Title: Bridging in vivo heart rate variability analysis with in vitro and in silico approaches

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Abstract
Heart rate variability (HRV) serves as a validated biomarker for autonomic nervous system function and overall health. HRV refers to the variation in time between successive heartbeats. At the cellular level, beat-to-beat variability (B2BV) represents an analogous phenomenon and has been studied in human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs). These cells provide an *in vitro* platform for investigating electrophysiological properties. However, the memory effects in beating dynamics and the relationship between interbeat interval (IBI) and action potential duration (APD) have not been systematically explored. Traditional HRV metrics cannot capture these dynamics.

This study introduces time-lagged cross-correlation (TLCC) analysis as a method to investigate B2BV in hiPSC-CMs, both experimentally and through computational modeling. TLCC uses IBI and APD time series to study their dynamic relationship. To investigate B2BV computationally, Paci2020 hiPSC-CM model is employed to replicate the observed effects in beating dynamics. In addition, the study examines the impact of a junctophilin-2 mutation in both experimental and simulated data.

The results show that hiPSC-CMs display a memory effect in their beating dynamics, closely resembling previously reported patterns in human RR-QT intervals from electrocardiogram data. Computational model initially failed to reproduce this effect, but the addition of biologically realistic pink noise enabled the simulations to match experimental findings.

By integrating measurement, modeling, and TLCC analysis, this work enhances the understanding of B2BV in cardiomyocytes and provides new insights into the memory effect in beating dynamics. These findings support the development of more realistic, patient-specific computational models for cardiac research.