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The parameter landscape of a mammalian circadian clock model
CRAIG JOLLEY, HIROKI UEDA, RIKEN Center for Dev. Bio., Laboratory for Systems Biology — In mammals, an intricate system of feedback loops enables autonomous, robust oscillations synchronized with the daily light/dark cycle. Based on recent experimental evidence, we have developed a simplified dynamical model and parameterized it by compiling experimental data on the amplitude, phase, and average baseline of clock gene oscillations. Rather than identifying a single "optimal" parameter set, we used Monte Carlo sampling to explore the fitting landscape. The resulting ensemble of model parameter sets is highly anisotropic, with very large variances along some (non-trivial) linear combinations of parameters and very small variances along others. This suggests that our model exhibits "sloppy" features that have previously been identified in various multi-parameter fitting problems. We will discuss the implications of this model fitting behavior for the reliability of both individual parameter estimates and systems-level predictions of oscillator characteristics, as well as the impact of experimental constraints. The results of this study are likely to be important both for improved understanding of the mammalian circadian oscillator and as a test case for more general questions about the features of systems biology models.

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