

Gene network models for circadian entrainment

Katharina Imkeller^{1,2}, Grigory Boryugov¹, and Hanspeter Herzel¹

Short Abstract — Circadian clocks of living organisms entrain to periodical environmental alterations like for example light-dark cycles. Recently a simple amplitude-phase model was used to systematically describe fundamental properties of this entrainment [1]. In the present work we show that the stated hypotheses, as for example the variation of entrainment phase, also apply for biologically more realistic gene network models. This work thus deals with the question of how simple or how complex a biological model can be in order to still provide meaningful results.

Keywords — circadian clock, entrainment, modeling

I. INTRODUCTION

CIRCADIAN rhythms are one of the fundamental properties of life on our planet. They mirror the adaptation to the rotation of the Earth and have evolved to synchronize the organism to periodical alterations of its environment, as for example dark-light cycles.

In mammals every single cell has its own circadian clock, i.e. circadian gene expression regulated by transcription-translation loops. These single clocks synchronize to build up circadian oscillations in organs and tissues. A master clock located in the suprachiasmatic nucleus processes environmental signals and orchestrates all subsidiary peripheral clocks. Nevertheless circadian rhythms are endogenous, which means that they persist even in absence of external time cues, so called Zeitgeber. The entrainment of this endogenous clock to Zeitgeber signals is crucial to understand phenomena like jetlag or human chronotypes, also known as owls and larks.

The dynamical behavior and the molecular mechanisms of circadian oscillations are of high complexity and for their investigation it is therefore obvious to use not only experimental methods but also theoretical approaches designed to study complex nonlinear systems [2]. Numerous theoretical models have been used to describe properties of the circadian clock [3]. Granada, Boryugov et al. [1] previously studied the dependence of entrainment on clock and Zeitgeber properties. For this purpose they used the Poincaré oscillator, a very intuitive amplitude-phase model. Their main result, the “180° rule”, states that the phase of circadian oscillations varies over a range of 180° within the entrainment range.

II. AIM OF THE WORK

In this study, we extend these observations to biologically more realistic gene network models using numerical simulations. Two models of different complexity are being considered to this purpose. The first one is composed by

three ordinary differential equations (ODE) and mimics a single transcription-translation feedback loop [4]. The second model is composed by nineteen ODEs and includes multiple feedback loops [5].

III. RESULTS

Figure 1 shows a typical graphical output of our simulations: the Arnold tongue indicates the phase differences between Zeitgeber and clock for different Zeitgeber periods and amplitudes. Entrainment of the clock to the Zeitgeber is only reached within the tongue. The “180° rule” holds true for weak Zeitgeber strengths in a biologically meaningful entrainment range of around ± 2 hours. We also computed phase response curves showing the phase shift of the model in response to different Zeitgeber pulses. The results were comparable to those obtained in experimental studies [6].

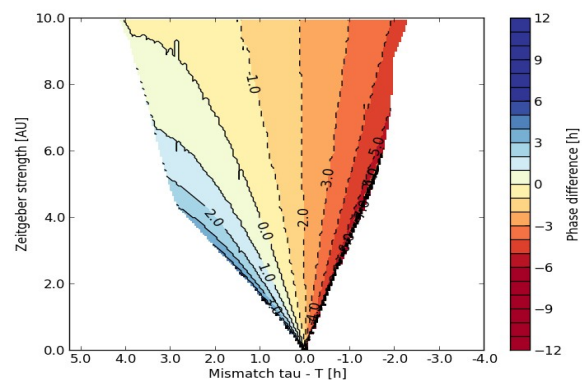


Fig. 1: Entrainment phase of 3 ODE model

IV. CONCLUSION

Generally seen, the gene network models studied in this work reflect the results previously seen with simpler models as well as experimental observations. The work provides good evidence that for fundamental properties of entrainment very simple models are sufficient to give meaningful results.

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¹ Institute for Theoretical Biology, Humboldt University, Berlin

² Master Program in Molecular Medicine, Charité Universitätsmedizin Berlin, Germany, E-mail: katharina.imkeller@charite.de