INTERNATIONAL INSTITUTE OF INFORMATION TECHNOLOGY
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Technology, Social Impact

Modeling the liver circadian clock control by nutrients

ABSTRACT

Circadian rhythms are oscillations with a period of 24 hours inherent in various biological processes. On a molecular level, the circadian clock is made of multiple feedback loops. The primary feedback loop of the circadian oscillator is CLOCK-BMAL1; PER-CRY feedback loop. As research into the mechanism has progressed, additional proteins have been identified that modulate the activity of the clock.

Experiments in recent years on mammalian circadian clocks have shown that external factors such as diet, nutrients and even blood gas concentrations have effects on circadian period, amplitude and phase. Molecular markers of these external factors have been found to regulate and be regulated by the circadian clock. Of note are mTOR and AMPK. mTOR is of importance in various cellular processes such as cell survival, growth, autophagy and protein synthesis. AMPK has a central role in metabolism and cellular energy homeostasis.

In this work, we have studied the effect of AMPK and mTOR on the circadian clock. mTOR and AMPK affect several clock proteins (Figure 1). Also AMPK is a known mTOR inhibitor. We studied the effect of HFD (AMPK Activity) and Nutrients (MTOR Activity) on the circadian clock. We also simulated the effect of the dual control of mTOR and AMPK on the clock.

METHODS

- The network was translated into a set of nonlinear ordinary differential equations, which describes the dynamics of clock components and mTOR.
- Mass action kinetics were used for interactions between mTOR and core clock components. AMPK's interaction with PGC1a and NAMPT were described with Michaelis-Menten equations.
- AMPK was described as a pulse oscillator based on experimental data (Wohler et al., 2016)
- Competition effects between Per1 and Per2 for Cry were modelled using mass balance.
- Model was simulated numerically using MATLAB to obtain the temporal profiles and time periods of oscillations

RESULTS

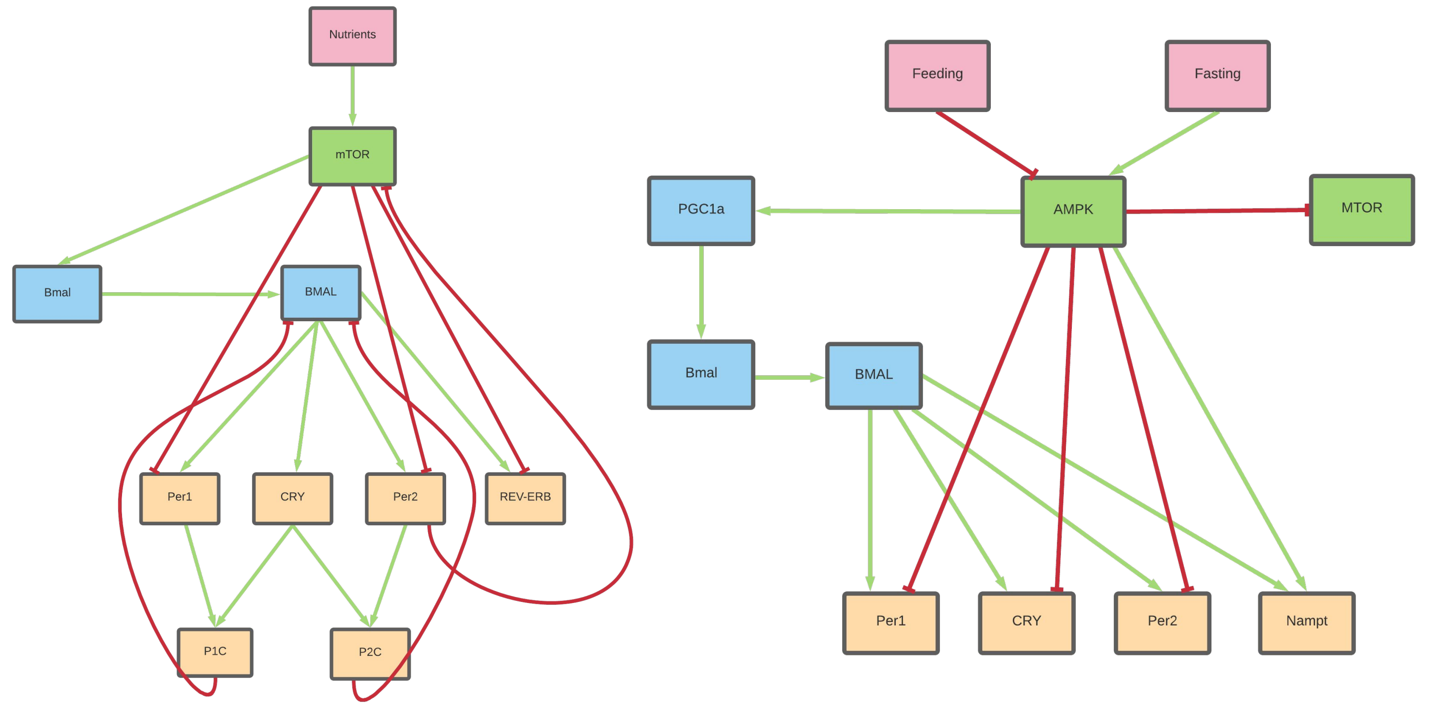

Figure 1. The regulatory network of circadian clock with AMPK and mTOR interactions. Some core circadian players and interactions between them have been left out for the sake of brevity.
1a (left). Regulatory network showing interactions between mTOR and Circadian Clock
1b (right). Regulatory network showing interactions of AMPK with mTOR and Circadian Clock

Cry Synthesis -> Competition factor (P1:P2)	1.0	1.2	1.4	1.6	1.8	2.0
0.4:0.6	No oscillations	No oscillations	28.4	26.3	24.6	22.2
0.5:0.5	No oscillations	29.2	26.5	24.5	23.07	21.87
0.7:0.3	No oscillations	29.1	25.5	21.9	20.6	19.6
0.9:0.1	26.3	23.57	21.82	20.44	19.3	18.3

Period	WT	Per1 (partial) KO	Per2 (partial) KO
BMAL MRNA	23.17	26.97	21.53
Per1 MRNA	23.17	27.01	21.53
Per2 MRNA	23.17	26.99	21.53

Table - 1 . Effect of competition of Per1 and Per2 for Cry to form Per(1/2) - Cry complex on time period of the clock.
Table 1a - (Top) Effect on time period of the circadian clock upon increasing Cry synthesis and Competition between Per1 and Per2
Table 1b - (Bottom) Experiments done in the model confirm observed time periods for Per1 and Per2 KO. (Tamiya et al. 2016)

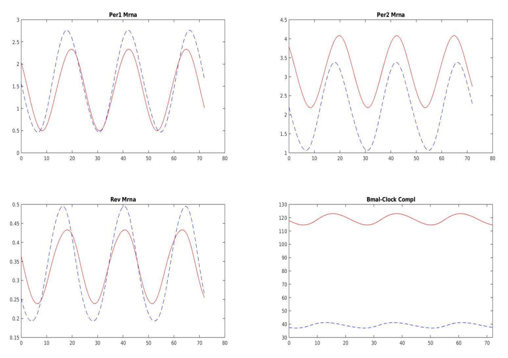

Figure 2. Effect of constitutive mTOR activation (Red) and mTOR Knockout (Blue) on the circadian clock. Per2 and BMAL protein (represented by CLOCK-BMAL complex) increases with increasing mTOR, Per1 and Rev-Erb decreases with increasing mTOR

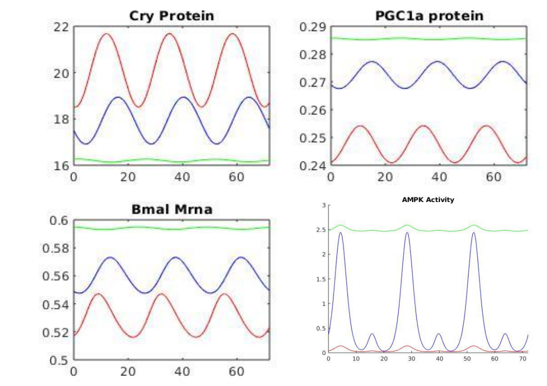

Figure 3. Effect of AMPK levels on Cry Protein (inhibited by AMPK) , PgC1α, BMAL mRNA (activated by AMPK). AMPK is modelled as a pulse oscillation with 24 hr period.
Red - HFD, Blue - Normal, Green - Starvation

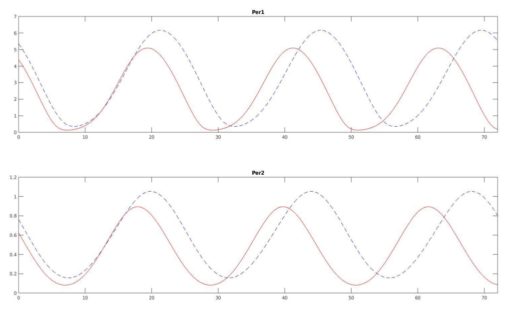

Figure 4. Effect of SIRT Knockout on the clock model.
SIRT KO causes a decrease in amplitude of Per1 and Per2 protein levels, in confirmation with experimental evidence by Foteinou et al (2018)

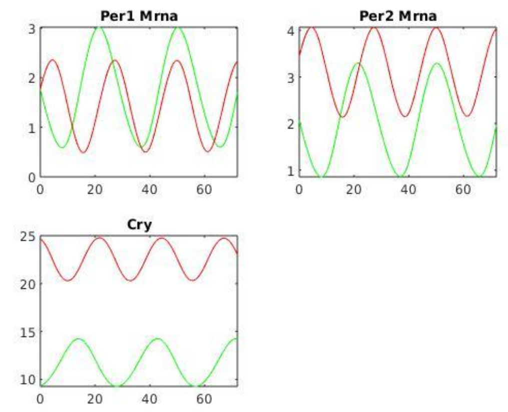

Figure 5. Combined effect of mTOR and AMPK on the clock (Red - Low AMPK, High mTOR ; Green - High AMPK - Low mTOR). Both amplitude effects of mTOR on Per1 and Per2 mRNA and of AMPK on Cry can be observed here

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