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A correctly set circadian clock, whatever the light intensity

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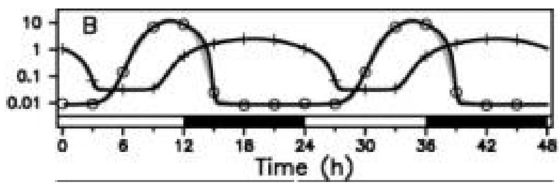

Evolution of the concentration of the products of two key genes of the circadian clock of the marine alga Ostreococcus tauri as a function of time. It can be observed that they self-regulate (the concentration of one increases while that of the other decreases) and that their concentration changes as a function of time over a 24h cycle. Credit: Marc Lefranc

How are circadian clocks able to synchronize themselves accurately to the day/night cycle without taking account of extreme light intensity fluctuations over the course of a single day or from one day to the next? The mathematical analysis of the activity profiles of two central genes of the circadian clock of a microscopic green alga has recently been carried out by French researchers from the Observatoire Oceanologique de Banyuls at CNRS. This study reveals that the circadian clock is only sensitive to light if it is out of sync and needs to be reset. This work has recently been published in the journal *PloS Computational Biology*.

Day/night alternation induces periodic variations in the environment (light, temperature) that most living organisms, including humans, anticipate thanks to what is known as an internal circadian or biological clock. These clocks operate over a period close to the diurnal lightness/darkness cycle. The "nuts and bolts" of these clocks are genes that interact so as to mutually modulate their activity: for example, an "A" gene produces proteins that activate a "B" gene, which in turn produces proteins which, when they are active, inactivate the "A" gene, and so on. The activity of these genes thus oscillates spontaneously, with a periodicity close to 24 hours. In the cell, it is thus possible to have an indication of what time it is by measuring the concentration of these proteins and thus their activity.

For this biochemical oscillation to be phase-locked to the day/night cycle requires one of the molecular bodies, at least, to be light-sensitive, especially since the key periodic events, namely daybreak and nightfall, vary throughout the year. Certain proteins for example are degraded more quickly in the evening while others are produced more actively in the morning. However, solar radiation can fluctuate significantly from day to day or even within the same day, depending on the cloud cover. These variations should therefore make the clock run out of sync in a random manner, rendering it inoperative... A collaboration between biologists and physicists has recently highlighted a simple mechanism that explains this mystery.

Researchers from the Observatoire Océanologique de Banyuls have analyzed the circadian clock of the green unicellular marine alga Ostreococcus tauri, the main properties of which can be explained by a two-gene oscillator. They measured the activity of these two genes and the proteins that they produce at regular intervals (every two/three hours) over 24 hours. Researchers from the Laboratoire de Physique des Lasers, Atomes, Molécules and the Institut de Recherche Interdisciplinaire then built mathematical models to try to reproduce the activity curves obtained. The simplest model fits the data perfectly: the two genes regulate each other and constitute an oscillator, which accurately locks onto the lighting cycle, to which it must therefore be sensitive.

Paradoxically, this mathematical model is only exceptionally coupled to light: the study shows that coupling to light is only activated at specific times of the day. Outside of these times, light has no effect on the synthesis and degradation of the measured proteins, and thus on their concentrations, because light information does not reach the oscillator. But that is not all! The moment when the coupling is activated, at least when the clock is correctly set, coincides with a period of insensitivity of the oscillator to external perturbations. The oscillator may in fact be compared to a swing that is pushed by a periodic movement. Depending on when the swing is pushed, the action can either slow down the movement, speed it up, or have no effect.

Thanks to this clever timing, the clock, when it is correctly set, is blind to the day/night cycle and thus to light fluctuations linked to cloudy episodes. On the other hand, if the clock is out of sync (for example in the case of a time difference or more simply through basic malfunctioning), the coupling to light occurs in a different phase of the oscillation, and may then act on the oscillator to reset it. It is thus a simple dynamic mechanism that explains the robustness of circadian clocks.

The researchers will now check whether these results can apply to all circadian clocks, particularly in humans, where some fifteen genes are involved. Existing models do not take account of light fluctuations within the day and from day to day. By subjecting them to such perturbations, scientists will be able to test the robustness of such models.

More information: *PLoS Computational Biology*, 11 November 2010. Article available at the following address: View web site

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