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Phenotyping whole-brain dynamics with modality-agnostic energy landscapes and cohort embeddings

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Comparing whole-brain dynamics across individuals and modalities remains challenging, particularly when seeking interpretable, cohort-scale metrics that respect the discrete, metastable nature of brain activity. We introduce a two-part framework that combines energy landscape analysis with a multi-subject dimensionality reduction stage to yield bias-minimal, scale-invariant, and modality-agnostic characterisations of brain dynamics from binarised time series.

First, we fit a pairwise maximum-entropy model to each subject's activity, using exact, pseudo-likelihood, or variational-Bayes estimators depending on system size. The model matches first and second moments only, avoiding strong distributional assumptions and remaining largely universal across any neuroimaging modality that can be meaningfully binarised. From the fitted parameters we construct basin graphs and disconnectivity graphs, derive Metropolis transition kernels, and compute a kinetic fingerprint comprising basin occupancies, barrier heights, dwell-time distributions, relaxation spectra, committors, and mean first-passage times. Two complementary accuracy indices quantify information gain over an independent baseline. Robustness is enforced by bootstrap confidence intervals, data-driven null thresholds for moment residuals, and quality control that verifies consistency between empirical and modelled moments.

Second, we embed subjects into a common feature space using a compact vector formed from the above geometric and kinetic descriptors. This multi-subject reduction preserves the most informative structure in each time series while enabling direct, universal comparisons across individuals. The representation supports unsupervised clustering, hypothesis testing, and cross-dataset transfer without re-engineering features for each modality.

Applied to functional ultrasound recordings from multiple mouse lines modelling distinct autism spectrum disorder subtypes, the joint pipeline yields statistically significant, stable clustering of the subtypes. Group differences are interpretable at the level of landscape geometry and kinetics, and the framework flags candidate regions with atypical dynamics for targeted follow-up. Because outputs are low-dimensional and atlas-ready, they can be aligned with high-resolution cytoarchitectonic and receptor maps to probe structure-function coupling across scales, and are directly applicable to neurodevelopmental and neurodegenerative cohorts as well as to cognitive and sensory paradigms.

This work provides a practical route to cohort-level, interpretable phenotyping of whole-brain dynamics. By unifying subject-specific energy landscapes with a common, population-level embedding, it offers a principled way to compare individuals in a single functional coordinate system and to integrate these dynamics with detailed anatomical resources. An accompanying repository and preprint will provide implementation details and extended results.

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