Intrinsic Complexity of RR and QT Intervals at the Cellular Level

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Introduction: Complexity of heart rate variability has been well established as an important measure in cardiac health, as it reflects the heart's ability to adapt to sudden perturbations. QT intervals also exhibit complex variability, which is useful in monitoring increased risks of fatal ventricular arrhythmias. In this study, we assessed for the first time the intrinsic complexity of RR and QT intervals at the cellular level by studying inter-beat intervals (IBIs) and field potential durations (FPDs) measured directly from clusters of spontaneously beating human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) under healthy and diseased conditions.

Method: Complexity is quantified by the sample entropy (SampEn) of a time series. We used the multiscale sample entropy (MSE) method, in which SampEn is obtained from a set of time series that are coarse-grained with a range of scales. The MSE analysis provides a physiologically valid measure of complexity that reflects the dynamics of long-range correlated signals.

Results: In a healthy condition, SampEn of RR and QT intervals retained constant values over most scales. SampEn of QT intervals peaked at the smallest scale, but reduced to a constant within the first few scales. Similar patterns were observed for hiPSC-CMs. The hiPSC-CMs with dilated cardiomyopathy and symptomatic long QT syndrome exhibited monotonically decreasing SampEn throughout the scale, showing a clear difference from the healthy cases.

Conclusion: RR and QT interval time series of a healthy heart exhibits scale-invariant SampEn, which is a characteristic of long-range correlation. The complexity is intrinsic at the cellular level, as a similar multiscale property, especially in the large scale (>10) regime, is present in IBI and FPD time series of healthy hiPSC-CMs. The intrinsic complexity is noticeably altered in hiPSC-CMs with hereditary cardiac diseases; their MSE patterns are similar to those of uncorrelated white noise, indicating the loss of complexity.