Information Processing in Post-Transcriptional Networks

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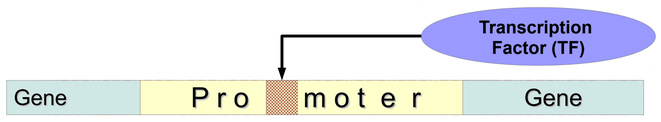
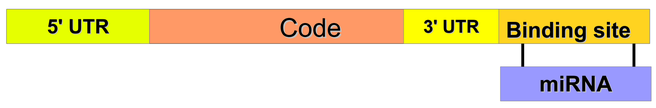
Introduction

Recently it had been shown [1] that RNAs can regulate each other by competing for miRNAs.
We aim to quantify this regulation focusing on 2 mechanisms that control mRNA concentration:

- **TF regulation on DNA level**

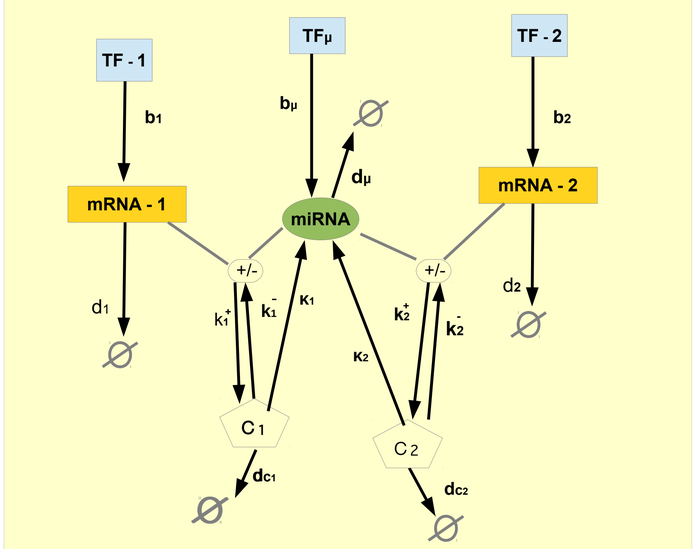


- **miRNA regulation on mRNA level**



Model

Consider 1 miRNA : 2 mRNA competing RNA model, with the TF control and complex composition-decomposition processes:



We separate 3 regimes [3]:

- Free (when the concentration of the miRNA is much smaller then the concentration of mRNA): F
- Susceptible (when the concentration of the miRNA is in the same order of the concentration of mRNA): S
- Bound (when the concentration of the miRNA is much higher then the the concentration of mRNA): B

State of The Art

Analytically dynamics of the model is given by the following ODE:

$$\frac{d[m_i]}{dt} = b_i n_{m_i} - d_i[m_i] - k_i^+[m_i][\mu] + k_i^- c_i + \xi_{m_i} - \xi_i^+ + \xi_i^-$$

mRNA · creation · degradation · complex association · complex dissociation · white noise

$$\frac{d[\mu]}{dt} = b_i n_\mu - d_\mu[\mu_i] - \sum_i k_i^+[m_i][\mu] + \sum_i (\kappa_i + k_i^-) c_i + \xi_\mu - \sum_i \xi_i^+ + \sum_i \xi_i^- + \sum_i \xi_i^\kappa$$

miRNA

$$\frac{d[c_i]}{dt} = k_i^+[m_i][\mu] - d_{c_i}[c_i] - (\kappa_i + k_i^-) c_i + \xi_{c_i} + \xi_i^+ - \xi_i^- - \xi_i^\kappa$$

complex · catalytic dissociation

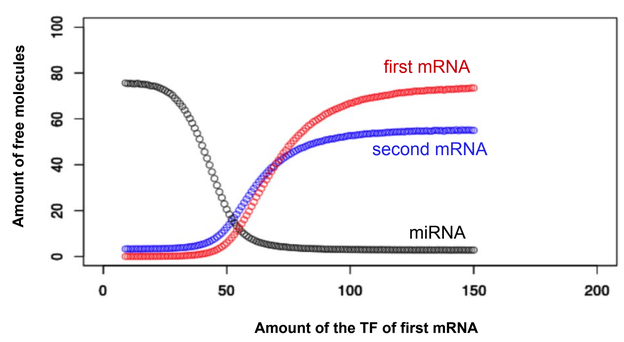
$$n_{m_i} = \frac{k_{on} f_{m_i}^5}{k_{on} f_{m_i}^5 + k_{off}}$$

TF · binding prob.

$$n_\mu = \frac{k_{on} f_\mu^5}{k_{on} f_\mu^5 + k_{off}}$$

binding prob. · TF binding rate. · TF unbinding rate.

System behaves as follows :



Optimization

We consider this network as a channel which transfers information between TF-1 (f_m) and mRNA-1/mRNA-2 (m).
Mutual information gives us quantitative estimation of the channel capacity:

$$I(f_m; m) = \int df_m\, dm\; p(f_m, m) \log_2 \frac{p(f_m, m)}{p(f_m)\, p(m)} \quad (1)$$

mutual information between TF(f_m) and mRNA (m) · Joint dist of input, output variables · TF (input) dist. · mRNA (output) dist.

Denote amount of TF when mRNA dynamical curves saturate by f_m^{max}. We choose this value as an upper bound for the input (TF).
Optimization can be done with respect to

- **input distribution,**
- **channel parameters.**

In the small noise limit with an assumption that we have a Gaussian channel, it is proven[2], that optimal input distribution is given by:

$$p_{opt}(f_m) \sim \left[\sum_{i=1}^{2} \frac{1}{\sigma_i^2(f_m)} \frac{d\bar{m}_i(f_m)}{d f_m}\right]^{1/2} \quad (2)$$

which corresponds to the mutual information equal to:

$$I(f_m, m_i) = \log_2 \int_0^{f_m^{max}} df_m \left(\frac{1}{2\pi e} \sum_{i=1}^{2} \frac{1}{\sigma_i^2(f_m)} \frac{d\bar{m}_i(f_m)}{d f_m}\right)^{1/2} \quad (3)$$

Variance of the output for given input · Derivative of the mean output in respect to input

Results

Consider following sub-networks:

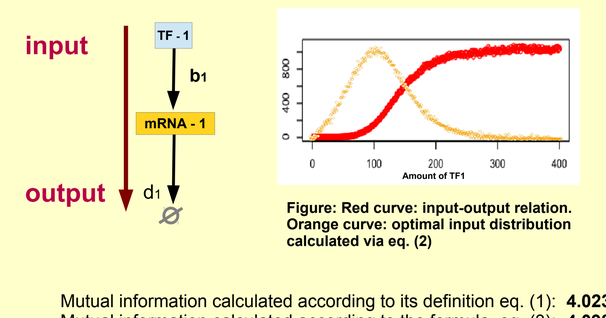


Figure: Red curve: input-output relation. Orange curve: optimal input distribution calculated via eq. (2)

Mutual information calculated according to its definition eq. (1): **4.023839 bit**
Mutual information calculated according to the formula eq. (3): **4.098728 bit**

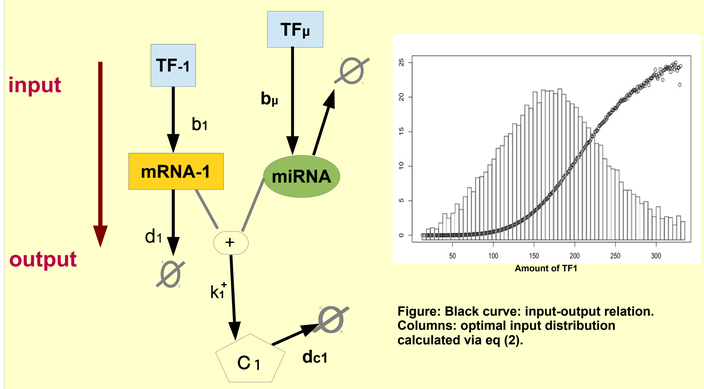
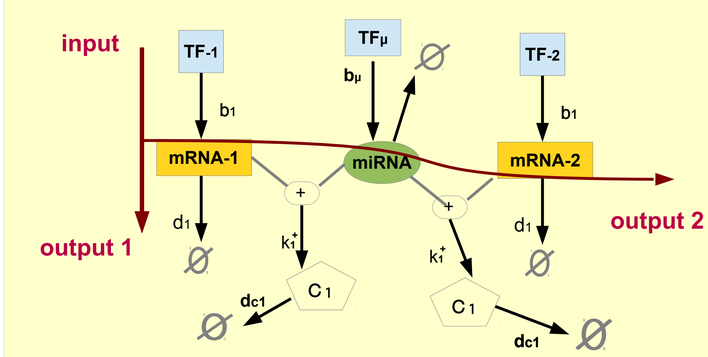


Figure: Black curve: input-output relation. Columns: optimal input distribution calculated via eq (2).

Mutual information calculated according to its definition eq. (1): **1.423926 bit**
Mutual information calculated according to the formula eq. (3): **1.889223 bit**



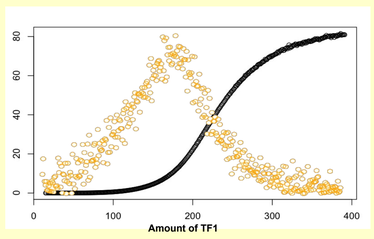


Figure: Black curve: input-output relation. Orange curve: optimal input distribution calculated via eq. (2)

Mutual information calculated according to its definition eq. (1): **1.887141 bit**
Mutual information calculated according to the formula eq. (3): **2.105024 bit**

Next Steps

> Do optimization with respect to channel parameters,
> Consider large PTR networks,
> Study out-of-equilibrium behavior of the system.

References

[1] Valencia-Sanchez M.A., J. Liu, G.J. Hannon, R. Parker. *Control of translation and mRNA degradation by miRNAs and siRNAs. Genes,* Dev 20, 515-524, 2006

[2] Gašper Tkačik, Aleksandra M. Walczak, William Bialek, *Optimizing information flow in small genetic networks*, Physical Review E 80, 031920, 2009

[3] Matteo Figliuzzi, Enzo Marinari, Andrea De Martino, *MicroRNAs as a selective channel of communication between competing RNAs: a steady state theory*, Biophysical Journal, 104(5), 1203-1213, 2013.

[4] Gašper Tkačik, Aleksandra M. Walczak, *Information transmission in genetic regulatory networks: a review*, Journal Physics: Condensed Matter, 23(15), 153102, 2011.