Lab Course: Modelling and Simulation (SS-2016, LSI) 5th -15th September 2016

Task 1: A simple model to explain the growth of organism is the exponential model given by dN/dt = rN where N(t) is the population at time t and r > 0 is the growth rate. But exponential growth is unrealistic. Therefore, to incorporate the ideas of overcrowding and limited resources, in the exponential growth model logistic equation is used. The following one-dimensional model is such a logistic equation:

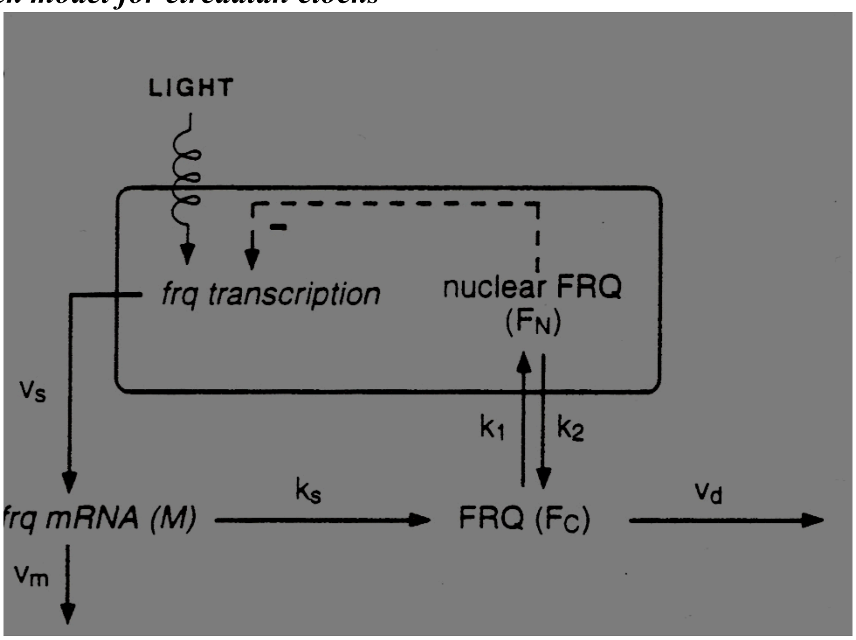
$$dN/dt = rN(1-N/K)$$

where N(t) is the population at time t , r > 0 is the growth rate and K is the carrying capacity.

i) Solve the above equation analytically and plot the result in a time series manner.
ii) Simulate it using numerical tools and compare the plots (try different solvers and step sizes)

Task 2:

Genetic feedback model for circadian clocks



We consider a ***3-dimensional Goldbeter model*** for expression and regulation of the *Neurospora* "frequency protein" (FRQ). For the concentrations of the mRNA ($\boldsymbol{M}$), the "frequency protein" ($\boldsymbol{F_C}$) synthesized in the **cytoplasm** and the successively built up protein concentration ($\boldsymbol{F_N}$) in the **nucleus**, we obtain the following ***system of three differential equations***:

$$dM/dt = V_s \frac{K^n}{K^n + F_N{}^n} - V_m \frac{M}{K_m + M}$$

$$dF_C/dt = k_s M - V_d \frac{F_C}{K_d + F_C} - k_{in} F_C + k_{out} F_N$$

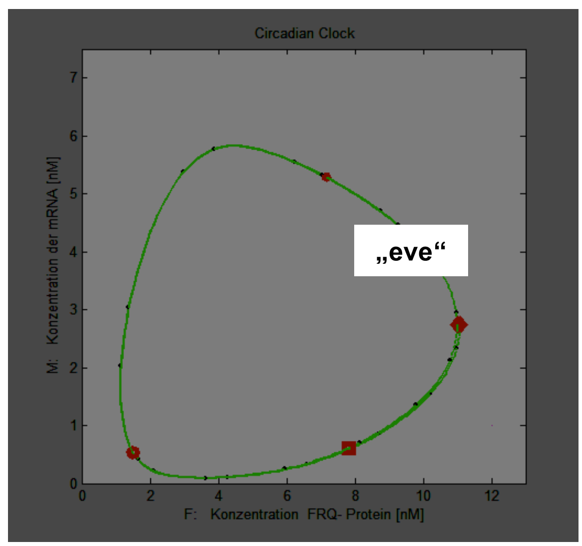
$$dF_N/dt = k_{in} F_C - k_{out} F_N$$

(1) Simulate this ***3-dim Goldbeter model*** with suitable parameters, whereby you should start with the following parameter set and try to alter it in order to obtain the experimentally observed intrinsic period ***P = 21.5 h (see below)***!

$$V_s = 1.5 \Leftrightarrow 2.0 \quad \textit{during dark or light, respectively} \quad [nM \cdot h^{-1}]$$
$$V_m = 1.5 \quad [nM \cdot h^{-1}], \quad V_d = 1.0 \quad [nM \cdot h^{-1}], \quad k_s = 0.5 \quad [h^{-1}]$$
$$K = 0.2 \quad [nM], \quad K_m = 0.15 \quad [nM], \quad K_d = 0.15 \quad [nM]$$
$$k_{in} = 0.02 \quad [h^{-1}], \quad k_{out} = 0.1 \quad [h^{-1}]$$
$$n = 4: \quad \textit{Hill number}$$

(a) Investigate the intrinsic “circadian clock” for different **transport rates k_{in}** and estimate the resulting **Period** in the time plot for M(t) and F(t). Which parameters produce a ***Period ≈ 21.5 h***, the value for *Neurospora* in constant darkness?

(b) During the ‘time loop’ determine a list of *time points* **T_eve**, where the cytoskeletal protein level **F(t)** is **maximal.** By the mean difference **mean(diff(T_eve))**compute the **Period** of the “clock”.



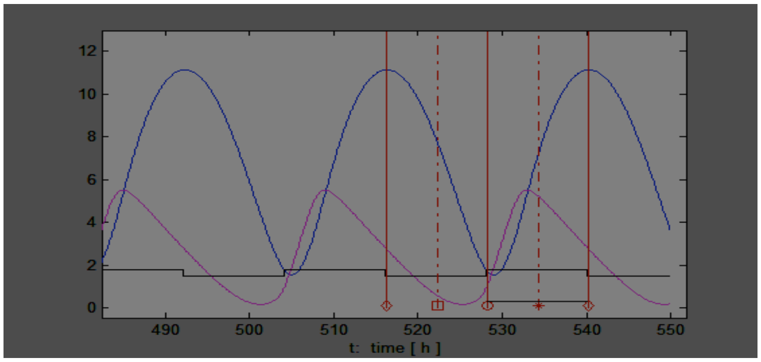
(c) Moreover, in the *state diagram* as well as in the time diagram, try to mark the “quarter phases”, when the intrinsic clock attains its “evening” (T_eve), “midnight”, “morning” and “noon”.

Task 3:

(2) Perform simulations to show, under which conditions a **12-12 h light-dark stimulus** is able to entrain the intrinsic *Neurospora* clock.

Take **Step = 0.5** for the **increase of transcription rate** altering the mRMA production speed **Vs** from **Vs0 = 1.5** (during 12 h darkness) to **Vs1 = Vs0 + Step** (during the following 12 h light).

- In the *time diagram* the stimulus level **Vs** is plotted as a stair function



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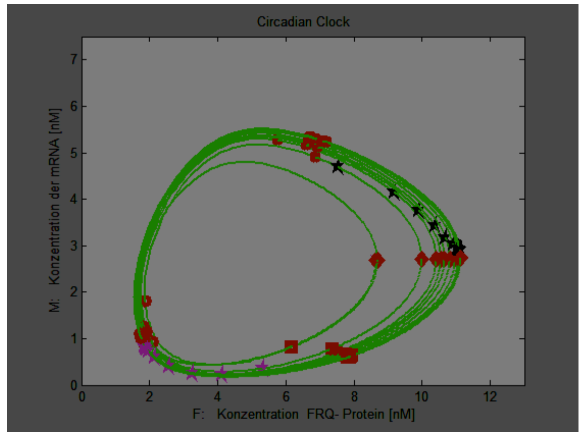
- In the *state diagram* mark the points of ***light switch on*** and***switch off (!)*** stimuli.



Will the intrinsic clock be entrained by the 24h cycle?

What is the ***minimal step increase*** in transcription rate (**Step**) that induces entrainment of the intrinsic *Neurospora* clock by the 12-12 h light-dark stimulus?

How does the outcome depend on the "phase" of first ***light switch off*** stimulus relative to the intrinsic clock cycle?

Task 4:

Perform simulations to show, under which conditions a **18-6 h light-dark stimulus** is able to entrain the intrinsic *Neurospora* clock. Modify the simulations of task 2 using 8 h of darkness and 16 h of light.

Good luck :)