Mathematical Models of the Mammalian Circadian Oscillator and Alcohol Dependency

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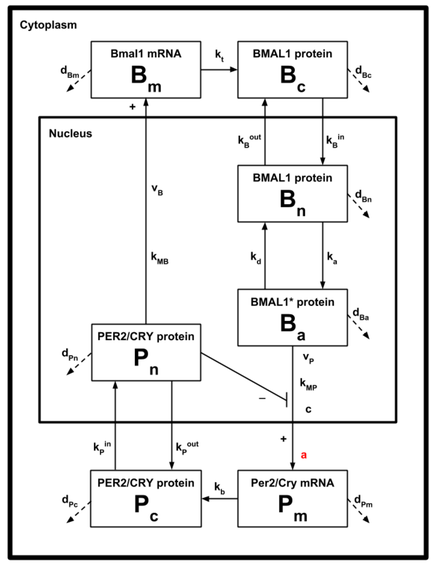
Introduction

The mammalian circadian oscillator is the body's internal clock that controls brain wave activity, energy production, and other biological activities.

- Acute or chronic alcohol consumption disrupts a regular circadian rhythm.
- A disrupted circadian rhythm affects mood regulation, sleep cycles, blood pressure, and other biological rhythms.
- The *Per2* gene of the mammalian circadian oscillator causes improper alcohol intake.

Goal: To understand the relation between alcohol and the circadian oscillator and to investigate the effects of alcohol on the system.



Model of the mammalian circadian oscillator.

Mathematical Model

$$\text{Per2/Cry mRNA} \quad \frac{dP_m}{dt} = \frac{\mathbf{a} \cdot v_P \cdot (B_a + c)}{k_{MP} \cdot (1 + (P_n/k_i)^s) + (B_a + c)} - d_{Pm} \cdot P_m$$

$$\text{PER2/CRY complex in the cytoplasm} \quad \frac{dP_c}{dt} = k_b \cdot {P_m}^q - d_{Pc} \cdot P_c - k_P^{in} \cdot P_c + k_P^{out} \cdot P_n$$

$$\text{PER2/CRY complex in the nucleus} \quad \frac{dP_n}{dt} = k_P^{in} \cdot P_c - k_P^{out} \cdot P_n - d_{Pn} \cdot P_n$$

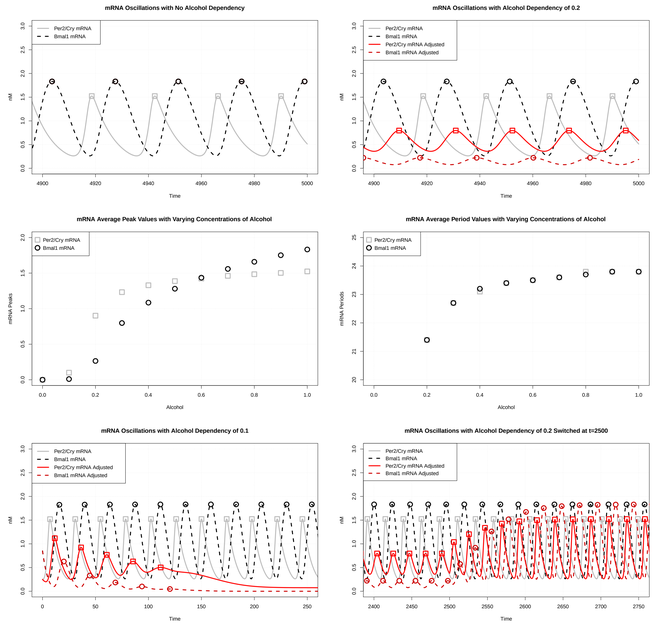
$$\text{Bmal1 mRNA} \quad \frac{dB_m}{dt} = \frac{v_B \cdot {P_n}^r}{k_{MB}^r + {P_n}^r} - d_{Bm} \cdot B_m$$

$$\text{BMAL1 protein in the cytoplasm} \quad \frac{dB_c}{dt} = k_t \cdot B_m - d_{Bc} \cdot B_c - k_B^{in} \cdot B_c + k_B^{out} \cdot B_n$$

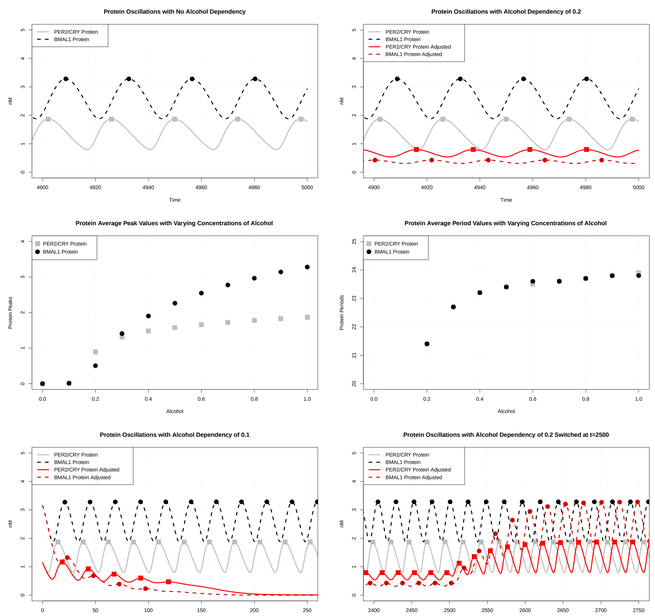
$$\text{BMAL1 protein in the nucleus} \quad \frac{dB_n}{dt} = k_B^{in} \cdot B_c - k_B^{out} \cdot B_n - d_{Bn} \cdot B_n + k_d \cdot B_a - d_{Ba} \cdot B_n$$

$$\text{Transcriptionally active form BMAL1} \quad \frac{dB_a}{dt} = k_a \cdot B_n - k_d \cdot B_a - d_{Ba} \cdot B_a$$

mRNA



Protein



Observations

mRNA

- *Bmal1* mRNA affected greatly by the change in alcohol parameter.
- *Per2* mRNA oscillations become more symmetric with the decrease in the alcohol parameter.

Protein

- *BMAL1* protein also affected greatly by the change in alcohol parameter.
- Protein oscillations flatten significantly with the decrease in the alcohol parameter.

Both

- The oscillations' periods shorten as the alcohol parameter decreases.
- When the alcohol parameter is greater than 0.2, oscillations are recovered at lower levels than if alcohol was not present.
- When the alcohol parameter is less than 0.2 (meaning an extremely strong effect of alcohol on the system), oscillations disappear entirely.
- It is possible to recover the control oscillations if the alcohol parameter is set to 1 (meaning no effect of alcohol on the system).

Impact

- Recovery of an unaffected circadian oscillation is possible after dependence on alcohol.
- Recovery time-lines can be created for the affected circadian oscillator.
- Targeting specific genes to decrease the chance of relapse.

Future Directions

- Investigate the effects when the alcohol parameter is less than 0.2 using bifurcation analysis.
- Create a more intricate model of the mammalian circadian oscillator to separate *Per2* and *Cry*.
- Build a similar model for drug dependency.

Acknowledgements and References

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- Caroline H. Ko and Joseph S. Takahashi. "Molecular components of the mammalian circadian clock." *Human Molecular Genetics* 15.2 (2006): 271-277. Oxford Academic. Web. Apr. 2017.
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