

Feedback loops of the mammalian circadian clock constitute repressilator

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Mammals evolved an endogenous timing system to coordinate their physiology and behaviour to the 24-h period of the solar day. While it is well accepted that circadian rhythms are generated by intracellular transcriptional feedback loops, it is still debated which network motifs are necessary and sufficient for generating self-sustained oscillations. We systematically explore a data-based circadian oscillator model with multiple negative and positive feedback loops composed of Delay-Differential Equations using a clamping strategy that allows examination of isolated parts of the model. In particular, the function of different negative feedback loops can be examined. We thereby identify a series of three subsequent inhibitions known as “repressilator” as a core element of the mammalian circadian oscillator. The central role of the repressilator motif is consistent with time-resolved ChIP-seq experiments of circadian clock transcription factors and loss of rhythmicity in core clock gene knockouts.