Controllability of Cardiac Alternans

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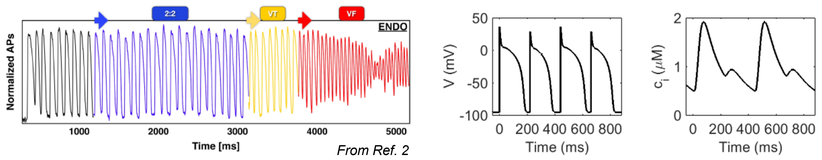
Overview

- Alternans is a beat-to-beat alternation (period-2 dynamics) in cardiac cellular action potential shape and duration that leads to alternans in the T-wave of the electrocardiogram. It often precedes more dangerous arrhythmias like ventricular fibrillation.
- Because alternans is one pathway to fibrillation, methods to understand when and how alternans can be controlled are important to study. However, many studies of alternans control have been conducted using models with only one mechanism for alternans.
- Here, we assess the suitability of controllability analysis to establish a theoretical basis for determining which control strategies are best for suppressing alternans and to determine how alternans mechanism impacts the best strategy.

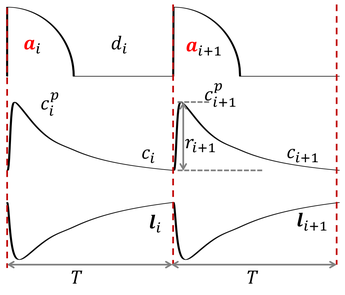
Alternans Mechanisms



- 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)
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)

APD restitution / APD coupling to Ca^{2+}

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

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

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

Ca^{2+} uptake

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

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:

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

Z. Qu, Y. Shiferaw, and J. N. Weiss, Phys. Rev. E **75**, *011927 (2007).*

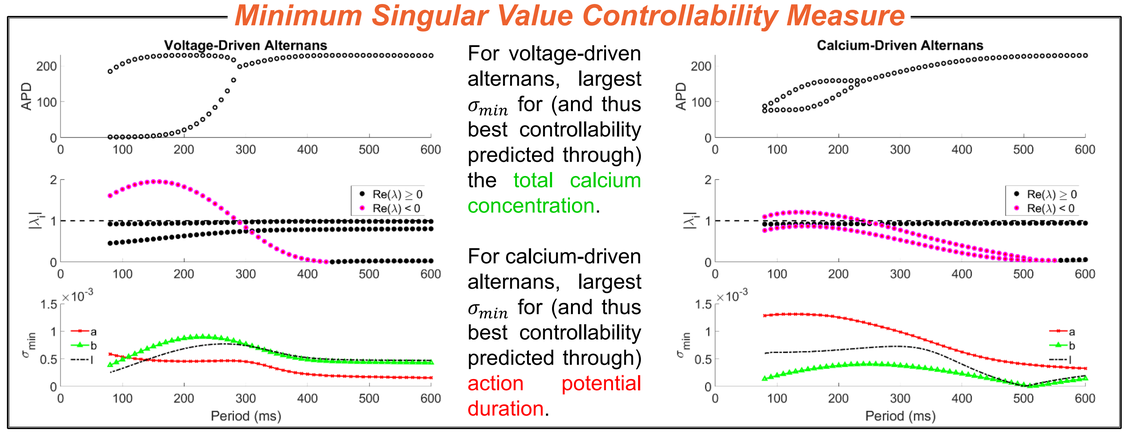
Controllability Assessment

- Linearize about a fixed point ($x_k = [a_k - a^*\ b_k - b^*\ l_k - l^*]^T$), add control input:
  $$x_{k+1} = Ax_k + Bu_k$$
  u_k: control input at step k
  B: control strategy; identifies input used to apply control
- Linearized model is ***controllable*** if for any initial and final states $x_{initial}$ and x_{final} there exists a final time index k_{final} and sequence of inputs u_k that will transfer $x_{initial}$ to x_{final} at time index $k_{final} = n$.
- Controllability matrix:
  $$P = [B\ AB\ A^2B \cdots A^{n-1}B]$$
  Thus, $x_n - A^n x_0 = P[u_{n-1} \cdots\ u_0]^T$.
- ***Minimum singular value controllability measure:*** P must have full rank for the system to be controllable. The minimum singular value σ_{min} of P can be used as a measure of how close P is to rank deficiency. Large σ_{min} is desired for controllability.
- ***Modal controllability measure:*** Compute cosine of controllability angle between each left eigenvalue w_i of A and input matrix B_j.
  $$\left|\cos\theta_{ij}\right| = \frac{|w_i^* \cdot B_j|}{\|w_i\|\|B_j\|}$$
  Larger values desired for any case with an alternans eigenvalue (negative real part) for controllability.

Results

Alternans was induced from a default parameter set with no alternans by varying either τ_0 (restitution curve steepness) to obtain voltage-driven alternans or ν (strength of calcium uptake to sarcoplasmic reticulum) to obtain calcium-driven alternans.

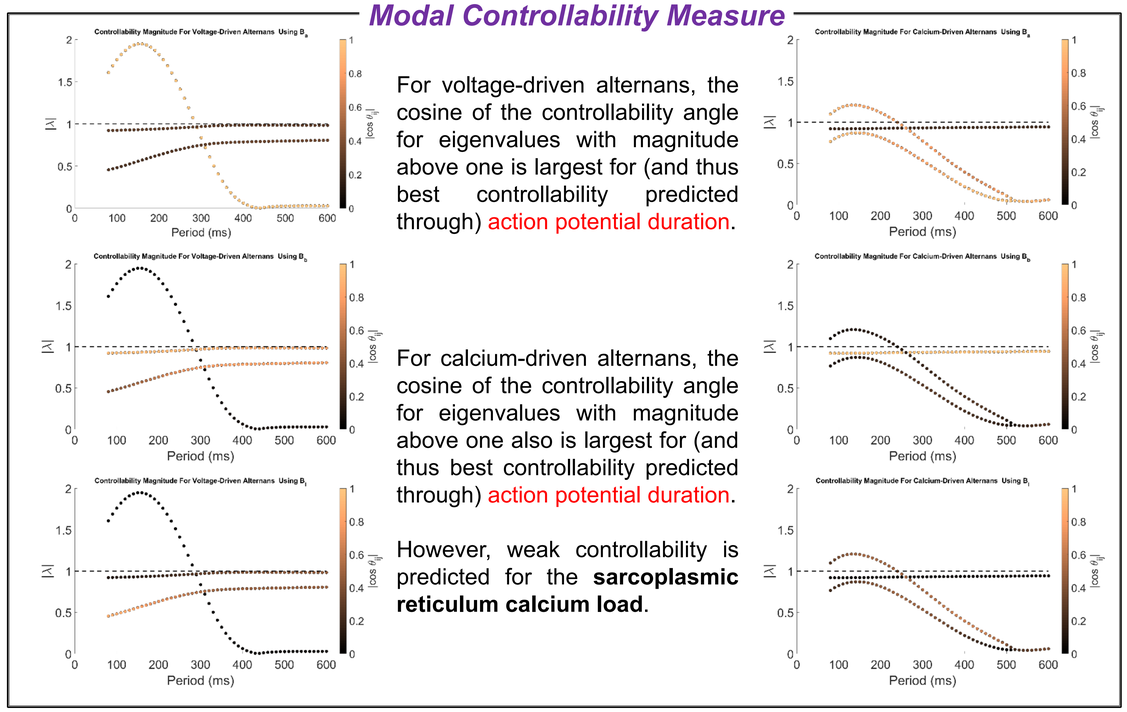
Minimum Singular Value Controllability Measure



For voltage-driven alternans, largest σ_{min} for (and thus best controllability predicted through) the total calcium concentration.

For calcium-driven alternans, largest σ_{min} for (and thus best controllability predicted through) action potential duration.

Modal Controllability Measure



For voltage-driven alternans, the cosine of the controllability angle for eigenvalues with magnitude above one is largest for (and thus best controllability predicted through) action potential duration.

For calcium-driven alternans, the cosine of the controllability angle for eigenvalues with magnitude above one also is largest for (and thus best controllability predicted through) action potential duration.

However, weak controllability is predicted for the **sarcoplasmic reticulum calcium load**.

State Feedback Control

- We assessed the accuracy of our controllability predictions using three types of state feedback controllers.
  - Single-variable state feedback.
  - Pole placement.
  - Linear quadratic regulator (LQR).
- Control was applied to a single representative cycle length for the voltage-driven and calcium-driven alternans cases.
- For voltage-driven alternans, all controllers favored (smaller target max eigenvalue/lower gain) control through action potential duration, matching the modal controllability measure but not the minimum singular value controllability measure.
- For calcium-driven alternans, the controllers generally favored (smaller target max eigenvalue/lower gain) control through the **sarcoplasmic reticulum calcium load**, although LQR results were fairly similar for control through action potential duration.

Summary + Future Work

- Voltage-driven case:
  - Minimum singular value measure: strong controllability through total calcium concentration.
  - Modal controllability measure: strong controllability through action potential duration.
  - State-feedback controllers favored control via action potential duration.
- Calcium-driven case:
  - Minimum singular value measure: strong controllability through action potential duration.
  - Modal controllability measure: strong controllability through action potential duration, weak controllability through **sarcoplasmic reticulum calcium load**.
  - State-feedback controllers favored control via either action potential duration or **sarcoplasmic reticulum calcium load**.
- Overall, modal controllability appeared to be the more useful controllability measure and action potential duration the most useful variable.
- Next we will extend our results to more complex models and seek closed-loop experimental validation.

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