Approaches for Control of Cardiac Electrical Dynamics

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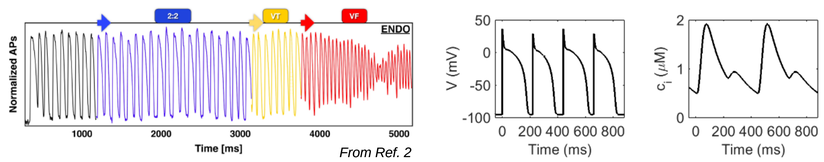
Overview

- Alternans is a beat-to-beat alternation (period-2 dynamics) in cellular action potential shape and duration that leads to alternans in the T-wave of the ECG.
- Alternans often precedes more dangerous arrhythmias like ventricular fibrillation.
- Because alternans is one pathway to fibrillation, methods to control alternans are an important area of study.
- Many methods proposed for controlling alternans have been tested using models with only one mechanism for alternans.
- We want to understand how the alternans mechanism affects the ability to suppress alternans.

Alternans Mechanisms

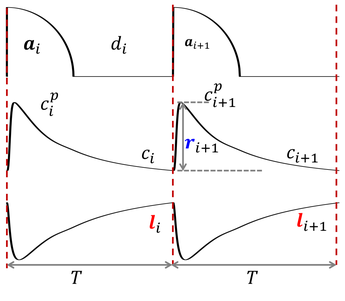


From Ref. 2

- Voltage-driven alternans: Instabilities in membrane potential lead to alternans.
  - Action potential duration to first order is predicted by the duration of the interval before that action potential (diastolic interval).
  - Alternans arises when changes in the intervals between action potentials cause even larger changes in action potential durations.
- Calcium-driven alternans: Instabilities in intracellular calcium cycling lead to alternans.
  - Calcium cycling is necessary for contraction.
  - Alternans arises at fast pacing rates when the cycling is unbalanced.

Model

Variable	Meaning (for iteration i)
$\boldsymbol{a}_i$	Action potential duration (APD) (ms)
$\boldsymbol{l}_i$	Sarcoplasmic reticulum calcium load (μM)
$\boldsymbol{r}_i$	Calcium released from sarcoplasmic reticulum (μM)
c_i	Cytoplasmic calcium concentration (μM)
$\boldsymbol{b}_i$	Total intracellular calcium concentration (μM)
d_i	Diastolic interval (ms)
c_i^p	Peak cytoplasmic calcium concentration (μM)
T	Period (ms)



Discrete model of Qu et al. (2007)[3]

APD restitution

$$\boldsymbol{a}_{i+1} = \frac{f(d_i;\tau_0)}{1-\gamma c_{i+1}^p}$$

APD coupling to Ca^{2+}

SR Ca^{2+} release restitution; SR load dependence

$$\boldsymbol{r}_{i+1} = q(d_i)\, g(\boldsymbol{l}_i)$$

Ca^{2+} uptake

$$\boldsymbol{l}_{i+1} = \boldsymbol{l}_i - \boldsymbol{r}_{i+1} + \nu u(T)\, h(c_{i+1}^p)$$

Period-dependent Ca^{2+} accumulation; Dependence on Ca^{2+} current

$$\boldsymbol{b}_{i+1} = \boldsymbol{b}_i - \kappa(c_i - c(T)) + \eta(\boldsymbol{a}_{i+1} - \boldsymbol{a}_i)$$

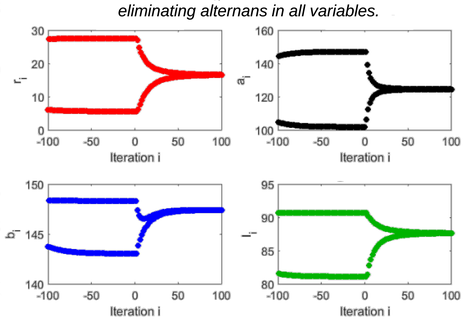
Derived quantities:

$$d_i = T - \boldsymbol{a}_i$$
$$c_i = \boldsymbol{b}_i - \boldsymbol{l}_i$$
$$c_{i+1}^p = c_i + \boldsymbol{r}_{i+1}$$

Control Methods

- Adjustments to stimuli timing:
  - Constant diastolic interval (DI) pacing[5]: adjust period to keep $d_n = T - a_n$ constant using the maximum, minimum, and average of the DIs occurring during alternans.
  - Early stimulus[1]: perturb period proportional to $APD_n - APD_{n-1}$.
- Feedback applied to state variables:
  - Feedback toward the approximate fixed point: apply feedback proportional to $z_n - z_n^*$ for a state variable z_n, where z_n^* is the average of the values of z_n during alternans.
  - Feedback to reduce variation[4]: apply feedback proportional to $z_n - z_{n-1}$ for a state variable z_n.

Iteration of state variables for calcium-driven alternans ($\nu = 0.35$) with a pacing period of $T = 170$ms using feedback applied to the APD variable a_n.Control is successful in eliminating alternans in all variables.

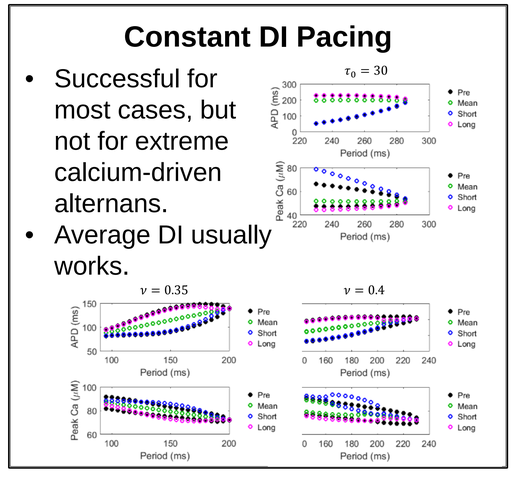


Results

- Alternans was induced from a default parameter set with no alternans by varying either τ_0 to obtain voltage-driven alternans or ν to obtain calcium-driven alternans.
- We studied effectiveness of control by directly iterating the system to establish an alternans state and then applying one of the control methods above.
- We studied the full range of periods with alternans and quantified the magnitude of alternans in APD and calcium before and after applying control.
- We also varied the feedback gain.

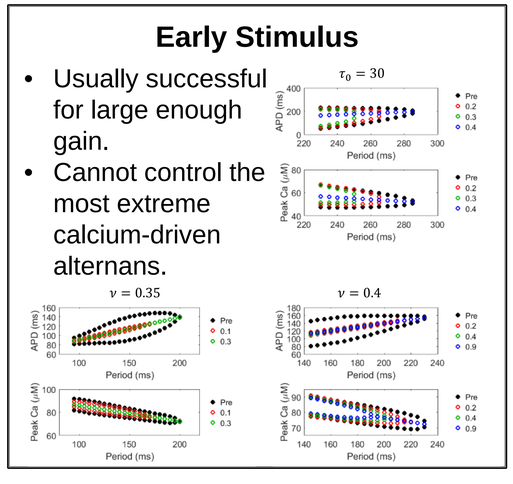
Constant DI Pacing

- Successful for most cases, but not for extreme calcium-driven alternans.
- Average DI usually works.



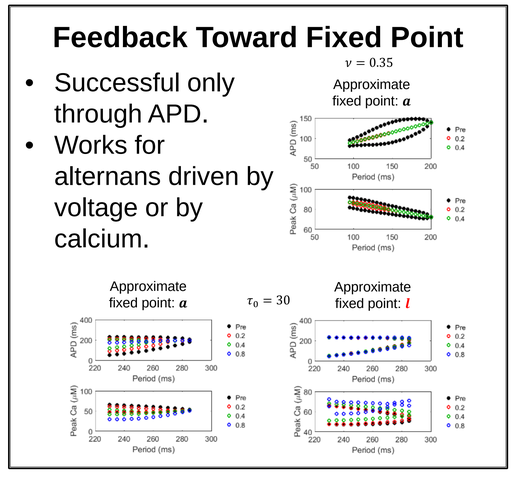
Early Stimulus

- Usually successful for large enough gain.
- Cannot control the most extreme calcium-driven alternans.



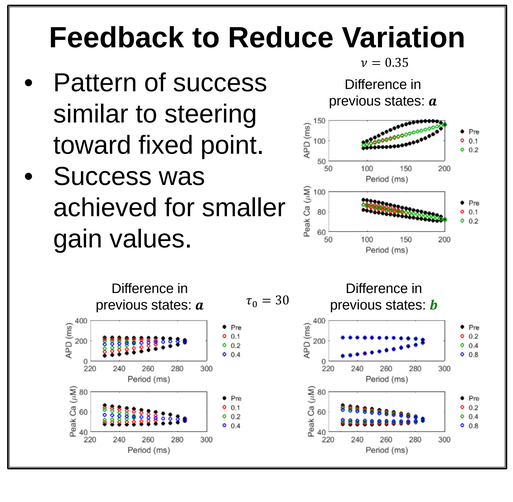
Feedback Toward Fixed Point

- Successful only through APD.
- Works for alternans driven by voltage or by calcium.



Feedback to Reduce Variation

- Pattern of success similar to steering toward fixed point.
- Success was achieved for smaller gain values.



Summary

- Constant DI can control APD alternans for all but the most extreme cases; care in DI selection is required only for extreme calcium-driven alternans.
- Early stimulus control (period feedback) works to control APD alternans in all cases except the most extreme Ca-driven alternans cases.
- Controlling APD alternans through APD is effective.
  - Feedback to reduce variation in the state variable requires a lower gain to be effective than steering toward the approximate fixed point.
  - Controlling through other state variables seldom is effective.
- Controlling Ca alternans is slightly more difficult; not all strategies that control APD alternans are effective.

Future Work

- Theoretical controllability studies:
  - Explain and understand our results in more detail.
  - Predict whether feedback from observations of multiple values will improve effectiveness.
- Extension to one spatial dimension and to states with more complex spatiotemporal dynamics.
- Compare our results with more detailed continuous-time models.
- Apply to real-world systems with heart tissue in the loop.

References

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