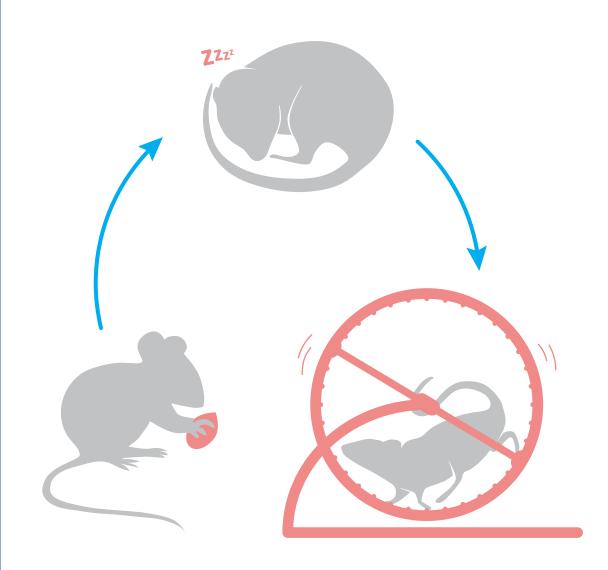
# Post-transcriptional regulation:

## major or minor role for circadian expression of transcripts?

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#### Introduction & Questions



Circadian clocks regulate many physiological processes in a cell-type specific manner. Composed of interlocked negative and positive feedback look, the core clock genetic network creates the oscillations in gene expression of a cascade of output genes. So far, rhythmic transcriptional regulation of gene expression is well characterized but little is known about post-transcriptional regulation of rhythmic transcripts.

Our aim is to quantify the half-lives of rhythmically expressed mRNAs and to identify those that are post-transcriptionally regulated by the clock.

How can we measure/infer post-transcriptional regulation?

(see Material & Methods panel)

What fraction of rhythmic genes have a circadian regulation after transcription? (see Results panel)

Can we characterize this post-transcriptional regulation?

(see Results panel)

What are the potential regulators? When do they act?

(see Conclusion & further work panel)

#### Conclusions & further work

Thanks to a model-based approach, we were able to indirectly predict the post-transcriptionnal regulation of mRNA.

We provide estimation of the half-lives for rhythmic transcripts in mouse liver and we found that a small fraction (about 20% of rhythmic transcripts) is characterized by half-lives shorter at given time of the day.

Our results suggest that the mRNA that undergo rhythmic degradation are less stable during the day (when the mouse is sleeping). We also observe that rhythmic degradation is used either to create oscillations of transcripts that are transcribed constitutively, either to adjust the time and the amplitude of transcripts that are rhythmically transcribed.

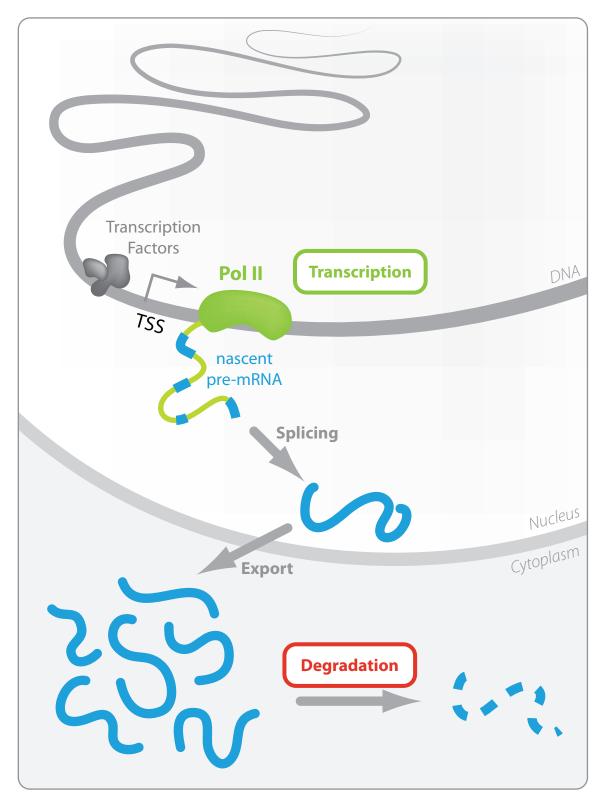
These results lead to other questions about this post-transcriptional regulation: What are the regulators?

miRNA? RNA Binding Proteins (RBPs)?

It has also been observed that some deadenylases (that trigger the degradation of mRNA) or associated proteins are rhythmically expressed.

The next step of this project is to first use bioinformatics tools to find whether some of the regulators can explain the specific post-transcriptional regulation of some transcripts. We then plan to experimentaly validate this regulation.

#### Material & Methods

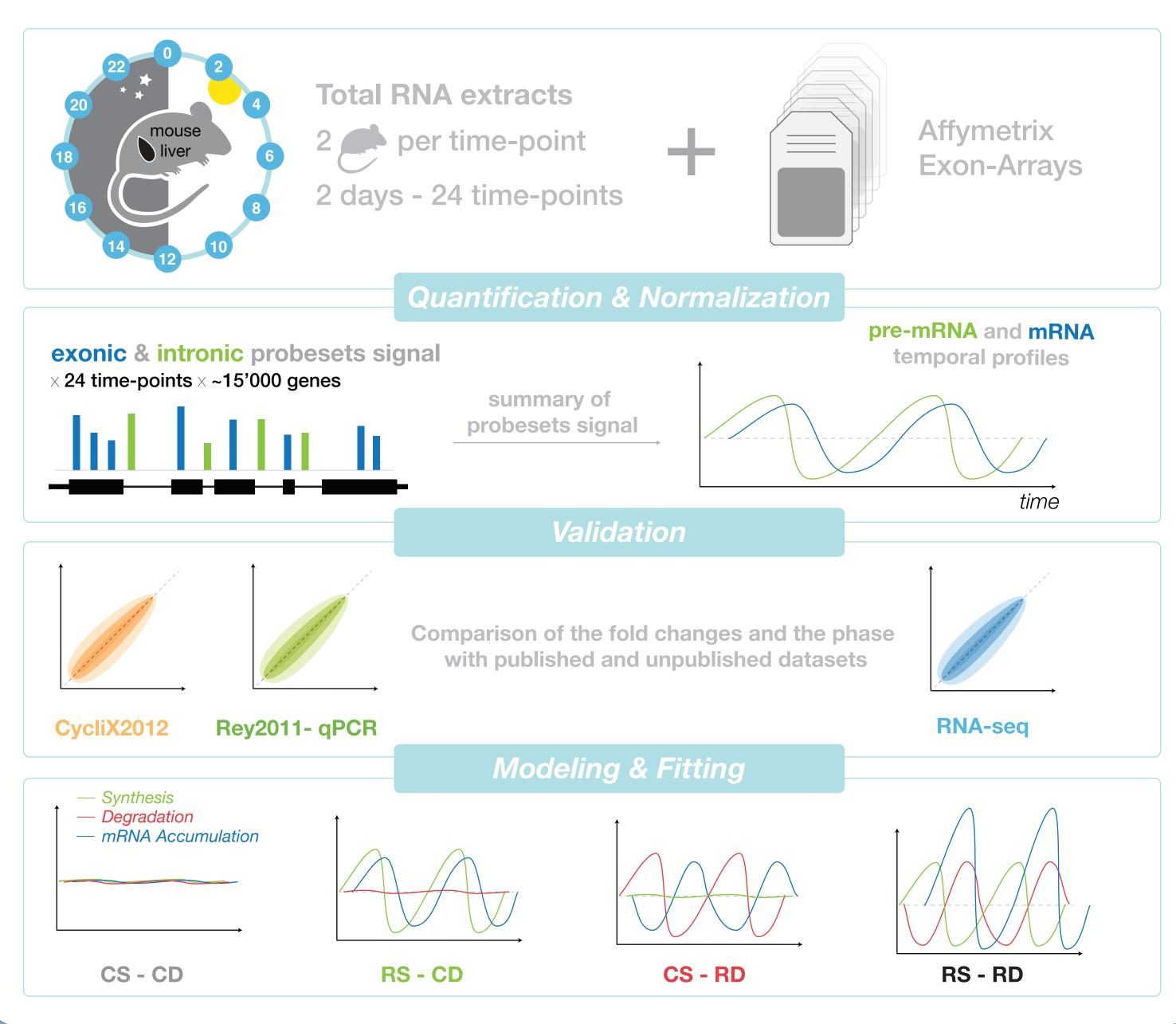


Direct measurements of degradation rates can be done by stopping transcription and measuring the decay of mRNA at different times of the day. However, in mouse liver, stopping transcription is technically impossible at the moment.

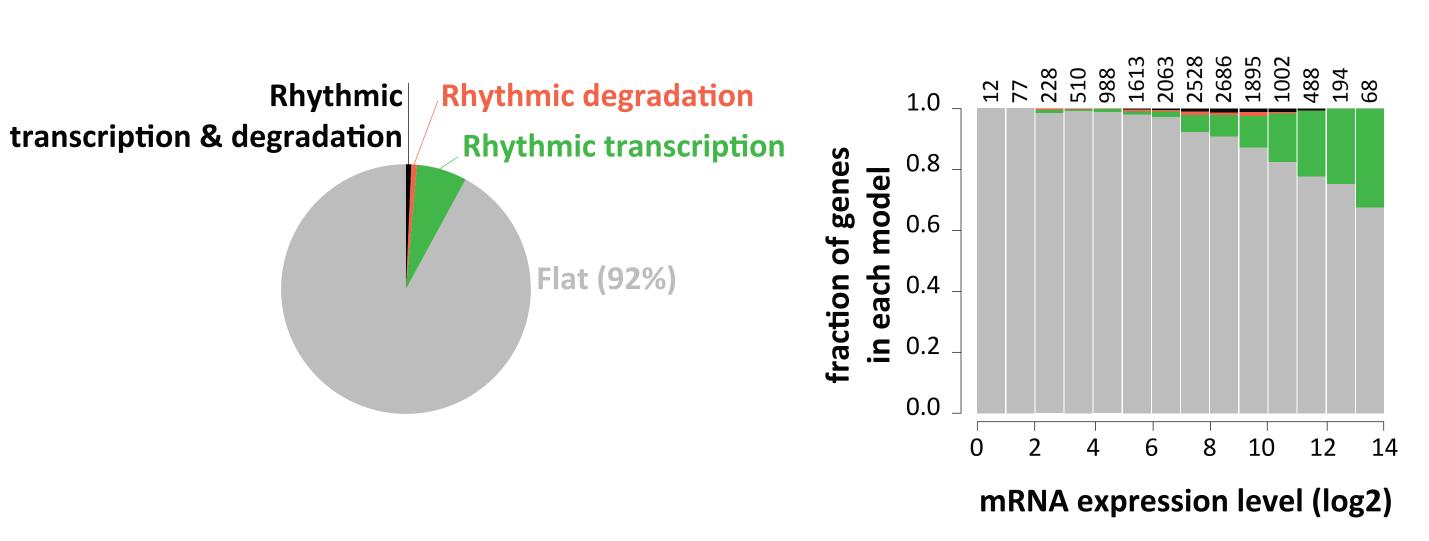
Thus, we use an indirect method to estimate degradation rates based on the measurement of transcription and accumulation rates and assuming that the accumulation of mRNA is the balance between transcription and degradation.

$$\dot{m}(t) = s(t) - \gamma(t)m(t)$$

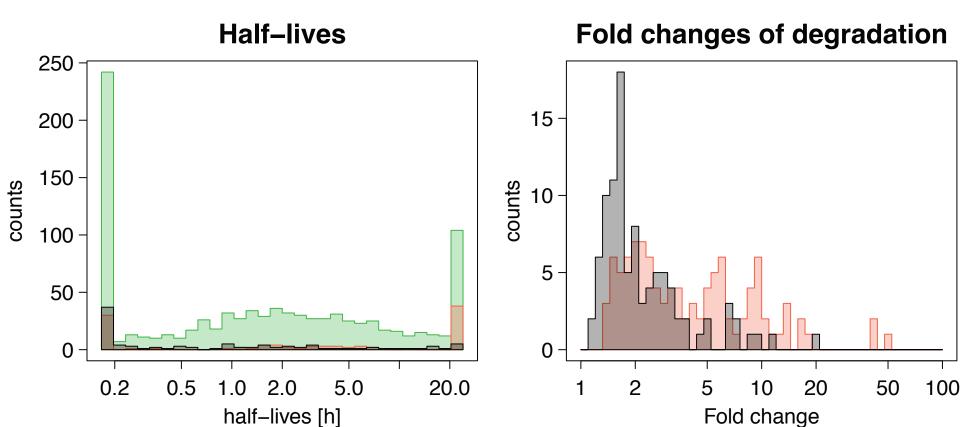
From measurements of pre-mRNA and mRNA in mouse liver, our method (profiles fitting and model selection) determines whether the temporal profile of a gene is explained by rhythmic transcription, degradation or both.



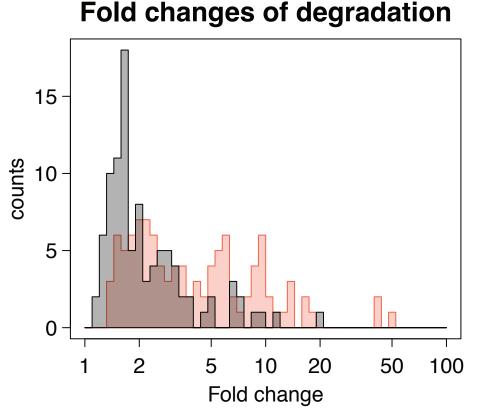
### (Preliminary) Results



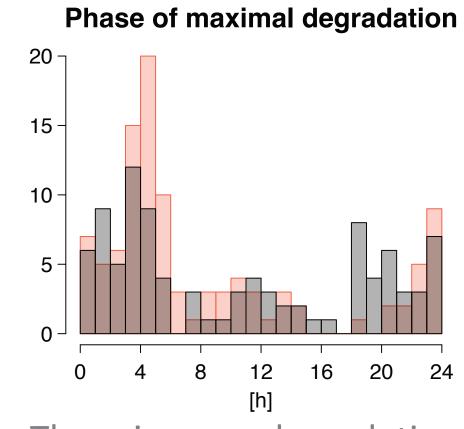
Most genes are not expressed rhythmically but that fraction increases with the level of expression. Among the rhythmic transcripts, only 20% of them have rhythmic degradation.



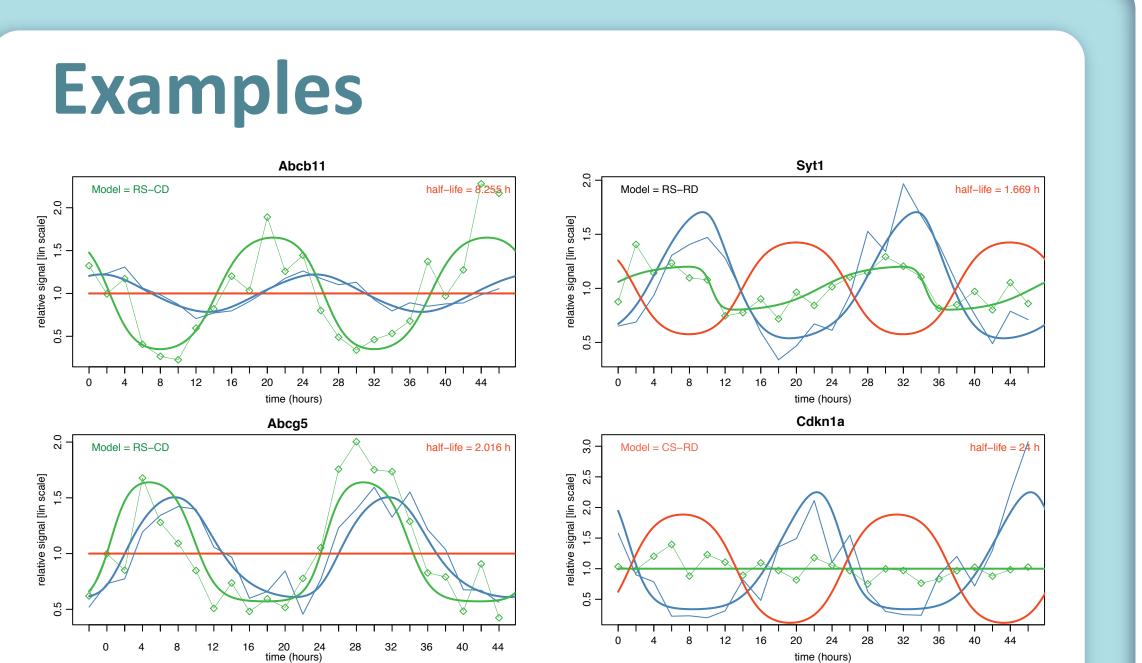
The median half-life is about 2h for rhythmic transcripts. We probably underestimate some of the half-lives due to our time resolution (2h)

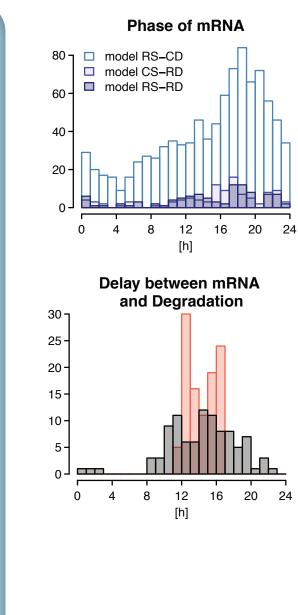


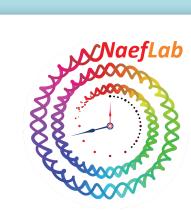
The fold changes of degradation are larger when the latter is the only responsible for oscillations.



There is more degradation in the morning, which is related to higher mRNA accumulation in the night (mice activity).







Félix Naef Nacho Molina Frederic Gachon Jingkui Wang & others for the biological samples





