TECHNISCHE UNIVERSITÄT DARMSTADT

Bachelor or Master Thesis: Channel Capacity of Amplitude- vs Frequency-modulated regulation

Cells transmit information by adapting their protein synthesis to the concentration of signalling molecules. In [1] it was investigated, how the transcription factor Crz1 in yeast cells regulates protein synthesis (Fig. 1a). Experimentally, the regulation was found to be frequency-modulated, while in principal also amplitude-modulated regulation is possible. The cell is assumed to aim at coordinating the simultaneous synthesis of proteins precisely. Particularly, the relative abundance of proteins should be robust at different Crz1 levels. In **amplitude-modulated regulation** (Fig. 1c), the following phenomenon occurs: At a weak concentration level of Crz1 the abundance of Prot A is higher than Prot B, whereas at a strong concentration level it is lower. This difference in relative abundance results from the functional response of both proteins to the Crz1 concentration levels (Fig. 1b). Let us now look at **frequency-modulated regulation** (Fig. 1d) which, in contrast, corrects this shortcome: the mean concentration level of Crz1 is now tuned by less frequent or more frequent bursts, rather than constantly low or high Crz1 concentration levels. (Yeast cells achieve this tuning by Calcium molecules.) On average the Crz1 concentration is the same as in the amplitude-modulated regulation. But note, that the abundances of Prot A and Prot B are proportionally the same in both the weak and the strong stages of Crz1. The regulation is thus more robust with respect to different Crz1 levels.

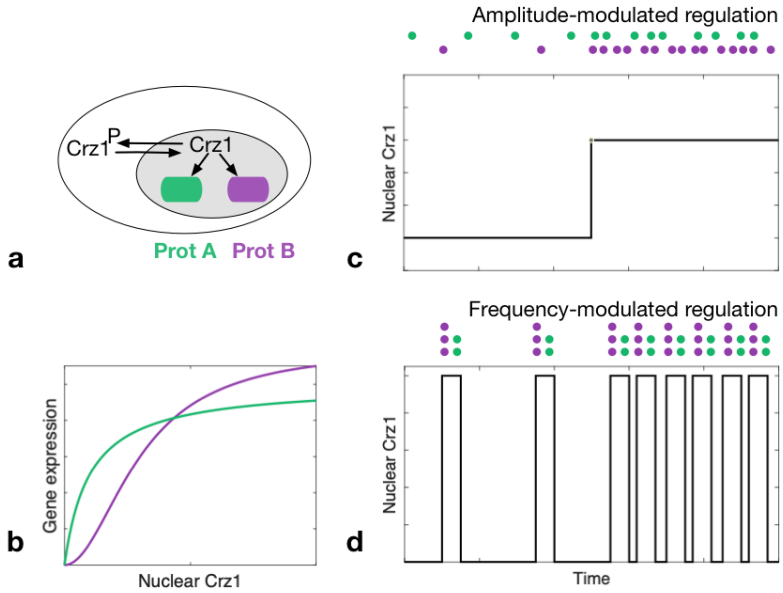

Figure 1. mimicking Figure 2 in [1] **a.** In yeast cells the transcription factor Crz1 enters the nucleus in its dephosphorylated form, where it enhances the synthesis of proteins, symbolically respresented by Prot A and Prot B. **b.** Functional response of Prot A and Prot B to different Crz1 concentration levels. **c.** Amplitude-modulated regulation **d.** Frequency-modulated regulation

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The reaction schemes of both regulations are abstracted in figure 2. The amplitude-strategy, on the one hand, stochastically switches between a weak and strong rate, that modulates protein synthesis bursts. This is known as a random telegraph model modulating a Poisson channel [2]. The frequency-strategy, on the other hand, switches between 1 (ON) and 0 (OFF), but the affinity of switching to the ON state stochastically alters between a weak and a strong affinity, resulting in periods of less and periods of more frequent bursts.

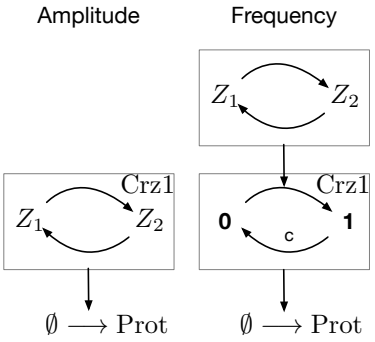

Figure 2. Abtract reaction schemes for the amplitude- and the frequency-strategy.

The mutual information between time-spanning signals provides a mathematical tool to assess the precision of signalling channels [3, 4]. On the one hand, a more robust regulation suggests that the information transmitted by the frequency-modulated channel is higher. Adding an additional layer of stochasticity, on the other hand, suggests that the mutual information is lower for the frequency-modulated channel. The goal of this project is to shed light on the difference between both channels from an information theoretic point of view.

Covered topics

- Filtering theory for point processes
- Finite state continuous time Markov chains, i.e. the random telegraph model
- Information theory for time-spanning signals
- Stochastic simulation algorithm for chemical reaction networks

Your advantages

- You will work on a clearly defined research question.
- You will enter an interdisciplinary group with expertise in stochastic processes, Bayesian parameter estimation, optimization, variational inference, single-cell measurements.
- Individual supervision with weekly meetings.

Expectations

- Affinity for applied mathematics, especially probability theory
- Literature research
- Programming simulation algorithms with Matlab or Python, etc.

For further information, please contact Mark Sinzger.

References

[1] Avigdor Eldar and Michael B Elowitz. Functional roles for noise in genetic circuits. *Nature*, 467(7312):167, 2010.

[2] Donald L Snyder and Michael I Miller. *Random point processes in time and space*. Springer-Verlag New York, 1991.

[3] Lorenzo Duso and Christoph Zechner. Path mutual information for a class of biochemical reaction networks, 2019.

[4] Robert S Liptser and Albert N Shiryaev. *Statistics of Random Processes II: II. Applications, vol. 2*, volume 737. 2001.