Cooperativity between Aryl Hydrocarbon Receptor and ß-catenin Binding Sites in Hepatocytes

Pascal Schulthess, Albert Braeuning, Alexandra Löffler, Michael Schwarz, and Nils Blüthgen

Cytochrome P450 (CYP)

- oxidate hydrophobic substances $\mapsto$ hydrophilic substances

  ➡ easier excretion

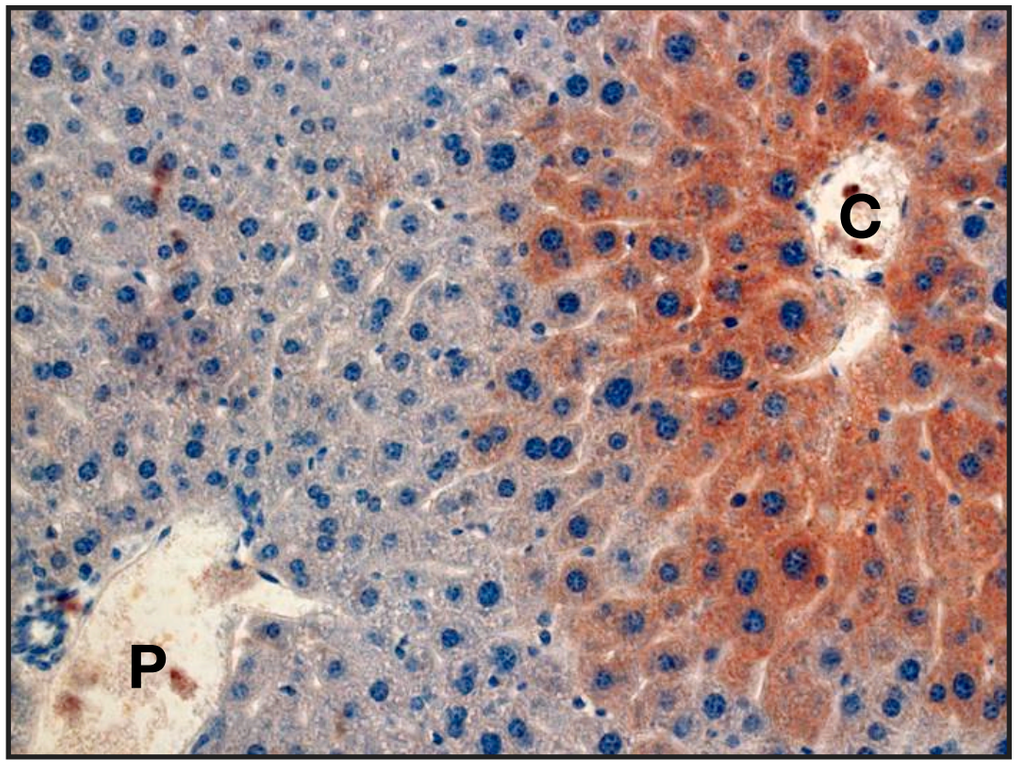
- essential for metabolizing many drugs & toxins

- strong expression in the liver & colon

CYP1A1 expression gradient in liver lobules

normal liver

CYP1A1



Braeuning, A. & Schwarz, M. Biol. Chem. 391, 139–148 (2010)

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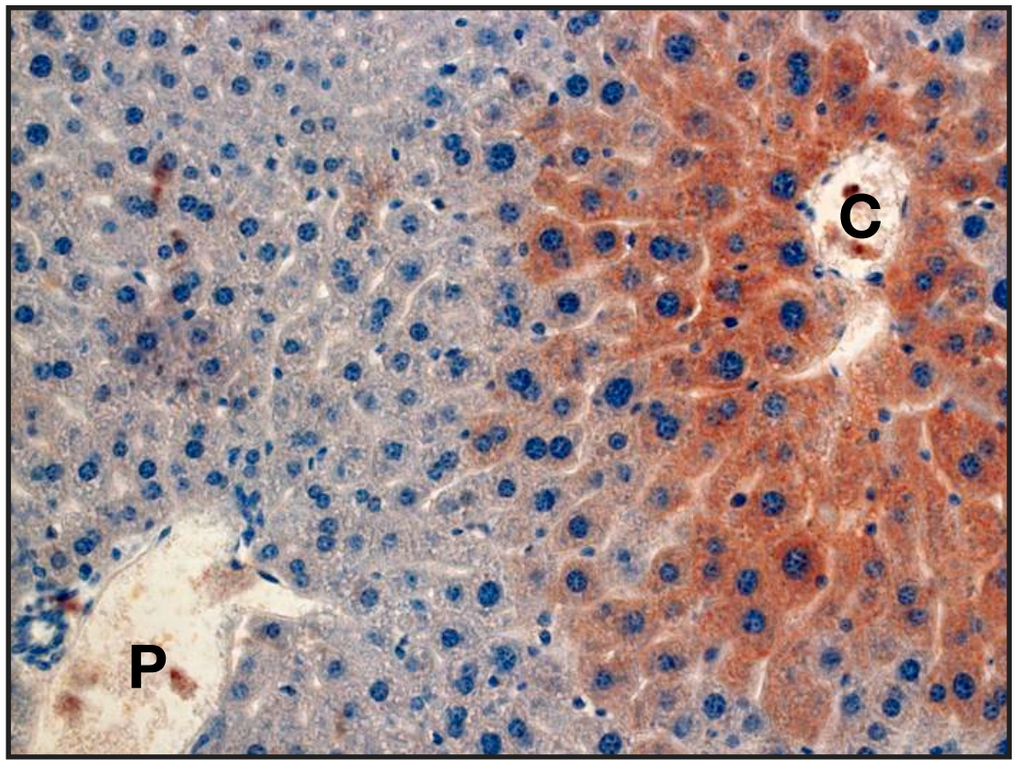
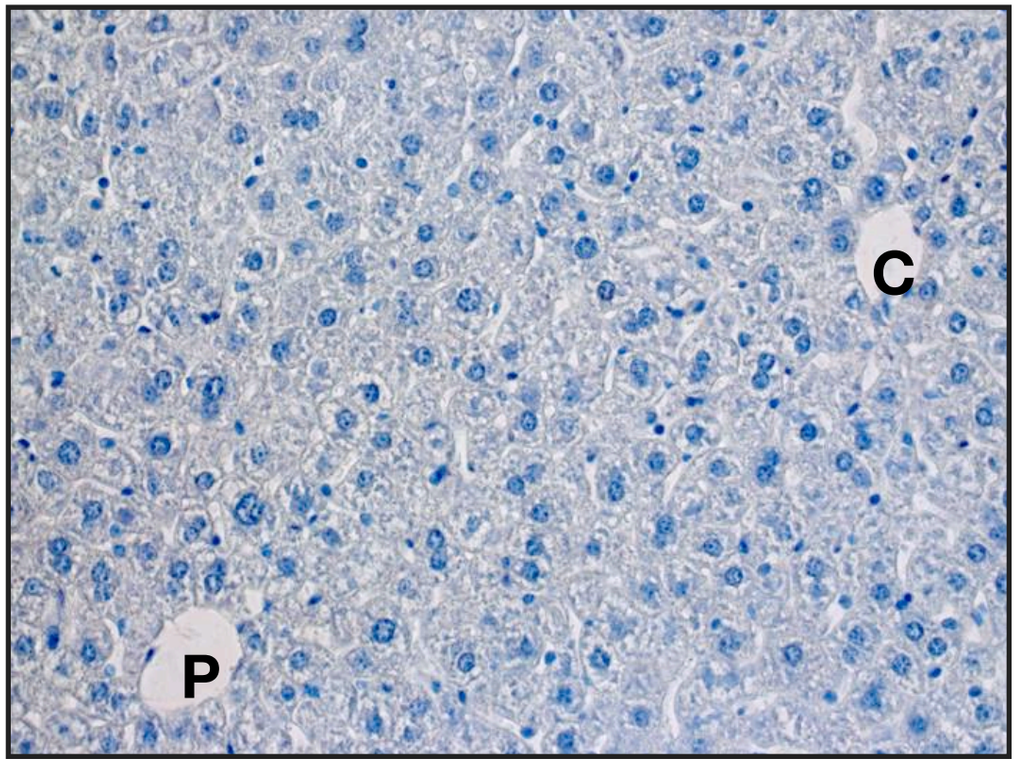


ß-catenin k.o.



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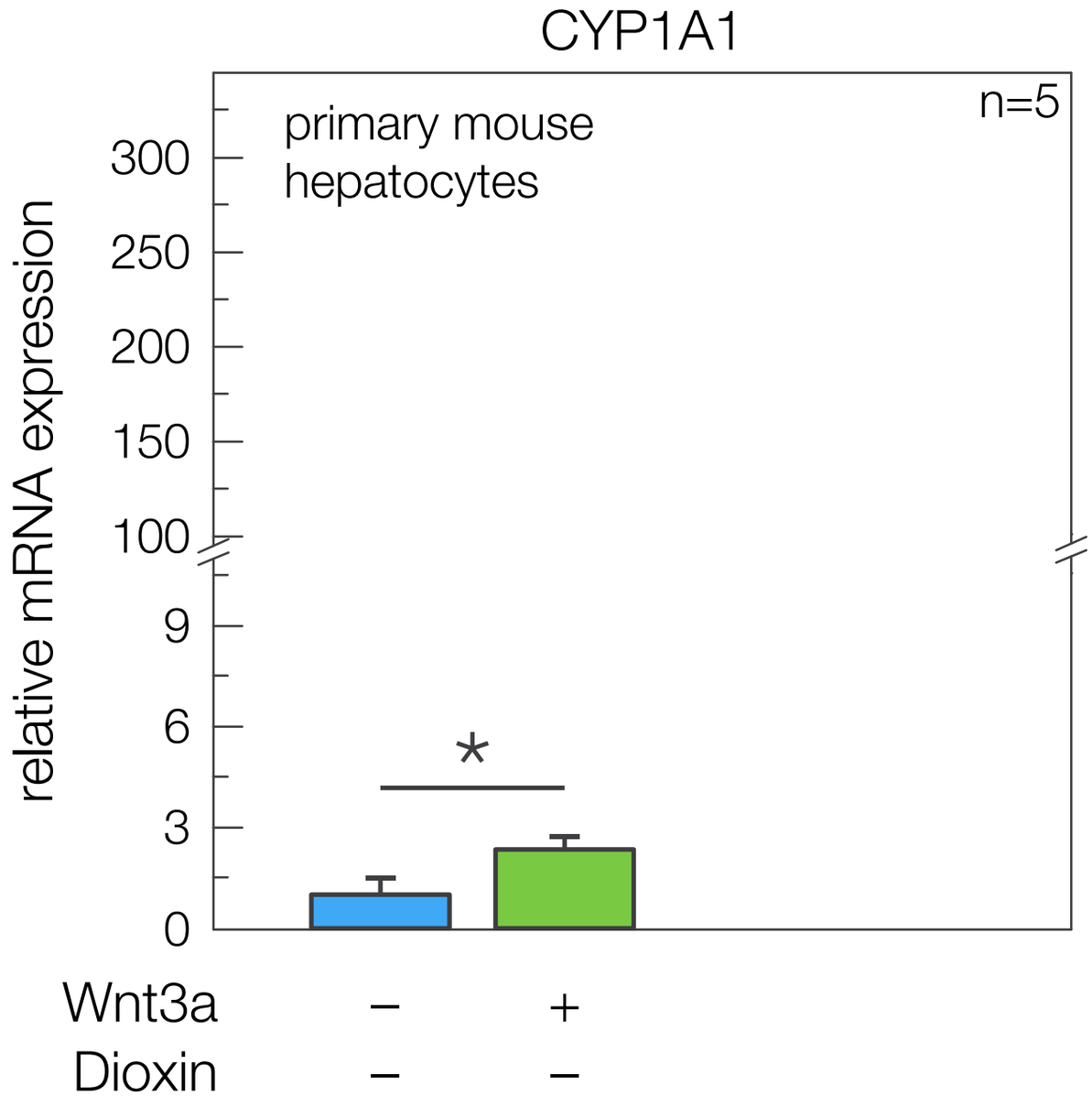
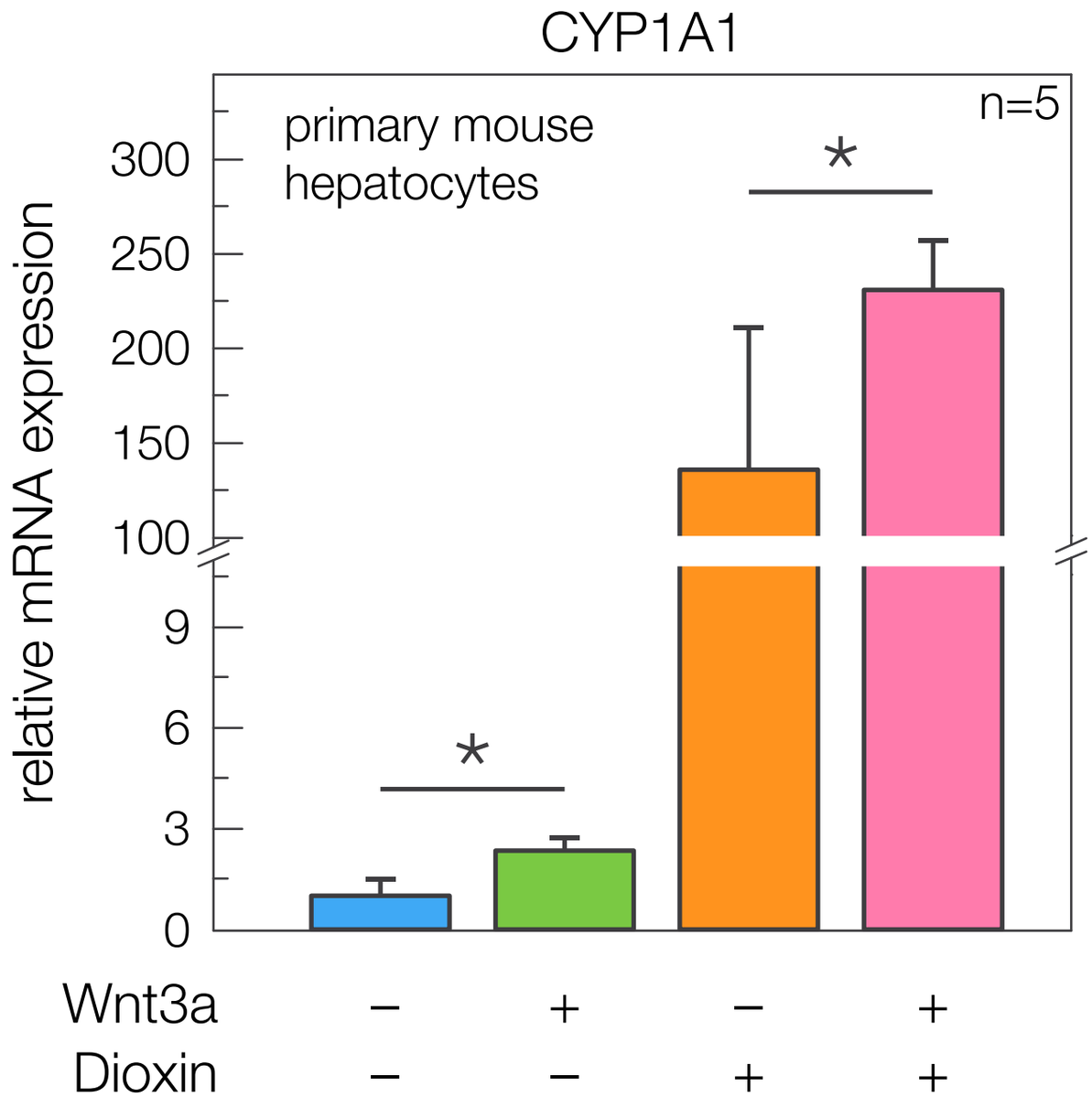
CYP1A1 expression induced by Wnt



Braeuning, A., Köhle, C., Buchmann, A. & Schwarz, M. Toxicol. Sci. 122, 16–25 (2011).

CYP1A1 expression induced by Wnt & Dioxin



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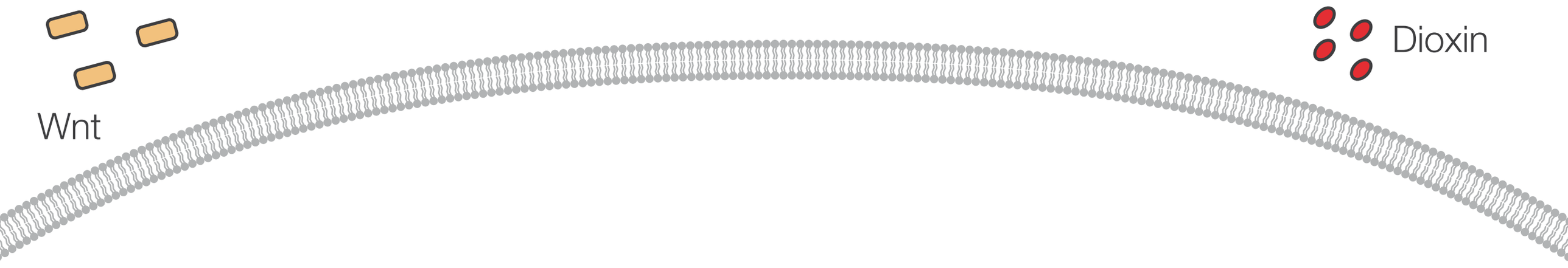
AhR and ß-catenin converge on CYP1A1 promotor



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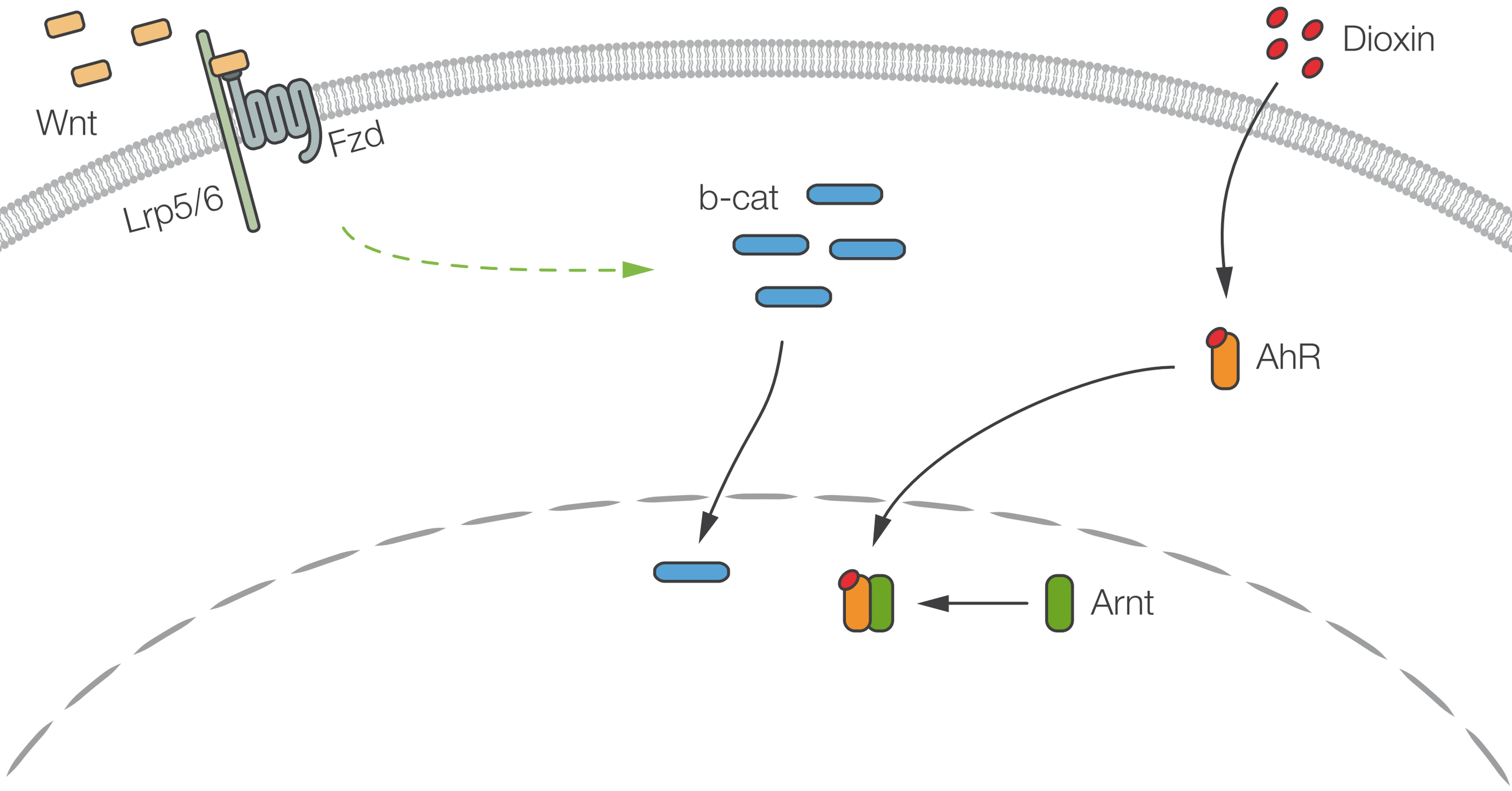

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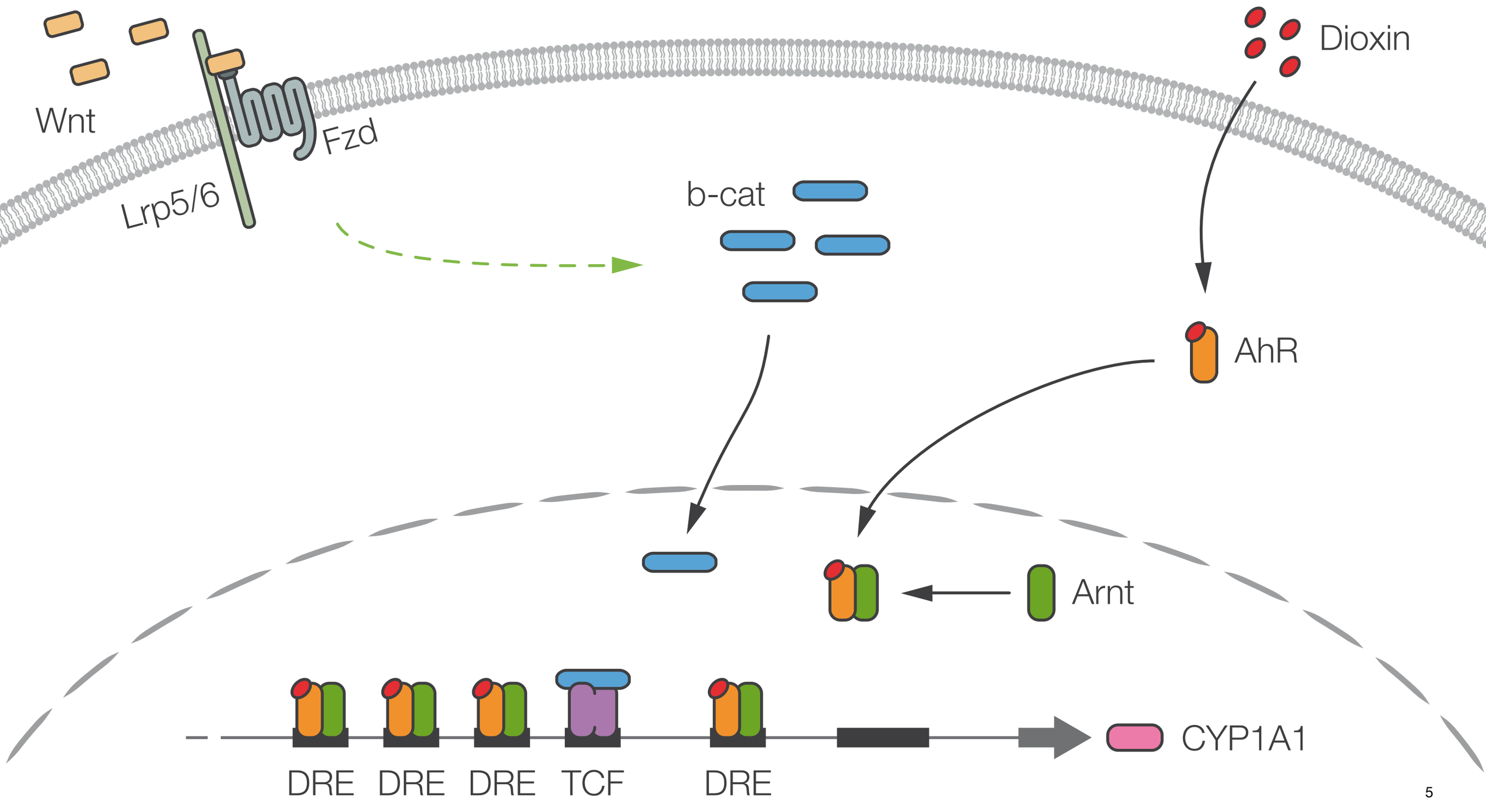


AhR and ß-catenin converge on CYP1A1 promotor

Wnt

Lrp5/6

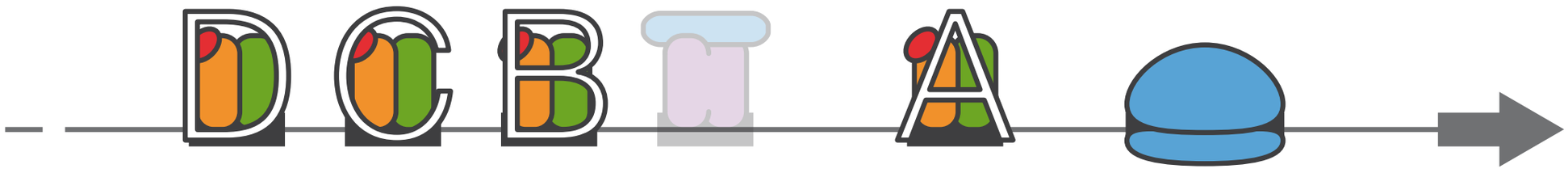
Dioxin

How do the binding sites cooperate?

hR

Arnt

15 human CYP1A1 promotor constructs



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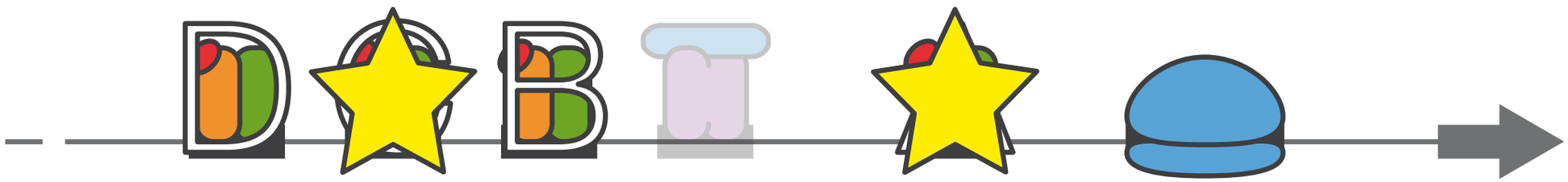
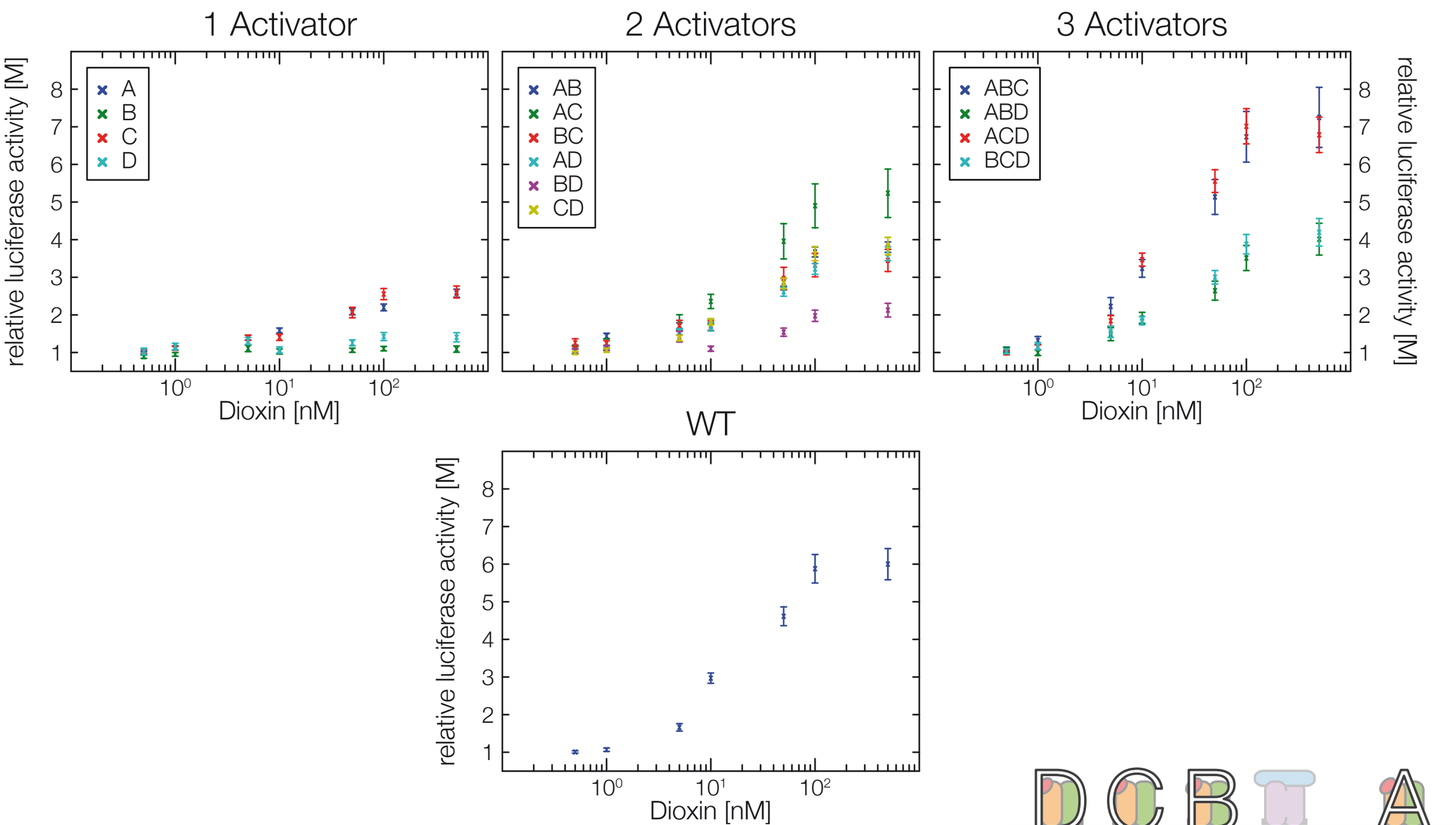
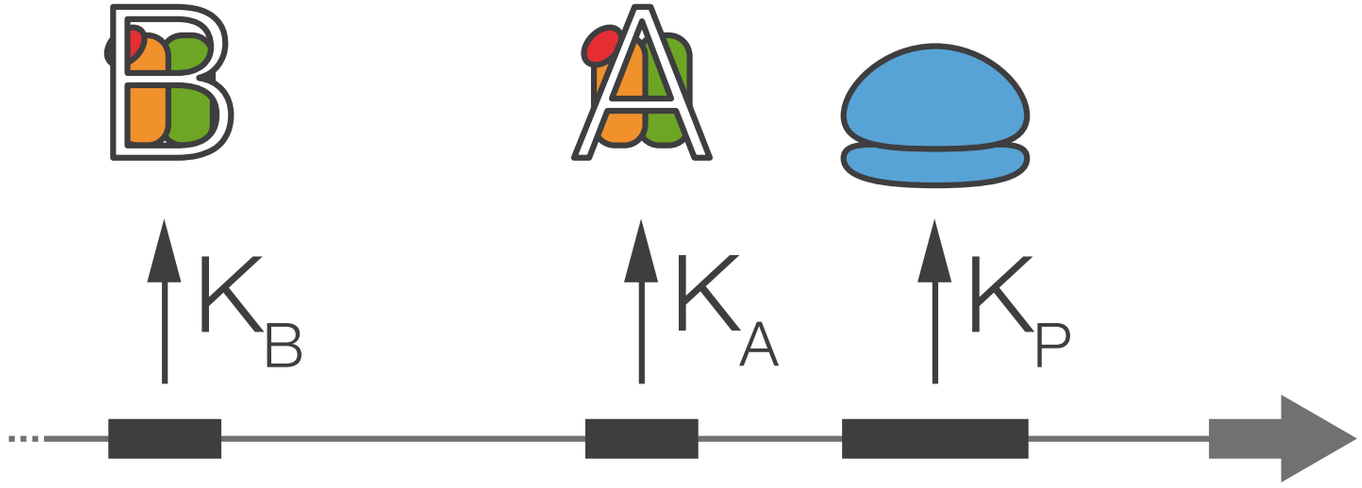


15 human CYP1A1 promotor constructs

Data show more-than-additive effects



Parameters of thermodynamic model



Bintu, L. et al. Curr. Opin. Genet. Dev. 15, 116–124 (2005).

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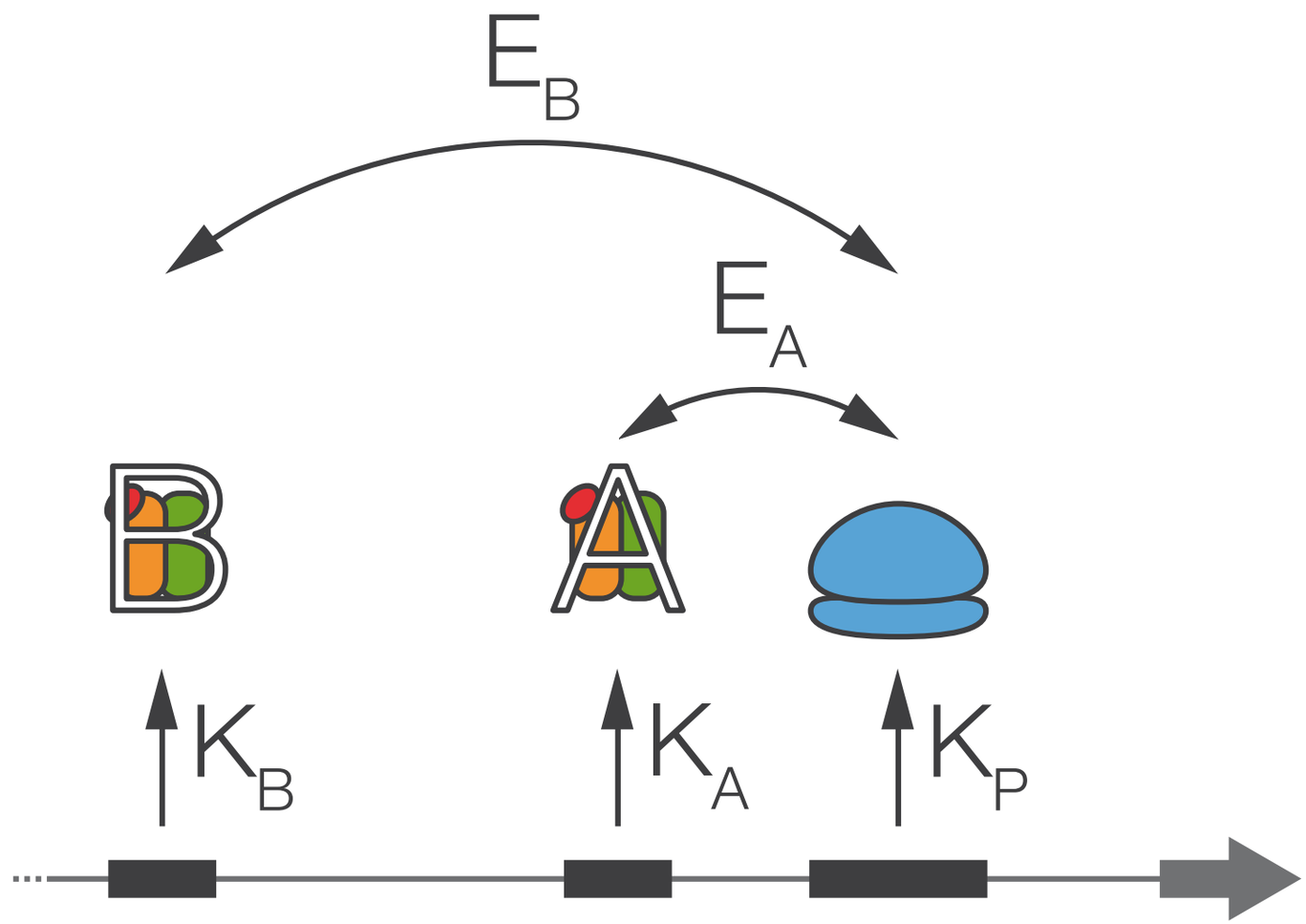

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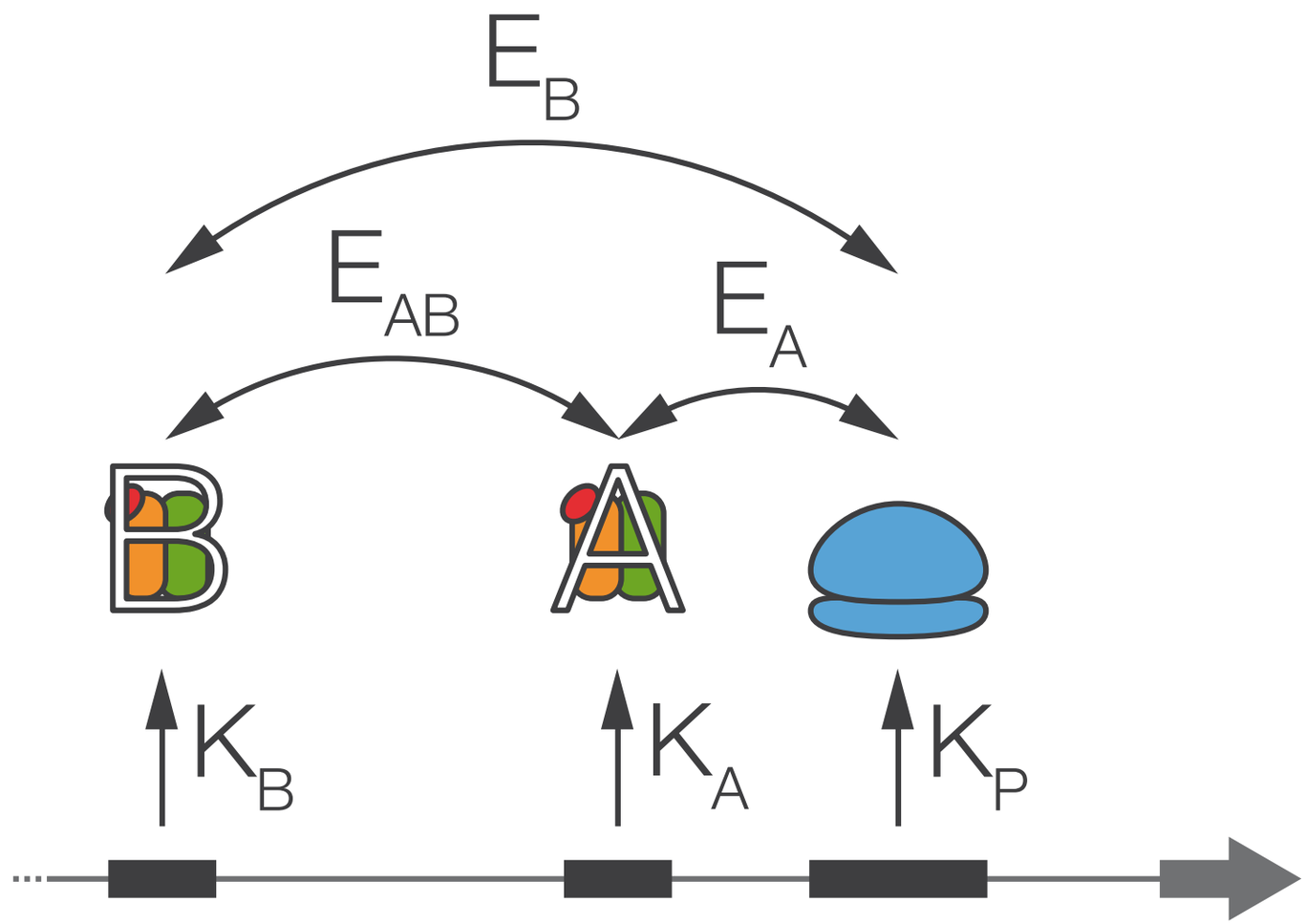
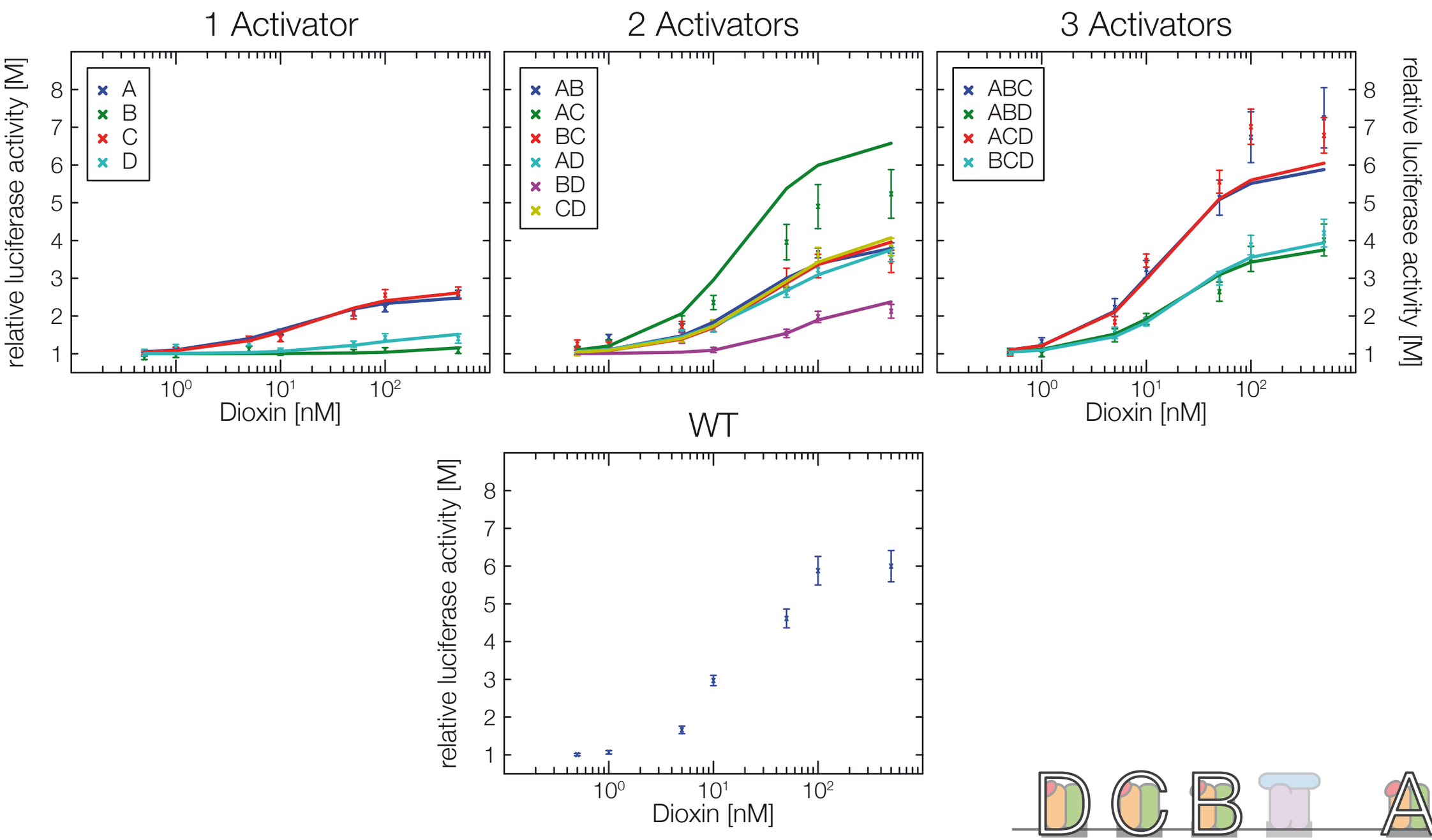


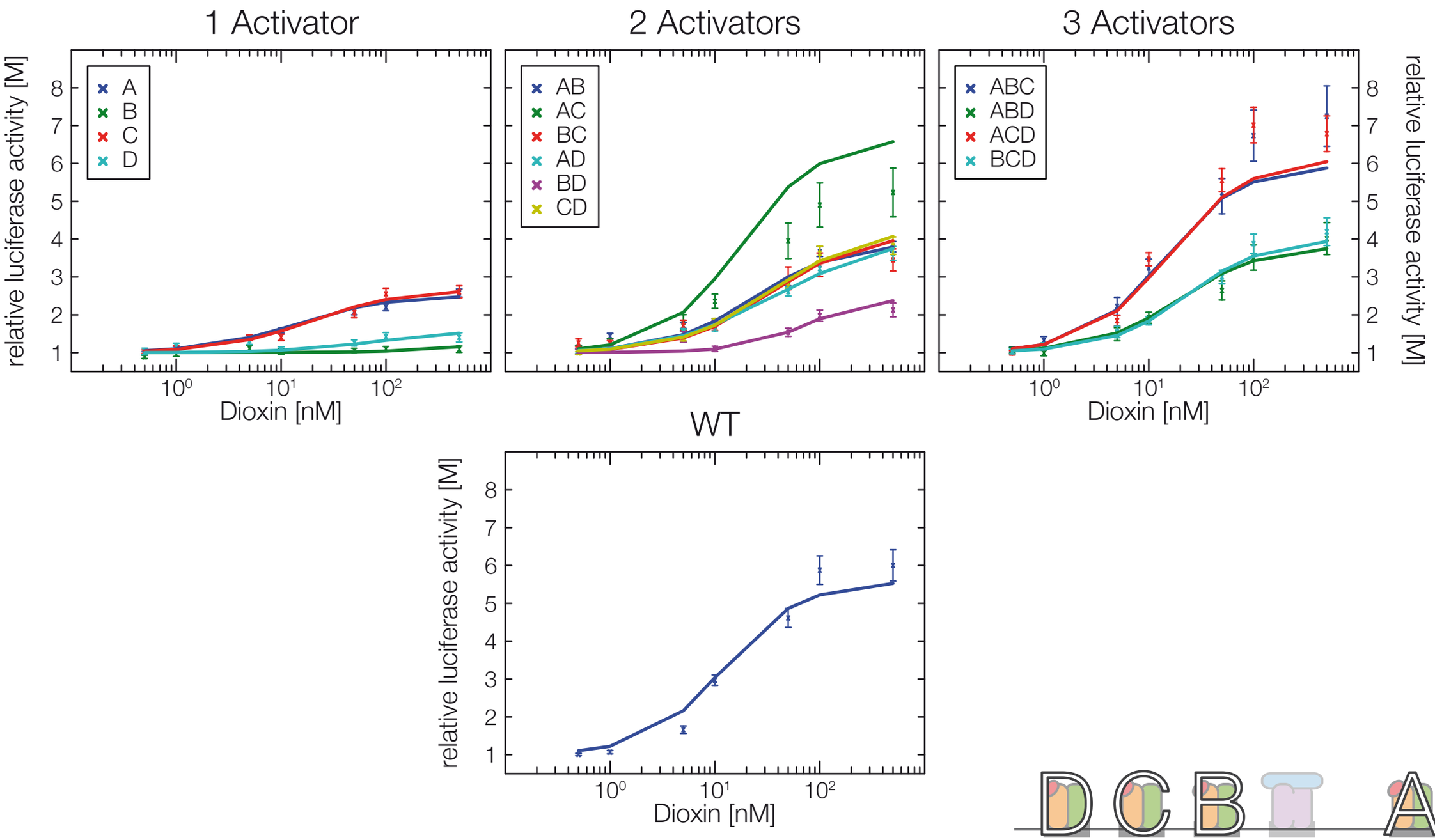
Fold change model expressed with mass action kinetics

Bintu, L. et al. Curr. Opin. Genet. Dev. 15, 116–124 (2005).

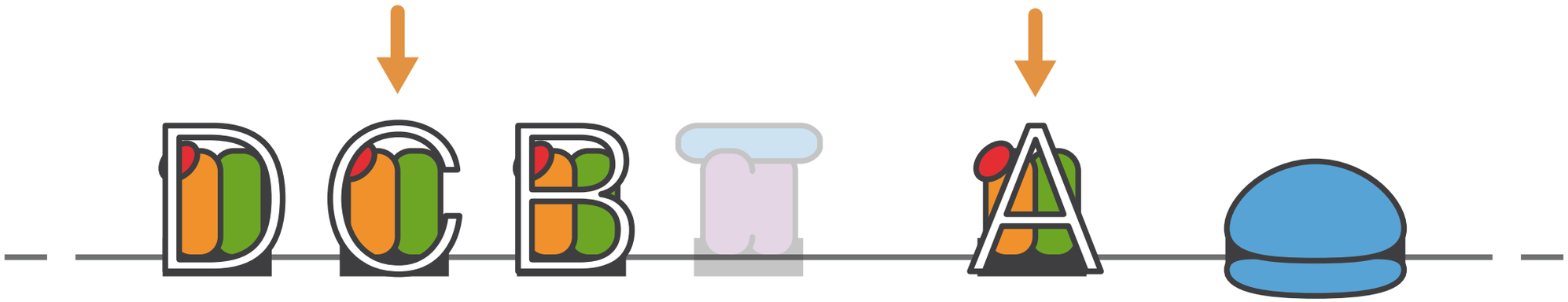
Maximum likelihood fit of thermodynamic model



Prediction of thermodynamic model

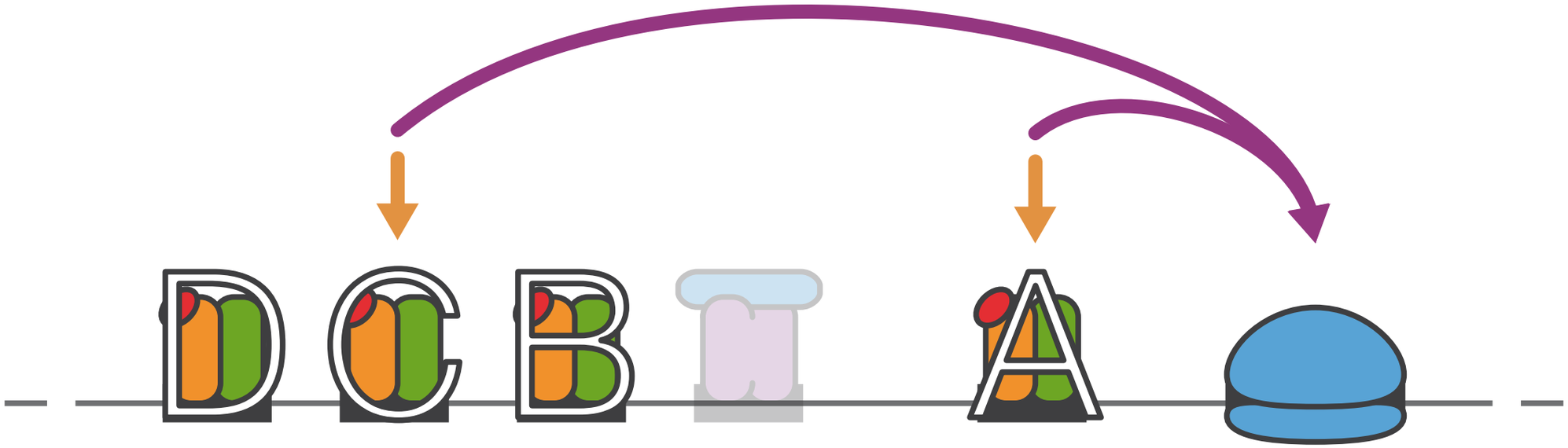


Interpretation of model parameters



strongest binding sites

Interpretation of model parameters



strongest binding sites | recruit RNA Polymerase

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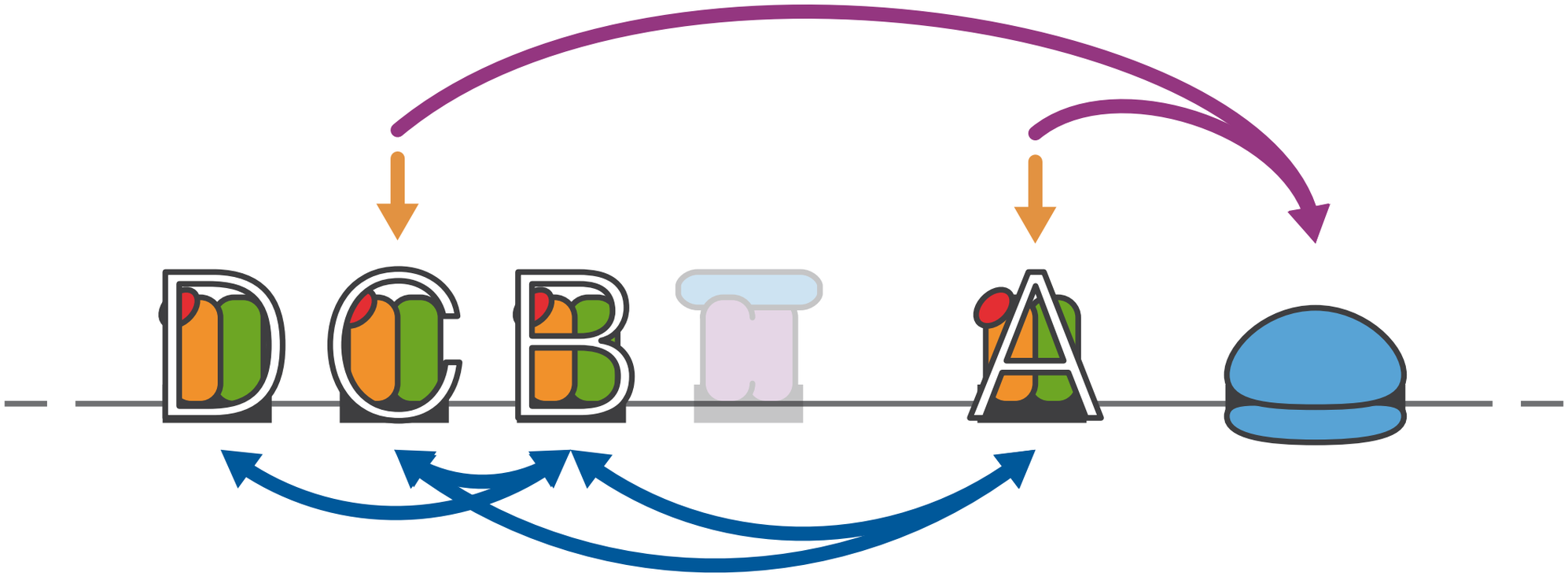


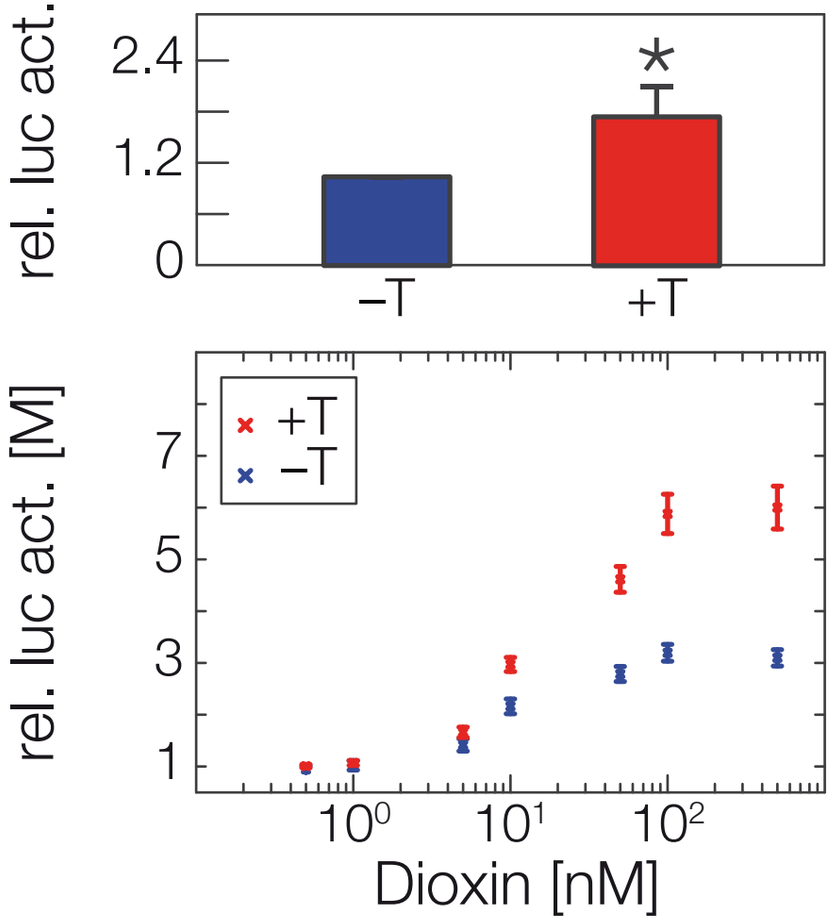
strongest binding sites | recruit RNA Polymerase

only some cooperations are essential

TCF binding site interactions

Experiments

Thermodynamic model



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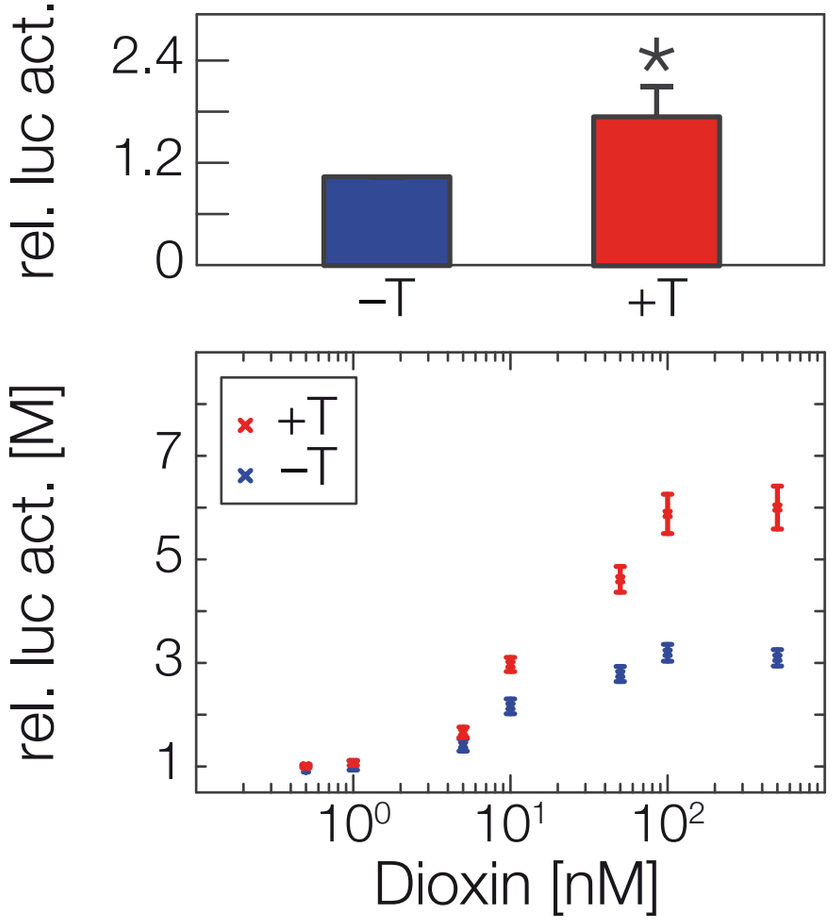
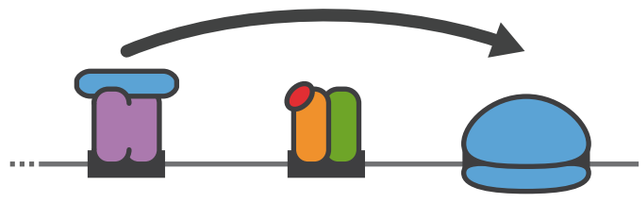
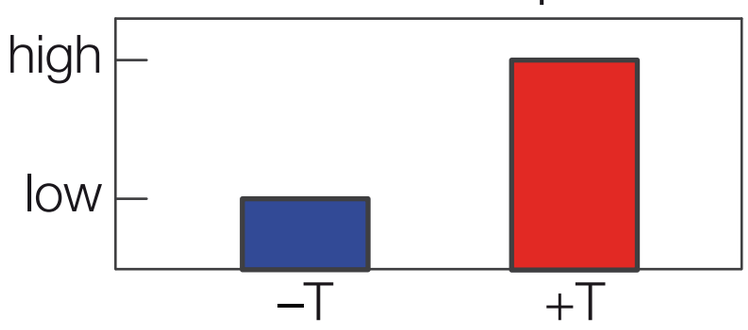
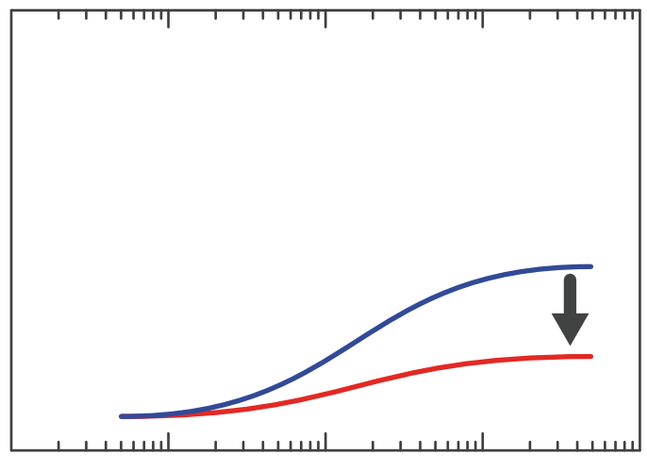


Thermodynamic model



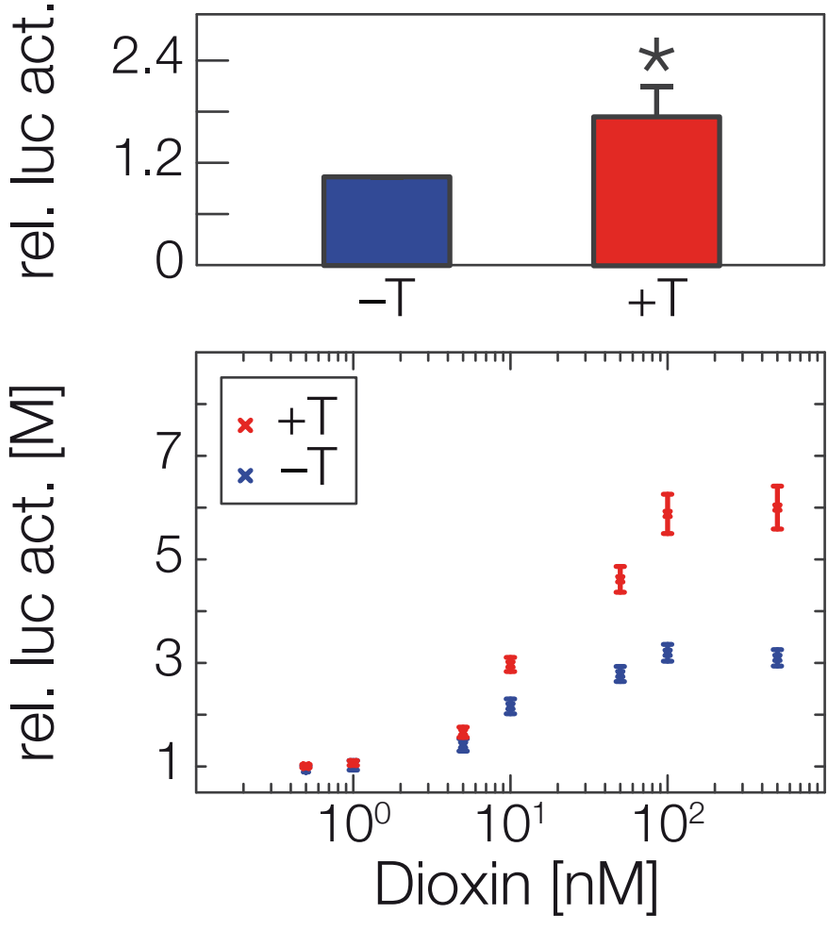
basal transcription





TCF binding site interactions not trivial

Experiments



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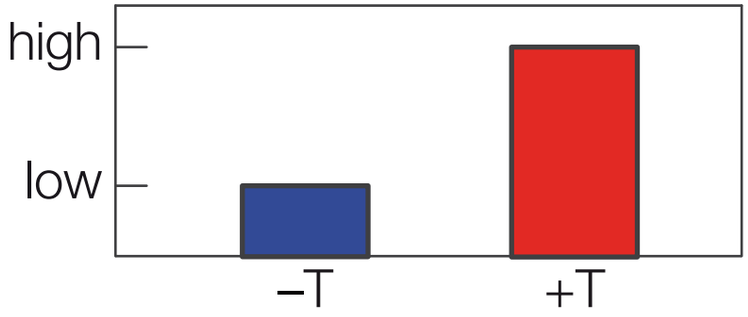

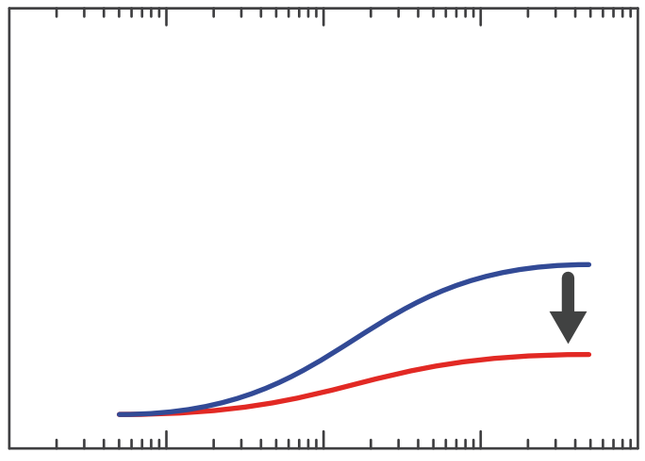

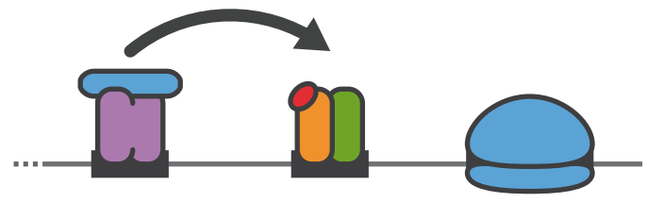

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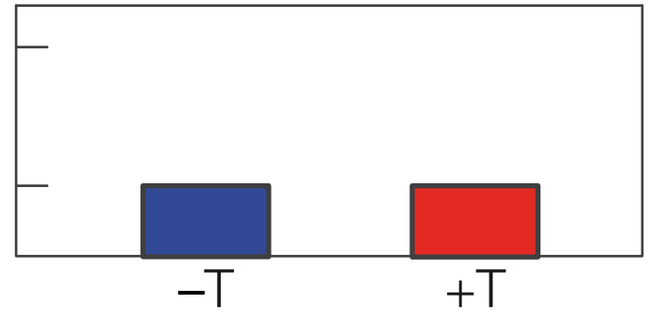

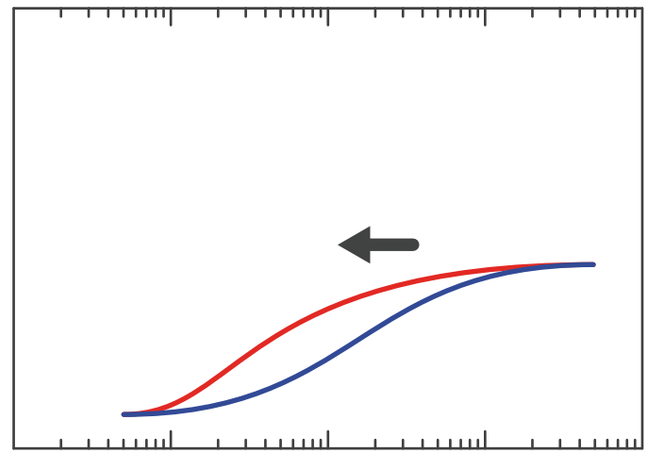

Conclusion

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- DRE binding sites
  - works according to convential paradigm of promotors
    - 2 strongest binding sites control recruitment of RNAP
    - cooperativity essential

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- DRE binding sites
  - works according to convential paradigm of promotors
    - 2 strongest binding sites control recruitment of RNAP
    - cooperativity essential
- TCF binding site
  - contradicts convential paradigm of promotors
    - needs active regulation
  - Mechanism?
    - needs further experiments

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