Generation of modified repressilator network(s) to model effect of light on Circadian rhythm

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Biological Background

Oscillatory networks like repressilators have been shown to be at the core of periodic processes in organisms. One ideal example would be Mammalian Circadian Rhythm (MCR). MCR is the machinery in mammals that regulates physiology towards the end goal of maintaining homeostasis. Data based and statistical approached indicate that a repressilator motif might between *cry1*, *per2* and *rev-erb-α* might be at the core of the MCR [1]. Out of these 3 nodes, 2 are directly correlated to external light conditions. On a related note, it has been observed that physiological features such as temperature, blood pressure, renal filtration are subject to variations correlated with sleep/light cycle of the subject [2]. These two keynote observations form the basis of this study.

One can hypothesize that external conditions of light and brightness must directly be affecting the repressilator motif at the core of MCR. One such way could be via frequency modulation of the motif, which would then affect downstream processes such as core body temperature, etc. Along the same lines, amplitude modulation of network could also result in said change in physiological conditions.

Question raised

Can a singular signal (potentially under indirect control of light) affect the repressilator network in such a way that signal levels determine the frequency of the oscillations (alternatively, the amplitude)?

Previous models employed

ODE based modeling of Repressilator motif was performed by Elowitz and group using Hill functions. These depicted stable oscillations of the motif under certain conditions and is something that can be adapted here [3]. Other important studies done worked on evolution of networks by introducing perturbations, and selecting networks based on certain fitness parameters, further subjecting them to such an evolution [4], [5], to arrive at networks performing stable oscillations. Such an approach has not yet been applied to repressilator networks as base.

Intended modeling and simulations

The preliminary model would aim towards quantifying zones under which repressilator performs stable oscillations. Ensuing this, the evolutionary algorithm would be adapted to use said repressilator with a specific set of parameters as base. Onto this, one node would be added (assumption is light conditions would be expressed as protein), whose levels would be sampled over a biologically relevant range. The interaction of this node with others would either be randomized, or progressively added based on said evolutionary algorithm. The interaction strengths would be sampled over a range. The fitness cost would be determined by relative change in frequency of protein expression wrt levels of signals. An alternative fitness cost could be

based on relative amplitude change wrt signal levels. Evolution over multiple steps and/or randomization over a large pool would be conducted.

Expected Outcome

The study, if successful would yield modifications of the repressilator motif under the control of a signal that directly modifies the frequency or the amplitude, based on signal levels.

Contribution of the study

The study could potentially shed light on possible gene regulatory networks and machinery by which physiological control is seen by the circadian rhythm. Further implications could be constructing and characterizing synthetic circuits of said network. The circuit can be then used to express desirable factors at intended frequencies and amplitude, that can be modulated potentially by chemical factors such as IPTG.

References

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