TimeTeller: quantifying circadian clock dysfunction

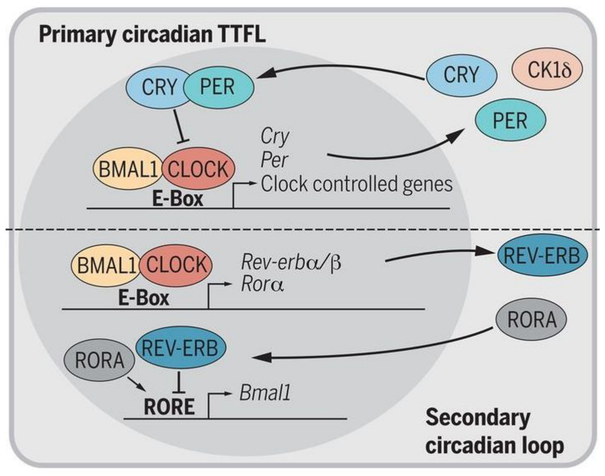
Maria Veretennikova[1*] , Laura Usselmann[2,3,4], Vadim Vasilyev[3,4,5], Robert Dallmann[3] , David Rand[5]
[1] COI, NDM, University of Oxford, [2] AstraZeneca, [3] Warwick Medical School, University of Warwick, [4] MRC DTP in IBR, University of Warwick, [5] Maths Institute, University of Warwick, UK
*Maria.Veretennikova@ndm.ox.ac.uk. *N.B. For Maria Veretennikova and Laura Usselmann the work was carried out whilst based at the University of Warwick, UK*.

Background

Circadian clocks (CC) manifest themselves in most cells of virtually all living organisms and their good condition is essential for optimal rhythmic daily variation in many internal processes.

The core of the clock mechanism comprises of a network of feedback loops in which clock proteins act as transcriptional factors/coregulators repressing/activating expression of their own genes or other core clock genes (see right).

There is evidence for a strong link between CC (dys)function level and onset, progression and therapeutic outcomes of treatment in diseases such as cancer.



Selected result

Train data: healthy mice (see Zhang et al.). *Test data*: Healthy control group vs. 24-hour starved mice (see Kinouchi et al.)

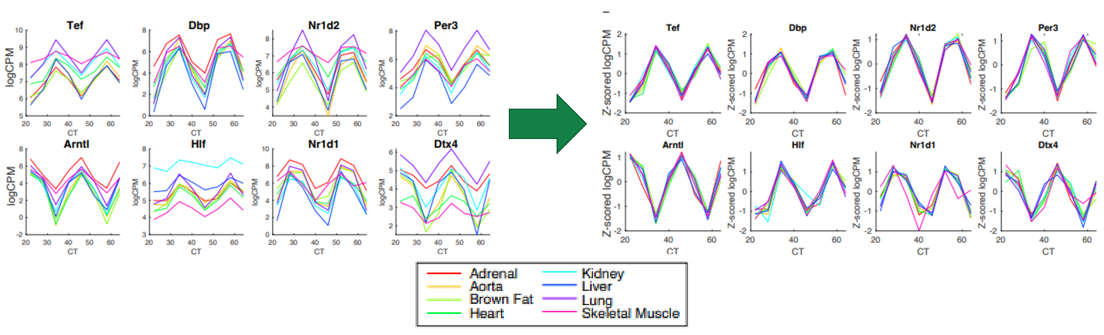
TimeTeller shows that:

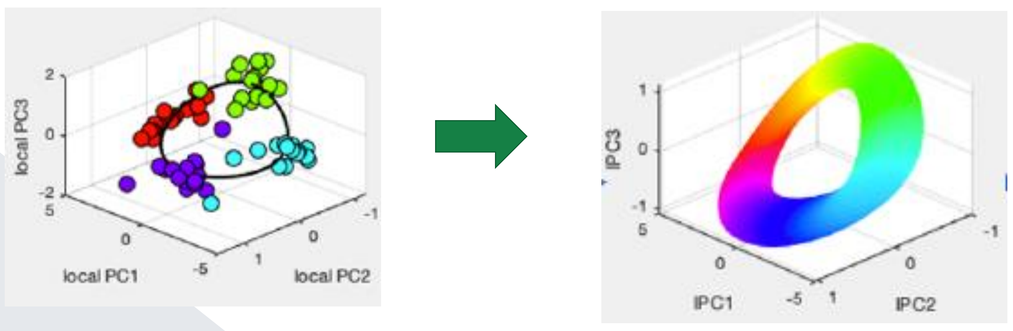
- The clock of the mice subjected to fasting has shifted away from the normal
- Theta values are significantly different between the groups
- Starved mice sampling time prediction displacements are higher.

TimeTeller model construction

TimeTeller is a machine learning approach, which allows to quantify the level of CC disruption from the multi-dimensional state of the clock given a single biopsy.

To construct the model one needs bulk RNASeq or microarray data around the clock at equally spaced time stamps with at least a few samples at each. After normalization data is projected onto local principal component spaces and Gaussian distributions are fitted to the train data in 3D.



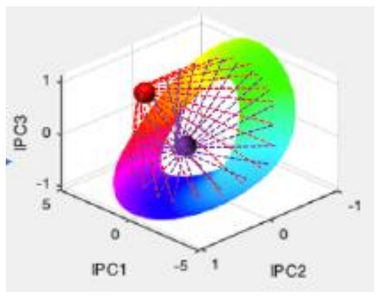


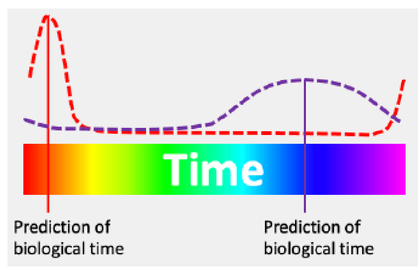
TimeTeller is built on the hypothesis that the more confident we can be in the sampling time estimate of the test data from our model, the better the clock functions as a system (high ***theta*** metric value), and the less confident we are, the worse the clock functionality.

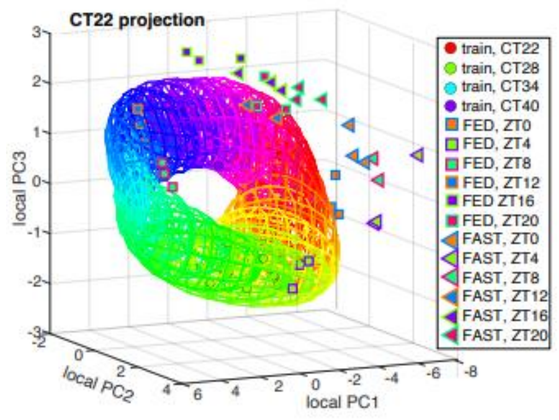
Test data analysis

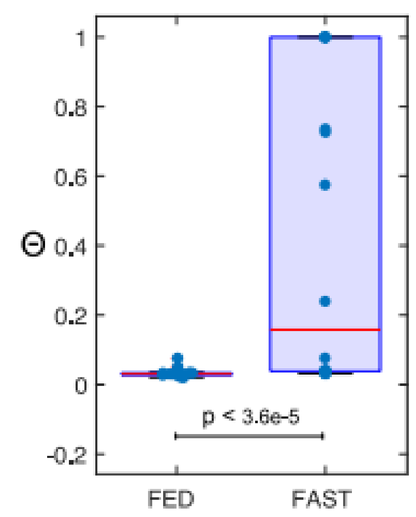
For a test data the likelihood of belongingness to Gaussian distributions centered at finely discretized ellipse points is calculated.

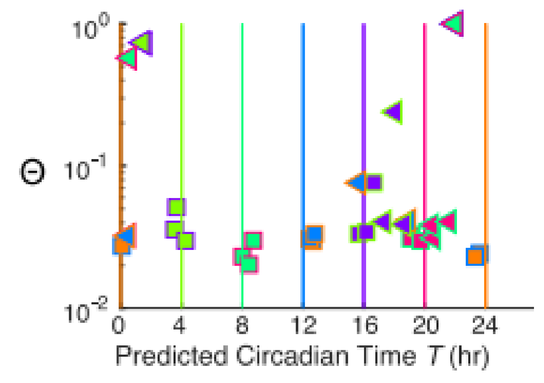
The maximum likelihood (ML) time point is found and the measure of confidence is taken as the clock disruption score ***theta***.











TimeTeller's key capabilities and strengths

- Only one biopsy is needed for quantifying clock dysfunction.
- Allows to compare control and perturbed test data to assess the extent to which the perturbed data is dysfunctional.
- Can provide a stratification of individual transcriptomes as well as serve as an independent biomarker for prognostic purposes e.g. in cancer studies.
- It is possible to combine microarray and bulk RNASeq data in the same model.

References

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- R. Zhang et al., *A circadian gene expression atlas in mammals: implications for biology and medicine*. Proc. Natl. Acad. Sci. U. S. A., 2014 Nov 11; 111(45):16219-24
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