Quantification of Circadian Locomotor Traits in the Hybrid Mouse Diversity Panel

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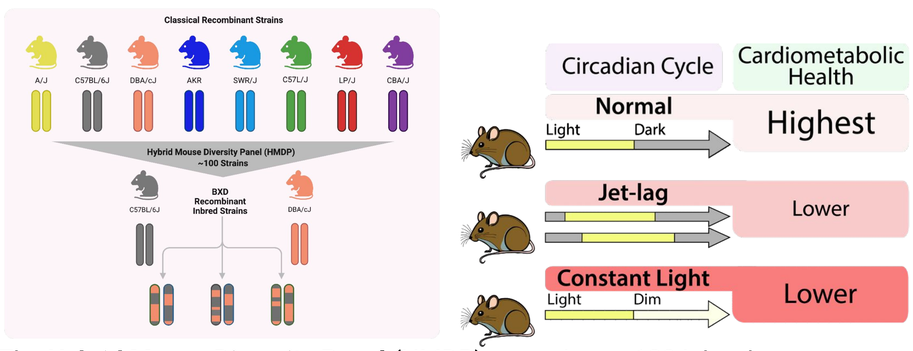
Background

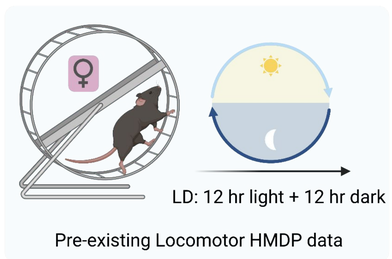
- **Circadian rhythms** are integral to the **regulation** of **physiological processes** such as sleep, metabolism and immune function
- **Disrupted** circadian rhythms are associated with **increased risk of disease**

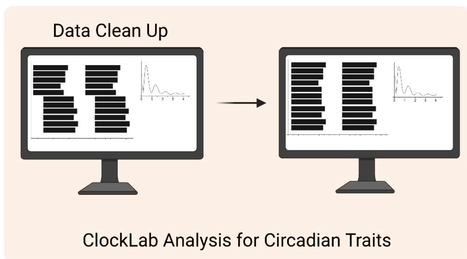


- The **Hybrid Mouse Diversity Panel** (HMDP) comprises ~100 inbred mouse strains, genetically identical within themselves but different from other strains
- The HMDP enables a **systems genetics approach** to link behavioral variation to genetic differences

Experimental Approach

- Utilized pre-existing **locomotor data** from the **exercise HMDP** and analyzed **circadian rhythm** parameters using Clocklab software





- Developed Custom R scripts to calculate onset and offset characteristics, activity levels during the active and inactive cycles, and bout characteristics
- Generated strain-ranked bar plots and ran trait-by-trait linear regressions to identify relationships for future analysis

In Progress

- Run a **Genome Wide Association Study (GWAS)** to allow mapping of loci influencing rhythmic behavior and uncover novel or underappreciated **regulators of circadian processes**

Trait Definitions

- **Interdaily Stability** (IS): Consistency of daily activity timing
- **Intradaily Variability** (IV): Degree of circadian disturbance within a day
- **Rhythm Power:** Strength of the dominant circadian rhythm from periodogram analysis
- Activity in the **Perceived Active/Rest Phase**: Total wheel revolutions per day
- Average **Bout Length** in Active/Rest Phase: Mean duration of activity bouts
- Average Active/Rest Phase Activity Duration: Total minutes per day spent active

Circadian Locomotor Trait Characterization

1: Strain Ranked Bar Plots of Circadian Locomotor Traits:

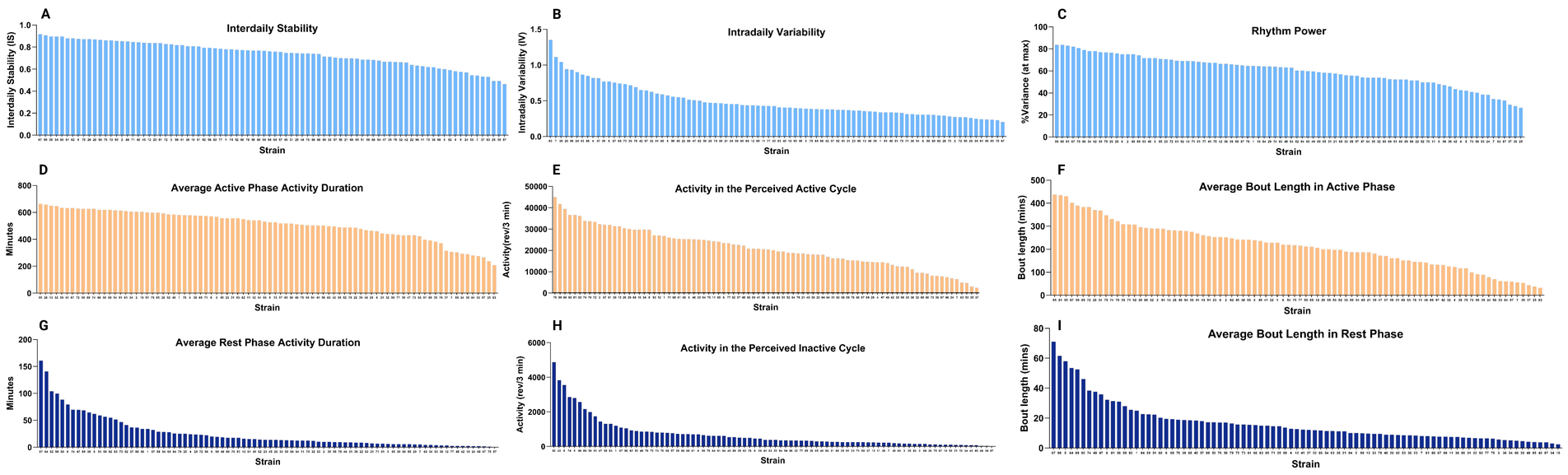


Figure 1. Strain ranked bar plots showing variation in nine circadian locomotor traits across HMDP strains: (A) Interdaily Stability, (B) Intradaily Variability, (C) Rhythm Power, (D) Active Phase Duration, (E) Active Phase Activity Counts, (F) Average Bout Length in Active Phase, (G) Rest Phase Active Time, (H) Rest Phase Activity Counts, and (I) Average Bout Length in Rest Phase.

2: Linear Regression Analyses on Trait by Trait Associations

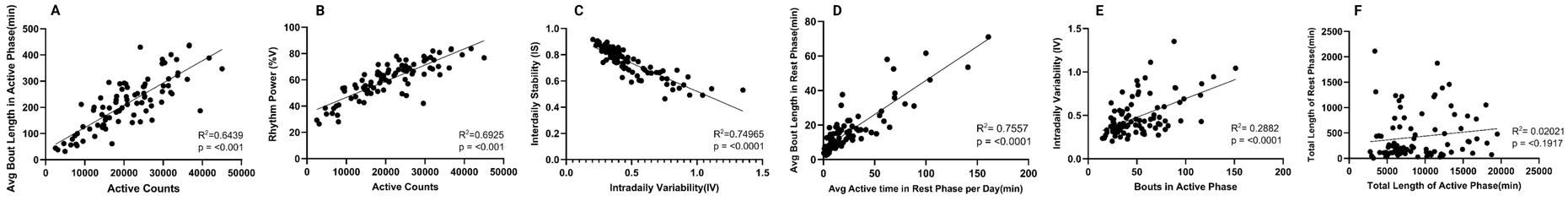


Figure 2. (A) Average bout length in the active phase vs active counts (B) Rhythm power vs active counts. Longer active phase bouts are linked with more activity and stronger rhythm power (C) Interdaily stability vs intradaily variability. Increased daily stability is linked with reduced circadian disturbance. (D) Active time in the rest phase vs average bout length in the rest phase. Longer bouts are fairly linked with more active time in the rest phase. (E) Intradaily variability vs number of bouts in the active phase. Increased intradaily variability is associated with more frequent active phase bouts, consistent with reduced activity consolidation. (F) Total length of rest phase vs total length of active phase. There seems to be no clear relationship between rest and active phase duration.

Conclusions

- The trait bar plots demonstrate **significant variation** in circadian trait manifestation across strains, indicating a **genetic basis** for **behavioral diversity**
- Different strains ranked highest for different traits, reflecting genetic influences on separate circadian behaviors
- Each trait represents a **distinct characteristic of circadian behavior**, such as rhythm stability and activity patterns, which may be relevant to **disease** states
- **Trait-by-Trait correlations** revealed relationships between traits and identified **outliers/cluster patterns** for **GWAS** to pinpoint circadian regulatory loci

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