Model learning to identify systemic regulators of the peripheral circadian clock

Julien Martinelli

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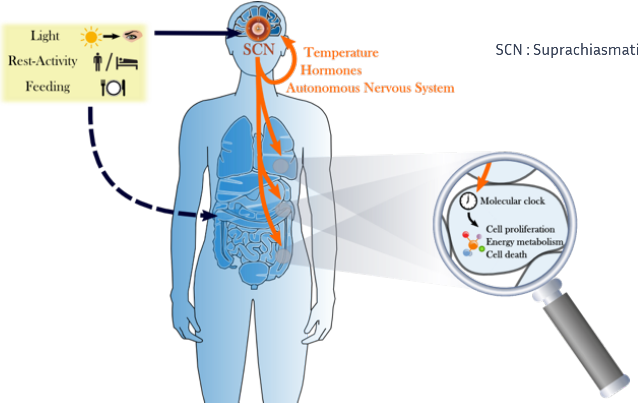
The circadian timing system



SCN : Suprachiasmatic Nuclei

- A master clock acting as an autonomous ≈ 24h-oscillator synchronised by external cues
- This master clock **entrains** the peripheral clocks in the cells *via* physiological signals
- The peripheral clock induces oscillations in key intracellular processes

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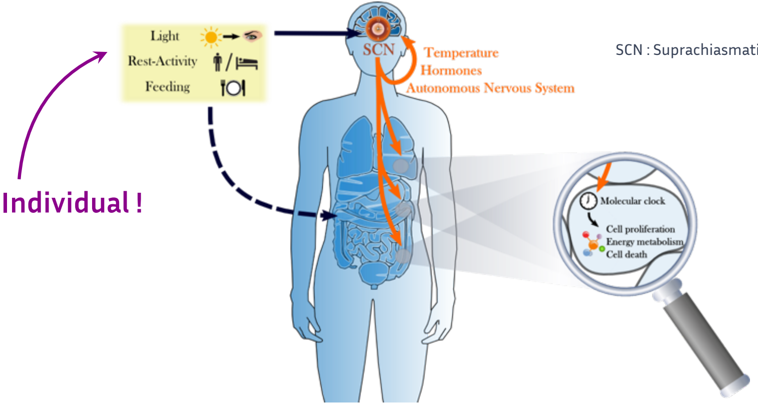

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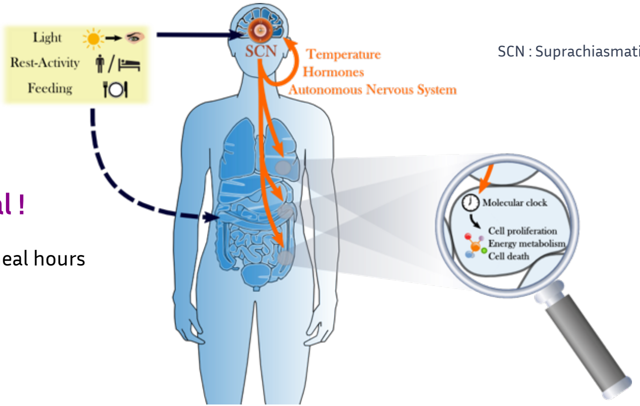

SCN : Suprachiasmatic Nuclei

Individual !

- ★ Different diet / meal hours
- ★ Work / Jetlag
- ★ ...

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Clock-induced oscillations in intracellular processes are individual

Repercussions e.g. cancer chronotherapy at the individual level

$\rightarrow$ **Precision medicine, but with what data?**

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Infer the links between measurable variables and the peripheral clock

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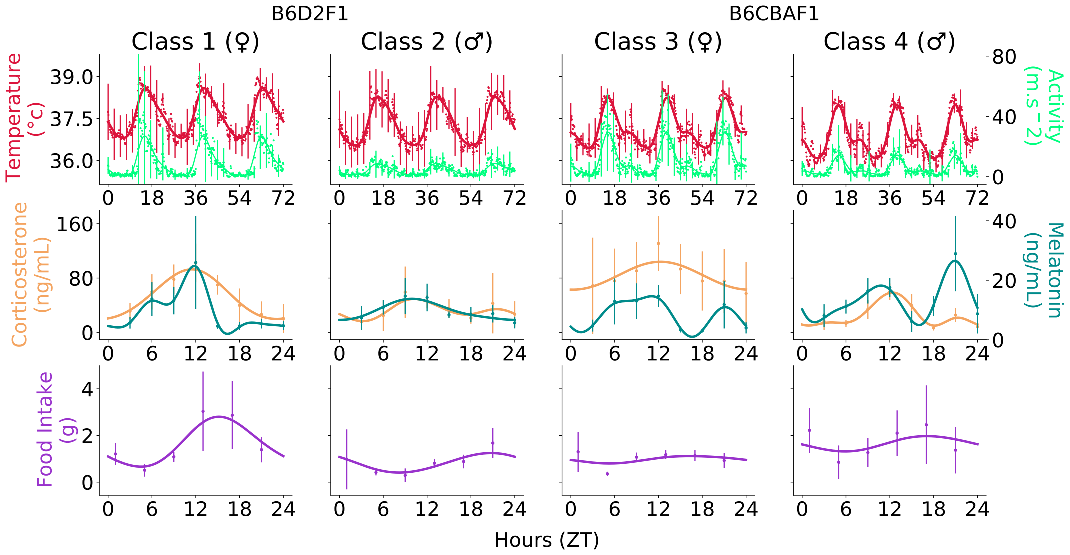
Infer the links between measurable variables and the peripheral clock

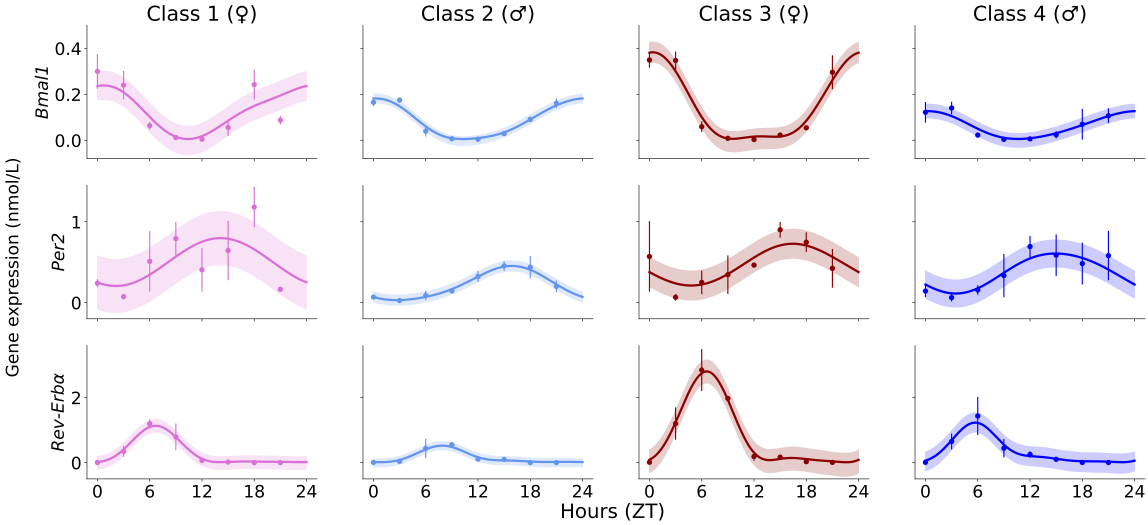
Focus on mice: data available both at the systemic and cellular level

Mouse class systemic regulators data



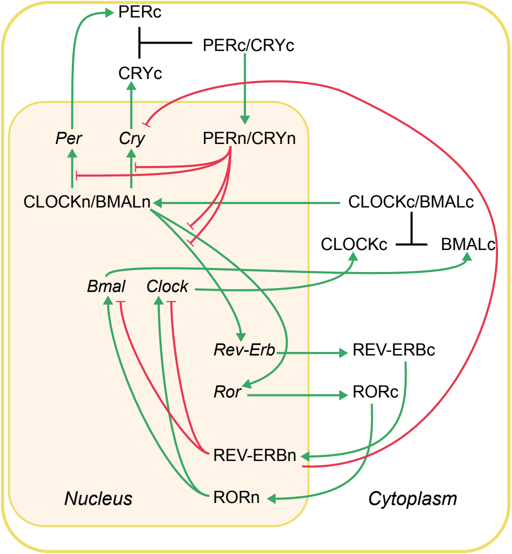
Gaussian process regression smoothing

Mouse class gene expression data (liver)



RT-qPCR acquired data. Gaussian process regression smoothing

A new model of the cellular circadian clock



Ordinary differential equations

$$n_{vars} = 18$$

$$n_{params} = 58$$

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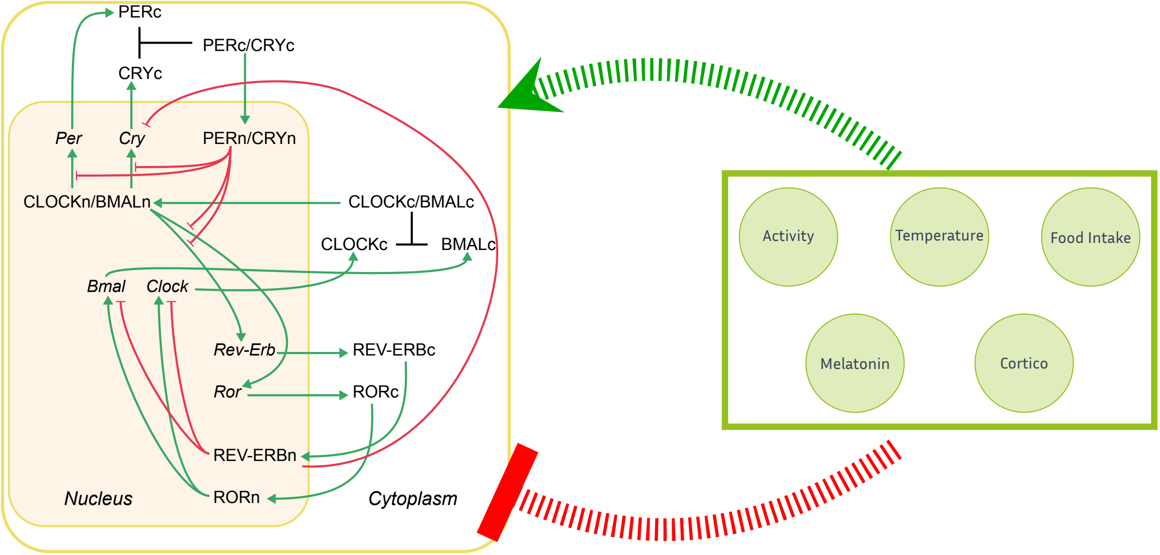

Systemic regulators identification as a regression problem

Hypothesis: Multiplicative control of systemic regulators z on gene transcription

$$\frac{dx^{vivo}}{dt} = f(\mathrm{z}) V_{\max} \mathsf{Transc}(\mathrm{M}, \gamma) - \alpha x^{vivo}$$

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Mouse class data $\bar{\mathrm{z}}$ $\bar{x}$

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Learn f using the samples $\left\{\left(\bar{\mathrm{z}}(t_i), y(t_i)\right) \;,\; i = \{1, \dots, N-1\}\right\}$

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Explicit form (unknown)

Systemic Regulators

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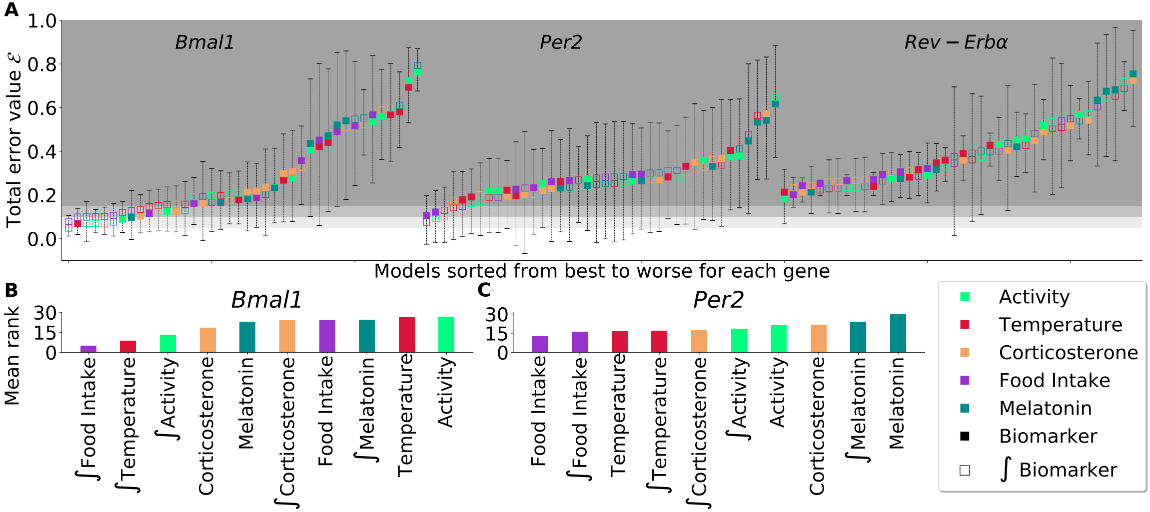
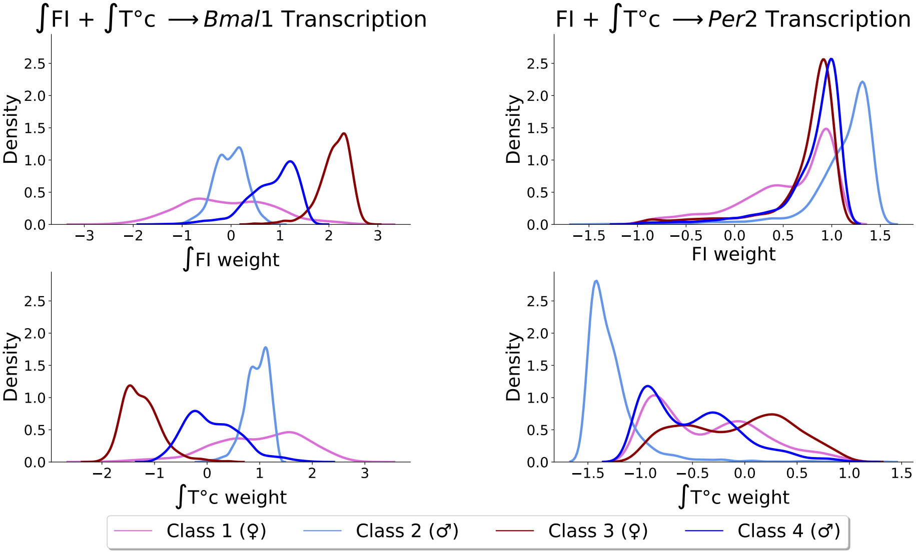
Systemic Regulators

$\rightarrow$ We consider linear models to learn f

2-term linear models ranking (lower is better)



Classwise weights analysis for best 2-term models



Want to know more? Paper to appear in *Bioinformatics* (ECCB21 Proceedings)

Julien Martinelli, Sandrine Dulong, Xiao-Mei Li, Michèle Teboul, Sylvain Soliman, Francis Lévi, François Fages, and Annabelle Ballesta. *Model learning to identify systemic regulators of the peripheral circadian clock*. working paper or preprint. Mar. 2021. url: https://hal.inria.fr/hal-03183579.