The Role of Incoherent microRNA-mediated Feedforward Loops in Noise Buffering

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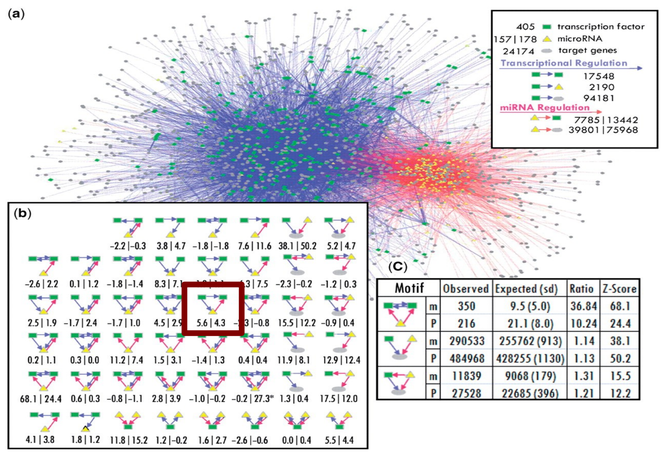
Introduction:



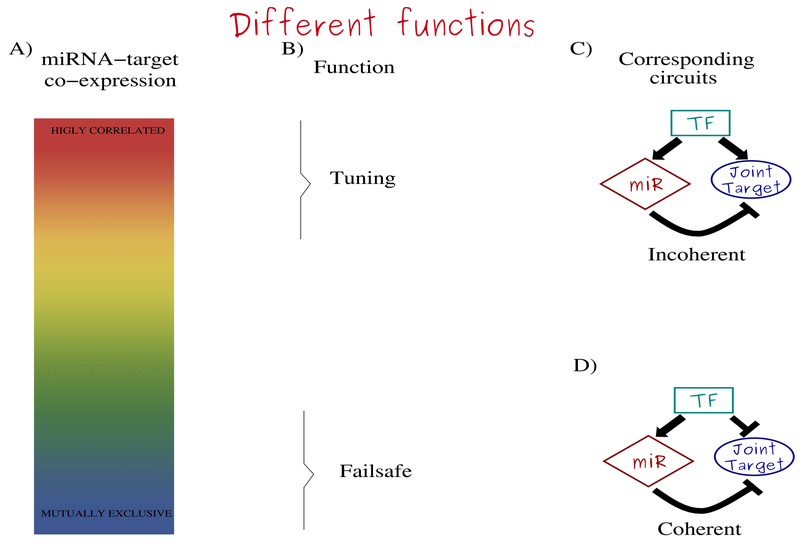
Motif		Observed	Expected (sd)	Ratio	Z-Score
	m	350	9.5 (5.0)	36.84	68.1
	P	216	21.1 (8.0)	10.24	24.4
	m	290533	255762 (913)	1.14	38.1
	P	484968	428255 (1130)	1.13	50.2
	m	11839	9068 (179)	1.31	15.5
	P	27528	22685 (396)	1.21	12.2

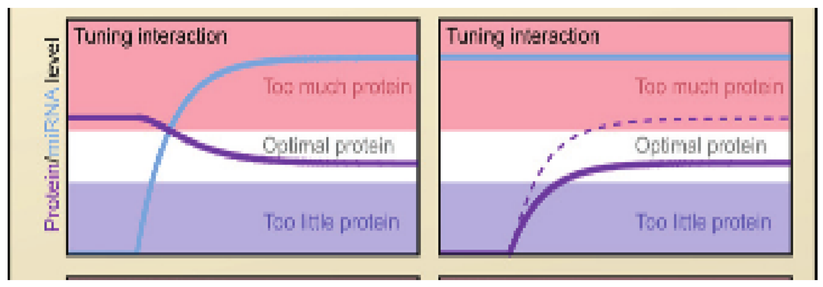
microRNA-mediated FFLs are network motifs in the mixed network of transcriptional and post-transcriptional regulations:
Selected by evolution for functional reasons

Different FFLs (coherent or incoherent)

Different expression patterns

Different functions



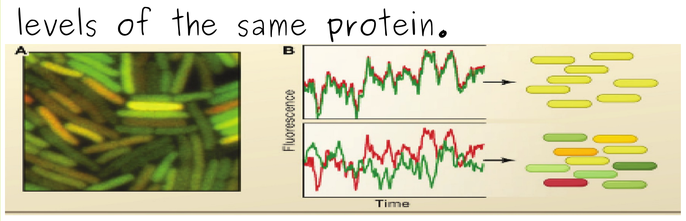


Incoherent FFLs lead to co-expression of the microRNA and its targets.

They can fine-tune the level of the target protein, setting it in its functional range.

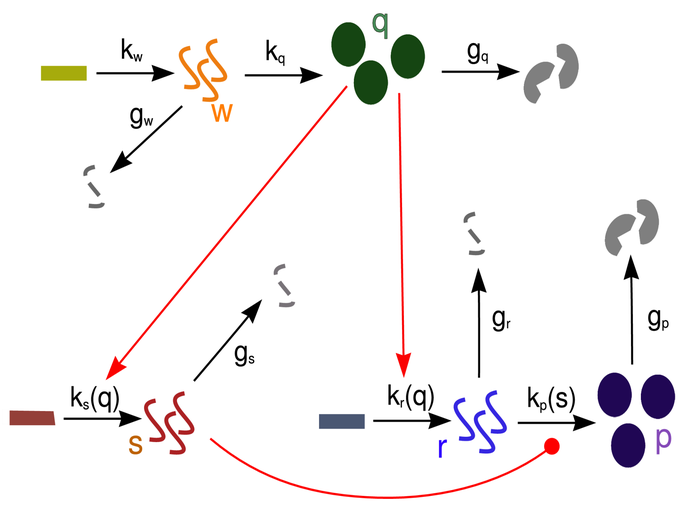
Question:

Gene expression is a stochastic process: isogenic cells can show very different levels of the same protein.



The fine-tuning is effective only if coupled with a control of fluctuations.
Can incoherent microRNA-mediated FFLs function as noise buffers?

Methods:



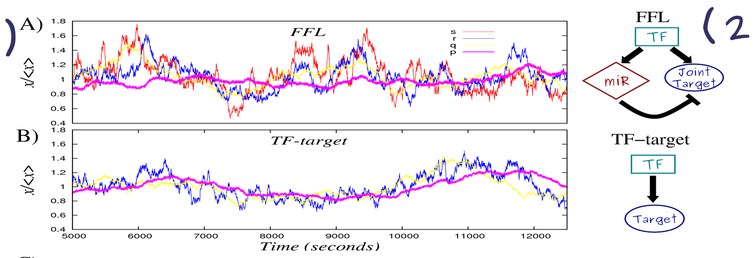
- Analytical solutions of master equations describing the regulative circuits in analysis, taking into account the essential features of transcription, translation, degradation and interactions between genes.
- Gillespie stochastic simulations.

Master Equation for the FFL

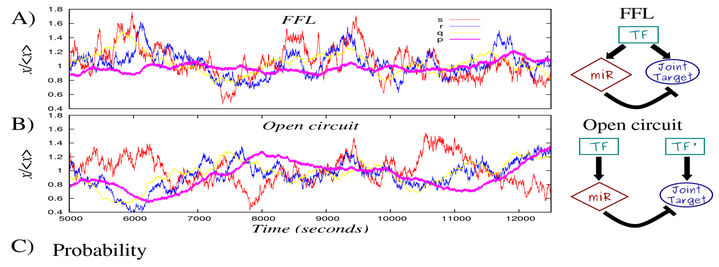
$$\begin{aligned}\partial_t P_{w,q,s,r,p} = \; & k_w(P_{w-1,q,s,r,p} - P_{w,q,s,r,p}) + k_q w(P_{w,q-1,s,r,p} - P_{w,q,s,r,p}) \\ & + k_r(q)(P_{w,q,s,r-1,p} - P_{w,q,s,r,p}) + k_s(q)(P_{w,q,s-1,r,p} - P_{w,q,s,r,p}) \\ & + k_p(s) r (P_{w,q,s,r,p-1} - P_{w,q,s,r,p}) + g_w\left[(w+1)P_{w+1,q,s,r,p} - wP_{w,q,s,r,p}\right]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

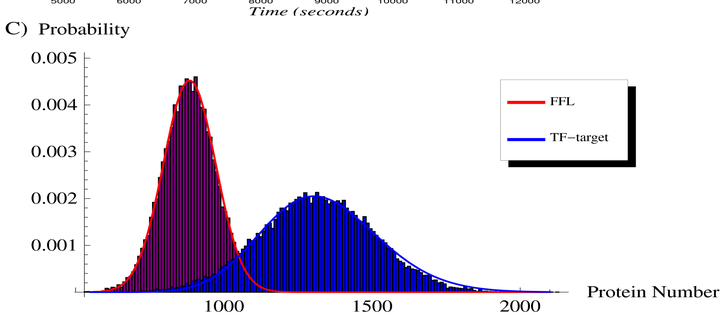
Results:

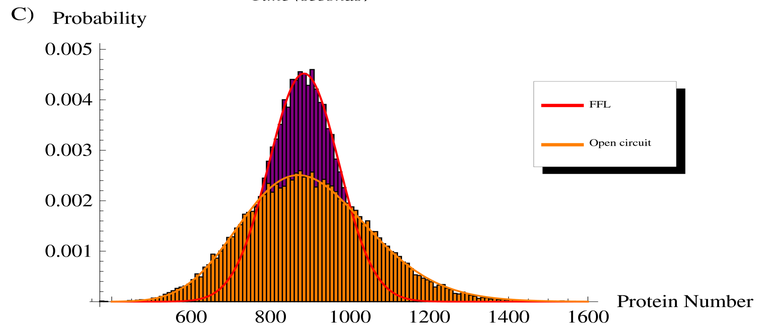
(1)



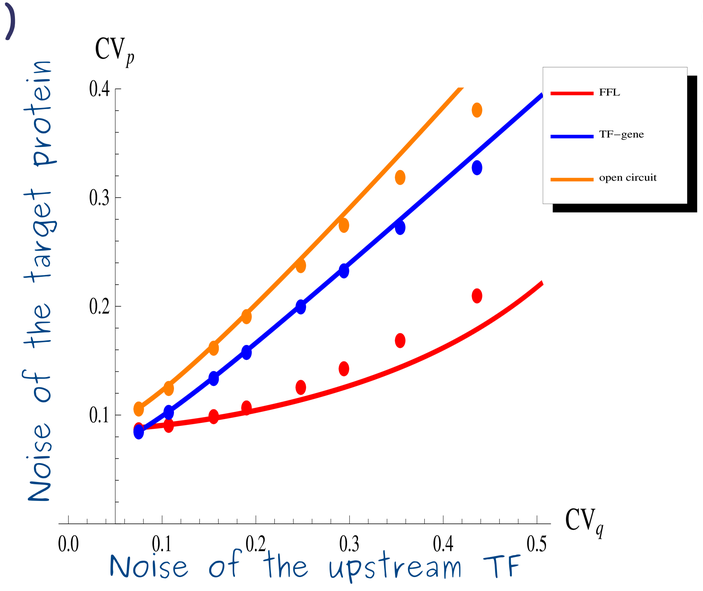
(2)



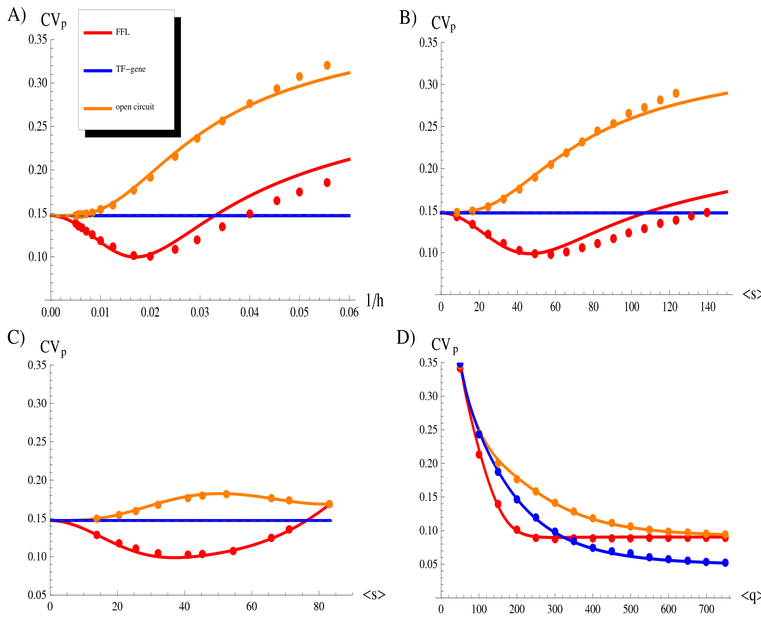




(3)



(4)



(1) miRNA-mediated FFLs can couple the fine tuning of target protein level with noise reduction. Adding a miRNA regulative pathway to the simple activation of a gene by a transcription factor reduces the target protein mean level together with fluctuations.

(2) The fine-tuning function does not require a FFL topology as it can be implemented using an independent microRNA (open circuit), but the FFL structure is mandatory to control the target fluctuations.

(3) Incoherent FFL are particularly effective in filtering fluctuations of upstream regulators, conferring robustness to the gene expression program even in the presence of noisy signals.

(4) Our model predicts that there is an optimal repression strength for noise attenuation. The optimal noise buffering requires only a weak suppression of the mean target expression, coherently with the fine-tuning function and with experimental observations that many miRNAs reduce the output of their protein targets of less than 50%. The U-shaped profile of the target noise can be tested in different ways (varying miRNA concentration, TF concentration, miRNA efficiency).

References

1) Yu et al 2008 Nucl Acids Res
2) Re et al 2009 Mol Biosyst
3) Bartel 2009 Cell
4) Tsang et al 2007 Molecular Cell
5) Karres et al 2007 Cell

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"The role of incoherent microRNA-mediated feedforward loops in noise buffering",
arXiv:1004.0336