Spatially discordant alternans and spiral waves

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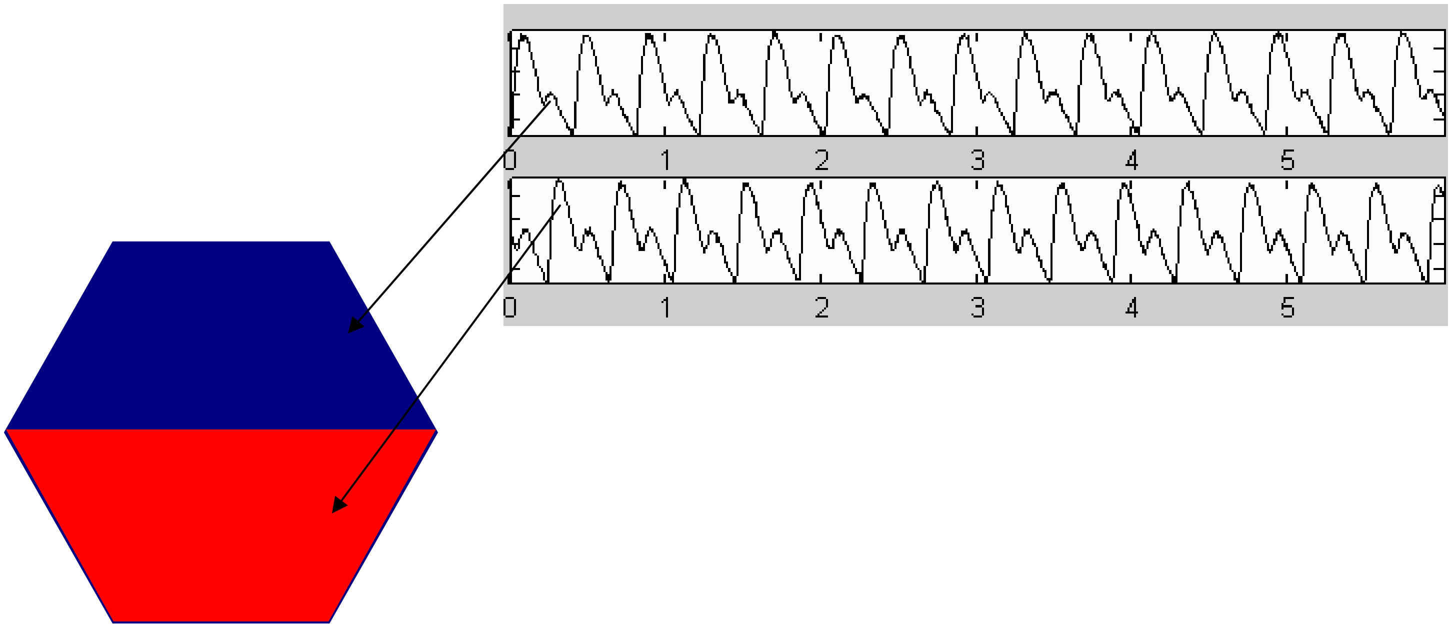
Background

- Spatial scale of cardiac propagation
- Pattern formation in cardiac tissue
- Arrhythmia mapping with high resolution
- Keeping up with models
- Need for sophisticated analysis tools

Background

- Spatially discordant alternans (SDAs)



SDAs

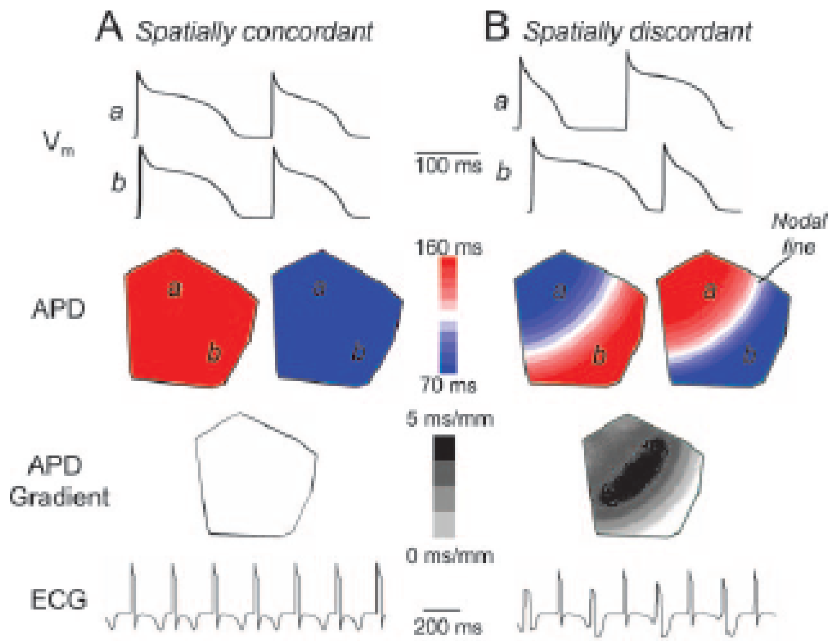


Figure 1. Spatially concordant (A) and discordant (B) APD alternans in simulated 2D cardiac tissue. A, Top traces show that simulated action potentials from sites *a* and *b* both alternate in a long-short pattern during pacing at 220-ms CL. Second panel shows that the spatial APD distribution is either long (blue) or short (red for each beat). Third panel shows that the APD dispersion (gray scale) for either long or short beats is minimal. Bottom panel shows simulated electrocardiogram (ECG), with T wave alternans. B, Top traces show that at a pacing CL of 180 ms, simulated action potentials from site *a* now alternate short-long, whereas at the same time, action potentials from site *b* alternate long–short. Second panel shows the spatial APD distribution, with a nodal line (white) with no APD alternation separating the out-of-phase top and bottom regions. Third panel shows that the APD dispersion is markedly enhanced, with the steepest gradient (black) located at the nodal line. Bottom panel shows simulated ECG, with both T wave and QRS alternans (attributable to engagement of CV restitution), as observed experimentally.[10] Simulations used a modified Luo–Rudy action potential model described previously.[11]

Weiss et al. 2006

SDAs

- Experimentally, ***spatially discordant alternans*** (***SDAs***) in APD have been documented to lead to ***reentrant (or spiral) waves, SW*** [1]:
  - SDAs have been proposed as a ***necessary*** condition for VT and VF
  - SDA's existence has been linked to ***base-apex gradient*** in tissue properties.

- Computer modeling investigations [2], however, point out the possibility to induce spatially discordant alternans in ***homogeneous tissue*** when engaging CV restitution or due to Turing pattern formation by the disparate scales of propagation of voltage and calcium alternans [3].

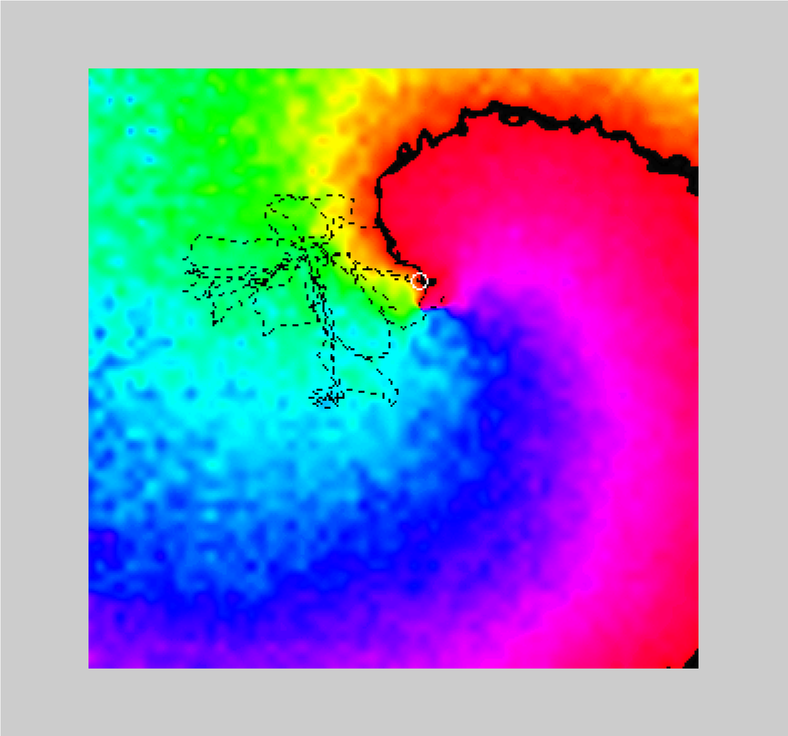
1 (Pastore et al., 1999;Pastore and Rosenbaum, 2000;Pham et al., 2003;Pruvot et al., 2004)

2 (Qu et al., 2000a;Qu et al., 2004;Watanabe et al., 2001)

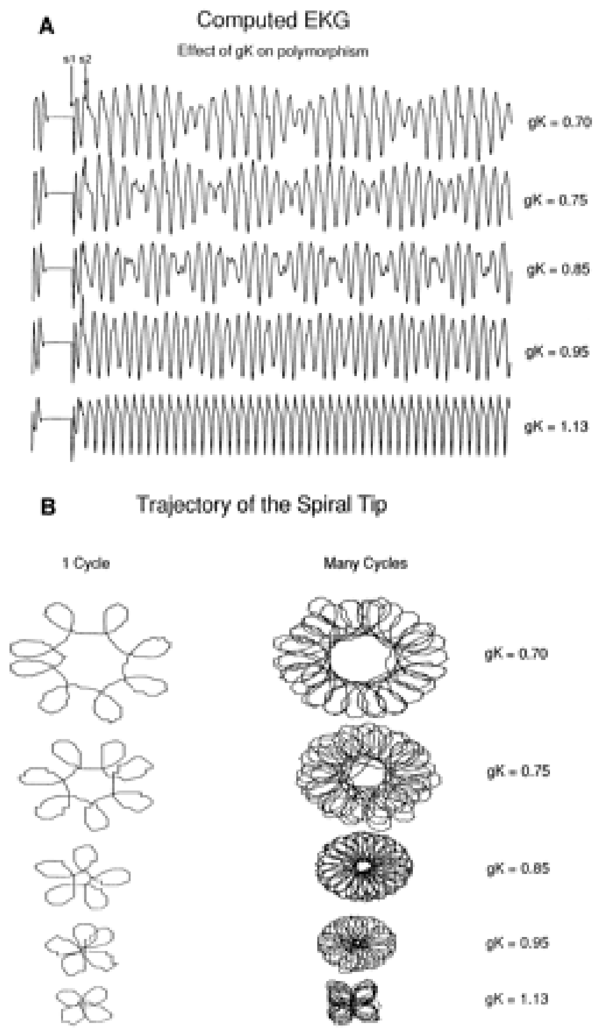
3 (Shiferaw and Karma,2006)

Background

- Meandering spiral waves (SWs)



SW Meandering



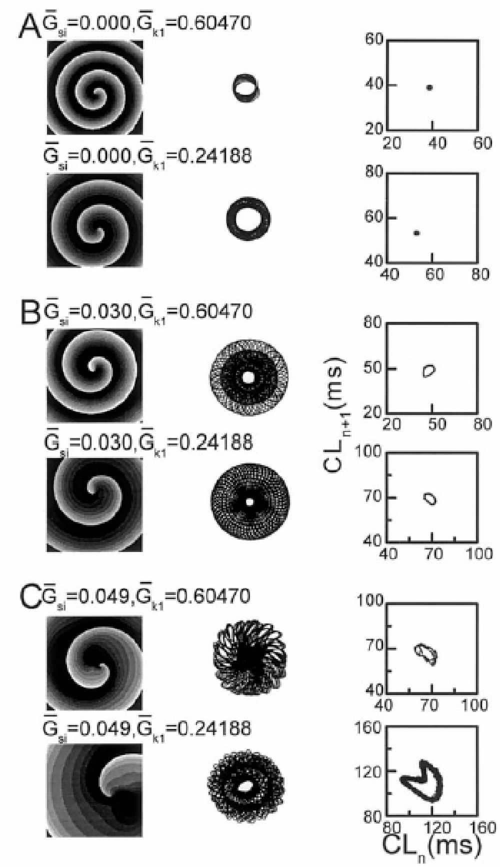
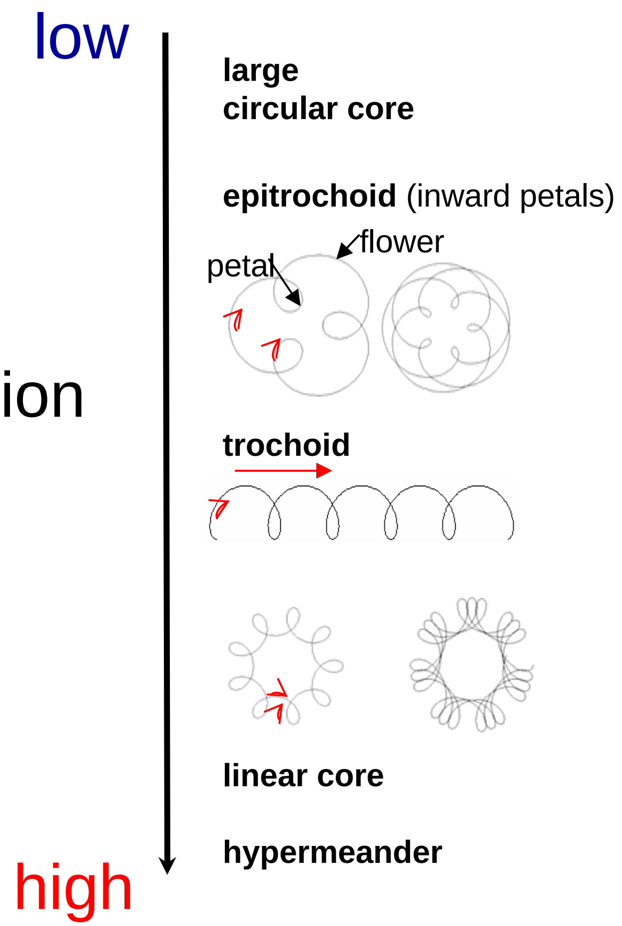


Fig. 1. Spiral wave dynamics as a function of the maximal conductance of the slow inward current ($\bar{G}_{si}$) when action potential duration (APD) is modulated by changing the time-dependent K^+ conductance ($\bar{G}_{K1}$) in homogeneous isotropic two-dimensional (2-D) tissue (80 × 80 mm). *A–C*: nearly stable ($\bar{G}_{si}$ = 0), meander ($\bar{G}_{si}$ = 0.030), and hypermeander ($\bar{G}_{si}$ = 0.049) regimes, respectively. Spiral wave behavior is shown both for the maximum (*top row*) and minimum (*bottom row*) values of $\bar{G}_{K1}$ (0.60470 and 0.21488) used to modify APD in subsequent simulations. *Left*: voltage snapshots at steady state (2 s after initiation of the spiral). White represents depolarized tissue at the wave front, and black represents repolarized tissue at the wave back. *Middle*: trajectory of the spiral tip. *Right*: Poincaré plots of successive cycle lengths (CL) of the spiral.

Starmer et al. 95, Xie et al., 2001

SW Meandering

Depolarization-repolarization
ion current balance

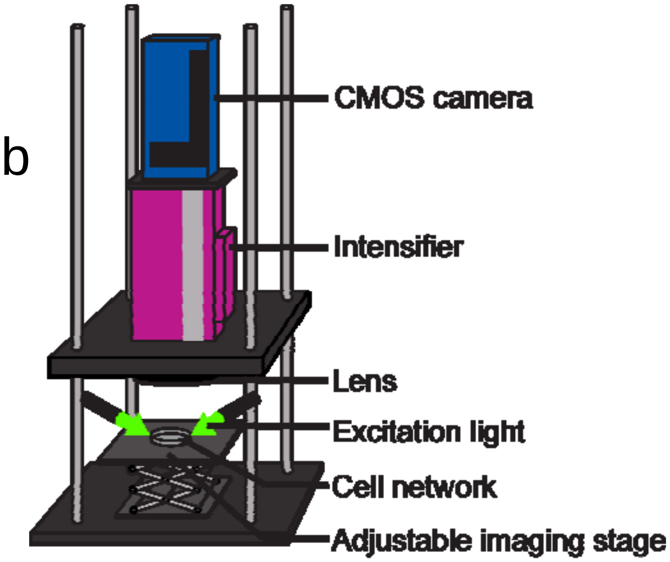


Questions

- **Can SDAs exist in isotropic tissue?**
- **Can whole-field SDAs coexist with spiral waves?**
- **How do SDAs and spiral waves (SW) interact?**

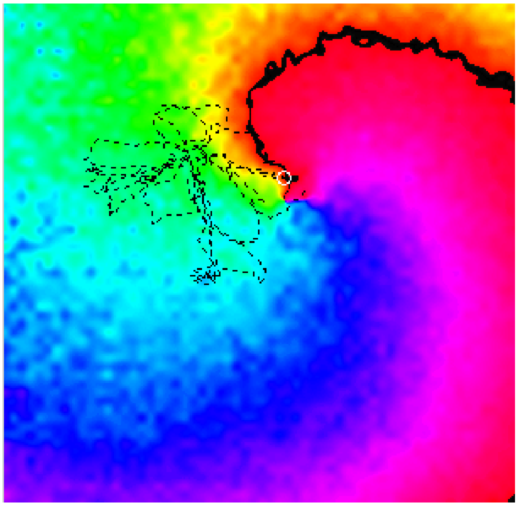
Methods

- Isotropic cultured cardiomyocyte networks
- $[Ca^{2+}]_i$ measured optically with Fluo-4
- Optical mapping system:
  - Intensified CMOS, 1280x1024, 200fps, 10b
  - Typical 14sec recording 7GB



Analysis

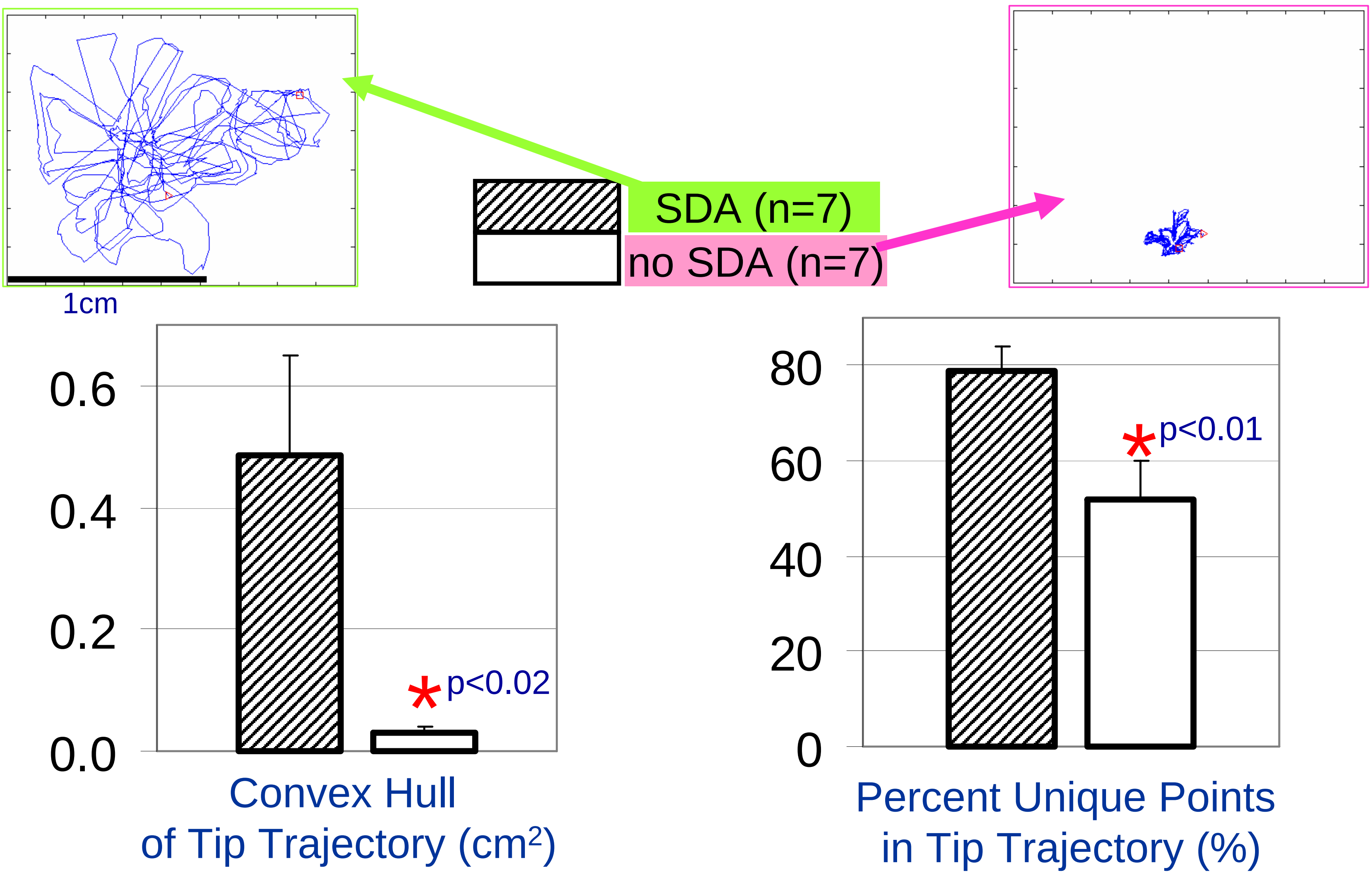
- **Spiral tip tracking**
  - **x-y-t** trajectory generated
  - Tip trajectory properties:
    - % unique (traversed once) points
    - Convex hull, centroid of trajectory



- **SDA Analysis**
  - Automatic adaptive **peak detection**
  - Spatial **alternans maps** over time after automatic beat matching
  - Binary-thresholded SDA regions

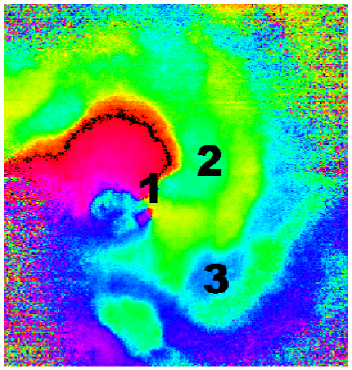
Results I:

Spiral waves with SDAs hypermeander

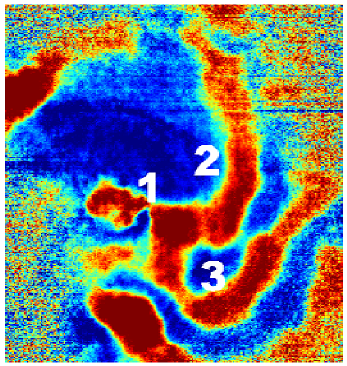


Results II:

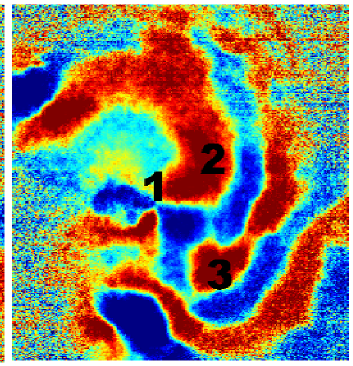
Spatial association of SDA regions with SWs



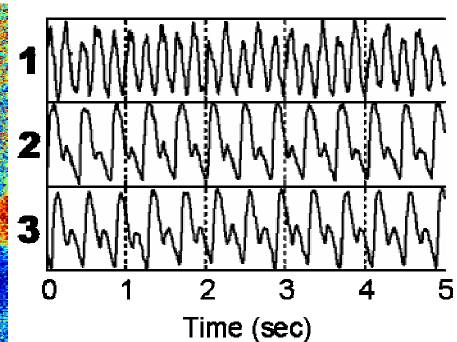
phase

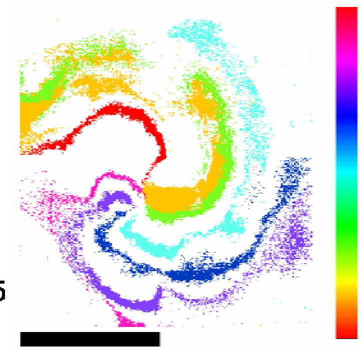


SDA
beat (n)

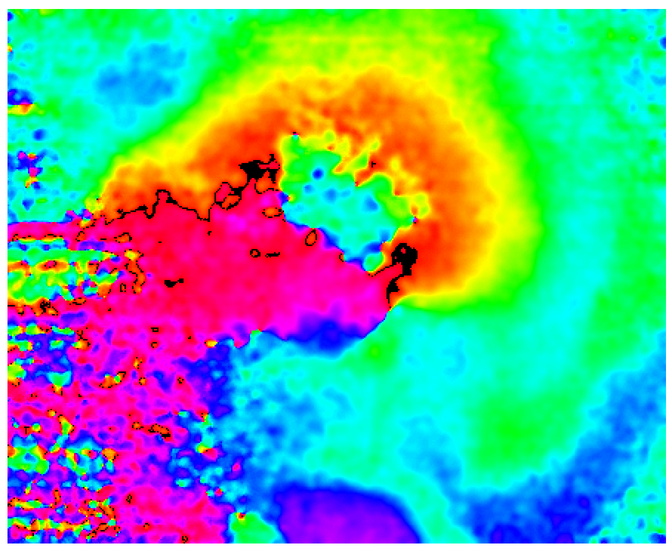


SDA
beat (n+1)

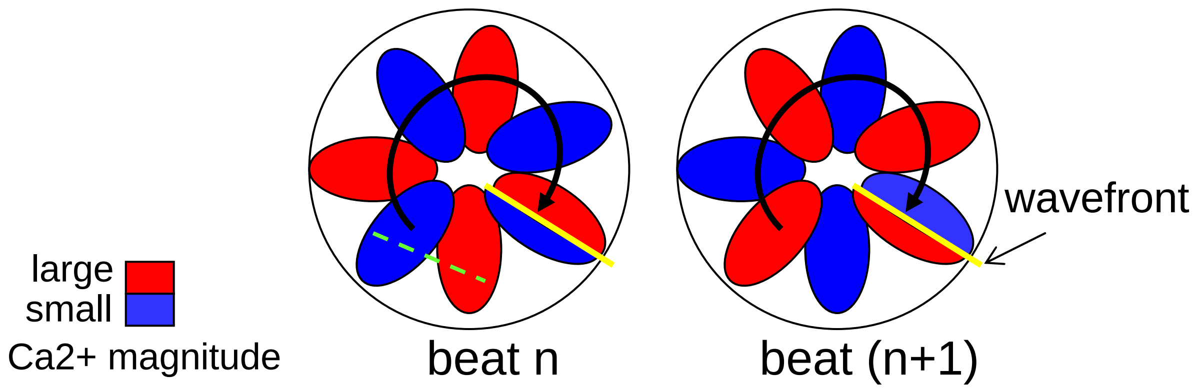




heterogeneous CV



Radial Arrangement of SDAs

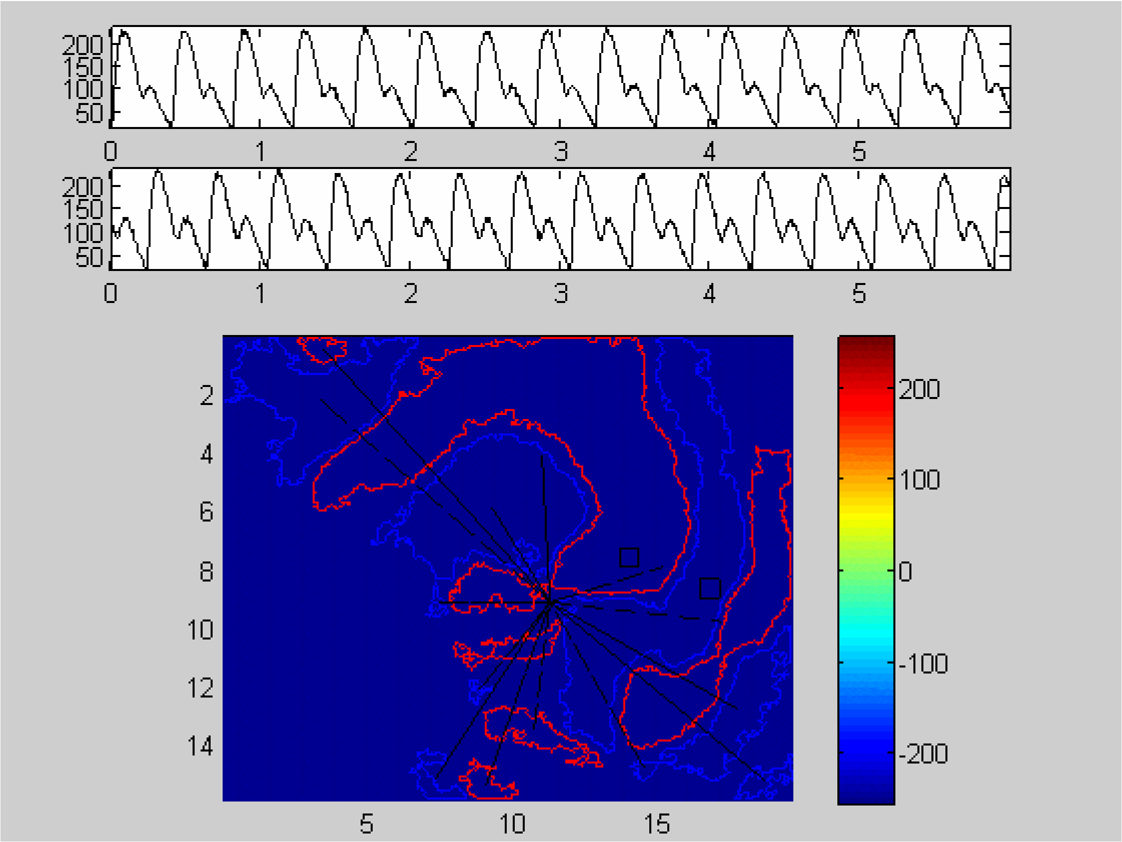


Results II:
Spatial association of SDA regions with SWs

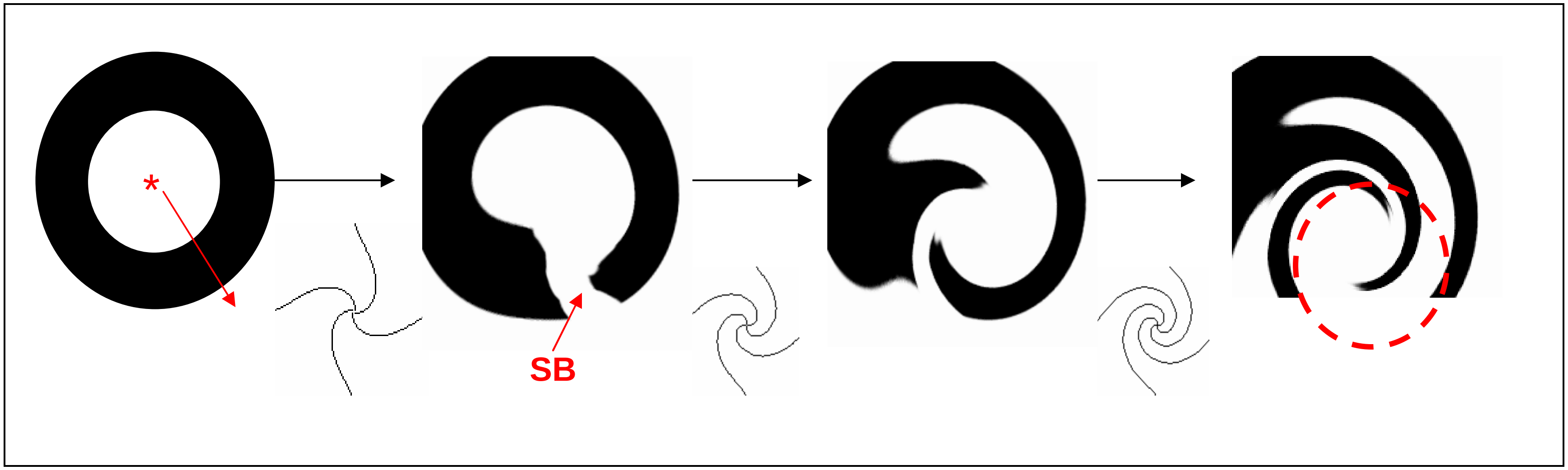
Radial arrangement of SDAs

- Unusual example of static SDAs (1/7)

- Coincidently, smallest convex hull of tip trajectory from all SDA-SW cases



A Possible Scenario



Discordant alternans (DA) established by external pacing or ectopic site (*)

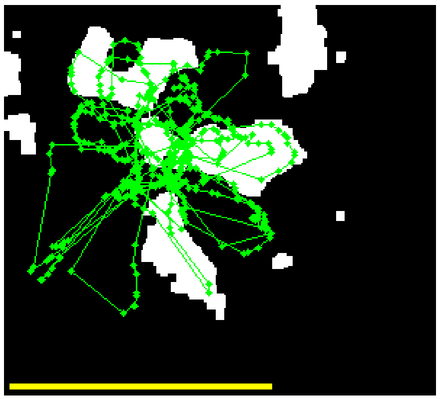
Symmetry break develops (SB) -> ***reentry induction***

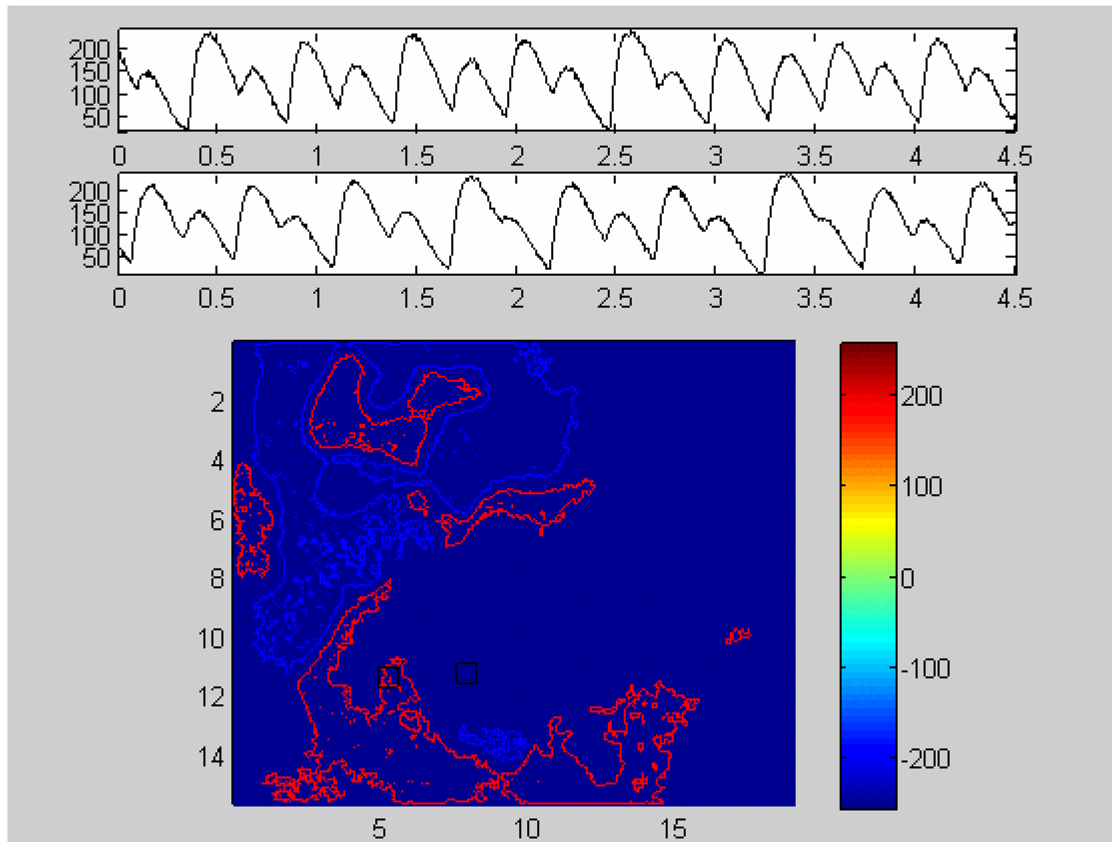
Reentrant wave acts as "***space warping***" transform on DA

DA perturb reentrant path -> ***hypermeandering***, *VF*

Results III:

SW tip trajectory follows nodal lines during SDA evolution





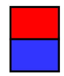
Summary

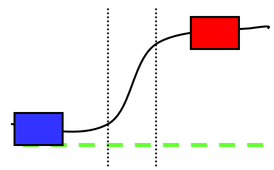
- SDAs can be induced in isotropic media and can coexist and directly interact with spiral waves causing **hypermeandering**
  - SW hypermeander in the presence of SDAs – tip trajectory spans large areas
  - Spatial association of SW reentrant path and the SDA domains, where the SW tip traverses primarily the nodal lines
  - SDA domains evolve in time along the SW path

Mechanism?

- **CV-restitution causing voltage SDAs**
- **Ectopic site causing voltage SDAs**
- **Turing mechanism of disparate scales of propagation for voltage and Ca^{2+} alternans**
- **Other?**

Spatial scale of SDAs?

large
small

Ca^{2+} magnitude



transition zone
between discordant alternans

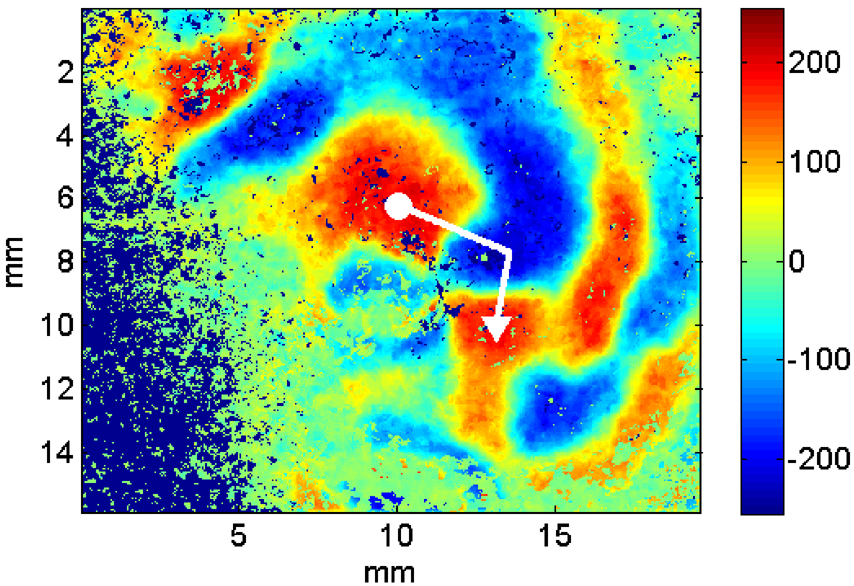
10μm
subcellular (Ca^{2+})

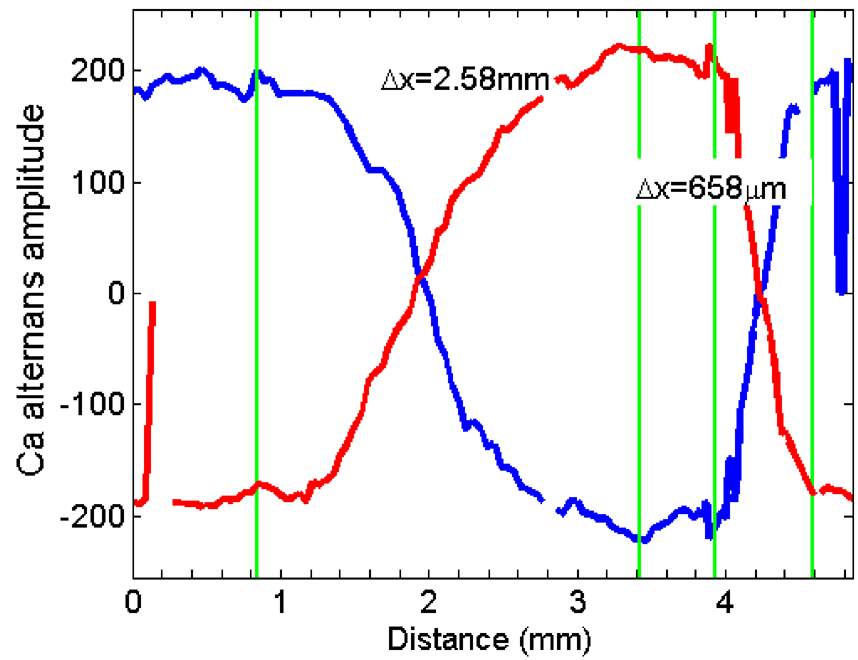
1cm
(voltage)

SDA region $$x \cong \Delta DI \left(\frac{\theta max \cdot \theta min}{\theta max - \theta min} \right)$$

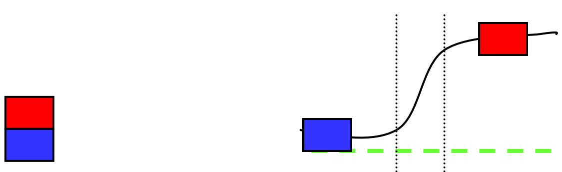
Watanabe et al., 2001, Shiferaw & Karma, 2006, PNAS

SDA transition zones vary in size





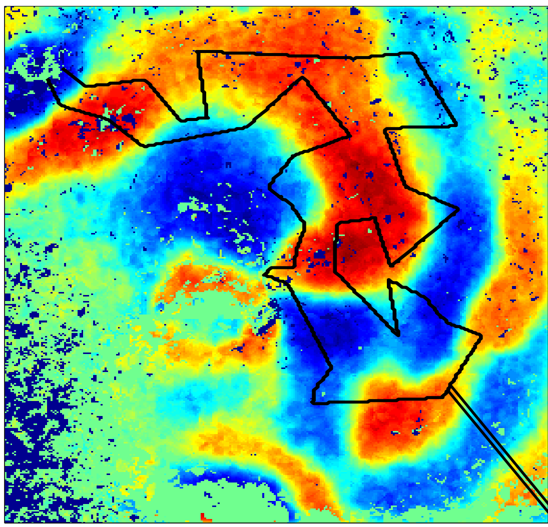
large
small
Ca2+ magnitude



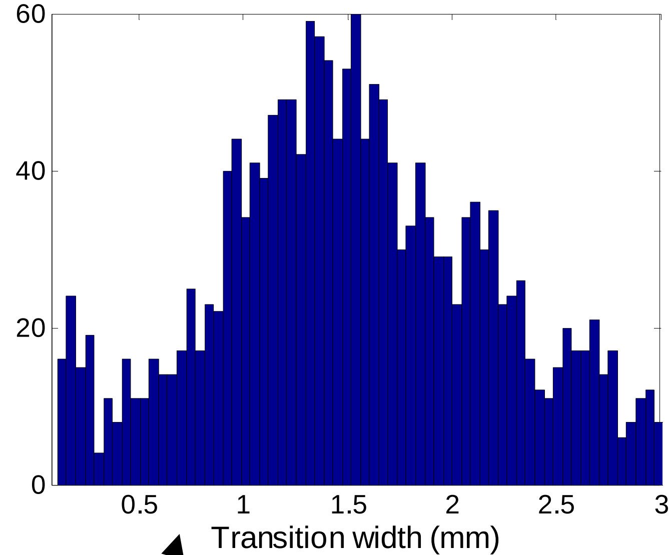
transition zone
between discordant alternans

SDA transition zones quantification

example path



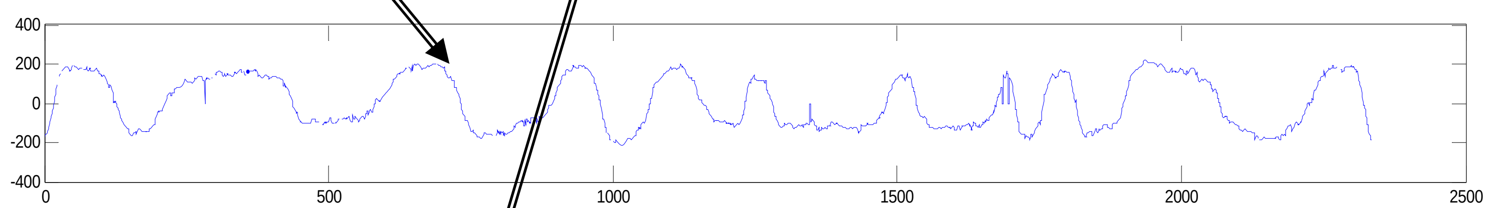
histogram of transition widths



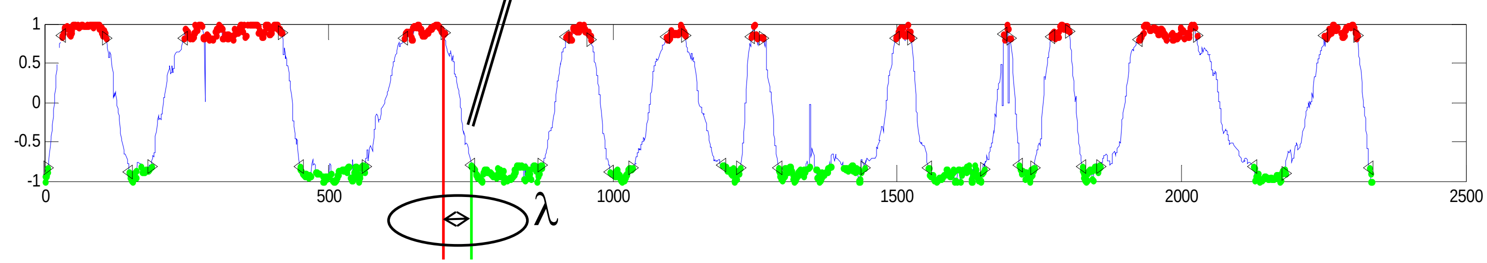
Q:
large range of values for λ: 0.1 to 3mm

predominant transition widths 1-1.5mm

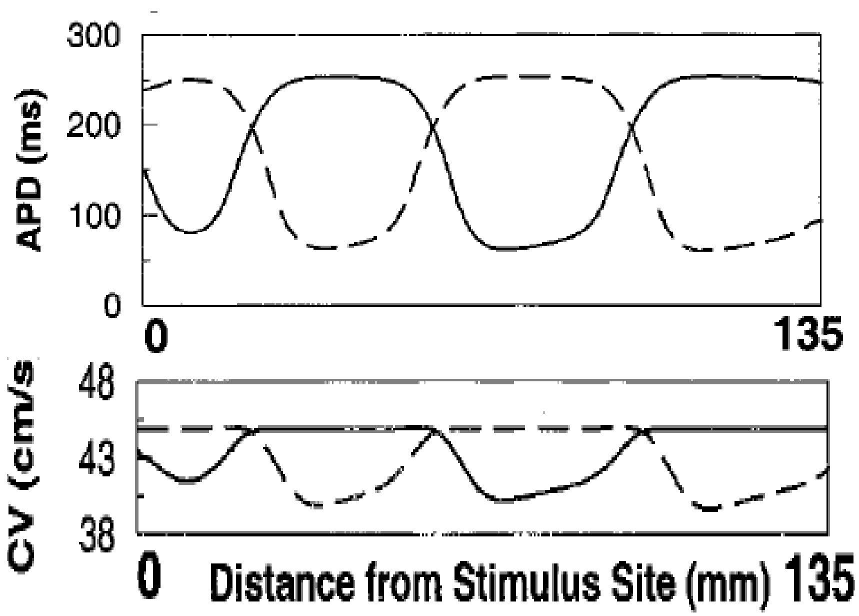
raw transitions

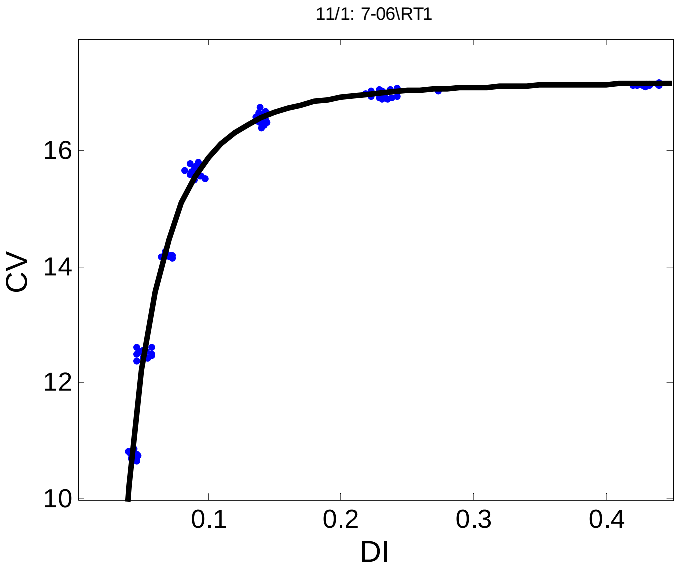


processed for calculation of 80% transitions



CV-restitution mechanism for SDAs

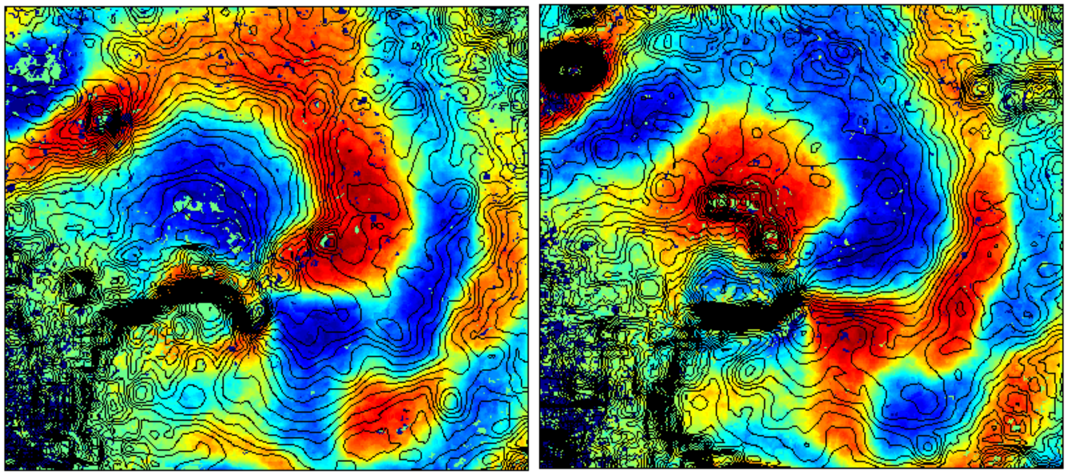




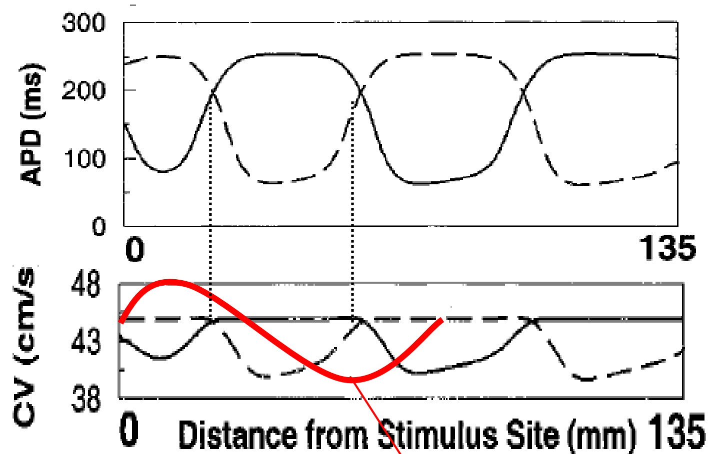
Watanabe et al., 2001

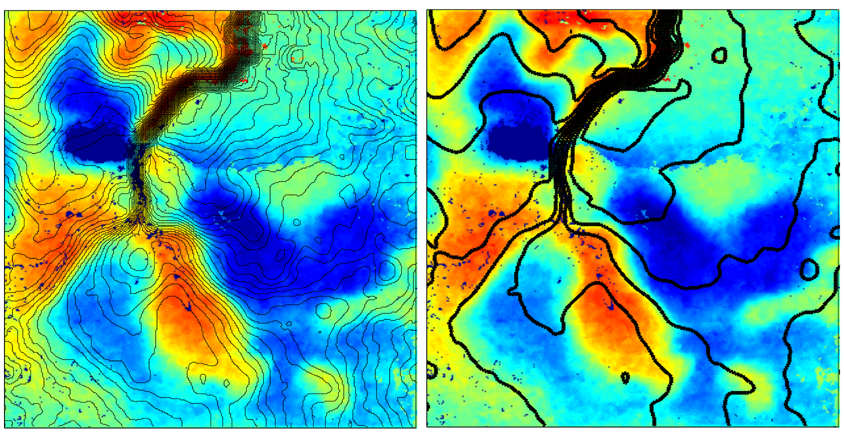
CV alternans

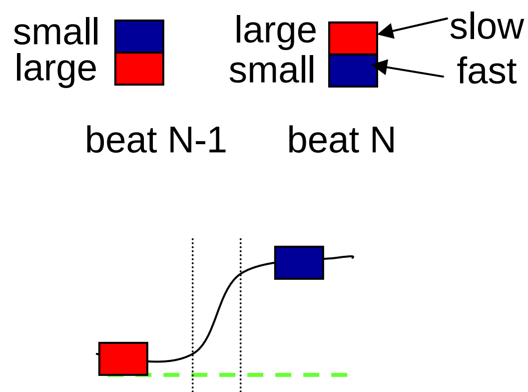
activation maps



beat N beat N+1





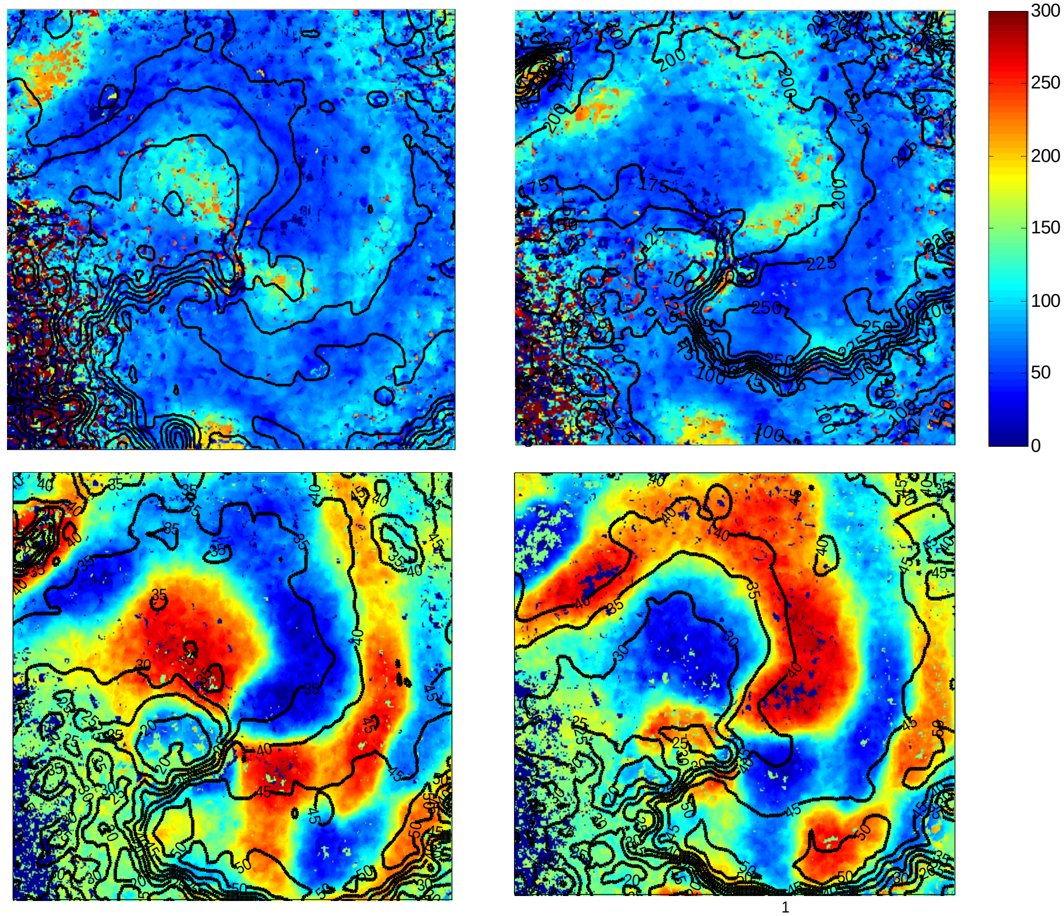


Q: min-max CV at the nodal lines?

DI Alternans

(preceding) DI maps

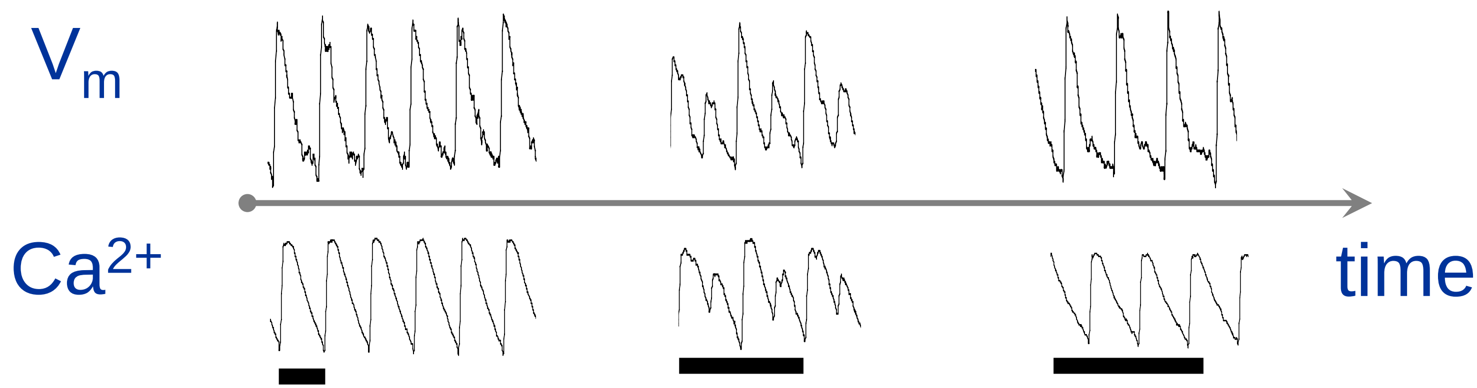
activation maps



beat N

beat N+1

Mechanism?



Vm-Ca2+ concordance

Shiferaw et al. 2004

Open Questions

- **Confirming mechanism of SDAs during SWs**
- **SDAs as modulators of SW meandering?**
- **What is different between our SDA and non-SDA samples with SW?**
- **Understanding the co-evolution of SDA regions and SW**
- **Perturbation strategy?**

Acknowledgements

- National Science Foundation
- American Heart Association

- Members of the Cardiac Cell Engineering Lab