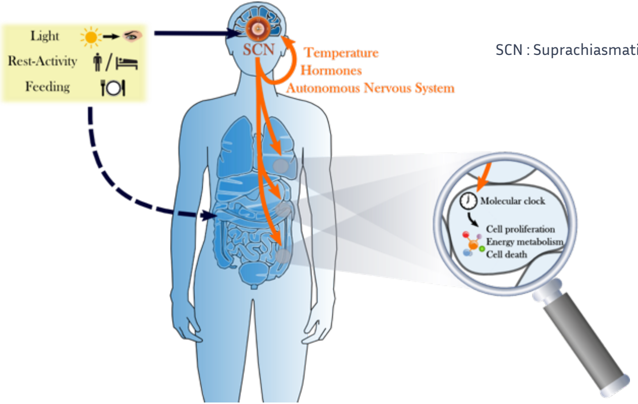
Identification de régulateurs systémiques de l'horloge périphérique circadienne par apprentissage de modèles

Julien Martinelli

June 21st, 2021

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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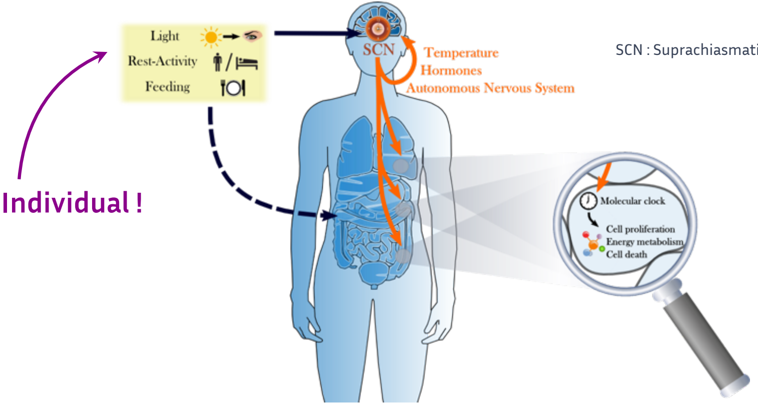

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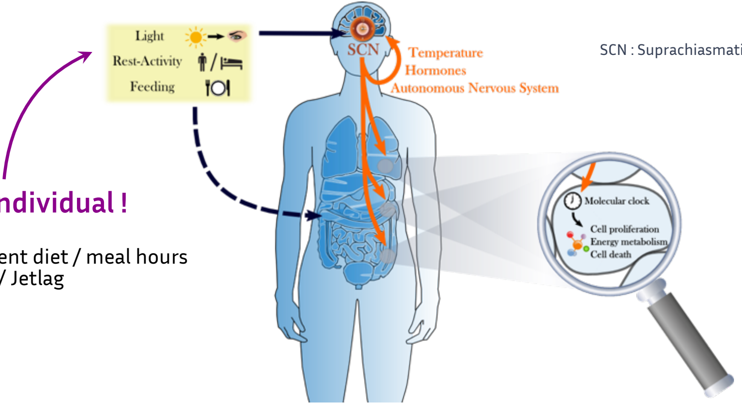

SCN : Suprachiasmatic Nuclei

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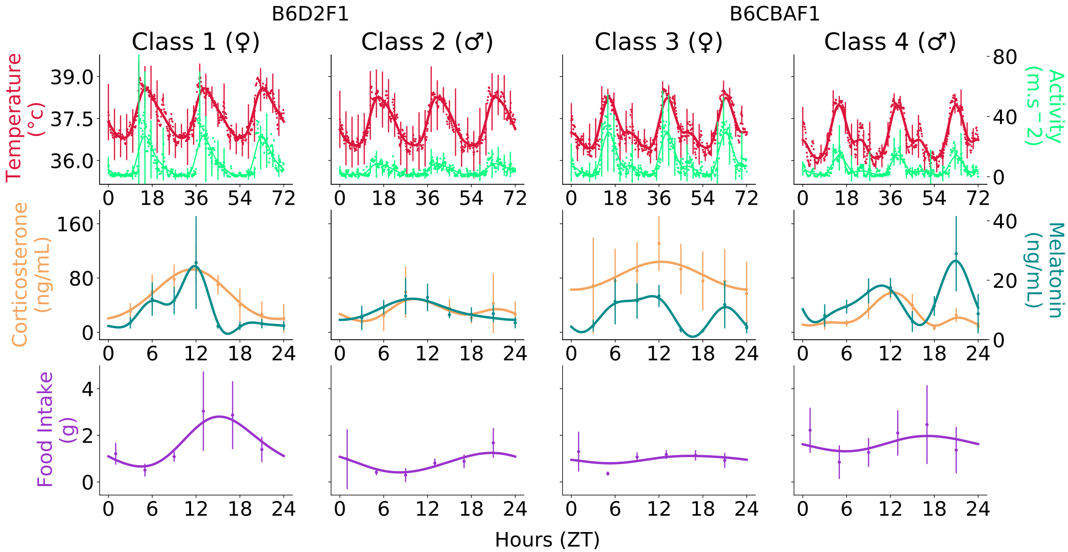
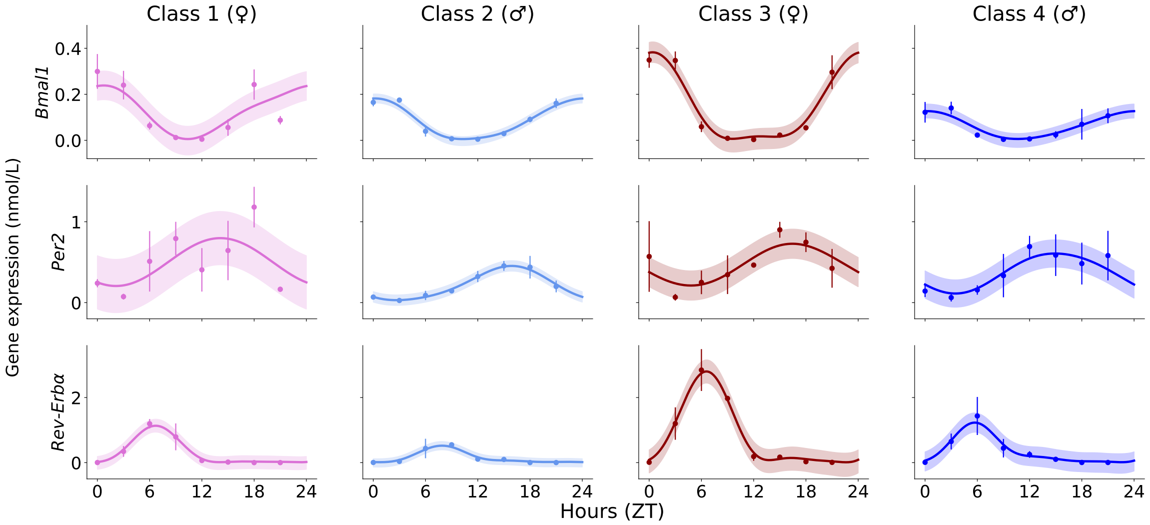
Focus on mice: data available both at the systemic and cellular level

Mouse class systemic regulators data



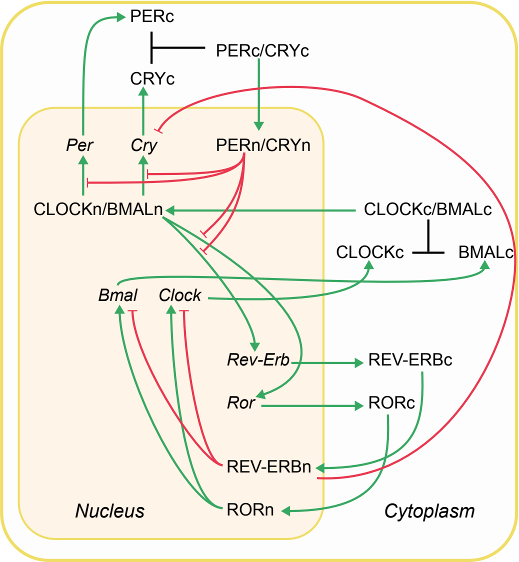
Solid lines: gaussian process regression smoothing

Mouse class gene expression data



RT-qPCR acquired data. Solid lines and stds: 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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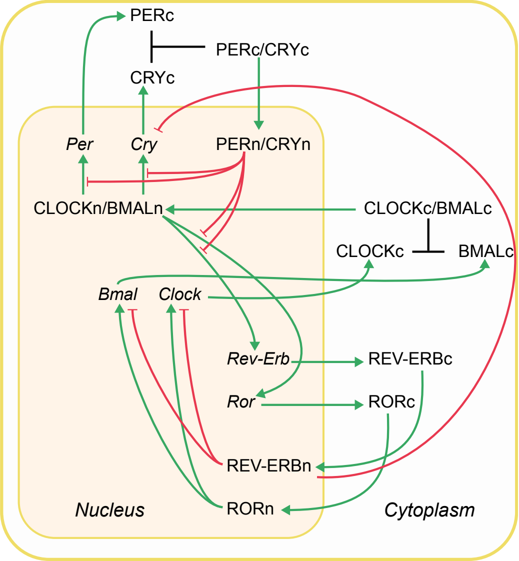

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Dynamics of gene expression:

Modulators

$$\frac{dx}{dt} = V_{\max}\text{Transc}(\mathrm{M}, \gamma) - \alpha x$$

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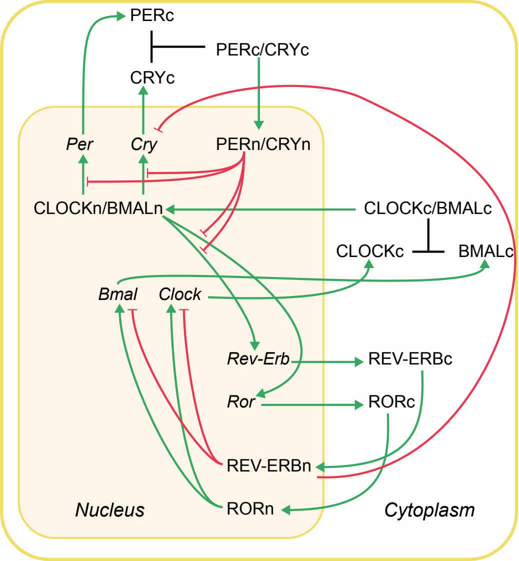

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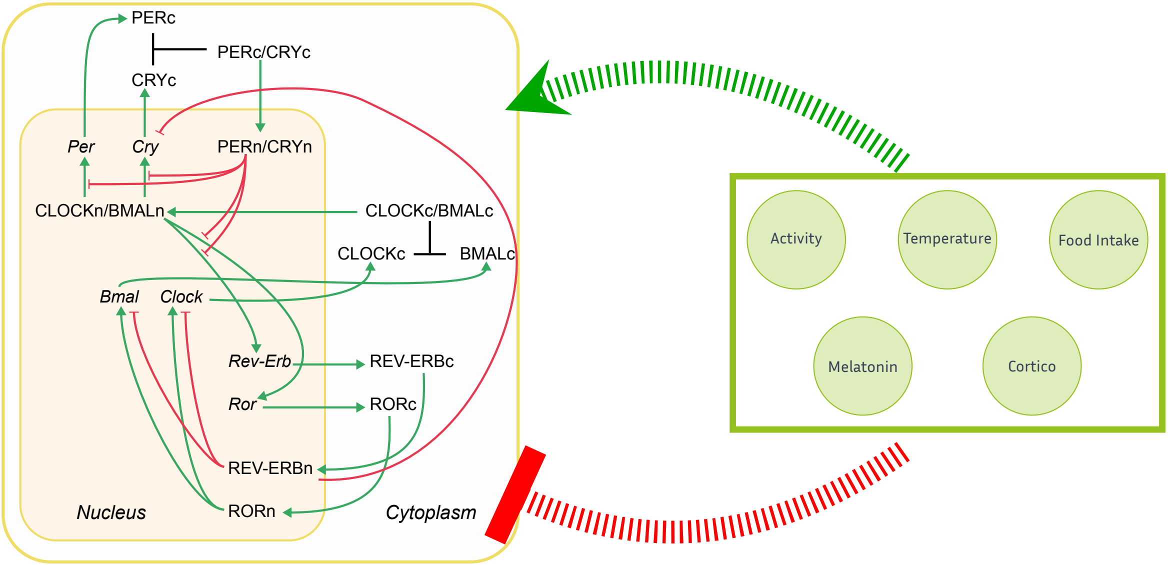
$$\text{Transc}_{Bmal1} = \frac{1+\gamma_1\left(\frac{\text{ROR}}{\gamma_2}\right)^{\gamma_3}}{1+\left(\frac{\text{REV-ERB}}{\gamma_4}\right)^{\gamma_5}+\left(\frac{\text{ROR}}{\gamma_2}\right)^{\gamma_3}}$$

Hill-like kinetics

A new model of the cellular circadian clock



Incorporating systemic regulators action on gene expression

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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$$\Leftrightarrow f(\mathrm{z}) = \frac{\frac{dx^{vivo}}{dt} + \alpha x^{vivo}}{\mathrm{Transc}(\mathrm{M}, \gamma)}$$

Data for x = *Bmal1*, *Per2* and *Rev-Erb*α

Systemic regulators identification as a regression problem

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

$$\Leftrightarrow f(\bar{z}(t_i)) \approx \frac{\frac{\Delta \bar{x}^{vivo}(t_i)}{\Delta t_i} + \alpha \bar{x}^{vivo}(t_i)}{\text{Transc}(\mathrm{M}, \gamma)} := y(t_i)$$

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

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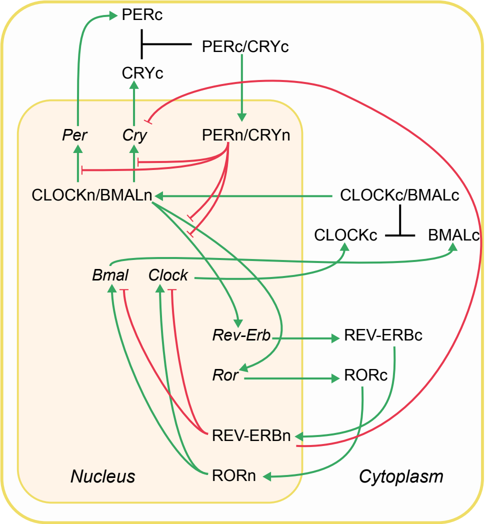
Systemic Regulators

Learning f usually boils down to solve

$$\underset{\hat{f} \in \mathscr{F}}{\operatorname{argmin}} \sum_{i=1}^{N-1} \left(y(t_i) - \hat{f}(\bar{z}(t_i))\right)^2$$

For this study, $\mathscr{F}$ will be the space of linear functions.

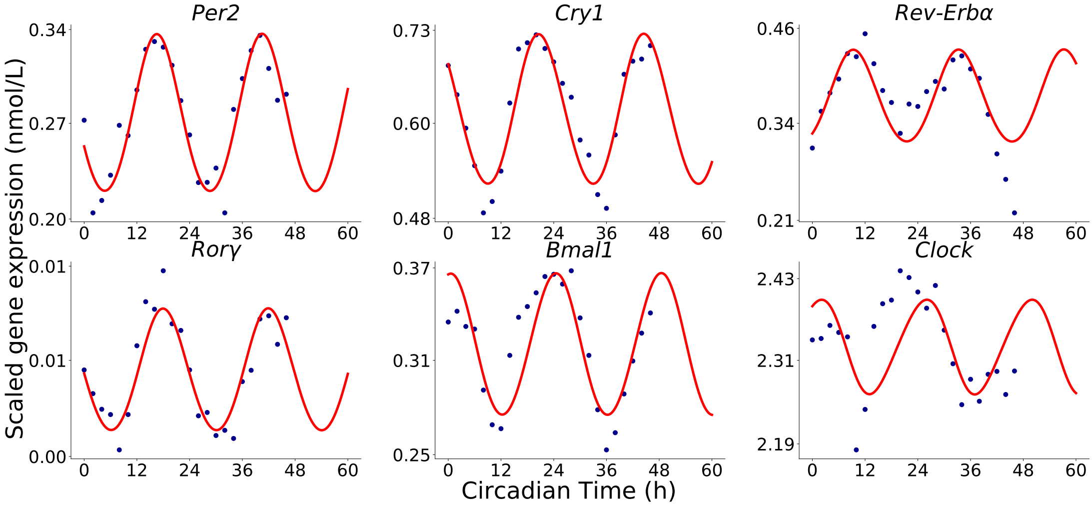
Computing residuals y: acquisition of clock parameters and protein levels



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

- *In vitro* setting $\Longrightarrow$ $f(z)$ constant
- Fit model on *in vitro* hepatocytes data (Atwood *et al.*, PNAS, 2011)

Clock model fit on *in vitro* hepatocytes data



$\Longrightarrow$ α, γ and $M(t)$ estimates obtained (fit performed with black-box optimizer *CMA-ES*)

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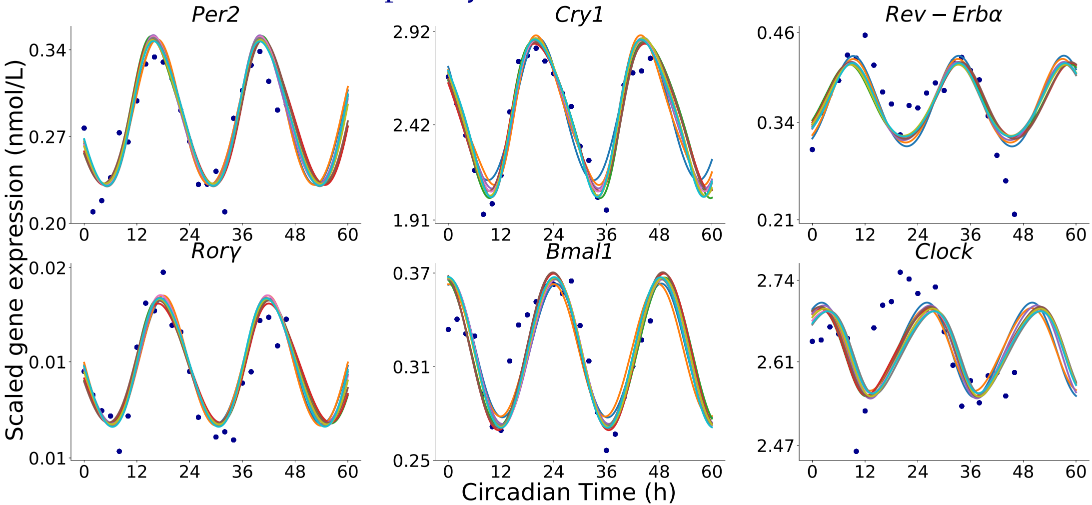

$\implies$ α, γ and $M(t)$ estimates obtained (fit performed with black-box optimizer *CMA-ES*)

Multiple α, γ and $M(t)$ $\implies$ multiple residual trajectories $y(t)$ for each gene / mouse class.

Linear regression

For each residual y, a linear model $\sum_j \beta_j z_j$ is fitted

- The **active regulators** of the fitted model should be the same classwise.
- **Different weights** β for a regulator from one class to another are allowed

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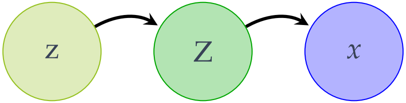
Need to account for the delay introduced by moving in different compartments

$\implies$ *Integral* regulators $Z_j(t) = \int_0^t z_j(s)ds$ are added: $\mathrm{z} \leftarrow (\mathrm{z}, \mathrm{Z})$



A regulator z_j and its integral Z_j are never found together in a model for all j

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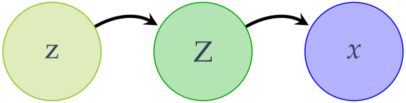

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0.8 Food Intake (Class 1)	0.7 Food Intake (Class 2)
+ 0.9 $\int$Food Intake	+ 0.6 $\int$Food Intake

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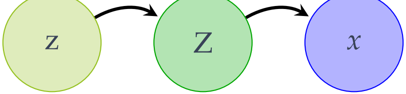

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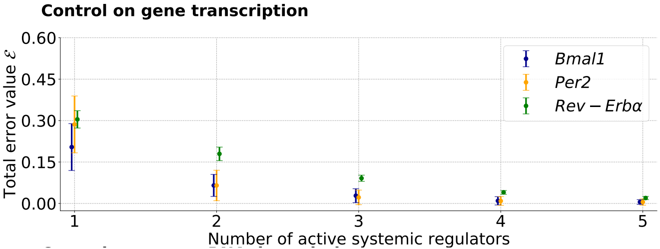
0.8 Food Intake (Class 1) + 0.4 $\int$ Melatonin

0.7 Food Intake (Class 2) + 0.2 $\int$ Melatonin

Total error as a function of the number of involved regulators



$$\mathscr{E}\left(y,\bar{z}\right) := \frac{1}{4n}\sum_{c=1}^{4}\sum_{k=1}^{n}\min_{\beta_k^{(c)}} \ell\left(y_k^{(c)},\bar{z}^{(c)},\beta_k^{(c)}\right)$$

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Input/output normalized $\implies$ $\mathscr{E}$ is an average % of unexplained variance

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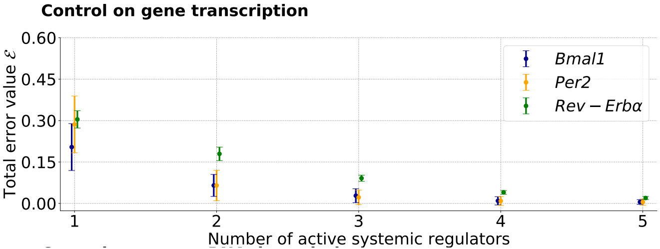

- *Bmal1* / *Per2* residuals well fitted with 2-term models, not *Rev-Erbα*
- F-test for nested models concludes on 2-terms

$\Longrightarrow$ No **linear** control of regulators on *Rev-Erbα* transcription

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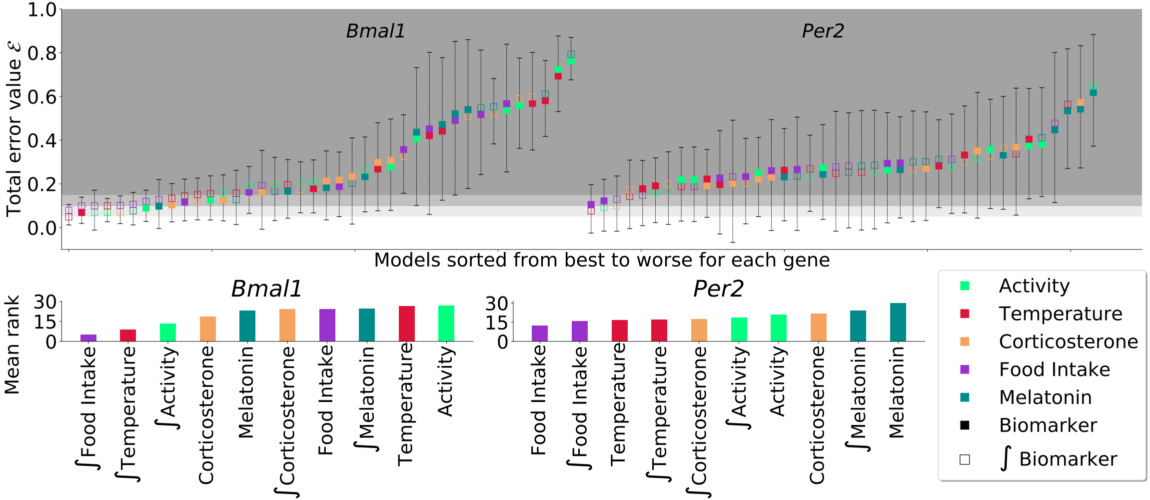
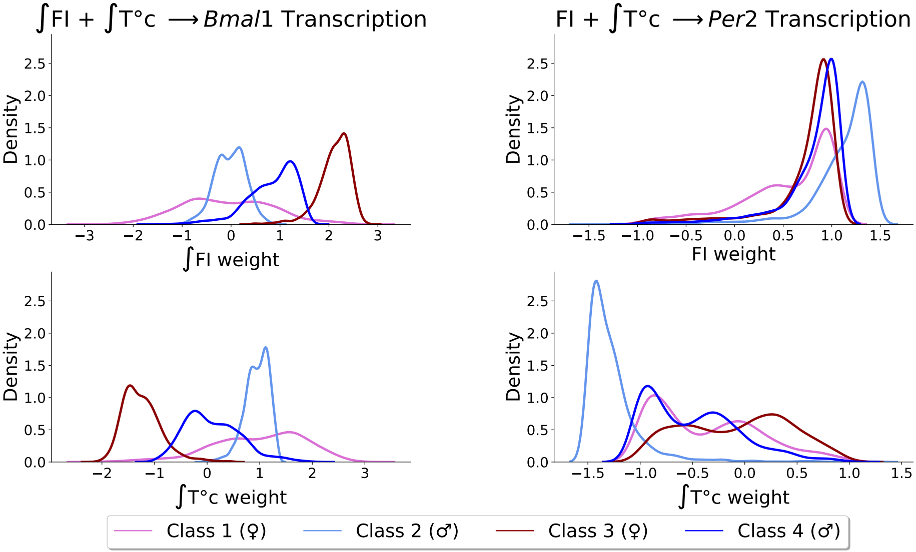
2-term models ranking



Classwise weights analysis for best 2-term models



Conclusion & Perspectives

Under all hypotheses:

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- Linear control of studied systemic regulators on gene mRNA degradation unlikely

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- Handle large number of variables within the sparse multi-task regression framework

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What's next:

- Integration of best regulator models back in the ODEs
- Validation on human data

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.