Gene Autoregulation via Intronic microRNAs and its Functions

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Annecy-le-Vieux 20-22/10/2010

OUTLINE

microRNA regulation

Mixed motifs

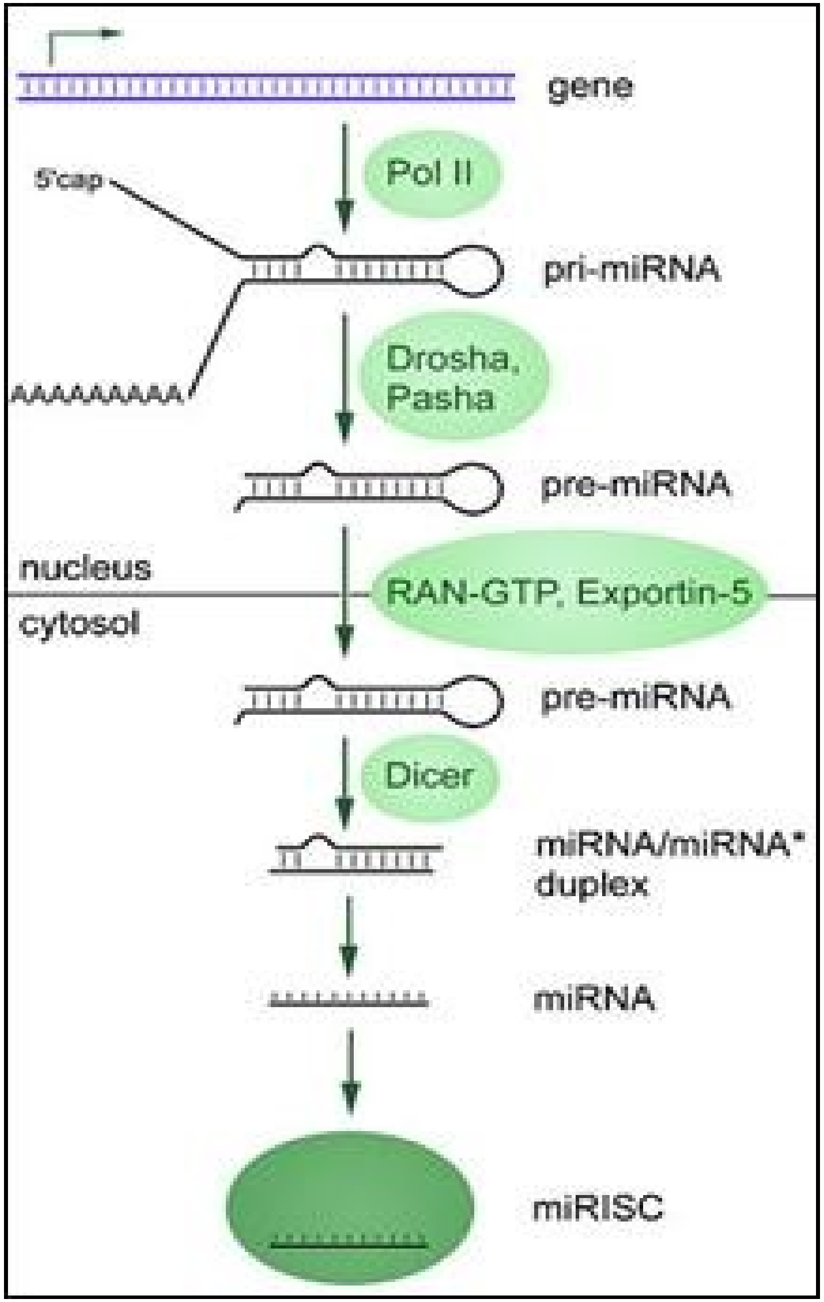
Focus on intronic microRNA-mediated self-loops

Models

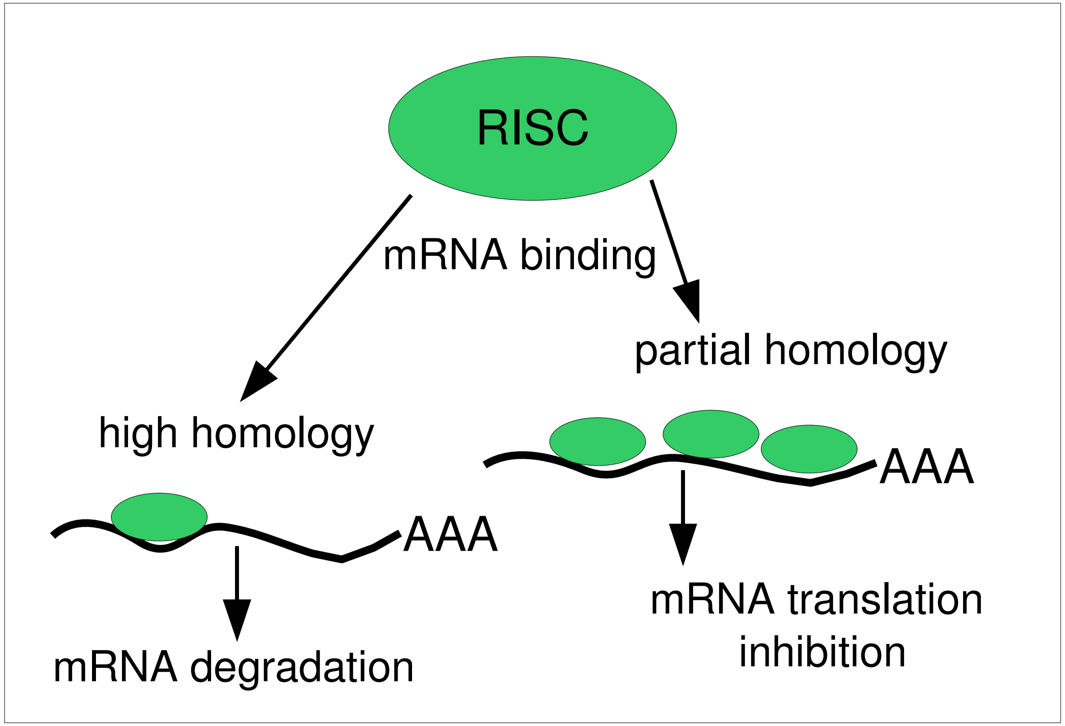
Results

Conclusions

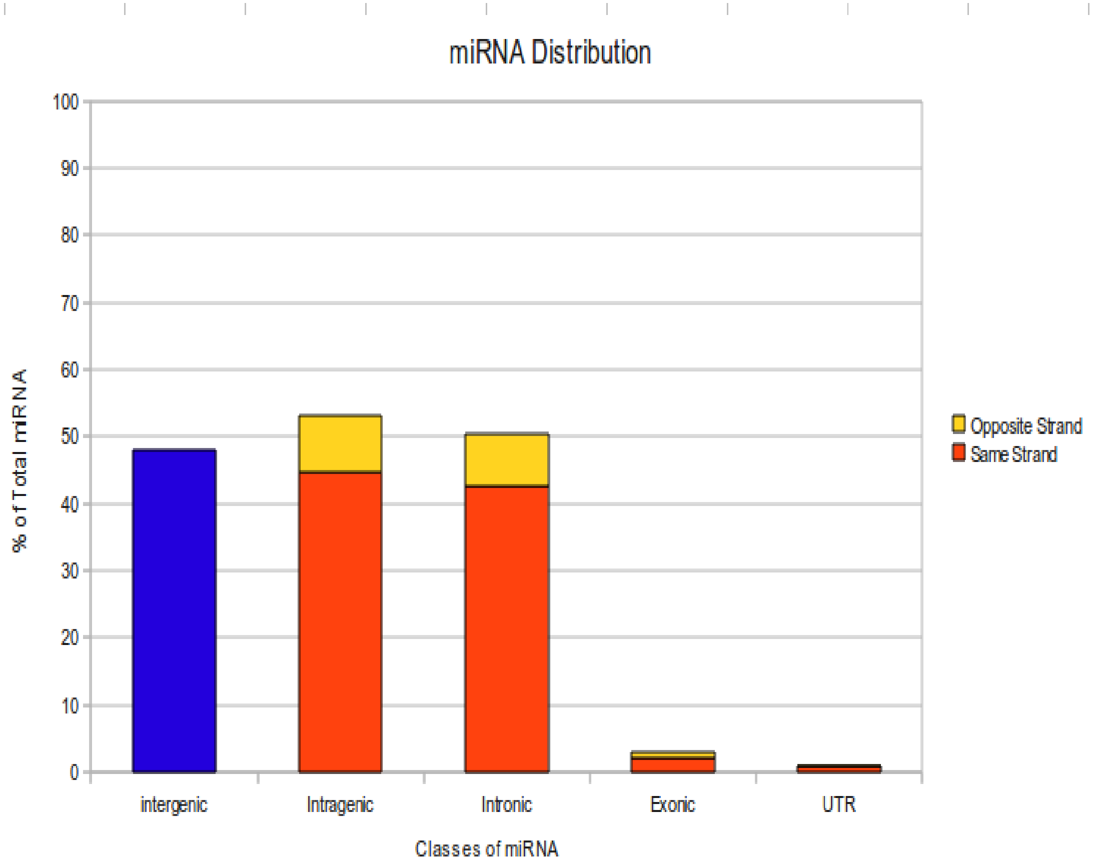
Regulation via microRNAS

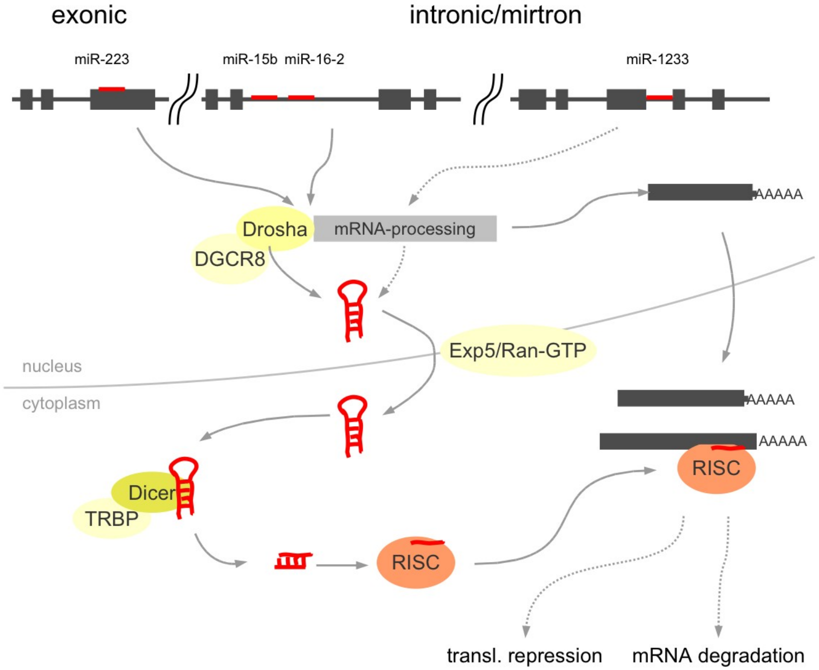


MicroRNAs (miRNAs) are a family of small RNAs (around 22 nucleotide long) which usually negatively regulates gene expression at post-transcriptional level thanks to the seed region in the 3'-UTR regions



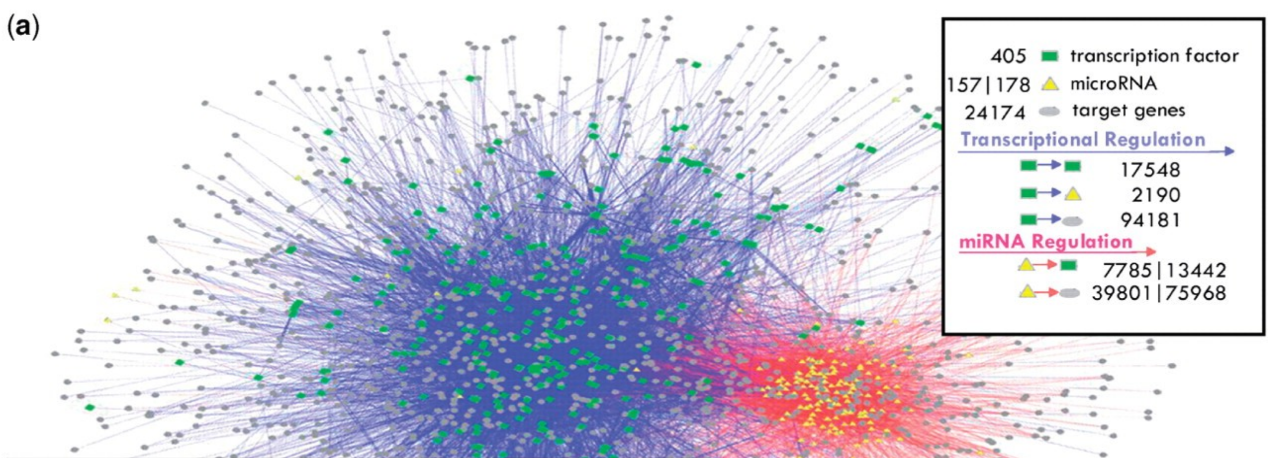
Regulation via intronic microRNAs

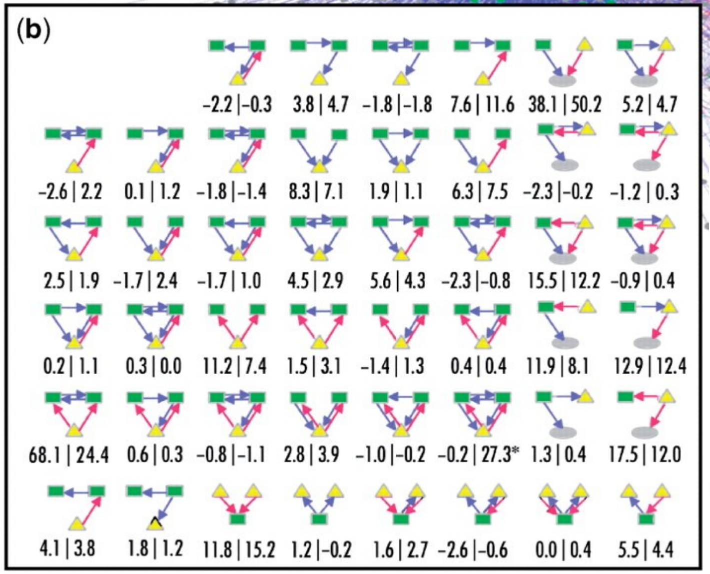




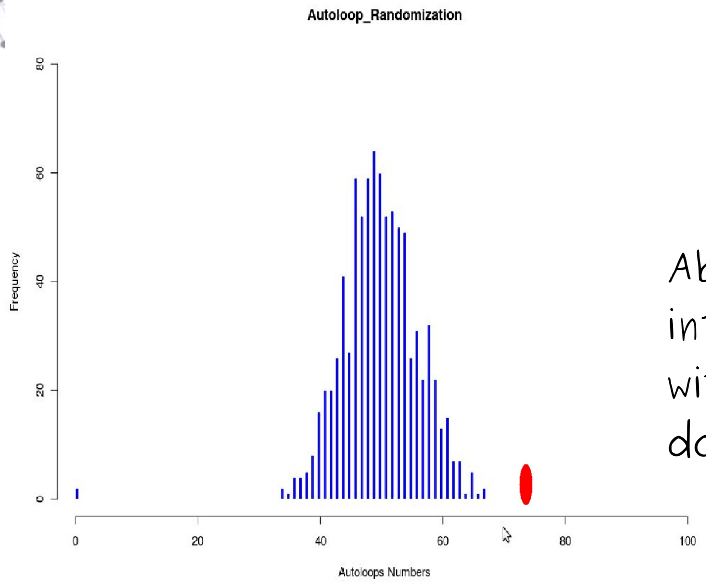
About half of human miRNAs are intergenic, the other half are intragenic (located within protein coding genes). Most miRNA genes are on the same strand as their host genes, suggesting common regulation

Intronic miRNA-mediated self-loop as network motif





Re et al, Mol Biosyst, 2009
Yu et al, Nucl Acids Res 36, 2008
Tsang et al, Molecular Cell 26, 2007
Megraw et al, Theor Chem Acc, 125, 2009



Network motifs: subgraphs that recur much more often than expected at random

Leading hypothesis: selected by evolutionary processes for functional reasons

About 24% of the human fully intronic miRNAs (same strand with their host genes) downregulate their hosts

Intronic miRNA-mediated self loop - models

Deterministic model

$$\frac{dw}{dt} = k_w - g_w w$$

$$\frac{dq}{dt} = k_q w - g_q q$$

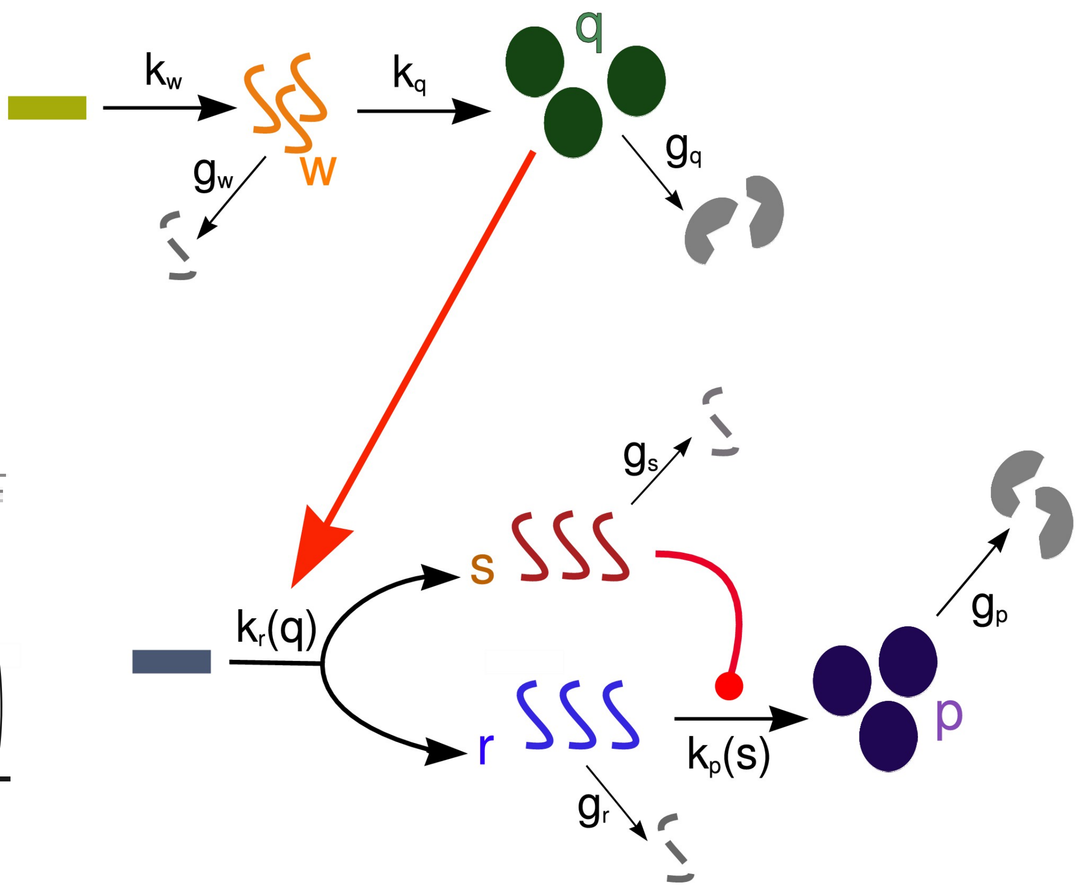
$$\frac{ds}{dt} = kr(q) - g_s s$$

$$\frac{dr}{dt} = k_r(q) - g_r r$$

$$\frac{dp}{dt} = r\, k_p(s) - g_p p$$

$$k_r(q) = \frac{k_r q^c}{q^c + h_r^c}$$

$$k_p(s) = \frac{k_p}{1 + (\frac{s}{h_p})^c}$$



Solvable mean field equations at steady state →

$$p_{ss} = \frac{k_p(s_{ss})\, k_r(q_{ss})}{g_p g_r}$$

Master equation

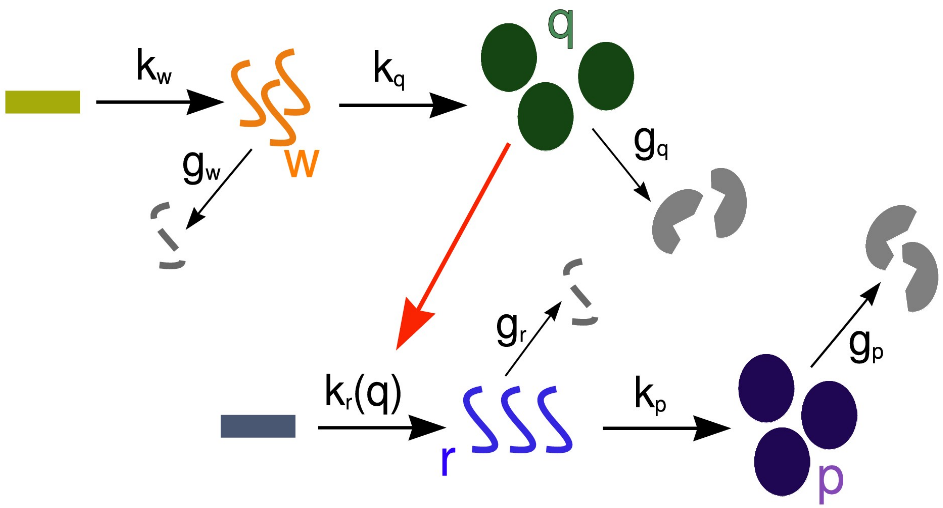
$$\begin{aligned}\partial_t P_{w,q,s,r,p} = {} & k_w(P_{w-1,q,s,r,p} - P_{w,q,s,r,p}) + k_q w(P_{w,q-1,s,r,p} - P_{w,q,s,r,p}) + \\ & + k_r(q)(P_{w,q,s-1,r-1,p} - P_{w,q,s,r,p}) + k_p(s) r(P_{w,q,s,r,p-1} - P_{w,q,s,r,p}) + \\ & + g_w\left[(w+1)P_{w+1,q,s,r,p} - wP_{w,q,s,r,p}\right] + g_q\left[(q+1)P_{w,q+1,s,r,p} - qP_{w,q,s,r,p}\right] + \\ & + g_r\left[(r+1)P_{w,q,s,r+1,p} - rP_{w,q,s,r,p}\right] + g_s\left[(s+1)P_{w,q,s+1,r,p} - sP_{w,q,s,r,p}\right] + \\ & + g_p\left[(p+1)P_{w,q,s,r,p+1} - pP_{w,q,s,r,p}\right]\end{aligned}$$

- The first two moments can be calculated with the moment generating function method

- Non linear model: post-transcriptional regulation always involves non linearity

Null models

Simple transcriptional unit



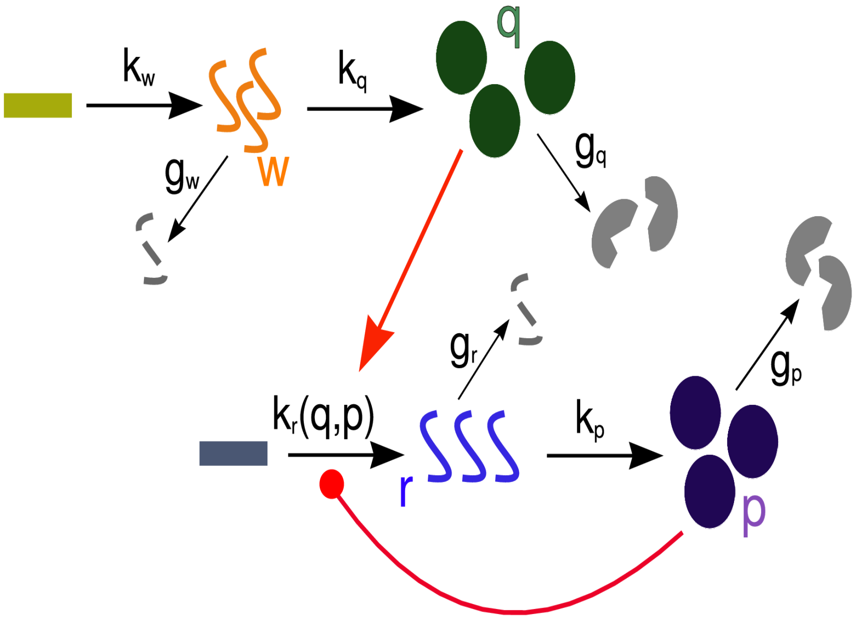
$$\frac{dr}{dt} = k_r(q) - r g_r$$
$$\frac{dp}{dt} = r k_p - p g_p$$

$$k_r(q) = \frac{k_r q^c}{q^c + h_r^c}$$

Master equation

$$\frac{\partial P_{w,q,r,p}}{\partial t} = k_w(P_{w-1,q,r,p} - P_{w,q,r,p}) + k_q w(P_{w,q-1,r,p} - P_{w,q,r,p})$$
$$+k_r(q)(P_{w,q,r-1,p} - P_{w,q,r,p}) + k_p r(P_{w,q,r,p-1} - P_{w,q,r,p})$$
$$+g_w\left[(w+1)P_{w+1,q,r,p} - wP_{w,q,r,p}\right] + g_q\left[(q+1)P_{w,q+1,r,p} - qP_{w,q,r,p}\right]$$
$$+g_r\left[(r+1)P_{w,q,r+1,p} - rP_{w,q,r,p}\right] + g_p\left[(p+1)P_{w,q,r,p+1} - pP_{w,q,r,p}\right]$$

Transcriptional autoregulation



$$\frac{dr}{dt} = k_r(q,p) - r g_r$$
$$\frac{dp}{dt} = r k_p - p g_p$$

$$k_r(q,p) = \frac{k_r q^c}{(q^c + h_r^c)(1 + (\frac{p}{h_p})^c)}$$

Possible functions performed by an intronic microRNA-mediated self-loop

Noise buffering

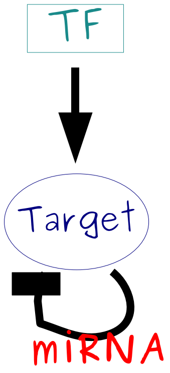
Alteration of the response time to upstream signals

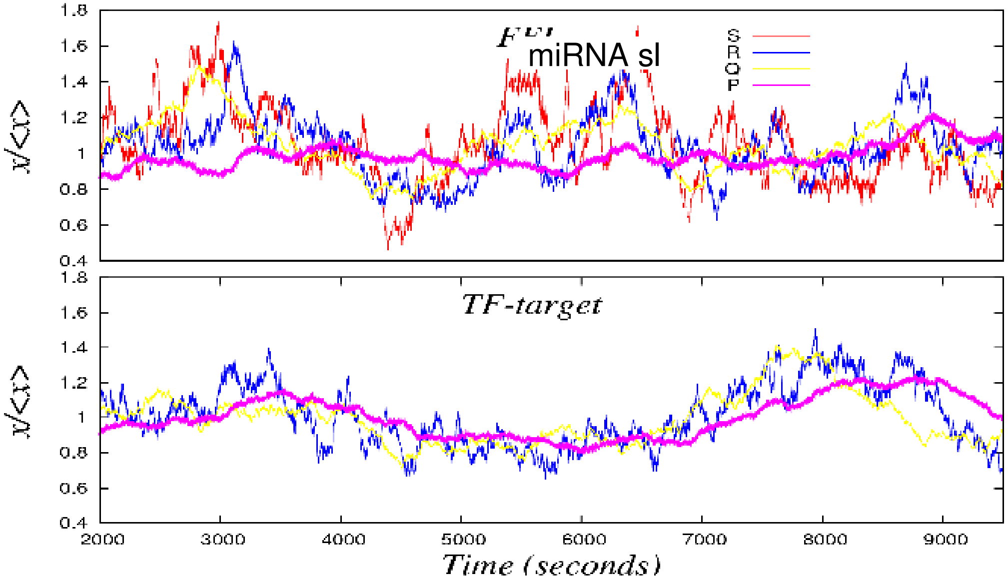
Adaptation and fold-change detection

Function of intronic miRNA-mediated self-loop (1)

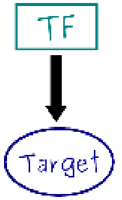
NOISE BUFFERING (A)

Biological hypothesis:
a microRNA-mediated self-loop can avoid large fluctuations in the target protein with noise reduction

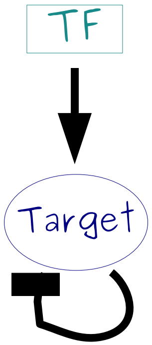


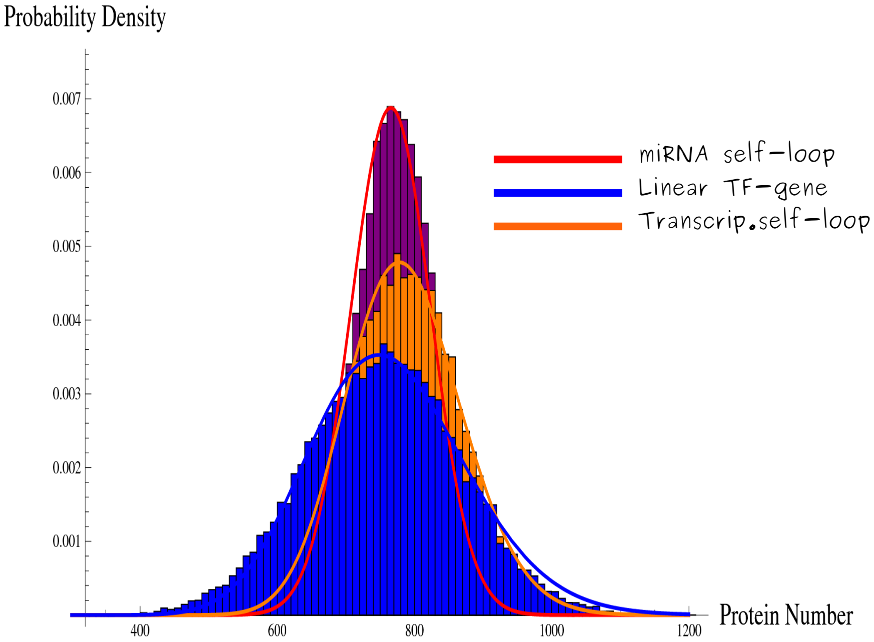


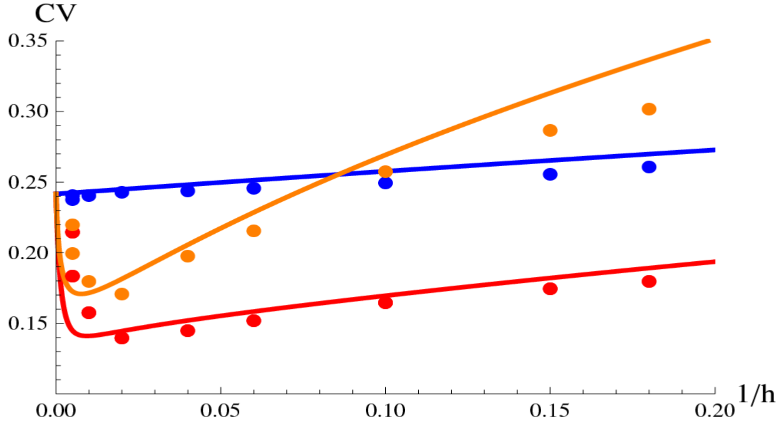
TF–target



transcr. sl



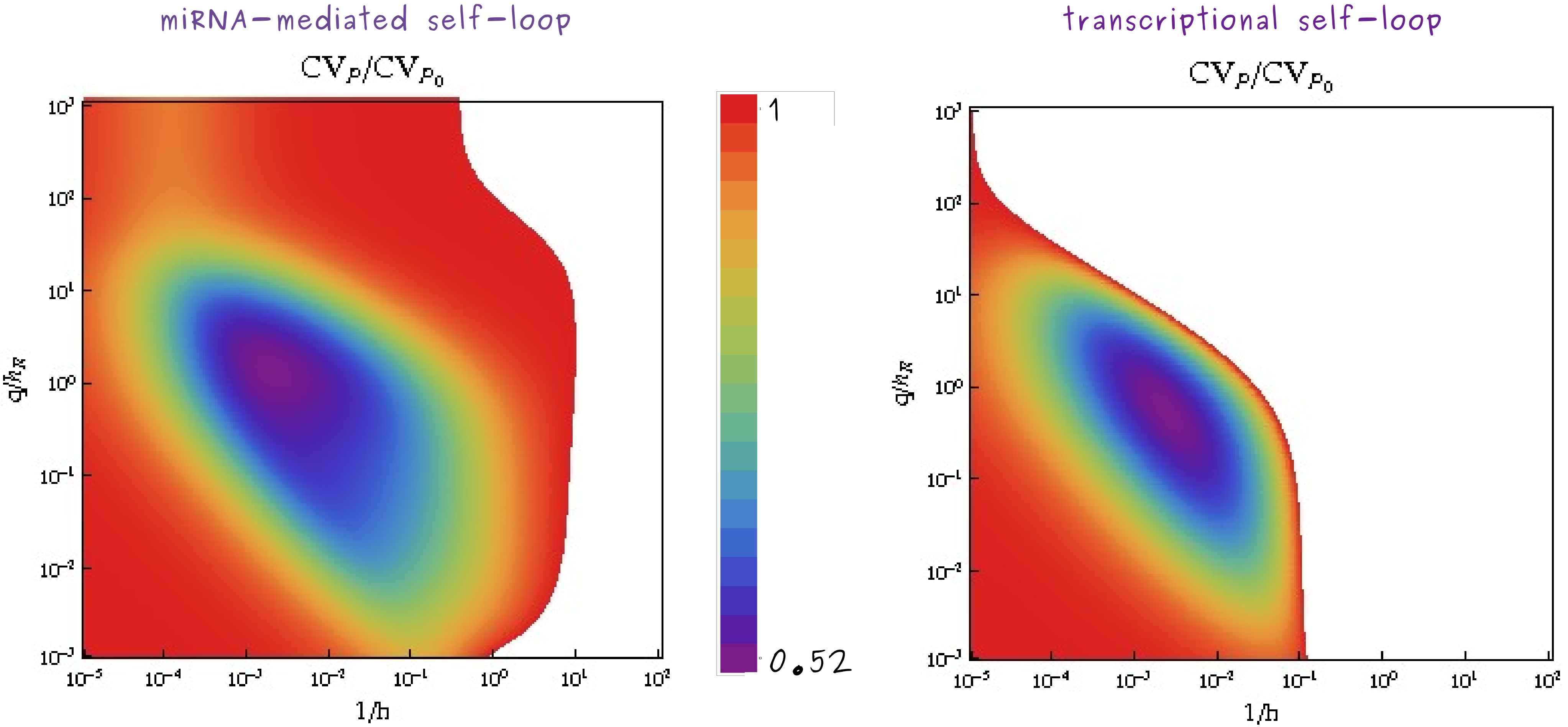




Influence of repression strength 1/h on the noise buffering effect. miRNA-mediated self loop shows an optimal repression strength (minimum noise), smaller than the one shown by the pure transcriptional self loop

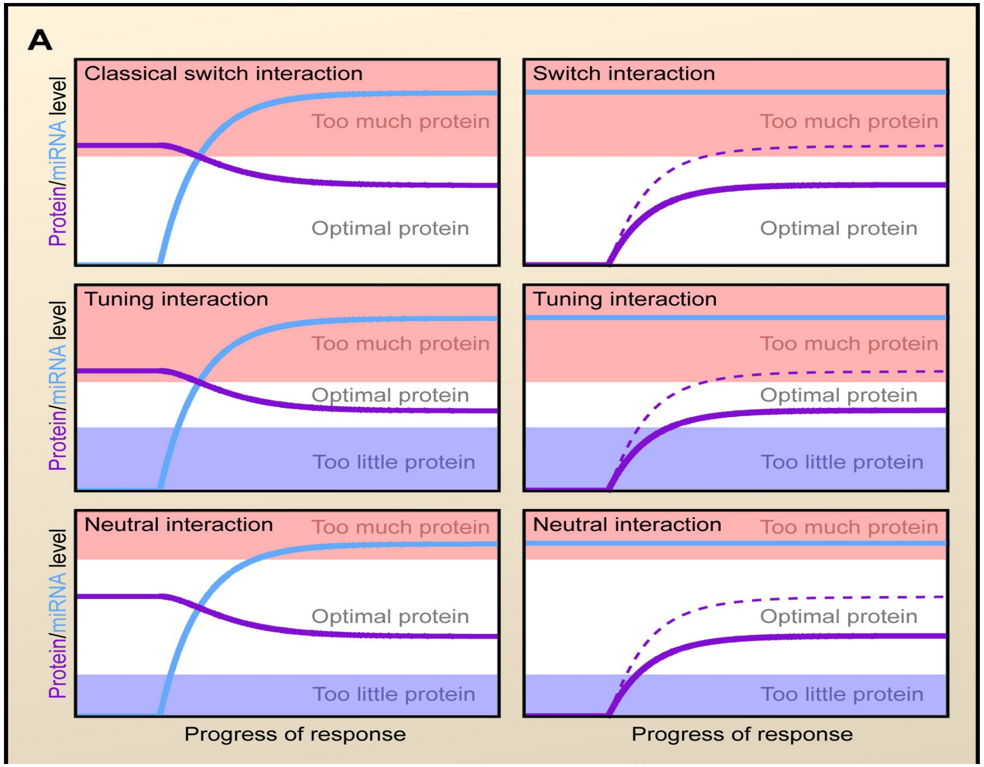
Function of intronic miRNA-mediated self-loop (1)

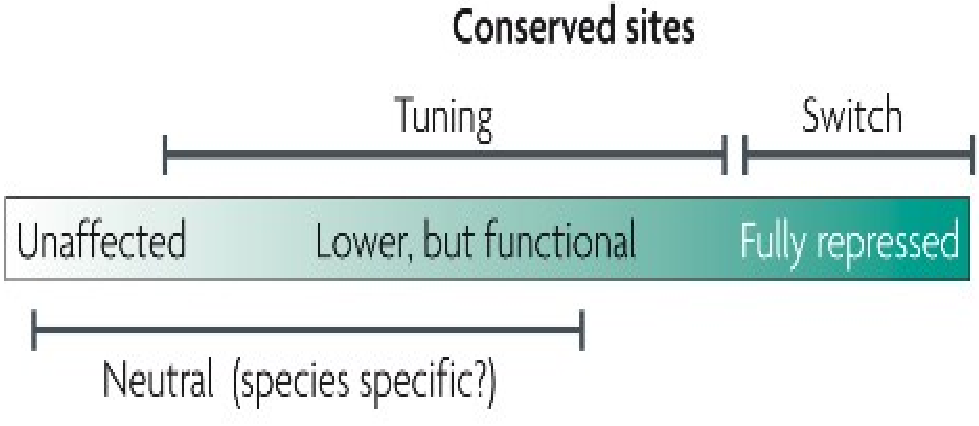
NOISE BUFFERING (B)



Target noise CV_P achieved by the miRNA-mediated self-loop and by the transcriptional self-loop. CV_P evaluated with respect to the constitutive expression noise (i.e. in absence of miRNA/autoregulation) for different $1/h$ and different q/h_R. The region where miRNA (protein) repression leads to larger fluctuations is shown in white. When a noise reduction is gained, the value CV_P/CV_{P_0} is reported with the color gradient in the legend.

Classes of miRNA regulatory interactions





Bartel, Cell 2009; Flynt Nat Rev Genet 2008

- Tuning interaction: set the optimal functional value of the protein through a miRNA repression

- Example: Drosophila miR-8 regulation of atrophin. miR-8 reduces the target protein output to a level that prevents neurodegeneration but not so low as to cause developmental defects (Karres et al. Cell 2007)

- In presence of fluctuations it is necessary to ensure uniform expression within a cell population, to avoid cells with an undesired protein level

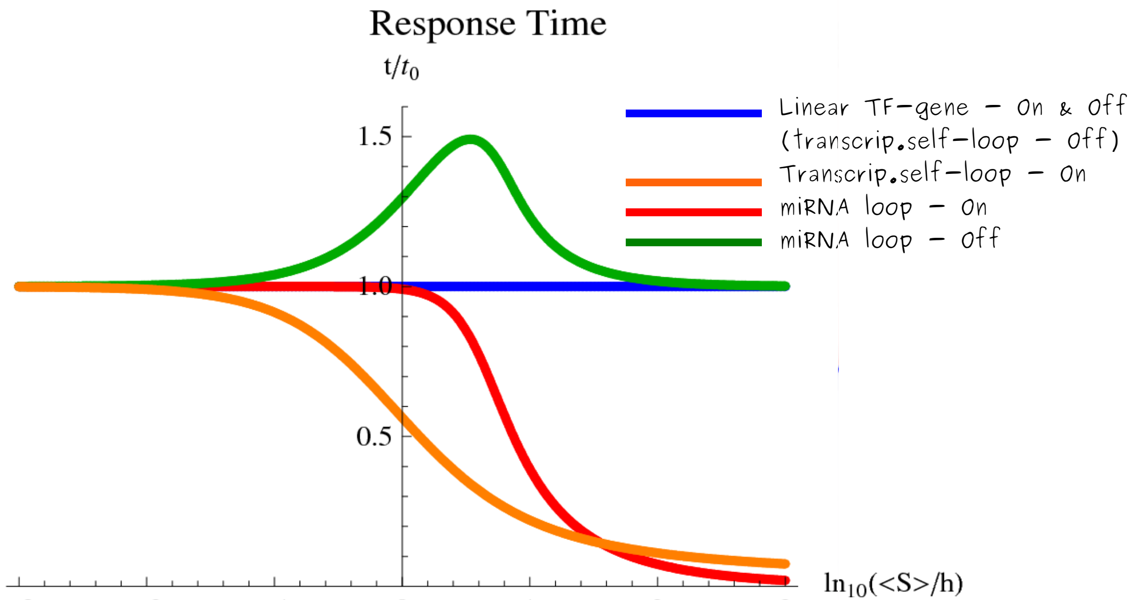
Function of intronic miRNA-mediated self-loop (2)

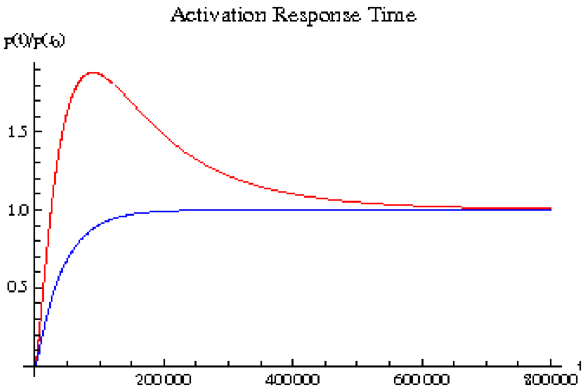
RESPONSE TIME (A)

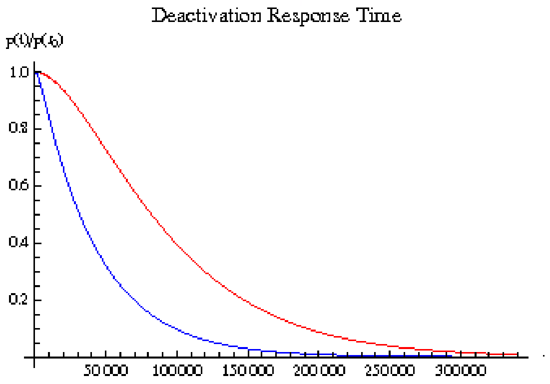
Response time: time needed to reach half of the final (or initial) steady state protein level.

Interest in studying the response time for the different circuits passing from a complete TF inactivation ($q \to 0$) to a total TF activation ($q \to$ infinity), i.e. saturation of the Michaelis-Menten.

The response time is evaluated with respect to the single gene response time (t_0) as function of an effective parameter given by $\langle S\rangle/h = k_R/g_{sh}$.

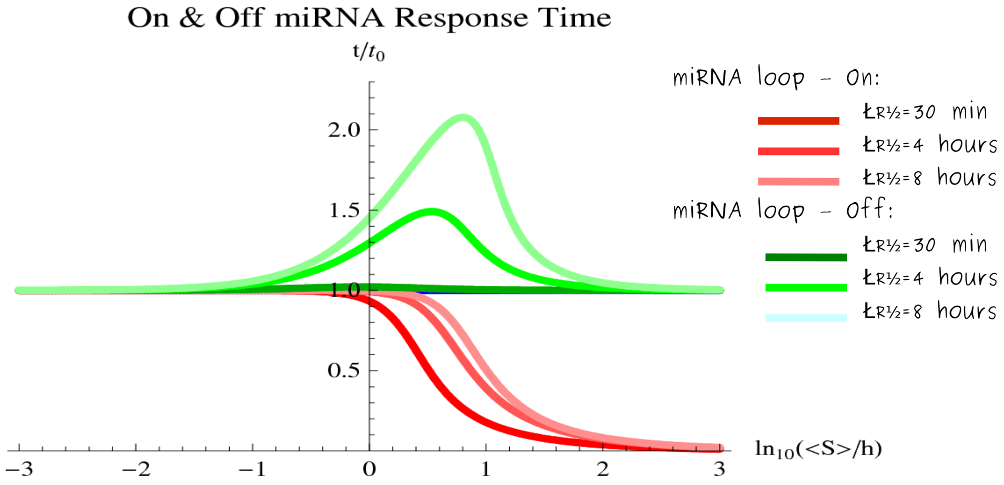






Function of intronic miRNA-mediated self-loop (2)

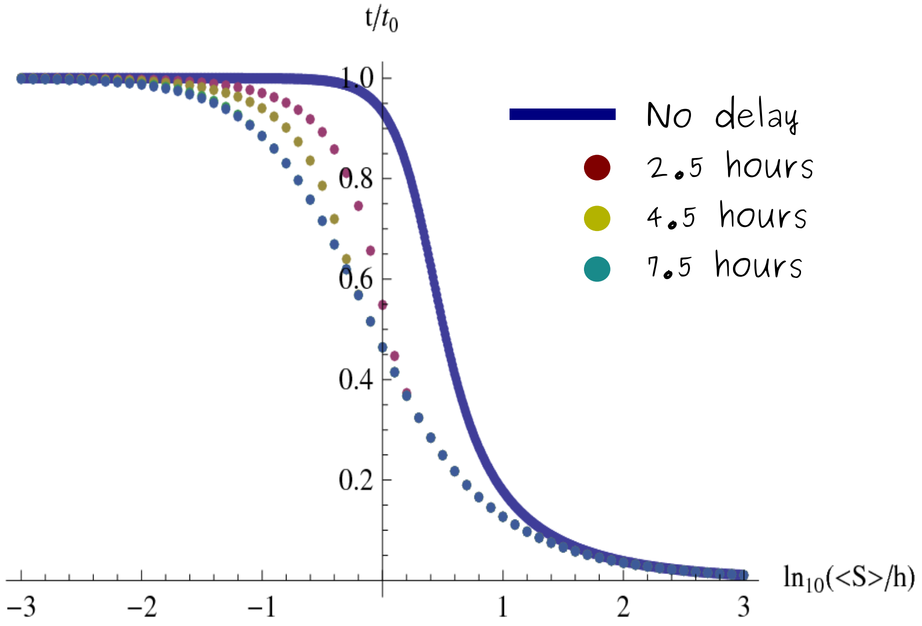
RESPONSE TIME (B)



Activation and deactivation response time for the post-transcriptional circuit varying the mRNA half-life. The mRNA half-life increases with the lightening of the colored curves.

Activation response time for the post-transcriptional circuit considered as acting or not with a delay (time needed for the miRNA to be processed, loaded in RISC, etc.).

The qualitative behavior is the same for the two cases. The shift towards left for the circuit with delay increases with the delay.



Function of intronic miRNA-mediated self-loop (3)

ADAPTATION & FOLD-CHANGE DETECTION (A)

ADAPTATION

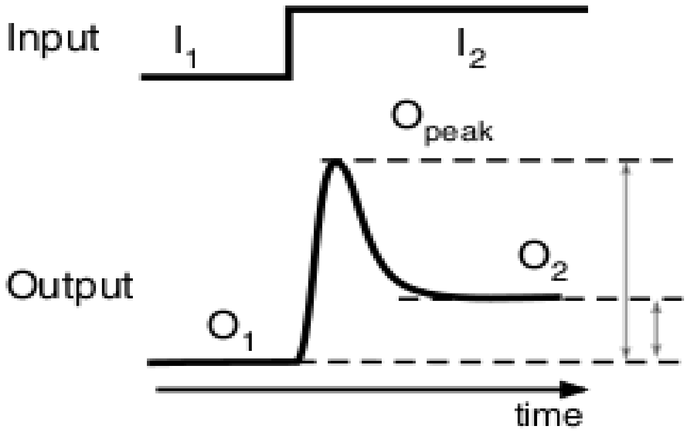
Ability of a system to respond to a change in input stimulus and then return to its prestimulated output level, even when the change in input persists ;

It is shown by many signaling systems ;

It is commonly used in sensory and signaling network to more accurately detect changes in the input and to maintain homeostasis in presence of perturbations

Conditions to have adaptation:

1) Precision > 10;
2) Sensitivity > 3 sigma;



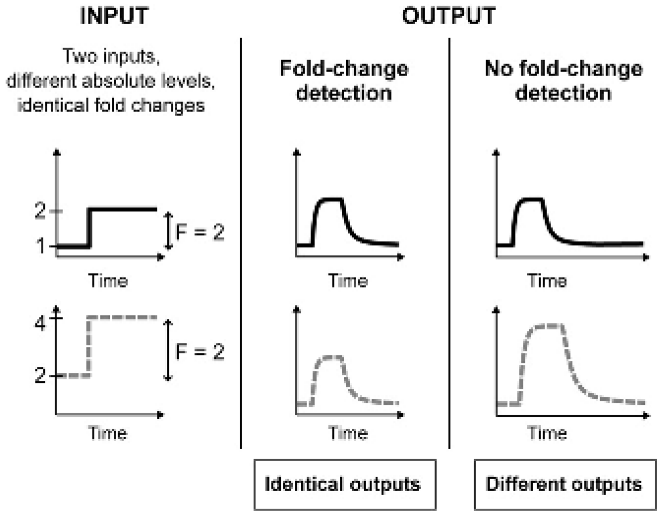
$$\textbf{Sensitivity} = \left| \frac{(O_{peak} - O_1)/O_1}{(I_2 - I_1)/I_1} \right|$$

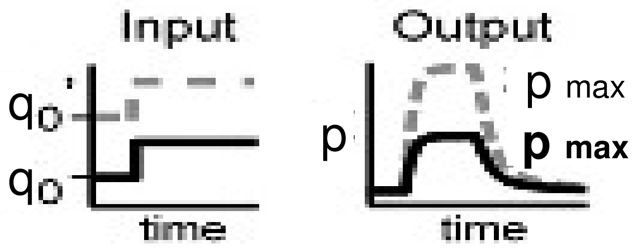
$$\textbf{Precision} = \left| \frac{(O_2 - O_1)/O_1}{(I_2 - I_1)/I_1} \right|^{-1}$$

Function of intronic miRNA–mediated self–loop (3)

ADAPTATION & FOLD–CHANGE DETECTION (B)

Fold–change detection → Weber's law (relationship between the physical magnitudes of stimuli and the perceived intensity of the stimuli)





$$\varepsilon = \left| \frac{p\ \mathrm{max} - \mathbf{p\ max}}{\mathbf{p\ max}} \right|$$

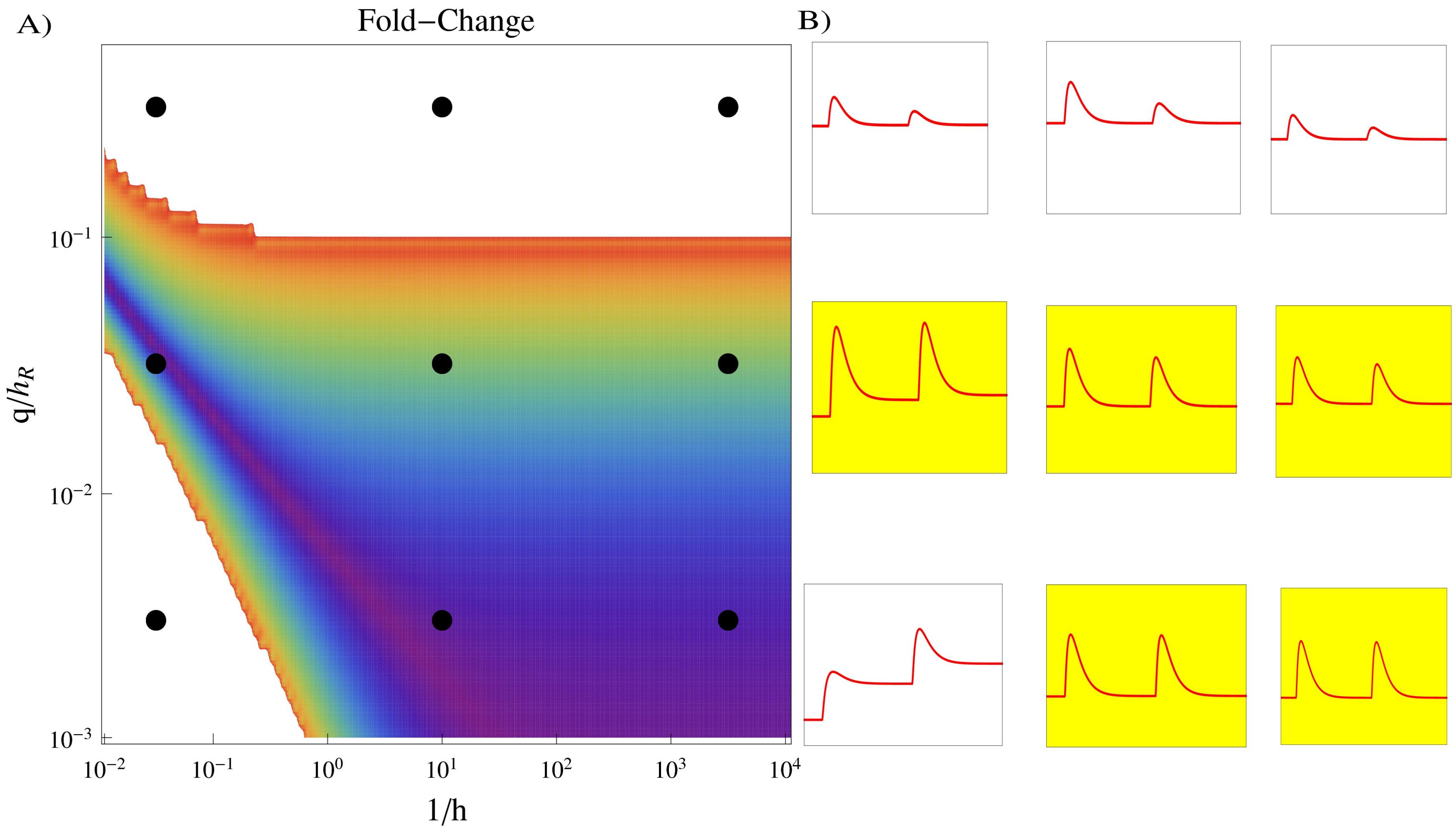
Fold–change detection features in signaling systems in cells (response depending on fold–change in input signal and not on its absolute value)

Fold–change detection generated by miRNA–mediated self loop

Conditions:

1) Linear transcription activation: kr(q)~(kr*q);
2) Strong repression: kp(s)~(kp/s);
3) Quasi–steady state for mRNA dynamics (r at steady state)

ADAPTATION & FOLD-CHANGE DETECTION (C)



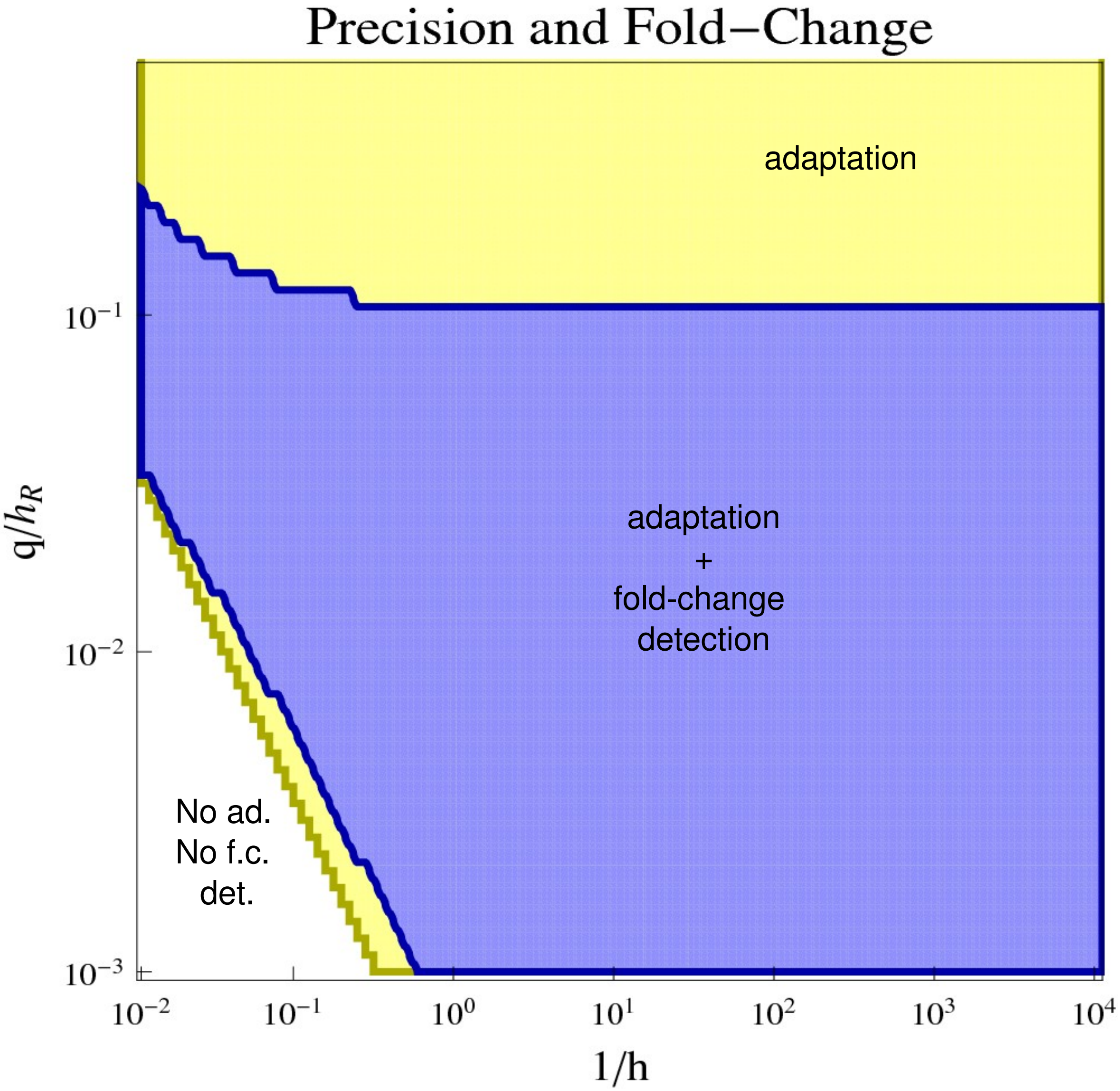
Conditions to have fold-change detection:

1) Linear transcription activation: kr(q)~(kr*q);
2) Strong repression: kp(s)~(kp/s);
3) Quasi-steady state for mRNA dynamics (r at steady state)

Function of intronic miRNA-mediated self-loop (3)

ADAPTATION & FOLD-CHANGE DETECTION

...summarizing...



CONCLUSIONS

PREMISE: Intronic microRNA-mediated self-loop are networ motifs

RESULTS:
our models suggest that microRNA-mediated self regulation, despite its simple topology, can perform different regulative tasks:

1) it can confer robustness to noise;

2) it can alter the response time of gene expression to upstream signals;

3) it can implement fold-change detection while adapting to external input signals;

FOR ALL THESE REASONS, POSSIBLE APPLICATION TO SYNTHETIC BIOLOGY

REFERENCES

M.Megraw, P.Sethupathy,K.Gumireddy,S.T.Jensen,Q.Huang and A.G.Hatzigeorgiou;
"Isoform specific gene auto-regulation via miRNAs: a case study on miR-128b and ARPP-21";
Theor.Chem.Acc (2009), 125:593-598

M.Osella,C.Bosia,D.Corà and M.Caselle;
"The role of incoherent microRNA-mediated feedforward loops in noise buffering";
arXiv:1004.0336V1

L.Goentoro,O.Shoval,M.W.Kirschner and U.Alon;
"The incoherent feedforward loop can provide fold-change detection in gene regulation";
Molecular Cell (2009), 36:894-899

W.Ma,A.Trusina,H.El-Samad,W.A.Lim and C.Tang;
"Defining network topologies that can achieve biochemical adaptation";
Cell (2009), 138:760-773

AKNOWLEDGEMENTS

A work with

Matteo Osella,
Mariama El Baroudi,
Davide Corà,
Michele Caselle

My group

Matteo Osella,
Mariama El Baroudi,
Alessandro Testori,
Michele Caselle

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THANK YOU FOR YOUR ATTENTION !