

# Systemic impact of microRNA-mediated regulation in animals

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## microRNAs in animals

microRNAs repress specific target mRNAs (recognized by sequence complementarity).

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Conservation of  
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## microRNAs in animals

microRNAs repress specific target mRNAs (recognized by sequence complementarity).

What is a miRNA target?

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### What is a miRNA target?

- ▶ Computational programs search for microRNA complementary sites that have been conserved in evolution.

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- ▶ A huge number of mRNAs exhibit such conserved sites (e.g.,  $\geq 60\%$  of human coding genes: Friedman *et al.*, 2009).

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- ▶ miRNAs only “fine-tune” most of their targets (Bartel and Chen, 2004).

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—→ microRNAs control every physiological process by fine-tuning some of its components.

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# An alternative hypothesis

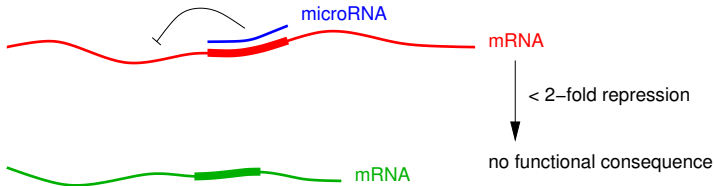
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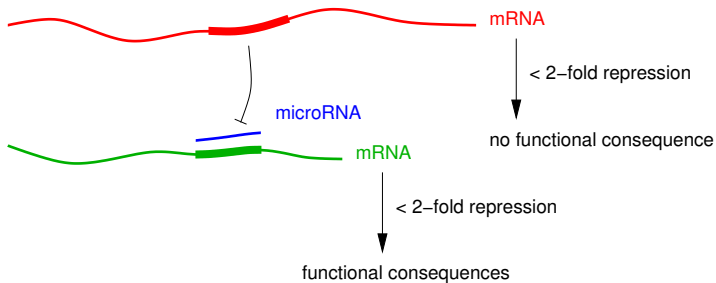
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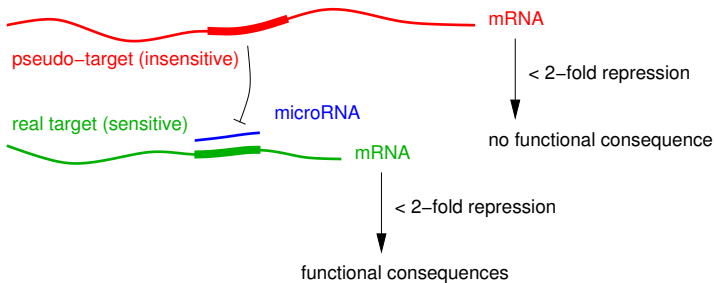
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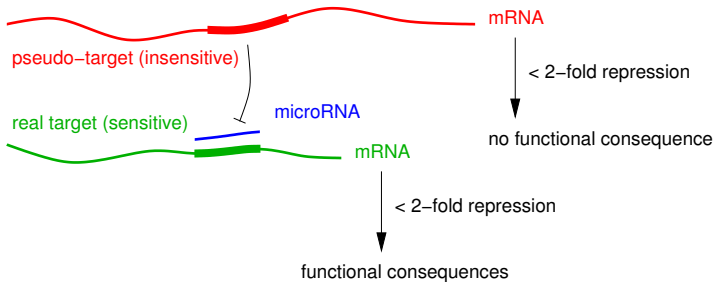
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(Seitz, 2009)

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# Discriminative predictions

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## Discriminative predictions

- ▶ miRNA binding sites on real targets are better conserved than on pseudo-targets;

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## Discriminative predictions

- ▶ miRNA binding sites on real targets are better conserved than on pseudo-targets;
- ▶ there could be non-coding pseudo-targets;

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## Discriminative predictions

- ▶ miRNA binding sites on real targets are better conserved than on pseudo-targets;
- ▶ there could be non-coding pseudo-targets;
- ▶ miRNA-mediated regulation is not amplified along regulatory pathways.

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## Conservation of real vs. pseudo-targets

Real targets have better conserved miRNA binding sites than pseudo-targets  $\iff$  the more dose-sensitive the gene, the more conserved its binding sites.

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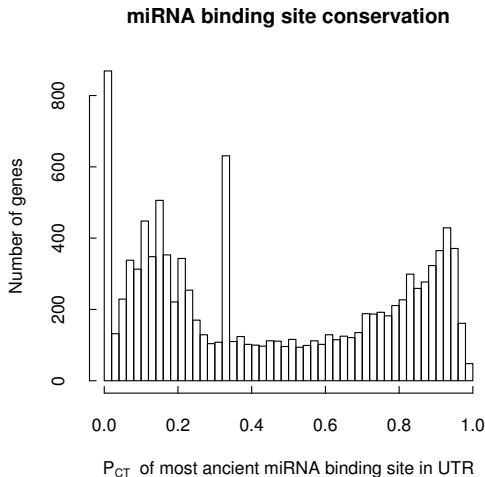
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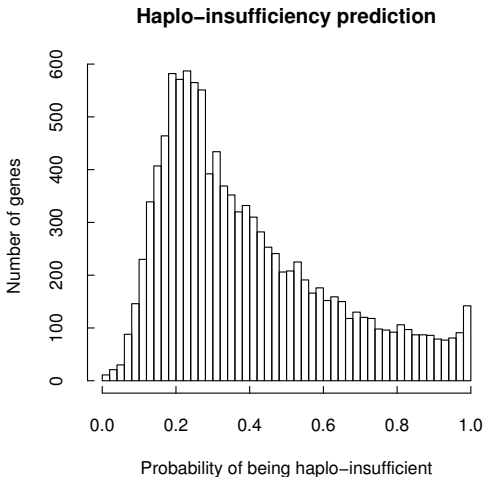
# Conservation of real vs. pseudo-targets

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regulation(data from Friedman *et al.*, 2009)

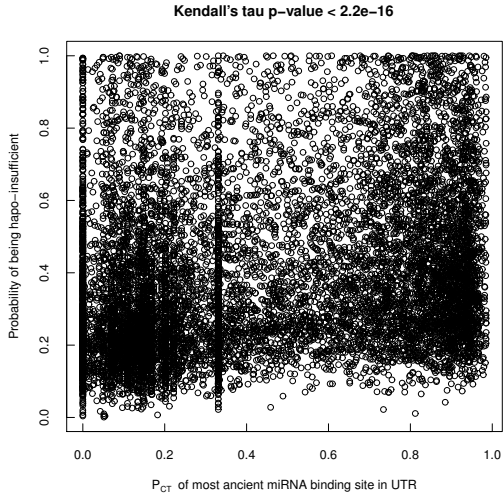
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(data from Huang *et al.*, 2010)

# Conservation of real vs. pseudo-targets



# Non-coding pseudo-targets?

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# Non-coding pseudo-targets?

Non-coding RNAs whose only function would be the titration of miRNAs.

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## Non-coding pseudo-targets?

Non-coding RNAs whose only function would be the titration of miRNAs (need to make sure that they do not have other functions).

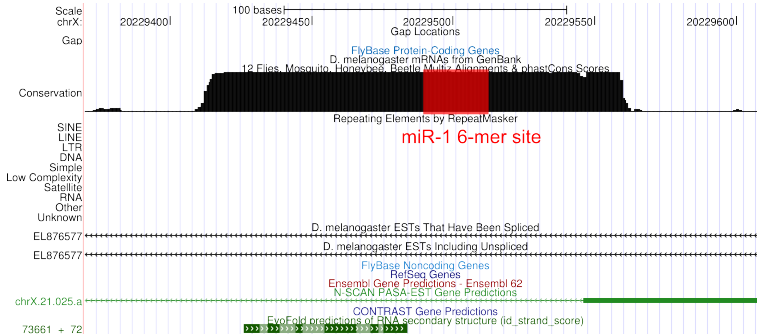
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# Non-coding pseudo-targets?



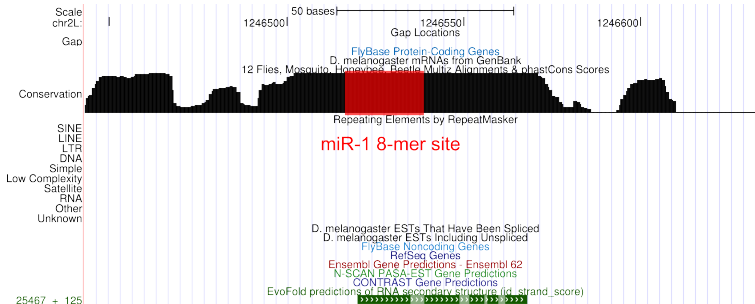
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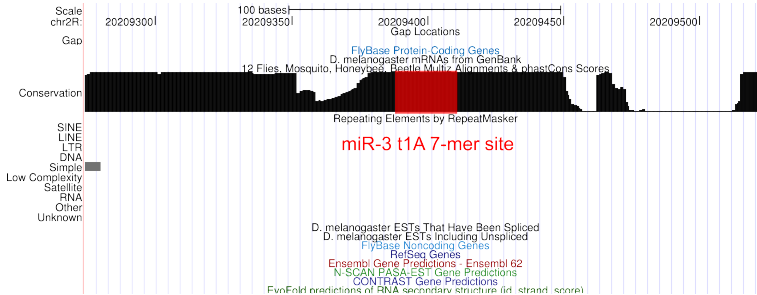
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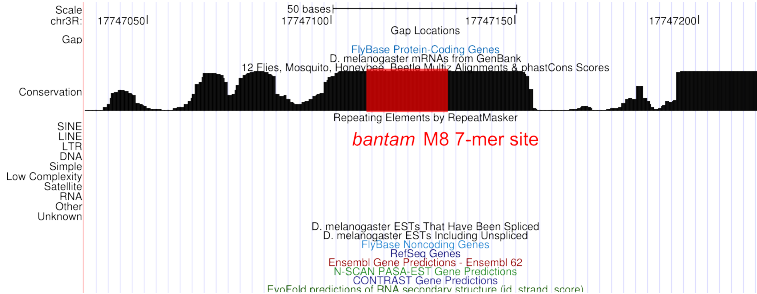
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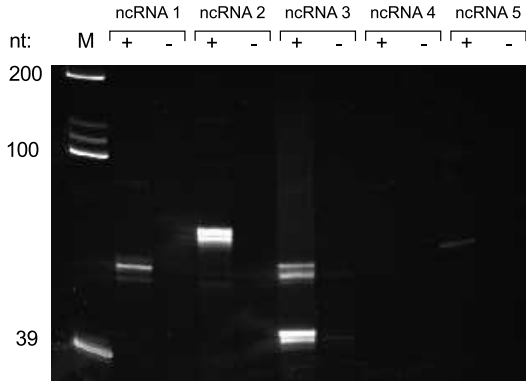
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# Non-coding pseudo-targets?

## Strand-specific RT-PCR:



"+": + RT; "-": - RT

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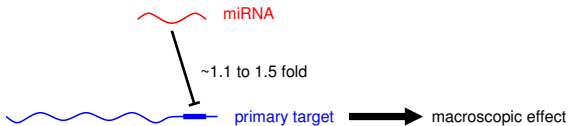
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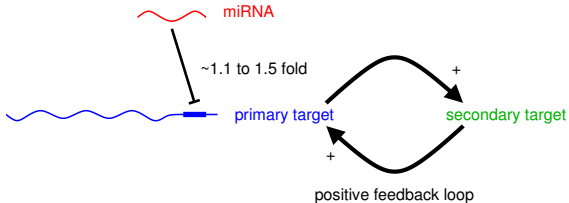
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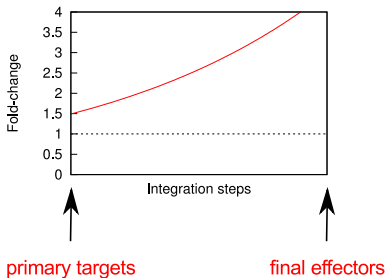
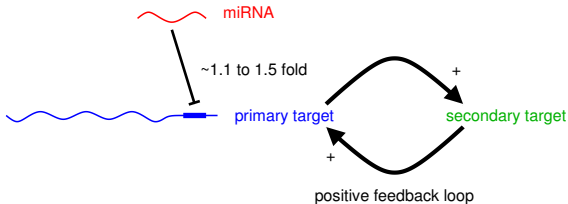
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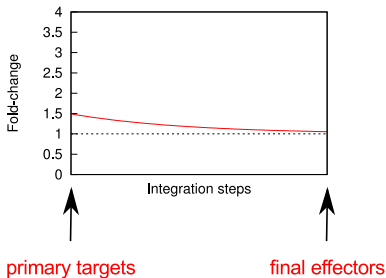
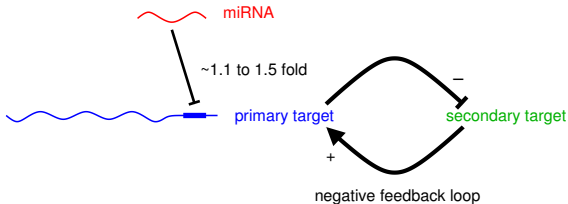
Non-coding  
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primary targets

final effectors

# Propagation of the regulation



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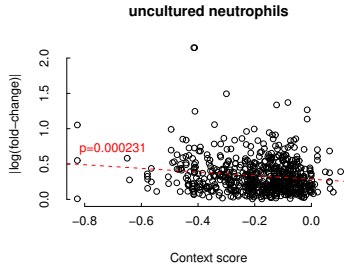
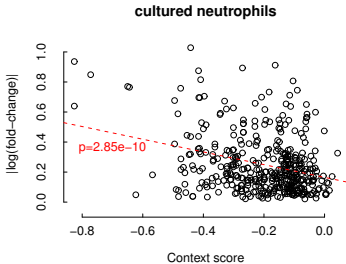
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miR-223<sup>-/-</sup> neutrophils in mouse.



(data from Baek *et al.*, 2008)

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# Acknowledgements

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