

Information Processing in Genetic Regulatory Networks



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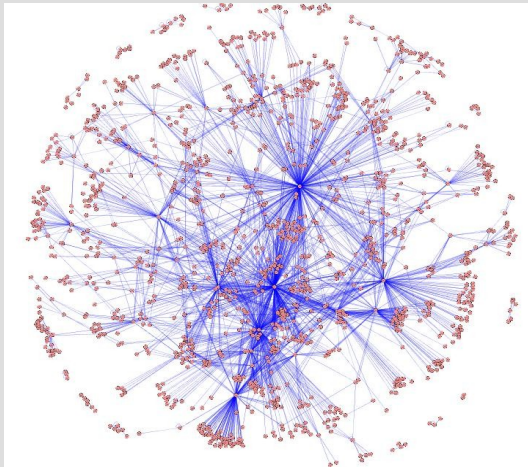
Pascale Romby

Pierre Fechter

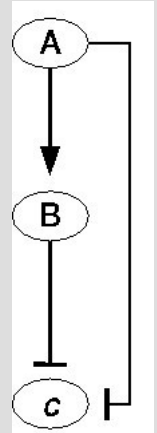
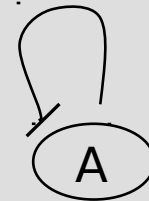
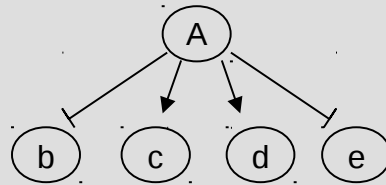
Network and motifs



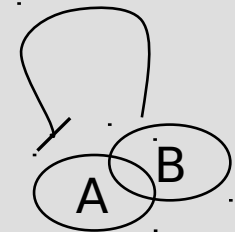
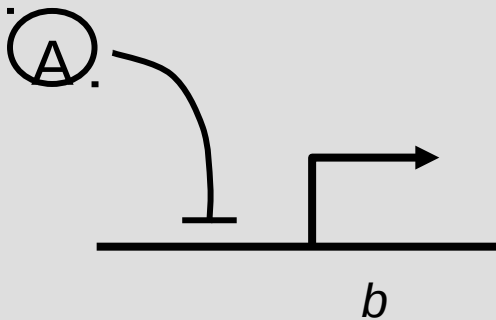
Transcriptional network of *E. coli*



Motifs



Other modules

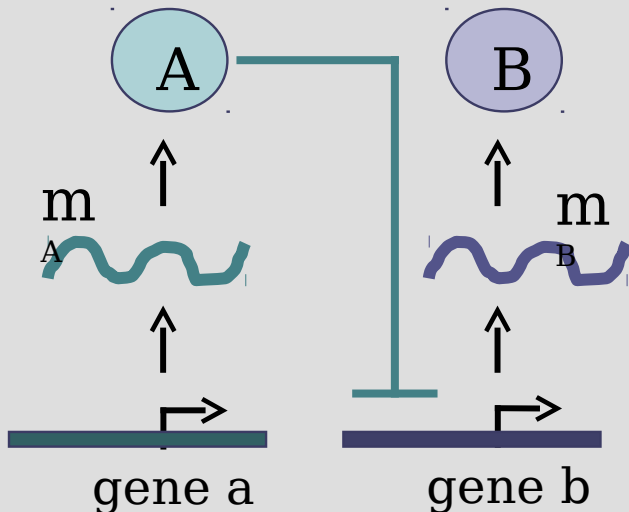


Regulation Mechanisms

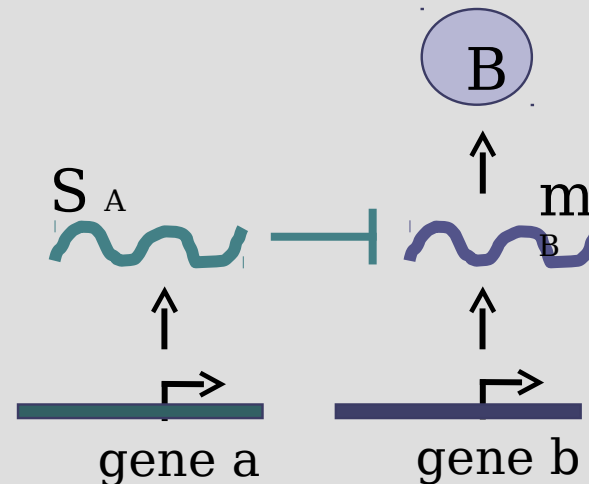


- Different levels of regulation
 - Transcriptional regulation
 - Post-transcriptional regulation (by sRNA-mRNA int.)
 - Post-translational regulation (by protein-protein int.)

Transcriptional regulation



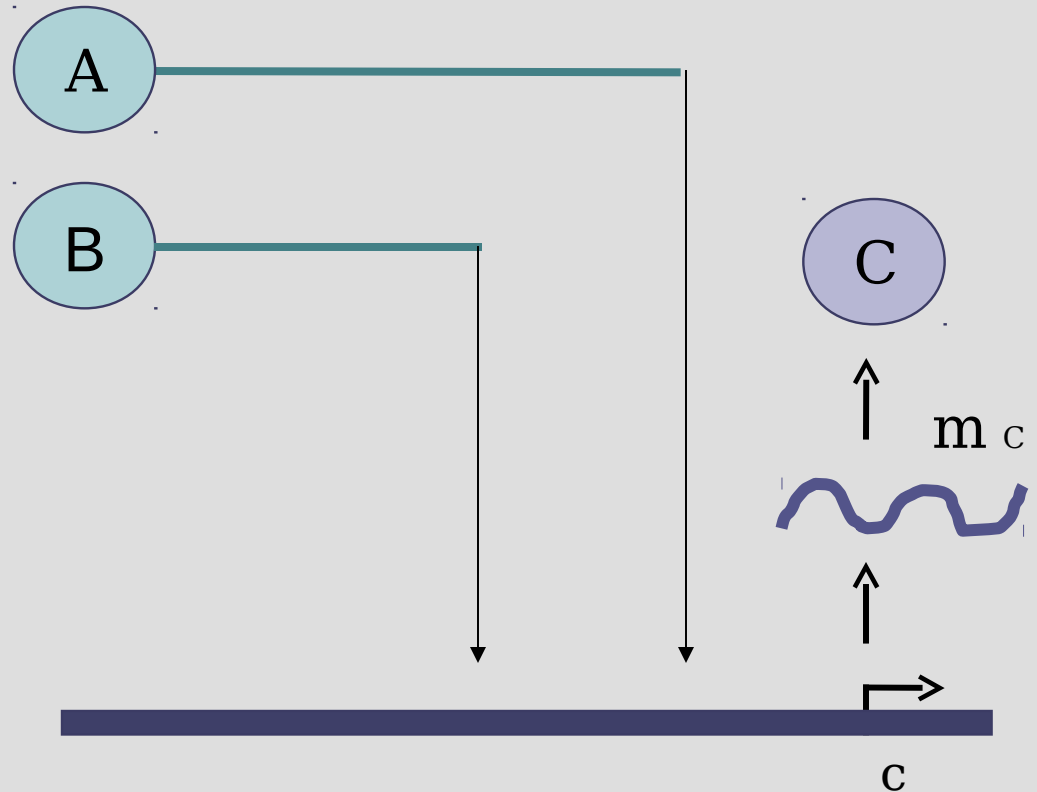
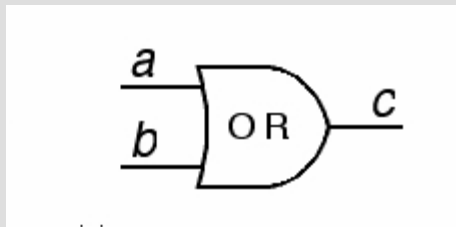
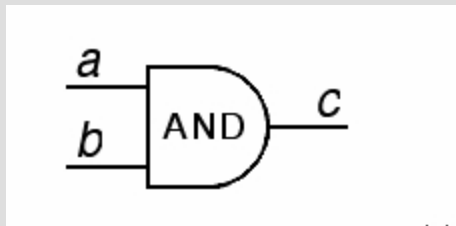
Post-transcriptional regulation



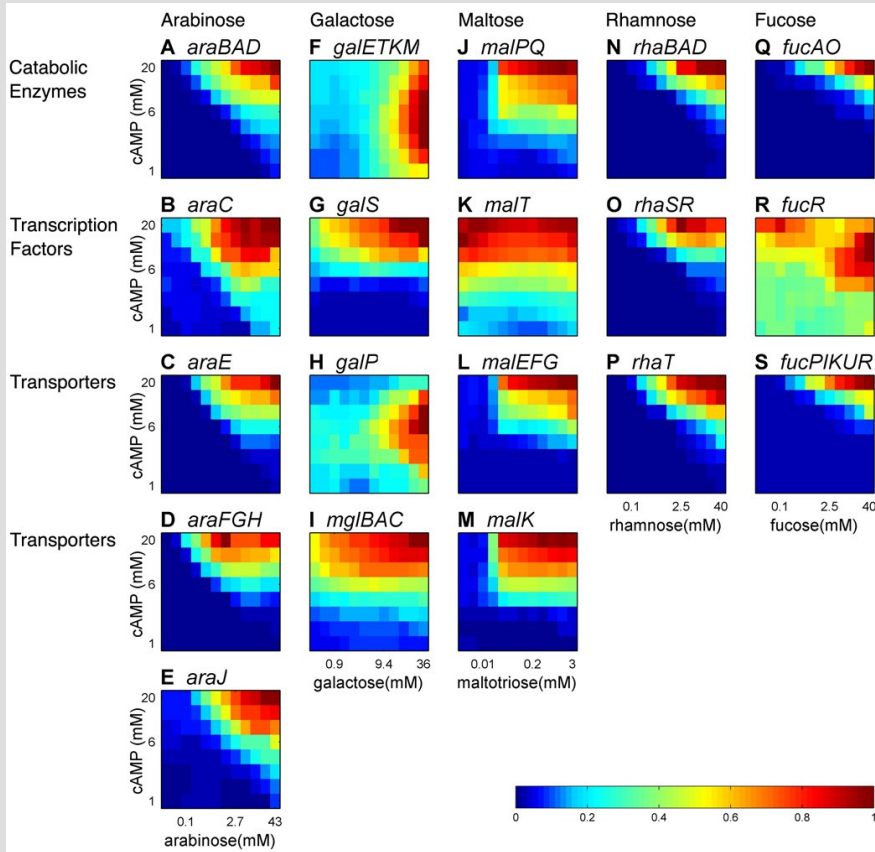
Information processing



Transcriptional regulation

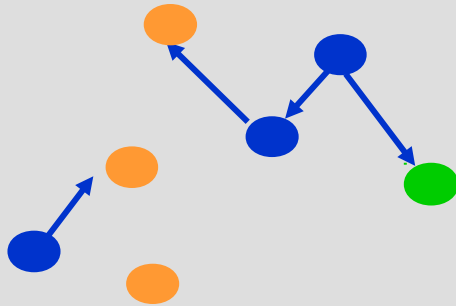


Input Functions

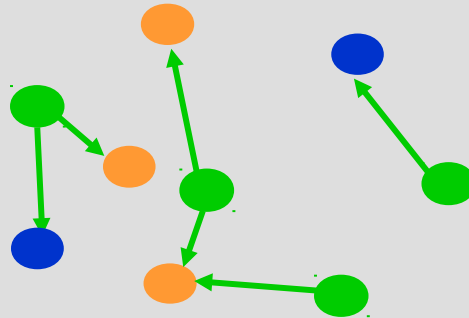


Diverse two-dimensional input functions control bacterial sugar Genes, Kaplan, Bren, Zaslaver, Dekel and Alon, Molecular Cell 29, 783 (2008).

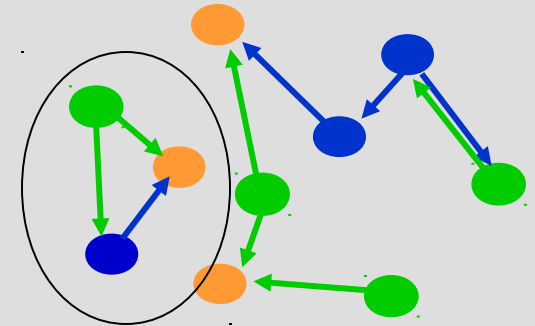
Multi-layer regulatory circuits



Transcription regulation



Post-transcriptional regulation by ncRNA



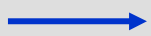
Multi-layer feed-forward loop



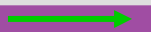
ncRNA



Transcription factor



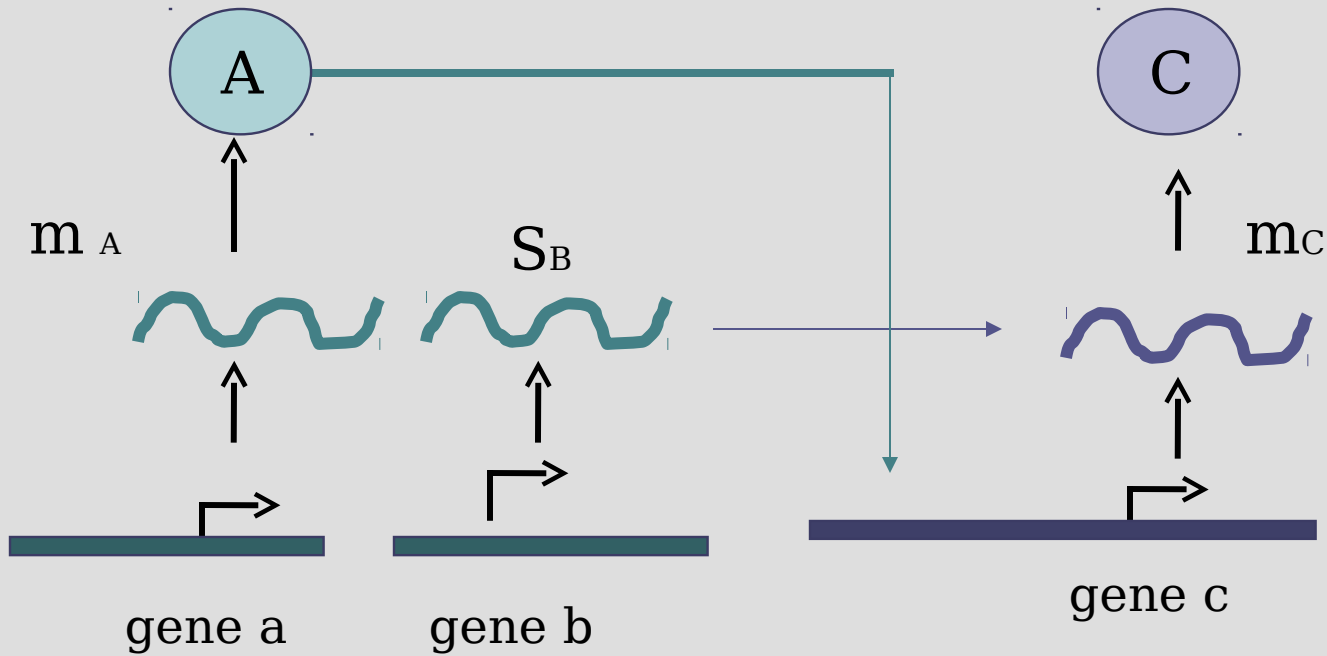
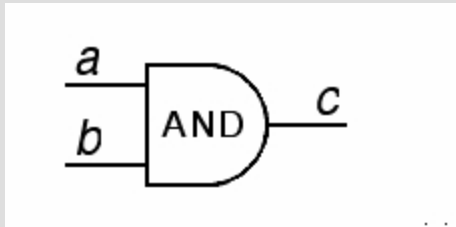
Transcription regulation



Post-transcriptional regulation

Asaf Peer, Mor Nitzan,
Zohar Itzhaki, Hanah Margalit

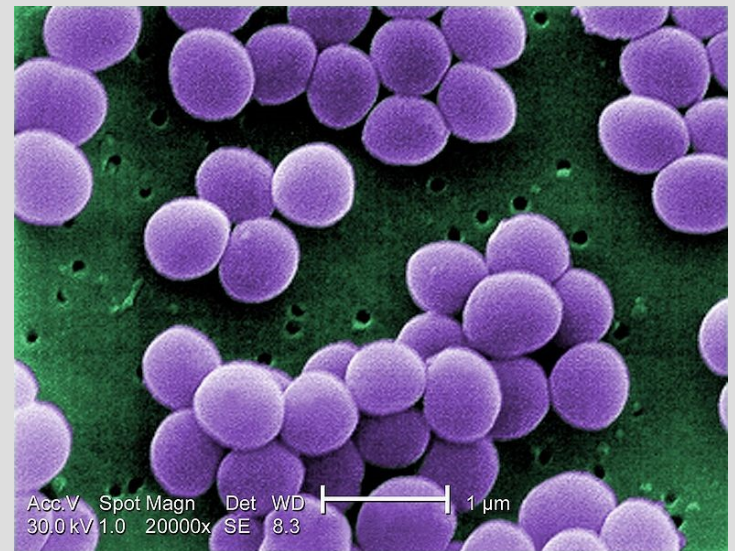
Combination of regulations at different levels



Staphylococcus aureus



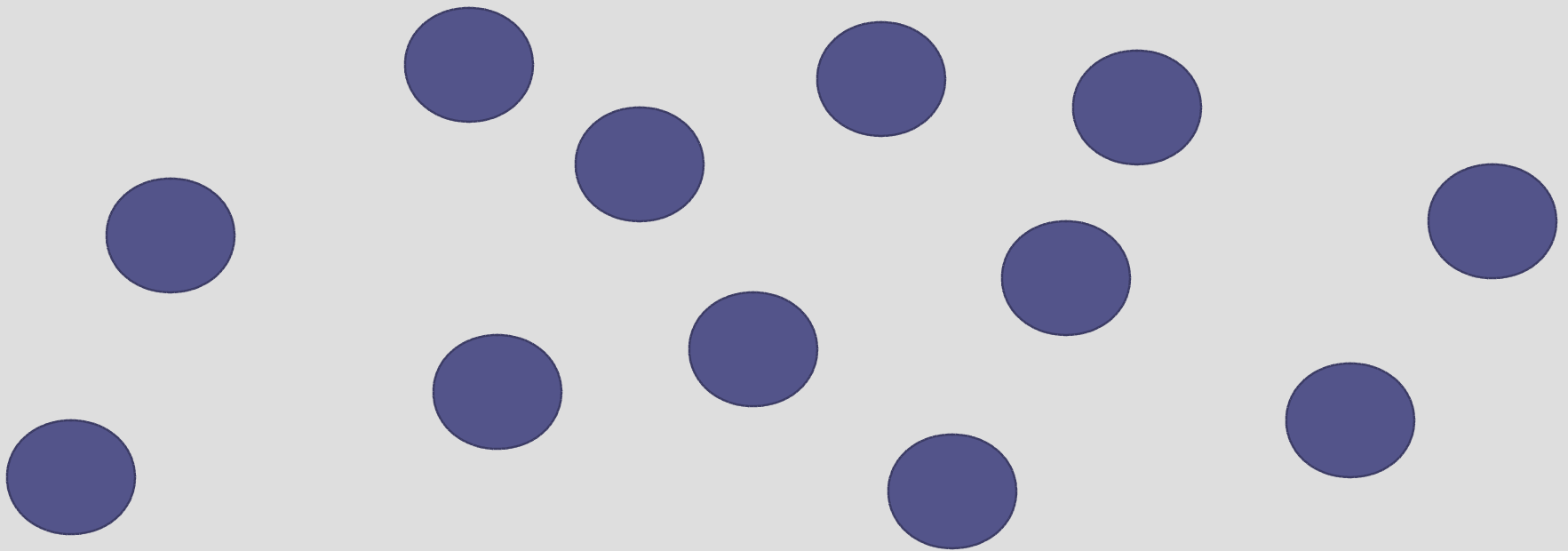
- Pathogenic bacteria
- Cause a wide range of human diseases
- Disease manifestations depend on the expression of numerous virulence factors
- Within *S. aureus* virulence pathways lies a regulator switch that is induced by a quorum sensing signal



Quorum sensing for a growing population



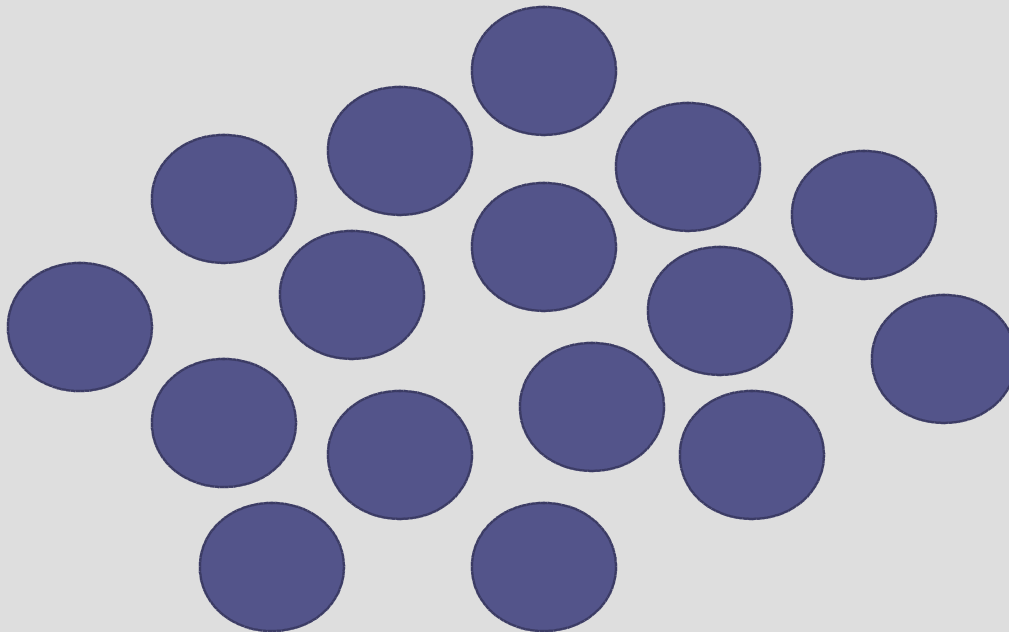
- At low numbers, violent bacteria will be quickly targeted for degradation
- Only at higher numbers, the bacteria become virulent.



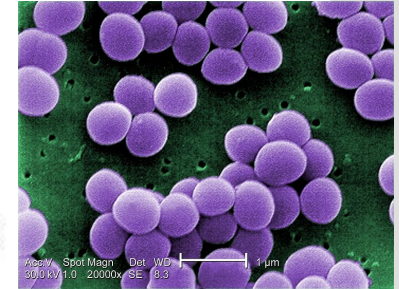
Quorum sensing for a dense population



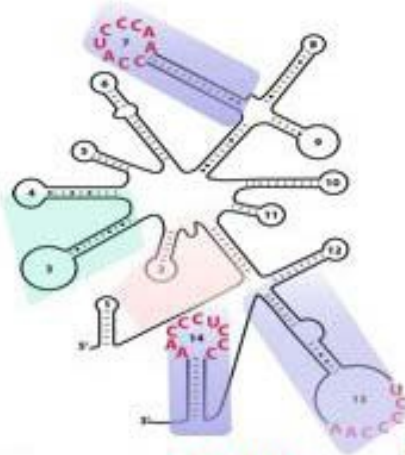
- Outer bacteria act as a shield
- Inner, protected bacteria excrete violent proteins



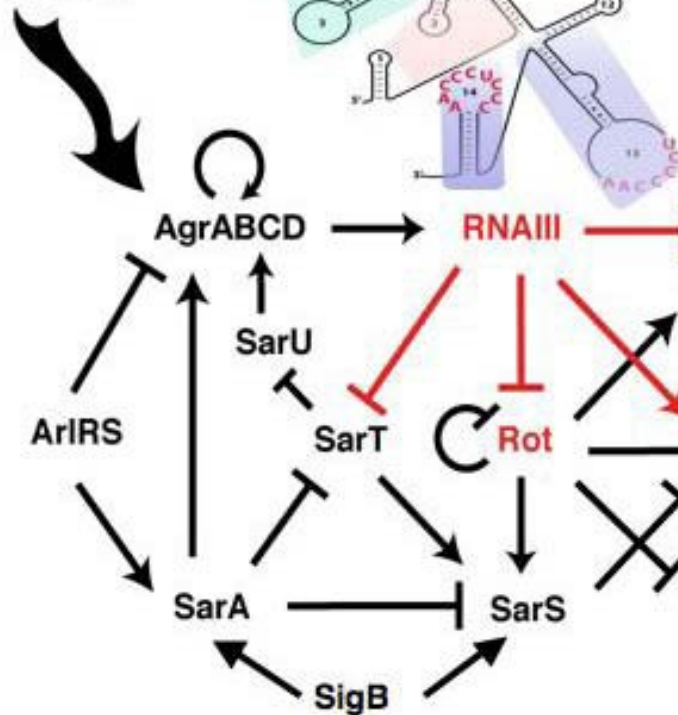
S. aureus virulence path



quorum sensing
cell density



response
virulence factors & other mRNAs



known targets:

coa (coagulase)
fib (fibrinogen binding protein)
spa (protein A)
SA2353 (SsaA-like)
lytM (peptidoglycan hydrolase)

hla (hemolysin)

aur (aureolysin)
geh (lipase)
hld (hemolysin)
spiABCDEF (serine proteases)
sspAB (serine proteases)

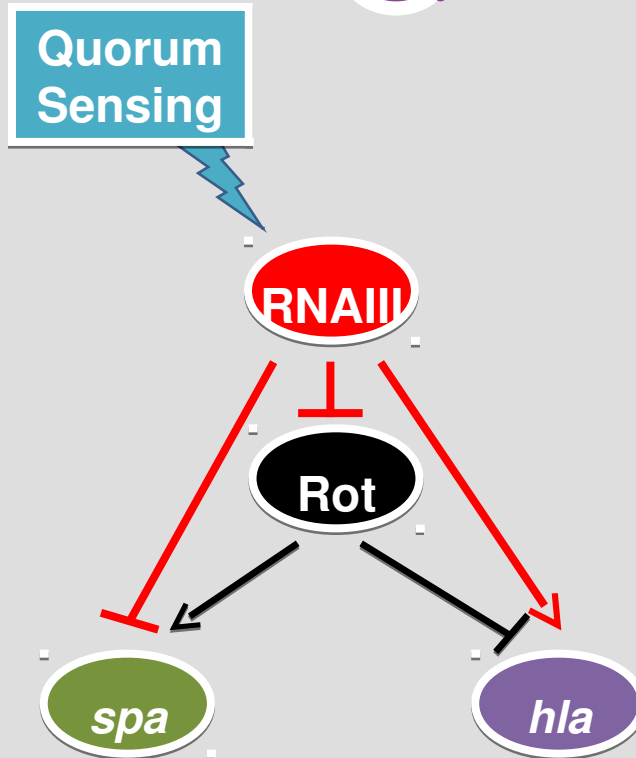
Adhesion



Dissemination



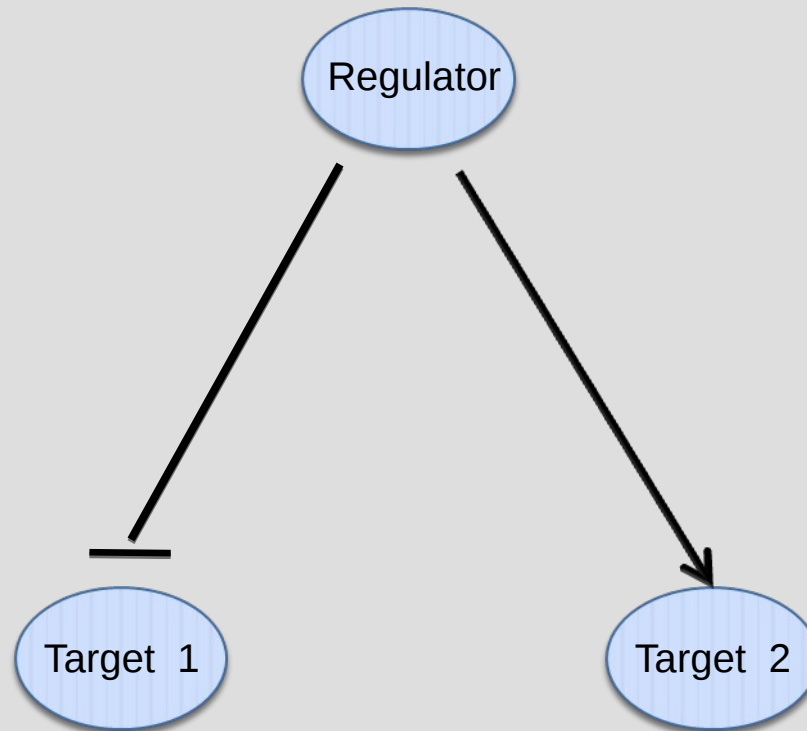
The Switch



**Adhesins, camouflage proteins
(defensive state)**

**Exotoxins,
 α -hemolysin
(offensive state)**

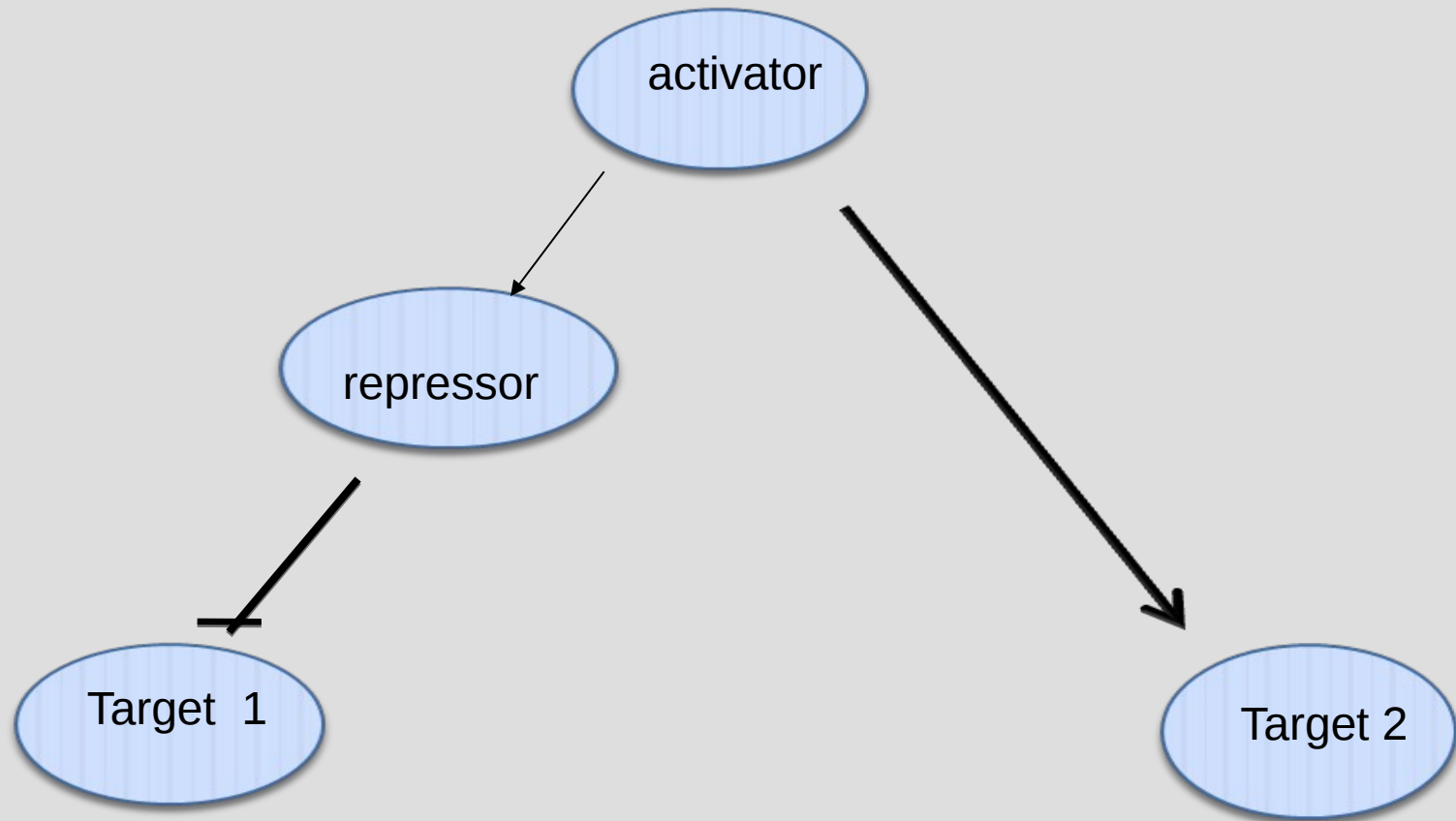
A Simpler Switch



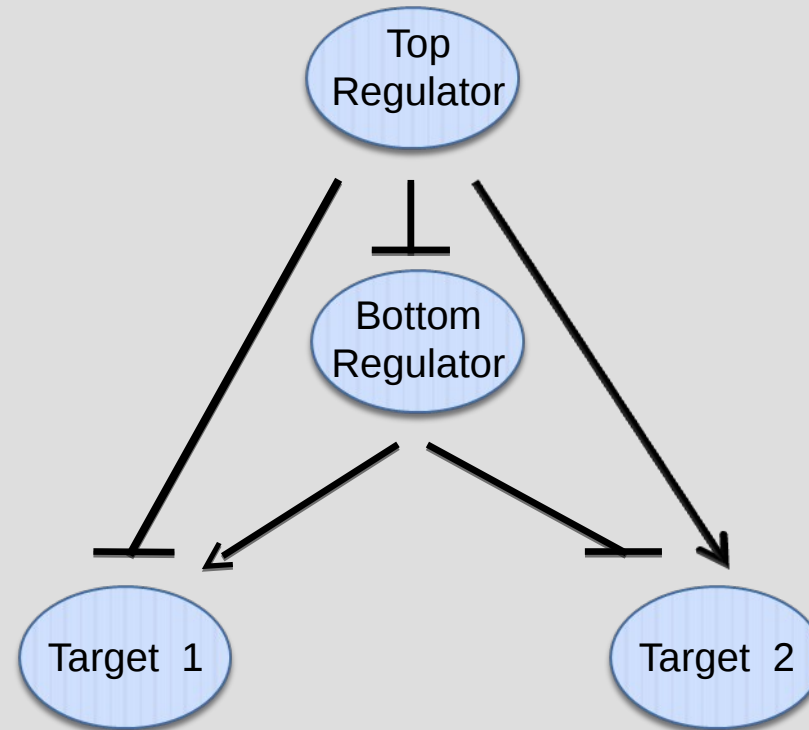
Selector Switch



Selector Switch without activator/repressor



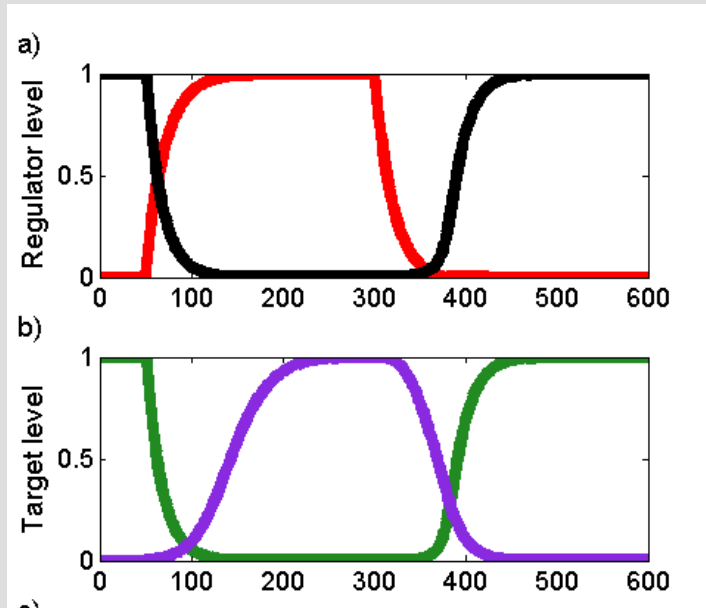
Double Selector Switch



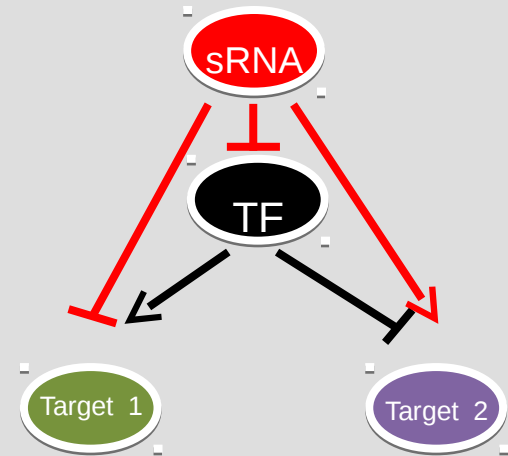
The model- rate equations

$$\frac{dN_S}{dt} = g_S - b_S N_S (N_{Rm} + N_{1m} + N_{2m}) - d_S N_S \quad (\text{sRNA regulator})$$
$$\frac{dN_{Rm}}{dt} = g_m - b_S N_S N_{Rm} - d_m N_{Rm} \quad (\text{mRNA transcripts of TF})$$
$$\frac{dN_{RP}}{dt} = g_P N_{Rm} - d_P N_{RP} - [b_R N_{RP} (1 - N_{R1}) - u_R N_{R1} + b_R N_{RP} (1 - N_{R2}) - u_R N_{R2}] \quad (\text{TF protein})$$
$$\frac{dN_{R1,2}}{dt} = b_R N_{RP} (1 - N_{R1,2}) - u_R N_{R1,2} \quad (\text{TF - promoter complexes})$$
$$\frac{dN_{1m}}{dt} = g_m N_{R1} - d_m N_{1m} - b_S N_S N_{1m} \quad (\text{mRNA transcripts of target 1})$$
$$\frac{dN_{2m}}{dt} = g_m (1 - N_{R2}) - d_m N_{2m} - b_S N_S N_{2m} \quad (\text{mRNA transcripts of target 2})$$
$$\frac{dN_{1P}}{dt} = g_P N_{1m} - d_P N_{1P} \quad (\text{Target 1 proteins})$$
$$\frac{dN_{2P}}{dt} = g_P^{S2} N_{S2} + g_P^{2m} N_{2m} - d_P N_{2P} \quad (\text{Target 2 proteins})$$
$$\frac{dN_{S1,2}}{dt} = b_S N_S N_{1,2m} - u_S N_{S1,2} \quad (\text{sRNA - target mRNA complexes})$$

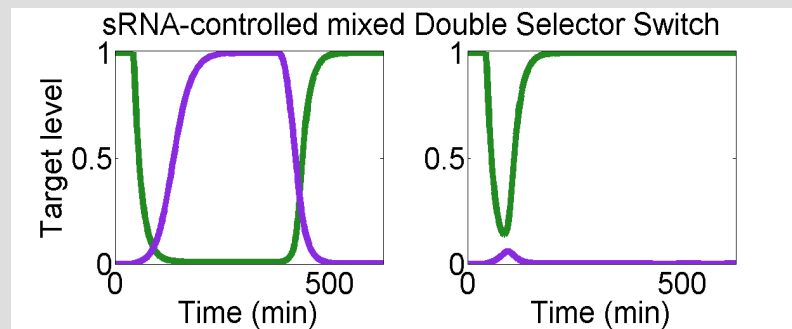
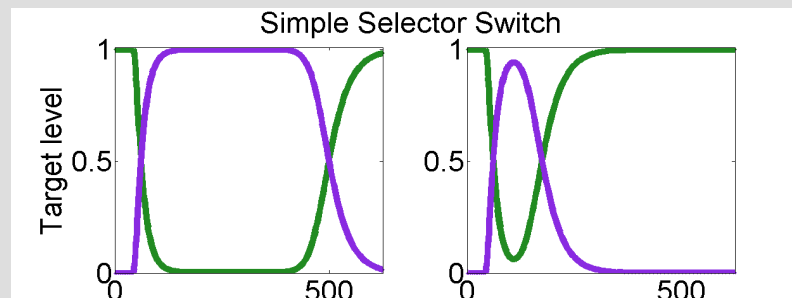
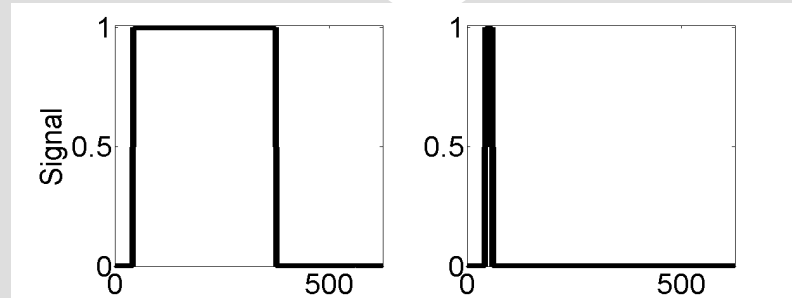
Switching on and off



Time (min)



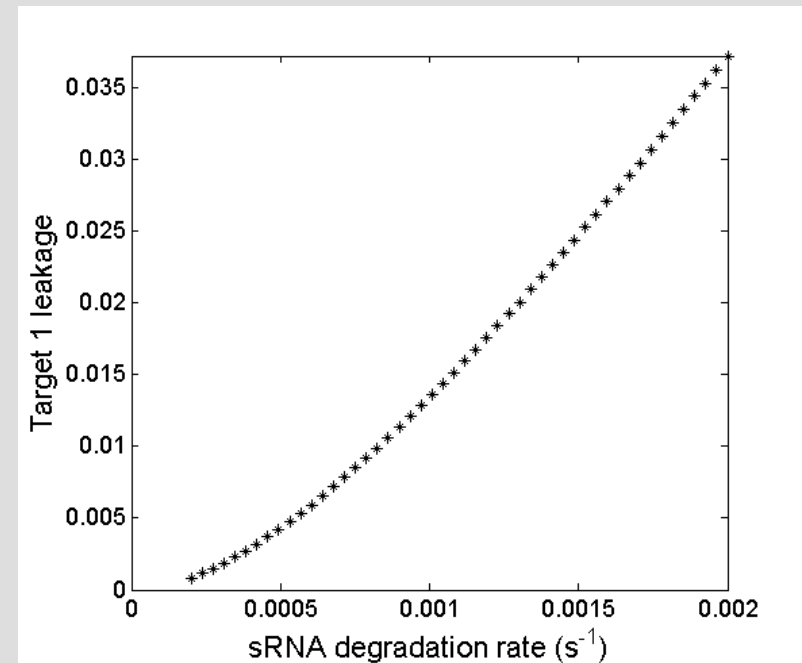
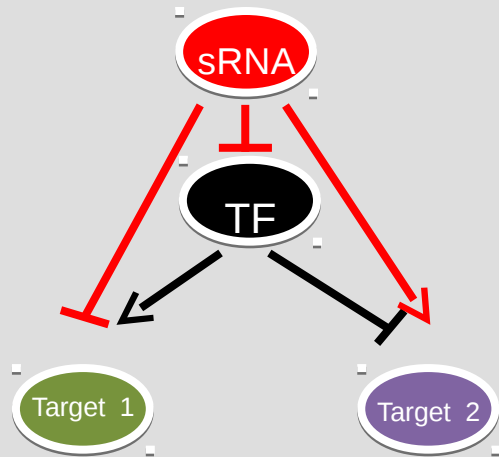
Response to a spike



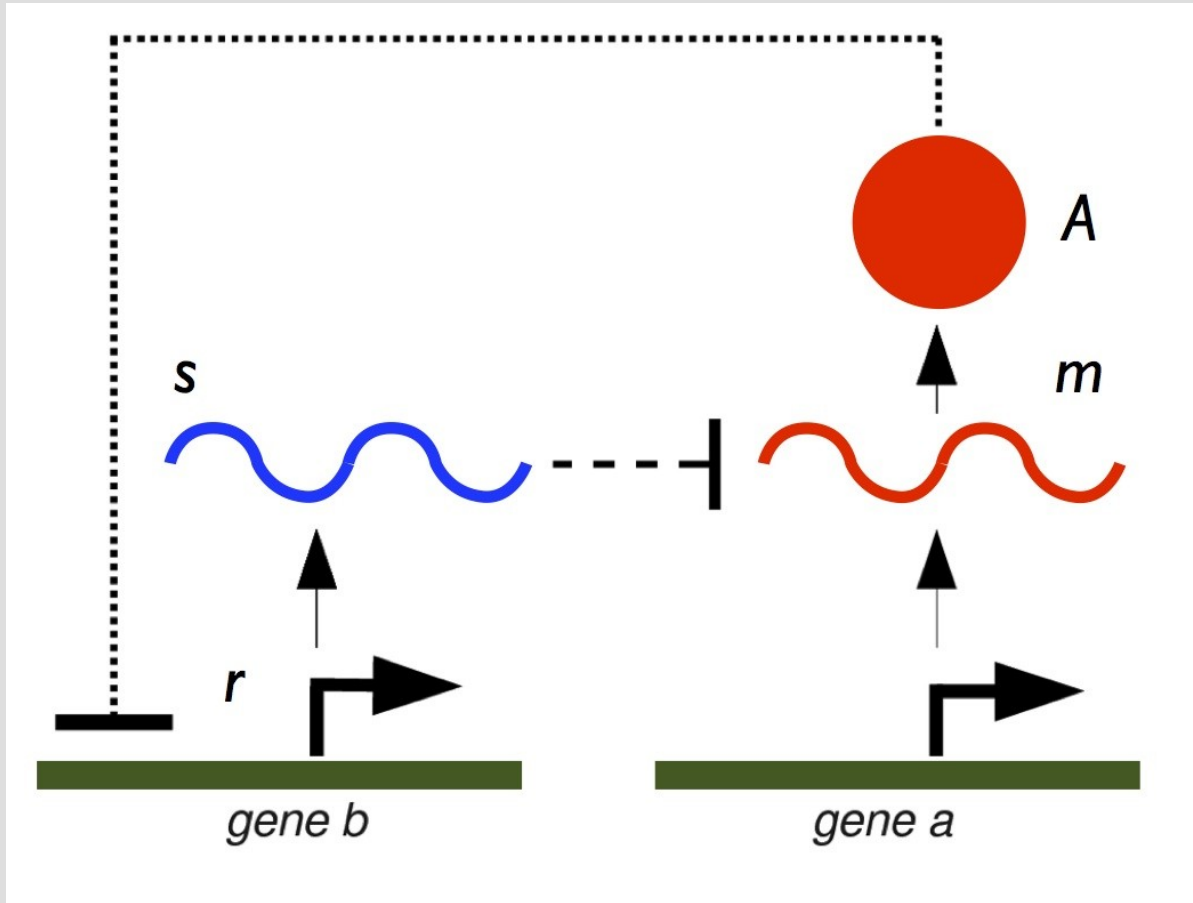
Leakage of Target 1



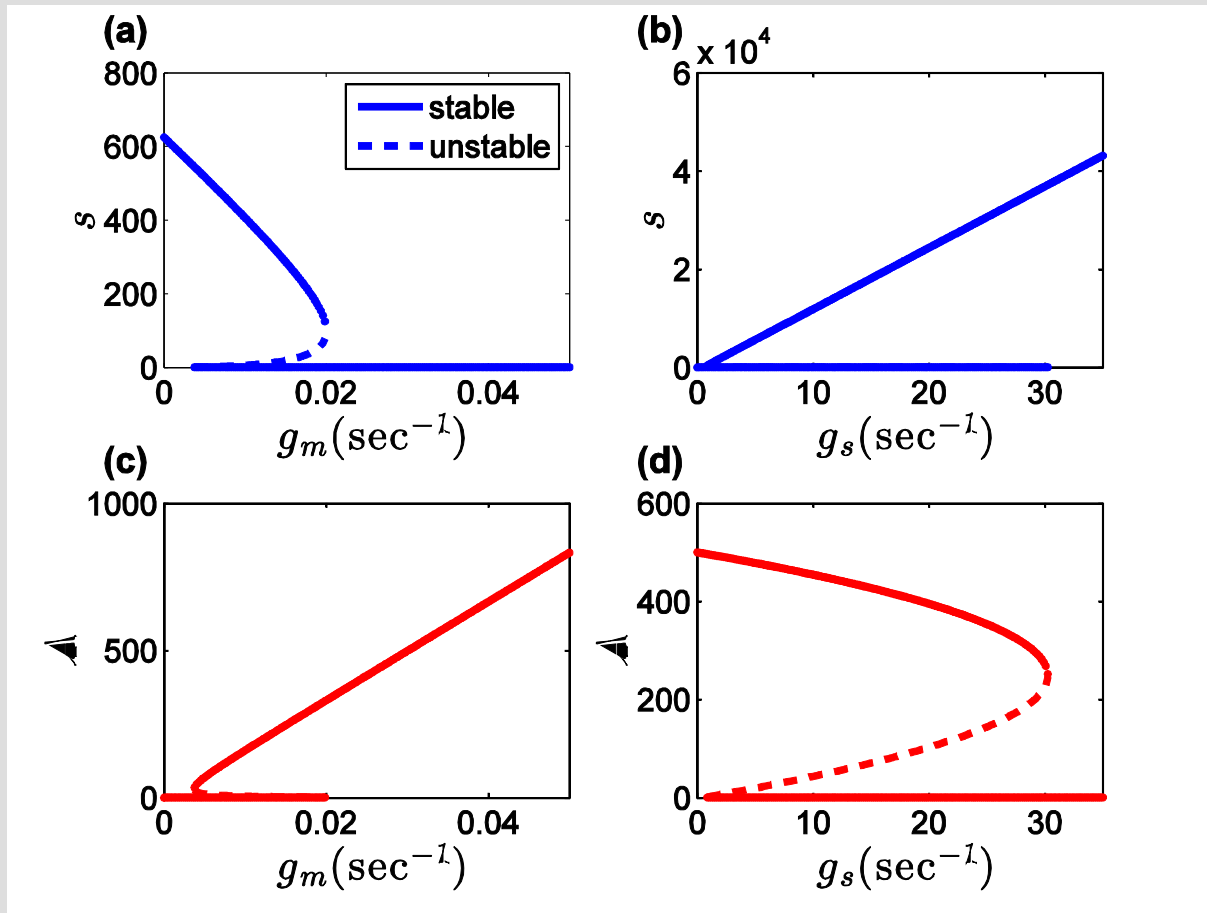
$$\text{Leakage} = \frac{\frac{b_T}{u_T} N_{TP}}{\left(1 + \frac{b_T}{u_T} N_{TP}\right)} \frac{1}{\left(1 + \frac{b_s}{d_m} N_s\right)}$$



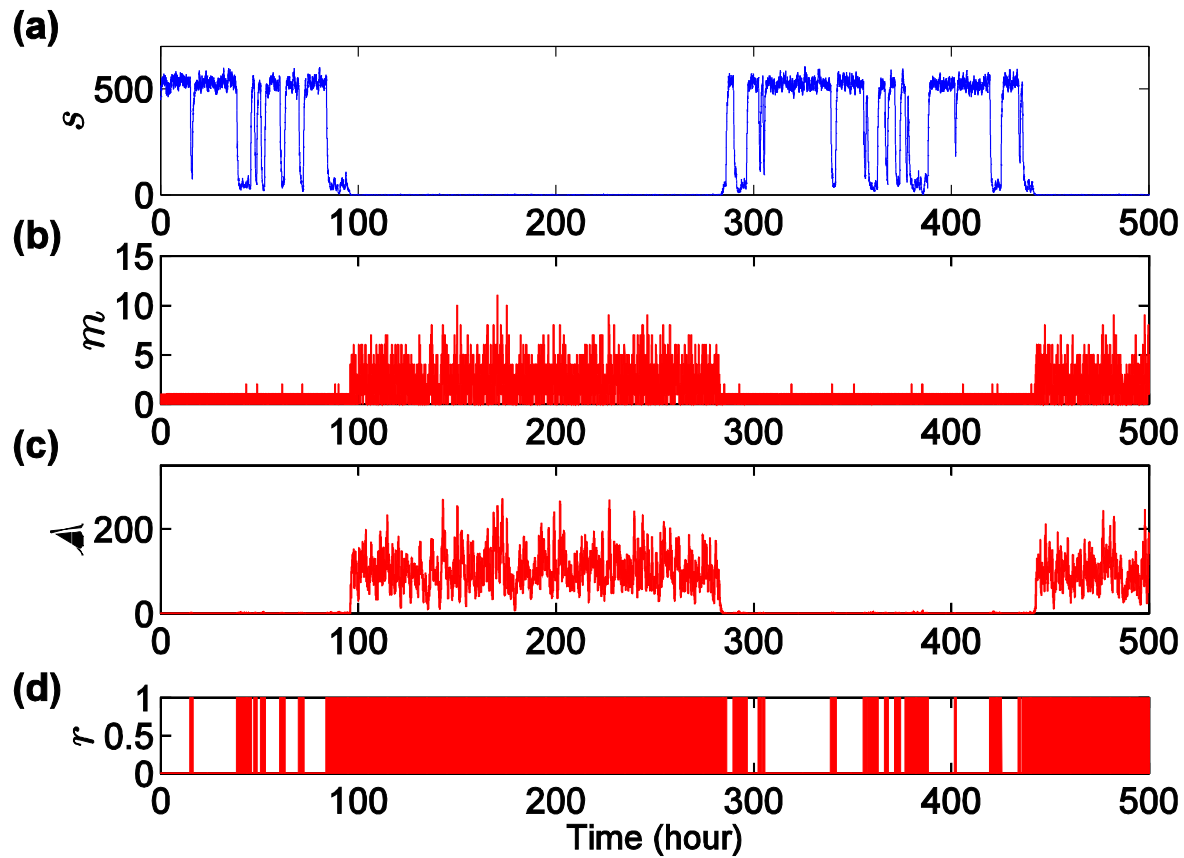
Mixed Feedback Loop



Bifurcation Diagrams



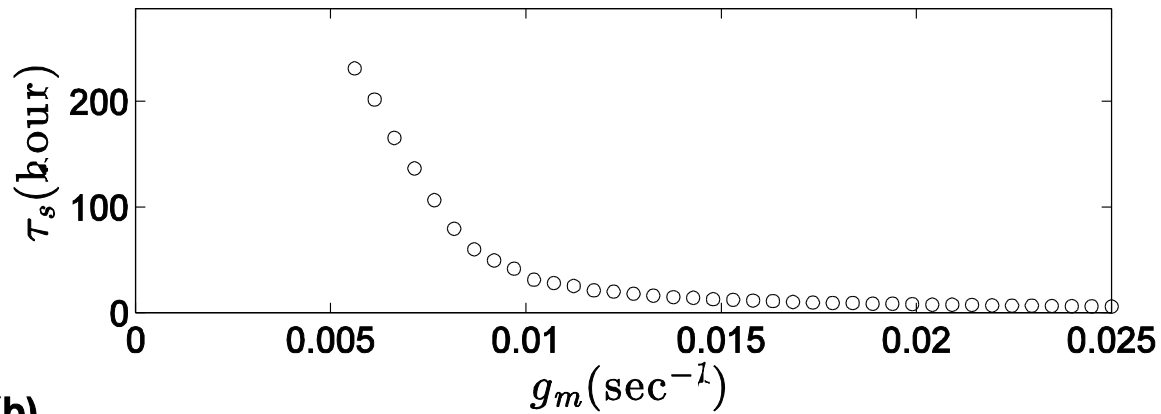
Stochastic Trajectories



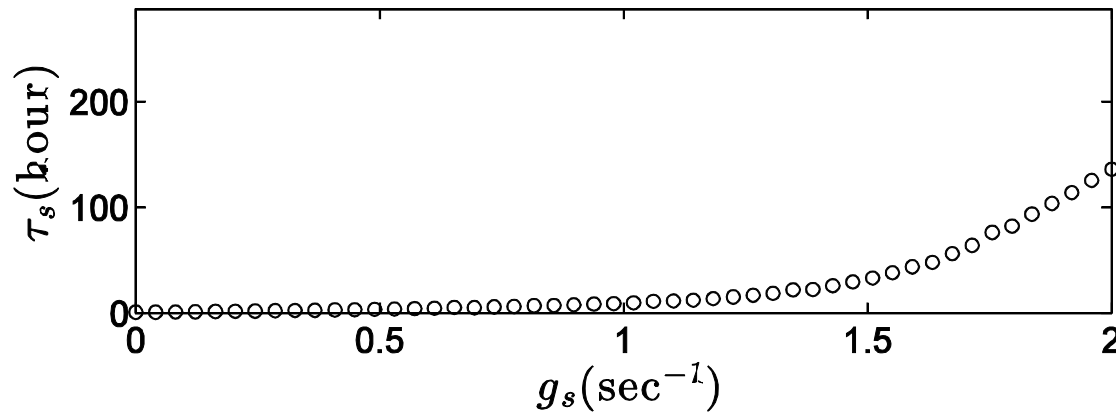
Life-times of bistable states



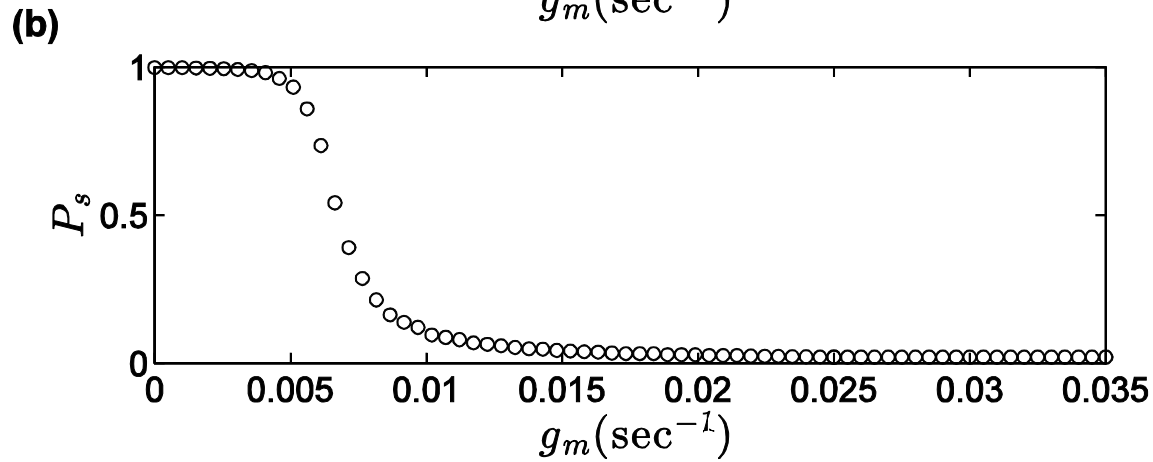
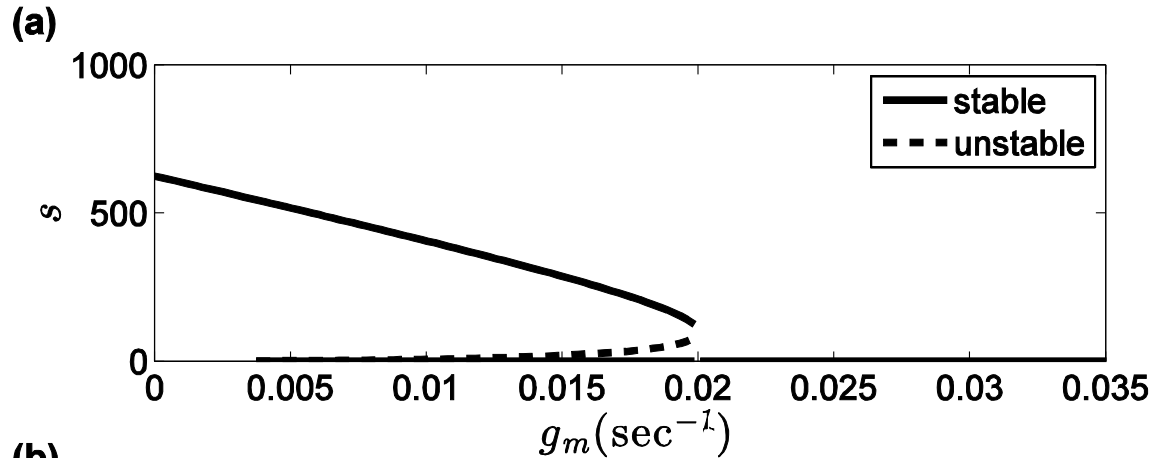
(a)



(b)

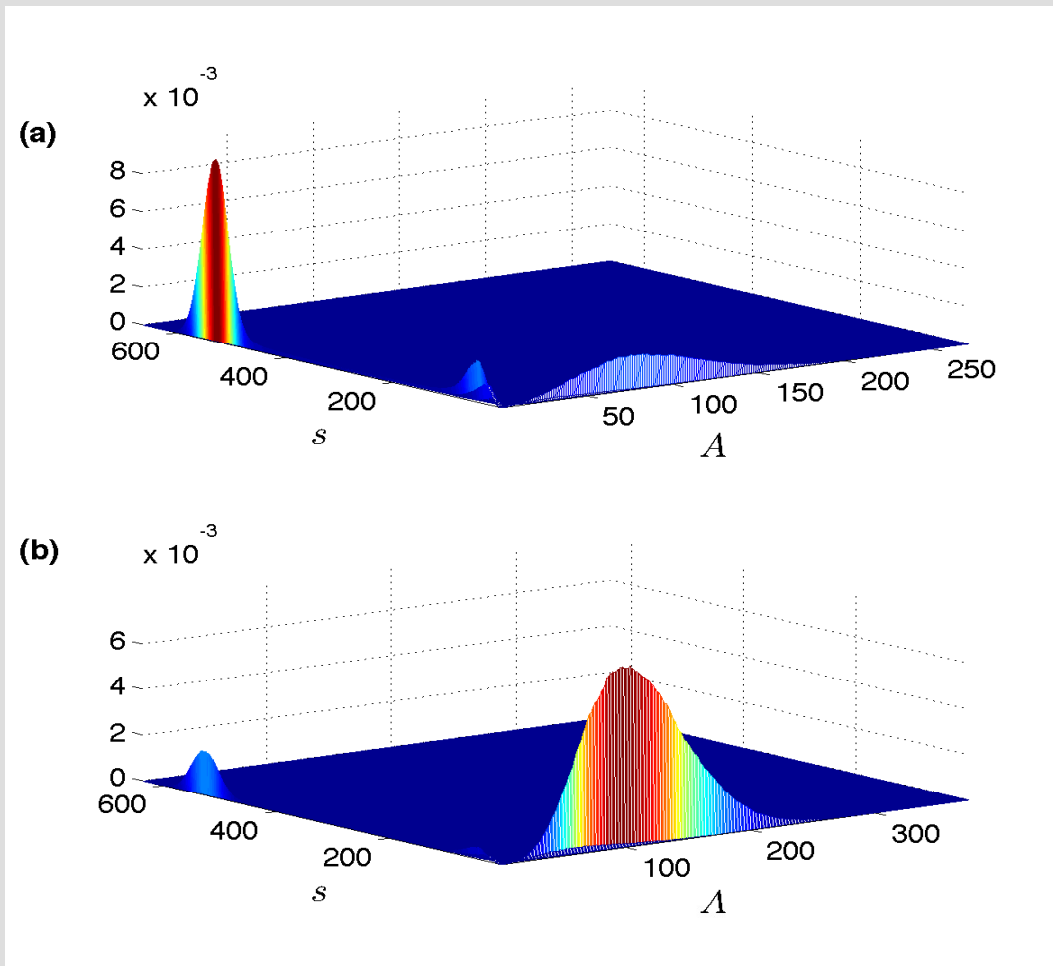


Deterministic vs. Stochastic Models

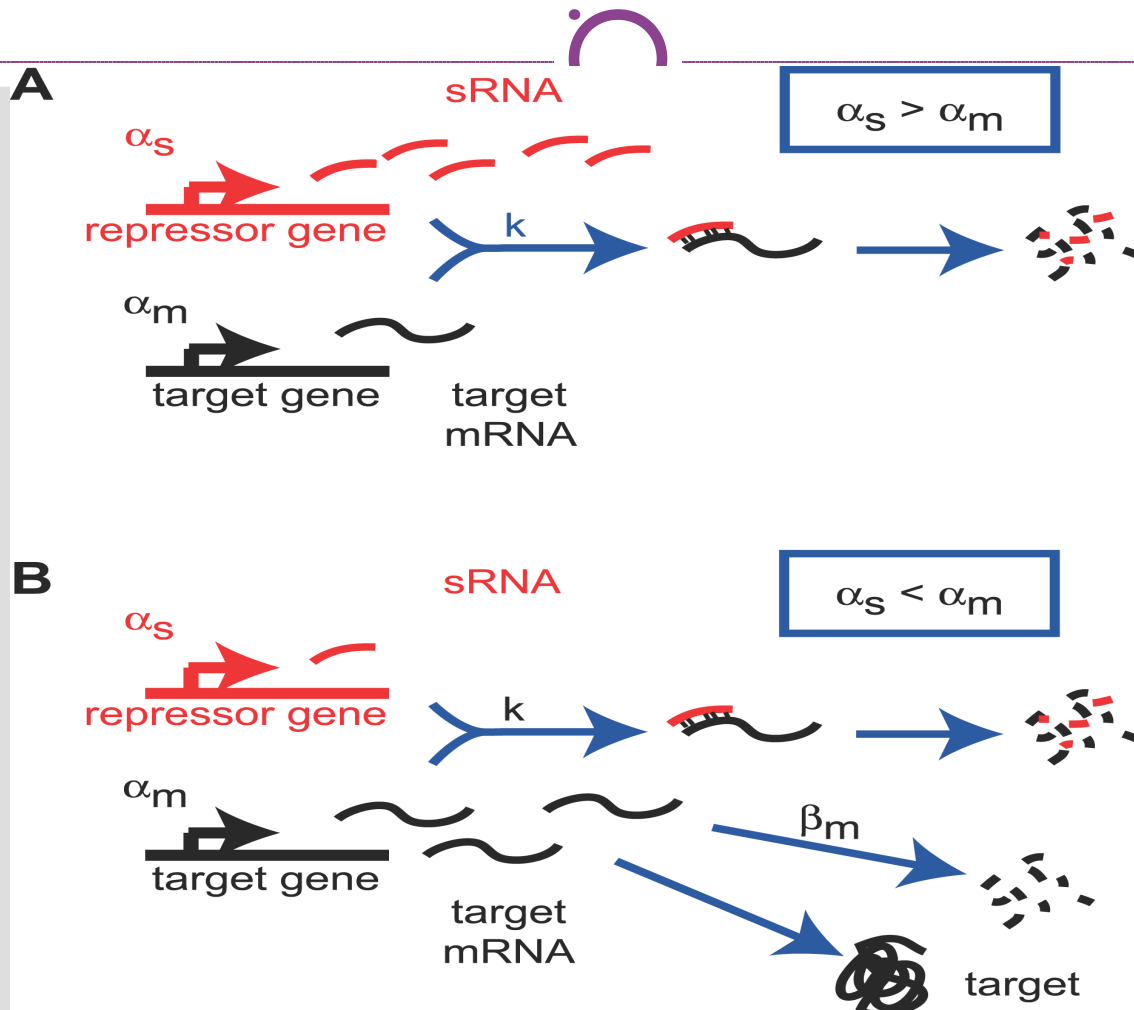


$$P_s = \frac{\tau_s}{\tau_s + \tau_A}$$

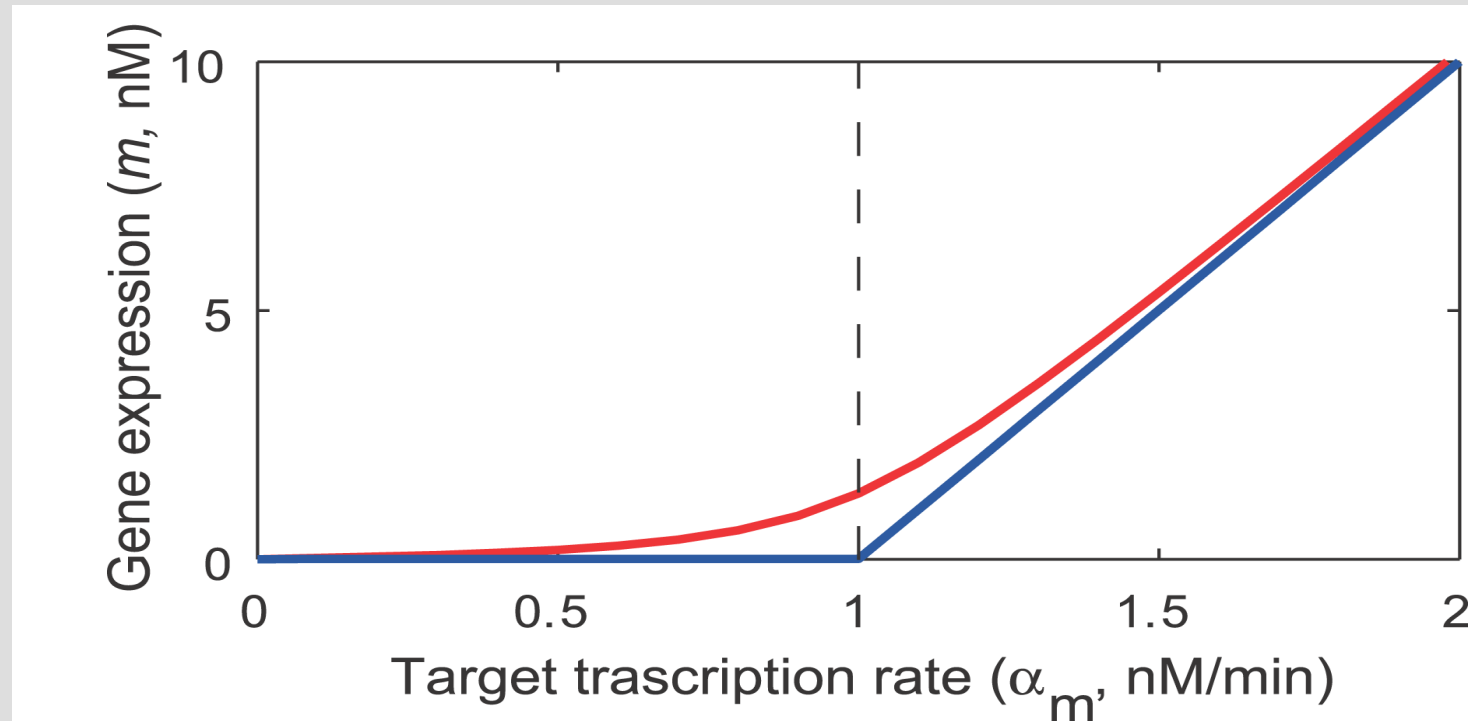
Probability Distribution



sRNA-target interaction



Fine-tuning of target expression

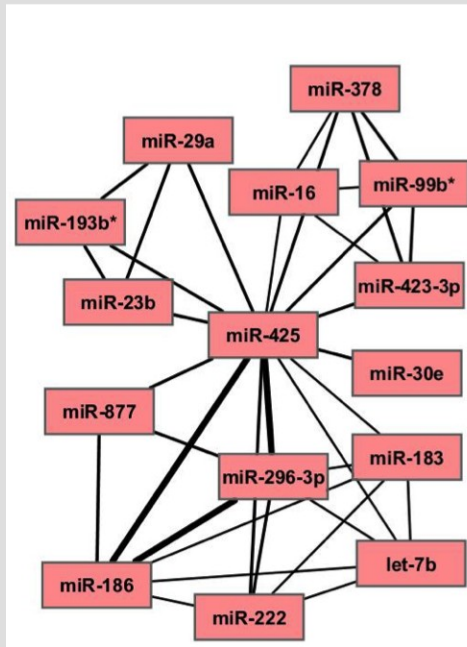


E. Levine, Z. Zhang, T. Kuhlman and T. Hwa, Plos. Biol. (2007)

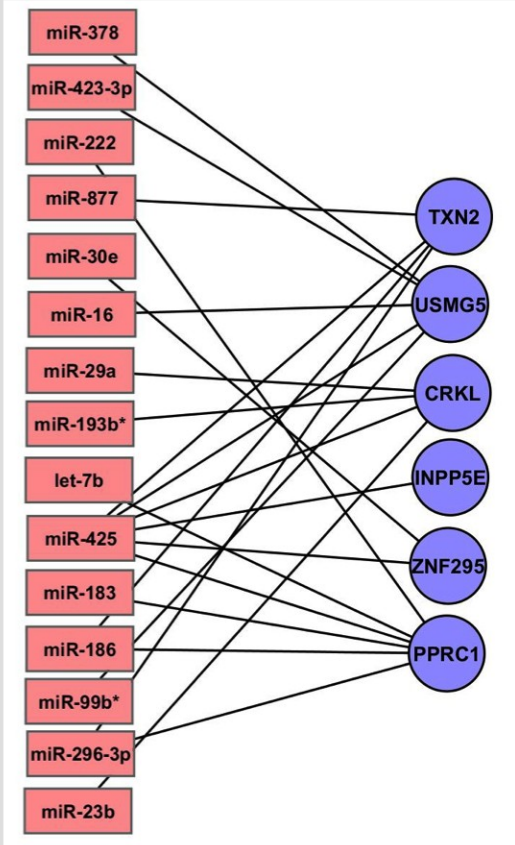
Post transcriptional network in HEK293 Cells



miRs

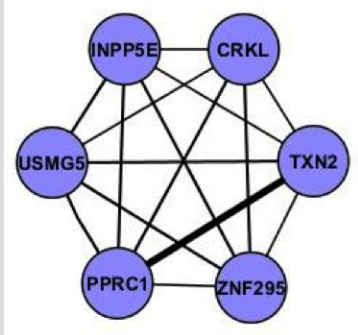


ASPL= 2.011
C= 0.755
 $\sigma = 4.015619$



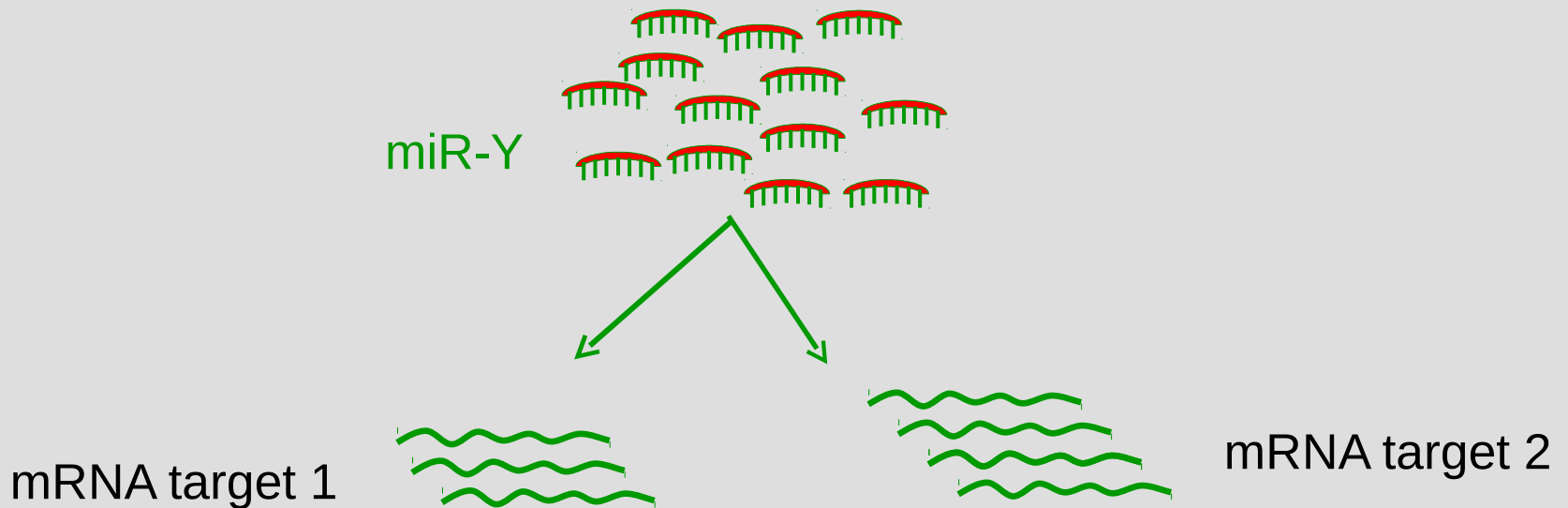
ASPL= 3.894

targets



ASPL= 1.9456
C= 0.8044
 $\sigma = 7.8$

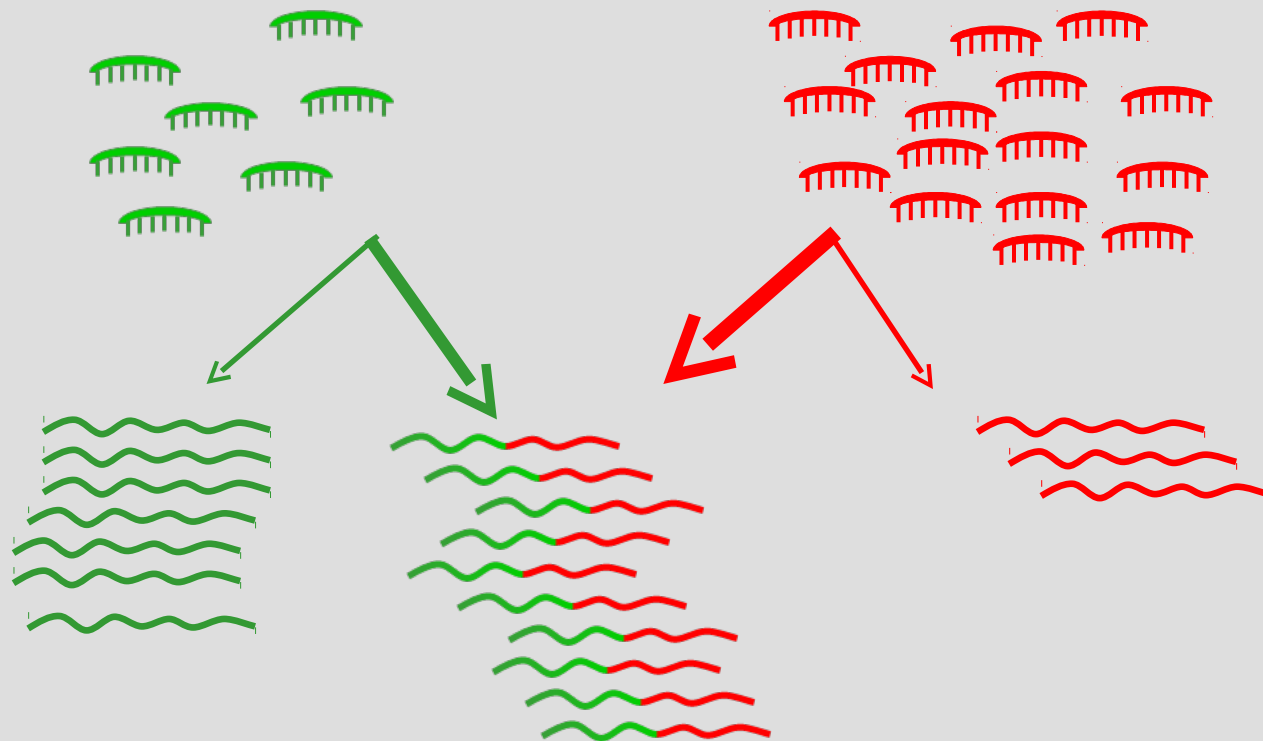
Crosstalk between Competing endogenous RNAs (ceRNAs)



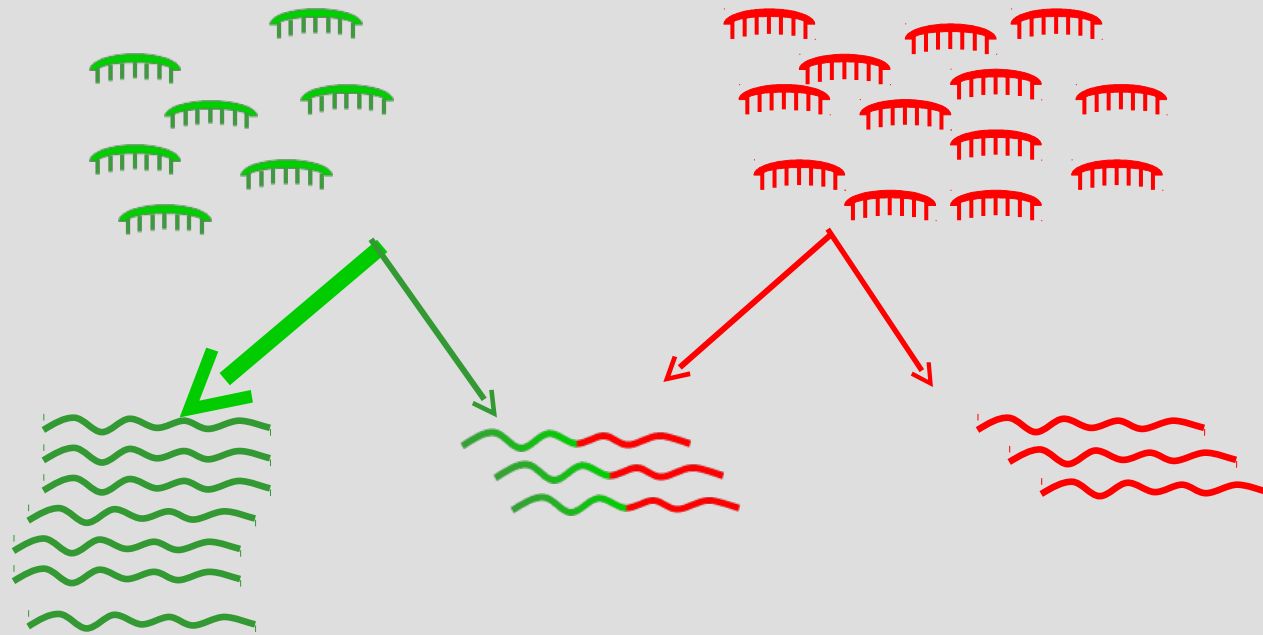
;Salmena et al., Cell 146, 353 (2011); Tay et al., Cell 147, 344 (2011)

Bosia et al., Plos One 8, e66609 (2013); Figliuzzi et al., Biophys J. 104, 1203 (2013)

Crosstalk between ncRNAs



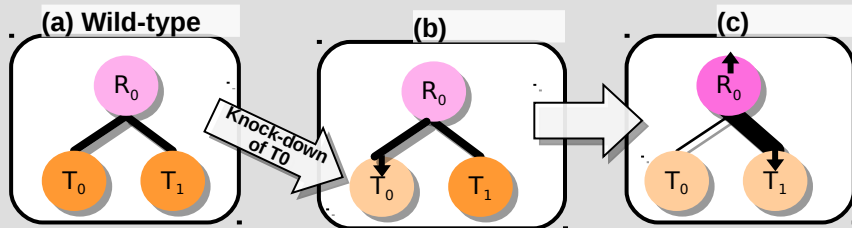
Crosstalk between mRNAs through their common regulators



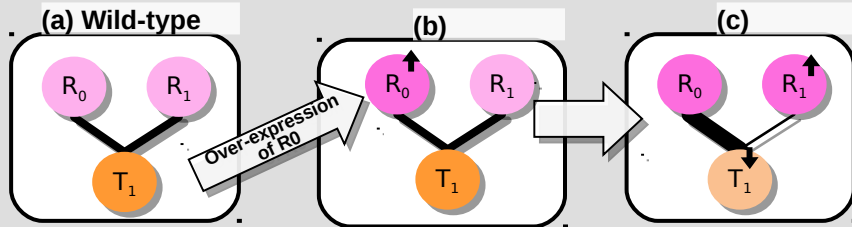
Fast Transmission of Signals



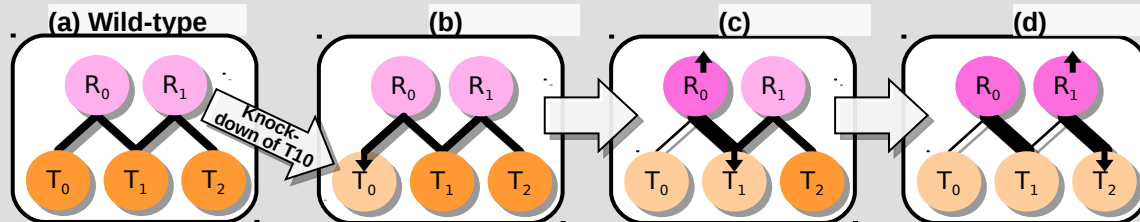
A



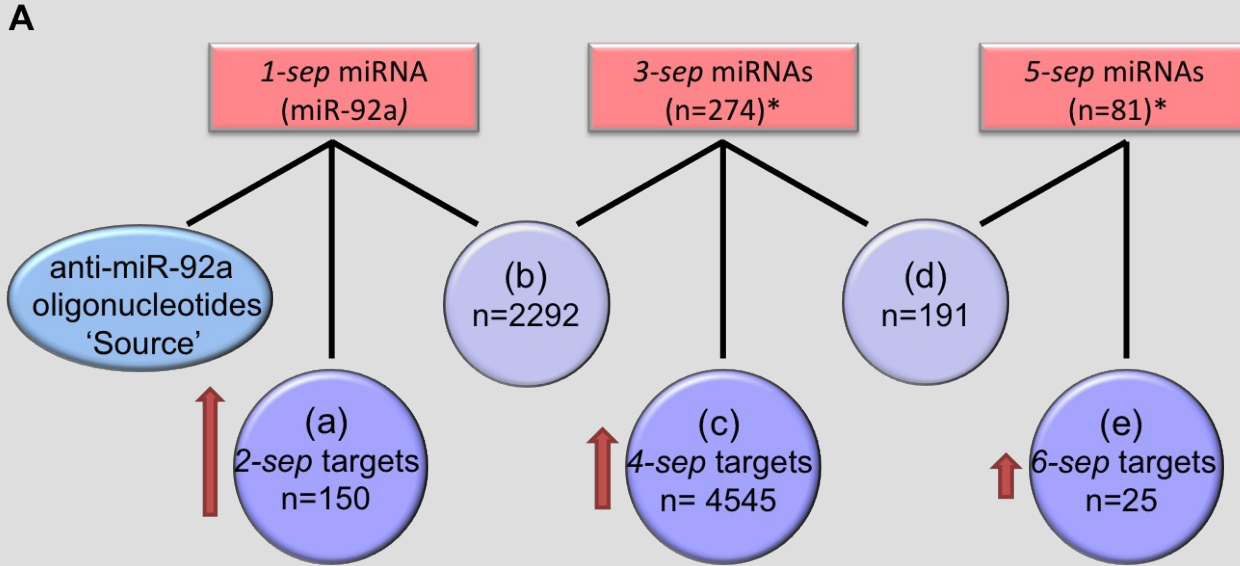
B



C

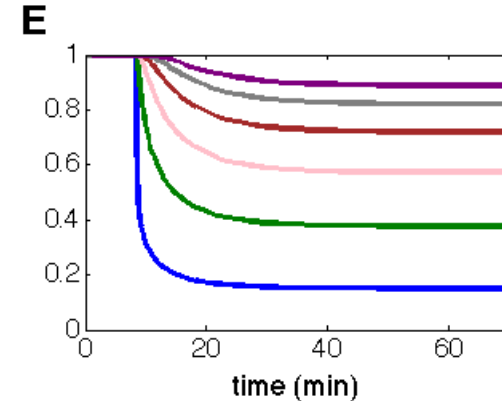
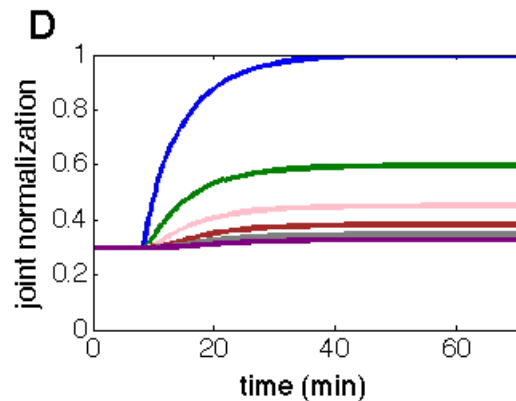
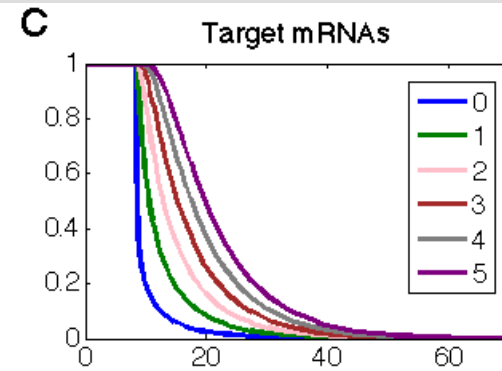
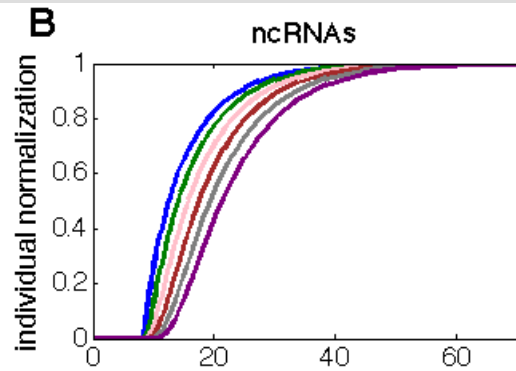
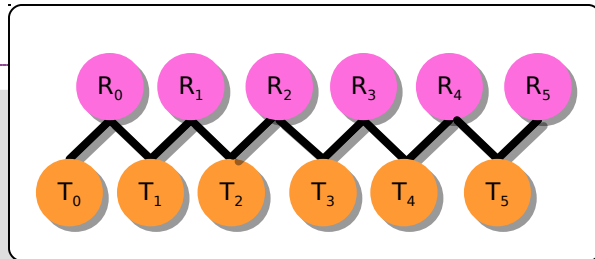


Signal Propagation - Experimental Data

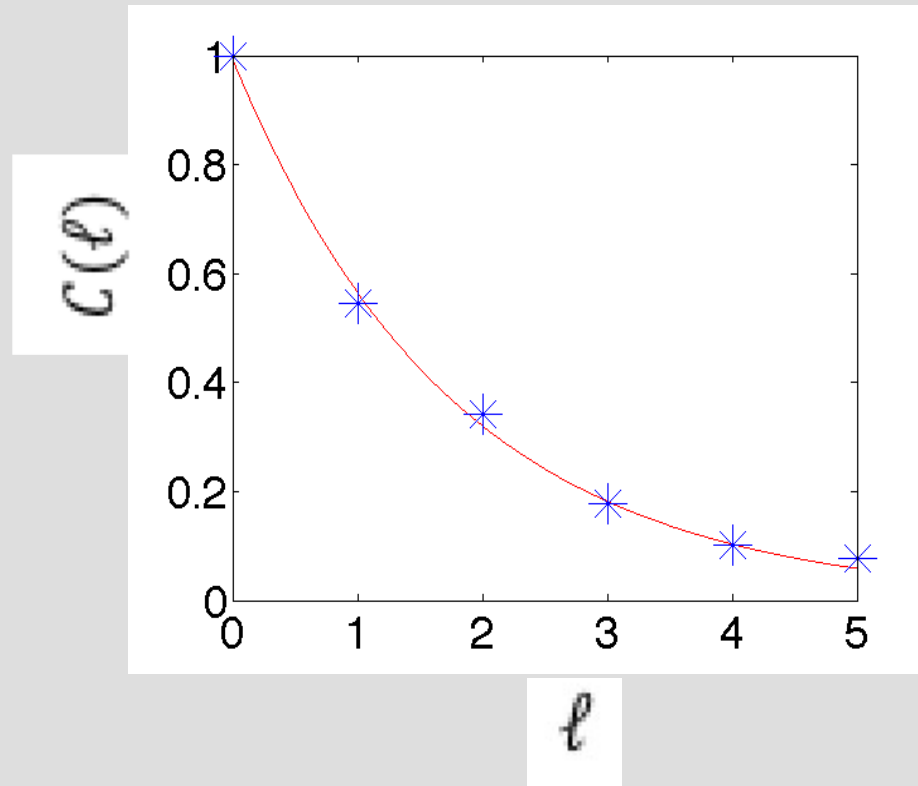
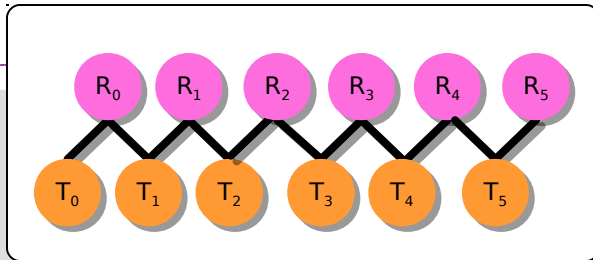


B

Subnetwork of sRNA Regulators and their Targets



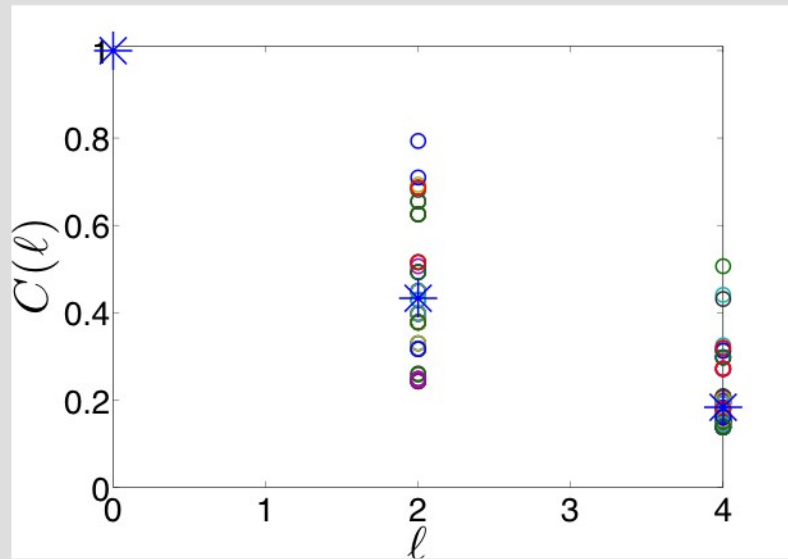
Decay Rate of the Signal



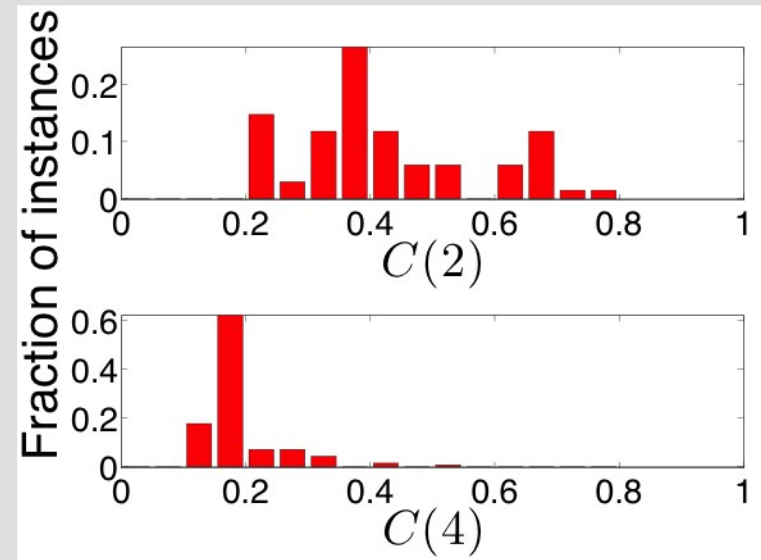
Correlations in the Network



A



B



Summary



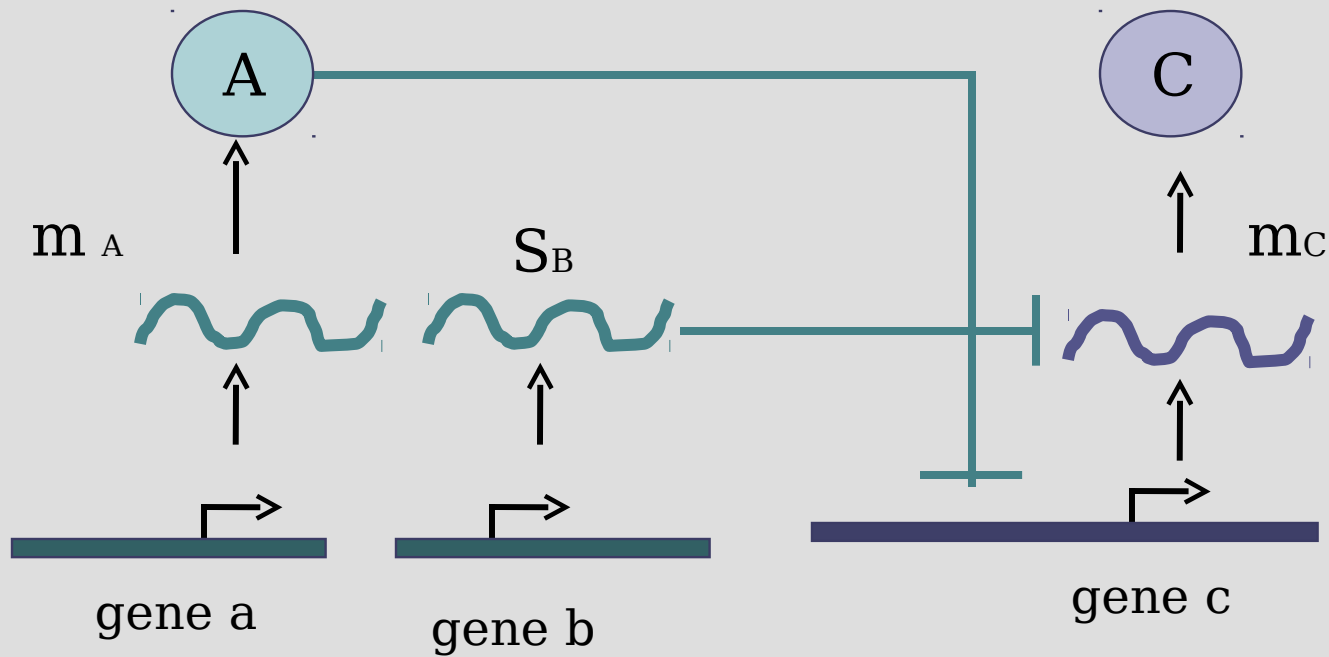
- We have studied information processing in genetic regulatory networks that involve different levels of regulation
- These networks combine sharp on/off type regulation with fine tuning processes, fast and slow processes, synchronization and subtle coordination
- Further progress will require experiments both at the single cell level and at the cell population level

Transcriptional vs. Post-transcriptional regulation

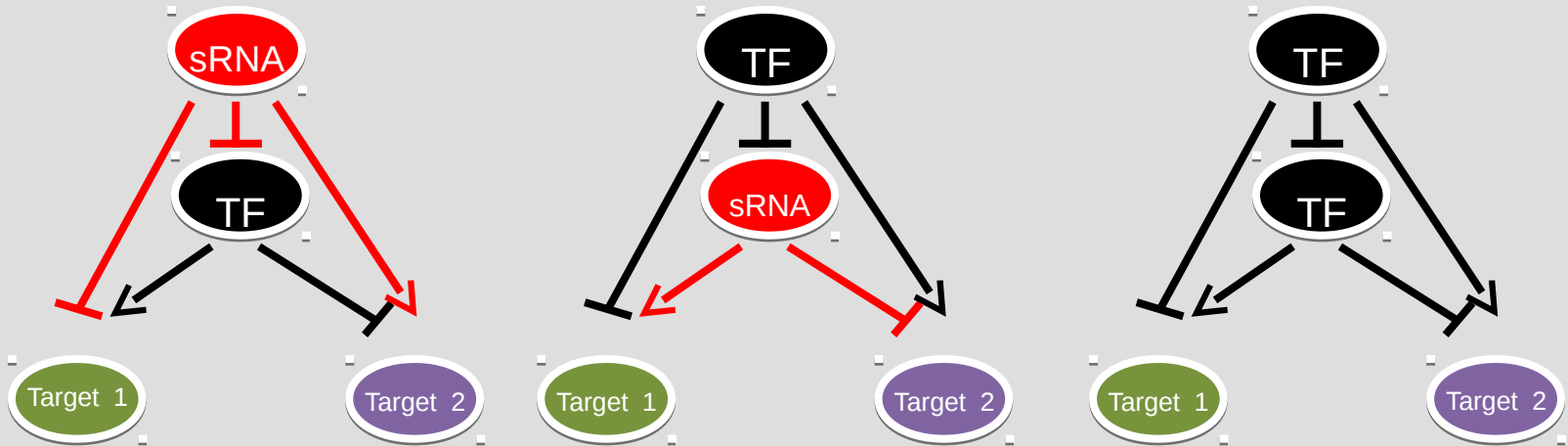


	Transcriptional	Post-transcriptional
Response time	Slow	Fast
Regulation type	Sharp On/Off	Enables fine-tuning
Regulator-target interaction	Non-stoichiometric	Stoichiometric
Regulation strength determined by	TF copy number and affinity to promoter	Relative copy numbers of sRNAs and mRNAs and their affinity
Directionality	Directional - from regulator to target	Bi-directional
Energetic cost	Protein synthesis	RNA synthesis

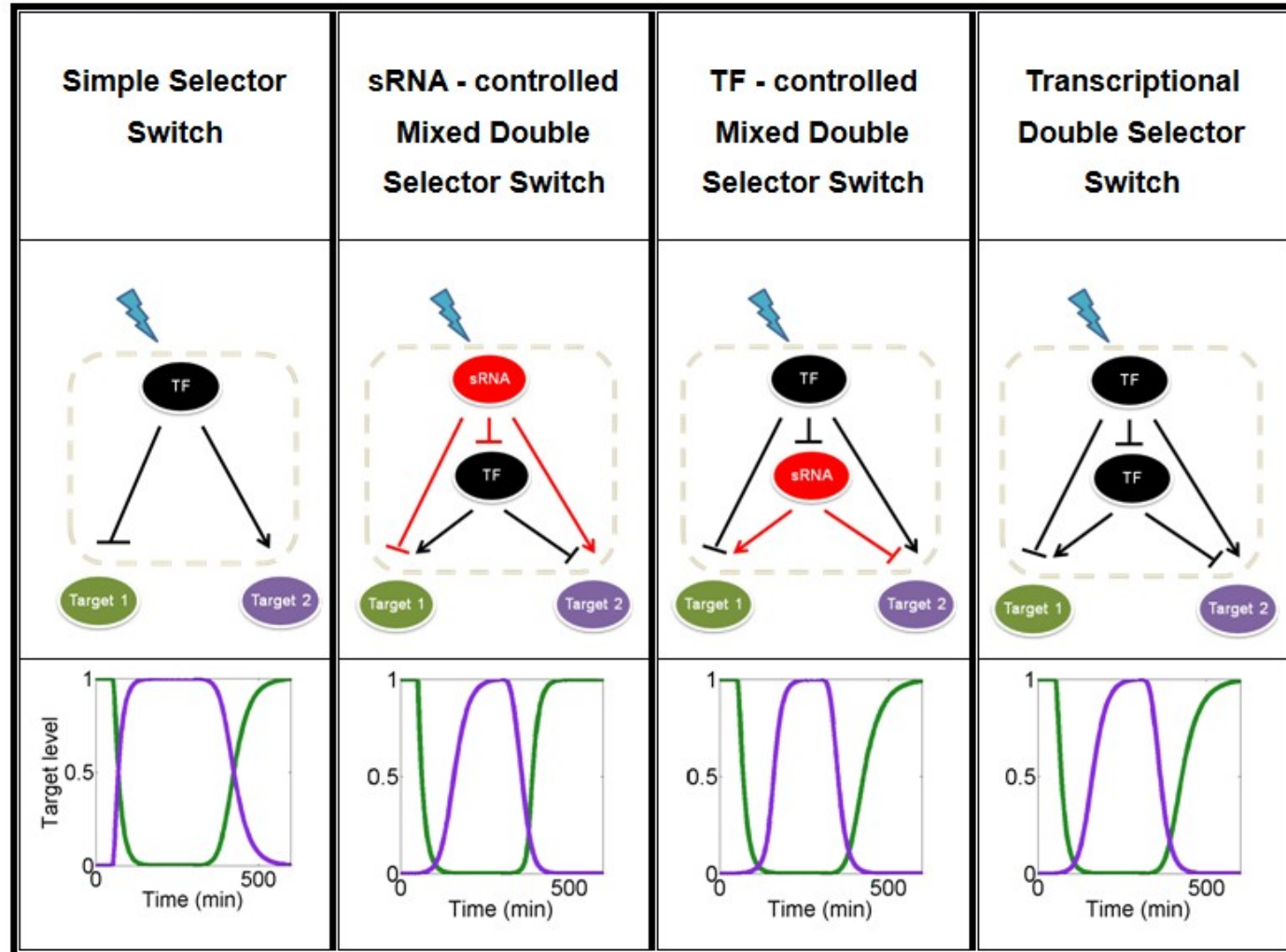
Combination of regulations at different levels



Three variants of the DSS



Dynamics of DSS variants



Leakage in target genes

