Modeling temperature entrainment in *Neurospora crassa*

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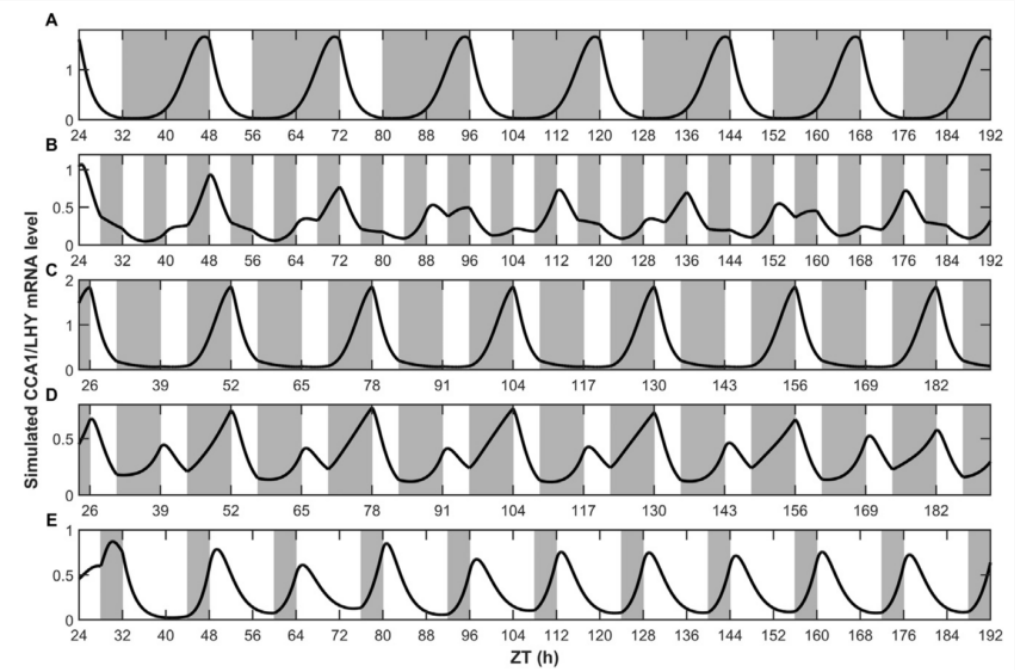
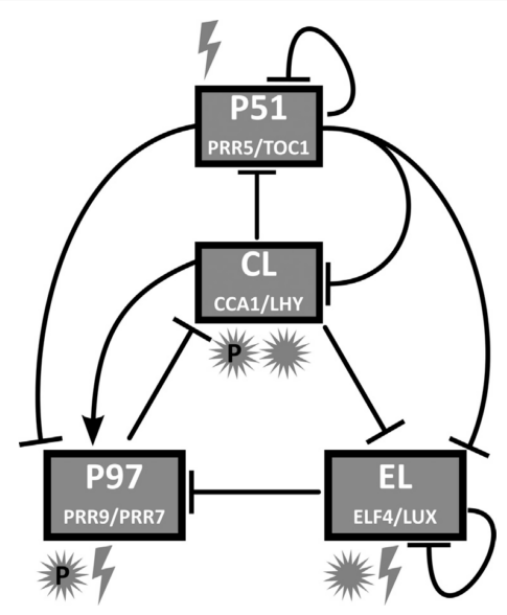
Table of contents

Introduction

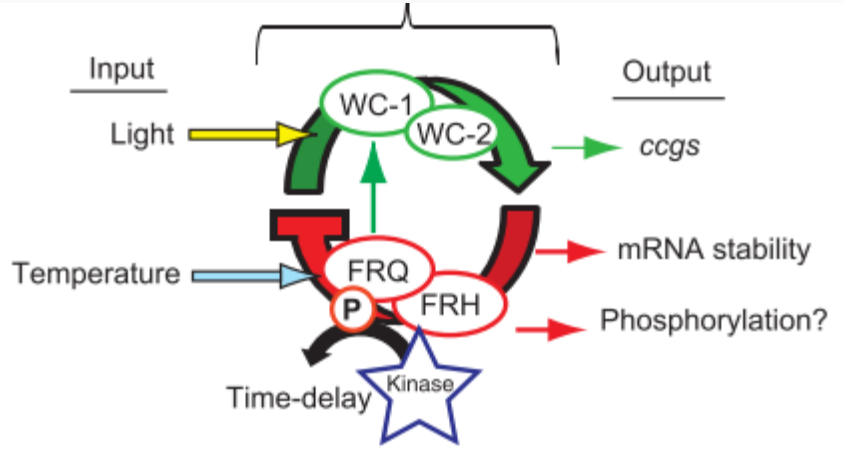
Photoperiodic entrainment in *Arabidopsis*





Caluwe et al. (2017)

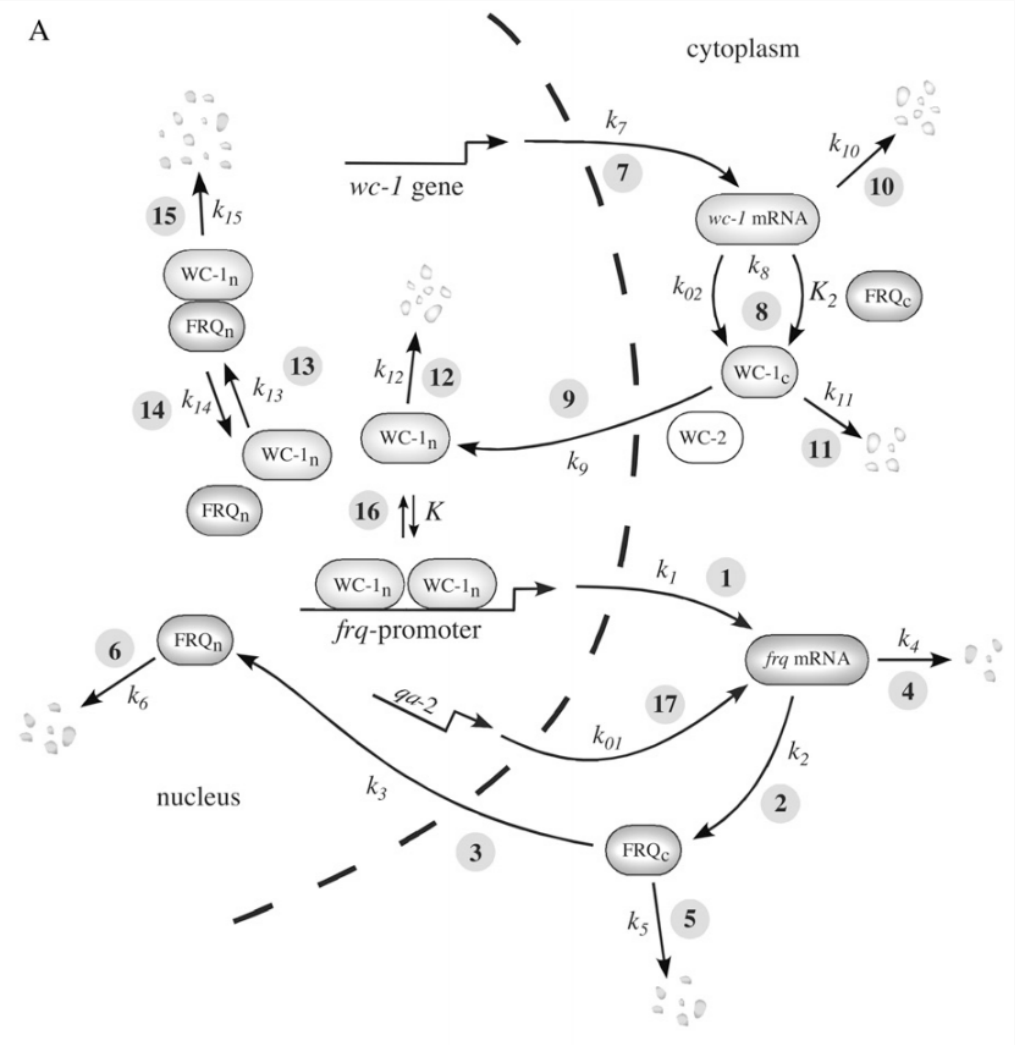
The circadian clock of *N. crassa*



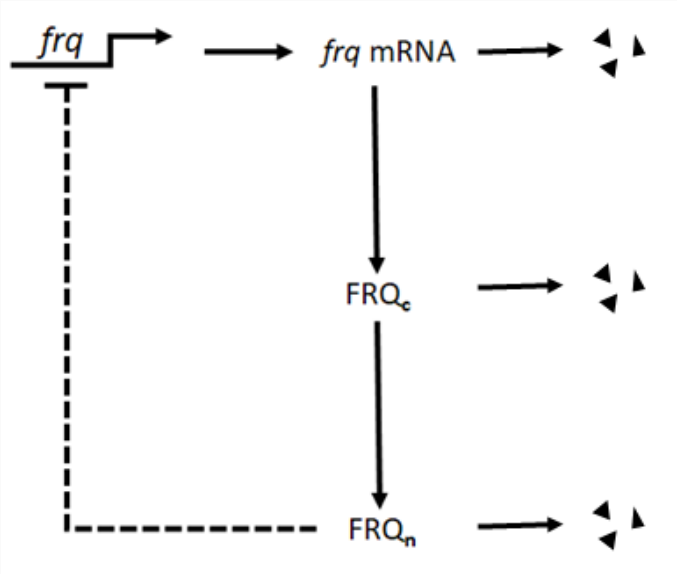
(Baker et al., 2012)

- How does temperature affect entrainment?
- We have a model (Hong et al., 2008)
- We have temperature entrainment data (C. Jyuthi, 2008)

The Hong model



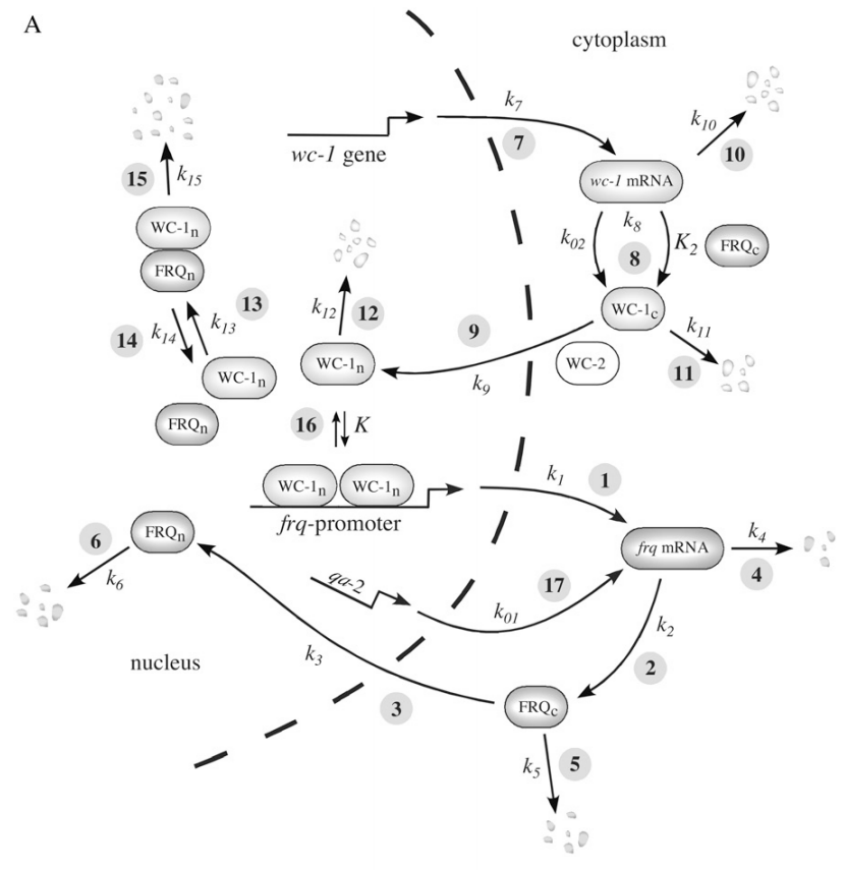
(Hong et al., 2008)



Goodwin oscillator

Hong model is an extended goodwin oscillator with an additional positive feedback loop

Hong model is described as a system of 7 ODEs



$$\frac{d[frq\,\mathrm{mRNA}]}{dt} = k_1 \frac{[\mathrm{WC\text{-}1_n}]^2}{K + [\mathrm{WC\text{-}1_n}]^2} - k_4[frq\,\mathrm{mRNA}] + k_{01} \tag{1a}$$

$$\frac{d[FRQ_c]}{dt} = k_2[frq\,\mathrm{mRNA}] - (k_3 + k_5)[FRQ_c] \tag{1b}$$

$$\frac{d[FRQ_n]}{dt} = k_3[FRQ_c] + k_{14}[FRQ_n : \mathrm{WC\text{-}1_n}] - [FRQ_n](k_6 + k_{13}[\mathrm{WC\text{-}1_n}]) \tag{1c}$$

$$\frac{d[wc\text{-}1\,\mathrm{mRNA}]}{dt} = k_7 - k_{10}[wc\text{-}1\,\mathrm{mRNA}] \tag{1d}$$

$$\frac{d[\mathrm{WC\text{-}1_c}]}{dt} = \frac{k_8[FRQ_c][wc\text{-}1\,\mathrm{mRNA}]}{K_2 + [FRQ_c]} - (k_9 + k_{11})[\mathrm{WC\text{-}1_c}] + k_{02}[wc\text{-}1\,\mathrm{mRNA}] \tag{1e}$$

$$\frac{d[\mathrm{WC\text{-}1_n}]}{dt} = k_9[\mathrm{WC\text{-}1_c}] - [\mathrm{WC\text{-}1_n}](k_{12} + k_{13}[FRQ_n]) + k_{14}[FRQ_n : \mathrm{WC\text{-}1_n}] \tag{1f}$$

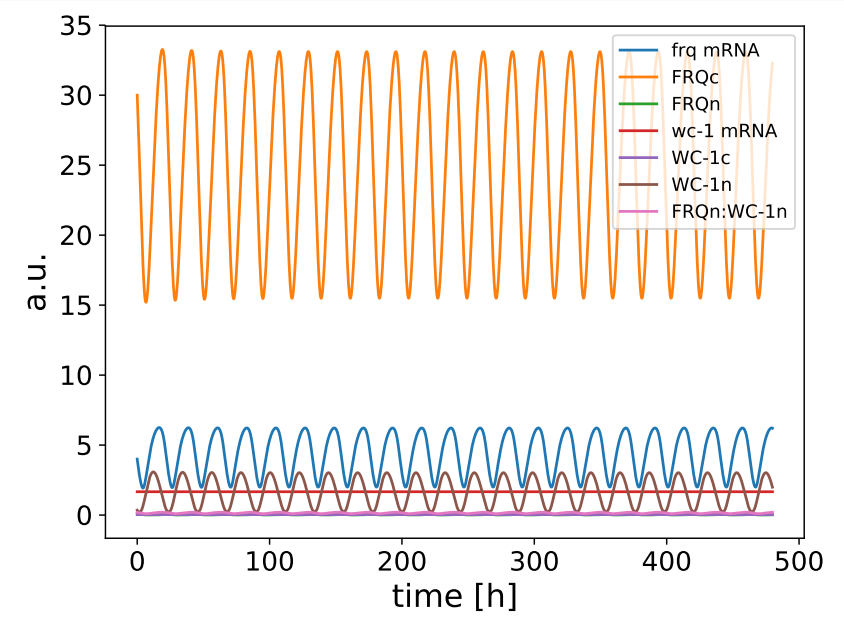
$$\frac{d[FRQ_n : \mathrm{WC\text{-}1_n}]}{dt} = k_{13}[FRQ_n][\mathrm{WC\text{-}1_n}] - (k_{14} + k_{15})[FRQ_n : \mathrm{WC\text{-}1_n}]. \tag{1g}$$

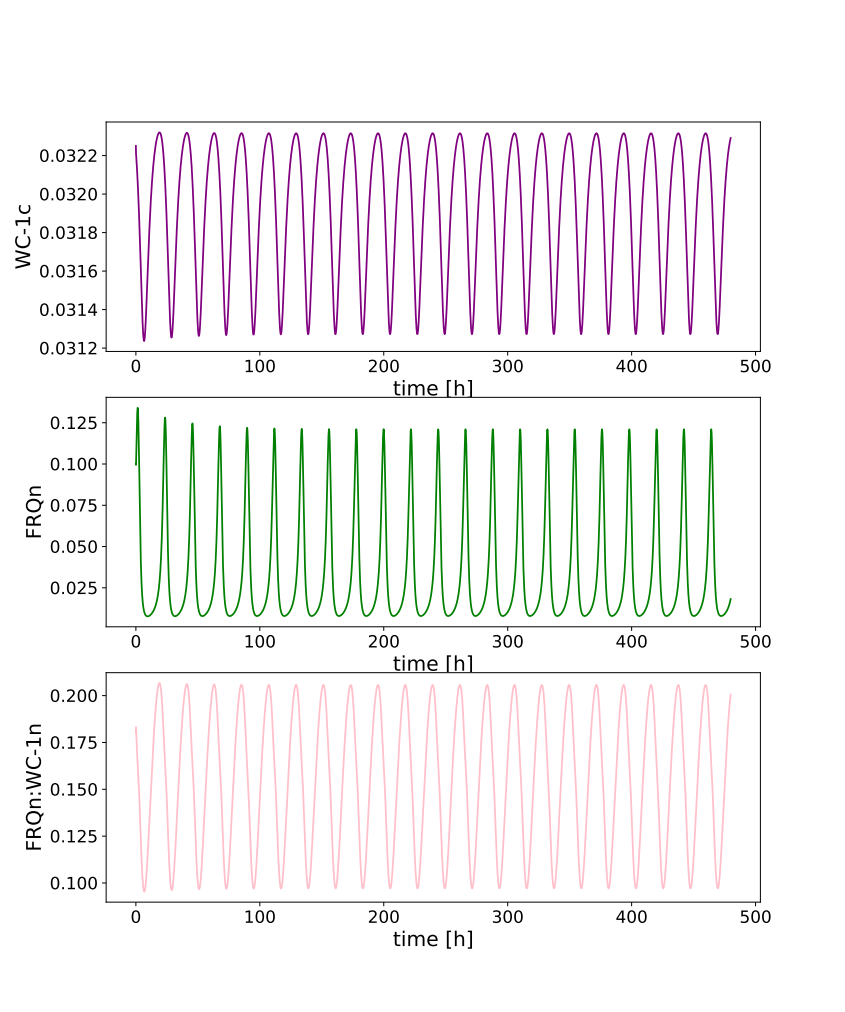
Aims

- Analyze Connies temperature entrainment data and compare with Hong model
- Step I: understand Hong model (bifurcations etc.)
- Step II: extend model to simulate temperature entrainment
- Step III: Compare model with Data

Model analysis

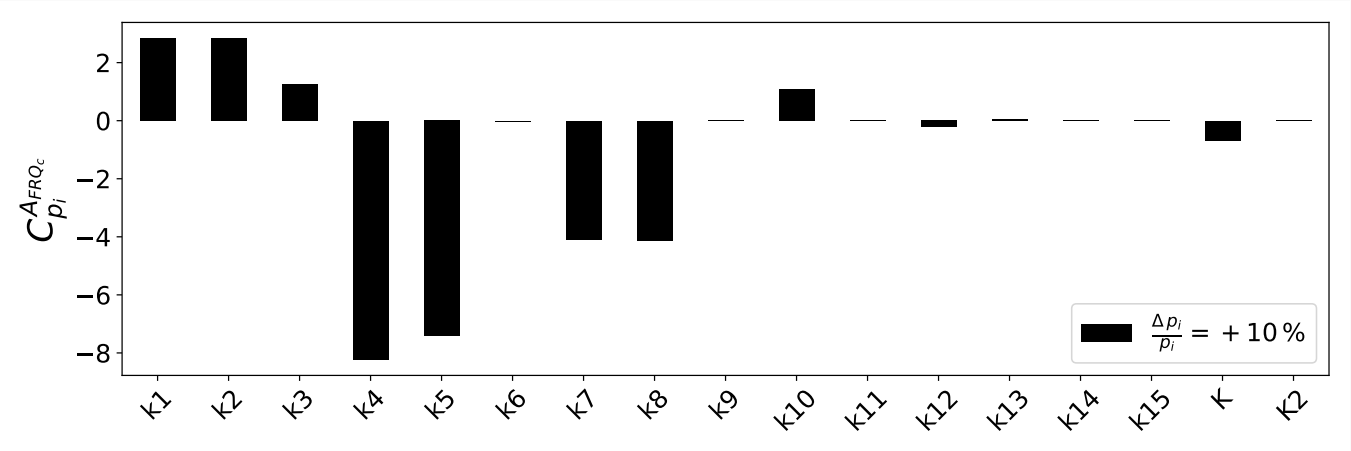
Model output

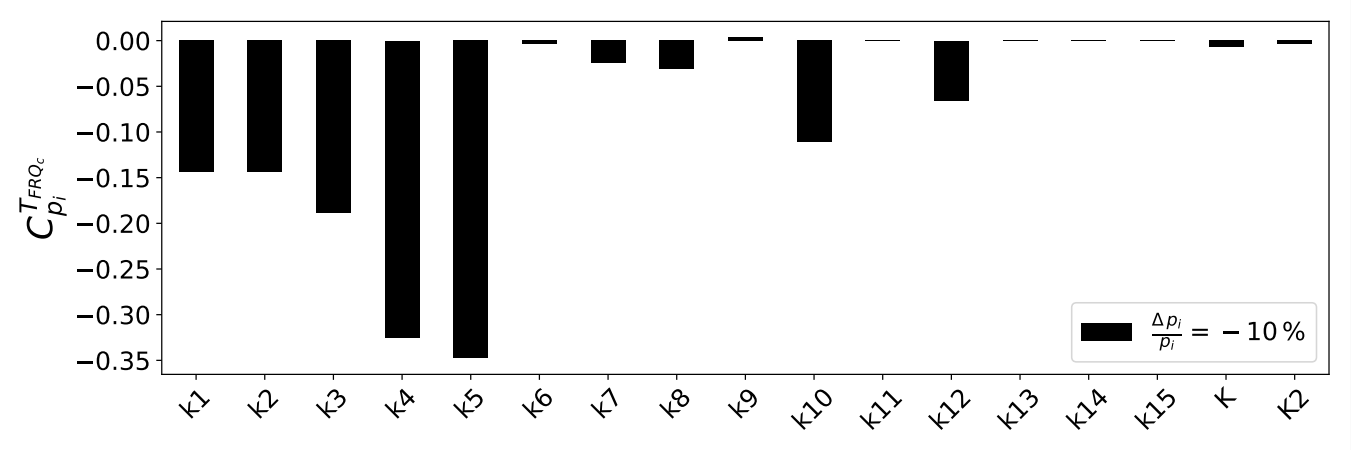




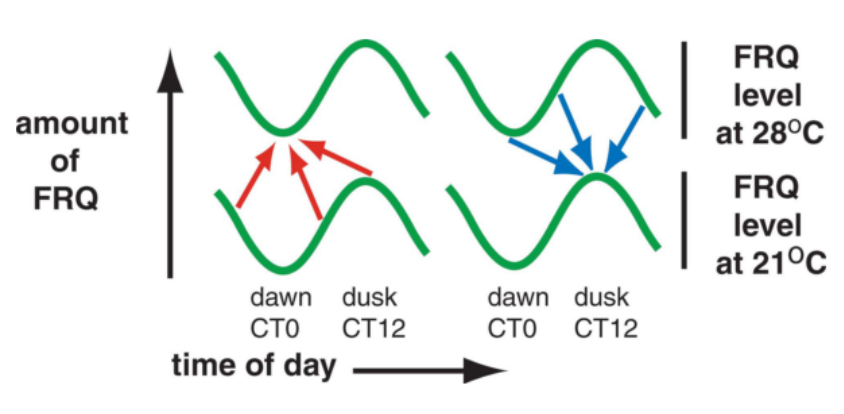
- model from publication can be reproduced
- model matches experimental observations

Sensitivity analysis



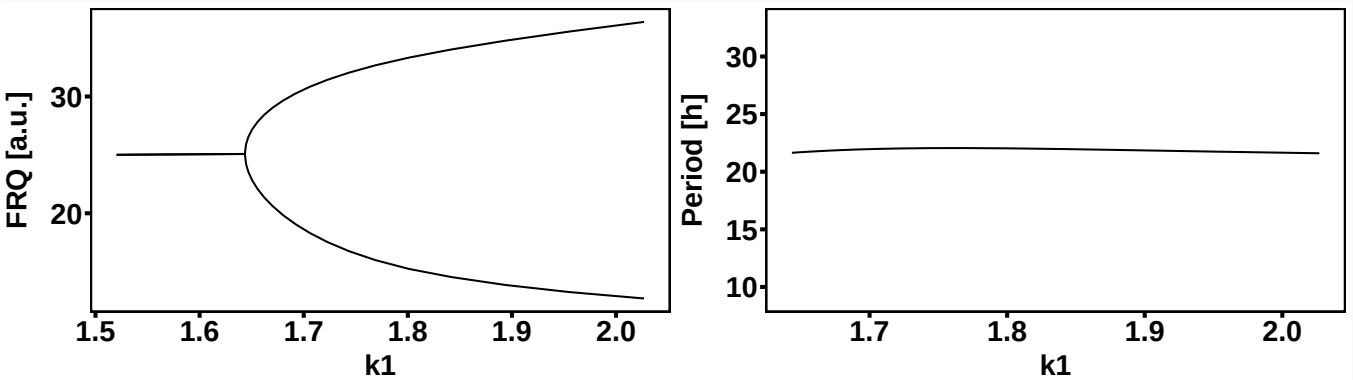


Effect of temperature on the *Neurospora* clock



(Dunlap and Loros, 2017)

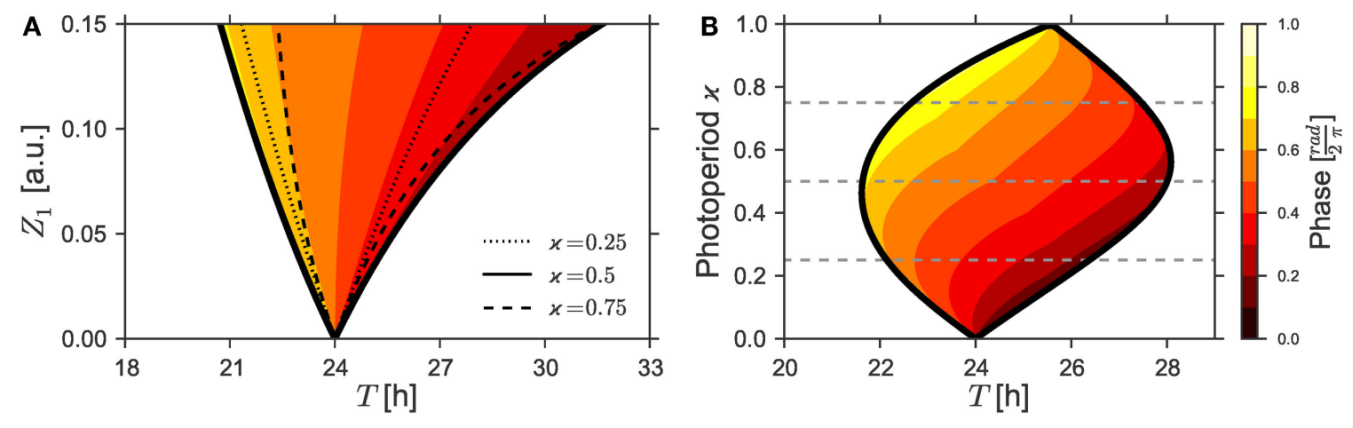
- Temperature might entrain the clock either by alternative frq mRNA splicing or by modulating FRQ magnitude



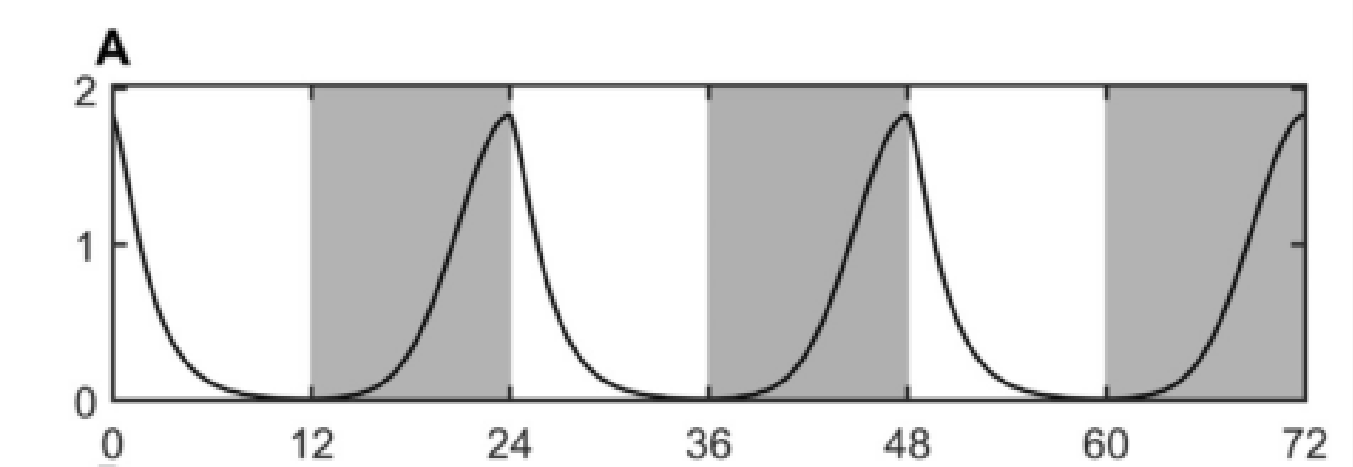
k1: (frq transcription rate) chosen as candidate paramter

Entrainment

Entrainment



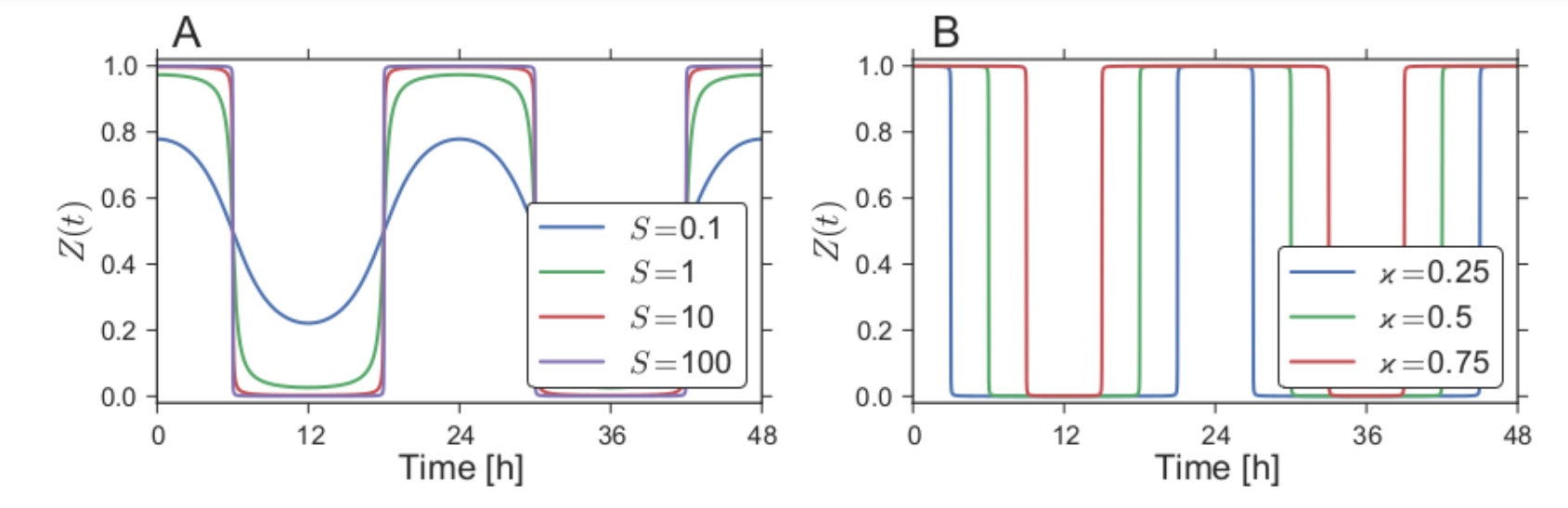
Schmal et al. (2015)



Caluwe et al. (2017)

Simulation of 1:1 entrainment in the plant circadian clock

Implementing a zeitgeber function in the model



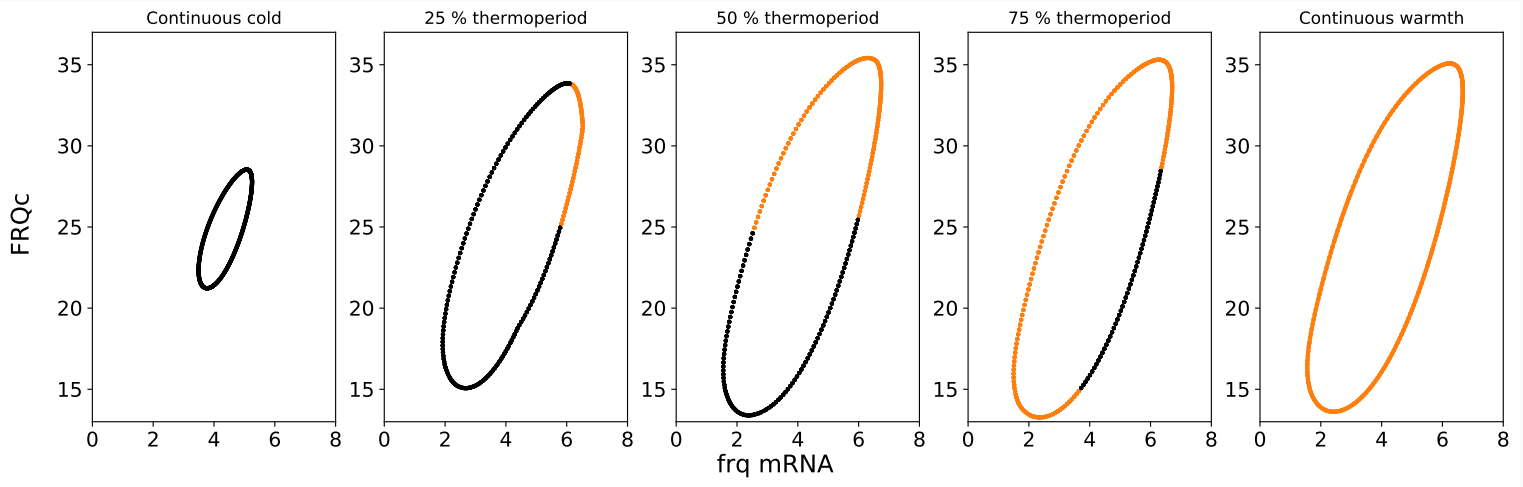
Schmal et al. (2015)

Modulate frq mRNA degradation rate $k_1 \cdot Z(t)$:

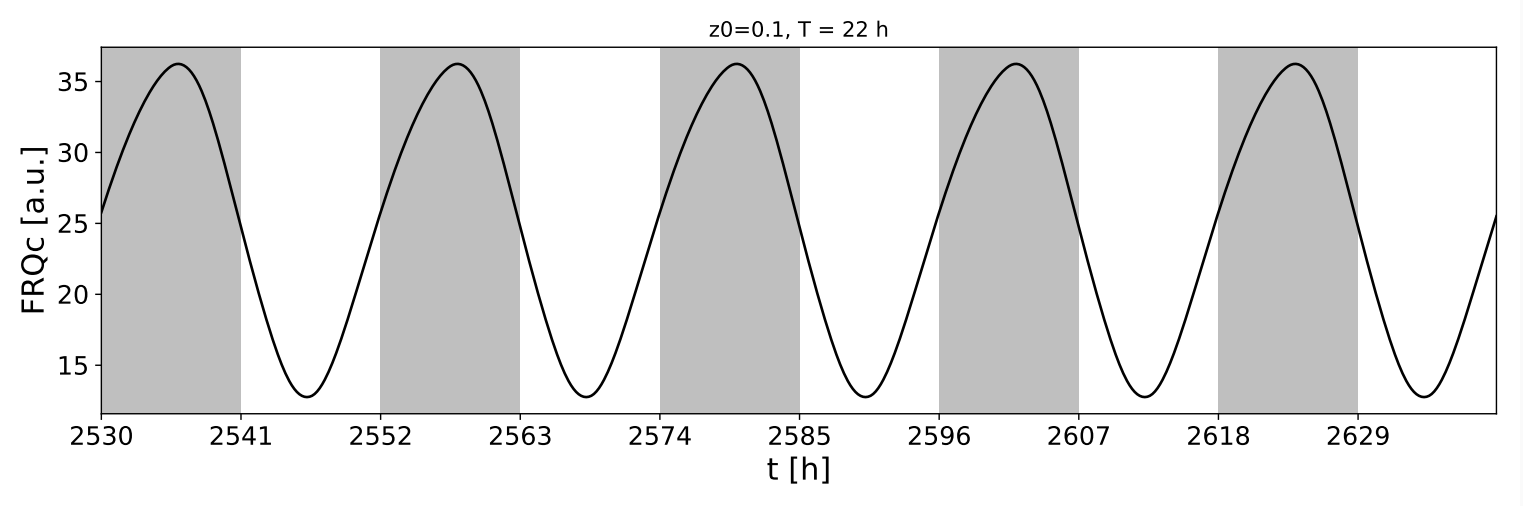
$$\frac{d[frqmRNA]}{dt} = Z(t) \cdot k_1 \frac{[WC-1_n]^2}{K+[WC-1_n]^2} - k_4[frqmRNA]$$

Implementing a zeitgeber function in the model leads to entrainment

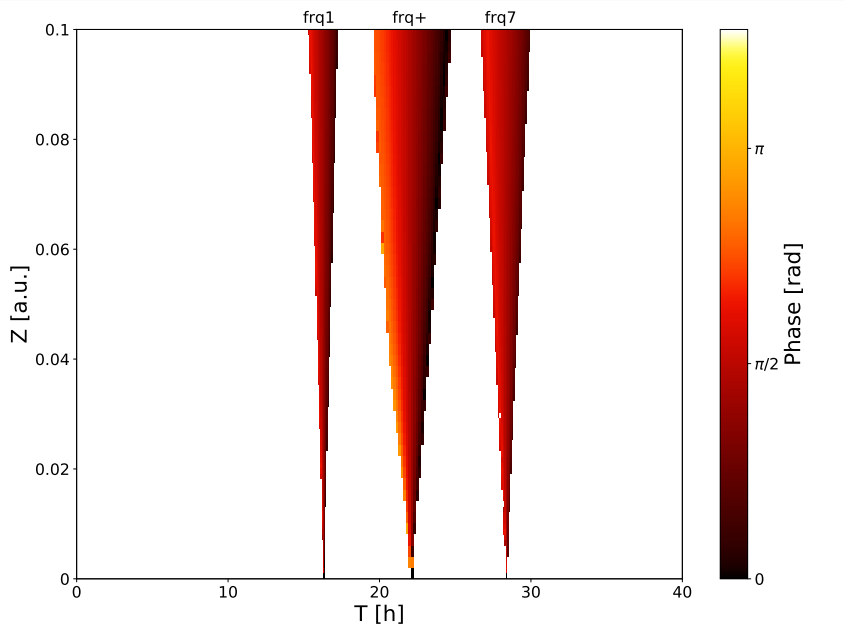
Evolution of the limit cycle with varying thermoperiod

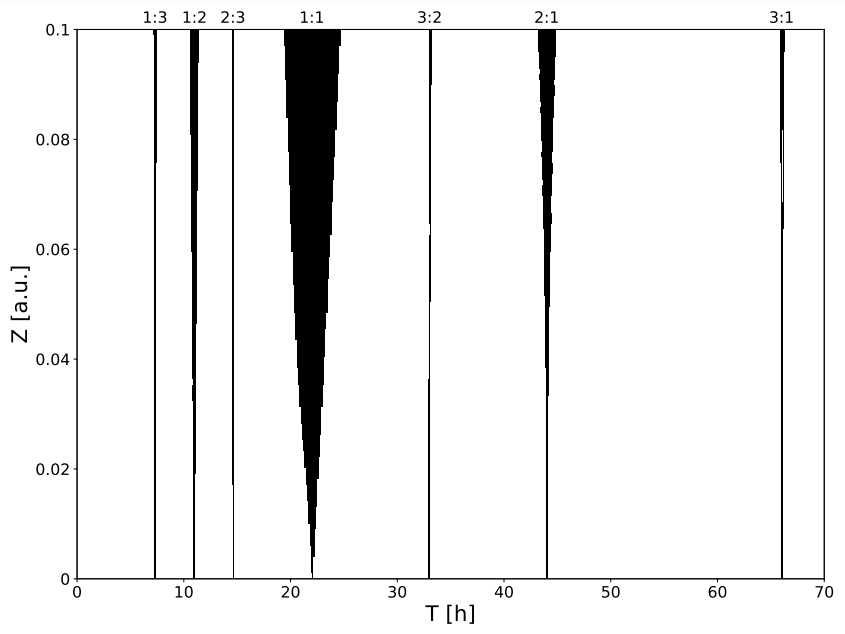


1:1 entrainment for constant zeitgeber strength

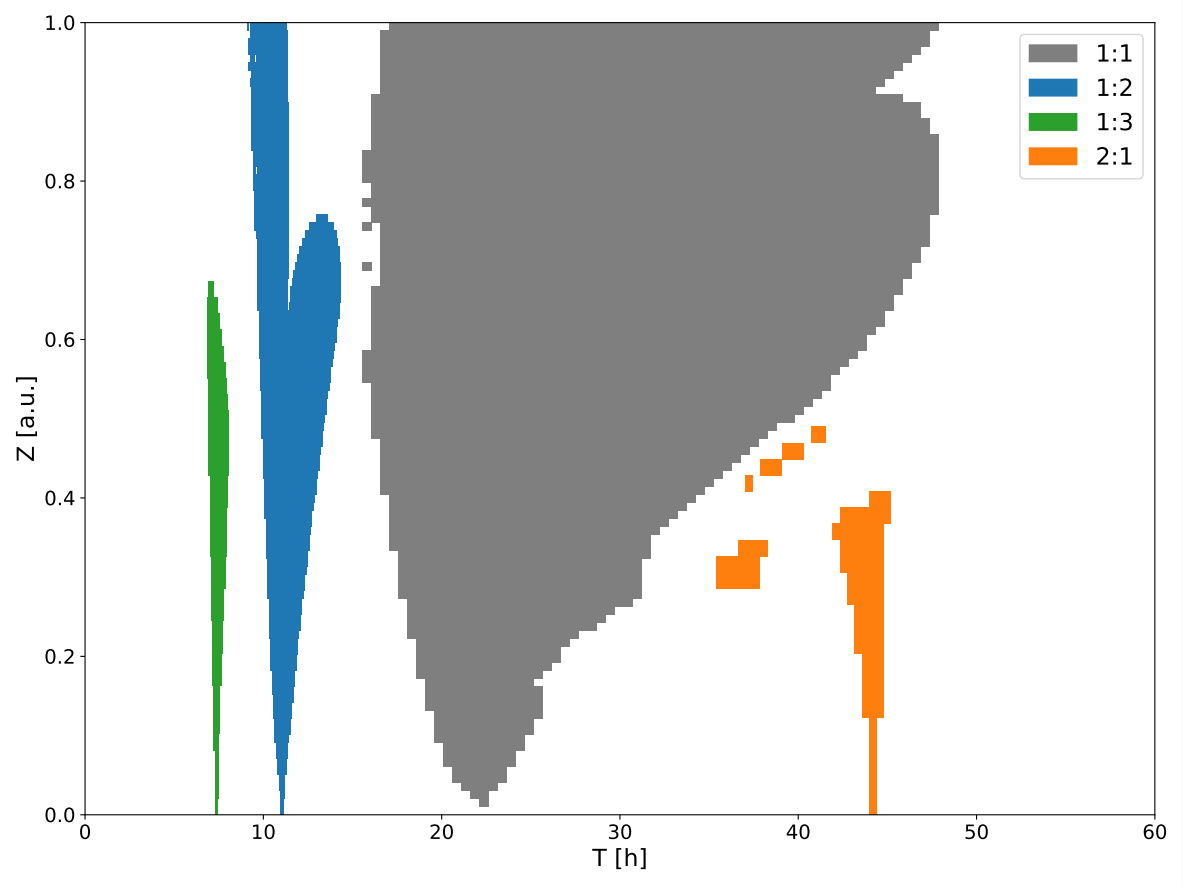


Entrainment in the Hong model



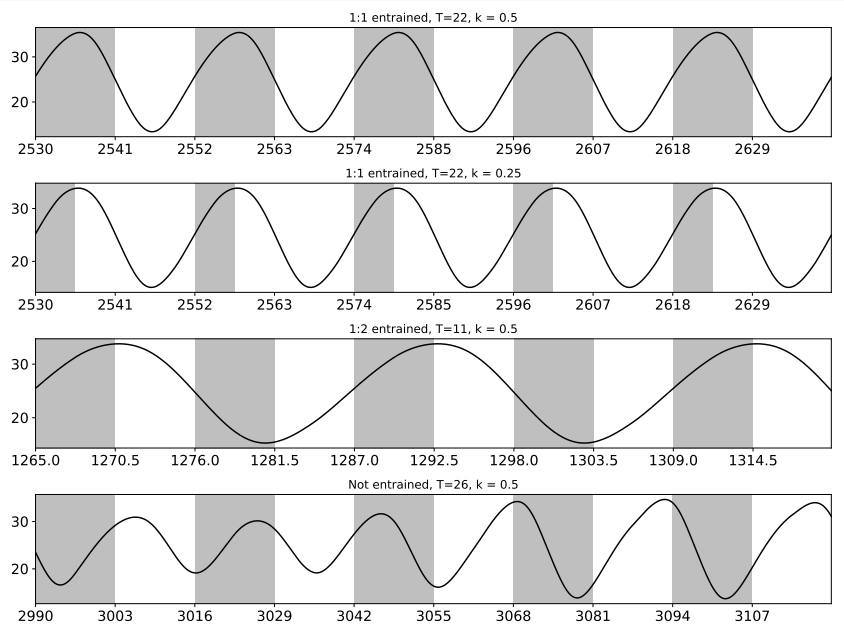


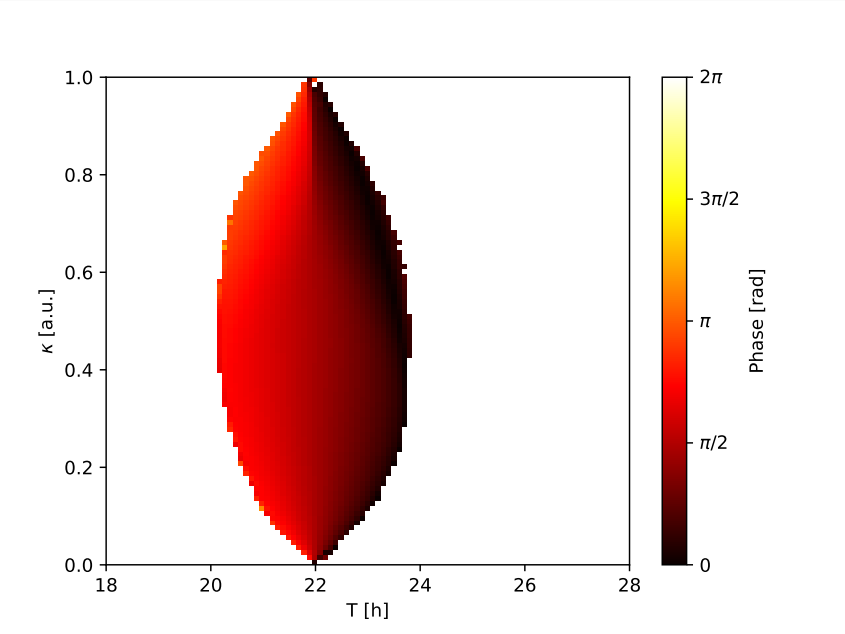
Arnold tongue structure is not so clear for stronger zeitgebers



- Next step: Understand bifurcation structure and 2:1 tongue

The extended Hong model has multiple entrainment regions

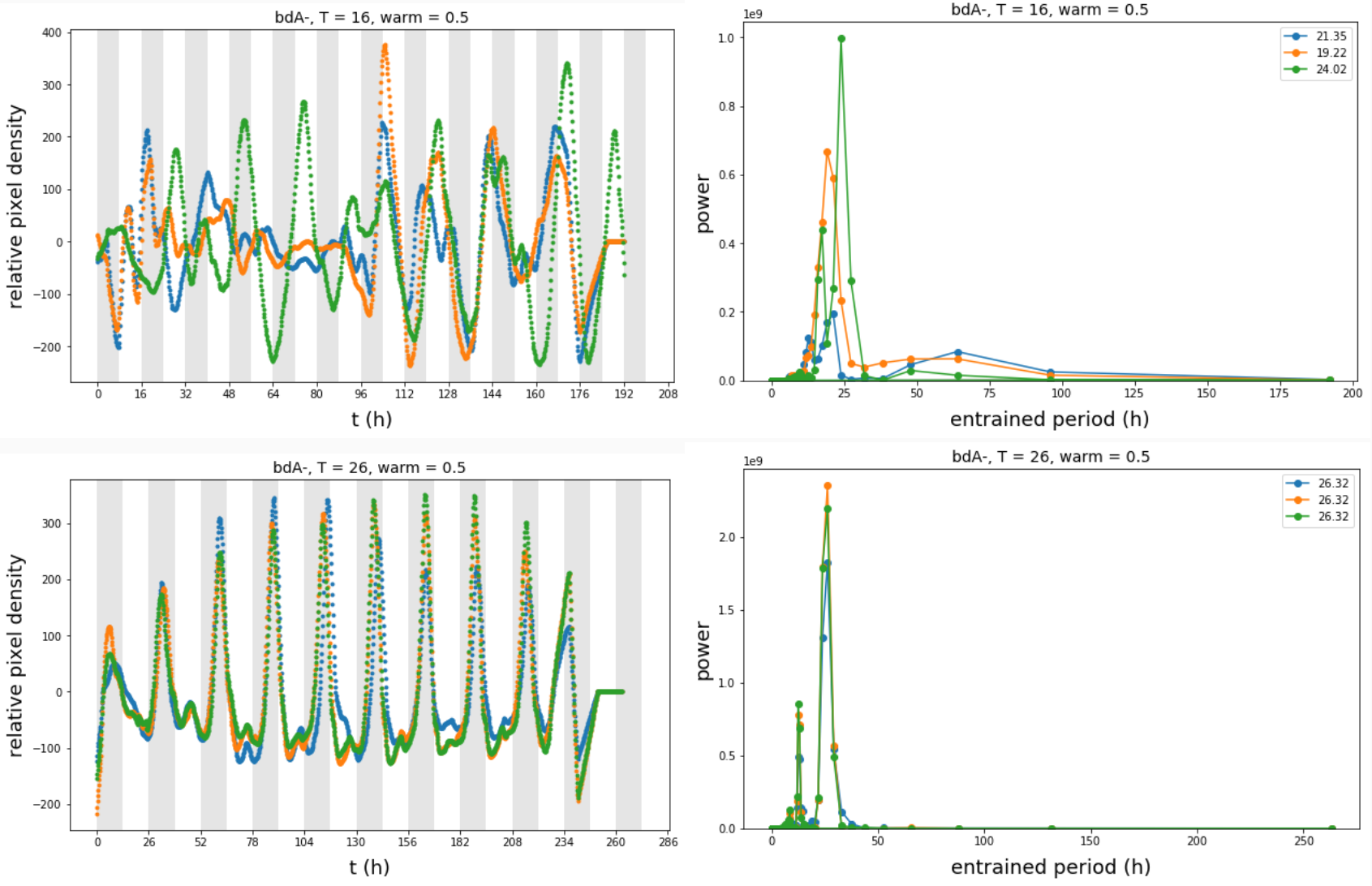




Next steps: compare simulations with data (and simulate onions for different strains and for other entrainment rations)

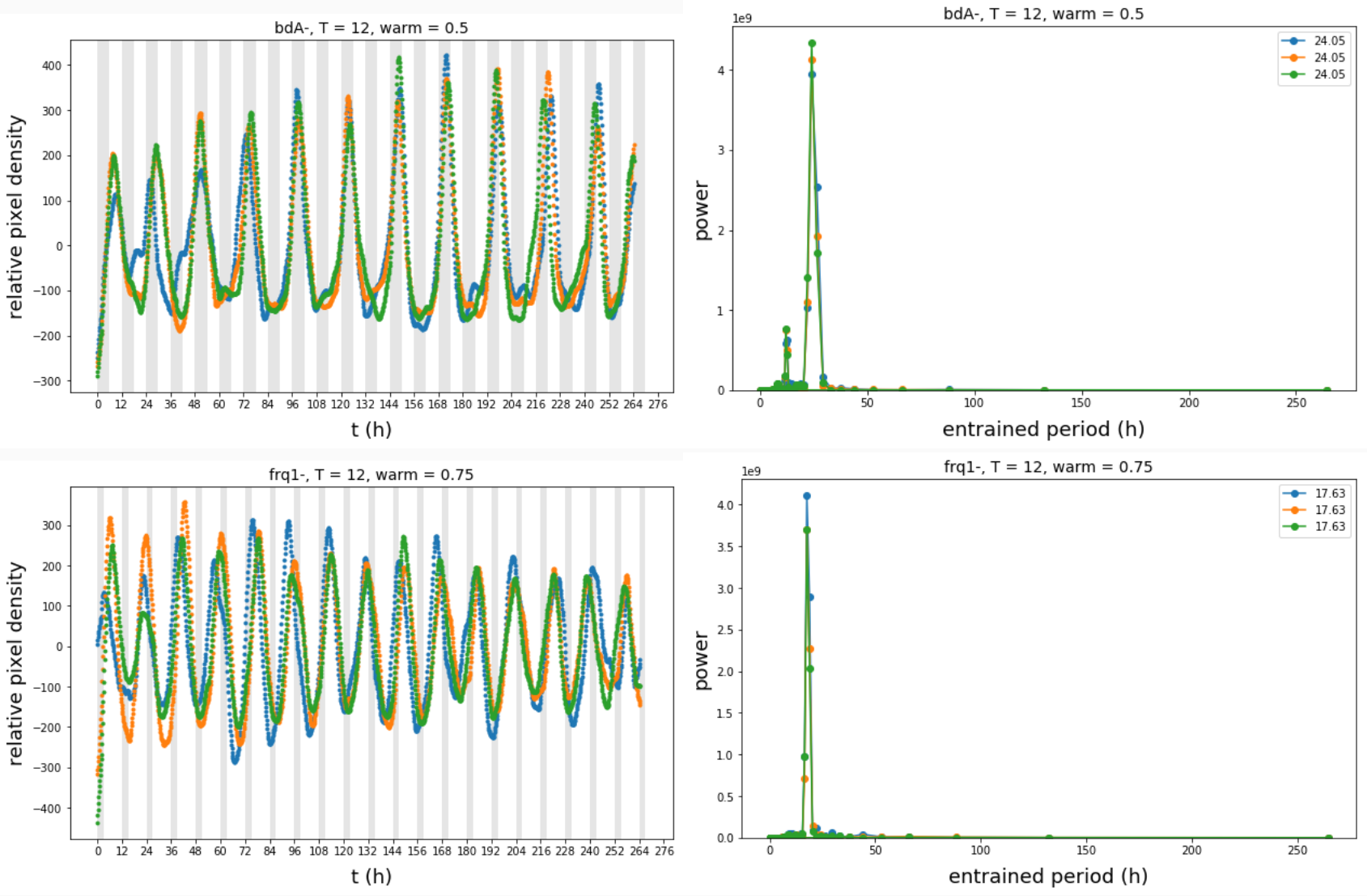
Data analysis

Neurospora entrains to some Zeitgeber periods and thermoperiods



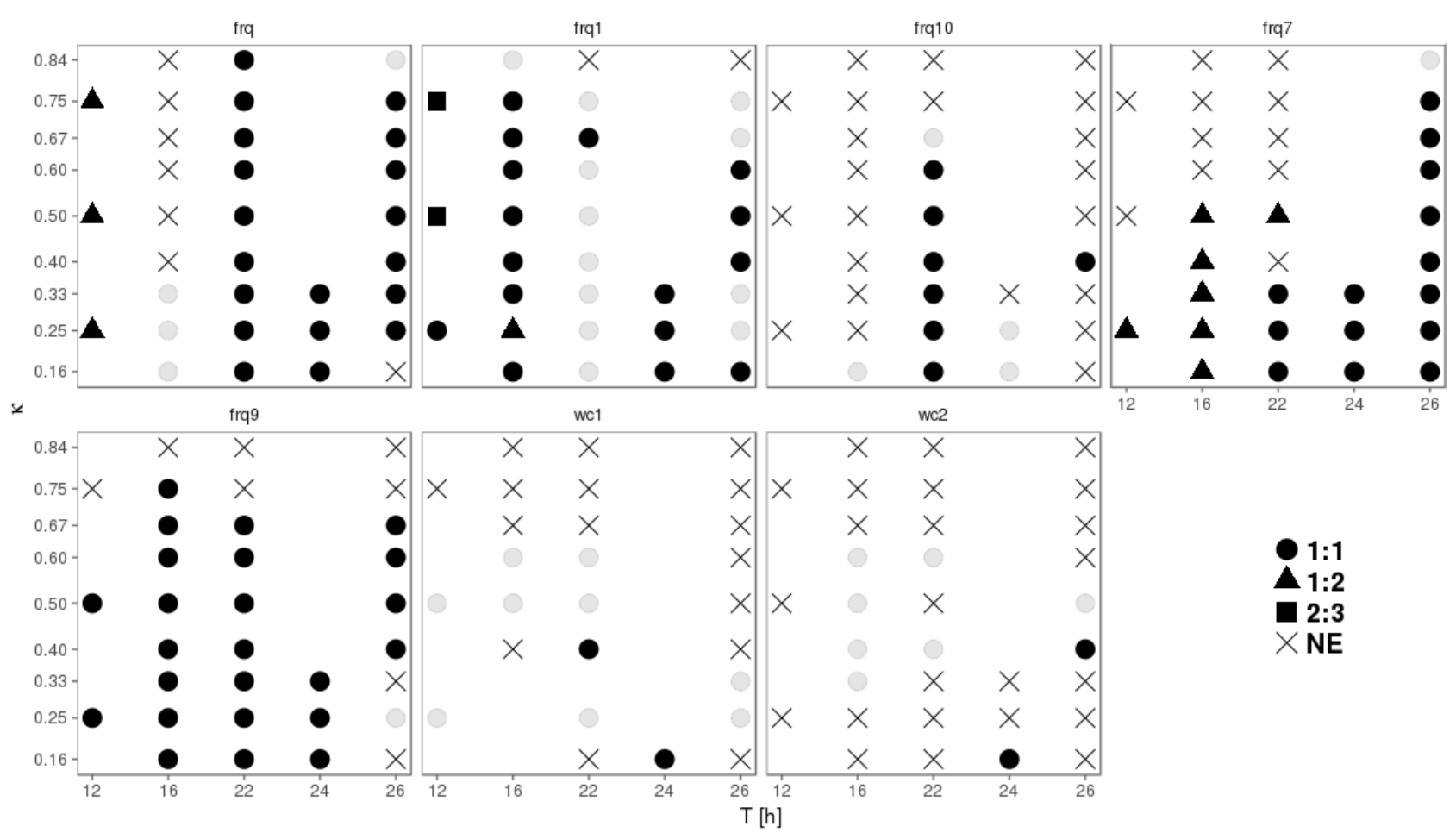
Thanks to Saskia Grabe

Neurospora also shows 1:2 and 2:3 entrainment



Thanks to Saskia Grabe

Data overview



κ: Thermoperiod

T: Period Zeitgeber

Summary

- The Hong model is reproducible and matches most experimental observations
- Entrainment in the model can be implemented by adding a Zeitgeber function
- Rythmic Neurospora strains entrain to varying Zeitgeber periods and thermoperiods
- Neurospora strains show 1:1, 1:2, 2:3 and no entrainment

To-Do List

- Improve understanding of arnold tongue structure and bifurcations
- Compare data with arnold onion simulations

References

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...Thanks!

Questions...?

(De Caluwe et al., 2017) (Jyuthi, 2008)