2018 Annual Meeting of the Society for Mathematical Biology & the Japanese Society for Mathematical Biology

Contribution ID: **89** Type: **Oral Presentation**

Dead zone formation by negative feedback loops in the circadian clocks

Thursday, 12 July 2018 11:00 (30 minutes)

Circadian clocks of many organisms consist of cell autonomous rhythms of gene expression in a pacemaker tissue. Negative feedback loops in clock gene regulation are responsible for the generation of the expression rhythms. One of the characteristics of the circadian clock is its phase responses to light input signals. A light signal changes the rates of biochemical reactions in the negative feedback loops and causes a phase shift depending on the state of the clock. The phase response curve (PRC) for short light stimulations in various organisms revealed the following features. A light pulse at morning advances the phase of the clocks, while a light pulse at evening delays the phase. Remarkably, light input signals cause only slight phase shifts during the day. Such time window where the phase of the circadian clock is insensitive to a light signal is referred to as dead zone. Several previous theoretical studies revealed that the presence of a dead zone in the PRC increased the robustness of the circadian clock. However, it remains unclear how a dead zone arises in the negative feedback loop underlying rhythmic gene expression. Here we reveal mechanisms that can produce the dead zone in the PRC using phase sensitivity analysis for Goodwin-type models. When light signals enhance degradation of repressor proteins such as TIMELESS in *Drosophila*, the cancelation of subsequent changes in transcription is critical for the dead zone formation. The influence of light signals can be nullified during the day, if the levels of repressor proteins are close to zero and transcription rate is already saturated. In contrast, when light signals induce transcription of clock genes like *Periods* in mammals, the saturation of translation of repressor protein can create a dead zone by removing the influence of excess amount of mRNA induced by the light signals. Taken together, our results suggest that the saturation of biochemical reactions in the negative feedback loops would be an underlying principle for a dead zone formation, regardless of the differences in how light signals modulate biochemical reactions in the clocks for different organisms.

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Session Classification: Multiscale modelling of sleep and circadian systems

Track Classification: Minisymposium: Multi-scale modelling of sleep and circadian systems