

EFFECTS OF DNA DAMAGE ON THE CELL CYCLE THROUGH THE CIRCADIAN CLOCK

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Importance and summary

Most cancer treatment induces DNA damage to eliminate highly proliferative cells. Cells respond differently to DNA damage depending on where they are in their cell cycle at the time of the treatment.

Intriguingly, circadian rhythms provide temporal information to the cell cycle machinery to control the timing of cell divisions.

The perturbation of the circadian clock and the cell cycle upon DNA damage was simulated and the consequences of this perturbation on the following cycles were analysed using phase-response curves.

Our results indicate that DNA damage induces an indirect effect on the timing of cell cycle through the Neurospora circadian clock.

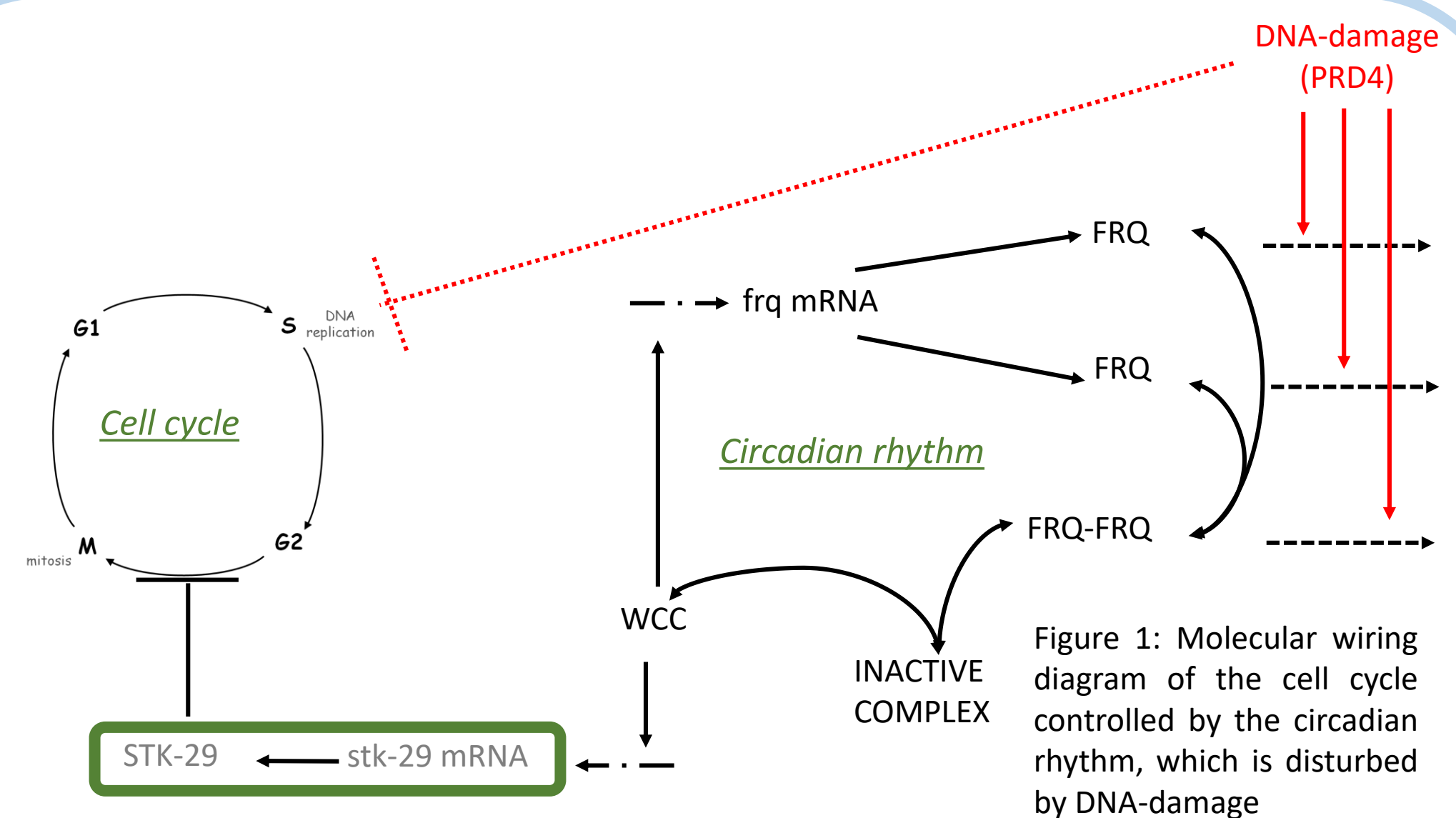


Figure 1: Molecular wiring diagram of the cell cycle controlled by the circadian rhythm, which is disturbed by DNA-damage

Methods

A mathematical model including coupling between cell cycle and circadian rhythm was built and *in-silico* experiments were performed for the complex system. A unified code in the Matlab programming language was composed for the analysis to simplify examinations.

Cell cycle without connection to the circadian rhythm

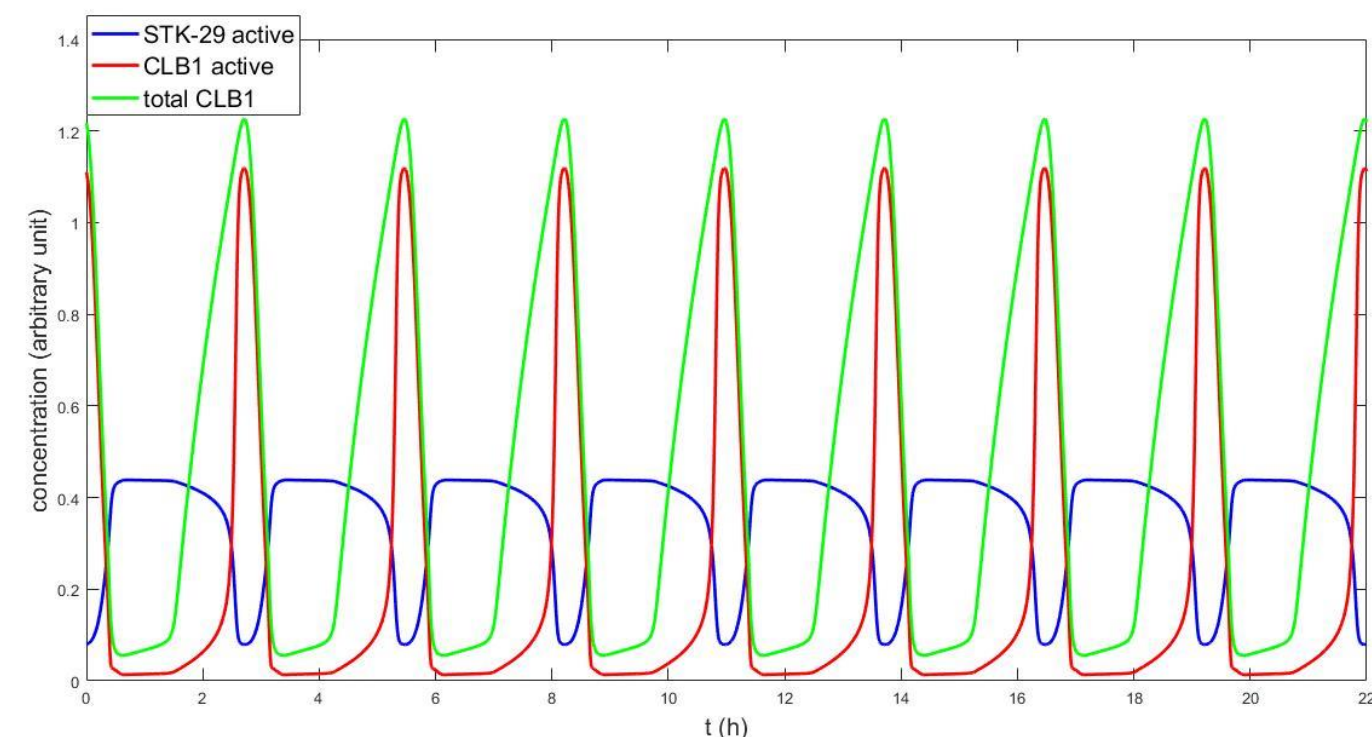


Figure 2: Main molecular components of the cell cycle without connection to the circadian rhythm

Circadian rhythm

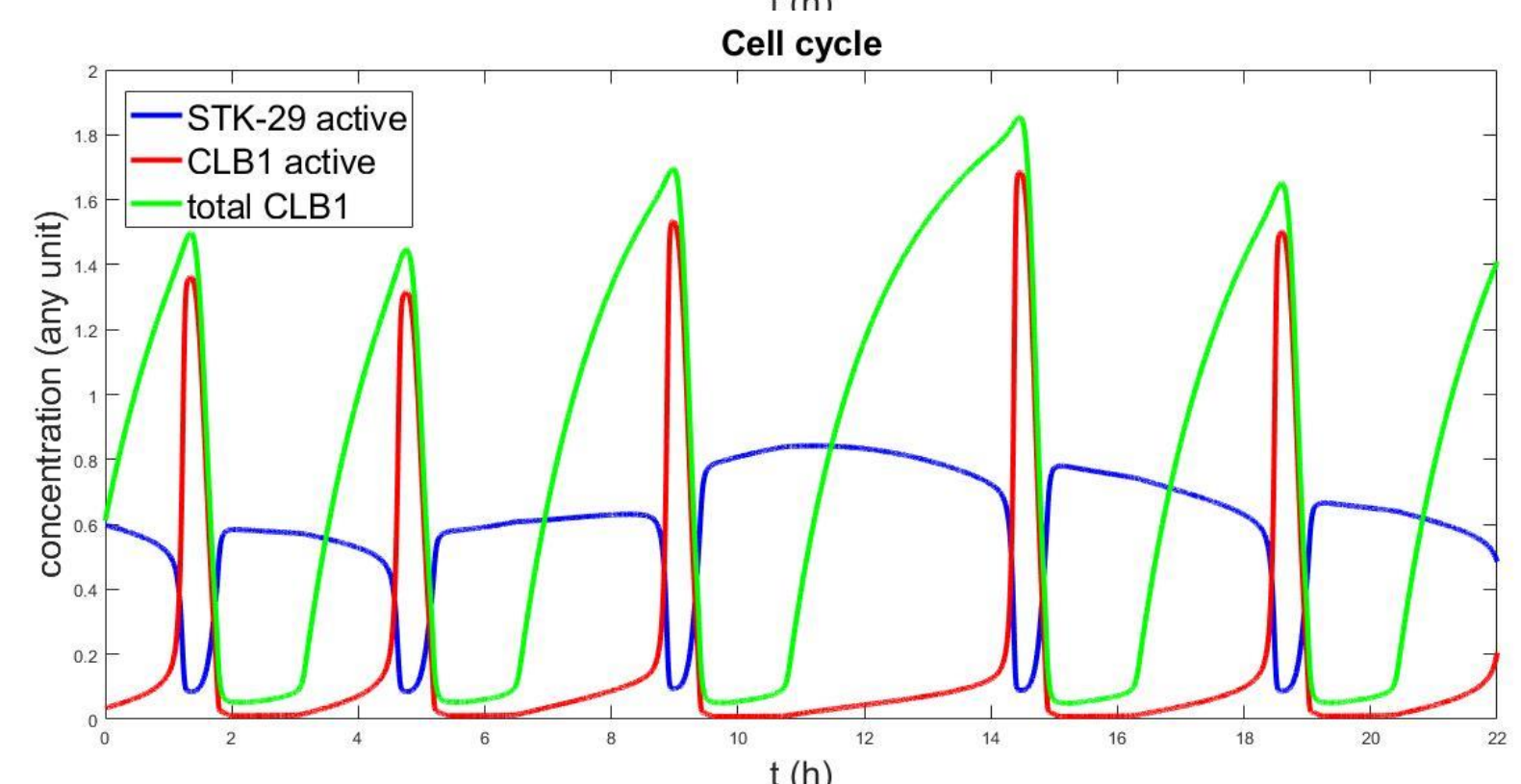
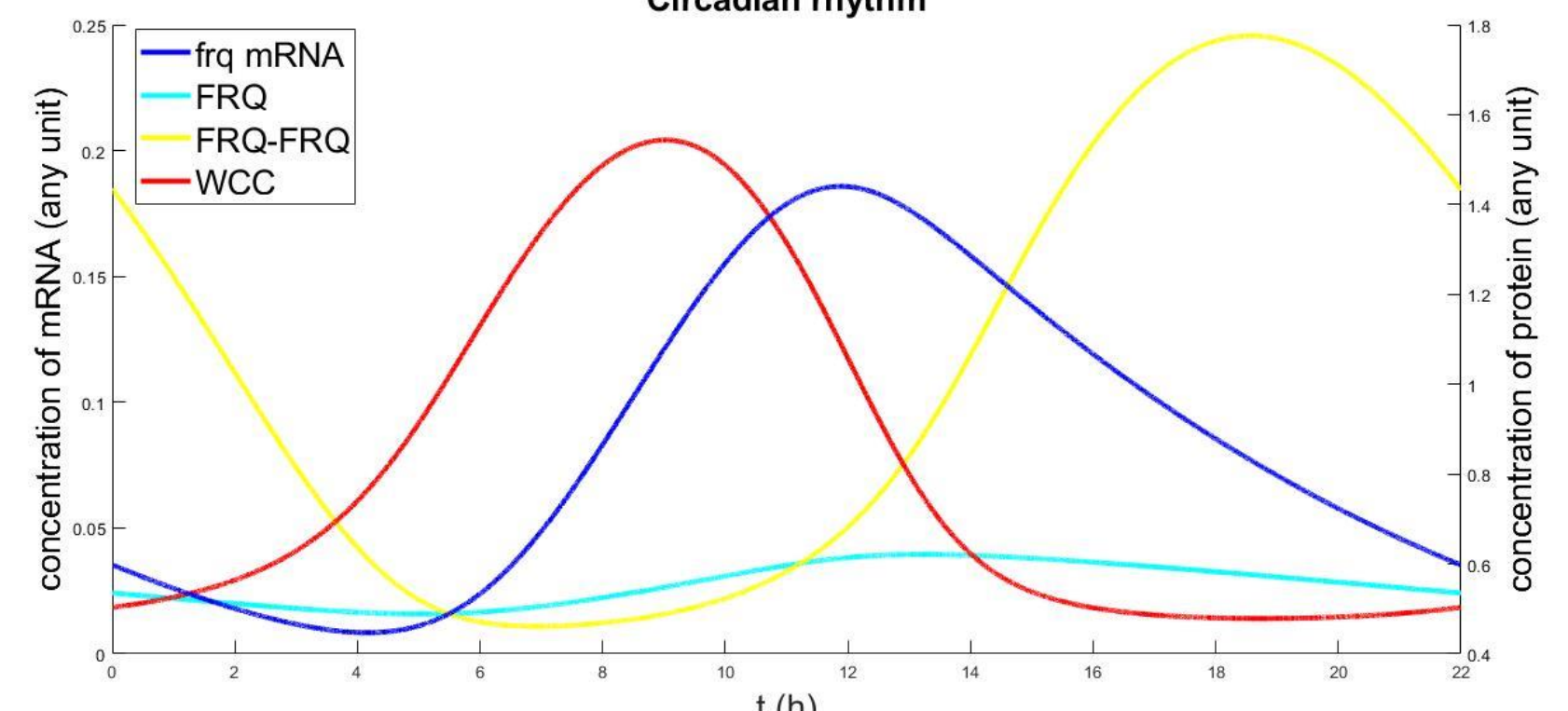


Figure 3: Main molecular components of the circadian rhythm and the connected cell cycle

Phase-response curve

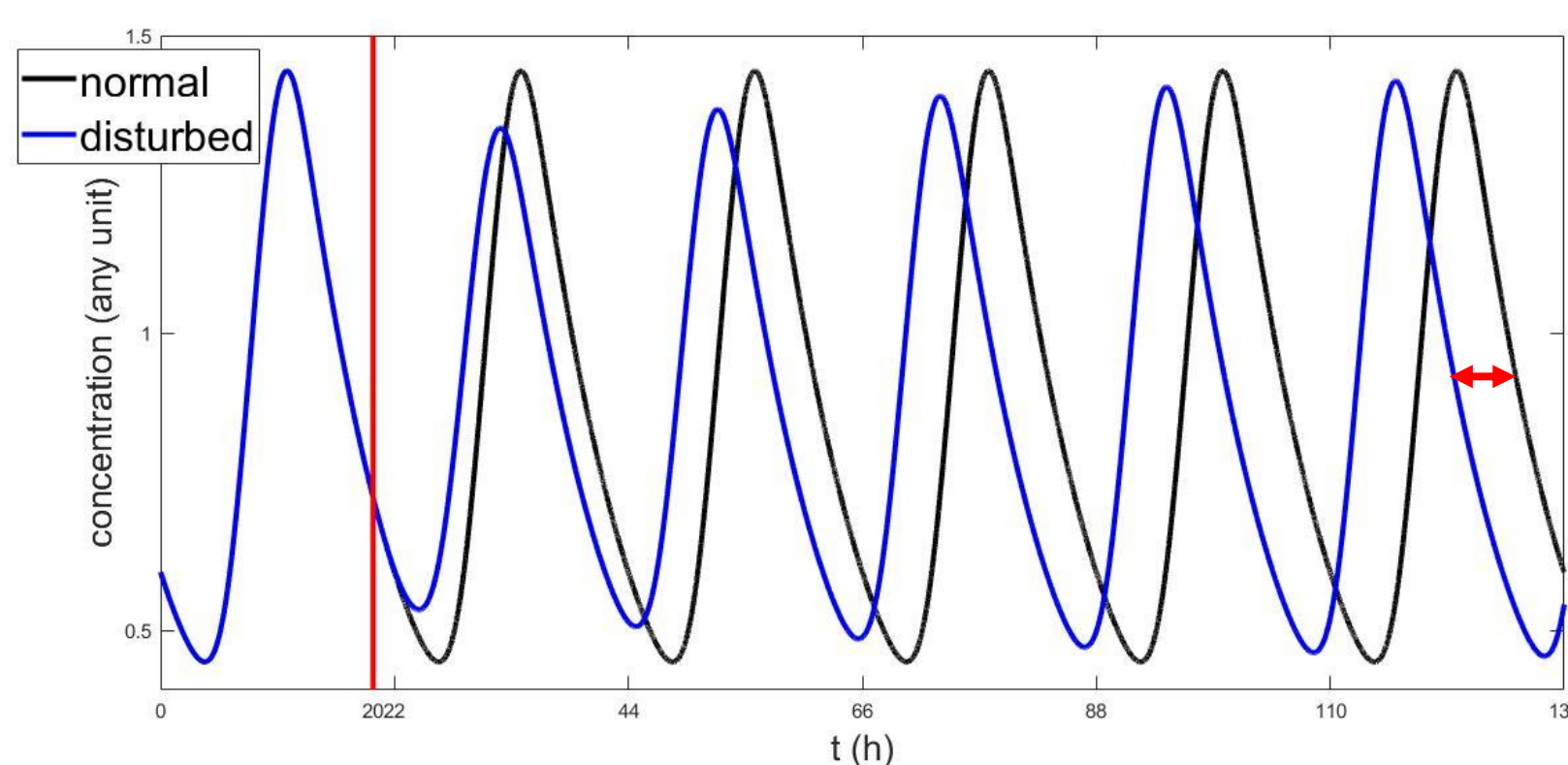


Figure 4: The diagram shows the effect of disturbance (DNA-damage) at 20 hours (blue line) compared to the normal one (black line).

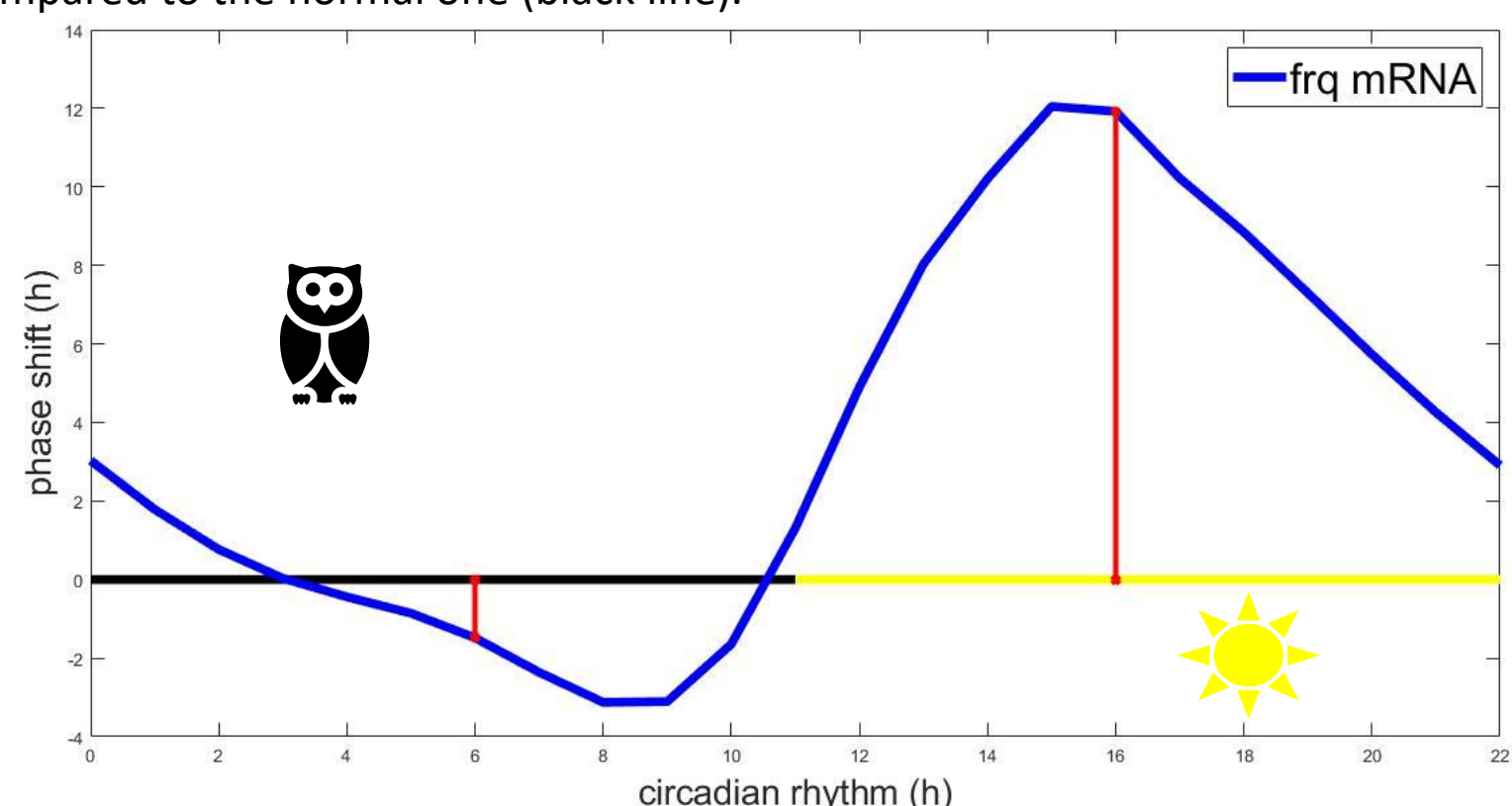


Figure 5: The diagram summarizes the result of disturbances at different time: phase-response curve (PRC) illustrates the phase shift in the cycle period of an oscillation induced by a perturbation as a function of the phase (subjective light or dark) at which it is received. The result at 6 and 16 hours is highlighted, because we examined the number of mitosis at these perturbations at Figure 6.

Behavior of cell cycle with stochastic connection to the circadian rhythm

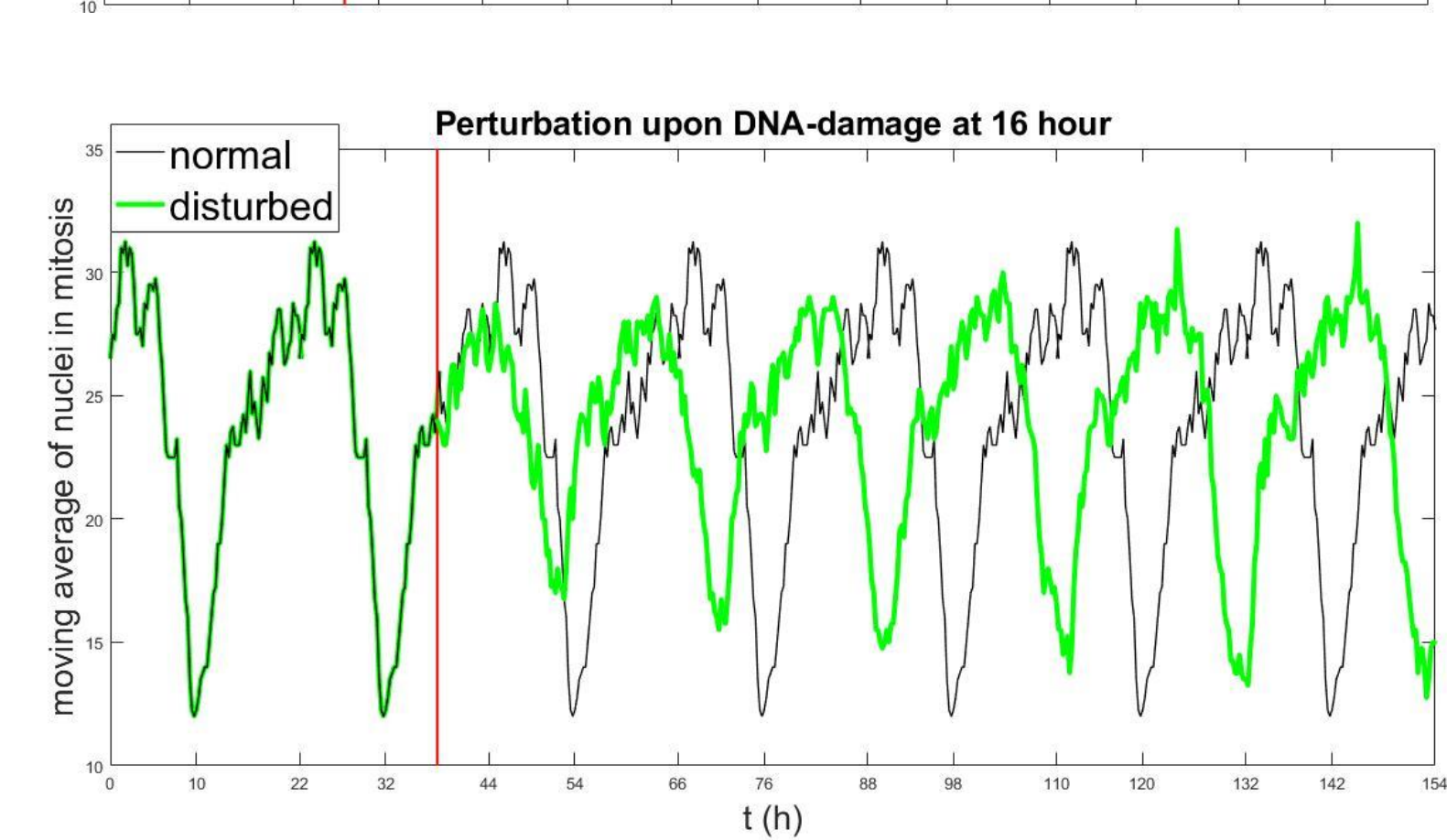
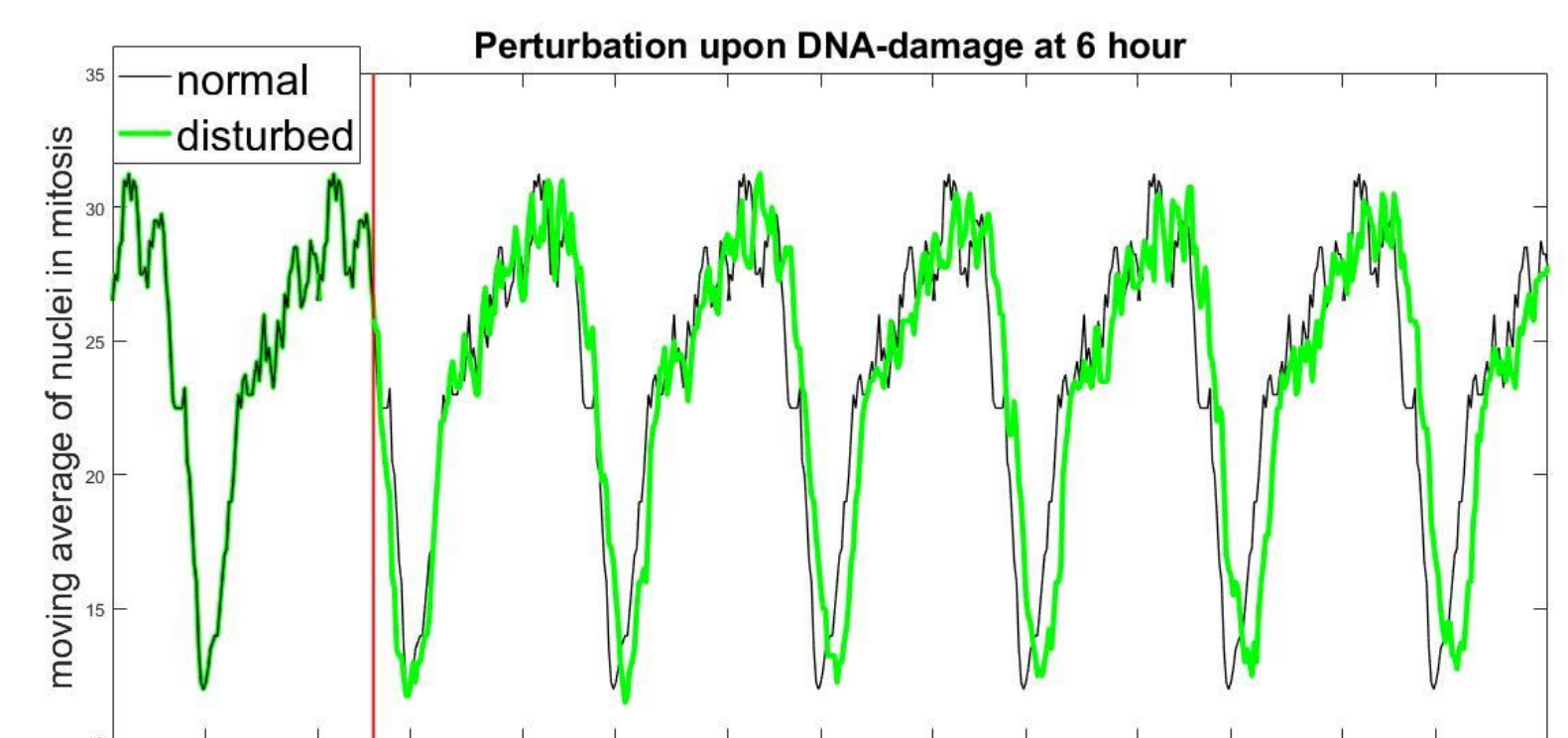


Figure 6: The effect of the DNA-damage highly depends on the time of disturbance: during subjective night (6 hours) it doesn't cause any relevant changes, but during subjective day (16 hours) a transient noise applies in the cell cycle for some days, after it regular periodic cycles with phase shift.

References:

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- Hong C. I., Zámboreszky J., Baek M., Labiscsak L., Ju K., Lee H., Larrondo L. F., Goity A., Chong H. S., Belden W. J., and Csikász-Nagy A., Circadian rhythms synchronize mitosis in *Neurospora crassa*, *PNAS*, 111 (4) (2014) 1397-1402