Consiglio Nazionale delle Ricerche

SAPIENZA
UNIVERSITÀ DI ROMA

STATISTICAL PHYSICS APPROACH TO POST-TRANSCRIPTIONAL REGULATION

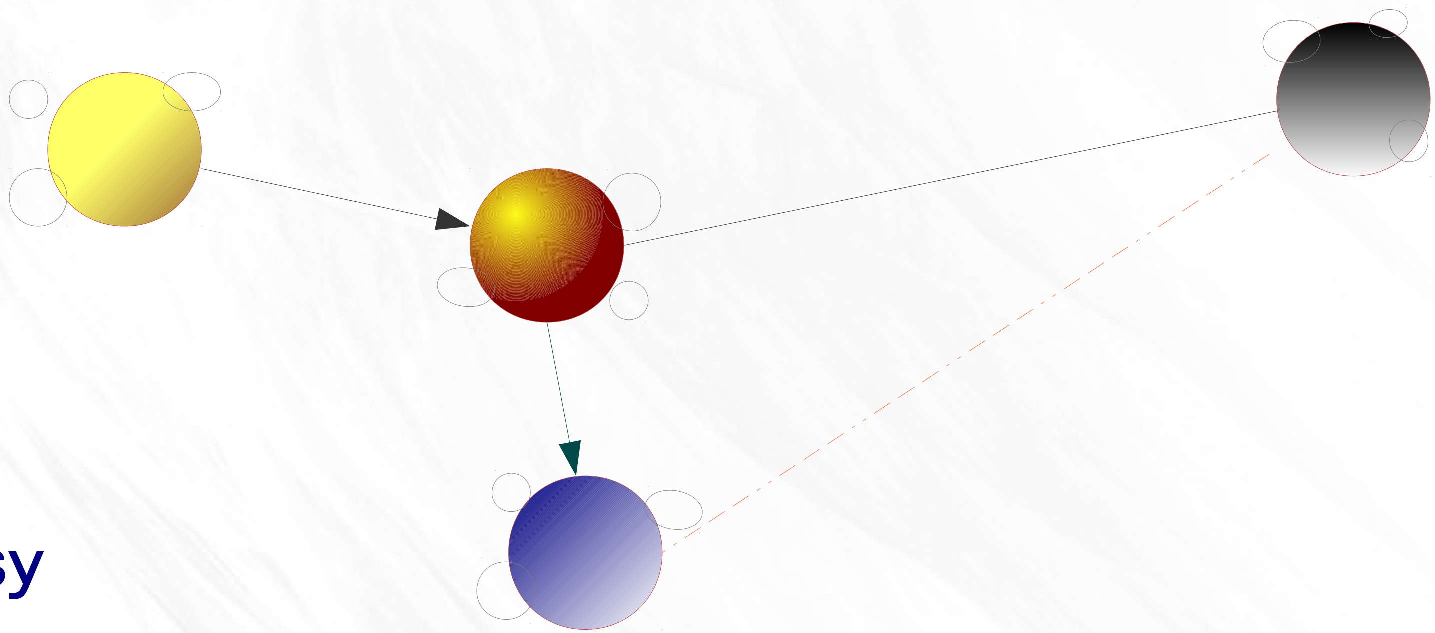
Araks Martirosyan

Advisors: Andrea De Martino, Enzo Marinari

Cortona, 07.07.2014

Project: Introduction

Models of Biological Systems



* Noisy

* Non linear

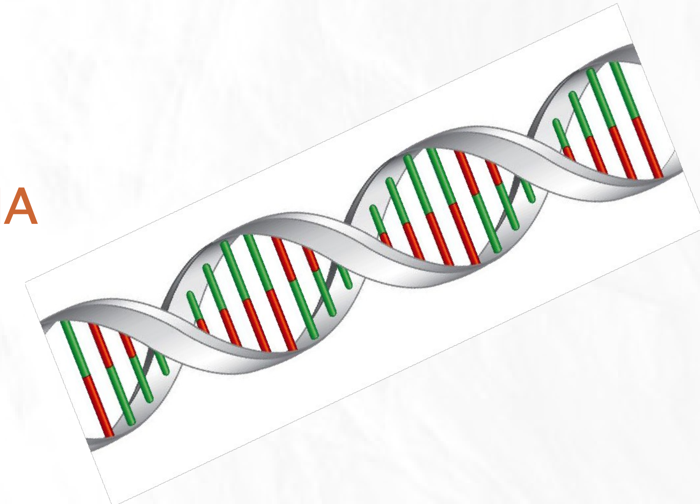
Channel: Gene Expression

Protein

Project: Introduction

Channel: Gene Expression

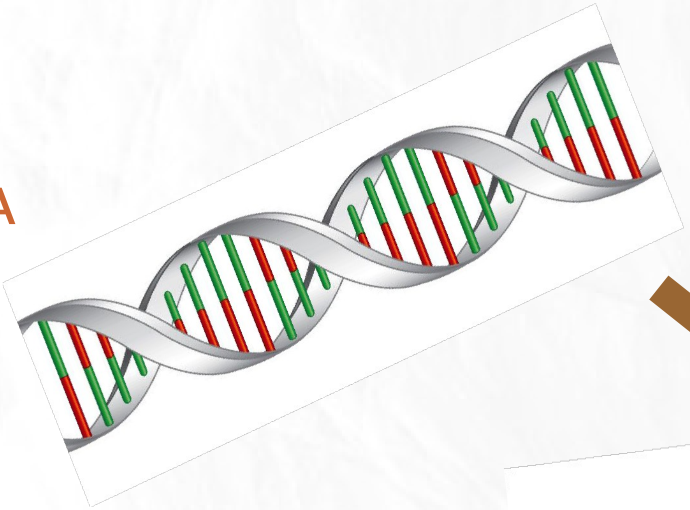
DNA



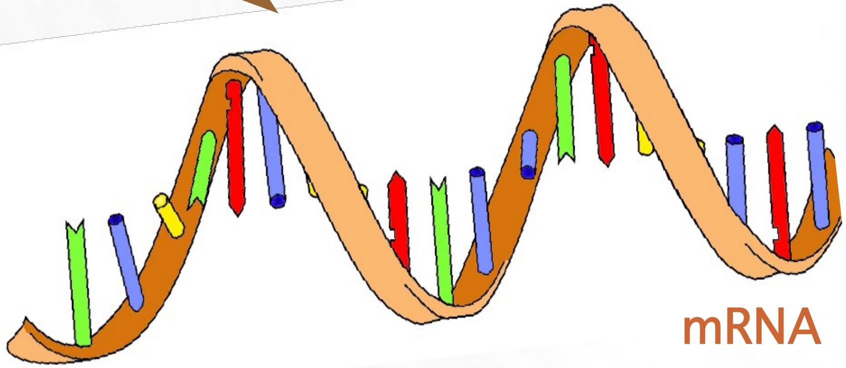
Protein

Channel: Gene Expression

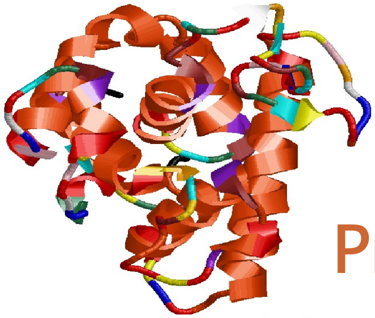
DNA



Transcription

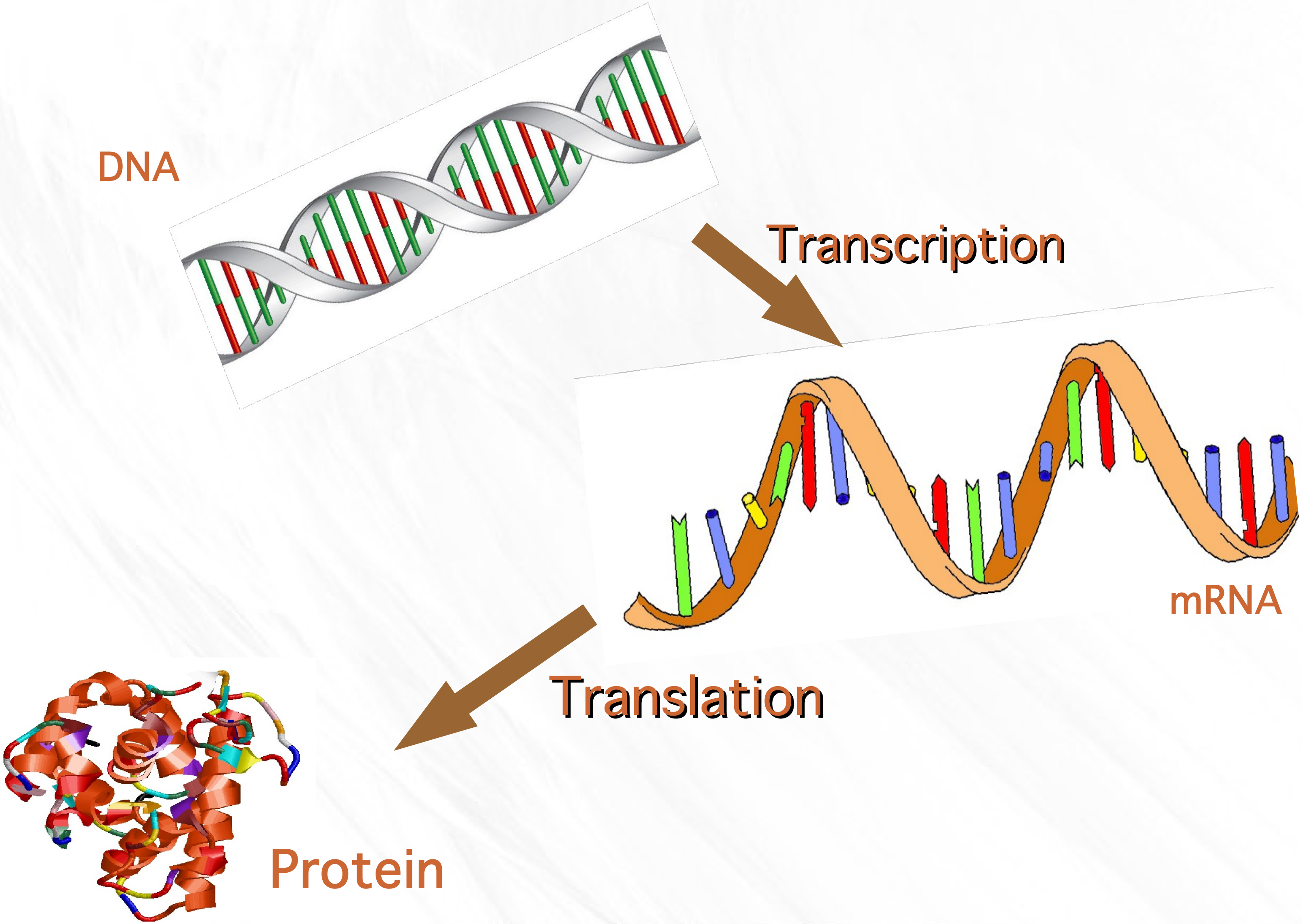


mRNA

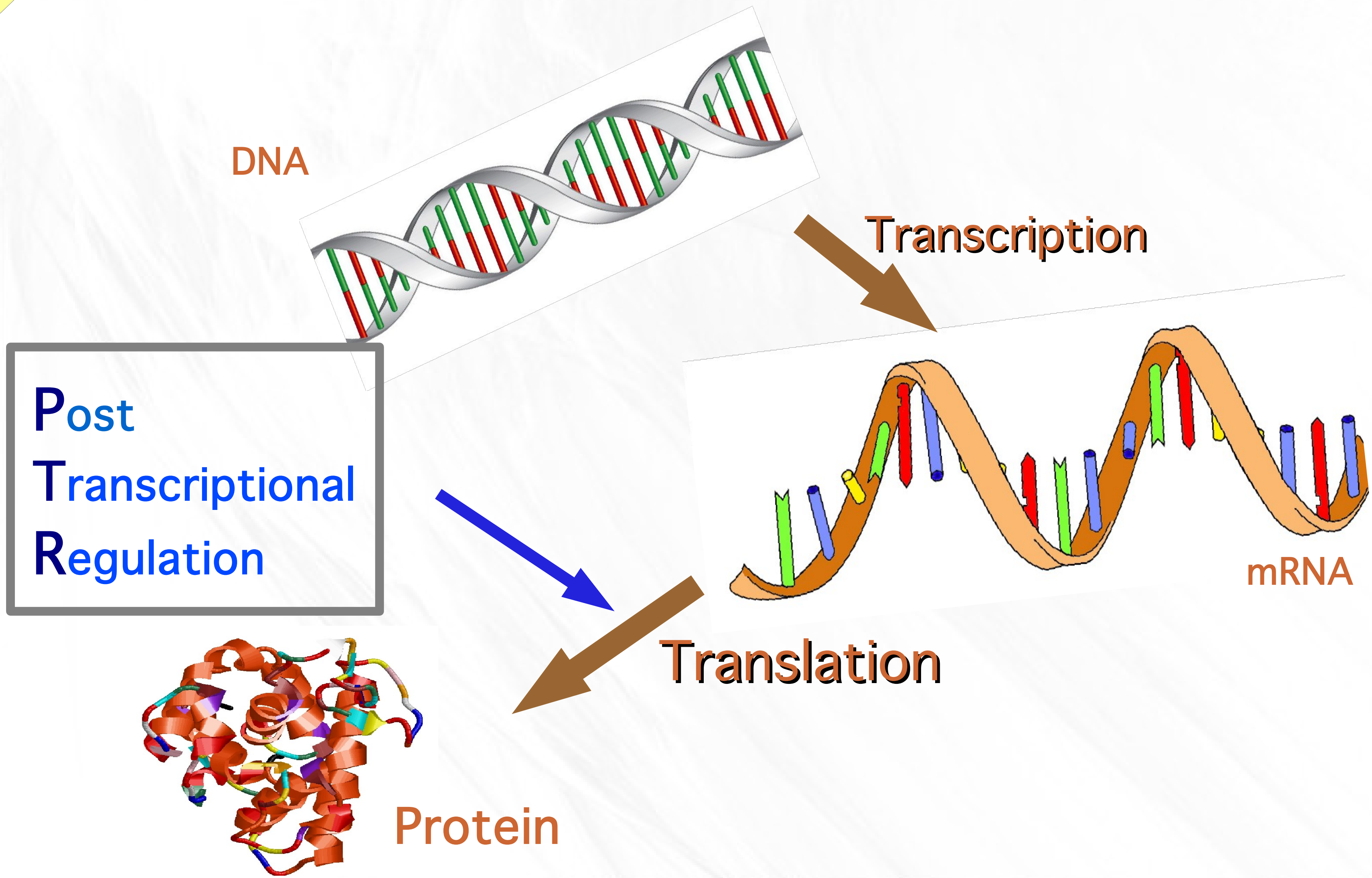


Protein

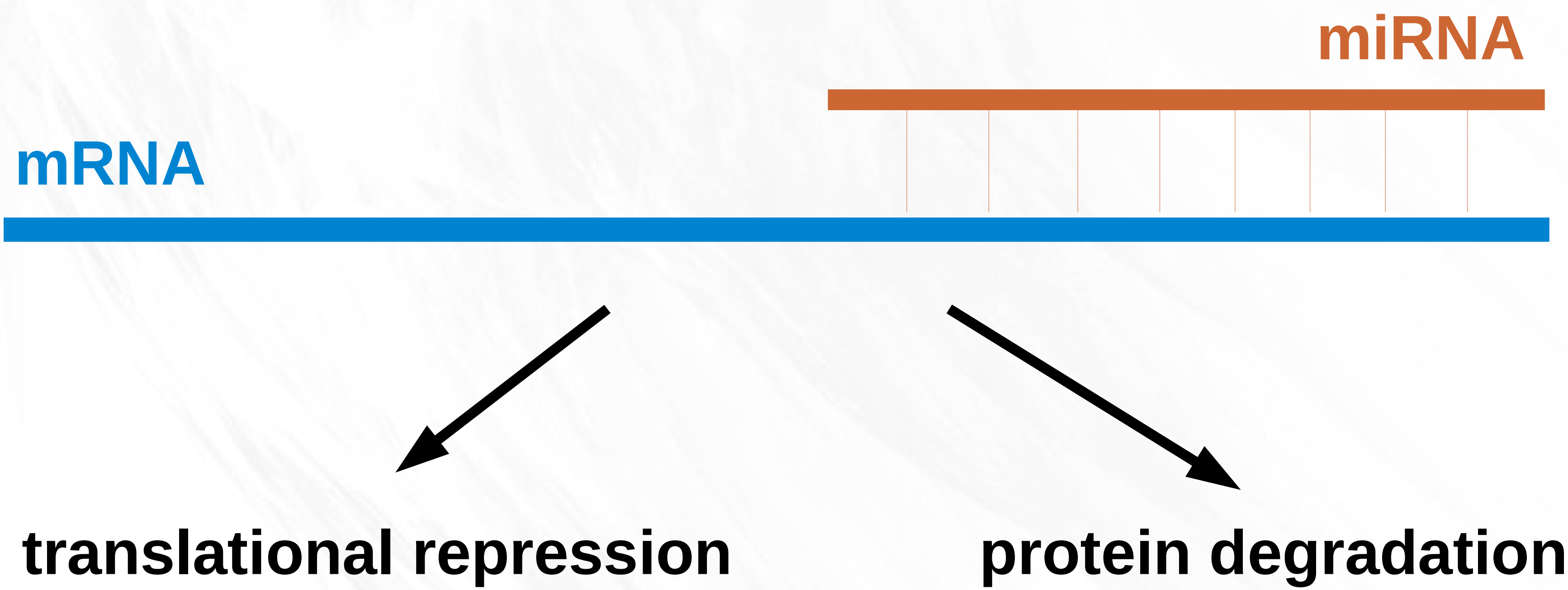
Channel: Gene Expression



Focus: PTR


DNA
Transcription
Post
Transcriptional
Regulation
mRNA
Translation
Protein

The Role of miRNA (microRNA)



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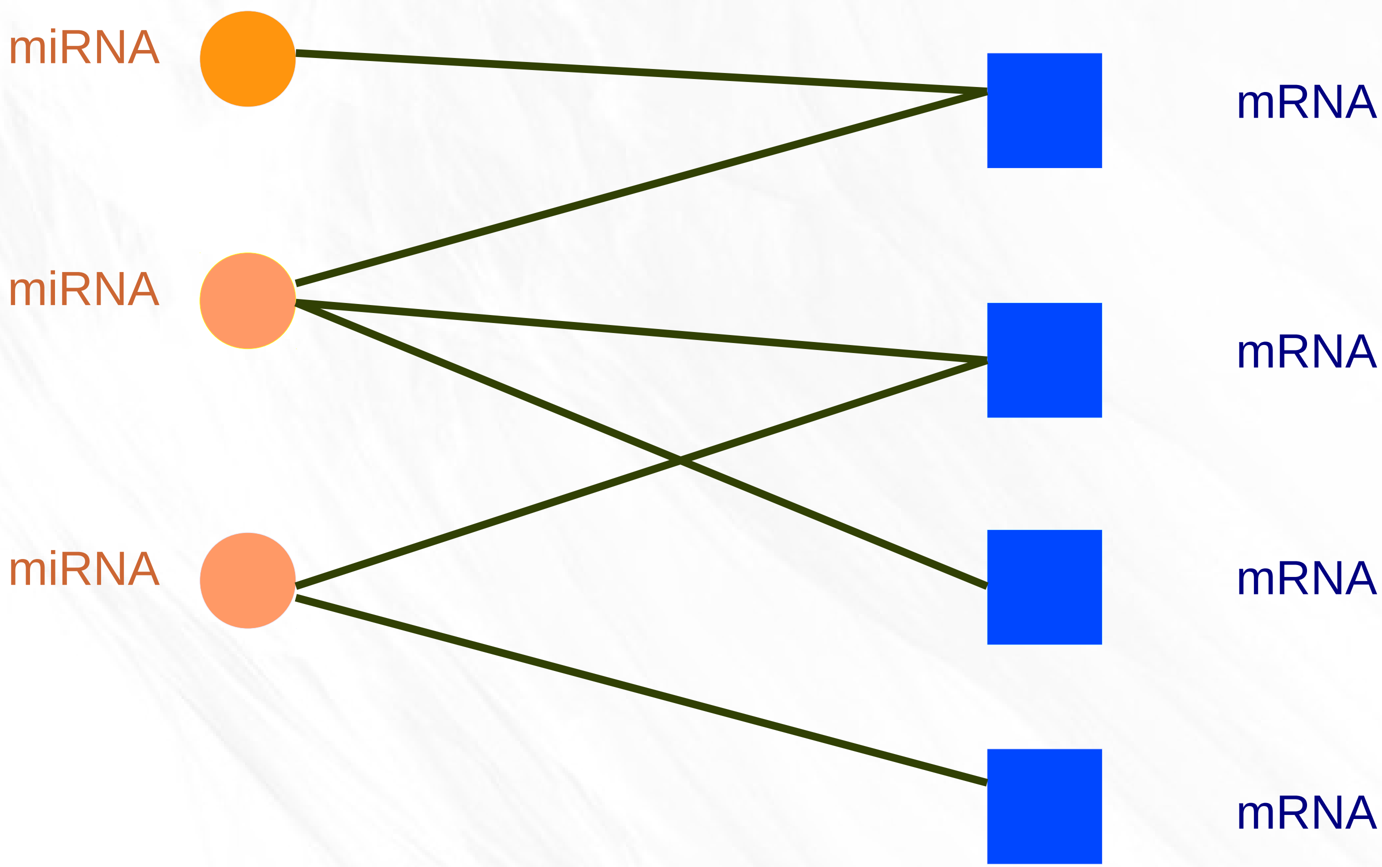
- Project
  - Part 1: Work done so far
    - Model
    - Analytical Methods: ODE approach
    - Computational Methods: Gillespie algorithm
    - Optimization
  - Part 2: Open Questions

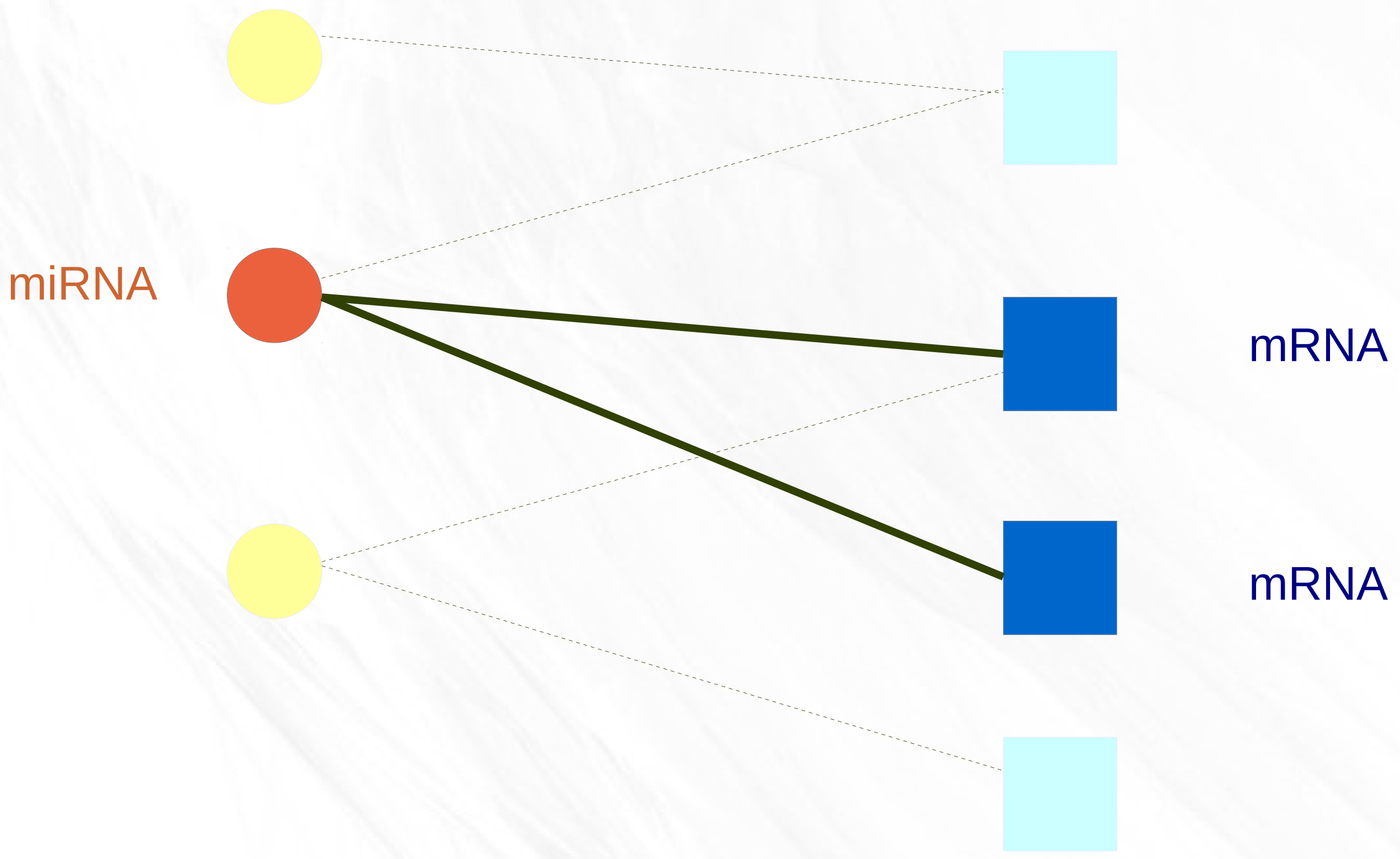
Network

Databases* => Network



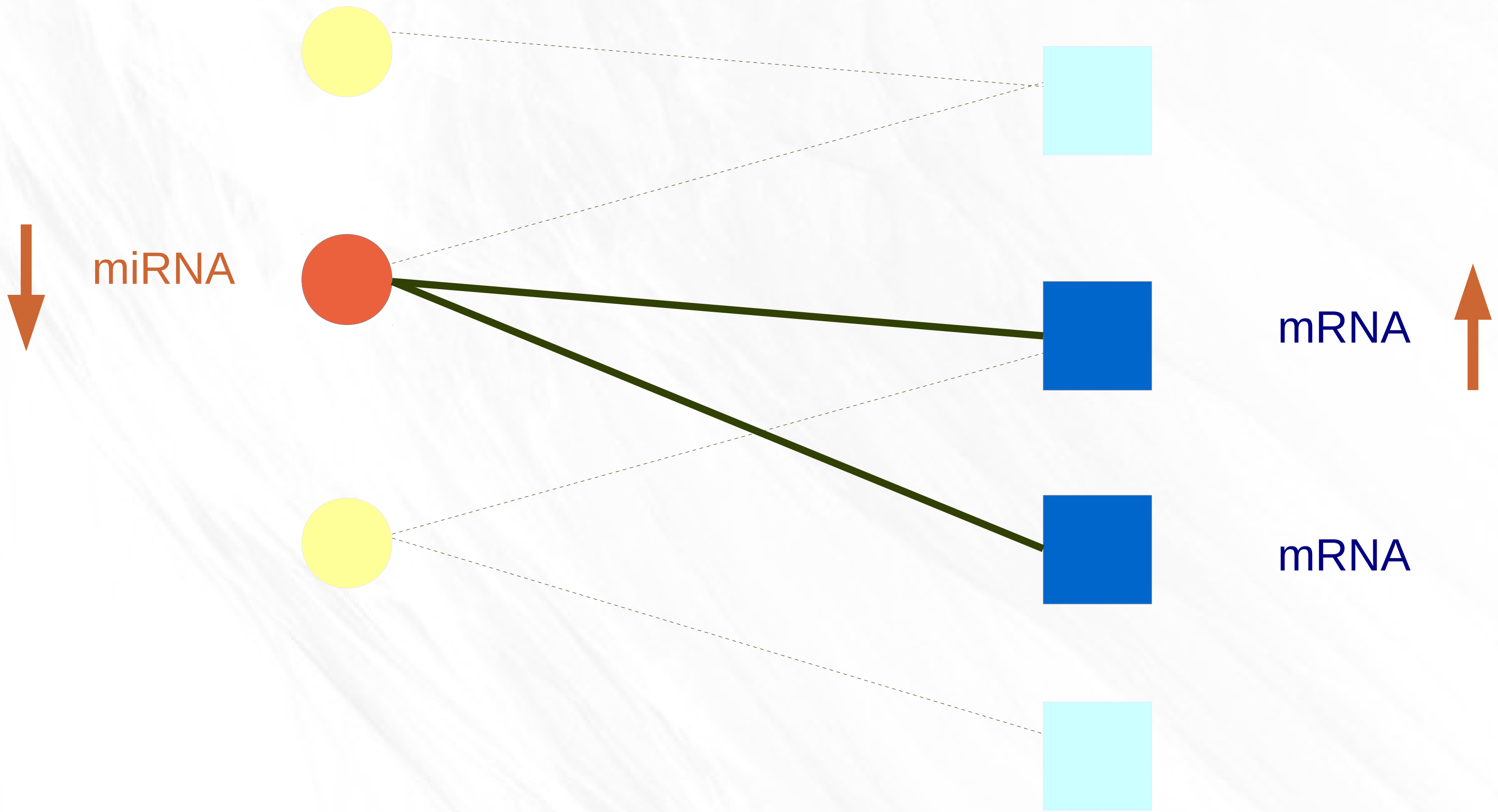
* TargetScan
MiRanda
MiRTarBase,

Ce-RNA Model



Model

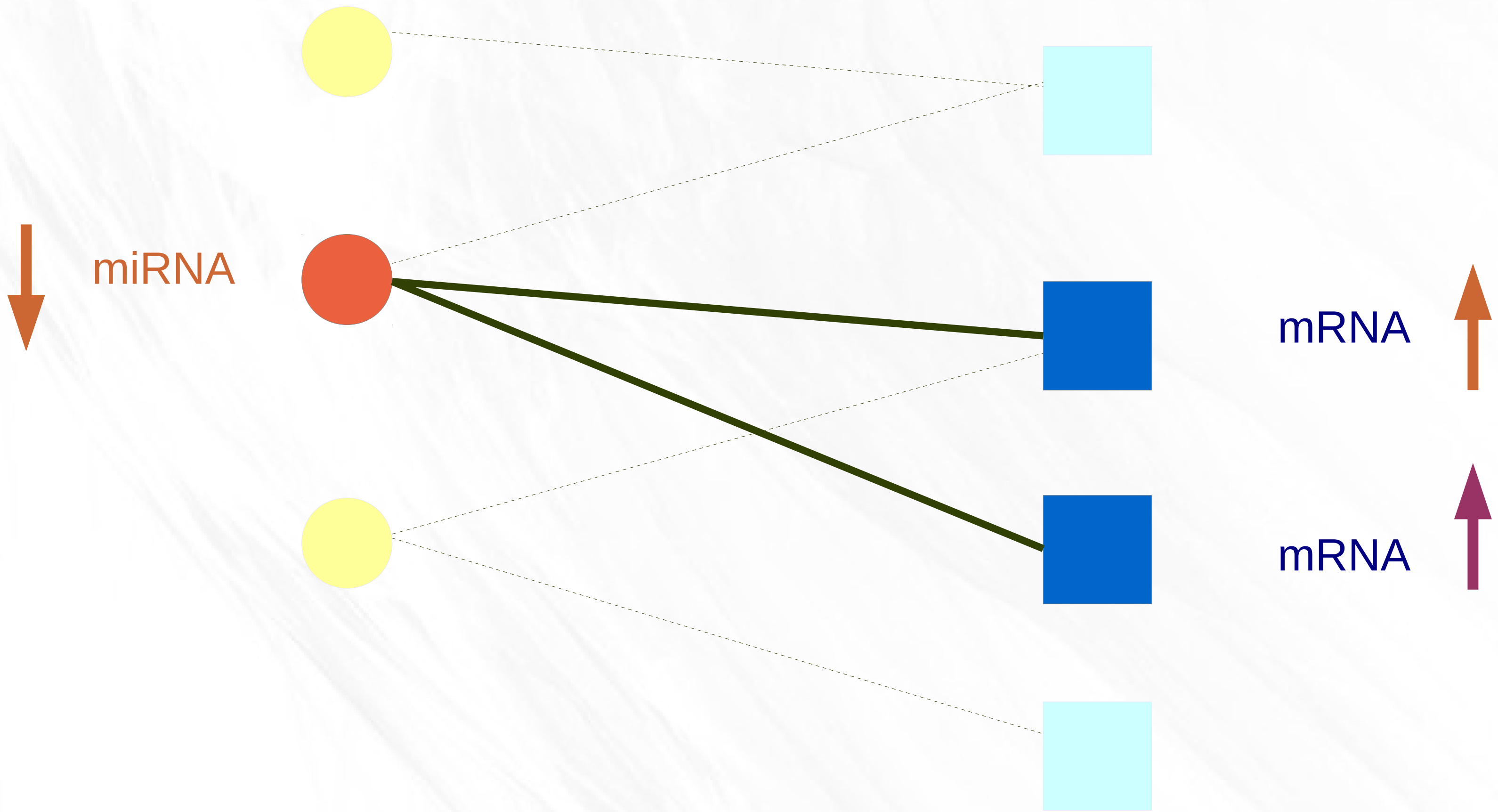
Ce-RNA Model



Ref: M. Figliuzzi, E. Marinari, A. De Martino,MicroRNAs as a selective channel of communication between competing RNAs: a steady-state theory, Biophysical Journal, 104(5), 1203-1213, 2013.

Model

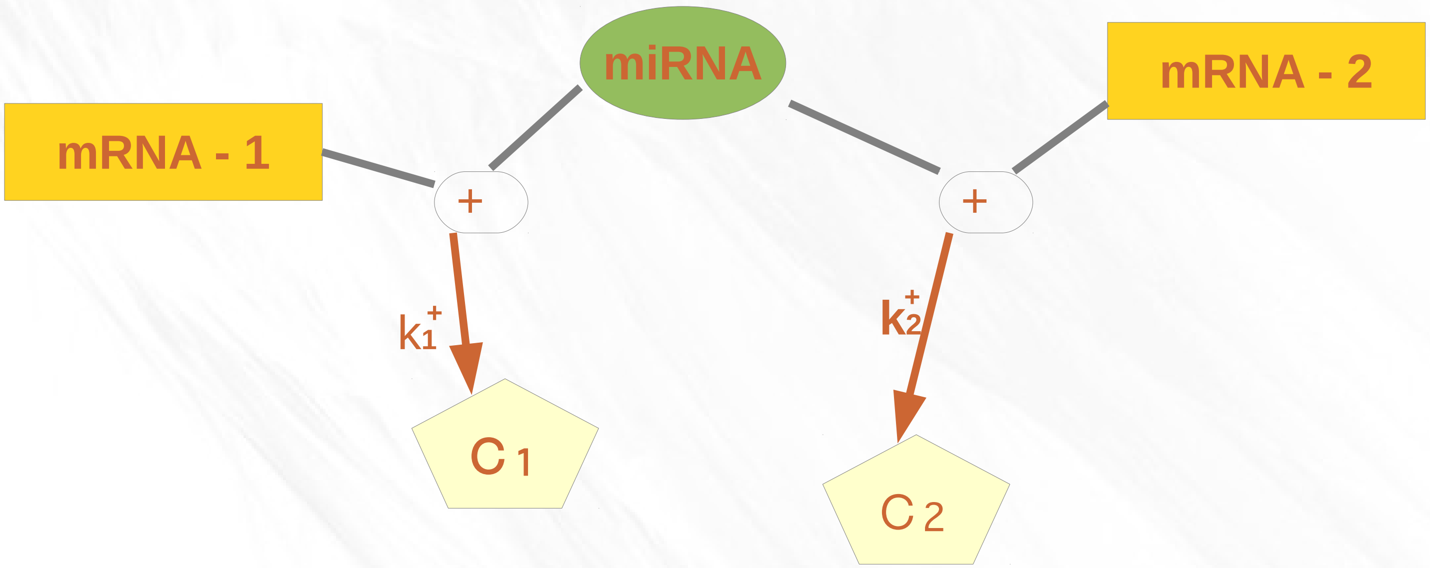
Ce-RNA Model



Ref: M. Figliuzzi, E. Marinari, A. De Martino,MicroRNAs as a selective channel of communication between competing RNAs: a steady-state theory, Biophysical Journal, 104(5), 1203-1213, 2013.

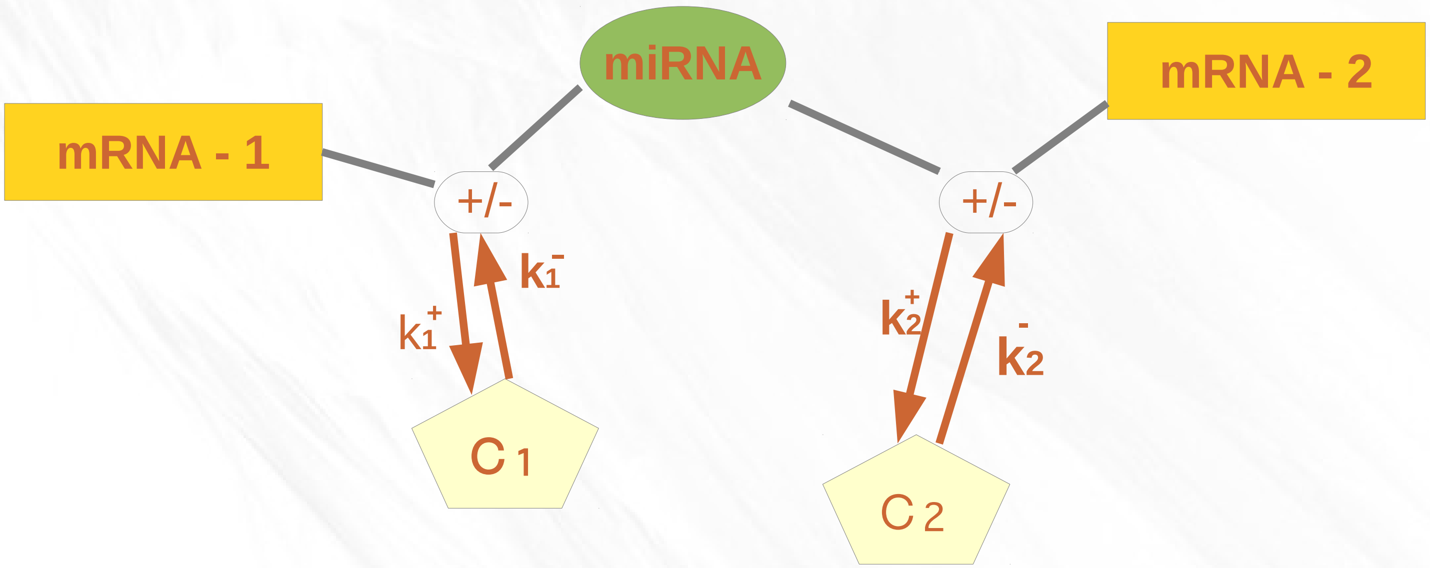
ODE Approach

ODE Approach



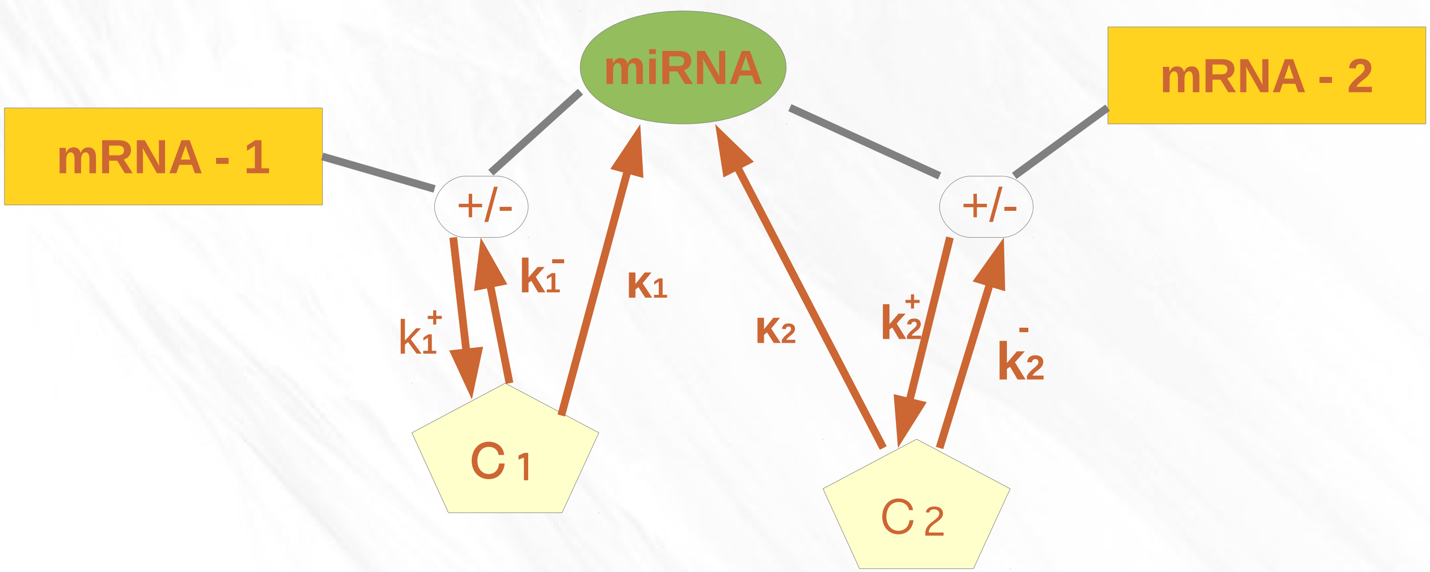
Analytical Methods

ODE Approach



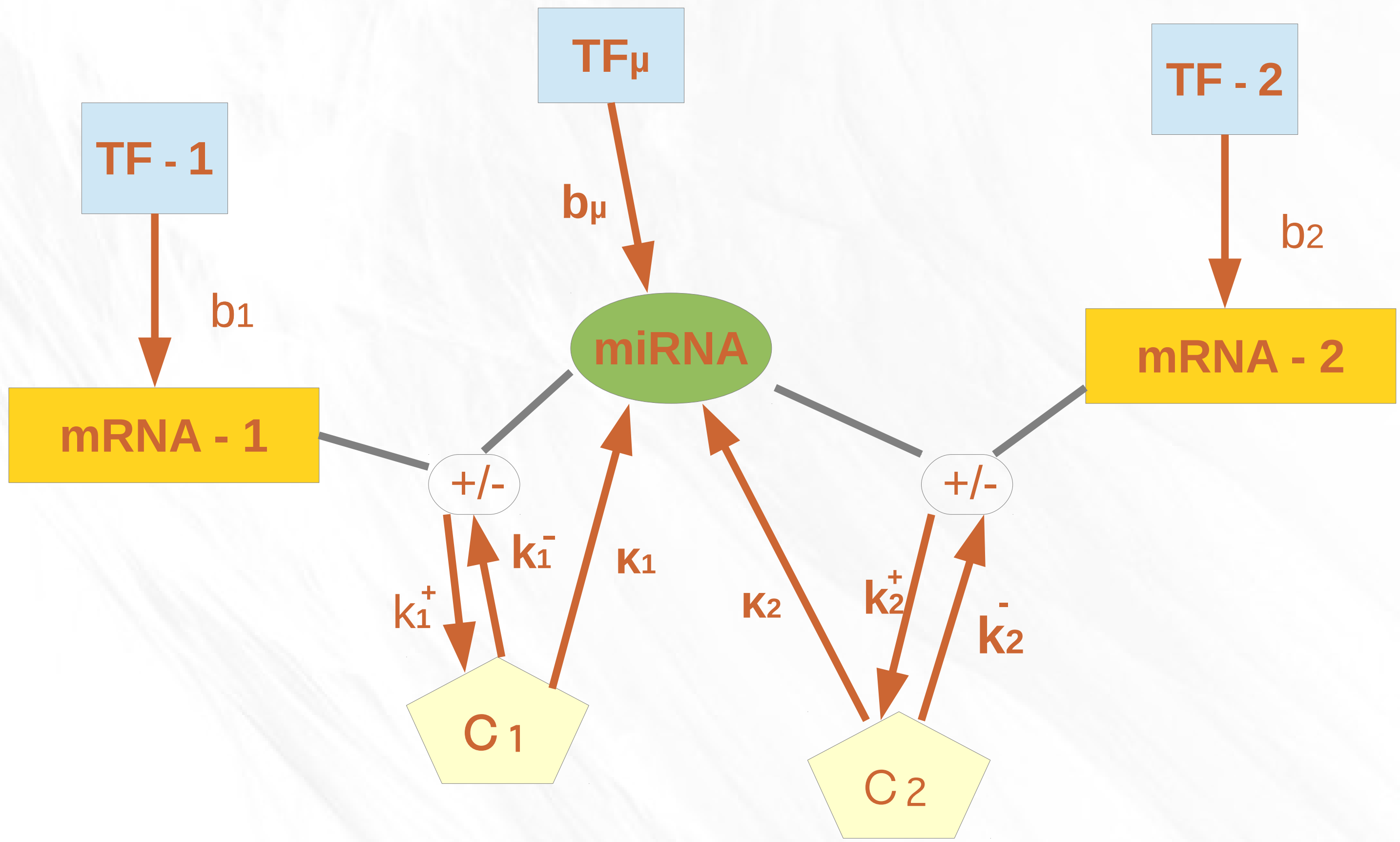
Analytical Methods

ODE Approach

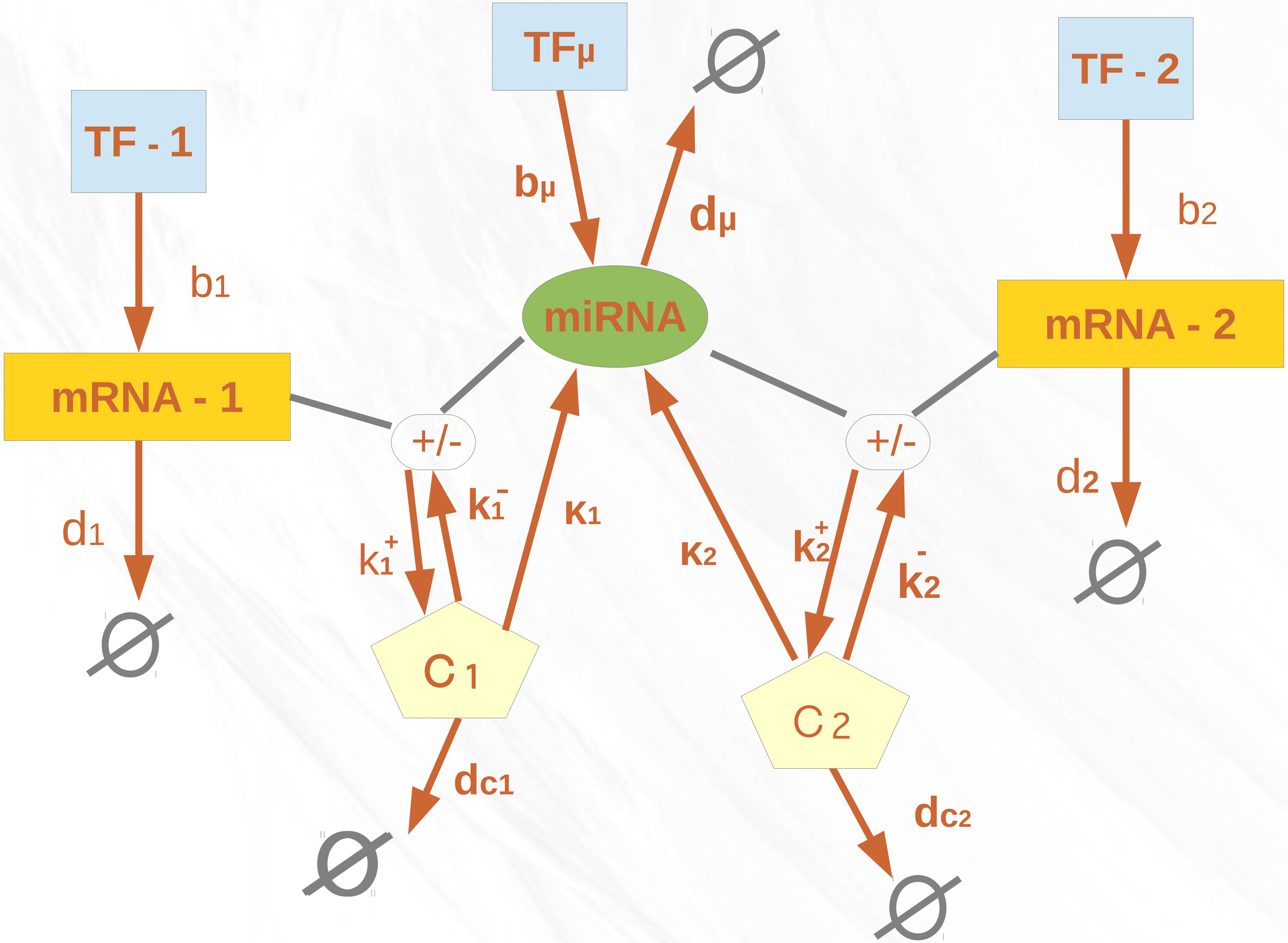


Analytical Methods

ODE Approach



ODE Approach



Analytical Methods

ODE Approach

mRNA $$\frac{d[m_i]}{dt} = b_i n_{m_i}$$

Analytical Methods

ODE Approach

mRNA $$\frac{d[m_i]}{dt}=b_i n_{m_i}-d_i[m_i]$$

Analytical Methods

ODE Approach

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

Analytical Methods

ODE Approach

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

Analytical Methods

ODE Approach

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

Analytical Methods

ODE Approach

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

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

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

TF binding prob. $$\frac{d\,n_{m_i,\mu}}{dt}=k_{in}f_{m_i}^x(1-n_{m_i,\mu})-k_{out}n_{m_i,\mu}+\xi_{n_i,\mu}$$

TF

ODE Approach

$$<\xi> = 0$$

$$<\xi_{m_i}(t)\xi_{m_i}(t')> = (b_i \bar{n}_{m_i} + d_i \bar{m}_i)\delta(t-t')$$

$$<\xi_{\mu}(t)\xi_{\mu}(t')> = (b_{\mu} \bar{n}_{\mu} + d_{\mu} \bar{\mu})\delta(t-t')$$

$$<\xi_{c_i}(t)\xi_{c_i}(t')> = d_{c_i} \bar{c}_i \delta(t-t')$$

$$<\xi_i^+(t)\xi_i^+(t')> = k_i^+ \bar{m}_i \bar{\mu} \delta(t-t')$$

$$<\xi_i^-(t)\xi_i^-(t')> = k_i^- \bar{c}_i \delta(t-t')$$

$$<\xi_i^{\kappa}(t)\xi_i^{\kappa}(t')> = \kappa_i^- \bar{c}_i \delta(t-t')$$

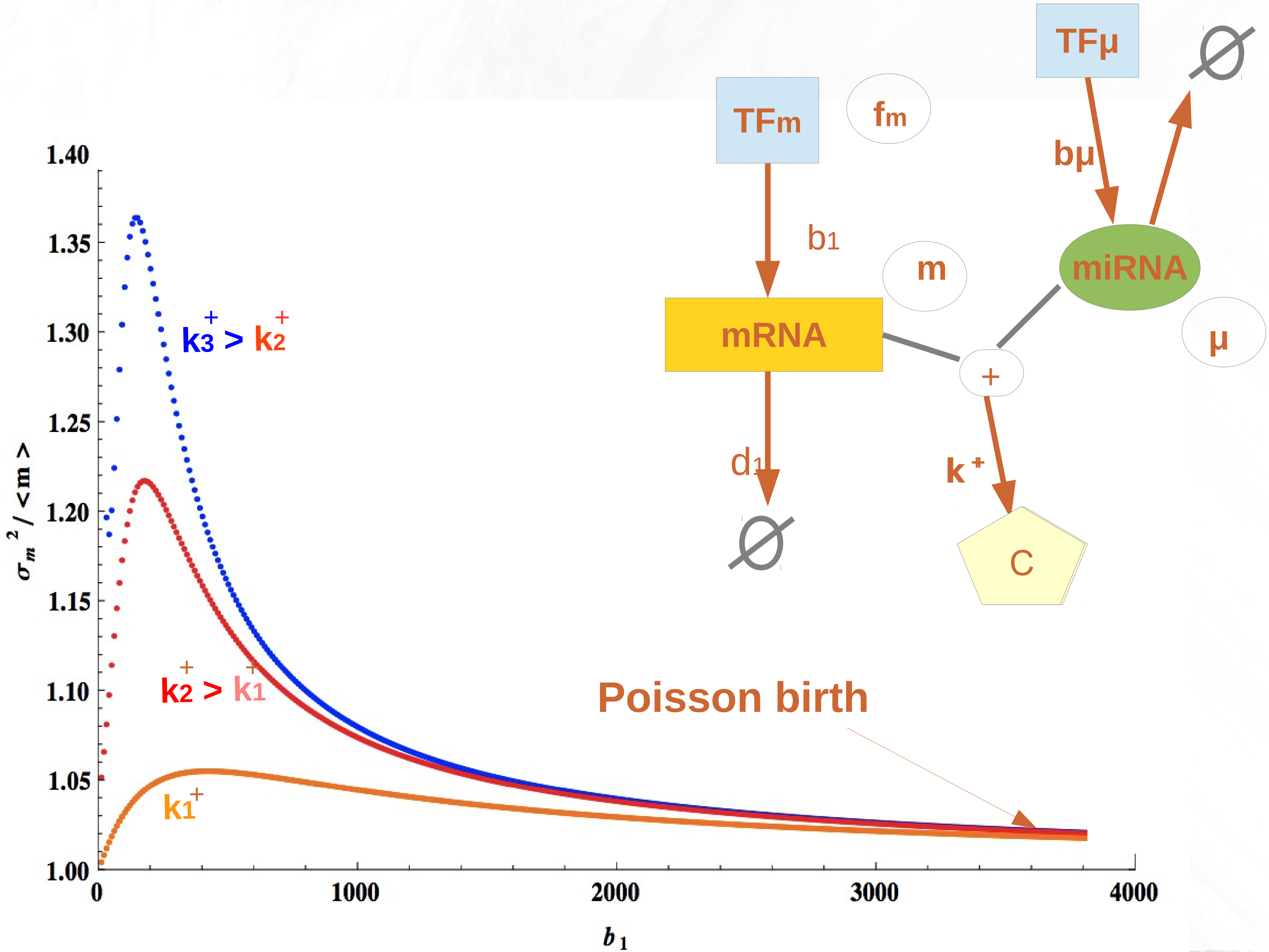
$$<\xi_{n_{i,\mu}}(t)\xi_{n_{i,\mu}}(t')> = (k_{in} f_{m_i,\mu}(1-\bar{n}_{i,\mu}) + k_{out} \bar{n}_{i,\mu})\delta(t-t')$$

Derivation of Noise

Given: $\frac{dX}{dt} = Ax + \xi$ $\quad < \xi > = 0$

$$< \xi_i(t)\, \xi_j(t') > = \gamma_{ij}\, \delta(t - t')$$

Question: calculate output noise: $< [x_i(t) - \bar{x}][x_j(t') - (\bar{x}_j)] > - ?$



1.40
1.35
1.30
1.25
1.20
1.15
1.10
1.05
1.00
$\sigma_m{}^2 / \langle m \rangle$
0
1000
2000
3000
4000
b_1
$k_3^+ > k_2^+$
$k_2^+ > k_1^+$
k_1^+
Poisson birth
TFm
fm
b1
mRNA
d1
m
TFμ
bμ
miRNA
μ
+
k+
C

Gillespie Algorithm

Denote the probability of reaction R to happen during next time interval τ by $p(\tau, R)$.

Step 0: initialize,

Step 1: generate random pair of (τ, R) according to $p(\tau, R)$,

Step 2: advance time by τ and change number of molecules according to reaction R,

Step 3: stop, if there are no more molecules left or if the termination time is reached, otherwise return to step 1.

Ref: T. Gillespie, A general method for numerically simulating the stochastic time evolution of coupled chemical reactions, Journal of Computational Physics, 22, 403-434, 1976

GA: Next reaction probability

c_i : reaction rate

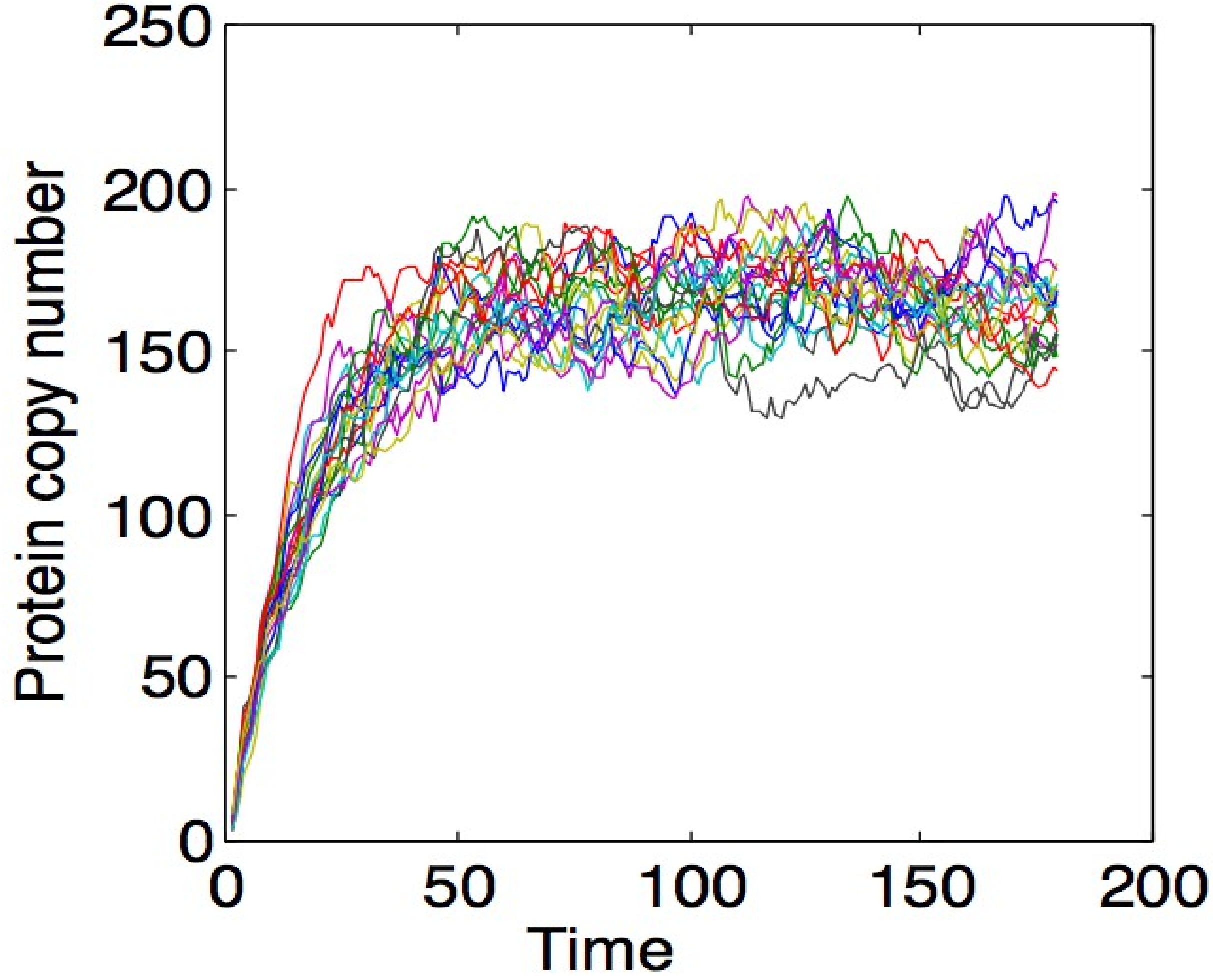
h_i : number of distinct molecular reactant combinations

$$p(\tau, R_i) = h_i c_i \exp\left(-\sum h_j c_j \tau\right)$$

Ref: T. Gillespie, A general method for numerically simulating the stochastic time evolution of coupled chemical reactions, Journal of Computational Physics, 22, 403-434, 1976

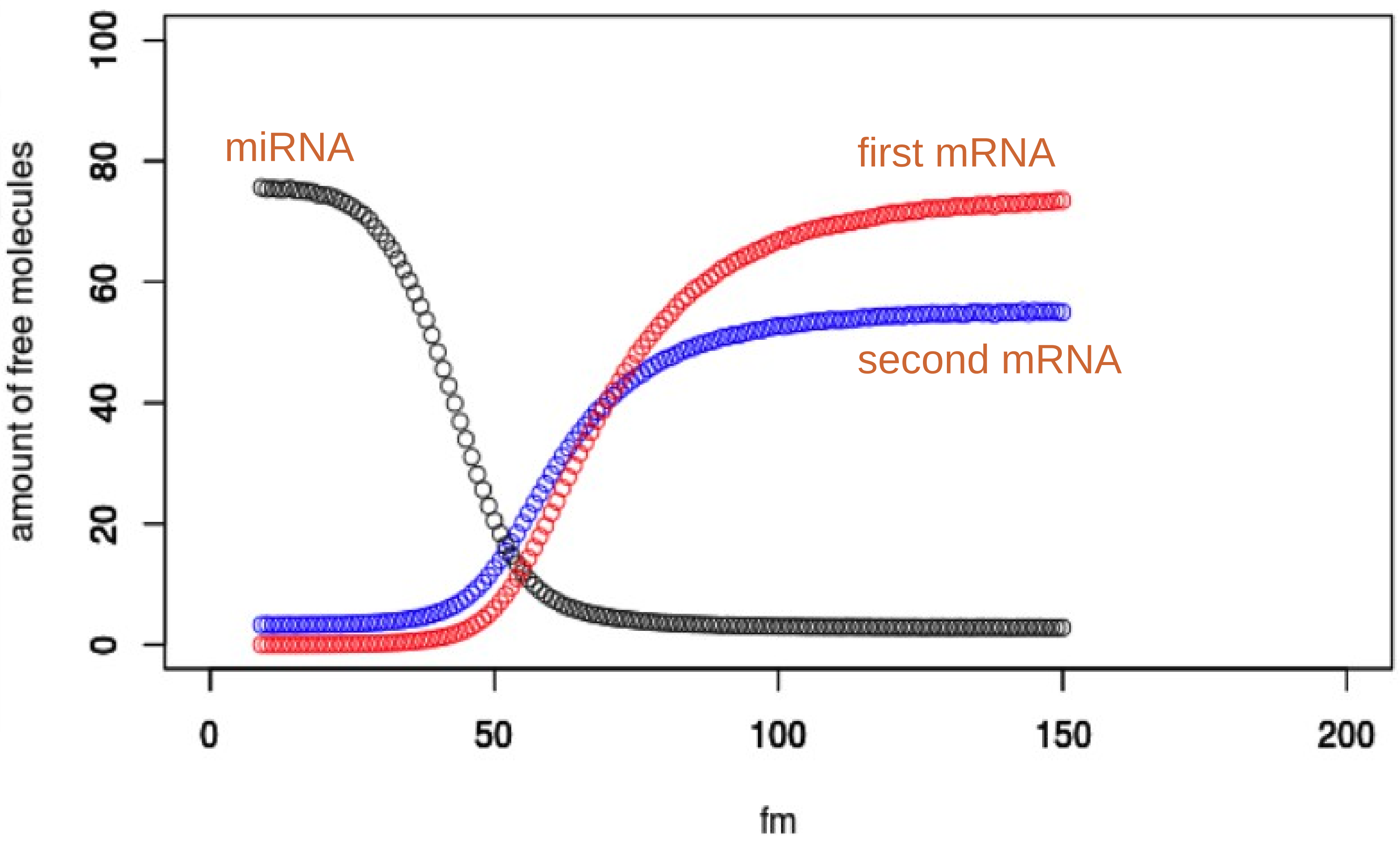
GA

Estimation of the Noise



GA

Behavior of The Steady State



MI

Mutual Information

as a measure of channel efficiency

$x, p(x) \longrightarrow$ Channel = f(x) $\longrightarrow o, p(o)$

Question: How much our ***uncertainty*** about output **o** ***reduces*** by knowing input **x**?

$$I(x;o) = \int dx\, do\, p(x,o) \log_2 \frac{p(x,o)}{p(x)\,p(o)}$$

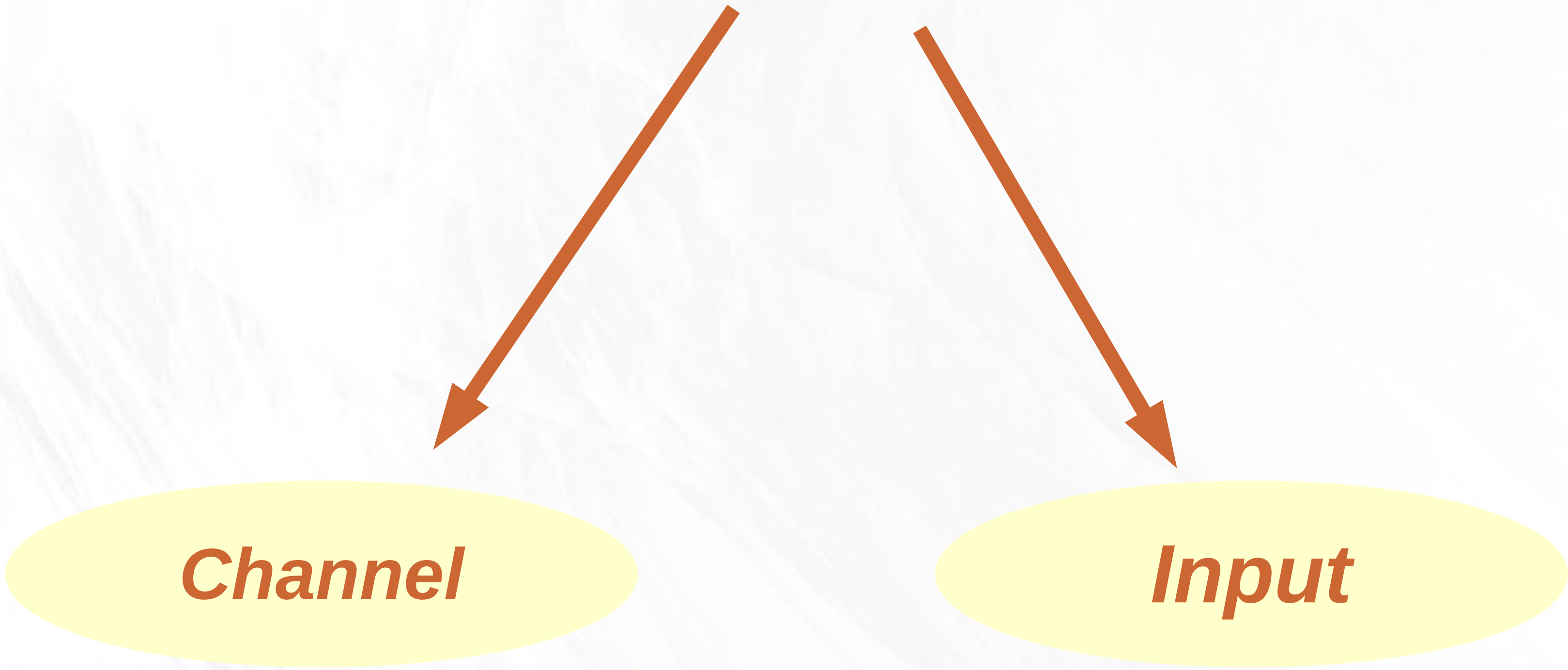
mutual information

joint prob. dist.

input variable prob. dist.

output variable prob. dist.

Optimization



Optimization over kinetic parameters, given p(x).

Optimization over p(x), given kinetic parameters.

Optimization

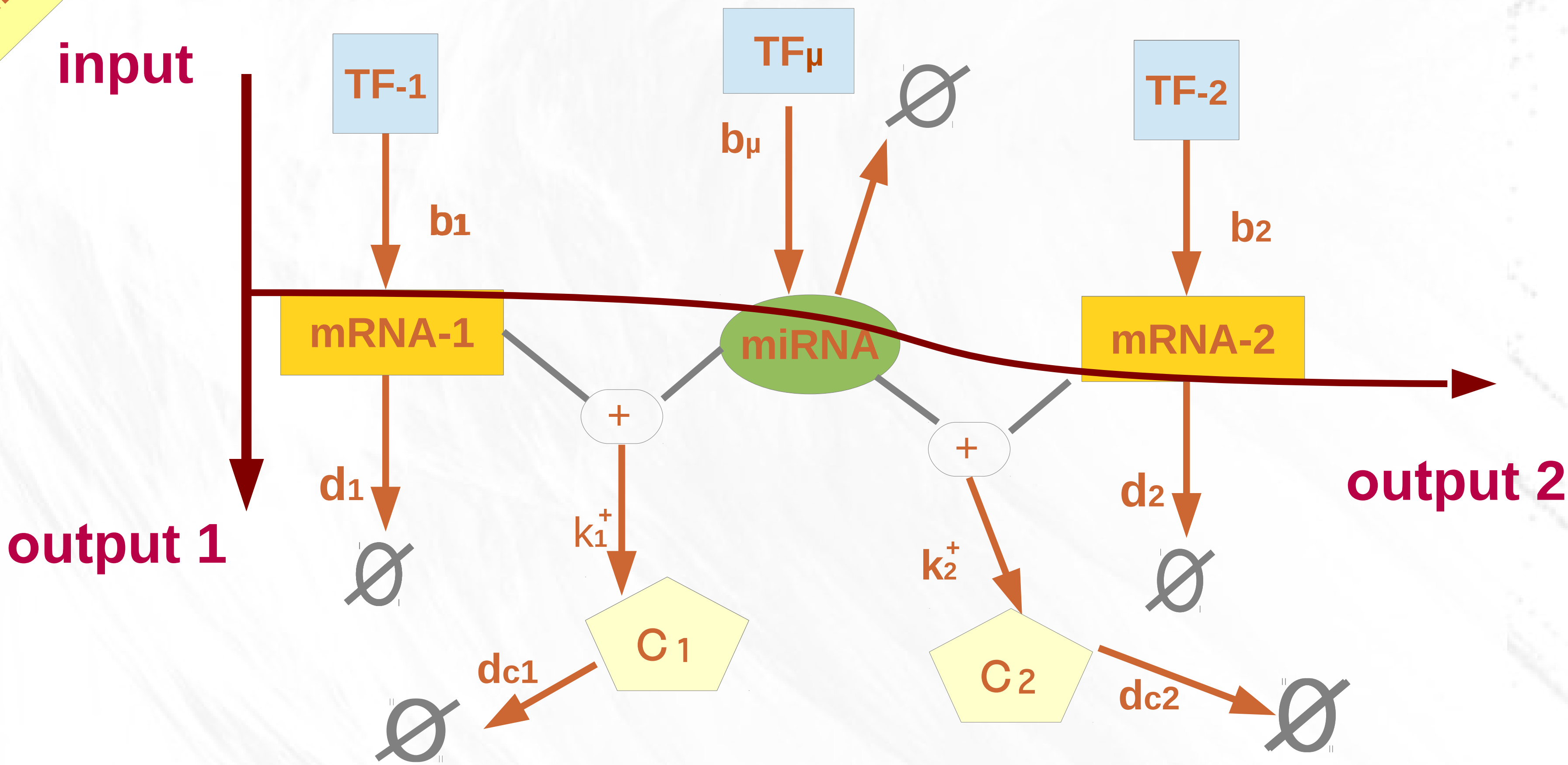
Channel

Optimization over kinetic parameters, given p(x).

Input

Optimization over p(x), given kinetic parameters.

Optimization: Channel

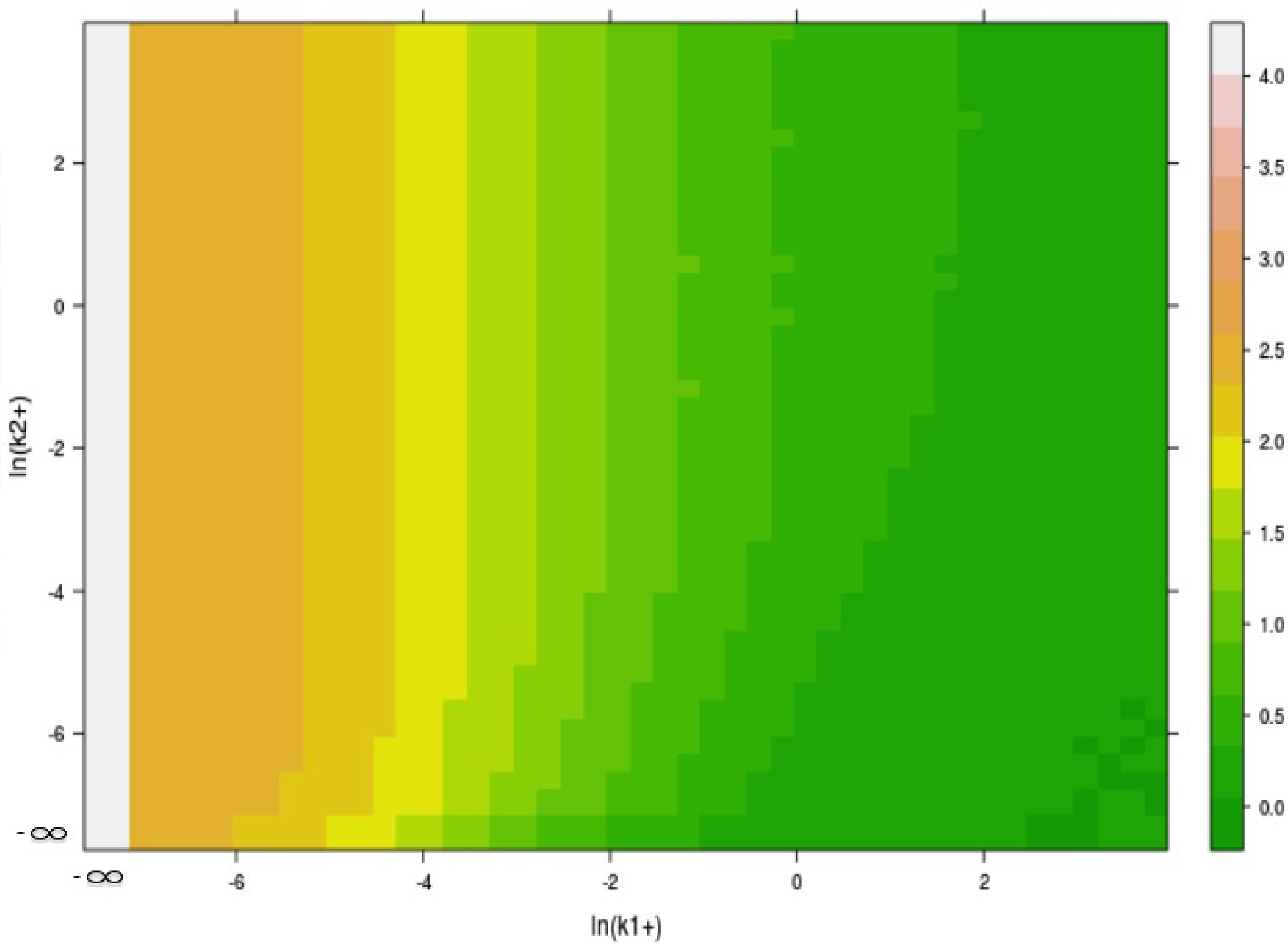


$$I_i(TF_1; m_i) = \int dTF_1\, dm_i\, p(TF_1, m_i) \log_2 \frac{p(TF_1, m_i)}{p(m_i)\, p(TF_1)}, i=1,2$$

$$I(TF_1; m_1, m_2) = \int dTF_1\, dm_1\, dm2\; p(TF_1, m_1, m_2) \log_2 \frac{p(TF_1, m_1, m_2)}{p(m_1, m_2)\, p(TF_1)}$$

Optimization: Channel

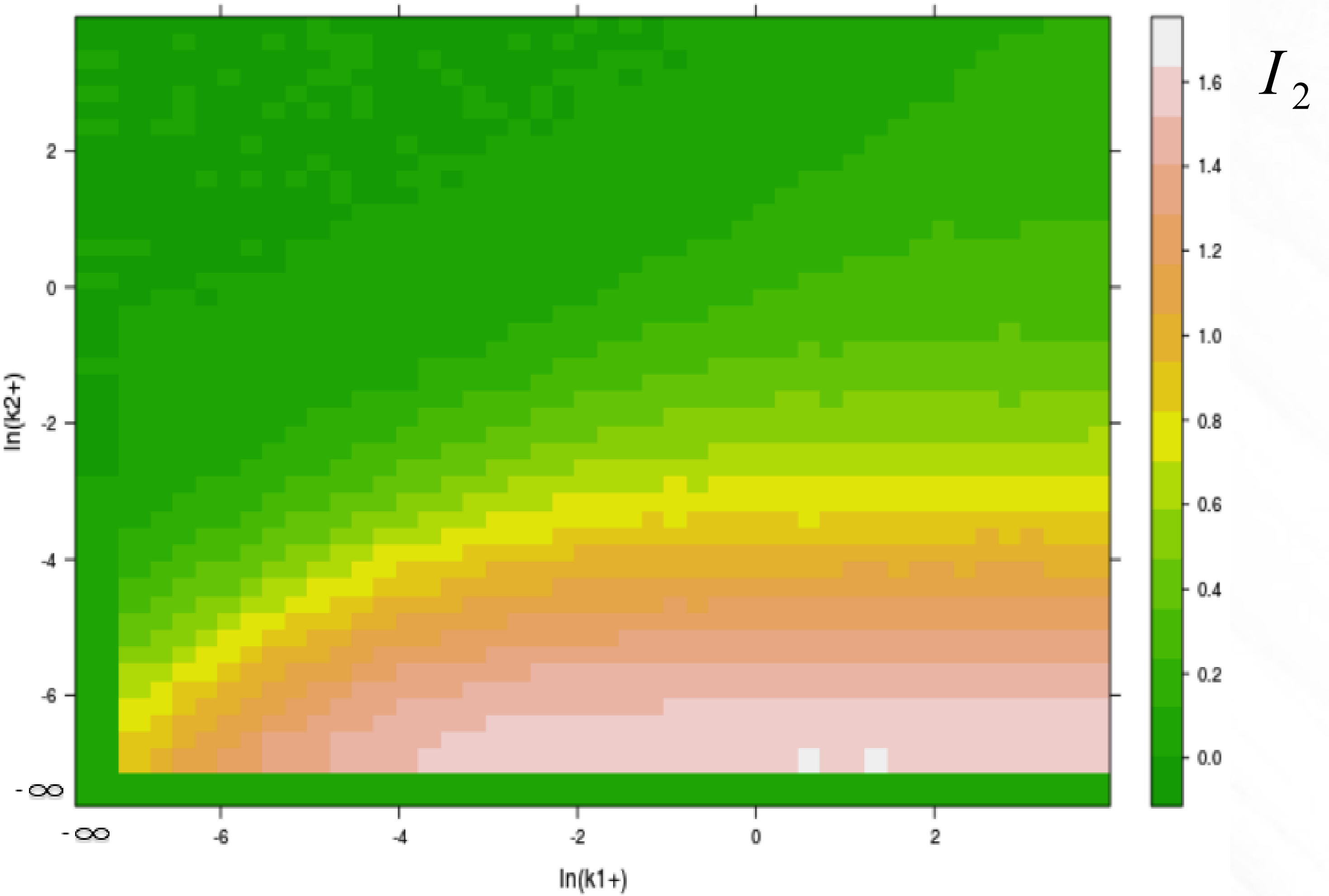
I_1



ln (complex association rate 2)

ln (complex association rate 1)

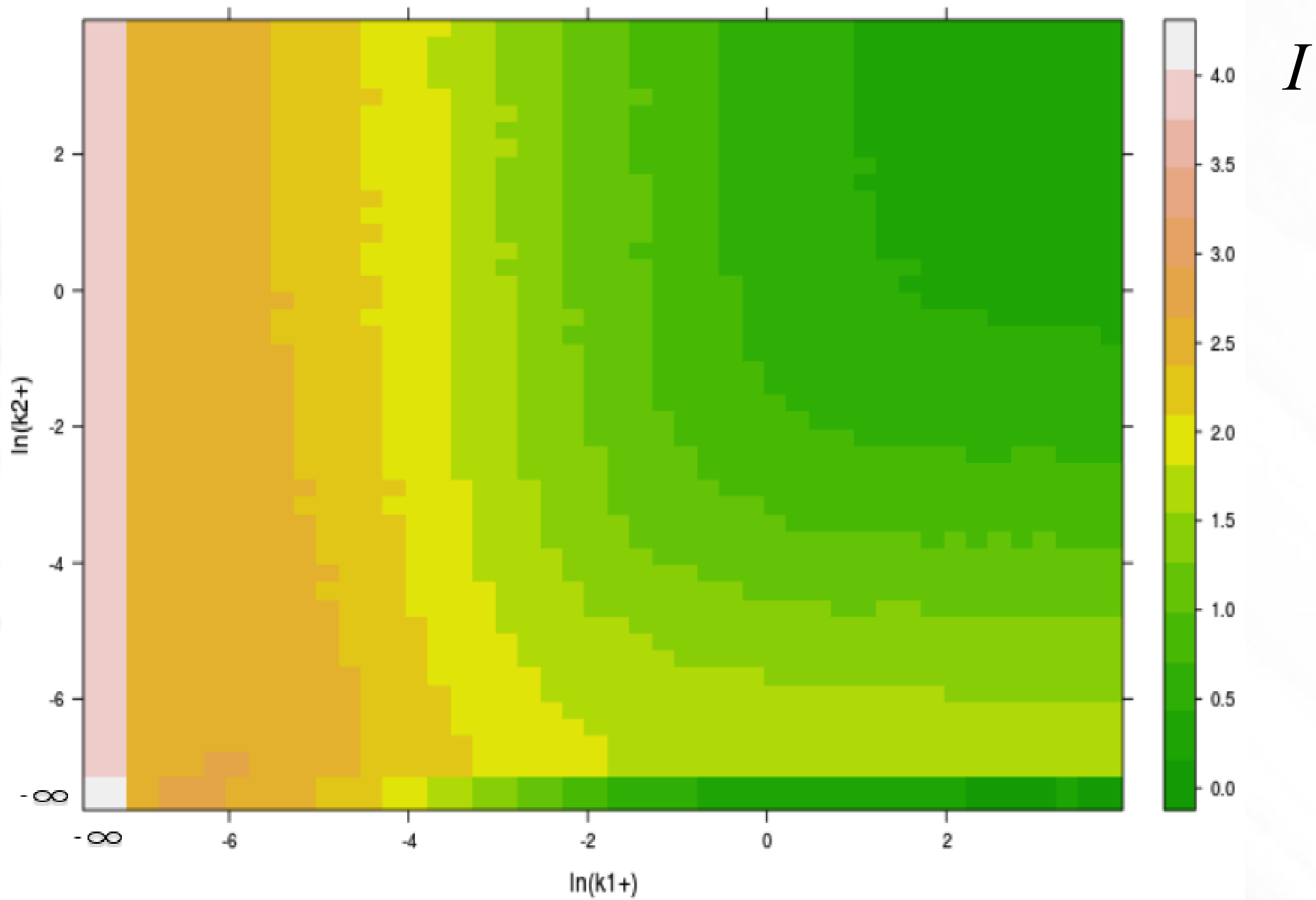
Optimization: Channel



ln (complex association rate 2)

ln (complex association rate 1)

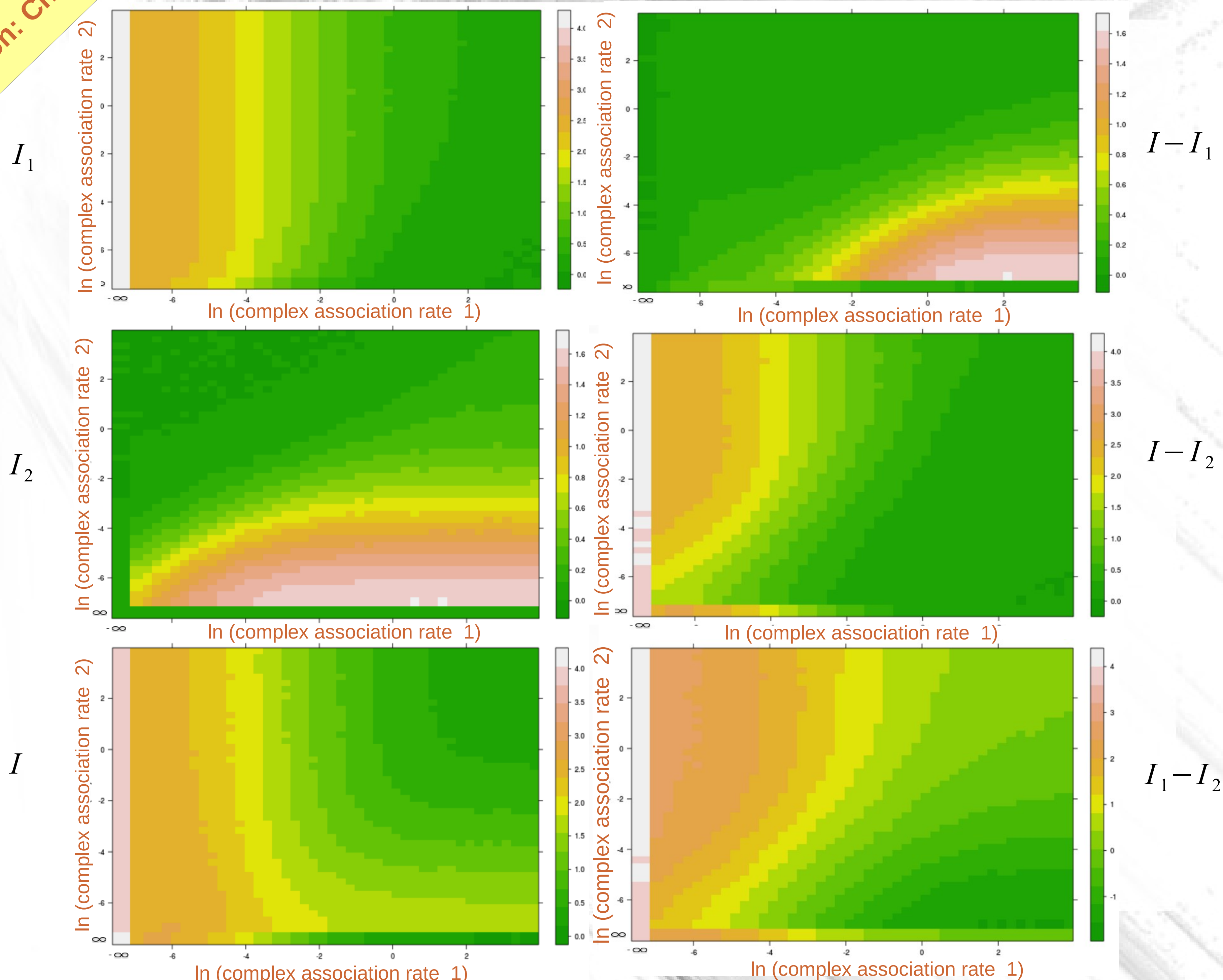
Optimization: Channel



ln (complex association rate 2)

ln (complex association rate 1)

Optimization: Channel



Optimization

Channel

Optimization over kinetic parameters, given p(x).

Input

Optimization over p(x), given kinetic parameters.

Optimization: Input

Optimization

with respect to the input distribution

Problem: Optimize mutual information in respect to input distribution given that noise is small and the channel is Gaussian.

$$I(x;o)=\int dx\, do\, p(x,o)\log_2\frac{p(x,o)}{p(x)\,p(o)} \qquad p(o/x)=\frac{1}{\sqrt{2\pi\sigma^2(x)}}\exp\left[\frac{-(o-o'(x))^2}{2\sigma^2(x)}\right]$$

$$limit:\sigma\rightarrow 0$$

Ref: G. Tkačik, A. M. Walczak, W. Bialek, Optimizing information flow in small genetic networks, Physical Review E, 80(3), 031920, 2009.

Optimization

with respect to the input distribution

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$$p(o/x)=\frac{1}{\sqrt{2\pi\sigma^2(x)}}\exp[\frac{-(o-o'(x))^2}{2\sigma^2(x)}]$$

$$limit:\sigma\rightarrow 0$$

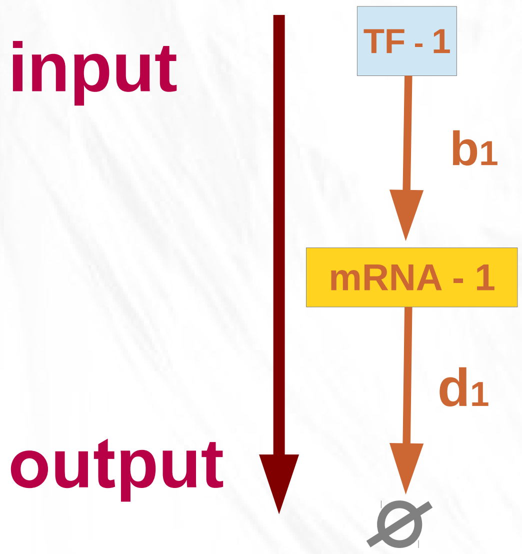
Solution:

$$p_{opt}(x)=\frac{1}{Z}[\frac{1}{2\pi e\sigma(x)^2}(\frac{d\,o'(x)}{dx})^2]^{1/2},$$

$$I_{opt}(x;o)=\log_2 Z$$

Ref: G. Tkačik, A. M. Walczak, W. Bialek, Optimizing information flow in small genetic networks, Physical Review E, 80(3), 031920, 2009.

Optimization
with respect to the input distribution



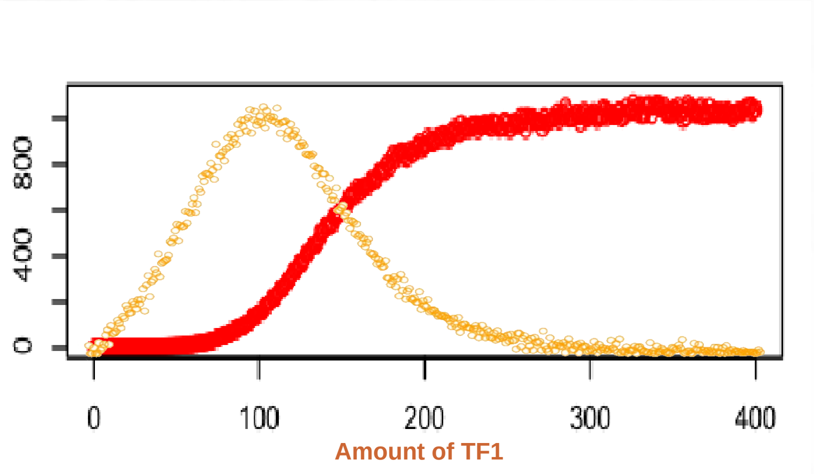
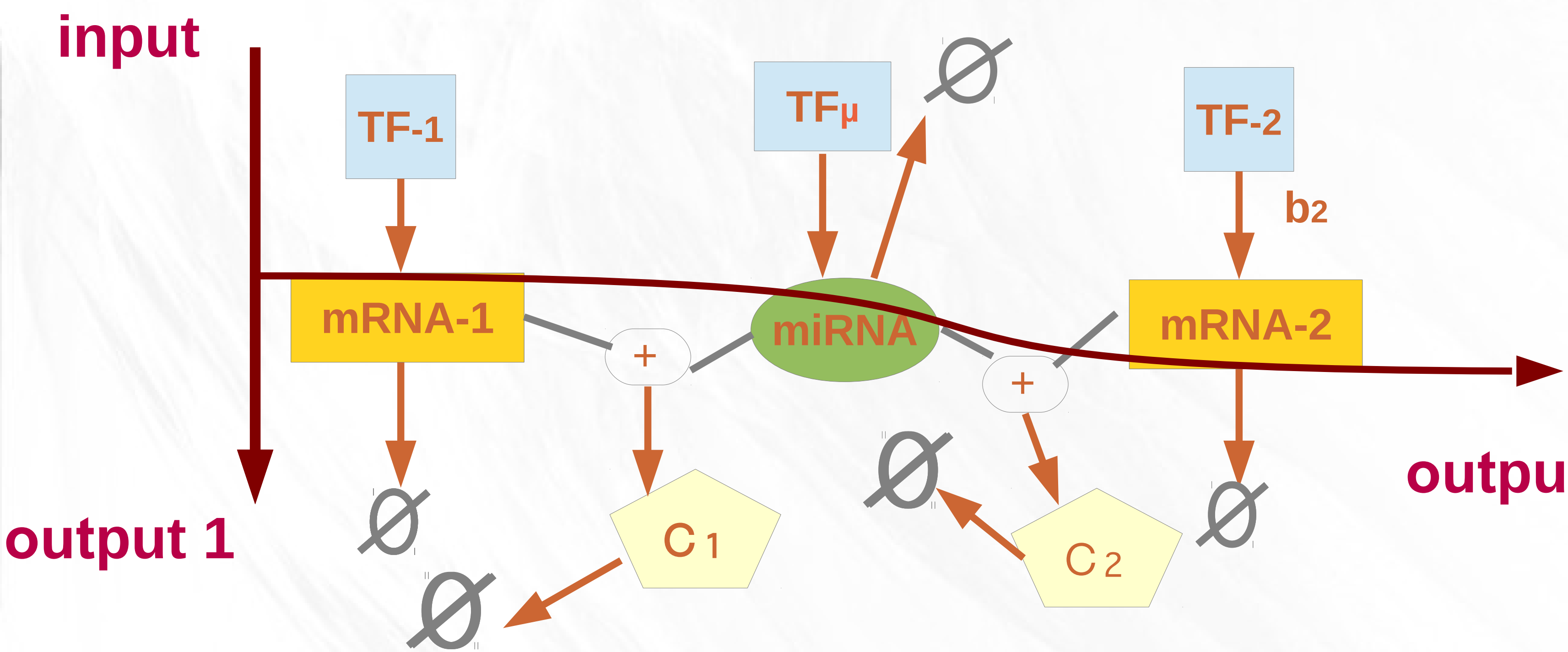


Figure: Red curve: input-output relation.
Orange curve: optimal input distribution.

MI calculated according to its definition: 4.023839 bit
MI calculated according to the formula : 4.098728 bit

Optimization
with respect to the input distribution



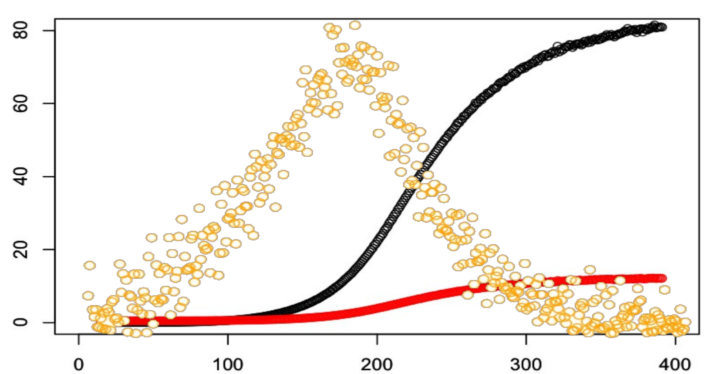


Figure:
Black curve: TF1-mRNA1 relation.
Red curve: TF1-mRNA2 relation.
Orange curve: optimal input distribution.

MI calculated according to its definition: 1.887141 bit
MI calculated according to the formula : 2.105024 bit

Open Questions

Conclusions

1) miRNA-mediated regulation on gene expression can be well-quantified by the mutual information.

Open Questions

Conclusions

1) miRNA-mediated regulation on gene expression can be well-quantified by the mutual information.

2)The principle of maximizing mutual information finds the best performance regime of the miRNA-regulatory element.

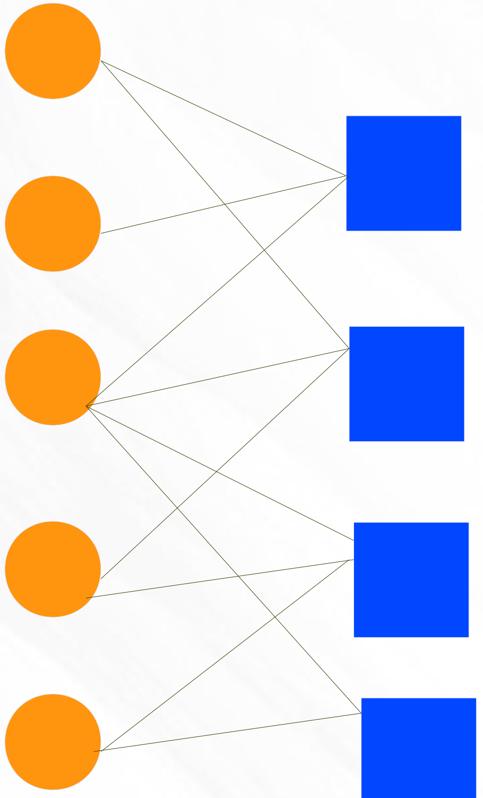
Open Questions

Open Questions

- Optimization
  Ongoing @ Sapienza, Rome

- Experiments, Integration of Other PTR
  Ongoing @ HUGEF, Torino

- Large Regulatory Networks
  To be started @ ICTP, Trieste



Thank you to:

- NETADIS
- Andrea De Martino, Enzo Marinari, Matteo Figliuzzi
- Andrea Pagnani, Riccardo Zecchina, Carla Bosia, Carlo Baldassi, Corinna Giorgi

- you, for your attention!