PhD thesis in cell metabolism (doctoral grant funded by I-SITE ULNE)

Synchronization of the mammalian circadian clock with metabolism: biosensor approaches coupled with mathematical modeling

TOPIC

In most living organisms, the circadian clock synchronizes to the day/night cycle and orchestrates many biological functions. There is increasing evidence that disruption of the mammalian circadian clock in metabolic organs (liver, pancreas, …) plays a key role in pathologies such as obesity or type 2 diabetes. To clarify the mechanisms involved, we have designed a mathematical model of the liver clock synchronized to feeding/fasting cycles through the intracellular factors NAD+ and AMP, which reflect the cellular bioenergetics (Woller et al, Cell Reports 17, 1087, 2016). Experiments are now needed to validate and extend this model, as well as to verify the biological hypotheses it has suggested.

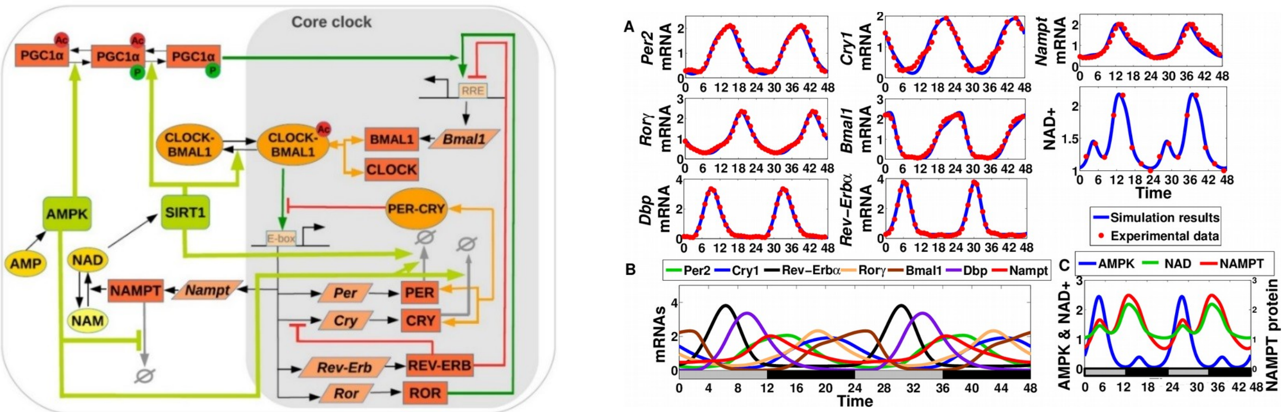

Figure 1. Left: molecular network synchronizing the mammalian liver circadian clock to metabolism ; (right) numerical simulations of the mathematical model (after Woller et al, 2016)

JOB DESCRIPTION

The PhD student will be in charge of acquiring relevant data to extend the model. For that purpose, she/he will transfect cells with fluorescence-based biosensors available in the lab and monitor the evolution of cell energy along the circadian clock. The main goals of the PhD thesis are summed up below.

Using reporters and biosensors for key metabolic actors such as NAD+/SIRT1 or AMPK, as well as for core clock genes (Bmal1, Rev-Erbα), the PhD student will quantify how various factors reset the circadian clock depending on the time of the day and compare measurements with model predictions.

The use of pharmacological or genetic tools will help unravelling the key components entraining the clock, which may be targeted to reset the clock through chronotherapic protocols.

There will be a strong interaction with the modeling part of the project, which is handled by a post-doctoral researcher. Contribution to this part will be welcome but does not represent a main task for the PhD student.

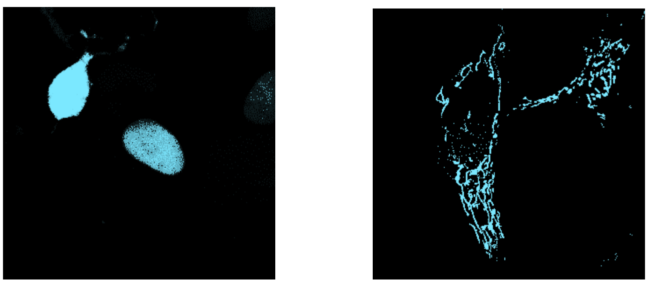

Figure 2. Cells transfected with NAD+ biosensors (nuclear and mitochondrial addressing sequences respectively)

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CONTEXT

Marc Lefranc at PhLAM has a long experience in developing data-driven mathematical models to describe the dynamics of the circadian clock, and will supervise the model refinement. Laurent Héliot at PhLAM has leading expertise in tracking molecular dynamics in living cells using real-time fluorescence-based biophotonic approaches, and will supervise the cell preparation and data acquisition within the imaging facility. This project is in tight collaboration with Bart Staels and Hélène Duez, experts in metabolic diseases (U1011, Institut Pasteur de Lille).

Marc Lefranc is coordinator of the “Mathematics and Physics for biology” axis of Labex CEMPI, which fosters interdisciplinary research.

Woller, A, Duez H, Staels B, Lefranc M. 2016. « A Mathematical Model of the Liver Circadian Clock Linking Feeding and Fasting Cycles to Clock Function ». *Cell Reports* 17 (4): 1087-97. doi:10.1016/j.celrep.2016.09.060

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Gross B, Pawlak M, Lefebvre P, Staels B. 2017 PPARs in obesity-induced T2DM, dyslipidaemia and NAFLD. *Nat Rev Endocrinol* doi: 10.1038/nrendo.2016.135

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Mayeuf-Louchart A, Zecchin M, Staels B and Duez H, Circadian control of metabolism and pathological consequences of clock perturbations, Biochimie 143, 42 (2017). doi: 10.1016/j.biochi.2017.07.017

PROFILE/SKILLS

Candidates should have a good biological background and experience with cell cultures, transfection and imaging. Since the student will interact closely with researchers in an interdisciplinary environment, relational abilities and good communication skills are required. A great motivation for quantitative biological approaches combining cell cultures and imaging with mathematical modeling is expected.

FUNDING /APPLICATION

The contract is for 3 years, starting from September 2019. Funding is already secured from the University of Lille Nord Europe ISITE project. It is aligned with the recently upgraded CNRS salary scale.

Candidates should send a cover letter stating their motivations and curriculum vitae, as well as two support letters, to Marc Lefranc (marc.lefranc@univ-lille.fr) and Laurent Heliot (laurent.heliot@univ-lille.fr).

WHERE

On the Science and Technology campus of the University of Lille, in Northern France. Lille is the dynamic core of the 4th French urban area (1.2 M people). It hosts many top research units in the various scientific disciplines. Will 67 000 students, the University of Lille is the largest french-speaking university.

Lille is connected by high-speed trains to Brussels (40 min), Roissy airport (50 min.), Paris (60 min), and London (80 min). With a lively atmosphere and a reasonable cost of living, Lille is an attractive place to stay.

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