Stanford MEDICINE | Department of Biomedical Data Science

Learning from rhythms of the heart and brain

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Abstract:

Rhythmic biology, from heartbeat to neuronal oscillations, produces rich waveforms that encode disease-relevant information, yet most genetic studies still rely on coarse summary measures (e.g., intervals) or hard-to-interpret black-box models. This talk presents a general, interpretable framework for learning from wave data and linking it to genome-scale variation to study rhythmic conditions using genome sequencing data and waveforms. We first introduce a frequency-resolved approach for genetic mapping of physiological signals by decomposing 12-lead ECGs from 47,052 UK Biobank participants with Daubechies wavelets to derive 84 lead-by-band "energy" traits, enabling GWAS that identifies 67 independent loci and fine-maps 101 high-confidence causal variants, while revealing that even ultra–high-frequency components (125–250 Hz) often treated as noise share genetic architecture with heart failure. Building on the idea that multiscale representations expose hidden biology, we then describe a unified rare-variant discovery model that learns nucleotide-level constraint from large sequencing resources (RGC Million Exome and All of Us), and integrates constraint with evolutionary conservation (GERP), structure-informed missense pathogenicity (AlphaMissense), and pLoF/missense annotations; applied to the ~54,000-sample Epi25 dataset, this meta-regression increases power to implicate epilepsy genes spanning ion channels and synaptic biology (e.g., KCNQ2, SCN2A, STXBP1) and calcium-handling pathways. Together, these two studies outline a unifying blueprint for multimodal "genome × waveform" discovery: transform raw waves into interpretable multiscale traits, prioritize sequence variation with biologically grounded priors, and connect genetic architecture to mechanism across rhythmic disorders.

Reading list:

- https://www.medrxiv.org/content/10.1101/2024.06.27.24309590v3
  A unified meta-regression model identifies genes associated with epilepsy