Model learning to identify systemic regulators of the peripheral circadian clock

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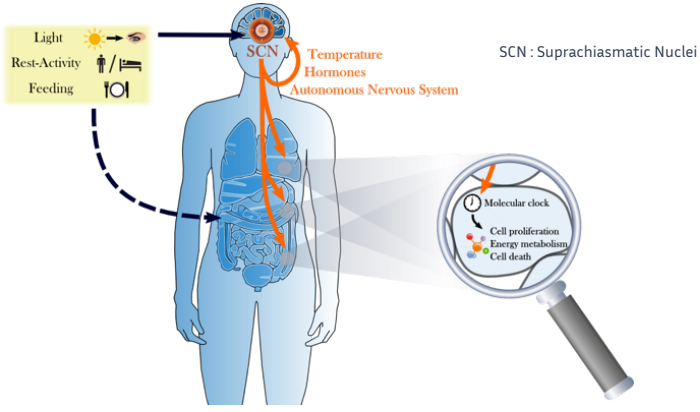
July 28th, 2021

The circadian timing system



- 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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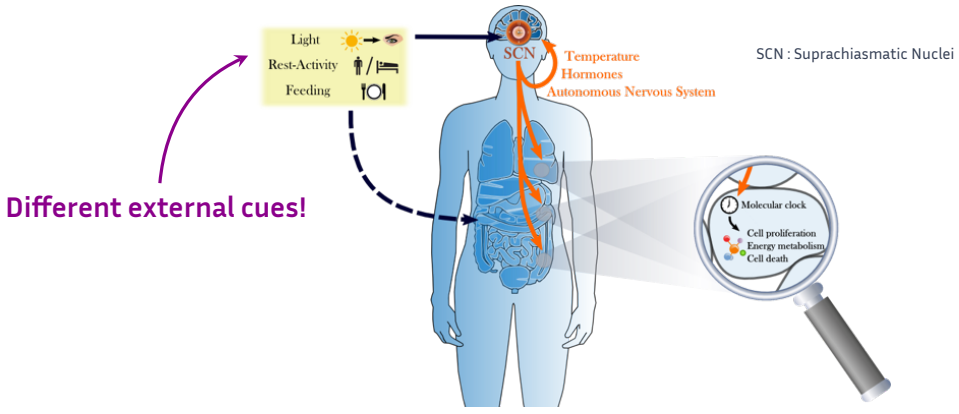

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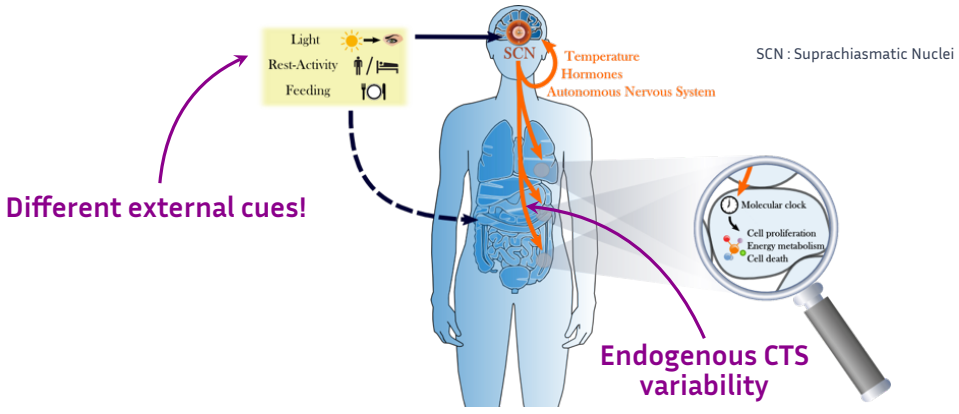

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Focus on mice: data available both at the systemic and cellular level

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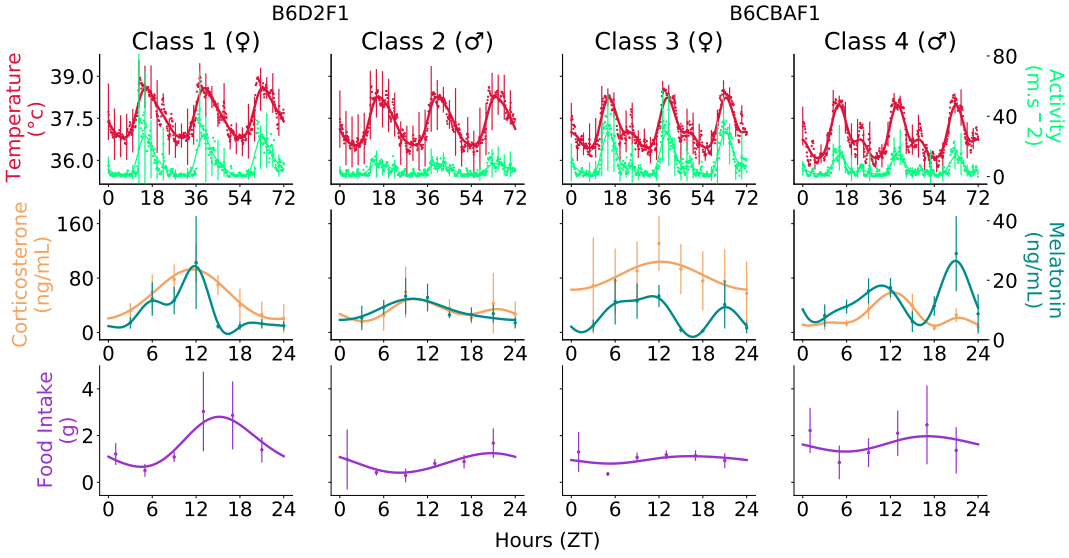
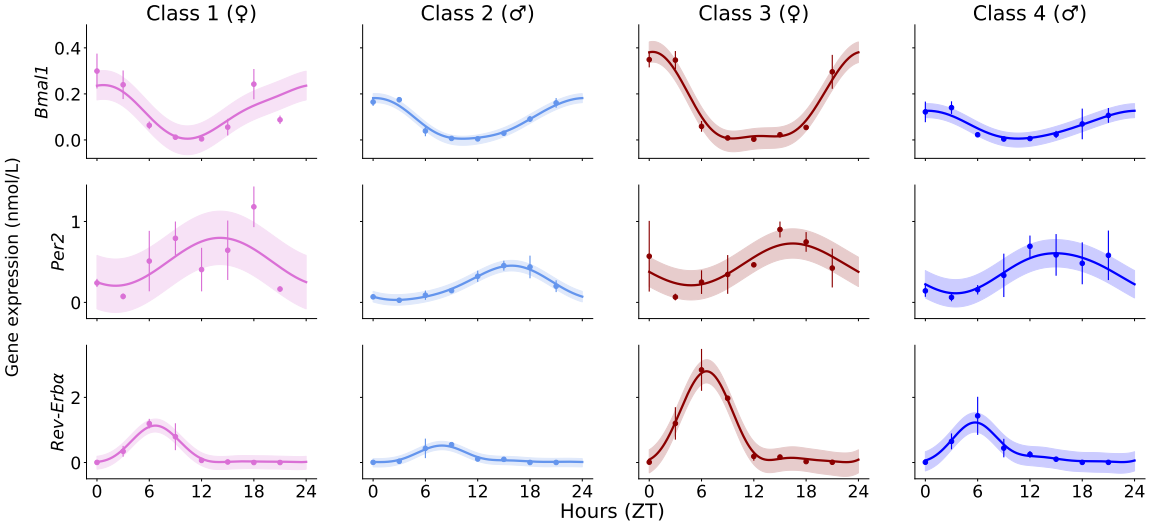
Mouse class systemic regulators data



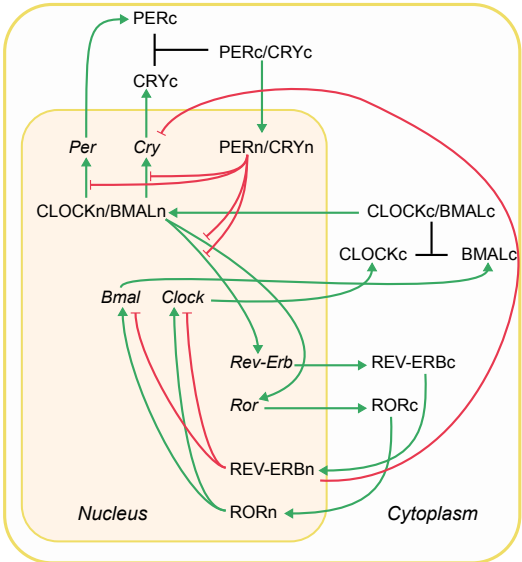
Solid lines: gaussian process regression smoothing

Mouse class gene expression data (liver)



RT-qPCR 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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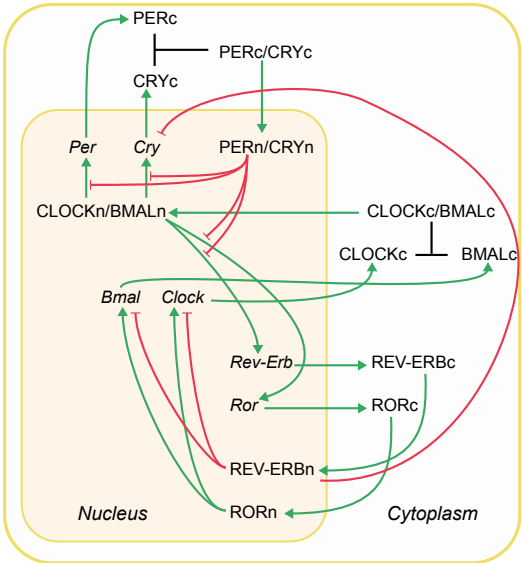

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Dynamics of gene expression:

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

Modulators

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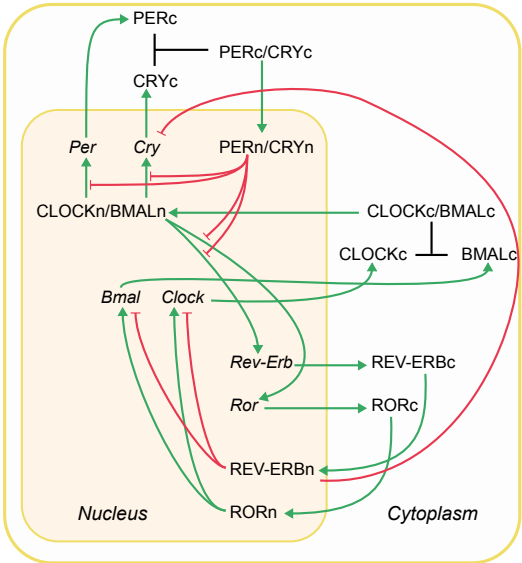

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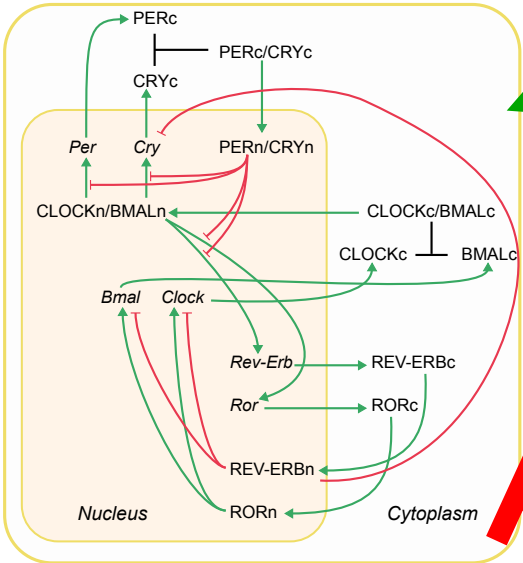
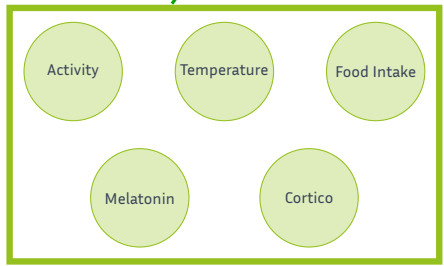
$$\frac{dx}{dt} = V_{\max}\text{Transc}(\mathrm{M}, \gamma) - \alpha x$$

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

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

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

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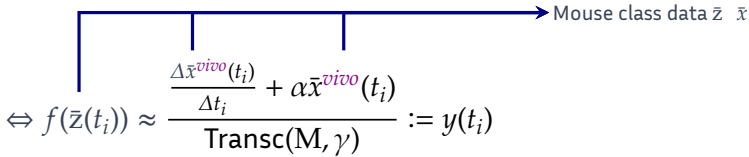
$$\frac{dx^{vivo}}{dt} = f(z)V_{\max}\text{Transc}(M,\gamma) - \alpha x^{vivo}$$

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

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

Systemic regulators identification as a regression problem



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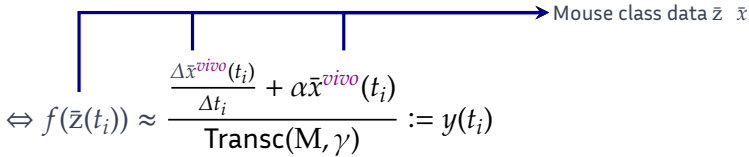

Learn f using the samples $\left\{\left(\bar{z}(t_i), y(t_i)\right)\ ,\ i = \{1, \dots, N-1\}\right\}$

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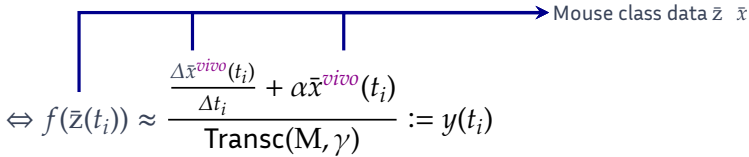

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Systemic Regulators

Systemic regulators identification as a regression problem

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

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

Residuals

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

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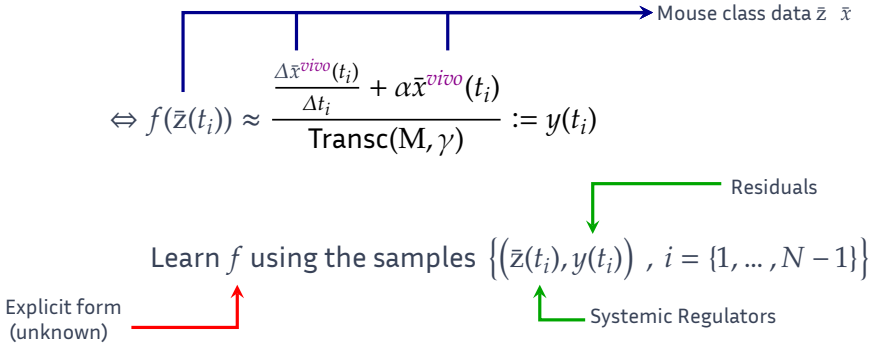

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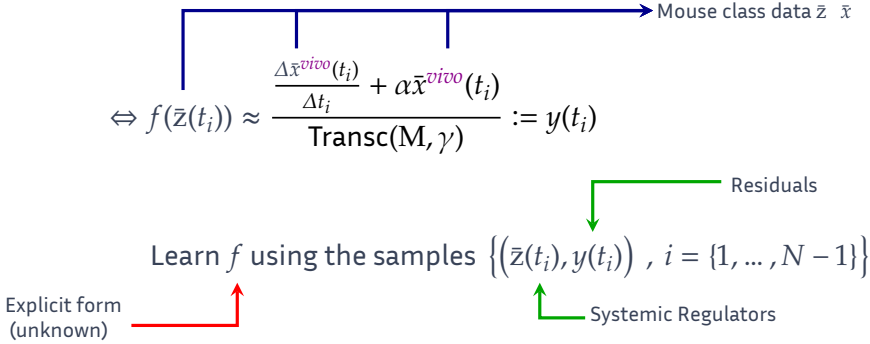
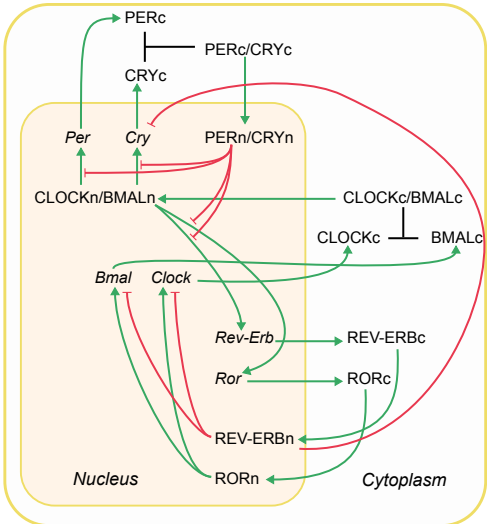


Learning f usually boils down to solve

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

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

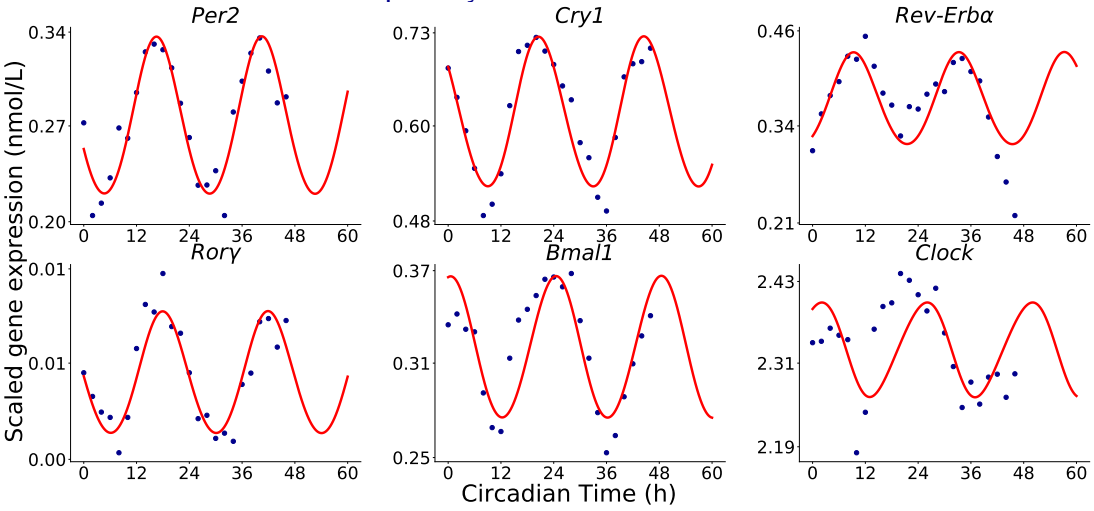
Computing residuals y: acquisition of clock parameters and protein levels



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

- *In vitro* setting $\Longrightarrow$ $f(\mathrm{z})$ 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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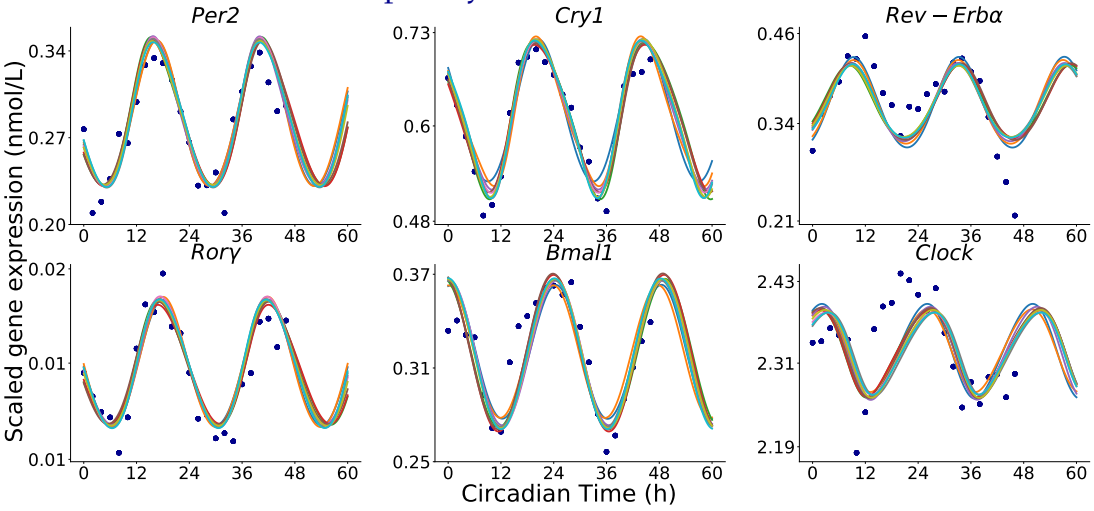

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Perturbations of parameter values to obtain multiple realistic residual trajectories $y(t)$

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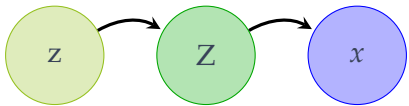
Need to account for the delay introduced by moving in different compartments

$\Longrightarrow$ *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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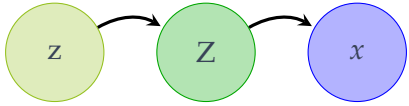

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+ 0.9 $\int$ Food Intake

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

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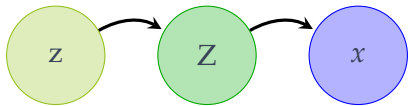

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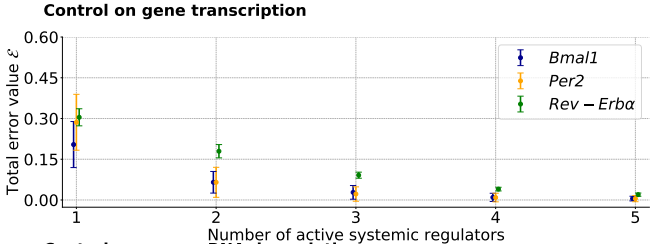
0.8 Food Intake (Class 1)
+ 0.4 ∫Melatonin

0.7 Food Intake (Class 2)
+ 0.2 ∫ 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 $\Longrightarrow$ $\mathscr{E}$ is an average % of unexplained variance

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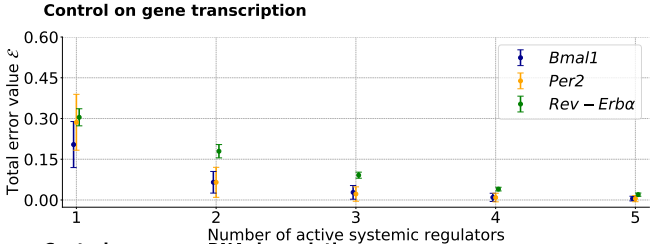

F-test for nested models or balance between DoF & error decrease:

- Assuming linear control on transcription, *Bmal1* / *Per2* associated trajectories conclude on **2-term models**
- **No linear control** for *Rev-Erbα* transcription
- **No linear control** for all 3 genes mRNA degradation

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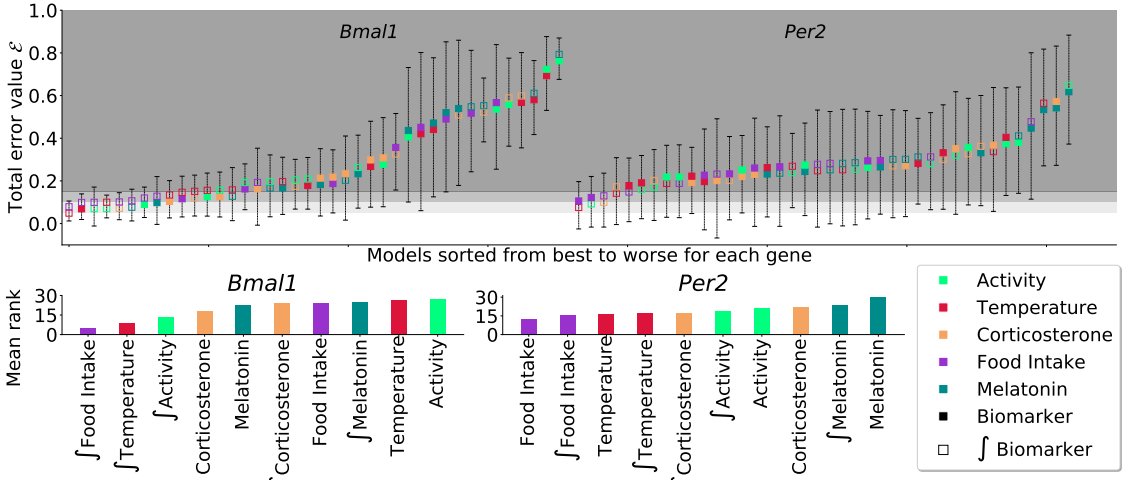
2-term models ranking



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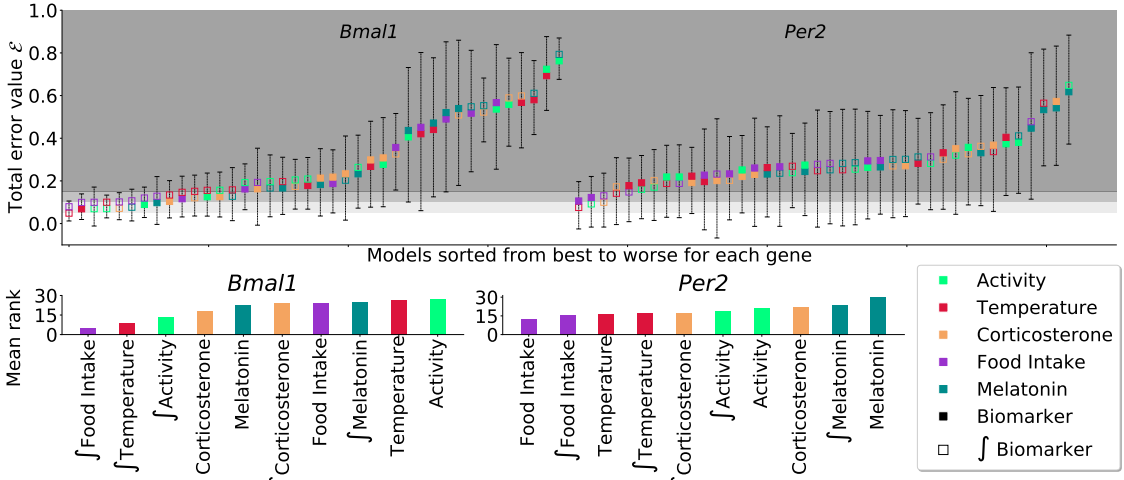
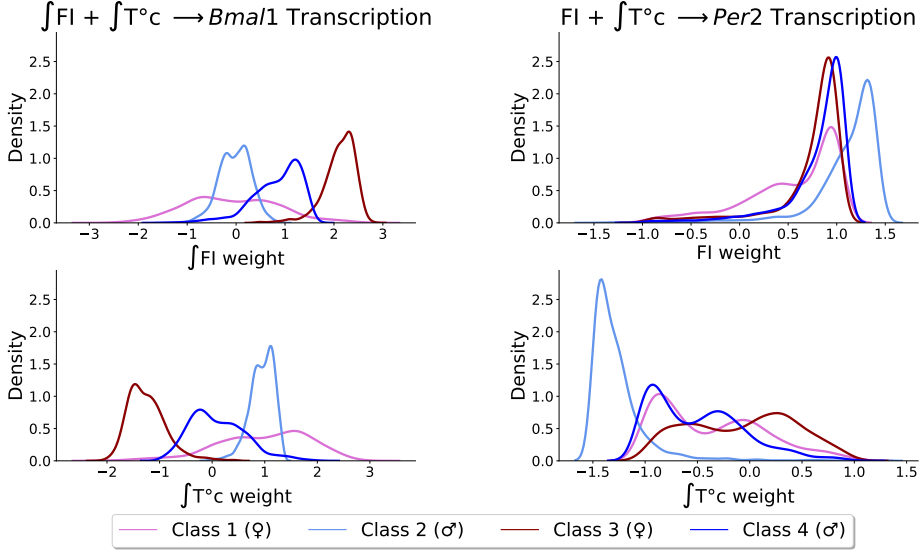


- Food Intake and Temperature stand out as best models key components.
- Melatonin included as negative control: validation of the approach.

Classwise weights analysis for best 2-term models



Conclusion & Perspectives

Biological insights and perspectives:

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