Bifurcation Analysis of Cardiac Alternans using δ-Decidability

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Award# CNS-1446725

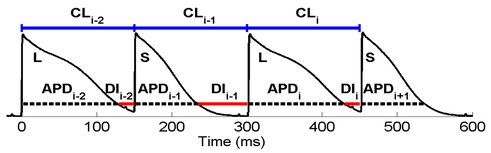
PROJECT SUMMARY

Electrical alternans is a phenomenon characterized by a variation in the successive Action Potential Durations (APDs) generated by a single cardiac cell or tissue. Alternans are known to initiate re-entrant waves and are an important physiological indicator of an impending life-threatening arrhythmia such as ventricular fibrillation. The bifurcation analysis we perform determines, for each control parameter τ of the MS model, the bifurcation point in the range of τ such that a small perturbation to this value results in a transition from alternans to non-alternans behavior. To the best of our knowledge, our analysis represents the first formal verification of non-trivial dynamics in a numerical cardiac-cell model.

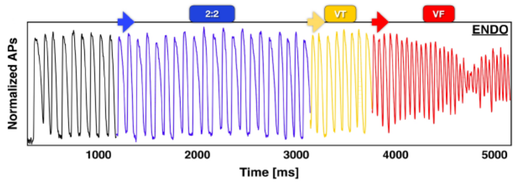
Our approach to this problem rests on encoding alternans-like behavior in the MS model as a 11-mode, multinomial hybrid automaton (HA). For each model parameter, we then apply a sophisticated, guided-search- based reachability analysis to this HA to estimate parameter ranges for both alternans and non-alternans behavior. The bifurcation point separates these two ranges, but with an uncertainty region due to the underlying δ-decision procedure. This uncertainty region, however, can be reduced by decreasing δ at the expense of increasing the model exploration time.

BACKGROUND & MOTIVATION

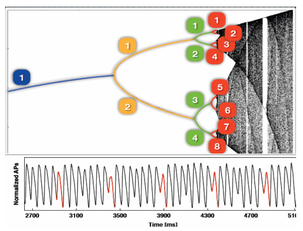
- Cardiac alternans appears as a beat-to-beat long-short alternation of action potential duration (APD)

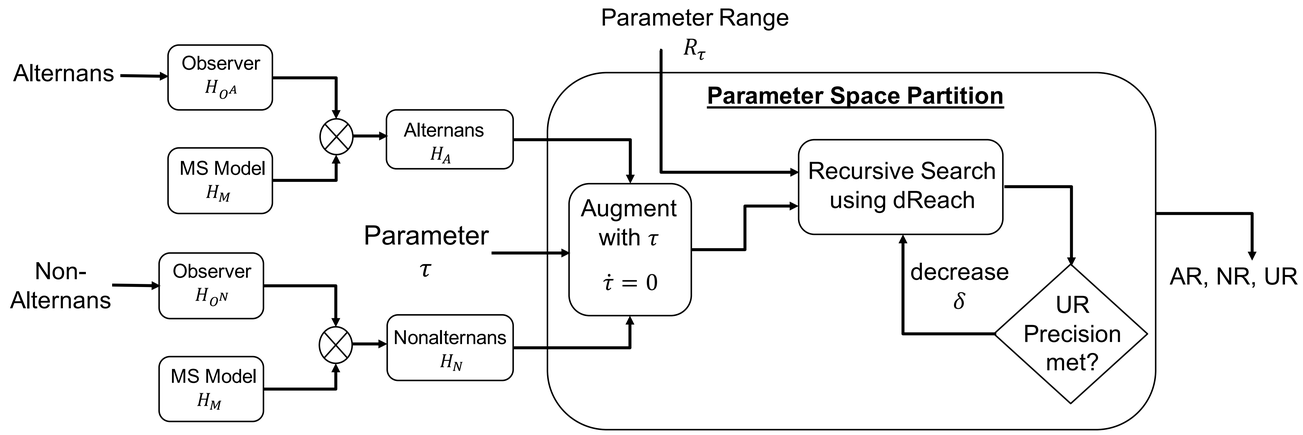


- Alternans often leads to fibrillation



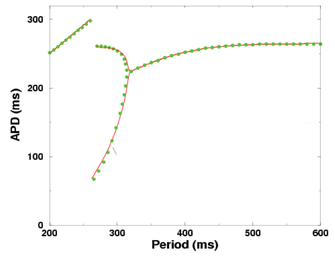
- Period-doubling leads to chaos



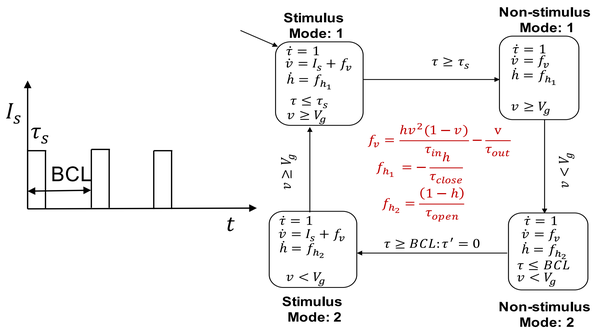


BIFURCATION ANALYSIS OF ALTERNANS

- Finding bifurcation points (BPs) that split the parameter space into alternans and non-alternans regions



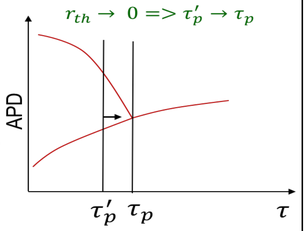
MITCHELL-SCHAEFFER (MS) MODEL



FORMAL DEFINITION OF ALTERNANS

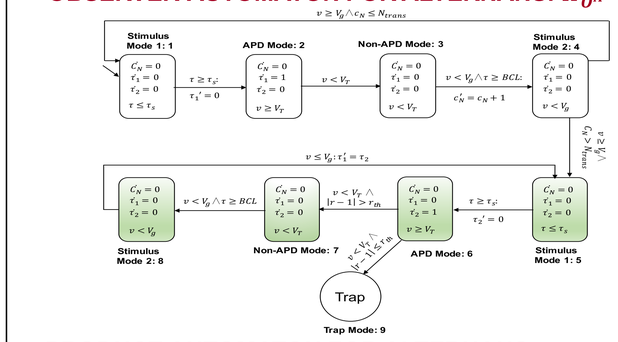
Given,

- σ: (possibly infinite) voltage signal
- $\tau_1 > 0$ and $\tau_2 > 0$: APDs two consecutive AP cycles where $r = \tau_2/\tau_1$

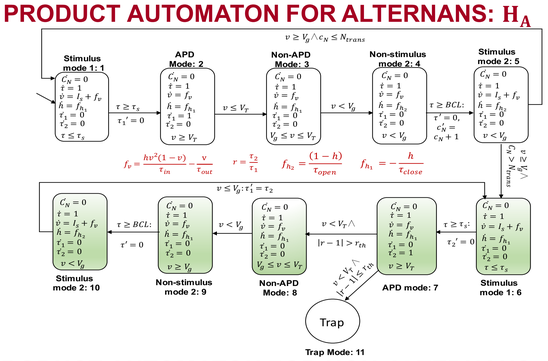


- σ exhibits: ***alternans (non-alternans)*** with respect to r_{th} when $|r-1| > r_{th}$ ($|r-1| \leq r_{th}$) is invariant

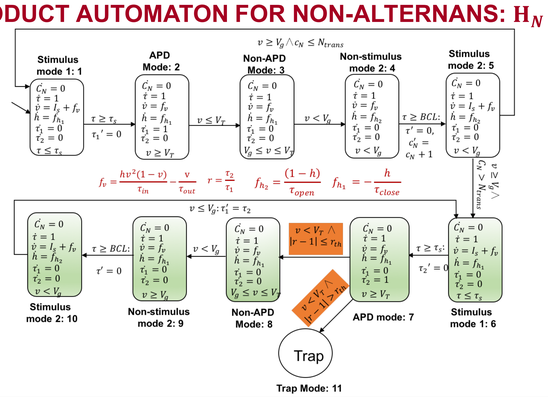
OBSERVER AUTOMATON FOR ALTERNANS: H_{O^A}



PRODUCT AUTOMATON FOR ALTERNANS: H_A



PRODUCT AUTOMATON FOR NON-ALTERNANS: H_N



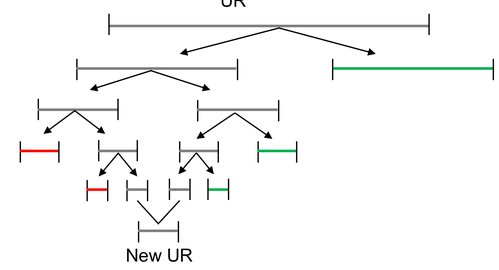
BIFURCATION ANALYSIS USING δ-DECIDABILITY

- Parameter (τ) Synthesis problem on H_A and H_N:
  - Augment both HA with $\dot{\tau} = 0$, where parameter range, $R_\tau = [\underline{\tau}, \overline{\tau}]$
  - Subrange $S_\tau \subseteq R_\tau$ produces alternans (non-alternans), if $\forall \tau \in S_\tau$, goal state of H_N (H_A) is not reachable

- Bifurcation Analysis using dReach:
  - Can not compute exact BPs (Undecidable problem)
  - Instead, by applying a recursive search procedure and refining δ on dReach, computes small intervals (URs) such that each one contains a BP. Additionally, it computes alternans (AR) and non-alternans (NR) regions
  - In search procedure, parameter synthesis problem is solved recursively on current subrange until dReach label the subrange as AR or NR or it becomes smaller than current δ on dReach

(a) Exact Analysis

(b) Steps in dReach-based Analysis



(b) Recursive search in action

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2. S. Kong, S. Gao, W. Chen, and E. M. Clarke. dReach: δ-reachability analysis for hybrid systems. In Tools and Algorithms for the Construction and Analysis of Systems - 21st International Conference, TACAS, London, UK, April 11-18, 2015.
3. S. Gao, S. Kong, W. Chen, and E. M. Clarke. Delta-complete analysis for bounded reachability of hybrid systems. CoRR, abs/1404.7171, 2014.