

# Research Highlights

## Article

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Systematic modeling-driven experiments identify distinct molecular clockworks underlying hierarchically organized pacemaker neurons,

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In *Drosophila*, the hierarchically organized master and slave clock neurons are widely believed to generate circadian rhythms via an identical negative feedback loop. However, their different roles in regulating those rhythms imply heterogeneity between their feedback loops. Indeed, the mutation disrupts rhythms in the master pacemaker, but not in the slave oscillator [1]. Here, we develop ordinary differential equation model describing the circadian clock in master and slave neurons. Using a global optimization method [2], we find  $10^3$  parameter sets of the models, and analyze them to identify key differences between two neurons. The predicted differences are validated through *in vivo* experiments. Importantly, further *in silico* analysis reveals that, due to this heterogeneity, the master neuron, but not the slave neuron, generates strong rhythms but also flexibly adjusts rhythms upon environmental perturbation. This explains how the circadian clock can have two contradictory properties, robustness and flexibility.

