Rhythmic Degradation Explains and Unifies Circadian Transcriptome and Proteome Data

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***Short Abstract* — In many mammalian tissues, 10% of all transcripts display a 24-hour rhythm in abundance. These abundane profiles are thought to be driven by the "circadian clock", a regulatory network of transcription factors.**

Recent studies have uncovered that these transcripts experience a widespread circadian post-transcriptional regulation. Using an ODE-model with time-dependent rates we have recently shown that the assumption of rhythmic half-lives can explain the mismatch of measured peaks of pre-mRNA and mRNA. The model predicts that peak phases of ca. 30% of oscillatory mRNA in mouse liver and fly brain are determined by rhythmic degradation. An expansion to a PDE allows us to include a measure for the molecule's age, and thus study oxidative protein damage or polyA-tail shortening.

***Keywords* — Circadian clock, rhythmic degradation, partial differential equation, transcriptome**

MANY behavioral, physiological, and biochemical activities show a circadian rhythm. This means they continue to oscillate under constant conditions with a period of about a day and are entrained to daily environmental cycles. On the cell level the circadian clock, a negative feedback loop in gene transcription and translation, influences several transcription factors [1]. Consequently, in many mammalian tissues 10% of all transcripts, and a possibly even higher percentage of all proteins, display a 24-hour rhythm [2,3].

Recent high throughput studies elucidate the circadian regulation on various levels of gene expression. Oscillating abundances can be found in nascent RNA, mature RNA and protein concentrations. The results have been enigmatic because transcript peak abundances do not always follow the peaks of gene-expression activity in time [4]. We posited that circadian degradation of mRNAs and proteins plays a pivotal role in setting their peak times. To establish guiding principles, we derived a theoretical framework that fully describes the amplitudes and phases of biomolecules with circadian half-lives [5]. We were able to explain the circadian transcriptome and proteome studies with the same unifying theory, including cases in which transcripts or proteins appeared before the onset of increased production rates. Furthermore, we estimate that 30% of the circadian transcripts in mouse liver and *Drosophila* heads are affected by rhythmic posttranscriptional regulation.

In a second approach we expand the view on a molecule's life and include a measure of a molecule's age. We address the question in which cases there is an advantage of rhythmic instead of constant degradation of long-lived proteins when they accumulate oxidative damage. Secondly, in a collaboration with Carla Green we use the same model to analyze sequencing data of poly(A) tails of mRNA in order to identify bottle necks in (rhythmic) mRNA degradation.

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