Model learning to identify systemic regulators of the peripheral circadian clock

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Personalized medicine aims at providing patient-tailored therapeutics based on multi-type data towards improved treatment outcomes. Chronotherapy that consists in adapting drug administration to the patient's circadian rhythms may be improved by such approach [1]. Recent clinical studies demonstrated large variability in patients' circadian coordination and optimal drug timing. Consequently, new eHealth platforms allow the monitoring of circadian biomarkers in individual patients through wearable technologies (rest-activity, body temperature), blood or salivary samples (melatonin, cortisol), and daily questionnaires (food intake, symptoms). A current clinical challenge involves designing a methodology predicting from circadian biomarkers the patient peripheral circadian clocks and associated optimal drug timing. The mammalian circadian timing system being largely conserved between mouse and humans yet with phase opposition, the study was developed using available mouse datasets.

We investigated at the molecular scale the influence of systemic regulators (e.g. temperature, hormones) on peripheral clocks, through a model learning approach involving systems biology models based on ordinary differential equations. Using as prior knowledge our existing circadian clock model [2], we derived an approximation for the action of systemic regulators on the expression of three core-clock genes: *Bmal1*, *Per2* and *Rev-Erbα*. These time profiles were then fitted with a population of models, based on linear regression. Best models involved a modulation of either *Bmal1* or *Per2* transcription most likely by temperature or nutrient exposure cycles. This agreed with biological knowledge on temperature-dependent control of *Per2* transcription. The strengths of systemic regulations were found to be significantly different according to mouse sex and genetic background [3].

References

[1] Annabelle Ballesta, Pasquale F. Innominato, Robert Dallmann, David A. Rand, and Francis A. Lévi. Systems chronotherapeutics. *Pharmacological Reviews*, 69(2):161–199, 2017.

[2] Janina Hesse, Julien Martinelli, Ouda Aboumanify, Annabelle Ballesta, and Angela Relógio. A mathematical model of the circadian clock and drug pharmacodynamics to optimize irinotecan administration timing in colorectal cancer, 2021. Under review.

[3] 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, 2021. To appear in *Bioinformatics*.