

Temperature compensation in circadian clock models

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From the mathematical study of simple models for circadian rhythm, we identified a clear effect of saturation in the enzyme kinetics in promoting or suppressing a sustained oscillation, then we discuss the mechanisms for the temperature compensation.

[1] In the models, a clock gene is transcribed to produce mRNAs, which are translated to produce proteins in the cytosol, which are then transported to the nucleus and suppress the transcription of the gene. The negative feedback loop creates sustained oscillation. All the enzymatic reactions are of Michaelis-Menten type. We prove mathematically that the saturation in any of the reactions included in the feedback loop (in-loop reaction steps) suppresses the oscillation, whilst the saturation of both degradation steps and the back transport of the protein to cytosol (branch reaction steps) makes the oscillation more likely to occur. In the experimental measurements of enzyme kinetics and in published circadian clock simulators, in-loop reaction steps have a small saturation index whilst branch reaction steps have a large saturation index.

[2] Circadian clock of organisms has a free running period that does not change much with ambient temperature. This property "temperature compensation" is studied when the rate of all reaction steps increase with temperature in the biochemical network generating the rhythm. The period becomes shorter when all the rate parameters are enhanced by the same factor. However, the period becomes longer as degradation rate of proteins and/or transcription rate of the clock gene increase (their elasticity is positive). This holds for a wide range of models, including N -variable model, and PER-TIM double oscillator model, provided that branch reactions (e.g. degradation of proteins or mRNAs) are strongly saturated, and that the cooperativity of transcription inhibition by nuclear proteins is not very large. A strong temperature sensitivity of degradation of PER proteins and/or temperature-sensitive alternative splicing of *per* gene, known for *Drosophila*, can be mechanisms for the temperature compensation of circadian clock.