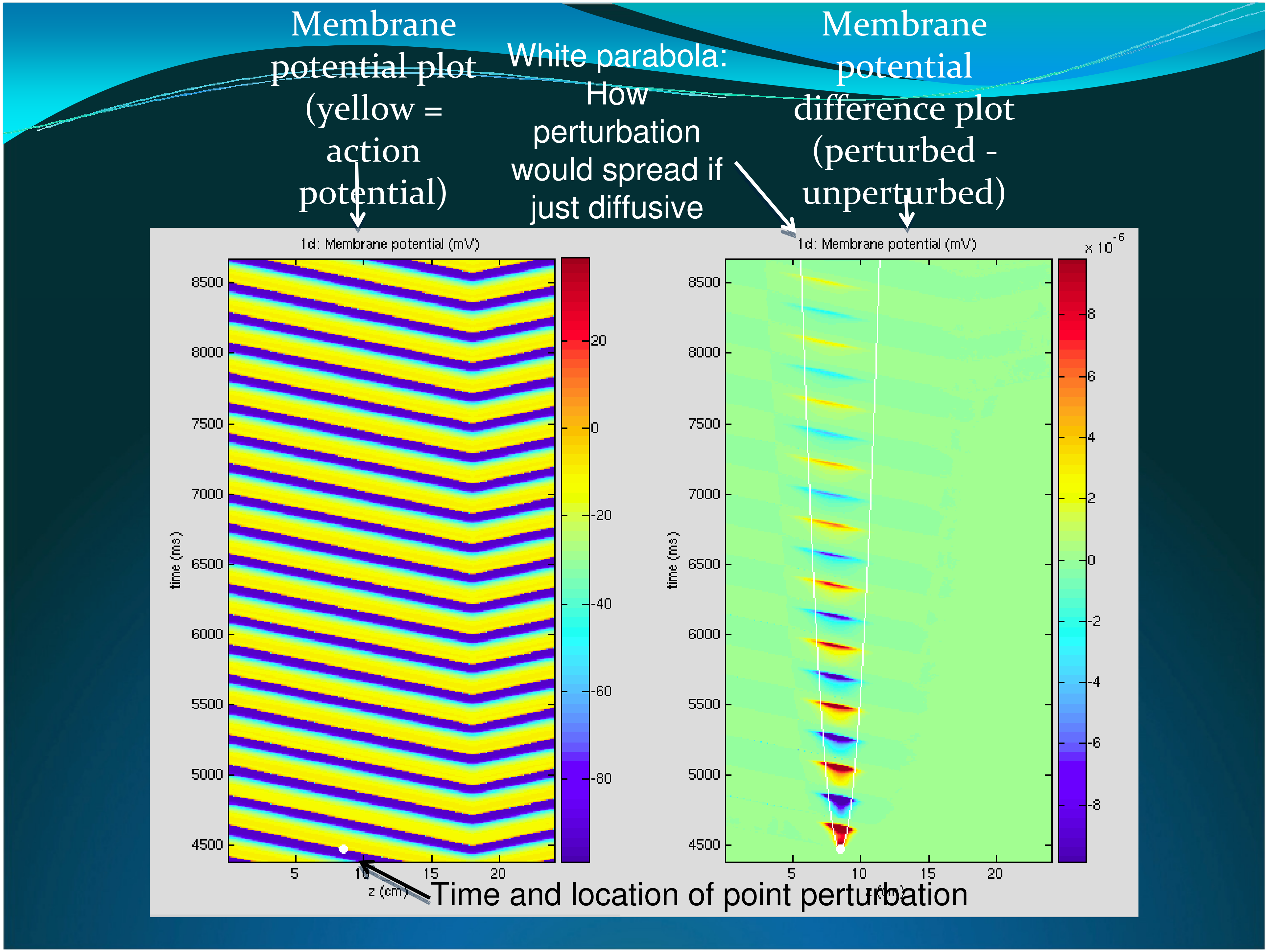
- Eigenmode methods are useful for:
  - Diagnosing the mechanism responsible for dangerous cardiac action potential morphology patterns such as APD alternans,
  - Designing cardiac rhythm control algorithms in single cells and small preparations, and
  - Studying the stability of rotating action potential waves in the heart
- Limitations:
  - Technically valid only for small departures from steady state! But from a practical point of view, still provides valuable insight.
  - System geometry modifies the behavior predicted by eigenmode theory.

3. Perturbation analysis

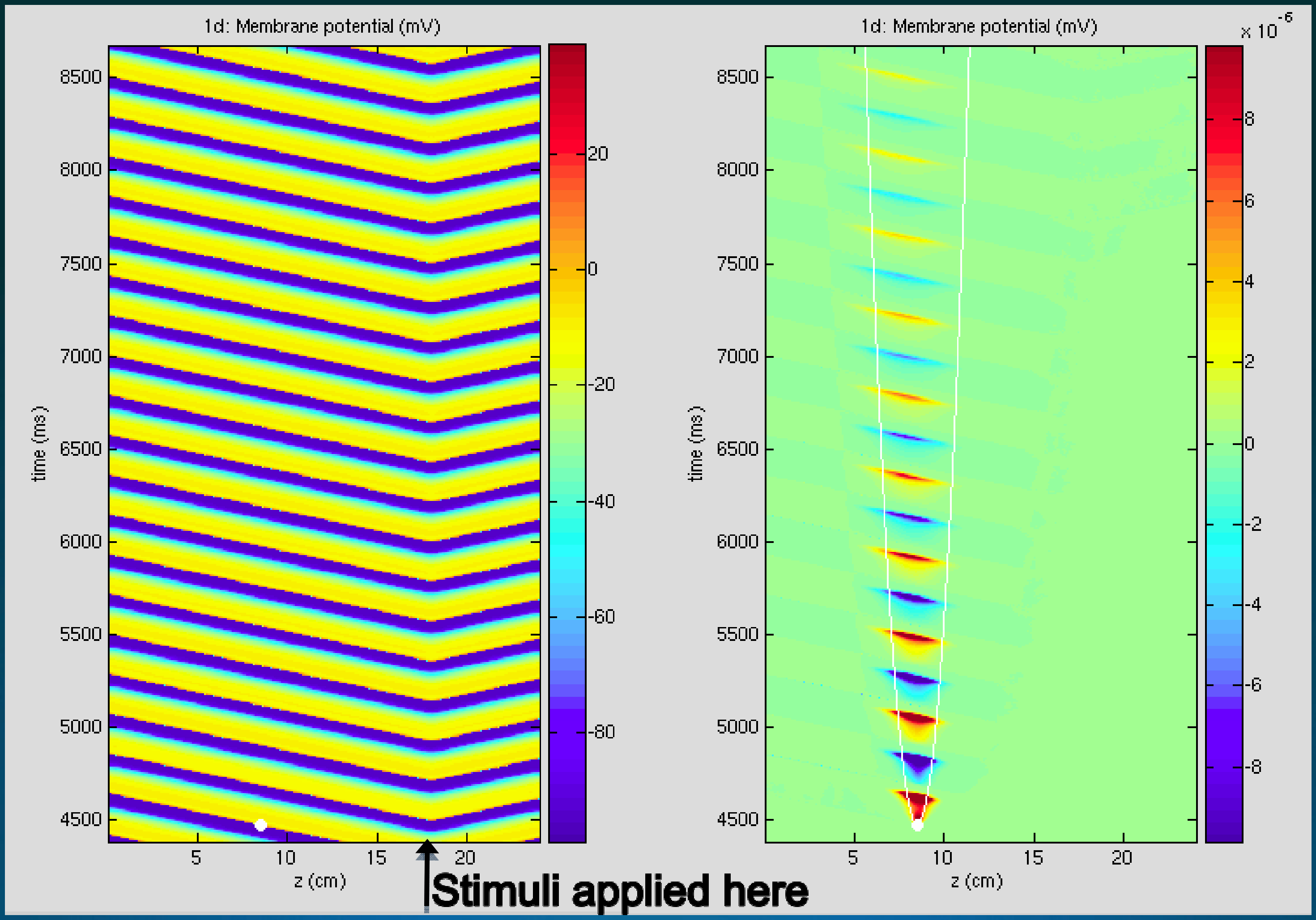
- What happens when we add a small perturbation to a propagating action potential?
- Uses:
  - Reveals something about the underlying dynamics
  - Shows the effective range control stimuli applied at a point.
- For spatially one-dimensional systems, e.g., fibers and rings, most easily studied by analyzing time vs. space diagrams.

Example of a time vs. space diagram

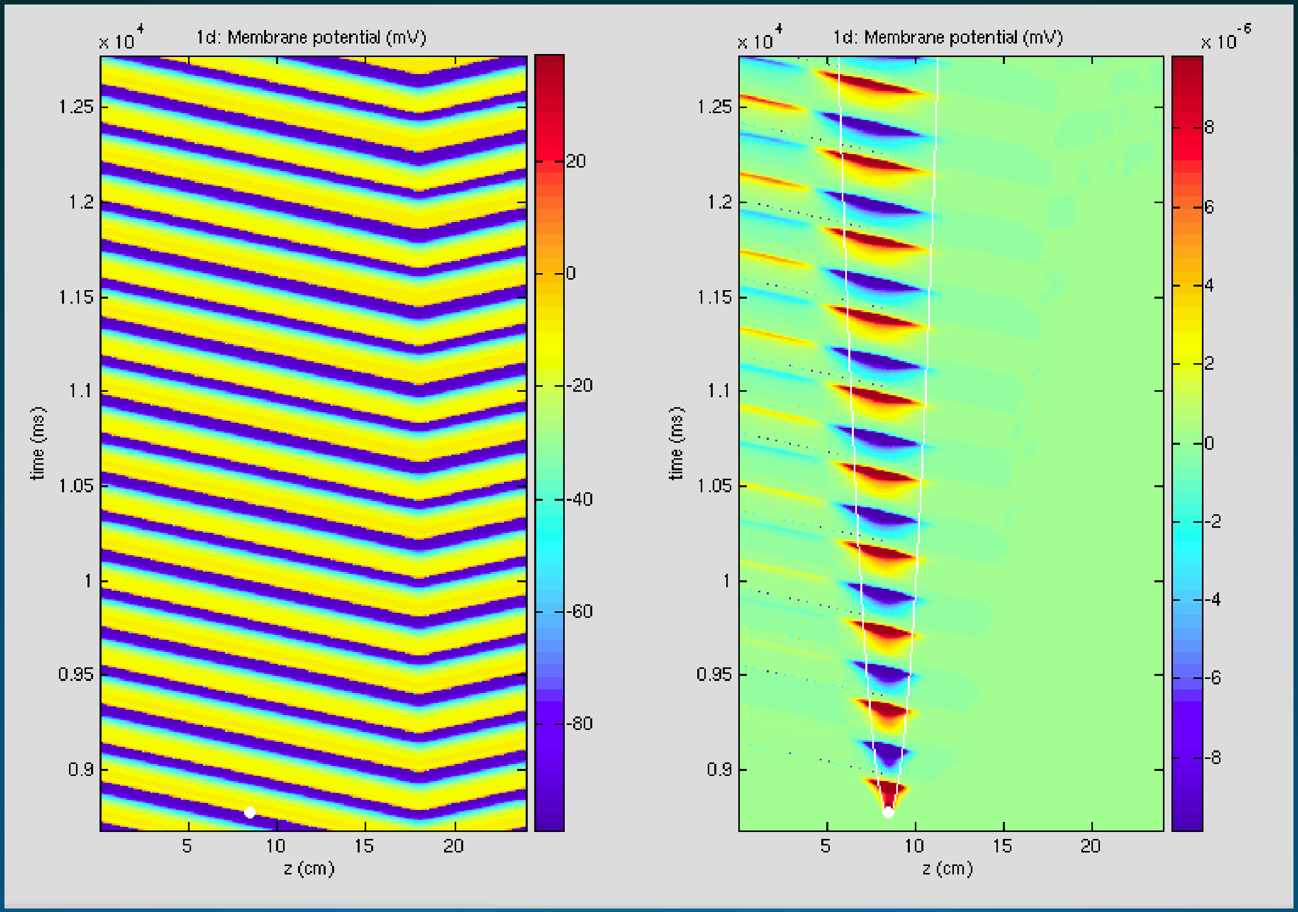



Membrane potential plot (yellow = action potential)
White parabola: How perturbation would spread if just diffusive
Membrane potential difference plot (perturbed - unperturbed)
1d: Membrane potential (mV)
time (ms)
z (cm)
1d: Membrane potential (mV)
time (ms)
z (cm)
× 10^-6
Time and location of point perturbation

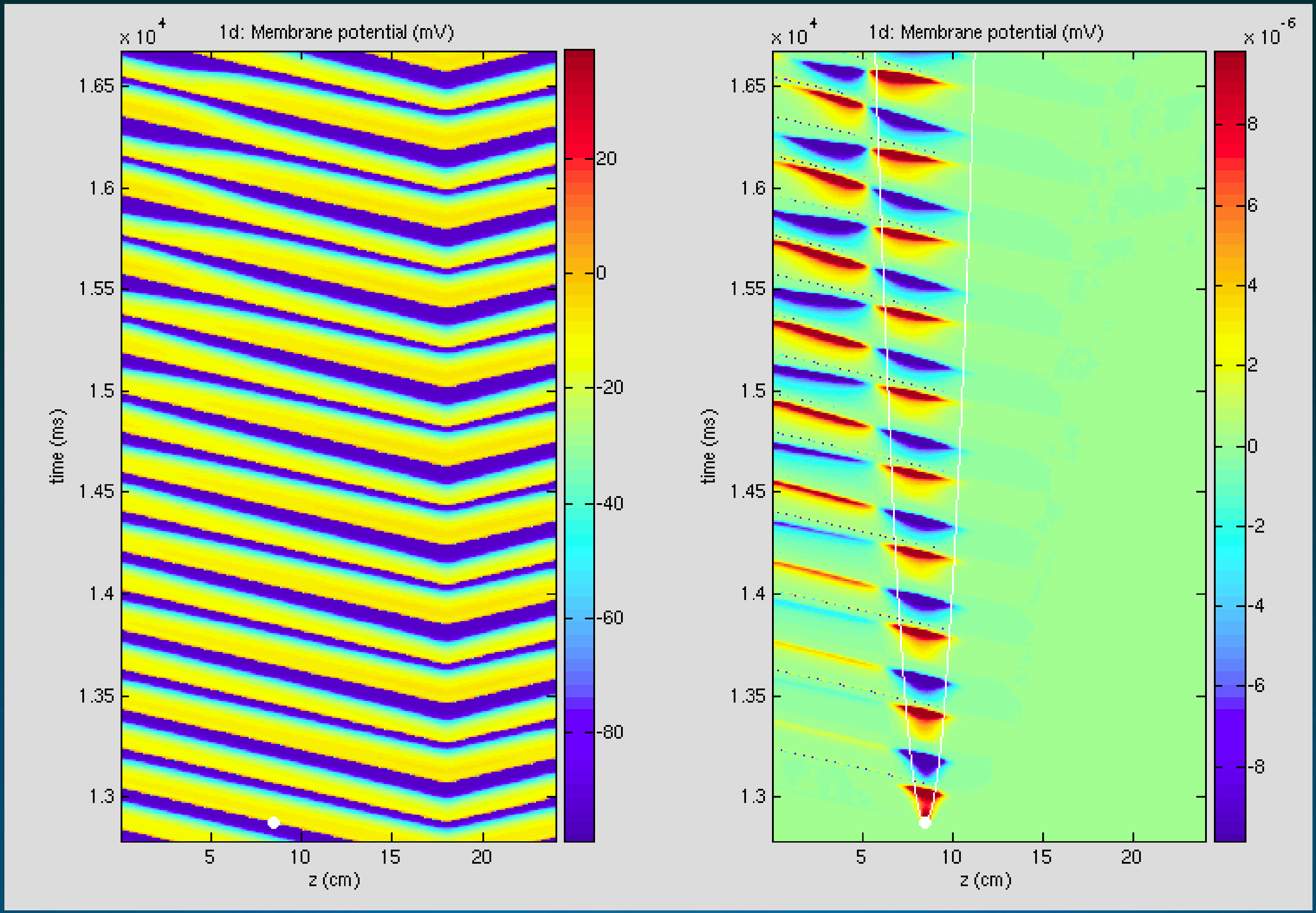
- Long stimulus cycle length (215 ms). No alternans. Perturbation stays within the parabola alternates, and decays with time.



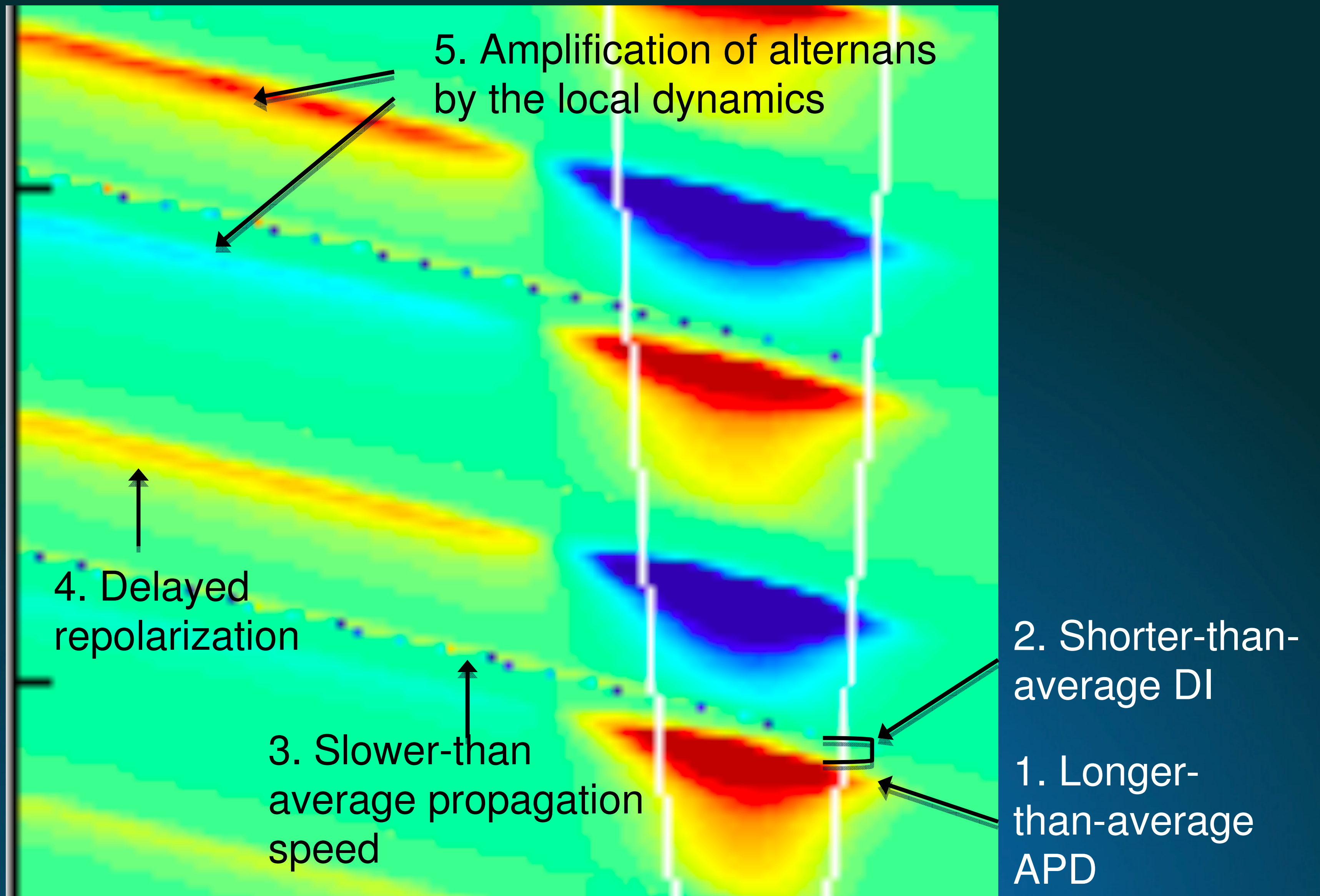
- Shorter stimulus cycle length (205 ms) produces small amplitude concordant alternans (left). Perturbation has two components (right). The component within the parabola decays only slightly with time. There is also a component downstream (i.e., to the left), induced by conduction velocity (CV) modifications in the parabolic region, and amplified by beat-to-beat dynamics.



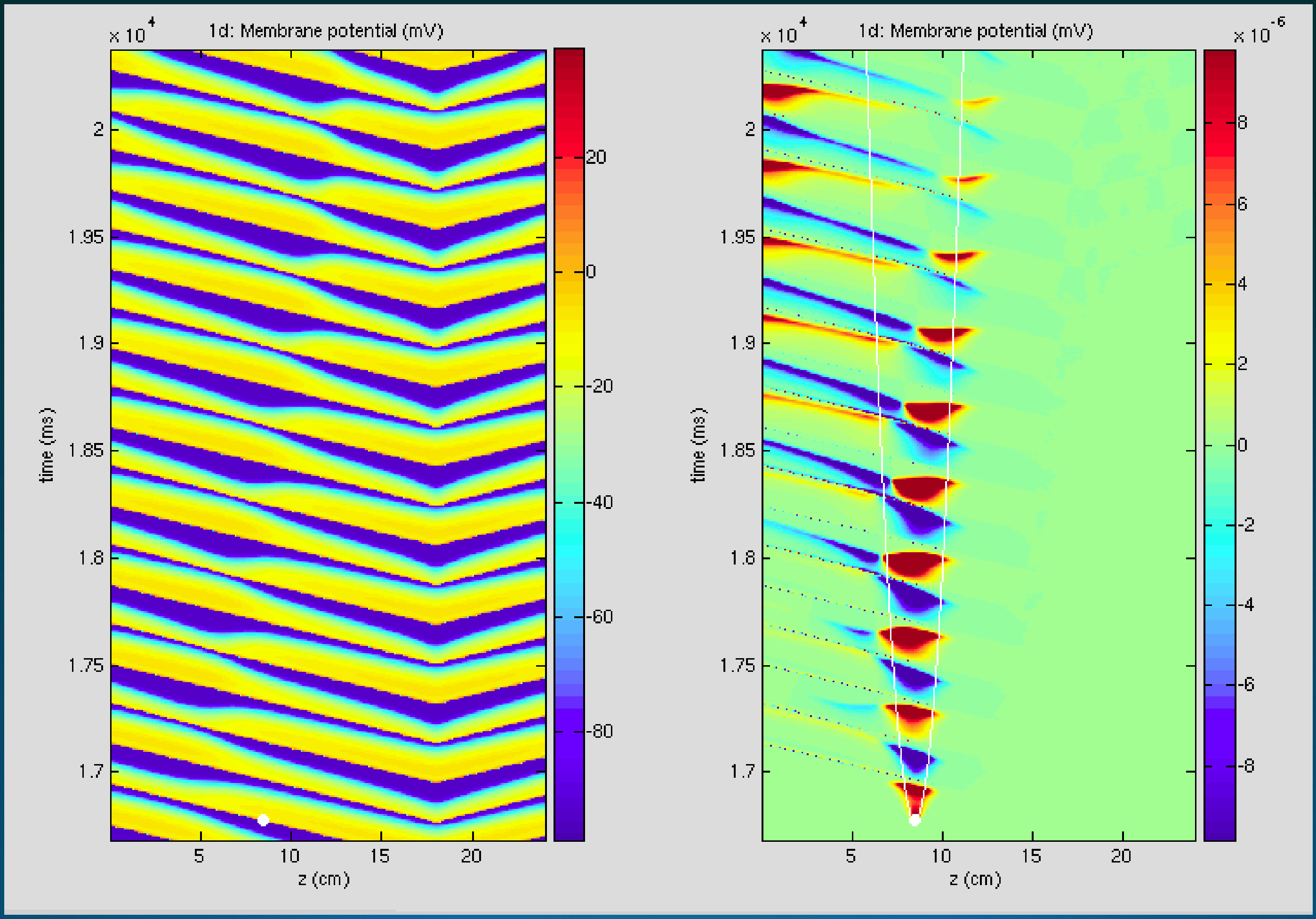
- Cycle length of 195 ms produces discordant alternans (left). The downstream disturbance is now much more prominent.



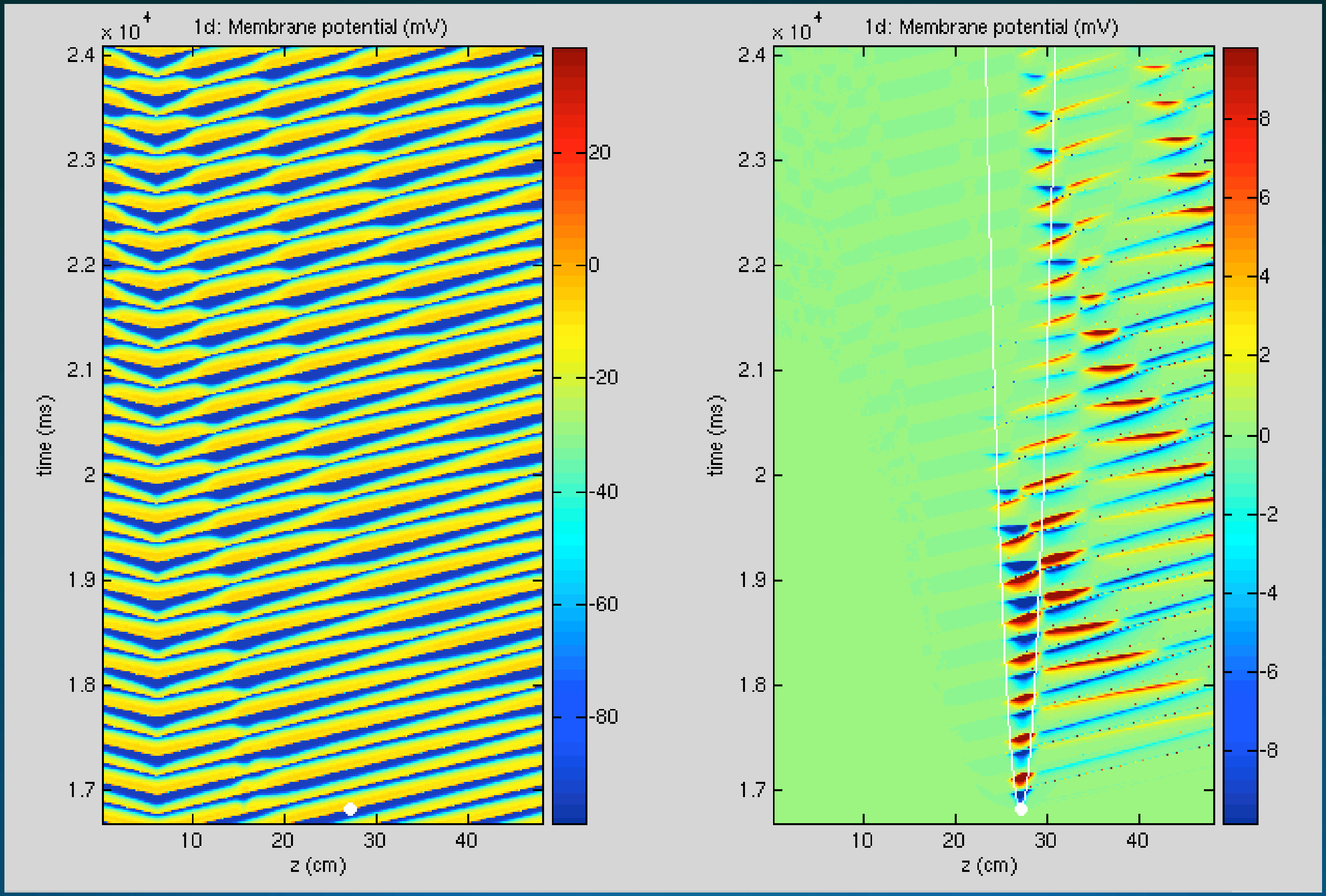
- Close-up of how downstream propagation of the perturbation occurs:



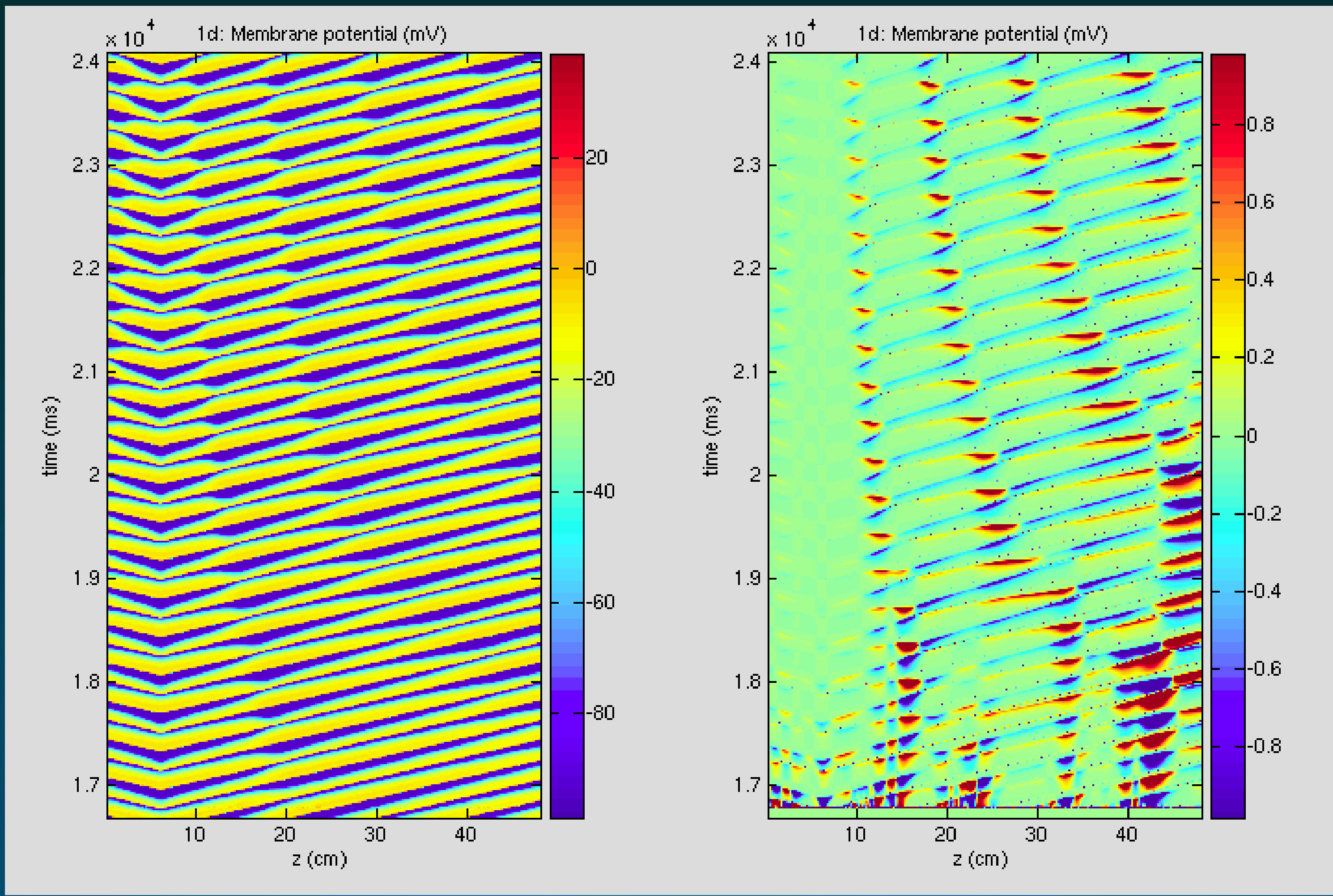
- Even shorter cycle length (185 ms) yields stronger discordant alternans (left). Perturbations now tend to localize in the nodes of the discordant alternans pattern.



- A clearer example of the congregation of the effects of perturbations in the nodes of the discordant alternans pattern. Note: no effect propagated upstream. (cycle length = 185 ms, larger system, different stimulus location)



- Applying a random perturbation at all locations at a single time again ultimately yields a similar pattern, with maximum effect in nodes:



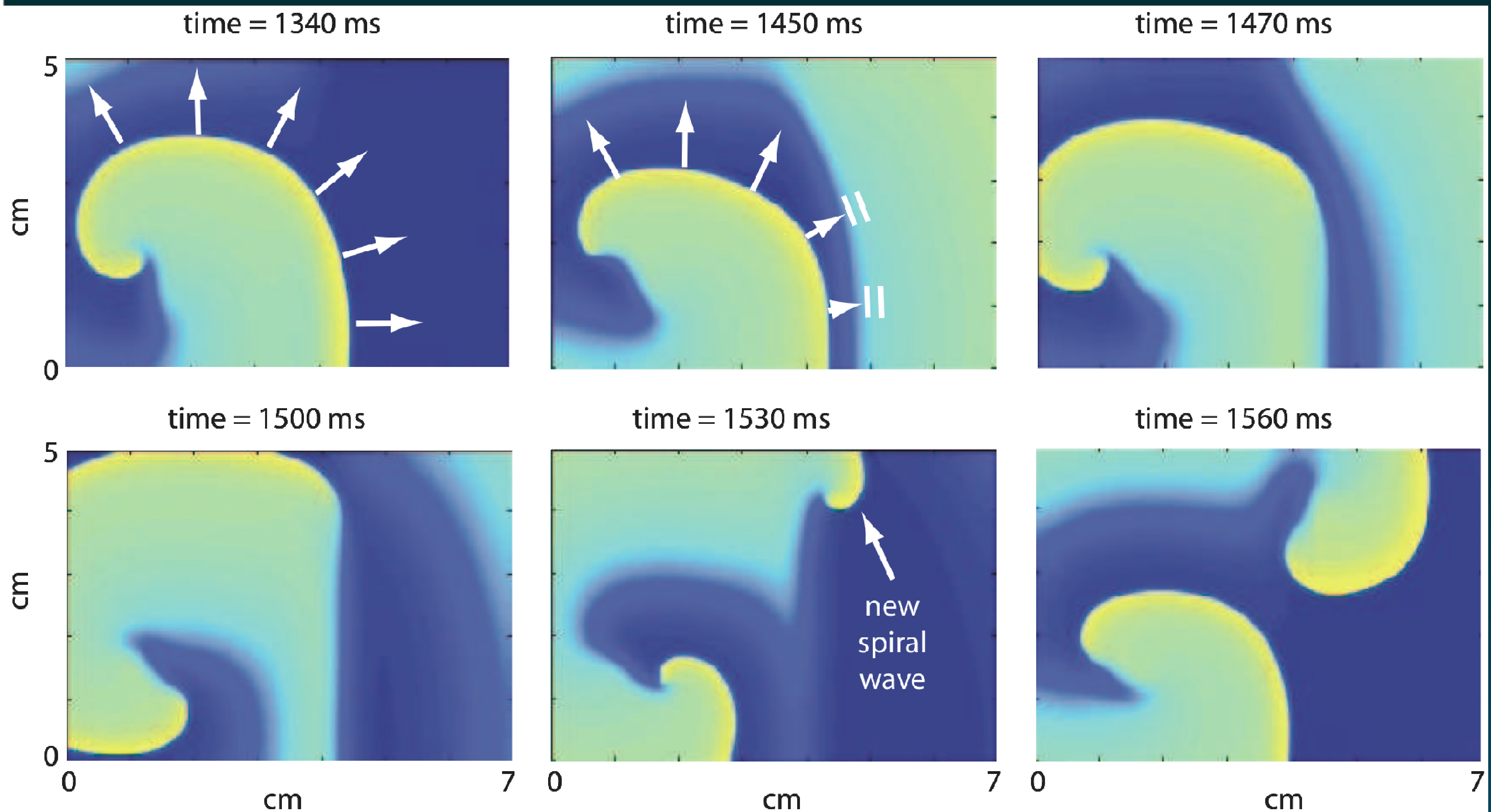
Perturbation analysis: Summary

- Provides some idea of how large a region of tissue can be controlled by a control stimulus applied to a single location.
  - Local dynamics (e.g., alternans) is seen in the vicinity of the applied perturbation
  - Also, the entire downstream region is affected by the perturbation, suggesting global control may be possible.
- However, effects of the perturbation tend to be concentrated in the nodes of the discordant alternans pattern, whereas we would like to have effects localized between nodes (i.e., where the alternation is occurring).

4. “Magic numbers” theory

- “Magic numbers”: a small number of irregularly spaced stimuli of that either cause or terminate fibrillation.
- So-called, because a simple dynamical model used to determine when conduction block at some distance from the stimulus site has been remarkably effective in when VF will be induced.
- Assumption: block at-a-distance does not occur across the entire wavefront uniformly, allowing some portion of the wave to continue, and subsequently reenter.

Example: block-at-a-distance causes reentry

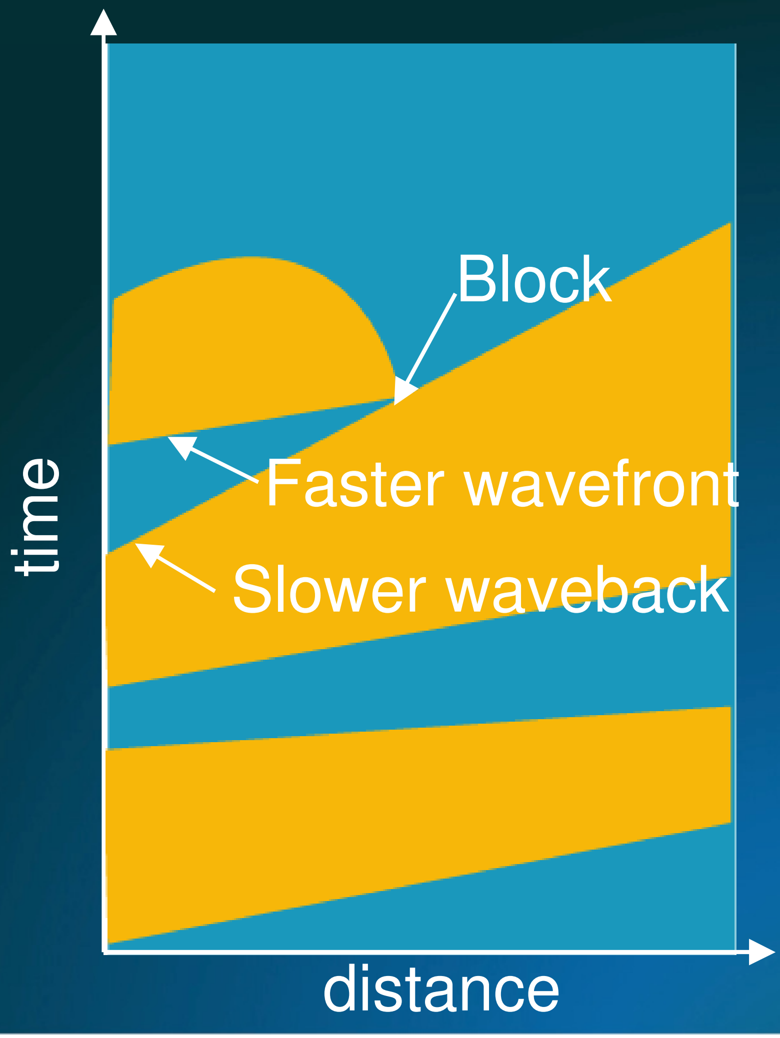


Approach

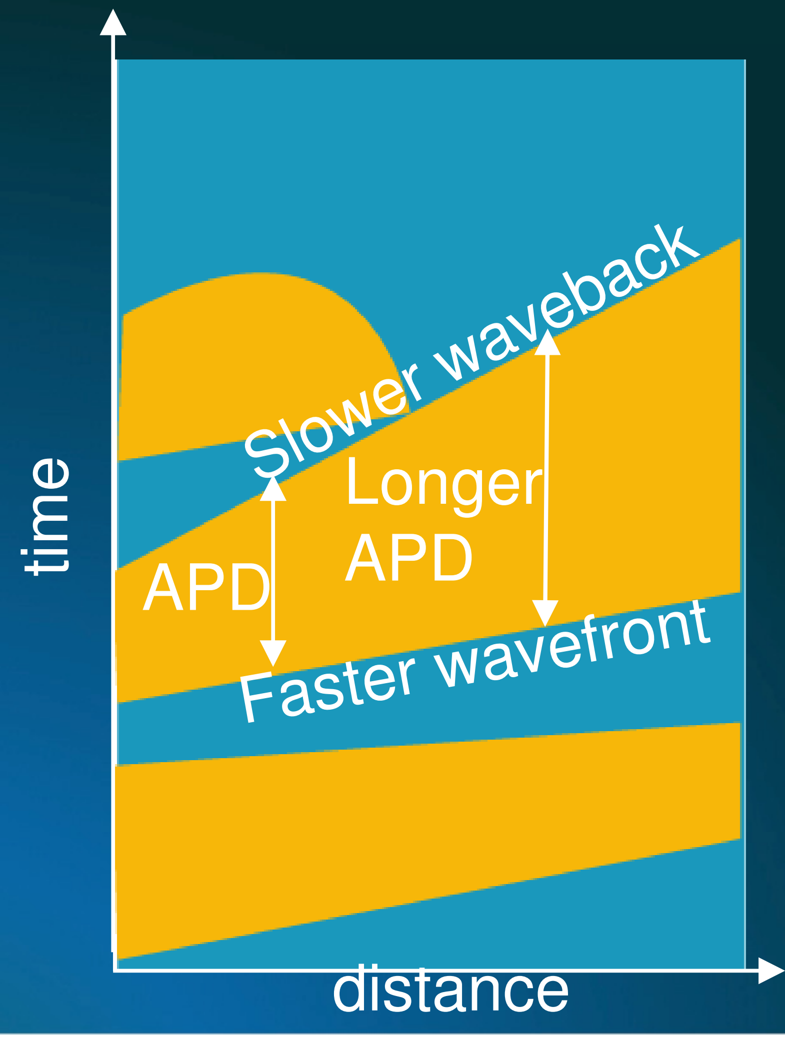
- Assume that conduction block occurs when a wavefront runs into the back of the wave in front of it.
- This occurs when the velocity of the wavefront just before it crashes is higher than the velocity of the waveback it is pursuing.
- Assume simple conduction velocity and APD restitution functions (APD=a(DI), CV = v(DI)) to do the dynamics.
- Use time vs. space diagrams to help with visualization of the situation.

How block occurs

Block occurs when a wavefront runs into the slower moving waveback of the previous wave:

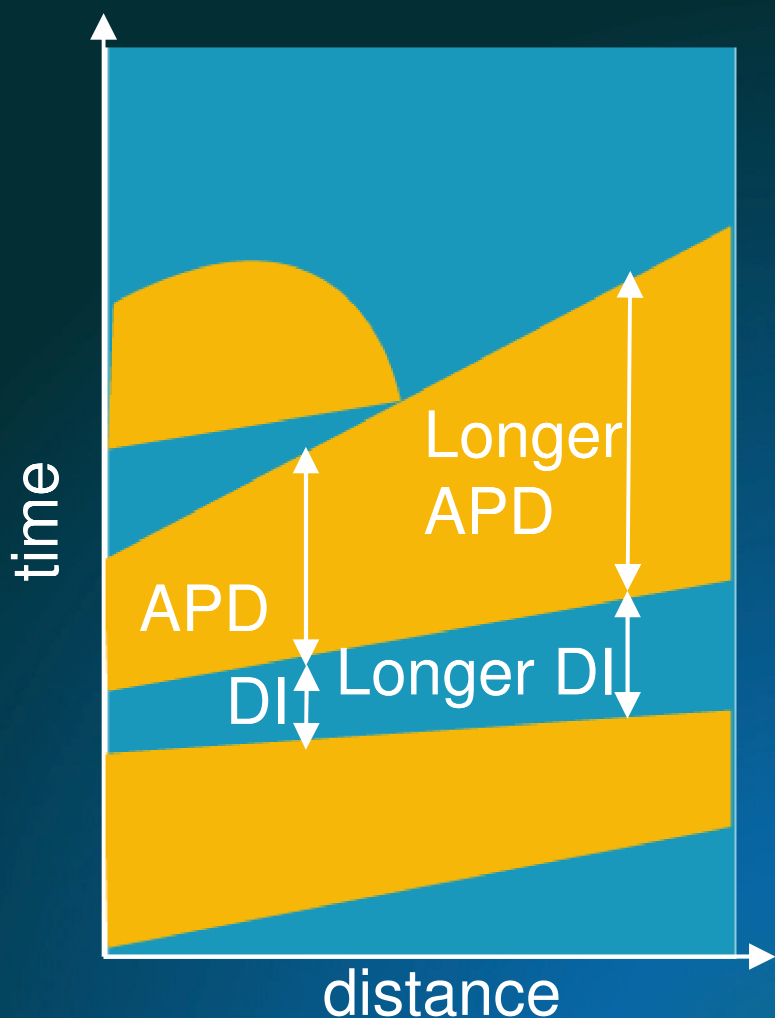


The slower waveback is created by a positive spatial gradient in the APD:

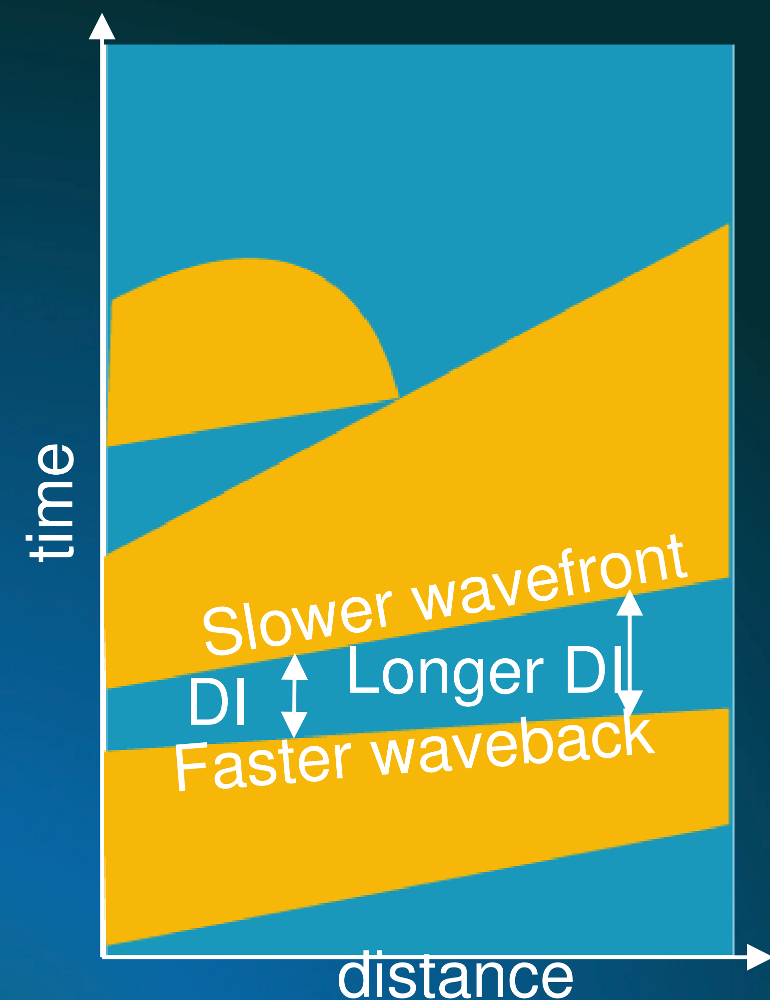


How block occurs

A positive APD gradient is derived from a positive DI gradient through the APD restitution function



The DI gradient comes from the difference in wavefront and waveback velocities, and so on:



How block occurs

These 4 relationships may be translated into 4 equations:

Block occurs when a wavefront is faster than the preceding waveback	$1/v(DI_{min}) - 1/v_{waveback} > 0$
Waveback velocity is slowed relative to wavefront velocity by a positive APD gradient	$1/v_{waveback} = 1/v(DI) + dAPD/dx$
Positive APD gradient is produced by a positive gradient in the preceding DI	$dAPD/dx = \boxed{a'(DI)}(dDI/dx)$
Positive DI gradient occurs when the wavefront velocity is slower than the preceding waveback	$dDI/dx = 1/v(DI) - 1/v_{previous\_waveback}$

How block occurs

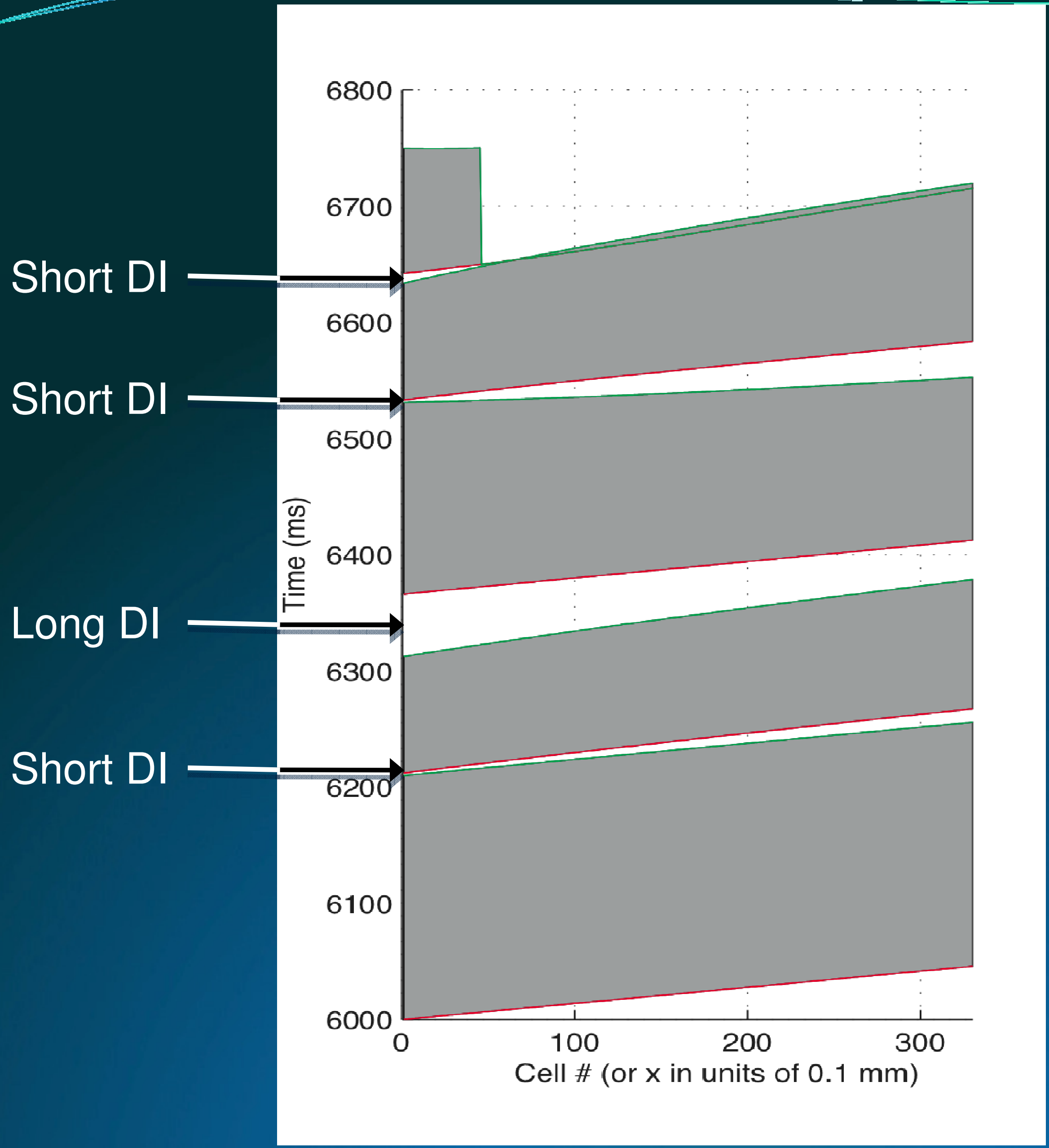
These 4 equations may be substituted repeatedly into one another to yield a condition for block for any given number of premature stimuli.

For example, for 4 premature stimuli, we obtain:

$$\frac{1}{v_{back}^{S4}} - \frac{1}{v(DI_{\min})} = \left(\frac{1}{v(DI_{S4})} - \frac{1}{v(DI_{\min})}\right) - \underline{a'(DI_{S4})}\underline{\left(\frac{1}{v(DI_{S3})} - \frac{1}{v(DI_{S4})}\right)}$$
$$+ \underline{a'(DI_{S4})a'(DI_{S3})}\underline{\left(\frac{1}{v(DI_{S2})} - \frac{1}{v(DI_{S3})}\right)} - \underline{a'(DI_{S4})a'(DI_{S3})a'(DI_{S2})}\underline{\left(\frac{1}{v(DI_{S1})} - \frac{1}{v(DI_{S2})}\right)} > 0$$

Note that the gradients in APD and DI are initiated by differences in consecutive velocities (in red) and amplified by the steep slope in the APD restitution function (in green) when present.

How block can occur

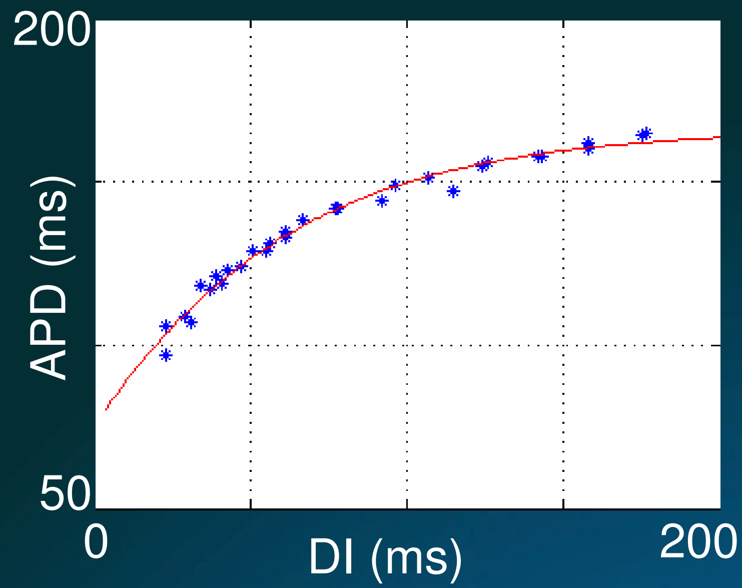


In vivo experiments

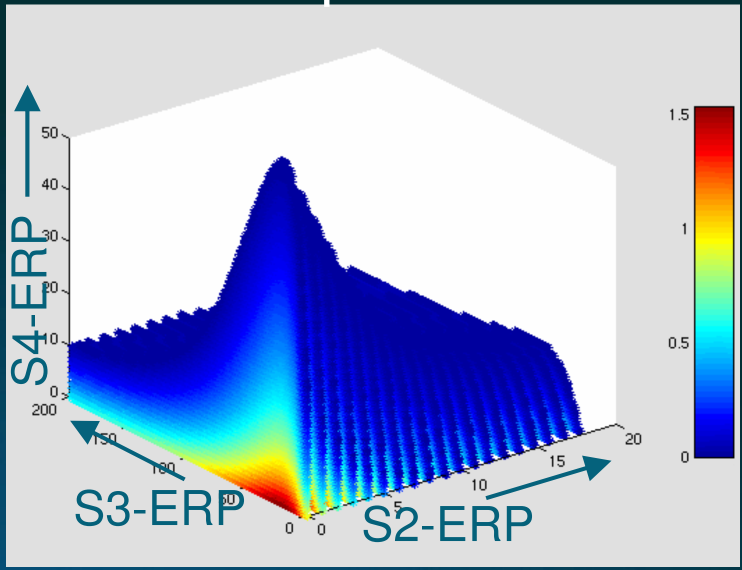
- Affected German shepherds were instrumented with catheters inserted into the right and left ventricles.
- A pacedown protocol was performed to determined the APD restitution function for each ventricle.
- Each restitution function was substituted into the block formula just derived to generated series of 4 premature pacing intervals predicted to produce block.
- These pacing intervals, and also intervals predicted not to produce block, were applied to the corresponding ventricle, to see if it would initiate ventricular fibrillation (VF).

Right ventricle results

APD restitution function



Pacing intervals that are predicted to produce block:

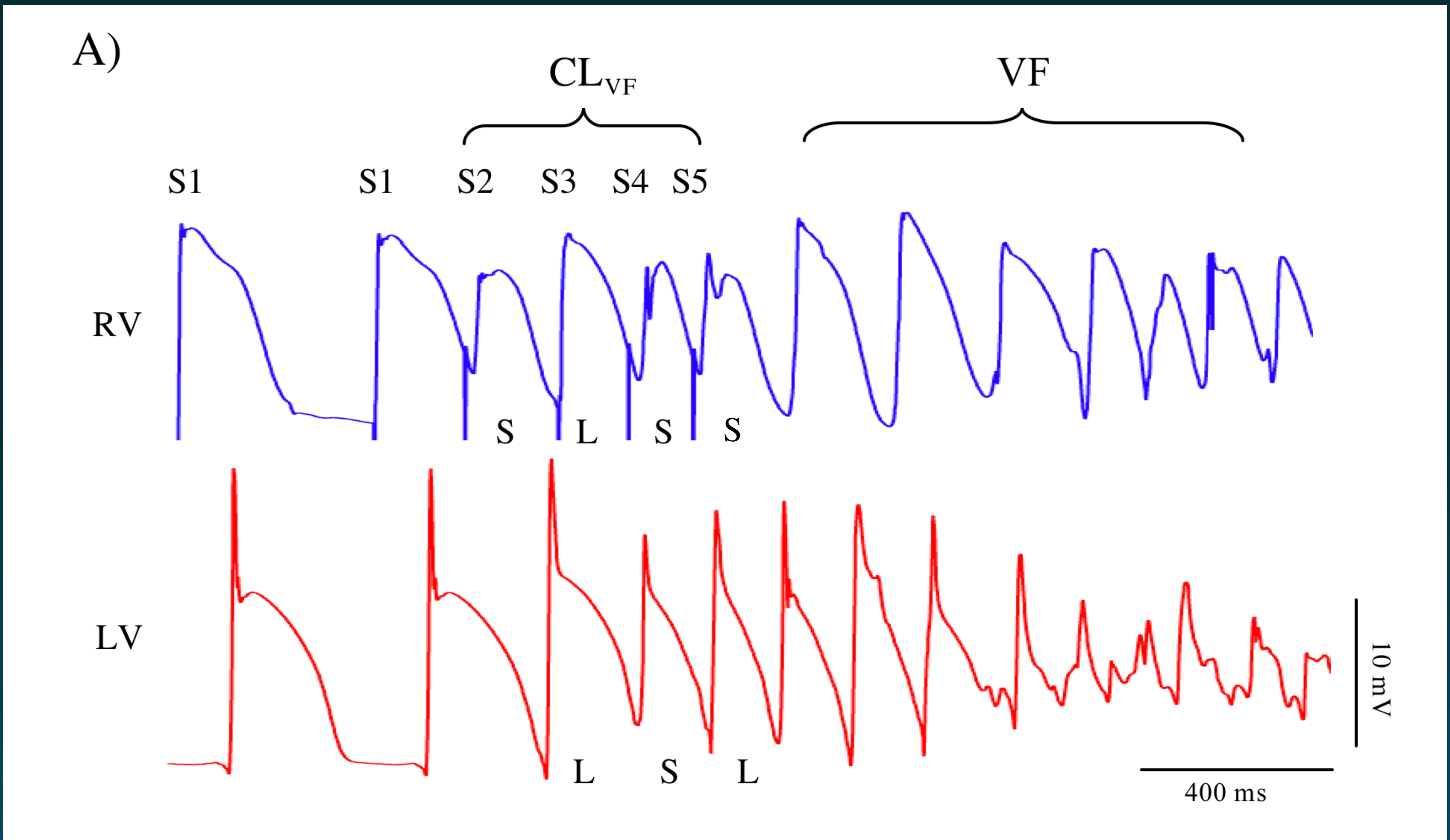


S2 - ERP = 1 ms “short”
S3 - ERP = 19 ms “long”
S4 - ERP = 1 ms “short”
S5 - ERP: always short

Experimental Results

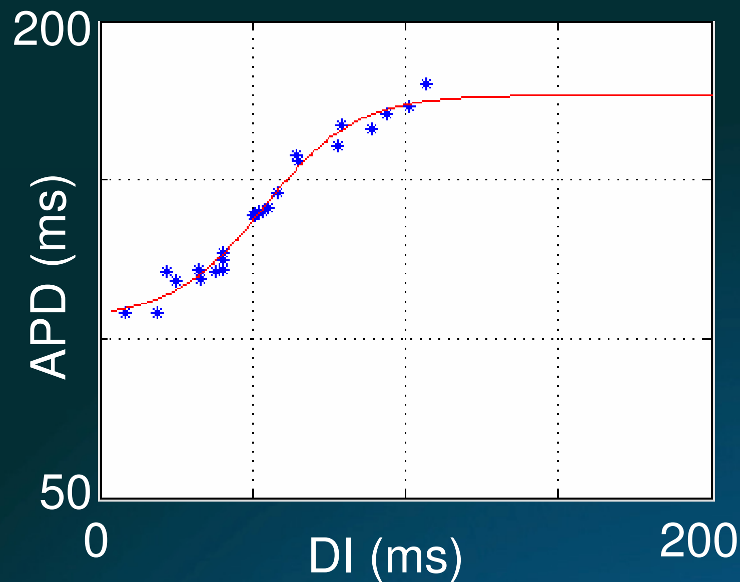
Short Long Short Short	Short Long Long Short
VF	No VF

In vivo experiment



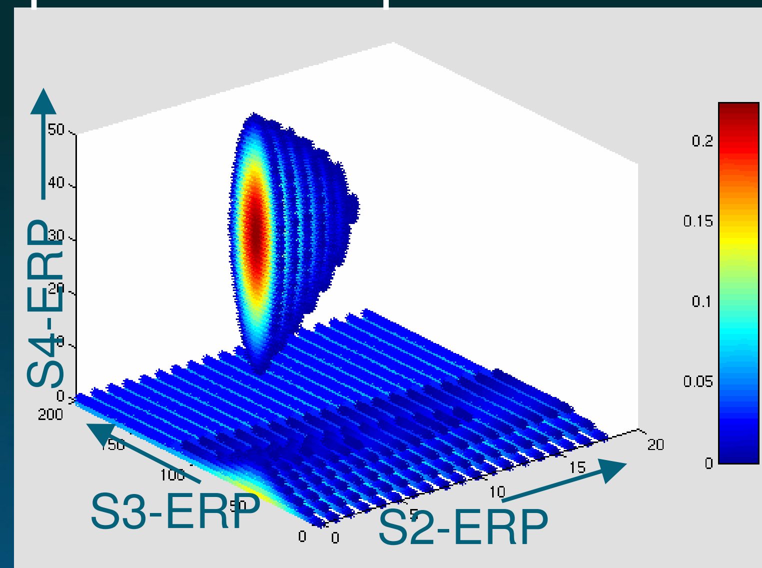
Left ventricle results

APD restitution function



S2 - ERP = 0 ms "short"
S3 - ERP = 51 ms "long"
S4 - ERP = 49 ms "long"
S5 - ERP: always short

Pacing intervals that are predicted to produce block:

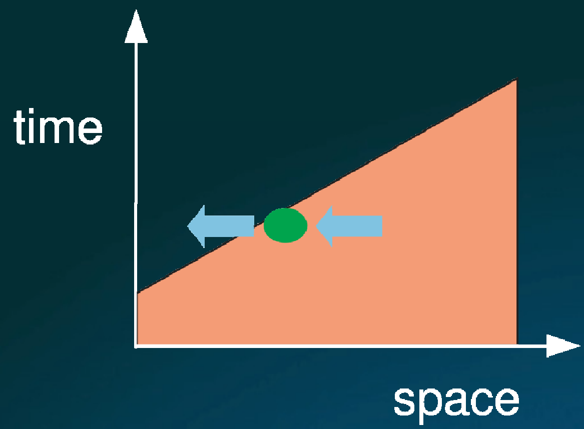


Experimental Results

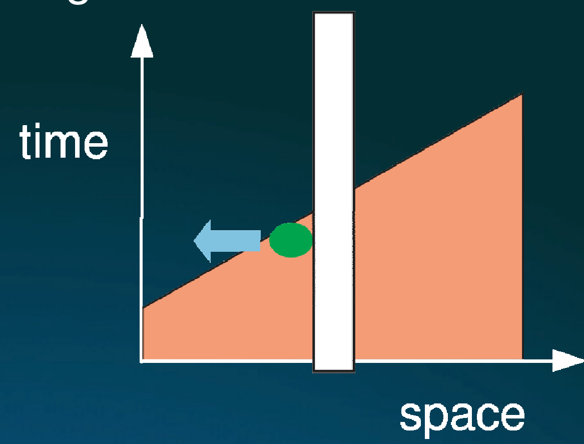
Short	Short
Long	Long
Short	Long
Short	Short
No VF	VF

Effect of walls

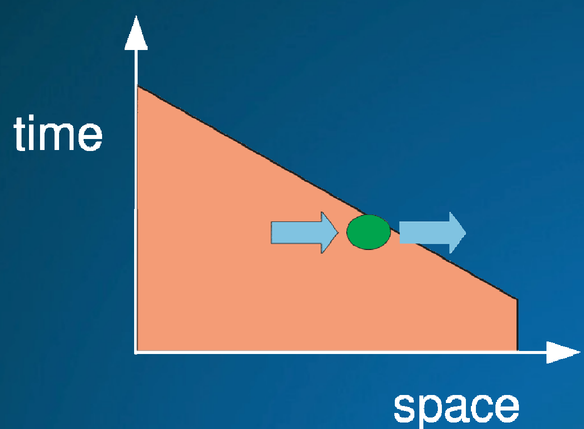
Propagation of waveback to right—no wall



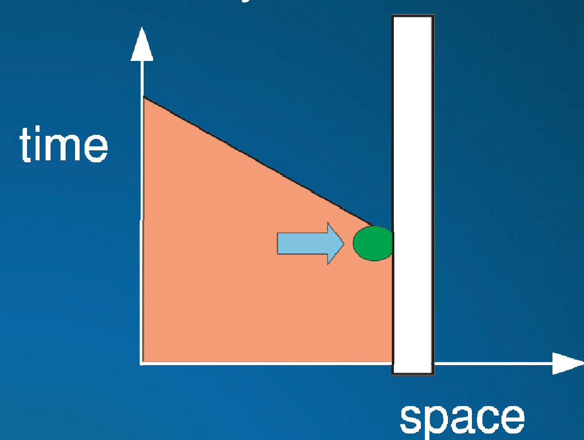
Propagation of waveback to right—towards wall



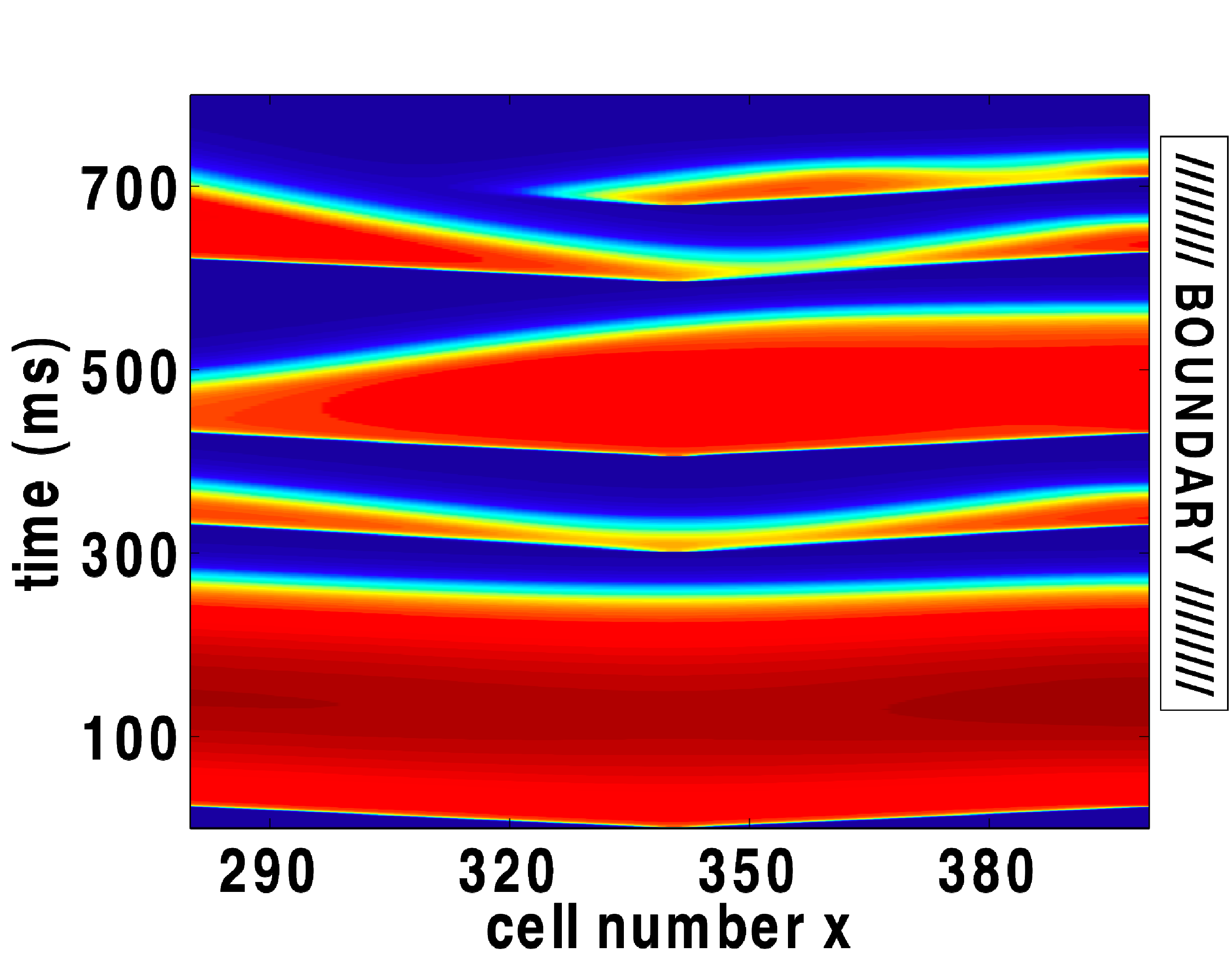
Propagation of waveback to left—no wall



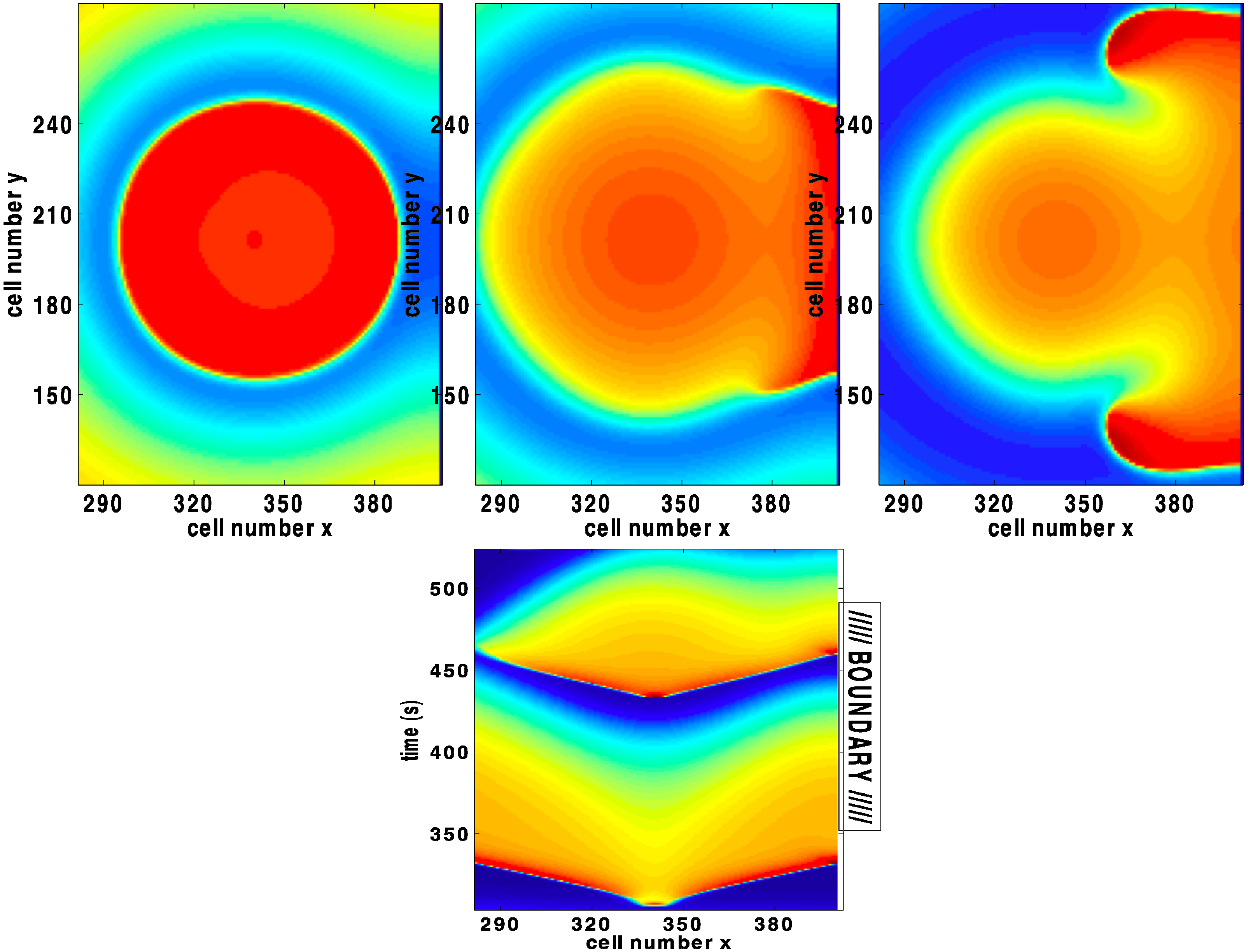
Propagation of waveback to left—away from wall



Effect of walls



Effect of walls



“Magic numbers”: summary

- A new dynamical theory has been developed that predicts when a series of premature stimuli will result in conduction block.
- Block is most likely to occur when differences in the conduction velocities of successive wavefronts are amplified by steep APD restitution.
- Steep APD restitution is greatly facilitates, but is not necessary, for block to occur.
- Preliminary experiments show a correlation between patterns of premature stimuli that theory says will produce block and the induction of VF.
- Geometric features, such as a wall, can modify the dynamics.

Conclusions

- Nonlinear dynamics can help us to understand systems that, when approached logically, lead to circular reasoning.
- Eigenmode methods can help to
  - Identify the physiological mechanism(s) underlying APD alternans, a possible precursor for VF
  - Suggest algorithms for their control

Conclusions

- Perturbation methods can determine the extent and localization of the influence of applied stimuli.
- Nonlinear dynamical analysis shows that certain combinations of stimuli can cause block-at-distance. These combinations tend to induce VF in *in vivo* experiments in canine hearts.
- Both dynamics and geometry are required for modeling of action potentials in the 3D heart.

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