04.03.2016

Thermodynamic modeling explains the regulation of *CYP1A1* expression in the liver

Thesis defense

Pascal Schulthess

COMPUTATIONAL MODELLING IN MEDICINE

CHARITÉ
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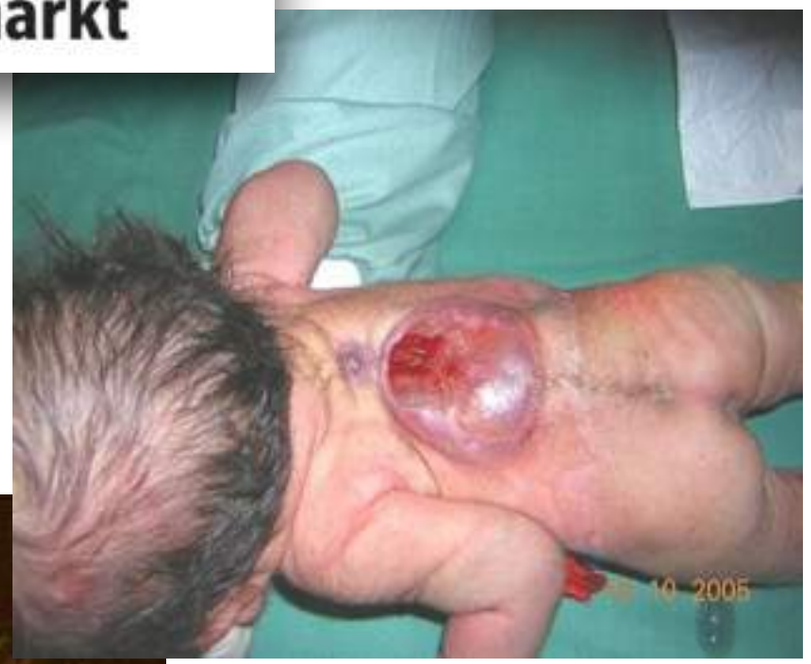
Exposure to dioxin through food uptake

EXPRESS

02.06.15, 08:15 Uhr

Wohl nicht gefährlich Schon wieder Dioxin-Eier in NRW! Gift-Eier gelangten in Supermarkt

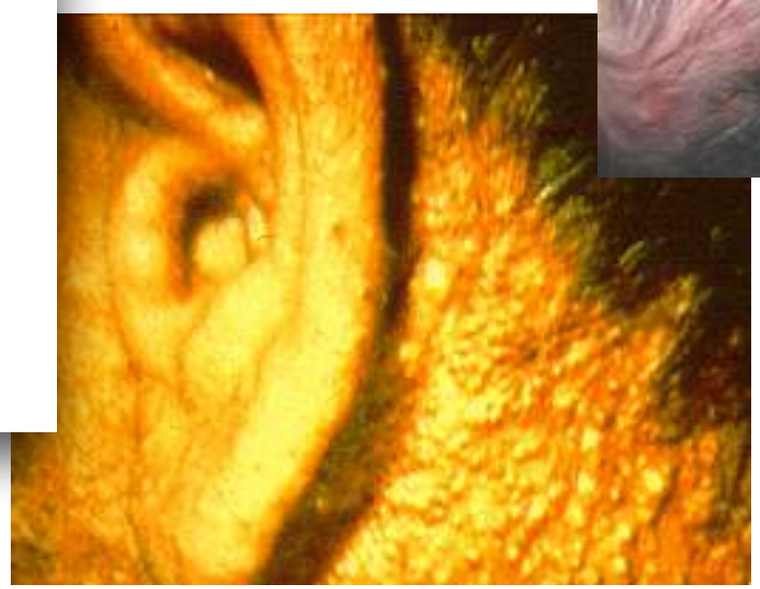


REUTERS

HEALTH

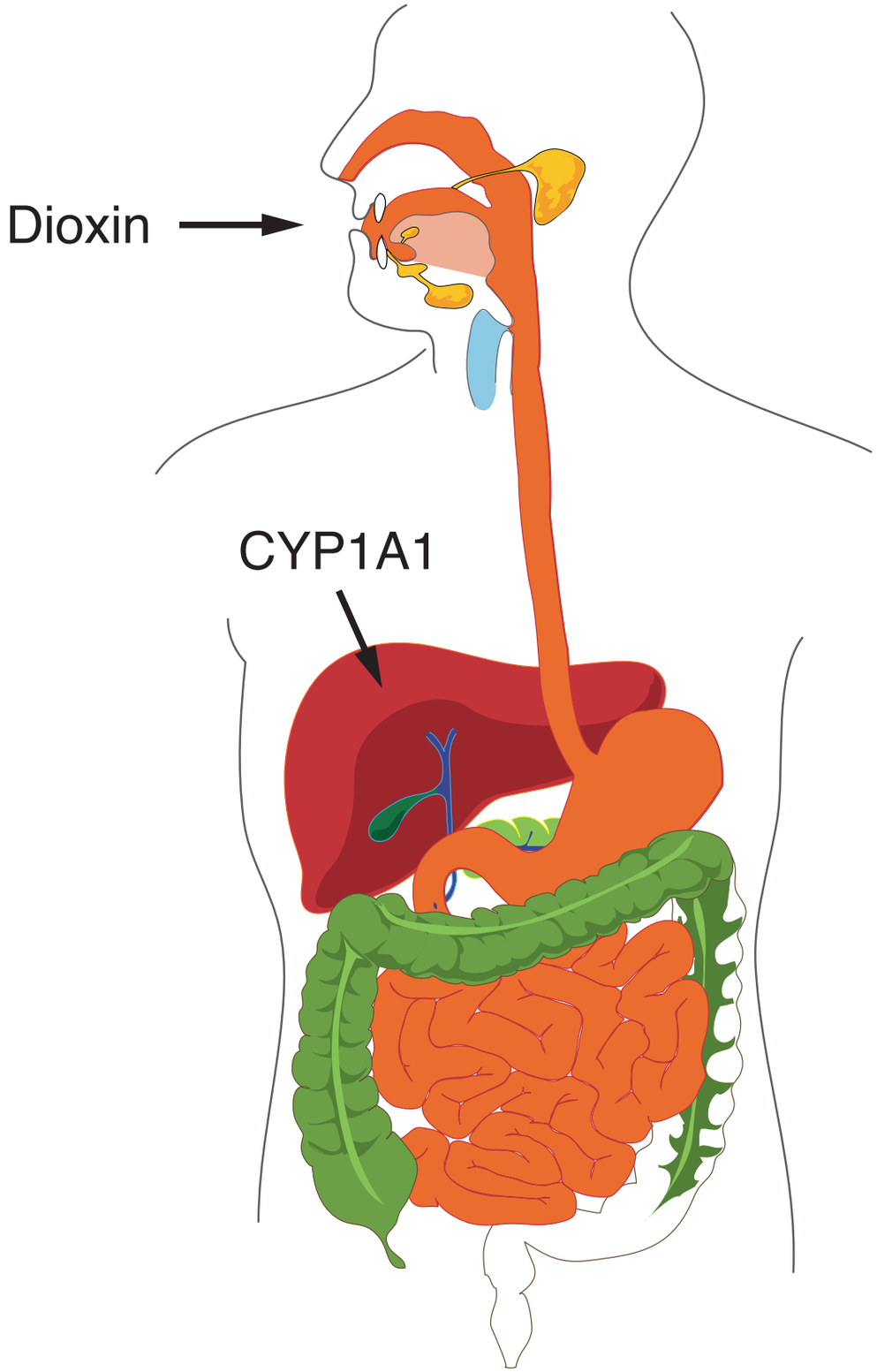
Wed Jan 12, 2011 | 12:55 PM EST

Dioxin-tainted pork possibly sold in Germany



welt.de, wikipedia.org, beyondthedish.wordpress.com

CYPs biotransform toxins

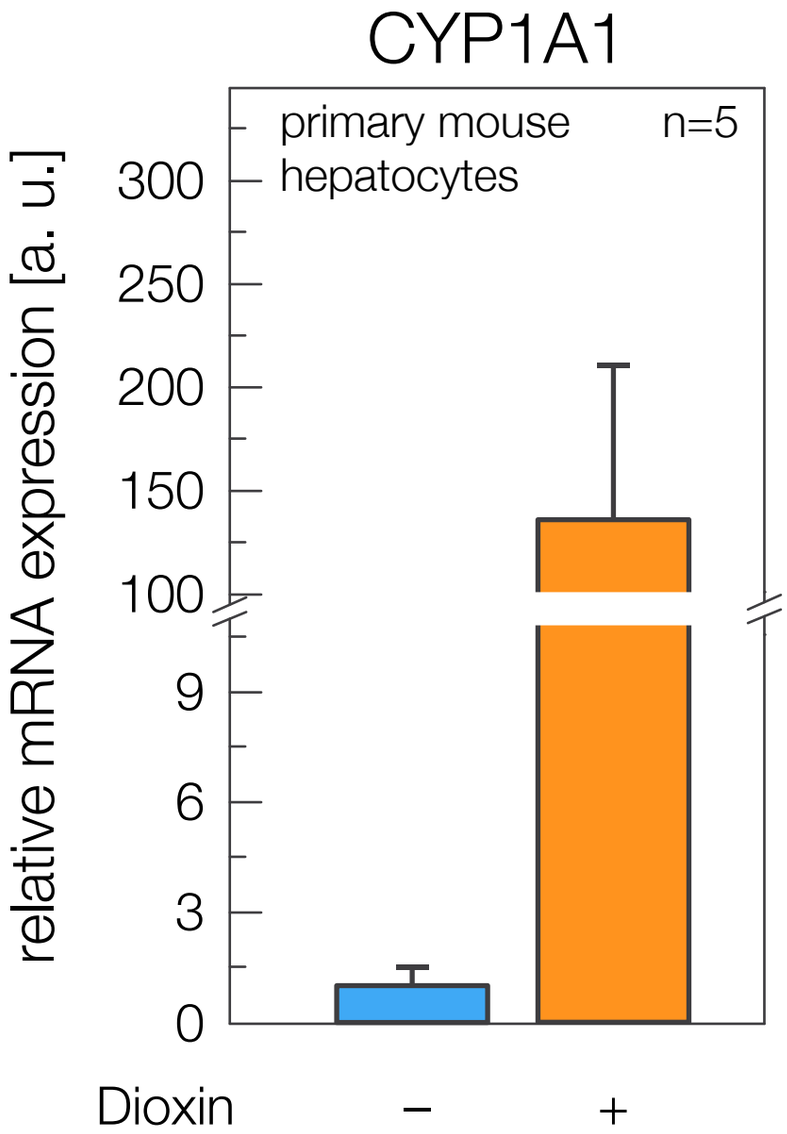


<u>Cytochrome P450s (CYPs)</u>

- major enzymes in detoxification
- harbor broad substrate specificity
- increase hydrophilicity of compounds to ease their excretion in bile or urine

wikipedia.org

Dioxin induces zonated expression of *CYP1A1*



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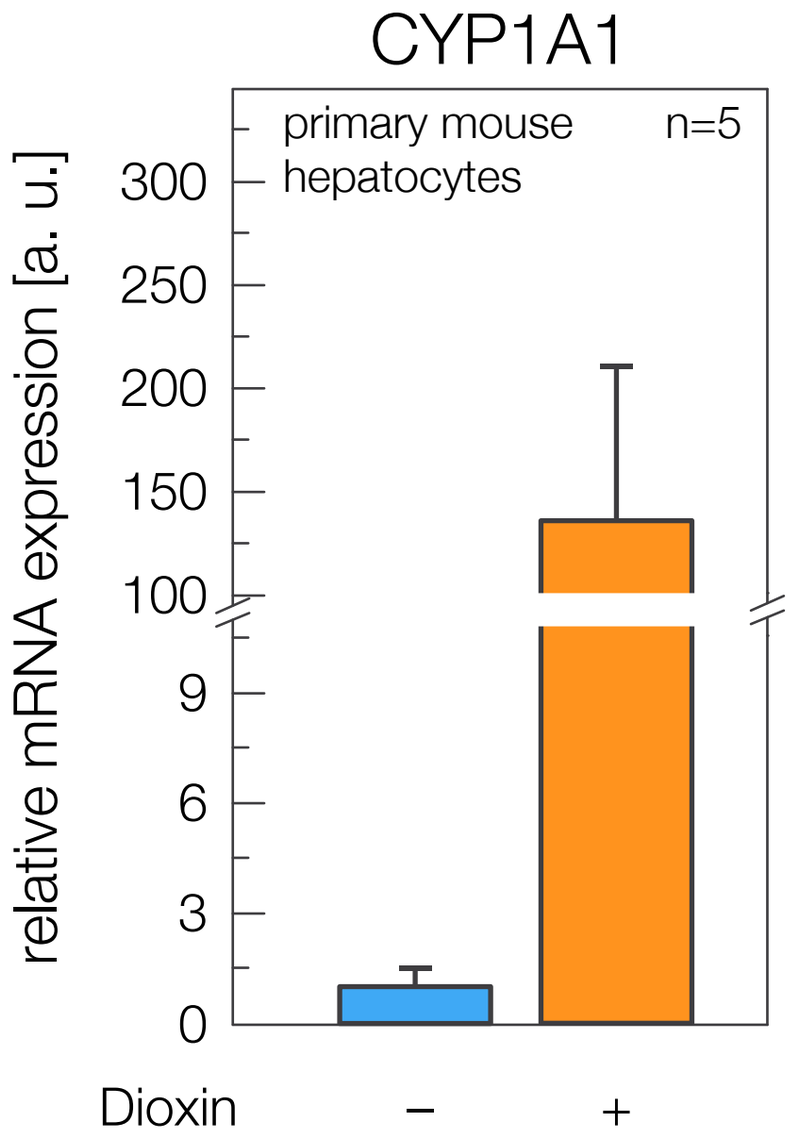

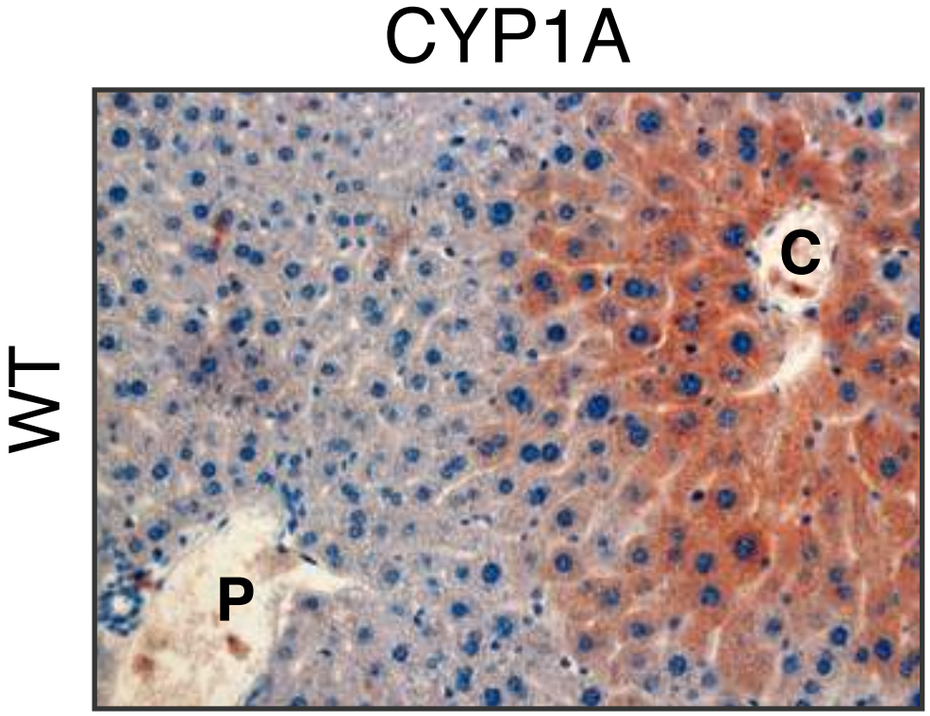

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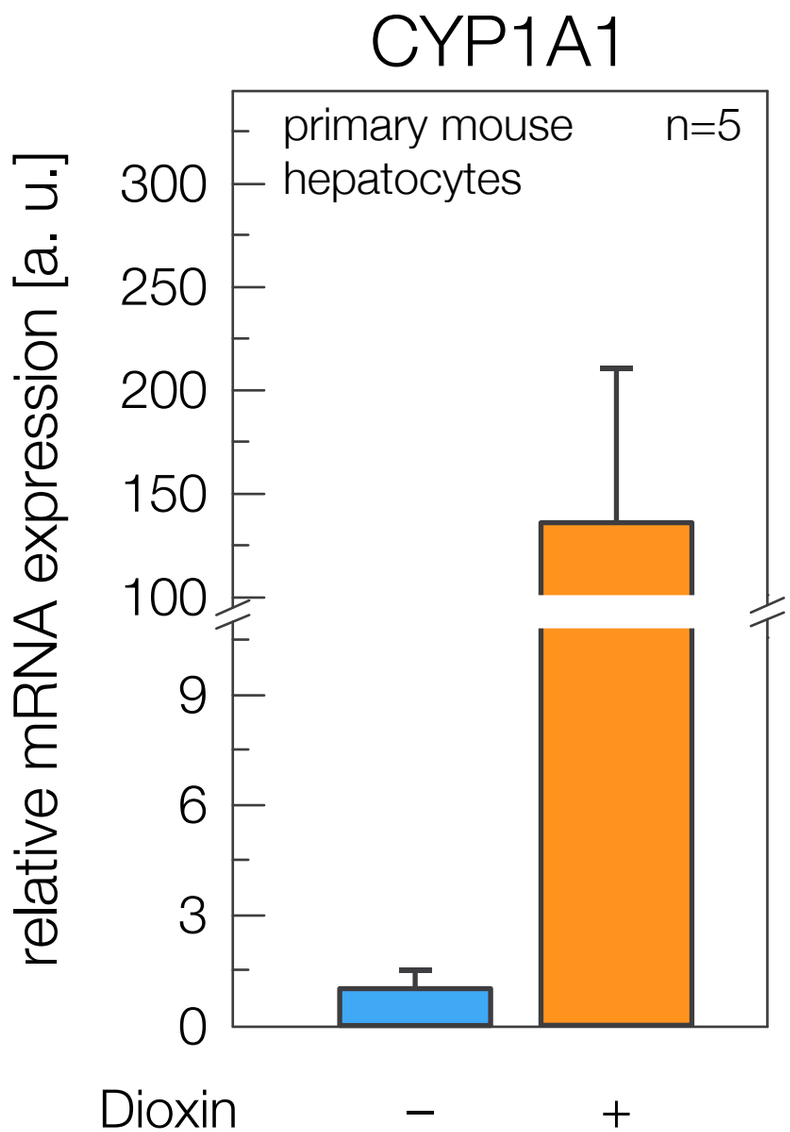

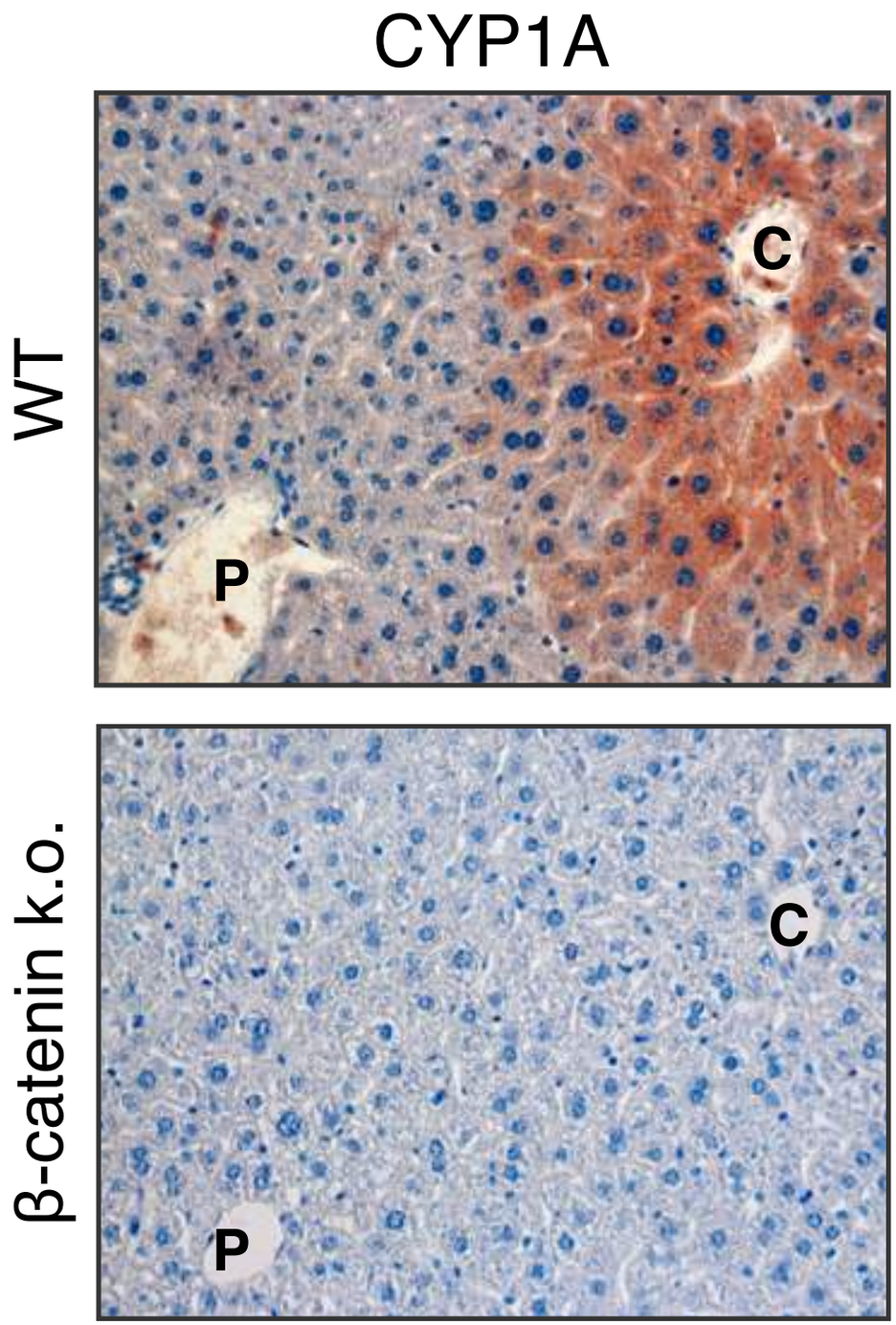

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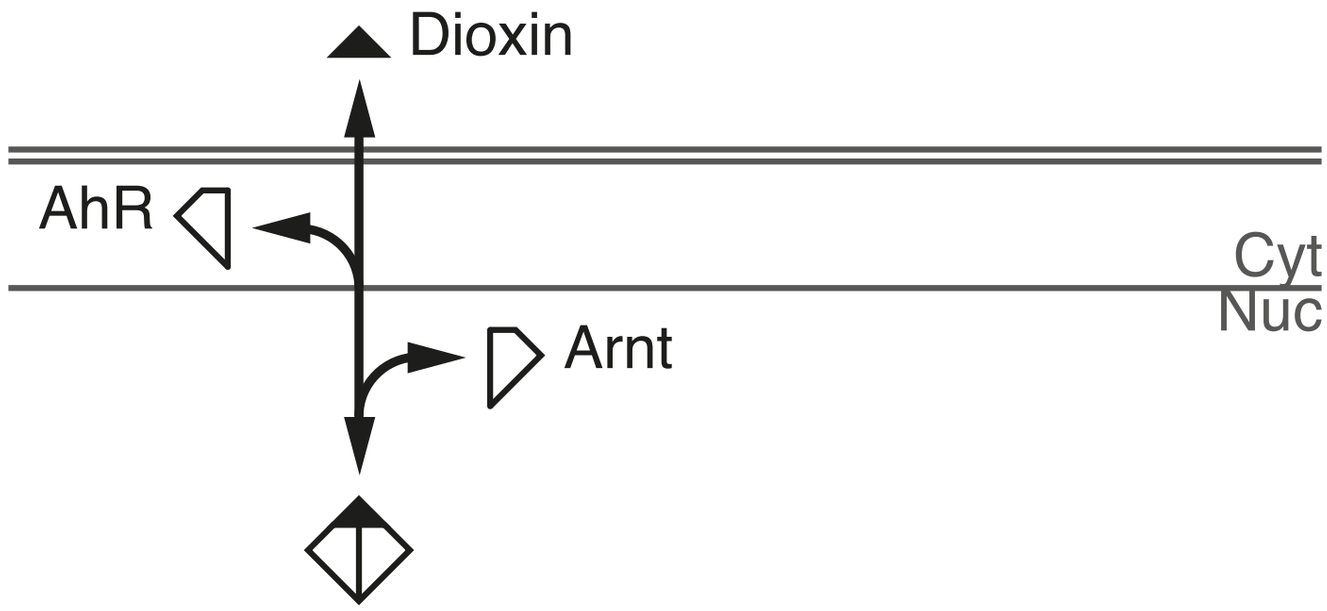
Dioxin and β-catenin signaling converge on *CYP1A1* promoter



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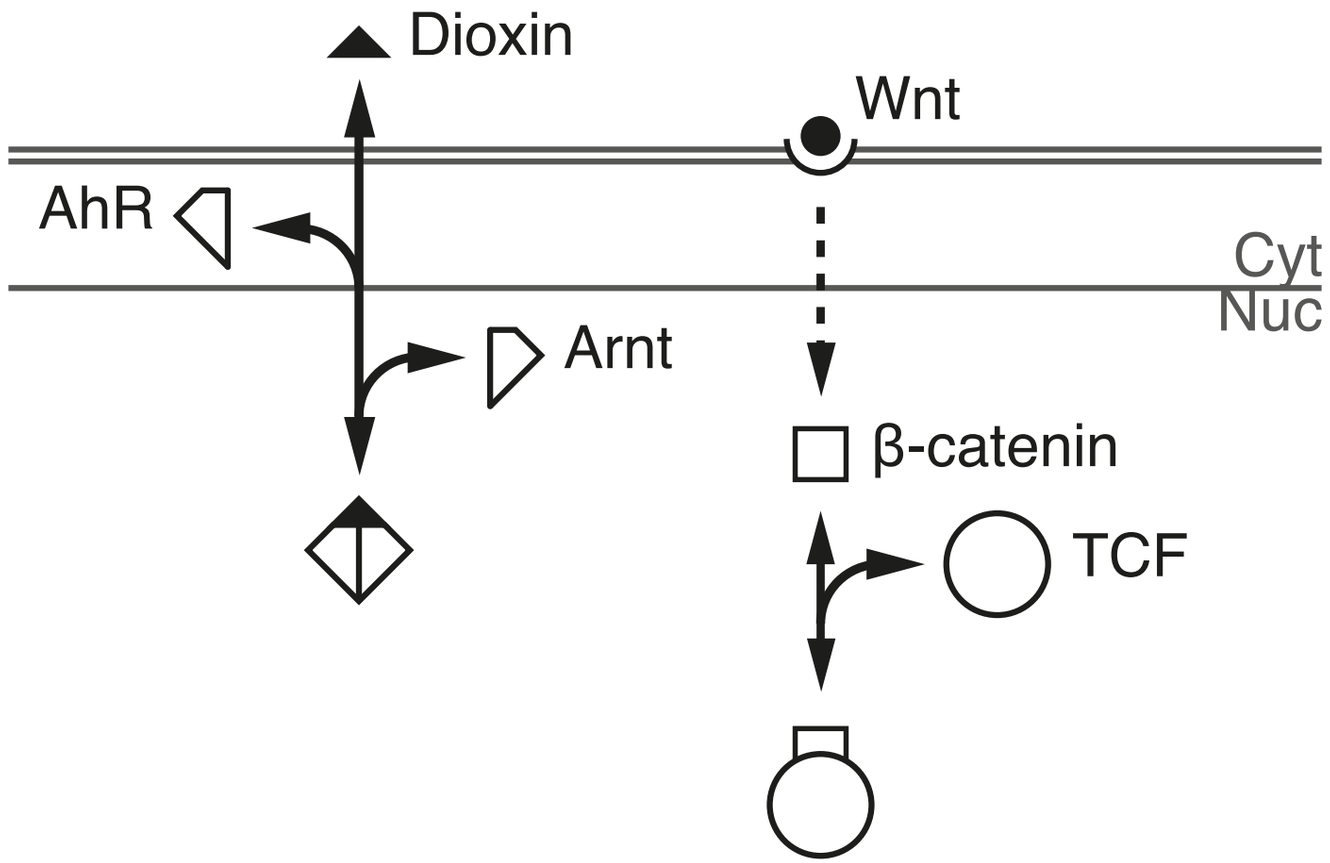

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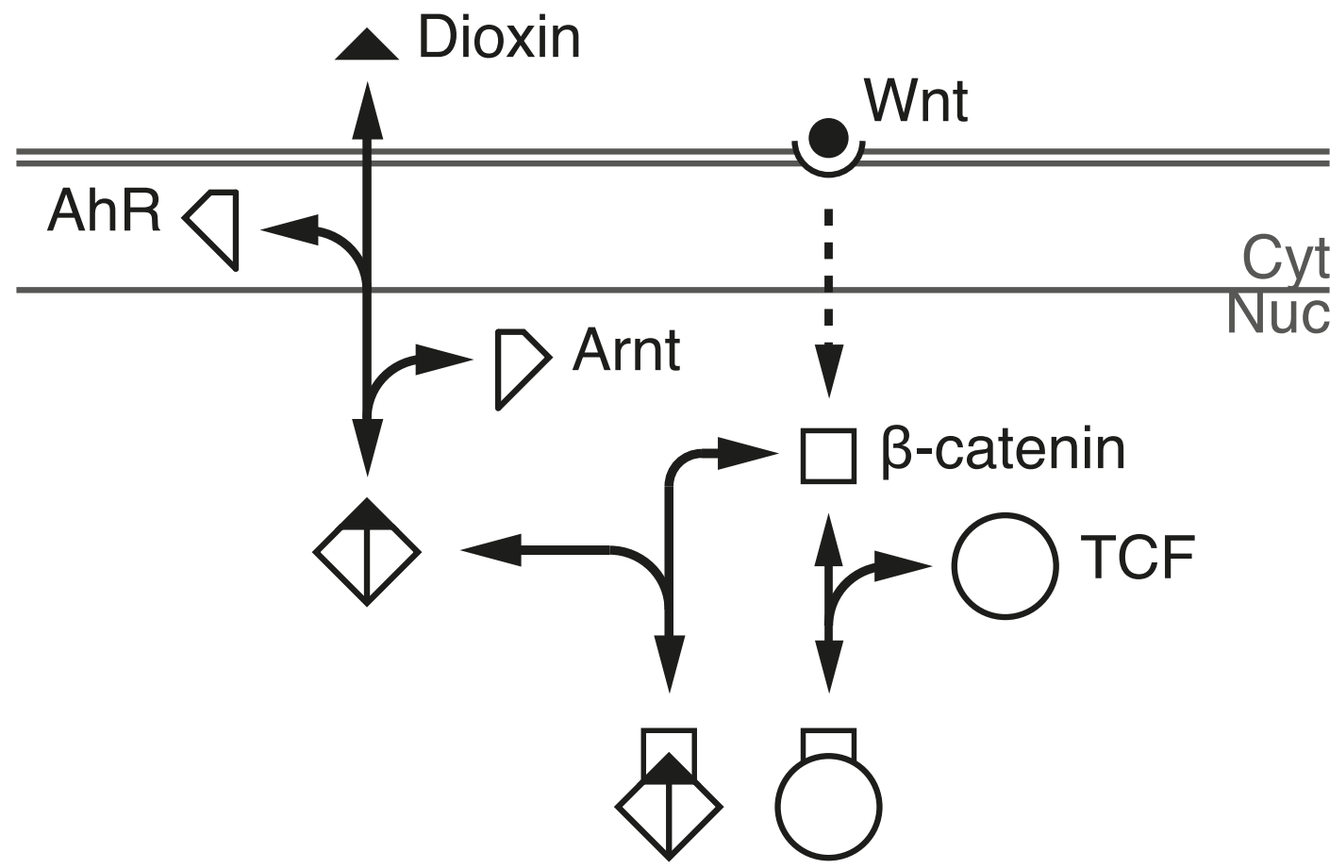
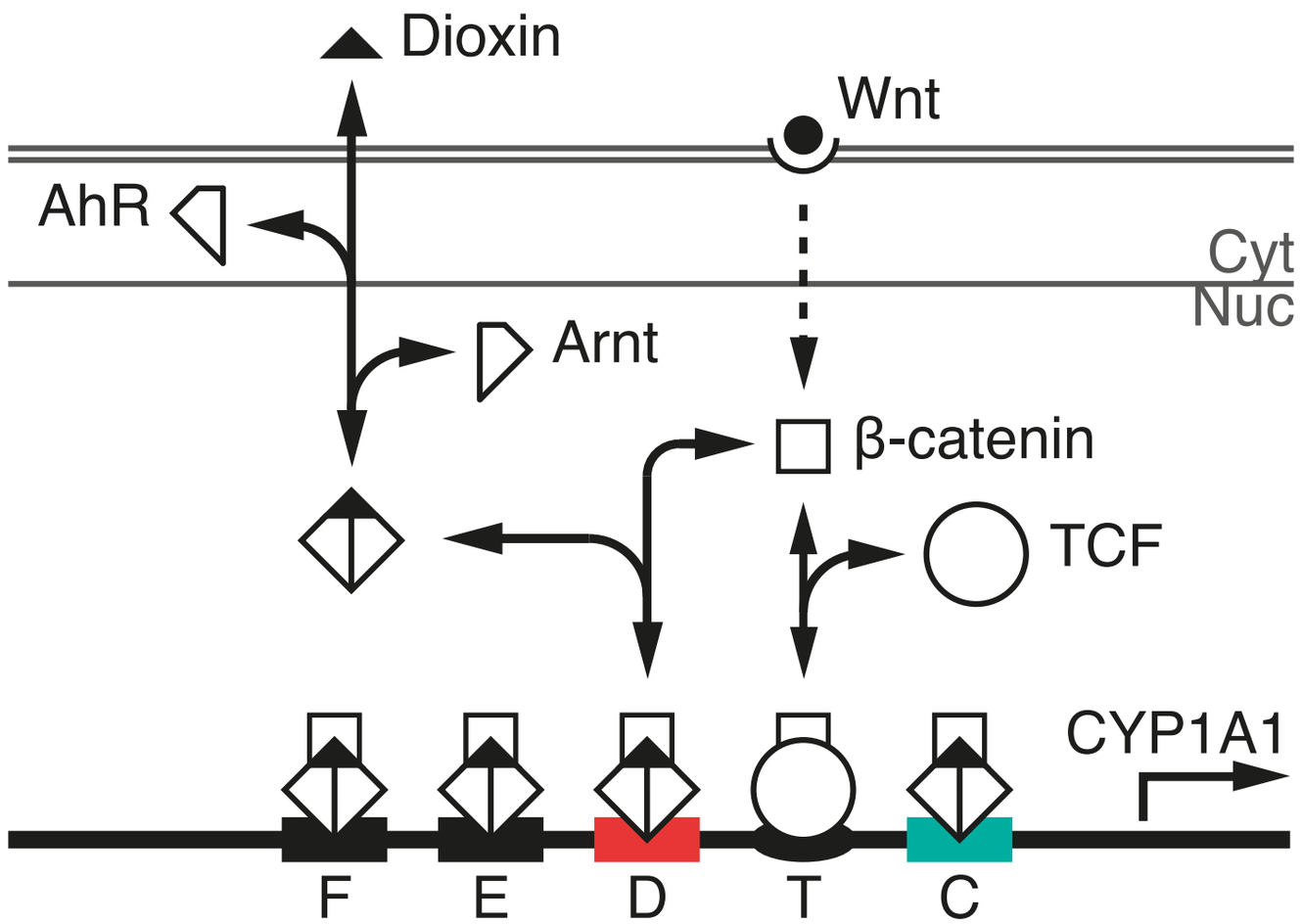


Dioxin and β-catenin signaling converge on *CYP1A1* promoter



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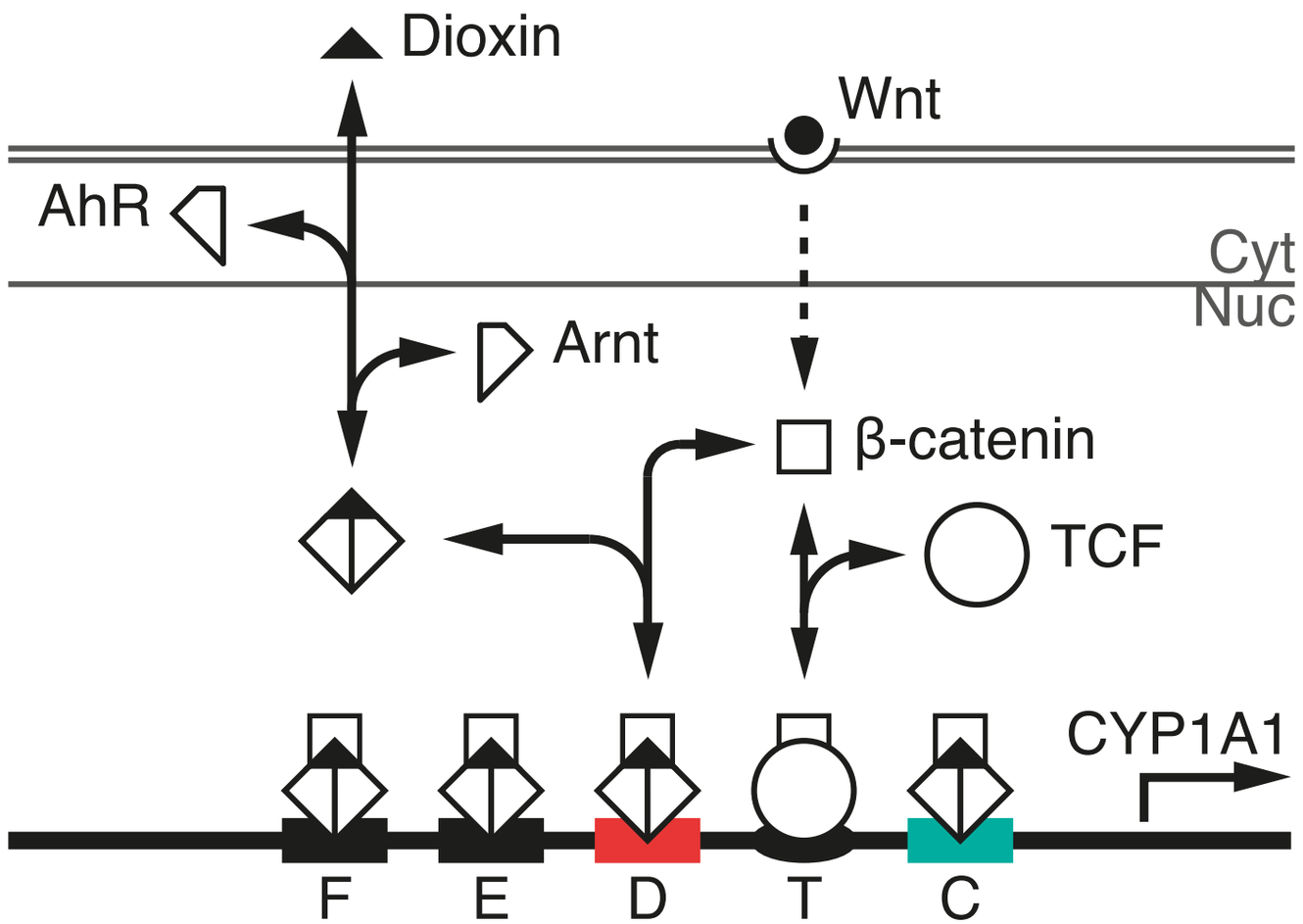
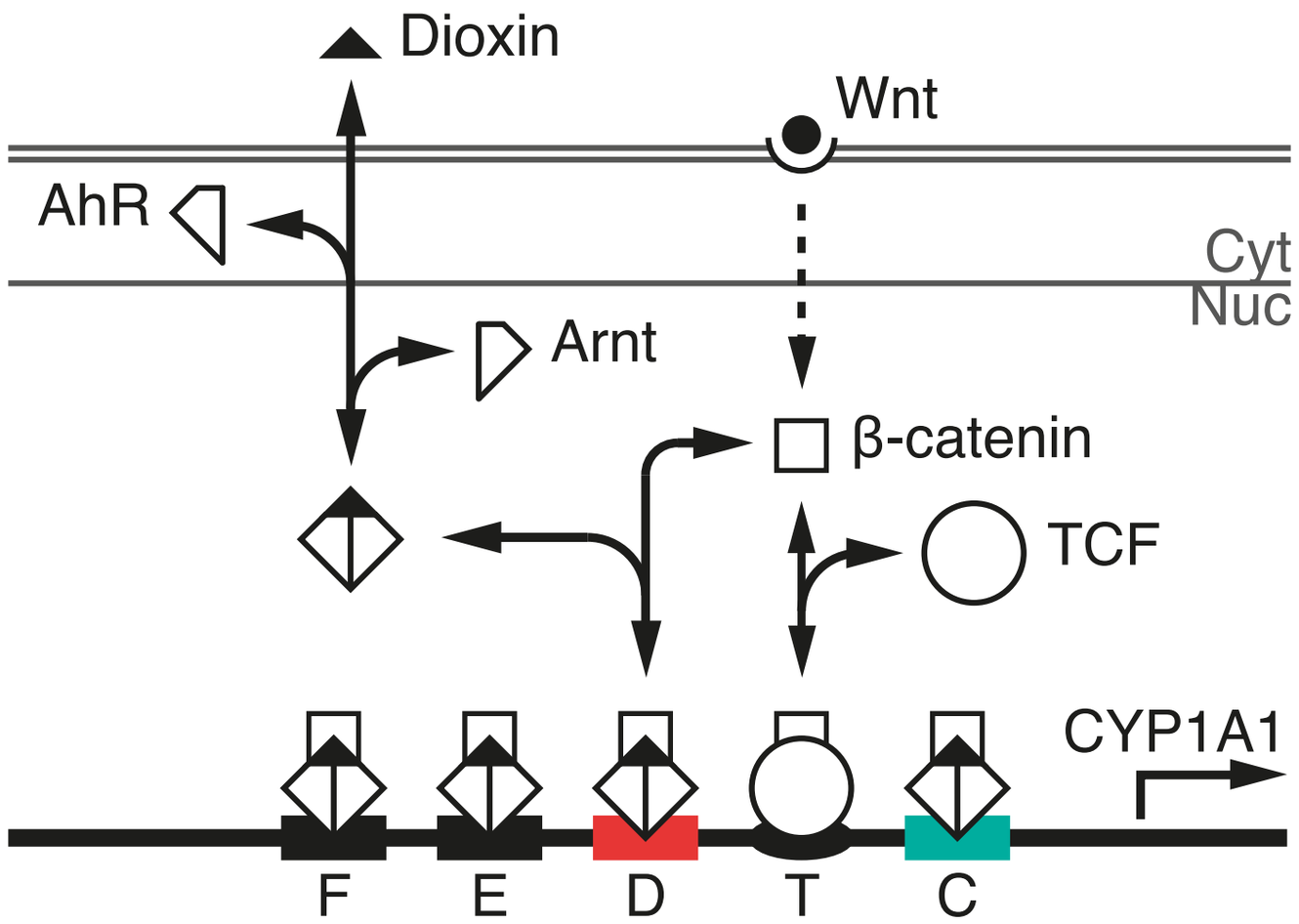


How are the two signals integrated?

Dioxin and β-catenin signaling converge on *CYP1A1* promoter



How are the two signals integrated?

How do binding sites cooperate?

Outline

1. Introduction of the modeling framework

2. Model of synthetic promoter

3. Model of wild-type *CYP1A1* promoter

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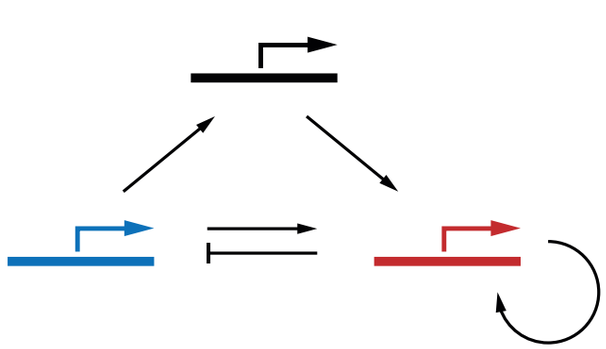
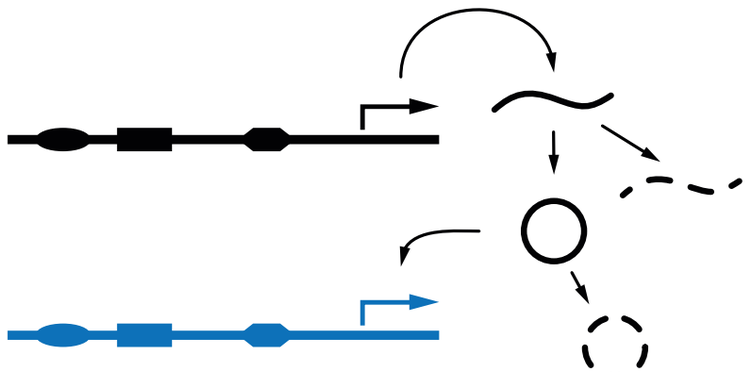
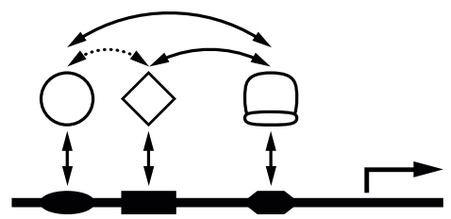
Modeling approaches for gene expression



(Un)directed graphs
Bayesian networks
Boolean networks
⋮



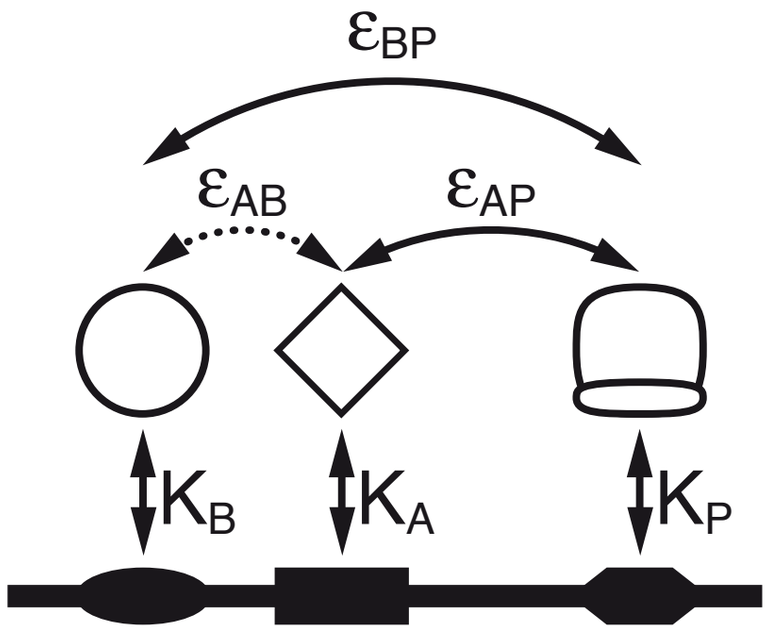
(Nonlinear) ODEs
PDEs
⋮

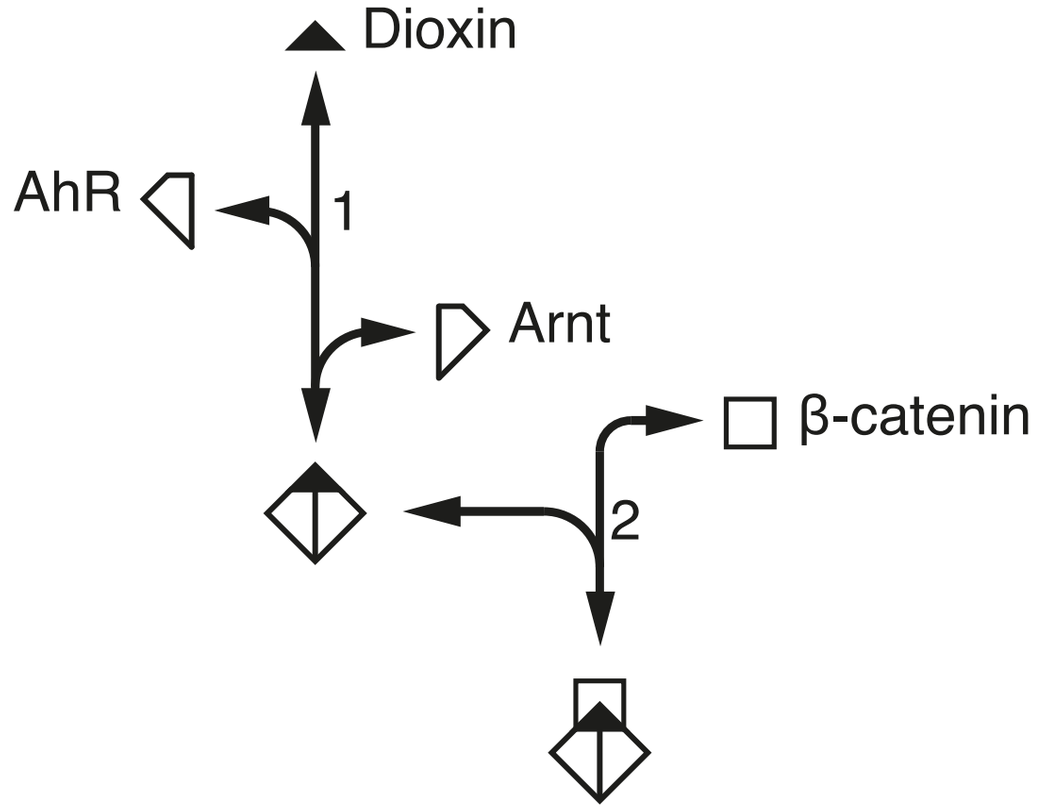


Thermodynamic
state ensembles

Level of detail

Mathematical model combines signaling and promoter logic





Thermodynamic model

Signaling model

Thermodynamic state ensemble model of gene expression

$$p_{\text{bound}}([P] \qquad) = \frac{\text{transcribing states}}{\text{all possible states}}$$

Sherman MS, Cohen BA, *PLoS Comput Biol* 8(3):e1002407 (2012)
Bintu L, et al., Curr Opin Genet Dev 15(2):116–124 (2004)

Thermodynamic state ensemble model of gene expression

$$p_{\text{bound}}([P] \qquad) = \frac{\text{transcribing states}}{\text{all possible states}}$$

$$= \frac{q_P}{1 + q_P}$$

with $q_i = K_i[i]$

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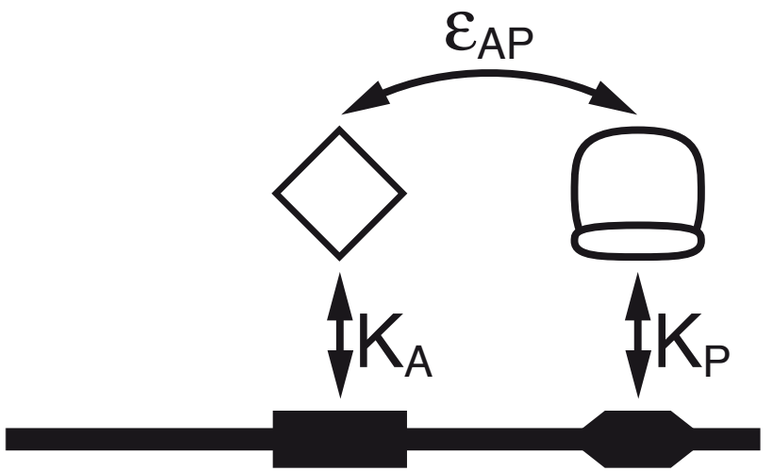

$$p_{\text{bound}}([P],[A]) = \frac{\text{transcribing states}}{\text{all possible states}}$$

$$= \frac{q_P + q_P q_A E_{PA}}{1 + q_P + q_A + q_P q_A E_{PA}}$$

with $q_i = K_i[i]$, and $E_{ij} = \exp(-\epsilon_{ij}/k_B T)$

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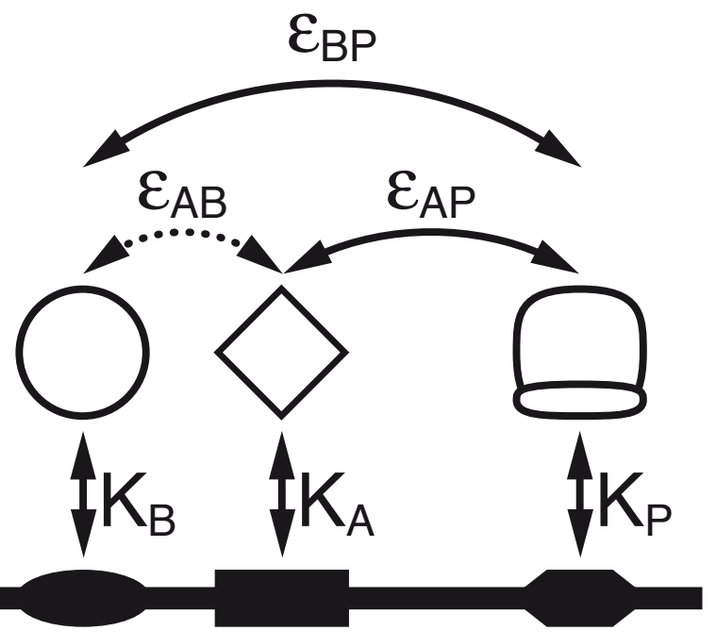

$$p_{\text{bound}}([P],[A],[B]) = \frac{\text{transcribing states}}{\text{all possible states}}$$

$$= \frac{q_P + q_P q_A E_{PA} + q_P q_B E_{PB} + q_P q_A q_B E_{PA} E_{PB} E_{AB}}{1 + q_P + q_A + q_P q_A E_{PA} + q_B + q_P q_B E_{PB} + q_A q_B E_{AB} + q_P q_A q_B E_{PA} E_{PB} E_{AB}}$$

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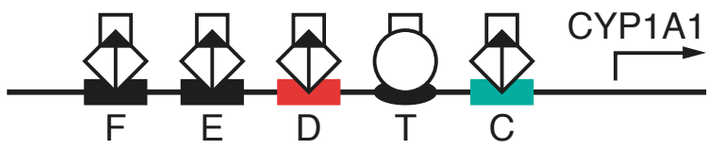

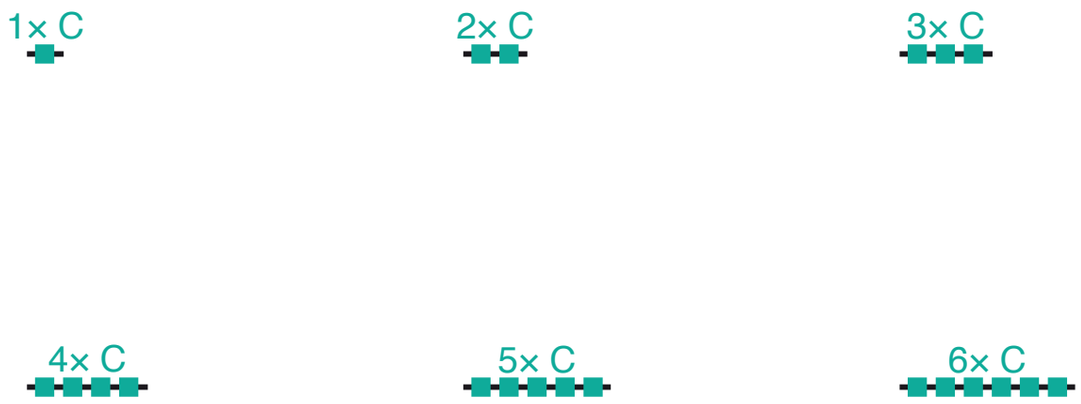

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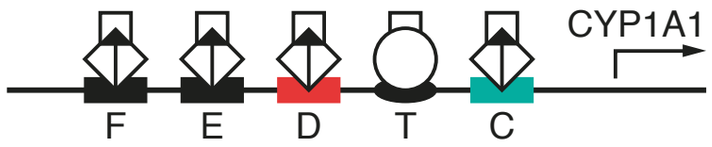

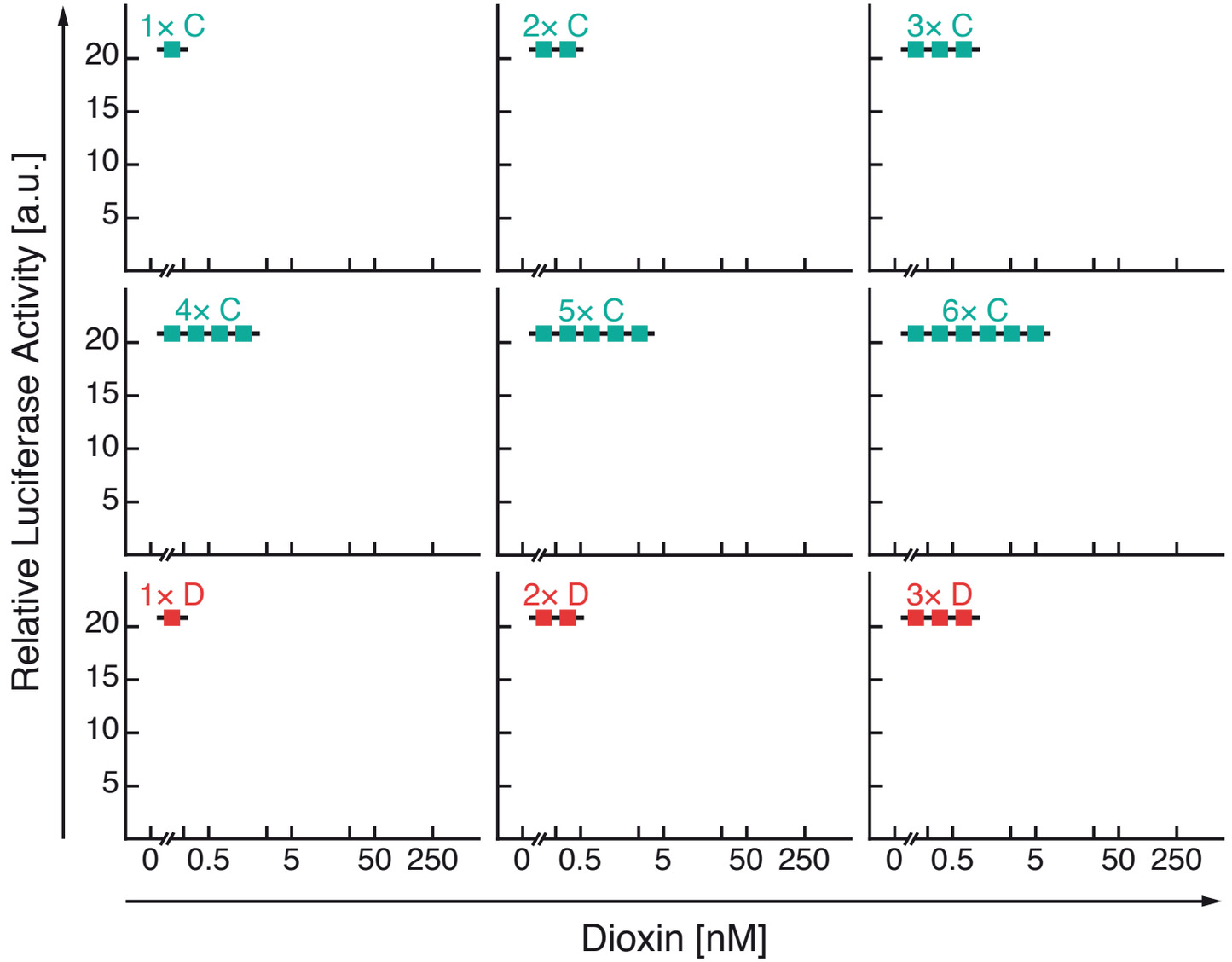

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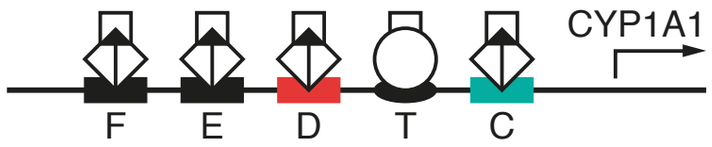

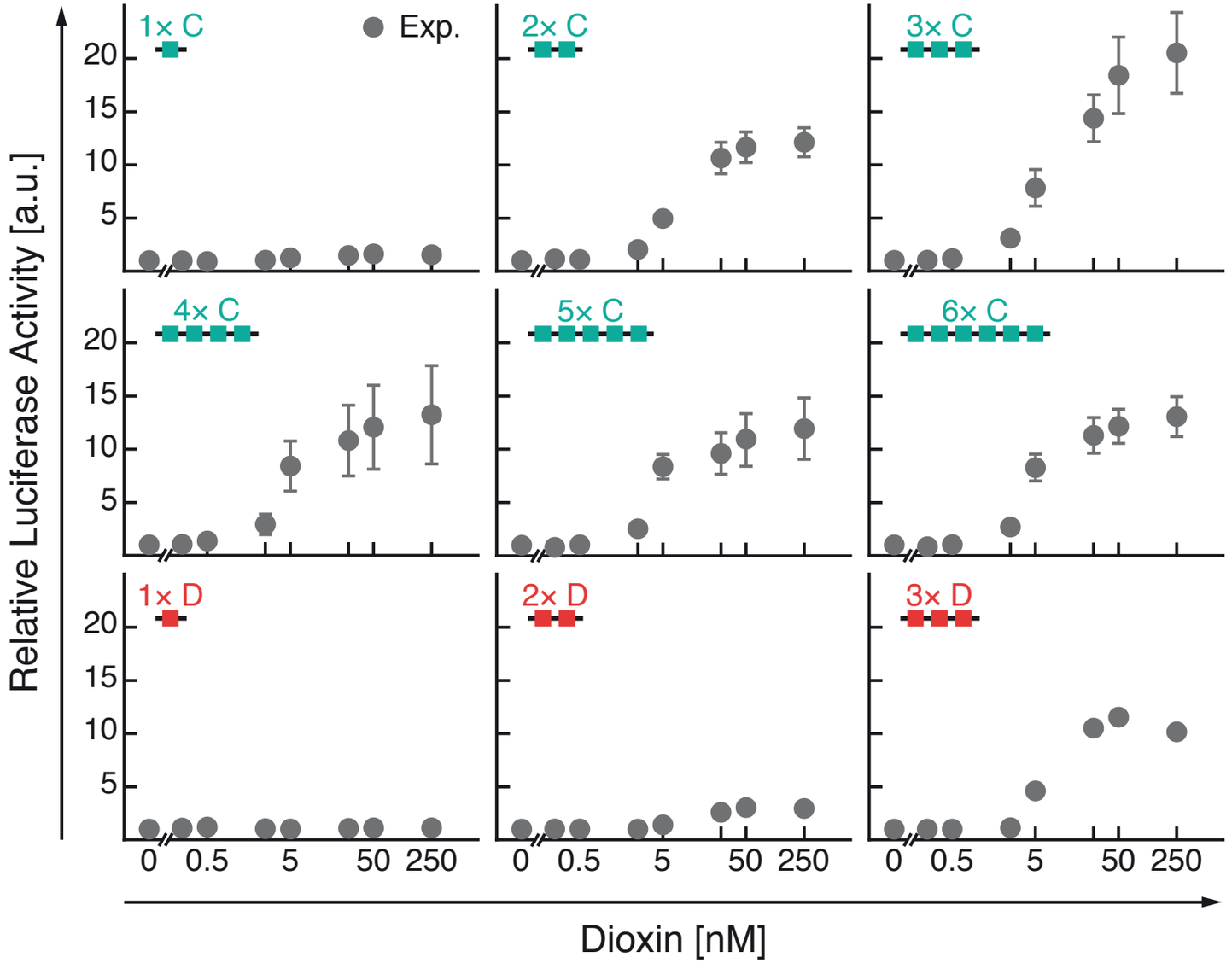

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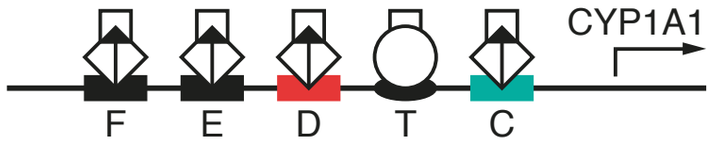
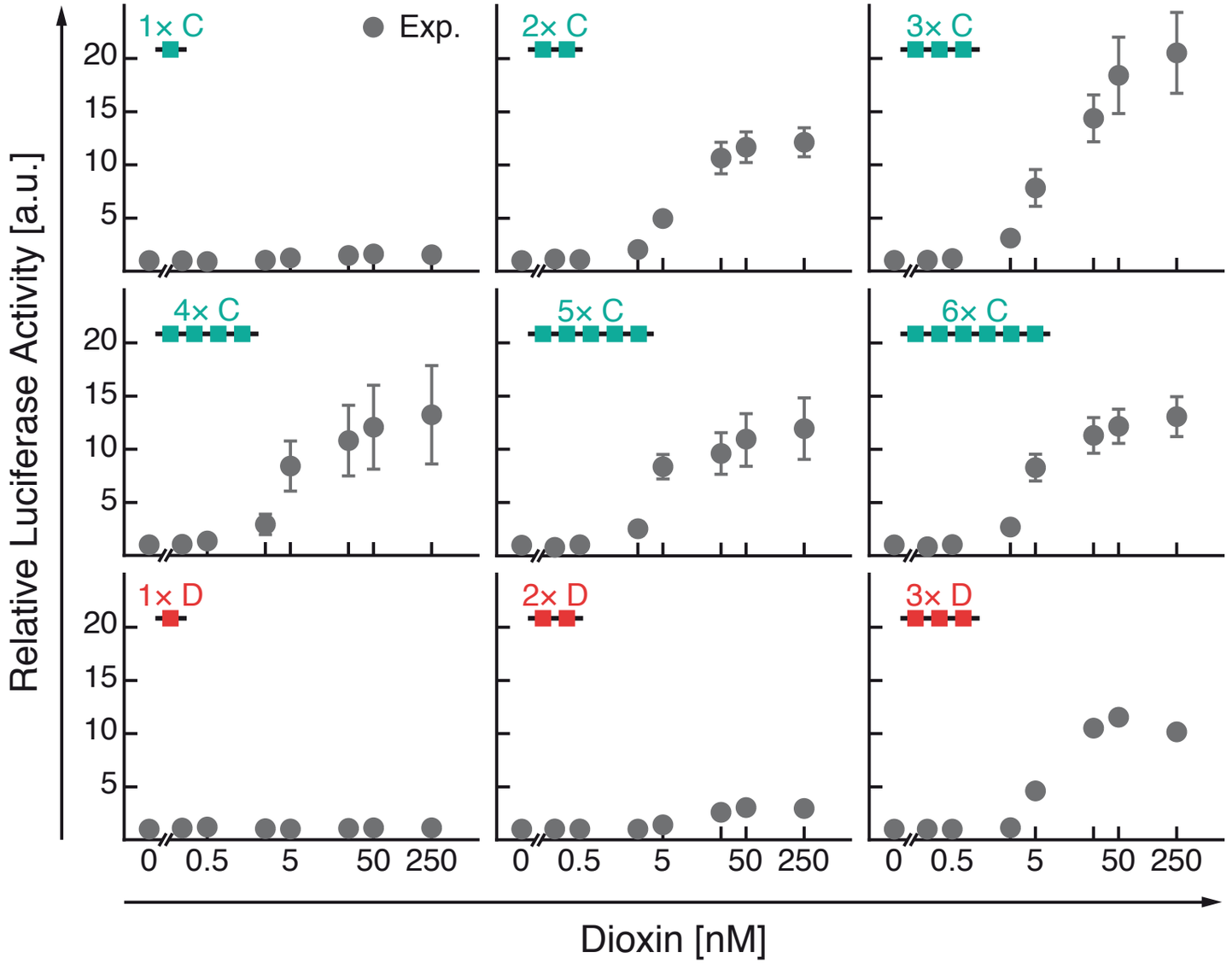
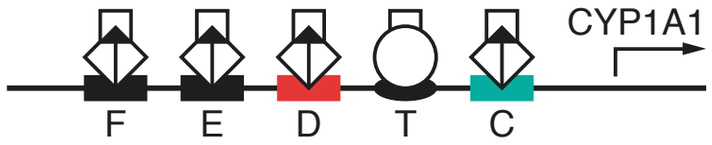
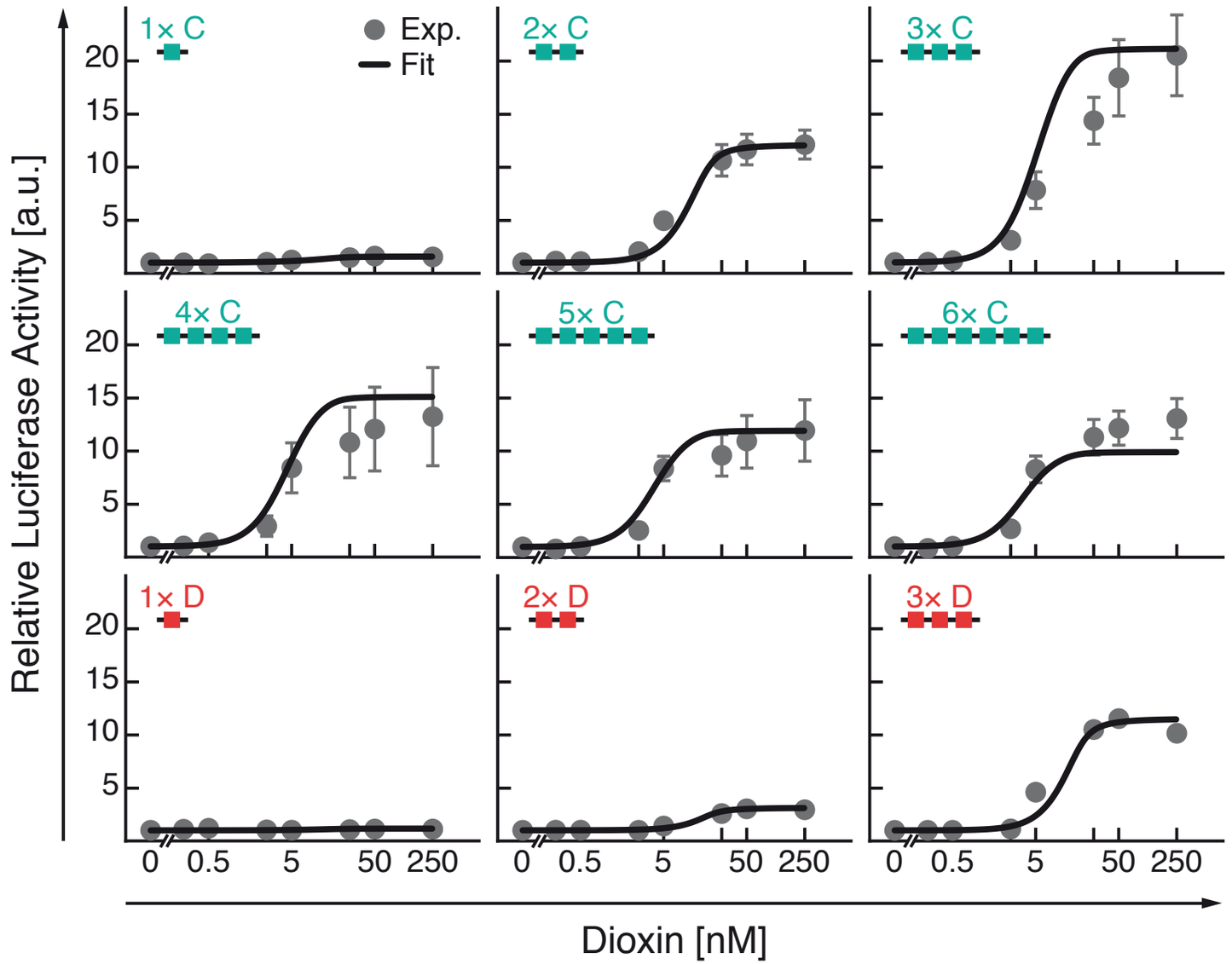




model	parameters
signaling	3
C constructs	13 (28)
D constructs	1 (9)

Model of synthetic promoters





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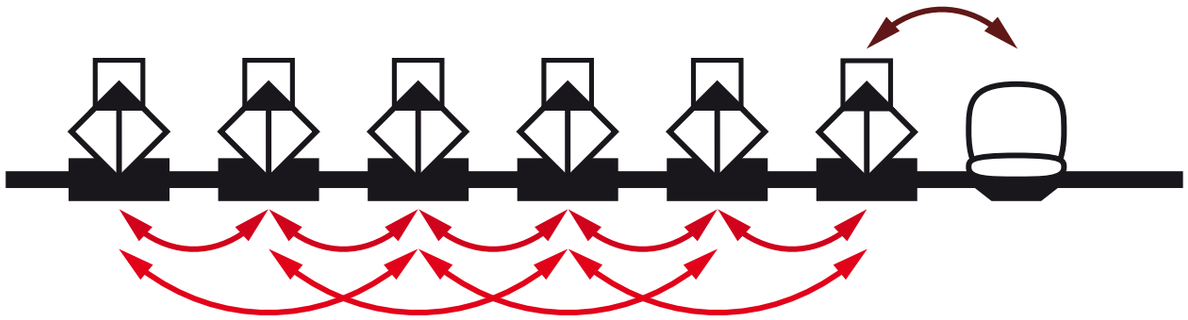
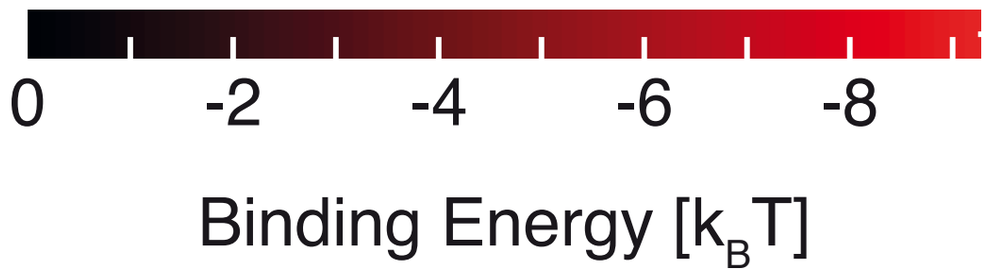
Model parameters unravel TF interactions





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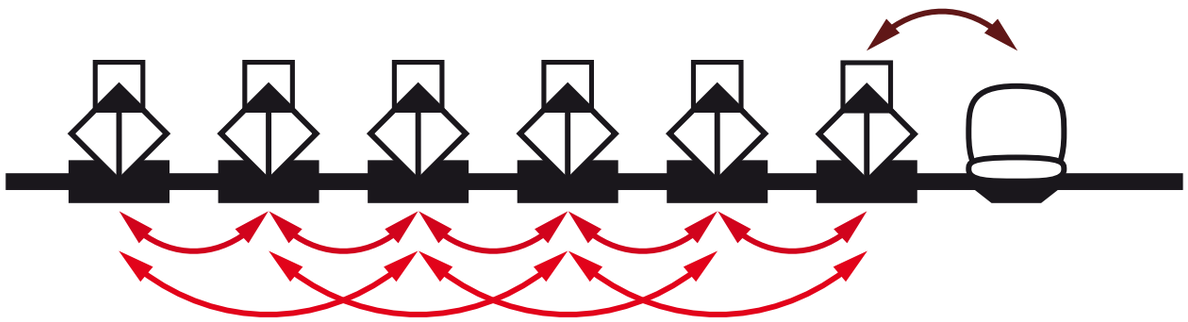
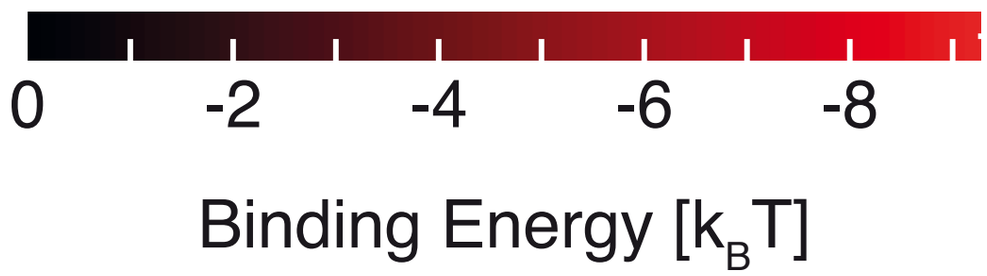
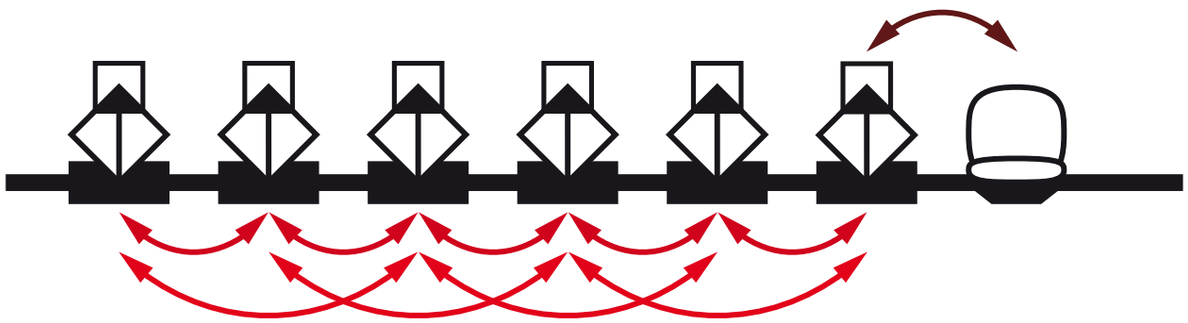
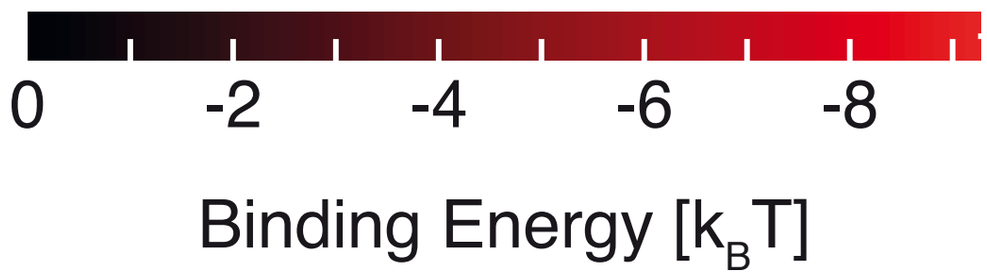




Only first TF interacts with polymerase

Model parameters unravel TF interactions

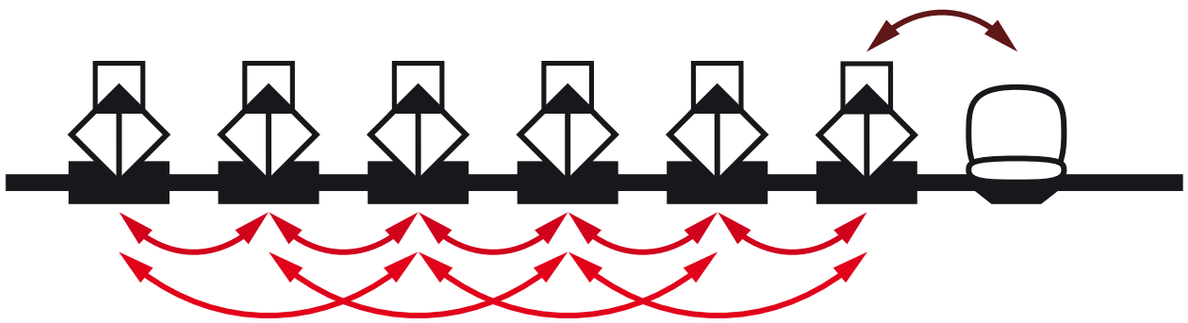


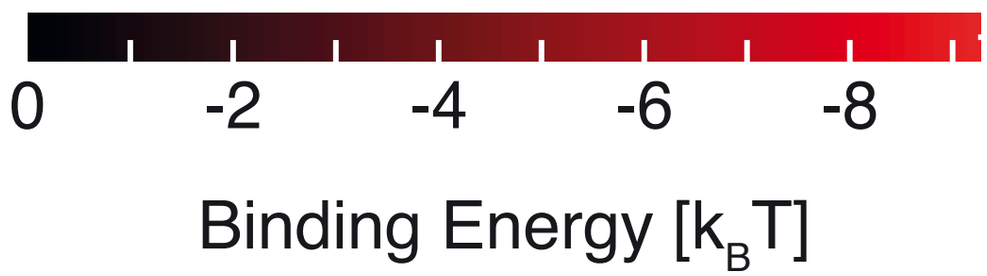


Only first TF interacts with polymerase

Only nearby TFs cooperate

Model parameters unravel TF interactions





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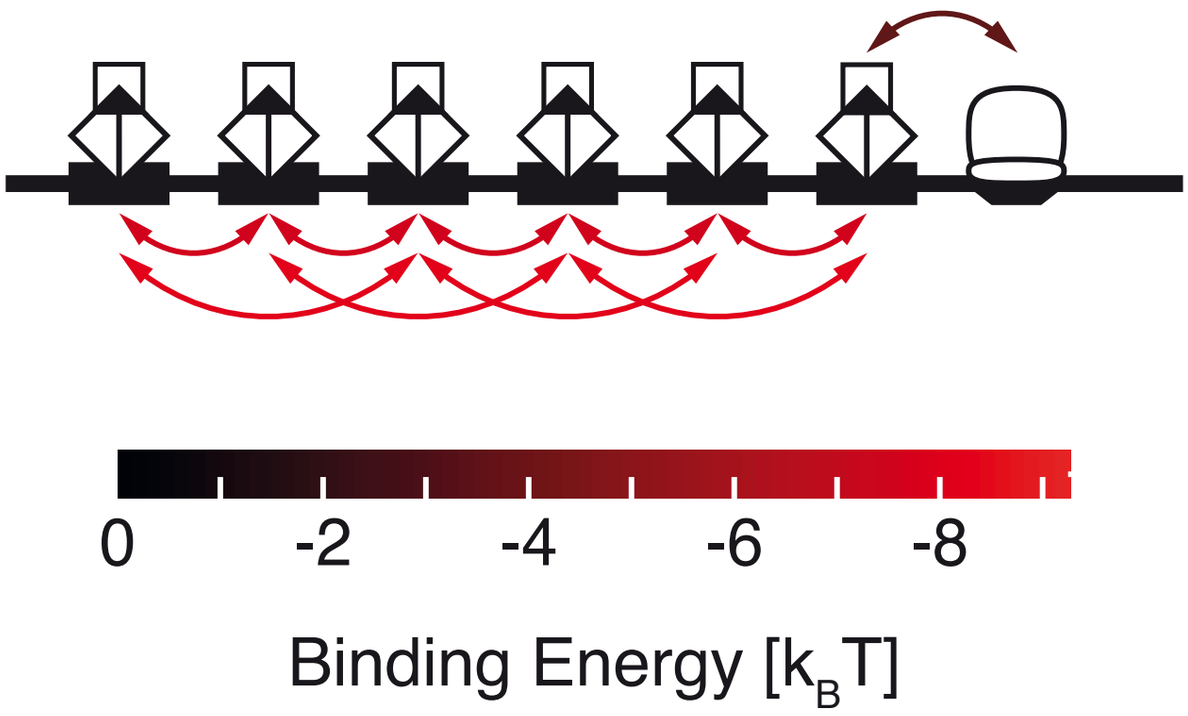
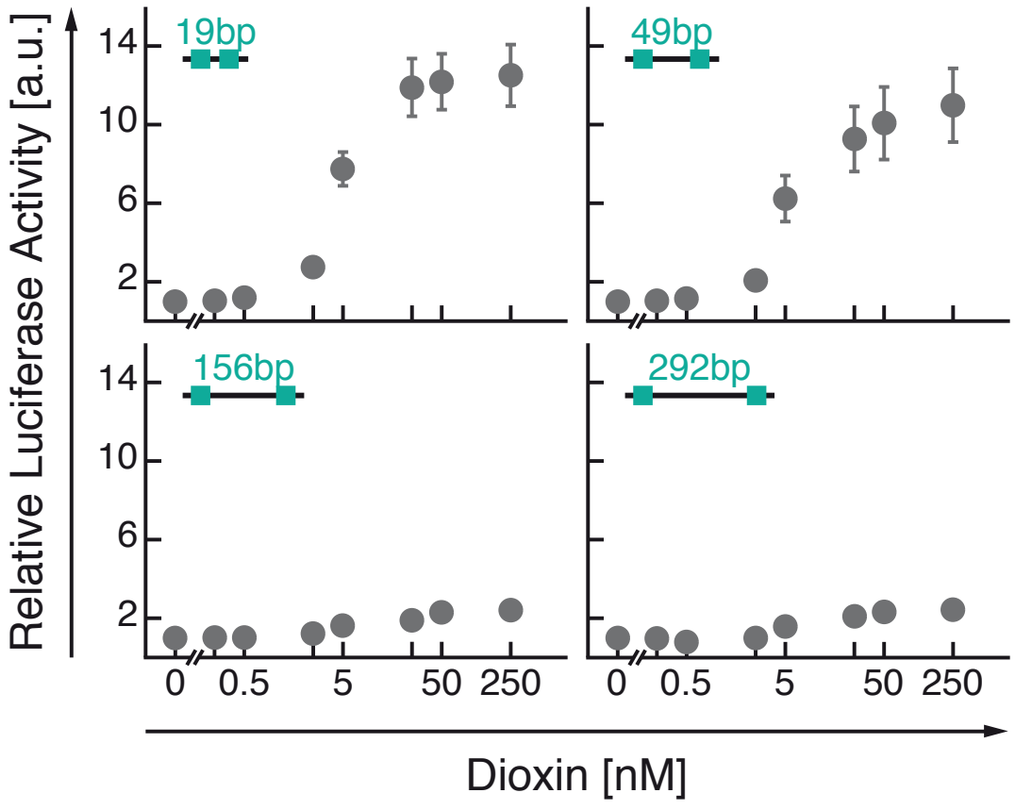
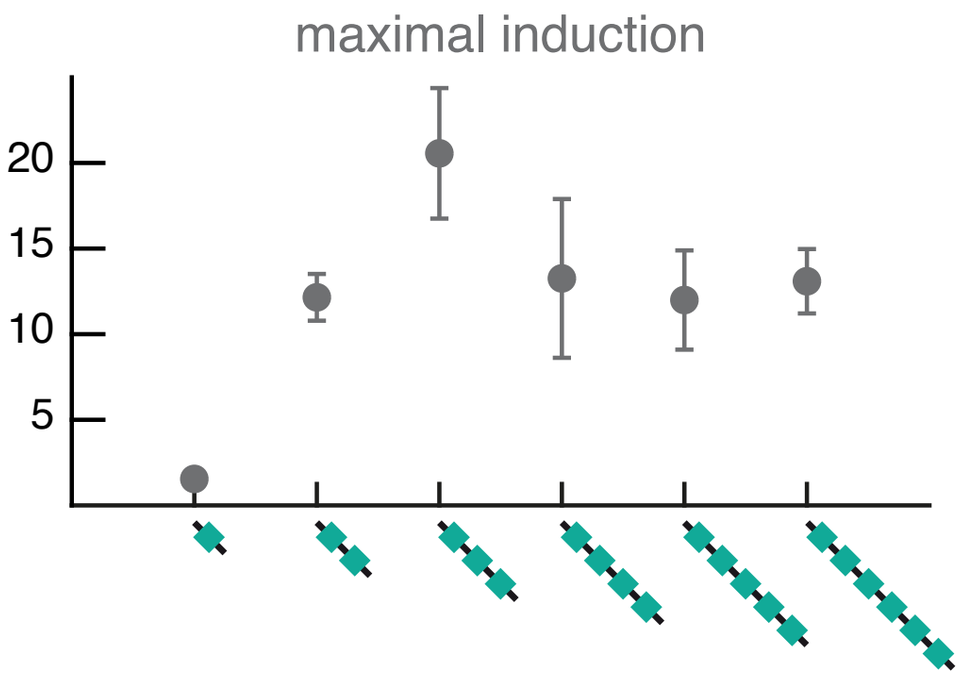


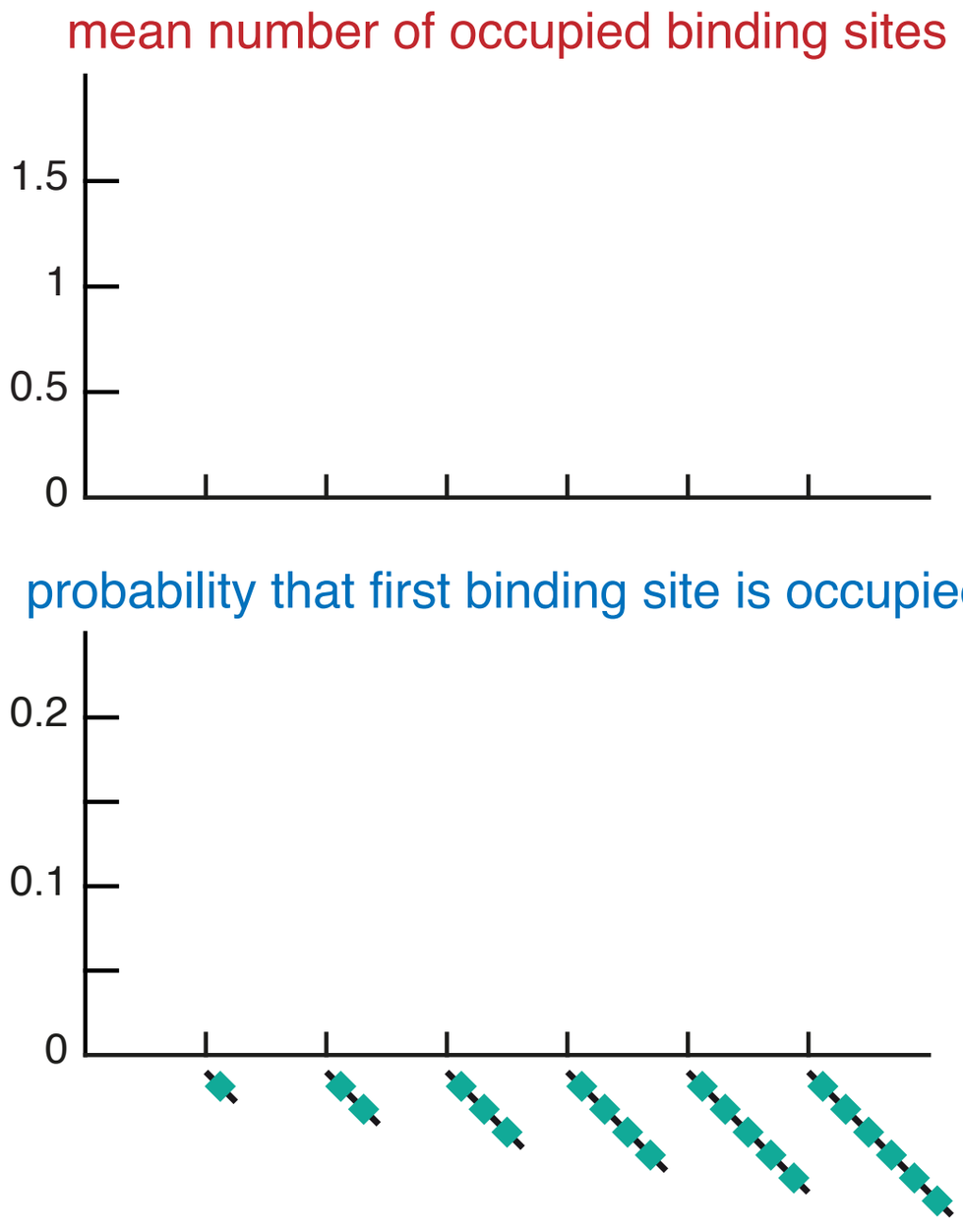


Only first TF interacts with polymerase

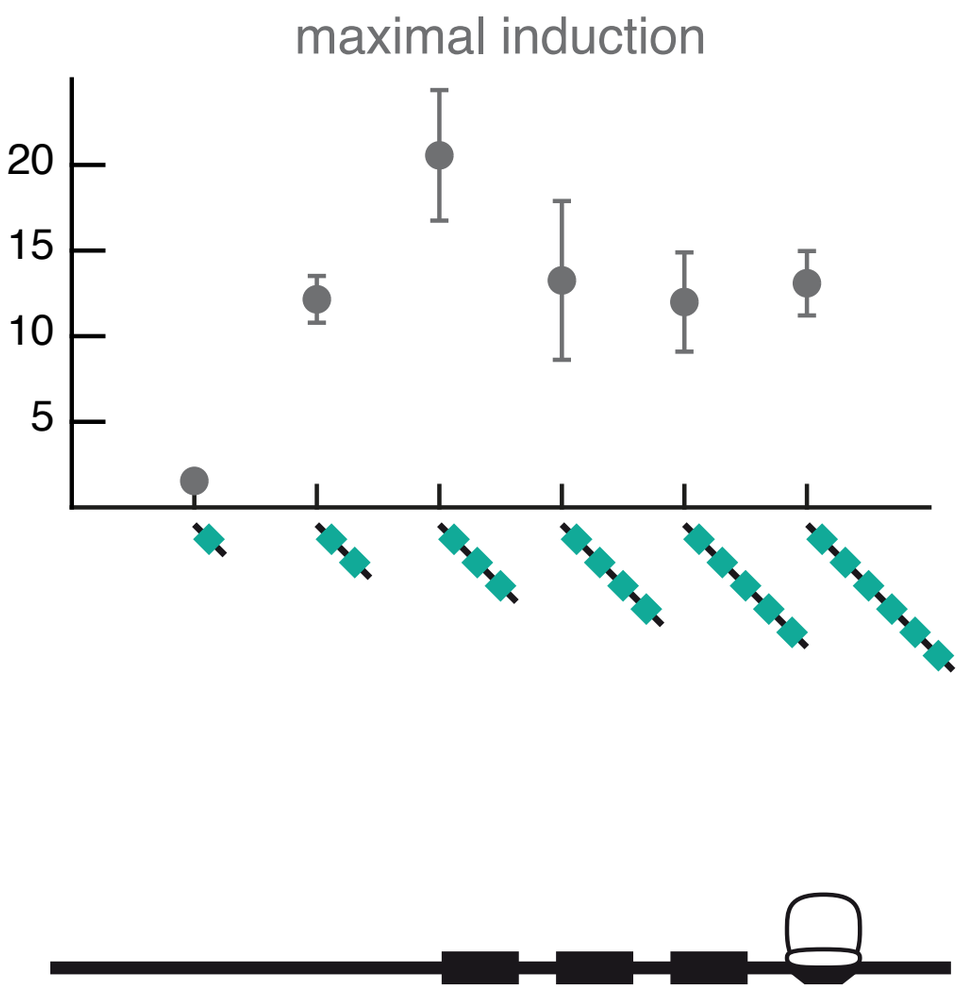
Only nearby TFs cooperate

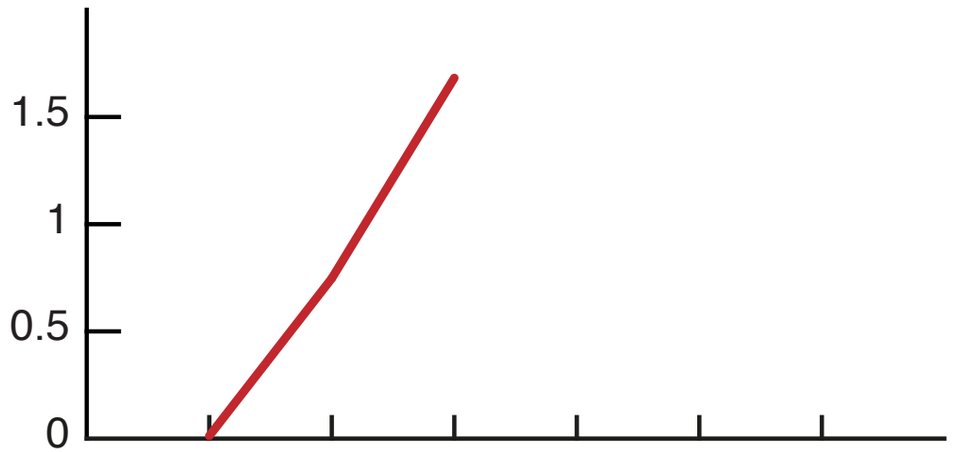
Reduced induction for 4+ binding sites

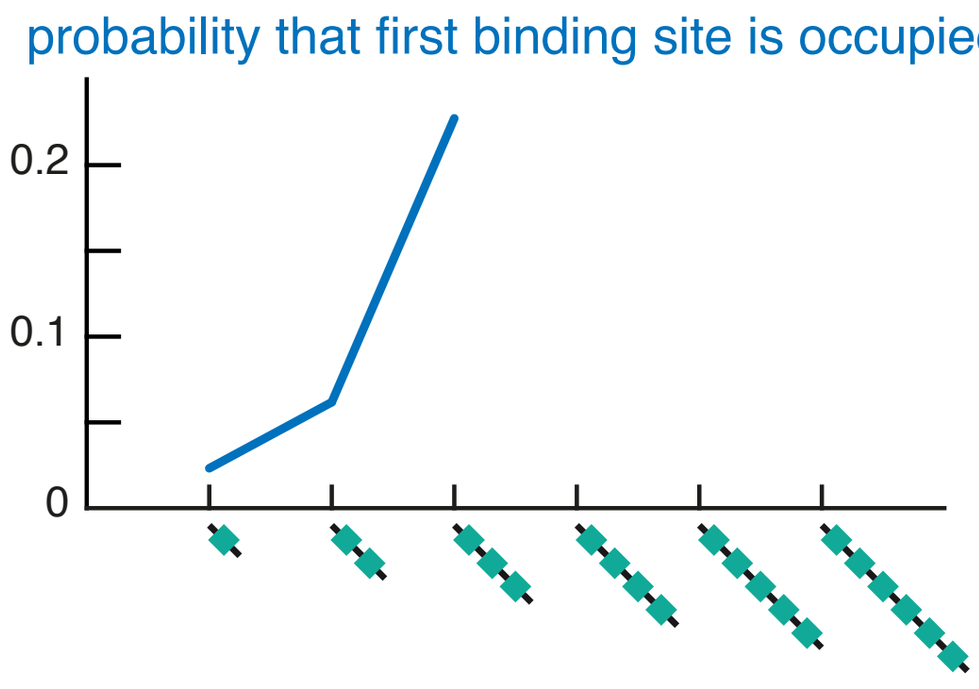




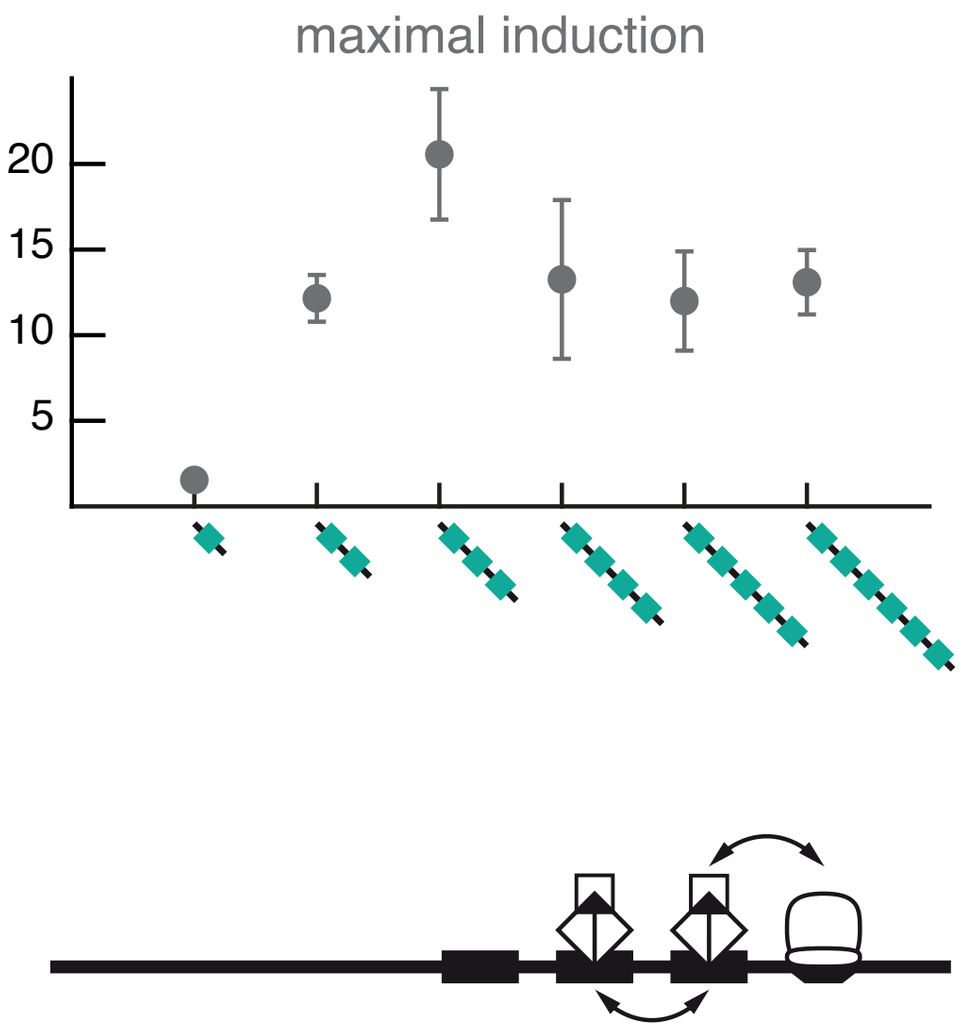
Reduced induction for 4+ binding sites

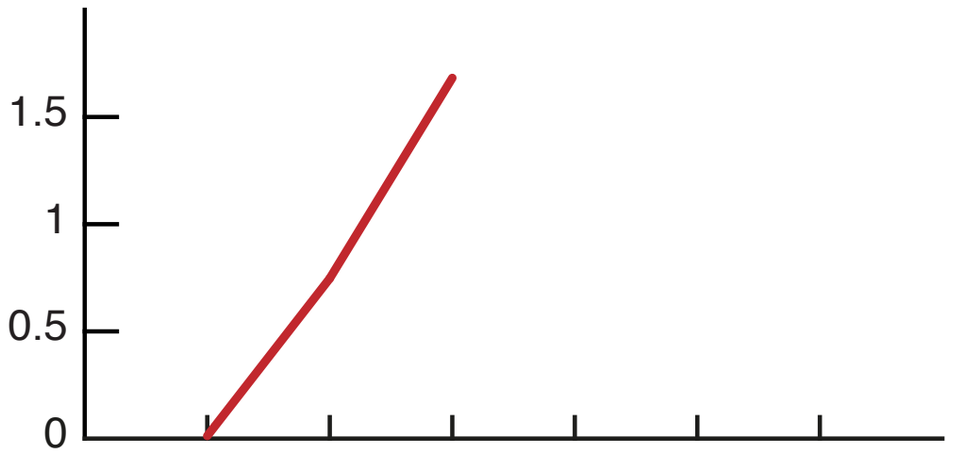


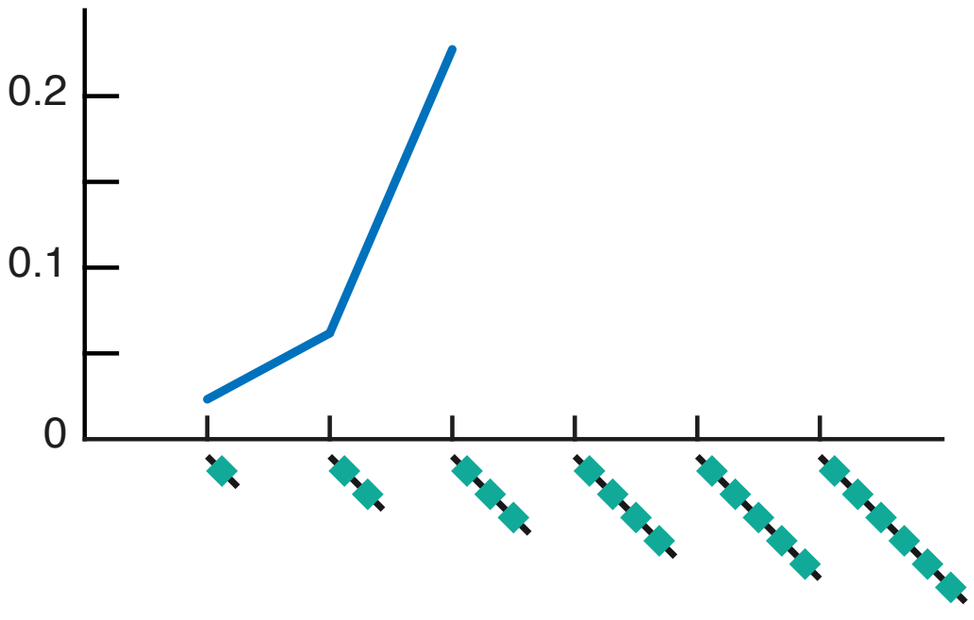




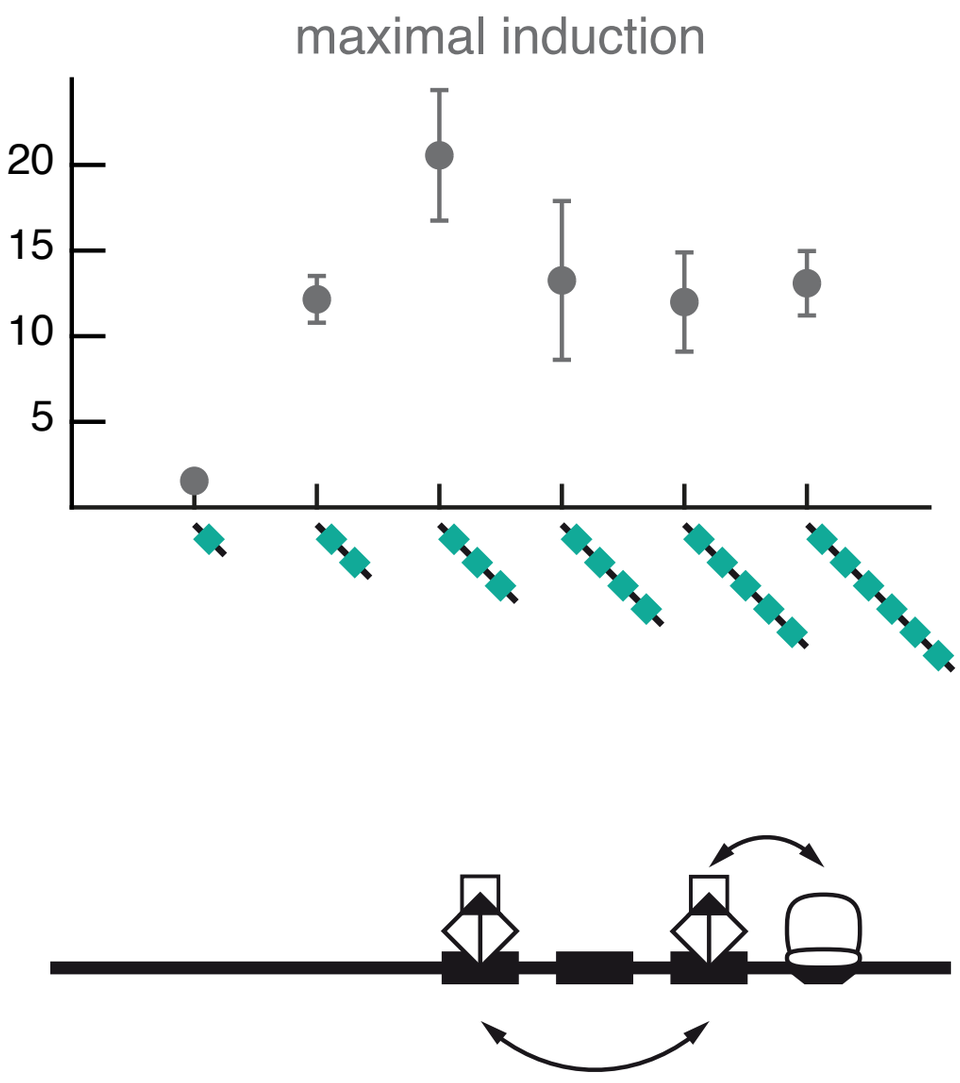
Reduced induction for 4+ binding sites

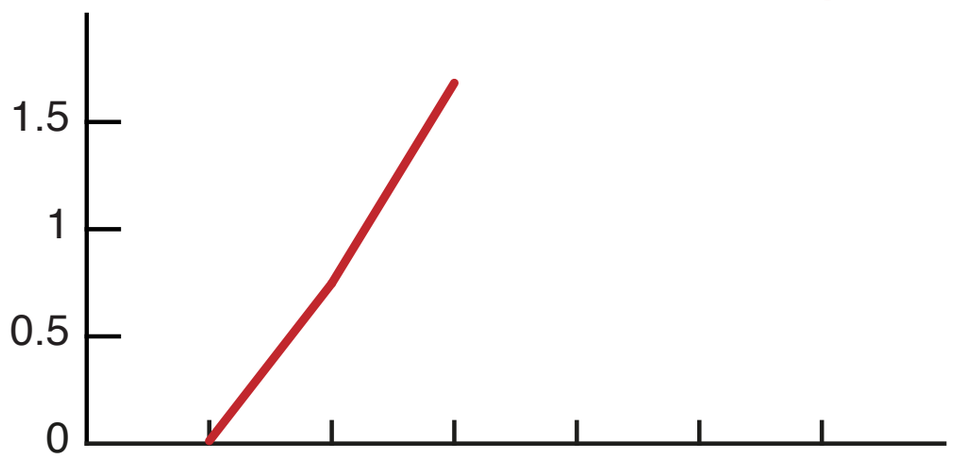


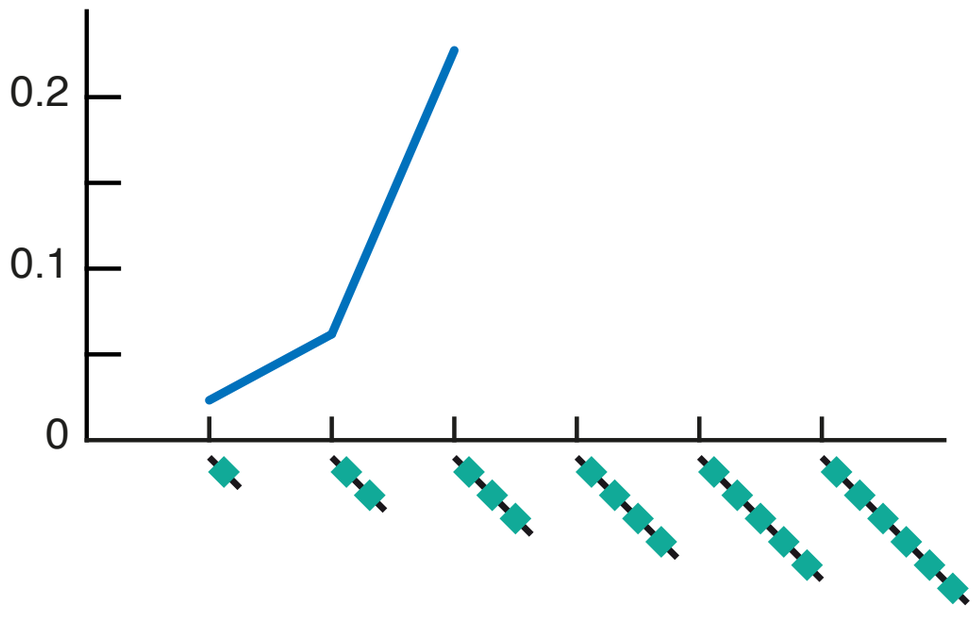




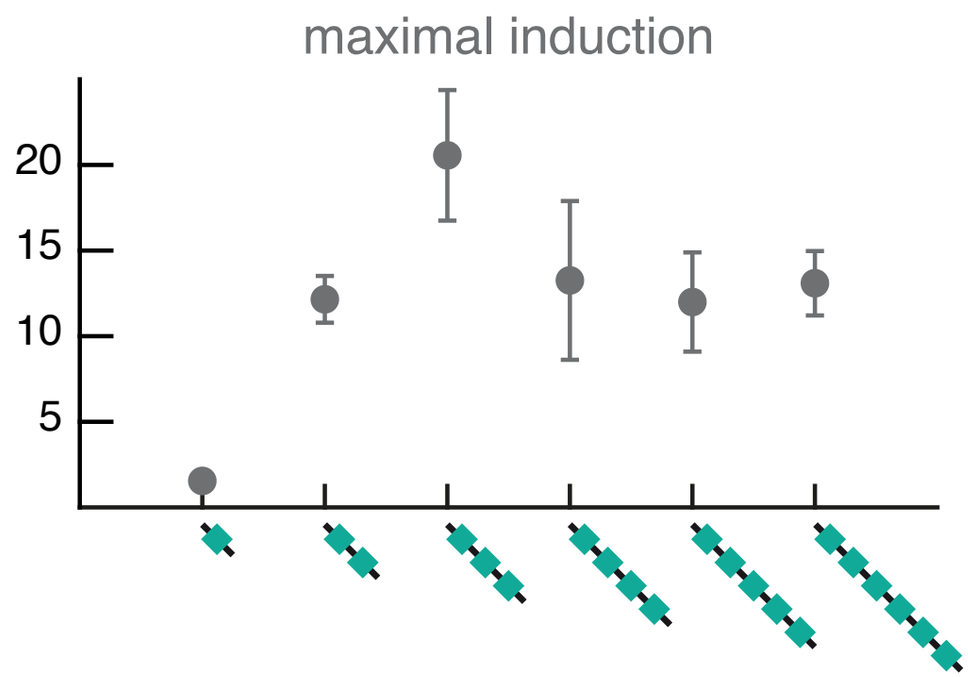
Reduced induction for 4+ binding sites

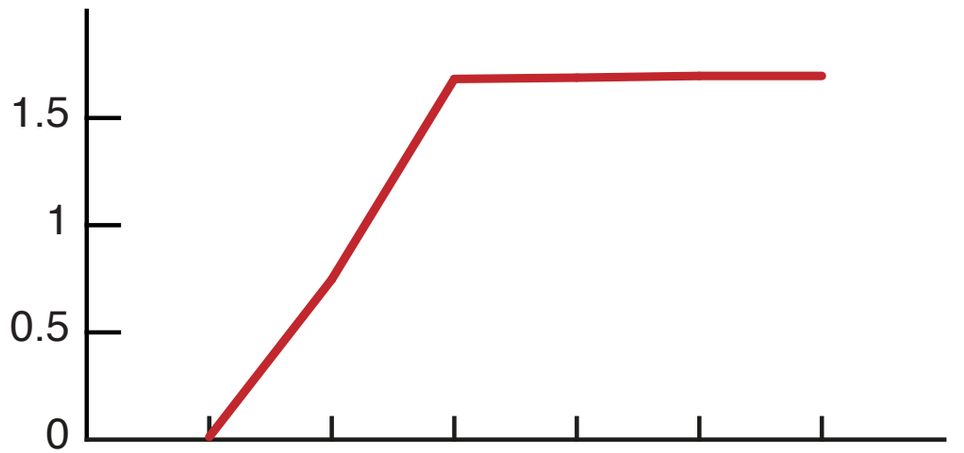


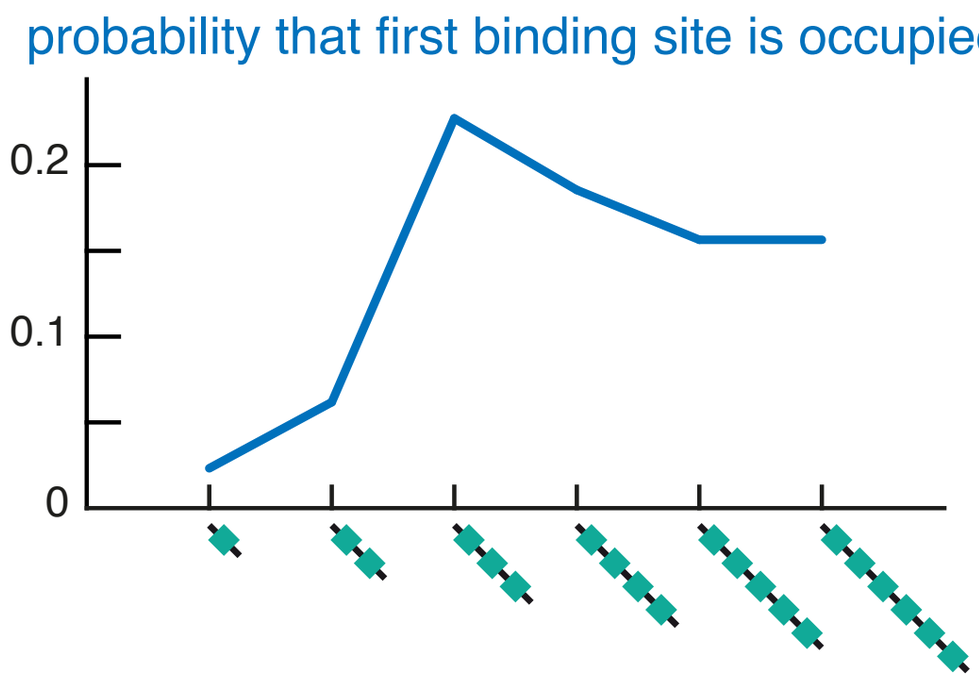




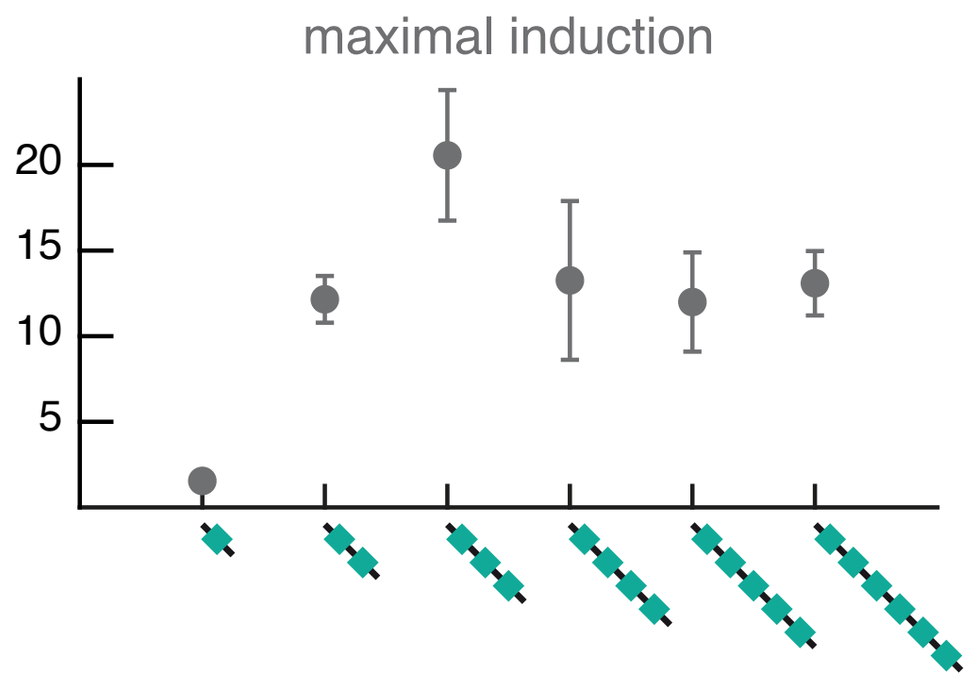
Reduced induction for 4+ binding sites

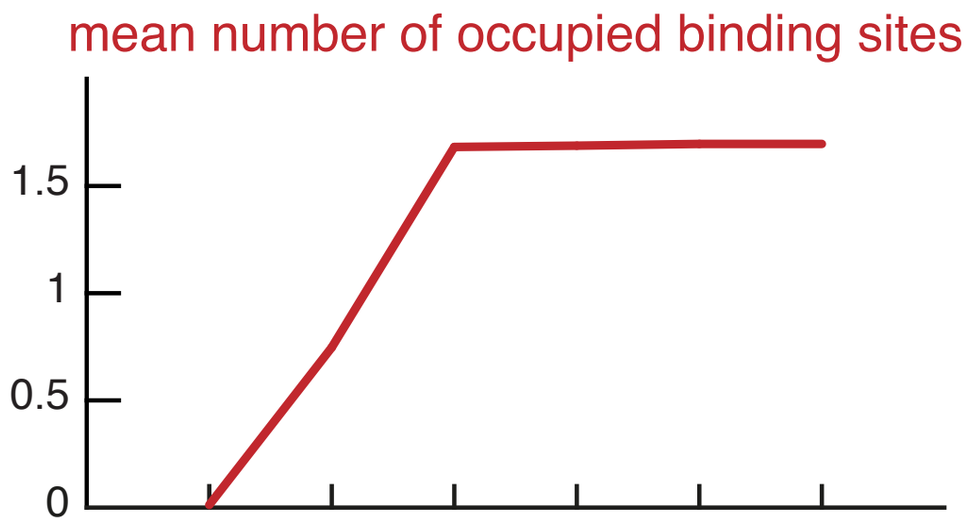


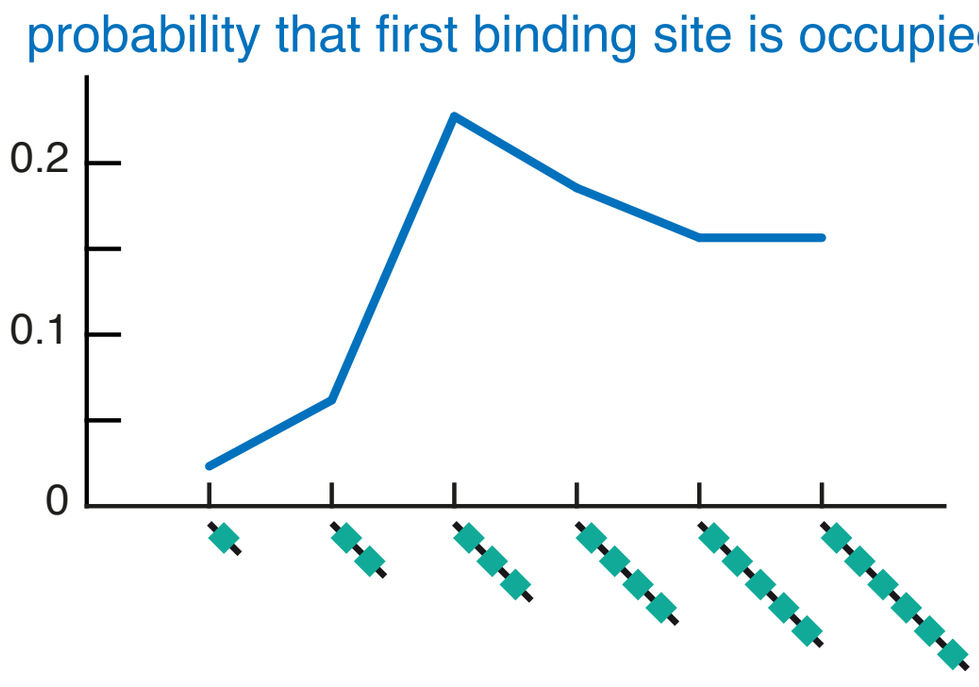




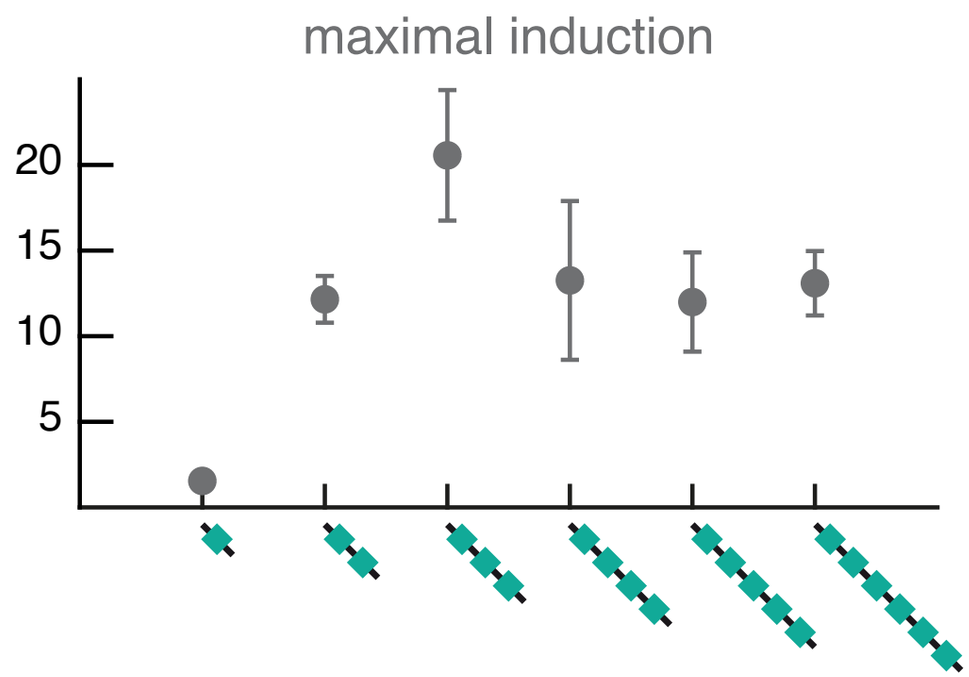
Reduced induction for 4+ binding sites

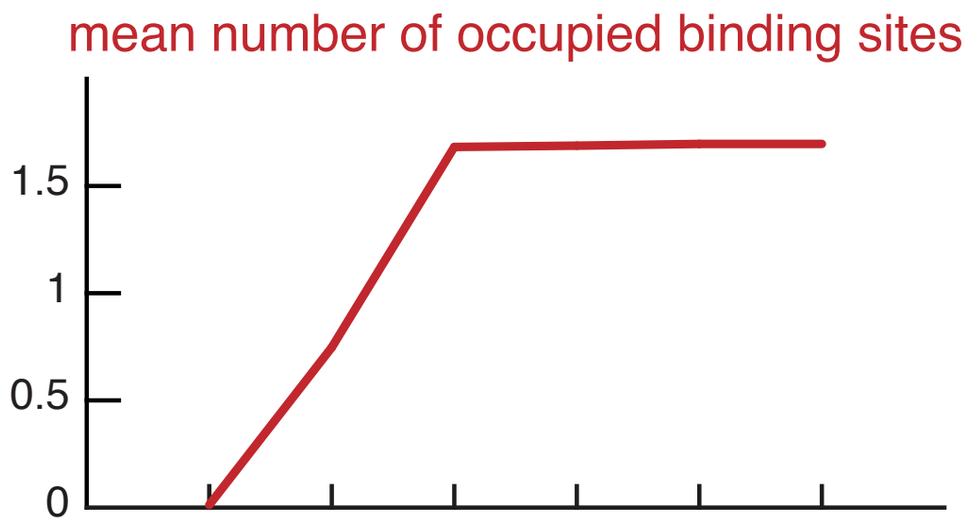


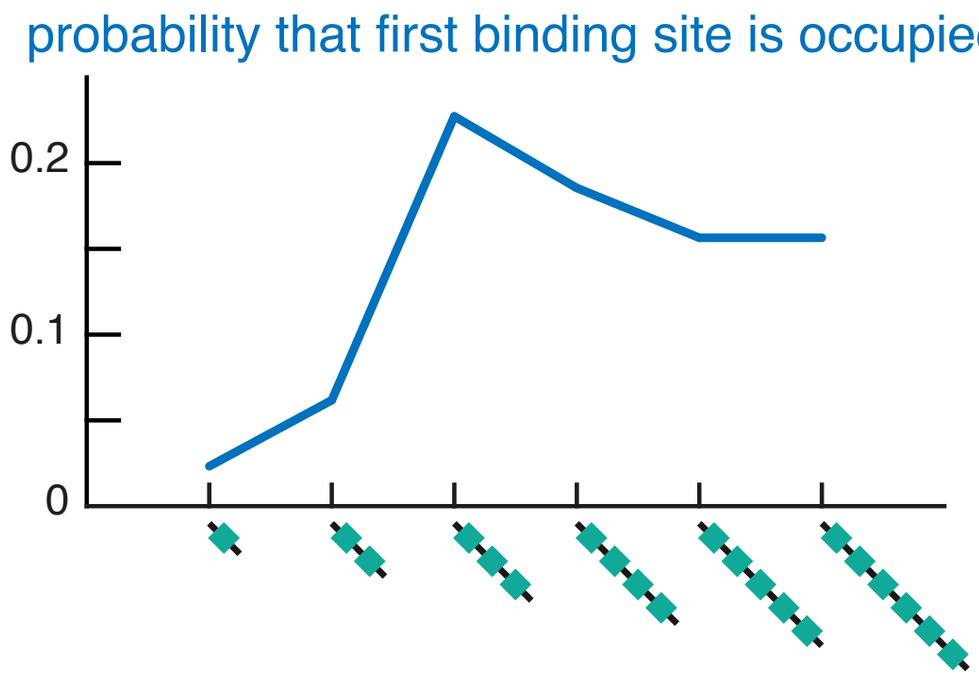




Reduced induction for 4+ binding sites

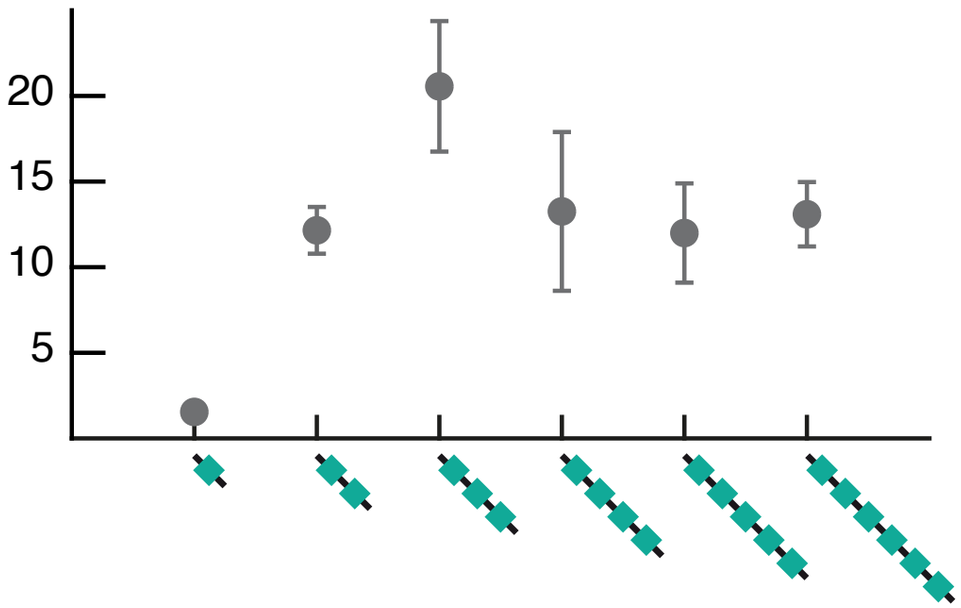




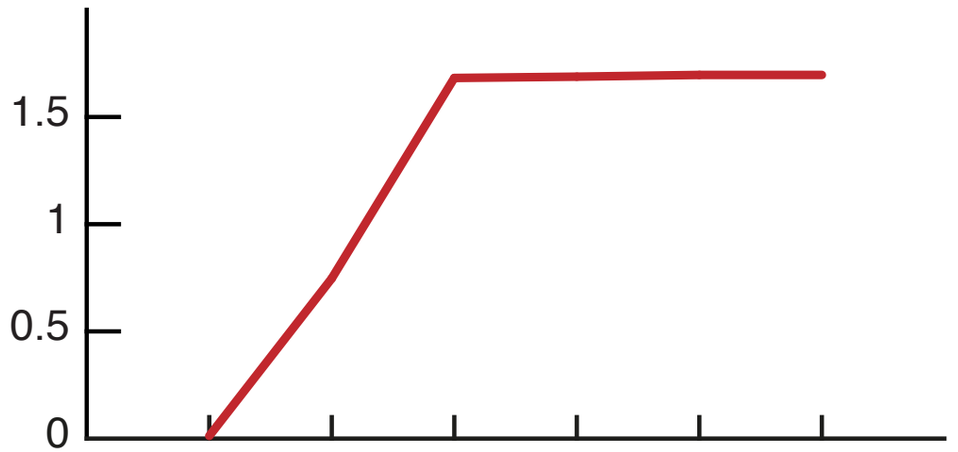


Reduced induction for 4+ binding sites

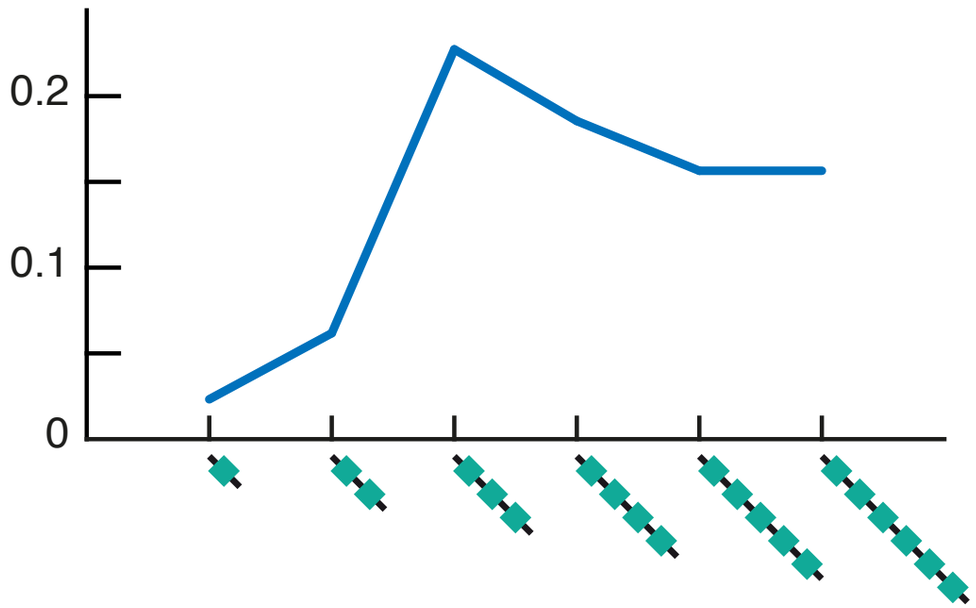
maximal induction



mean number of occupied binding sites

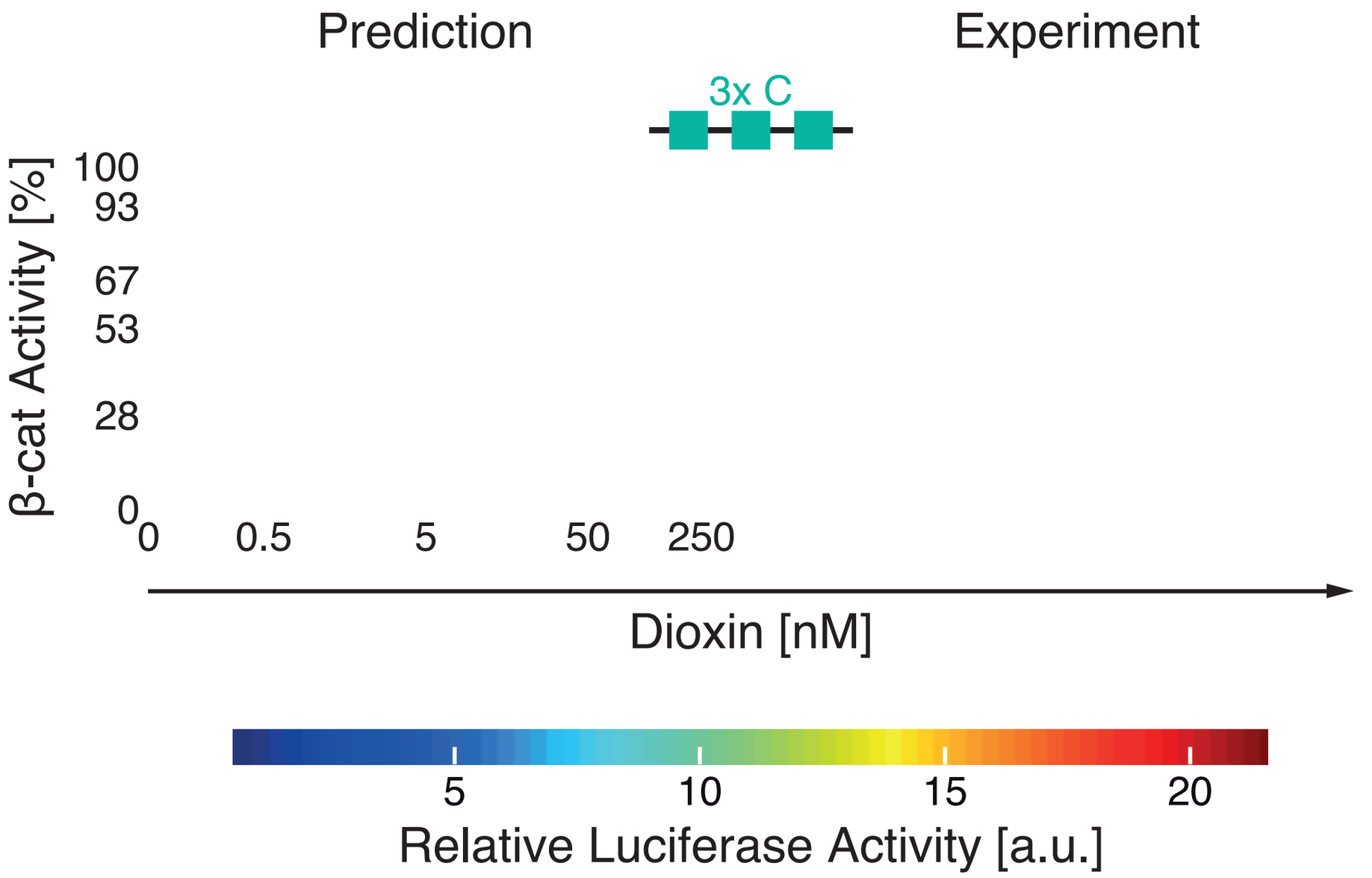


probability that first binding site is occupied

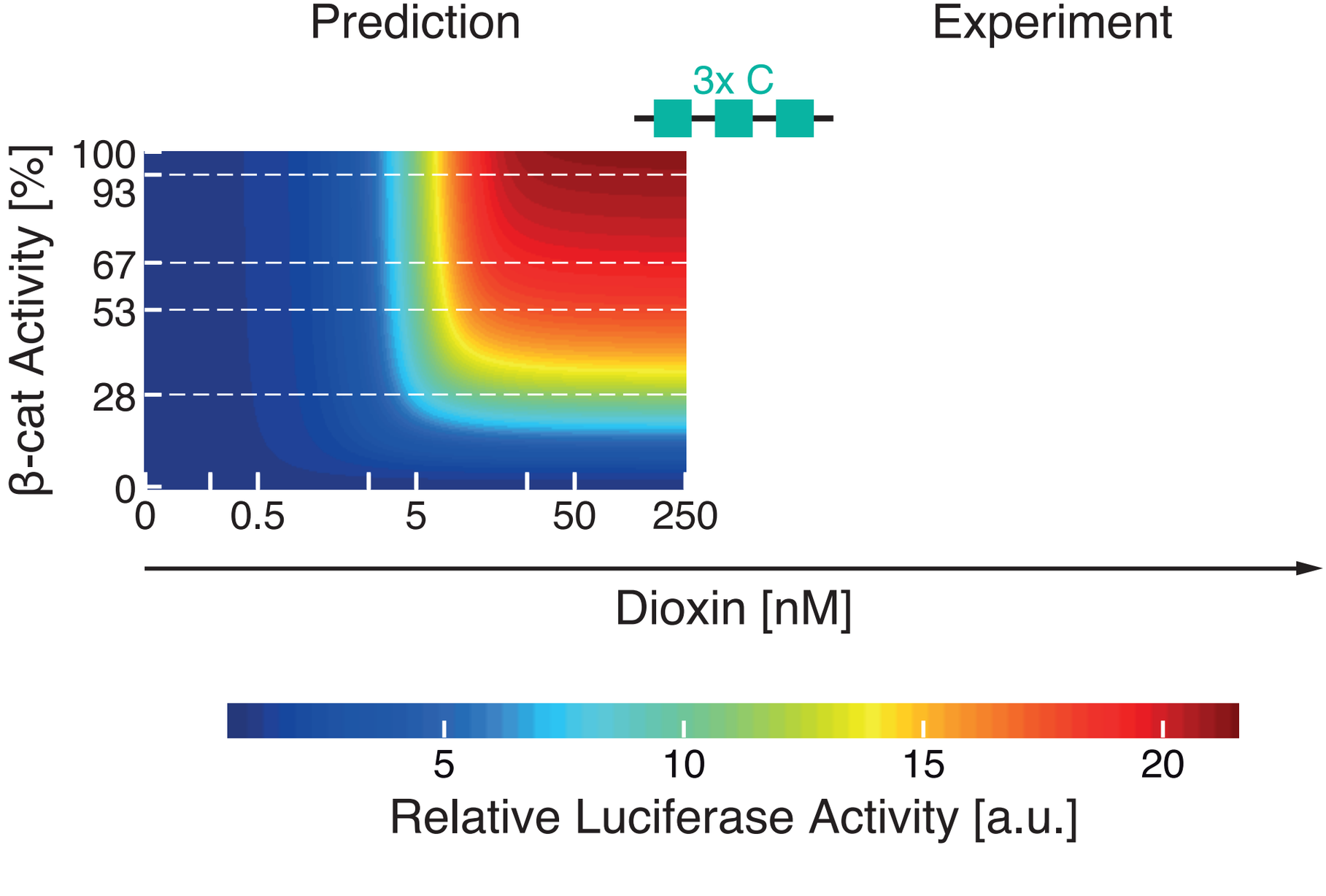


Sequestration responsible for reduced induction

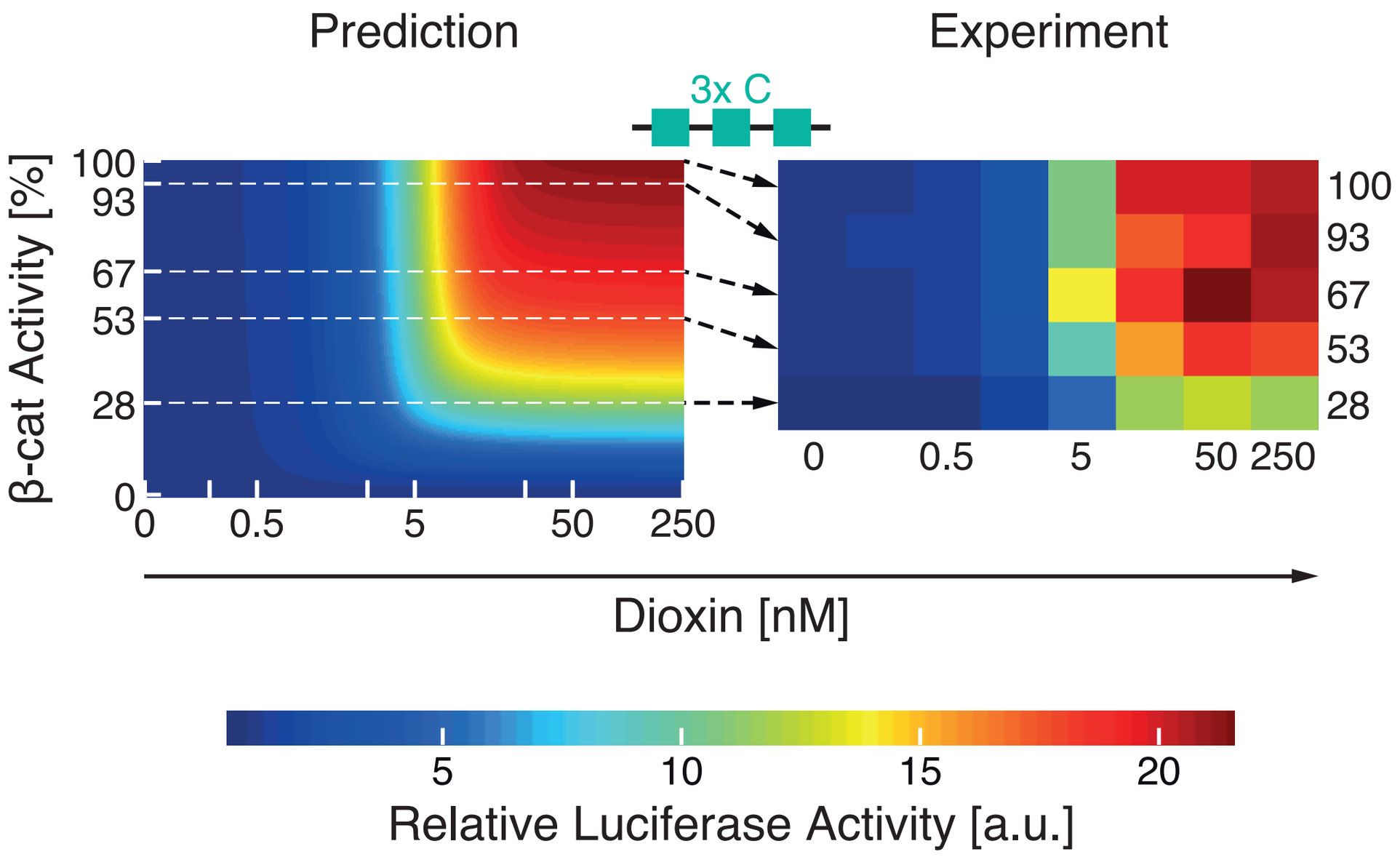
Prediction of dioxin and β-catenin signaling integration



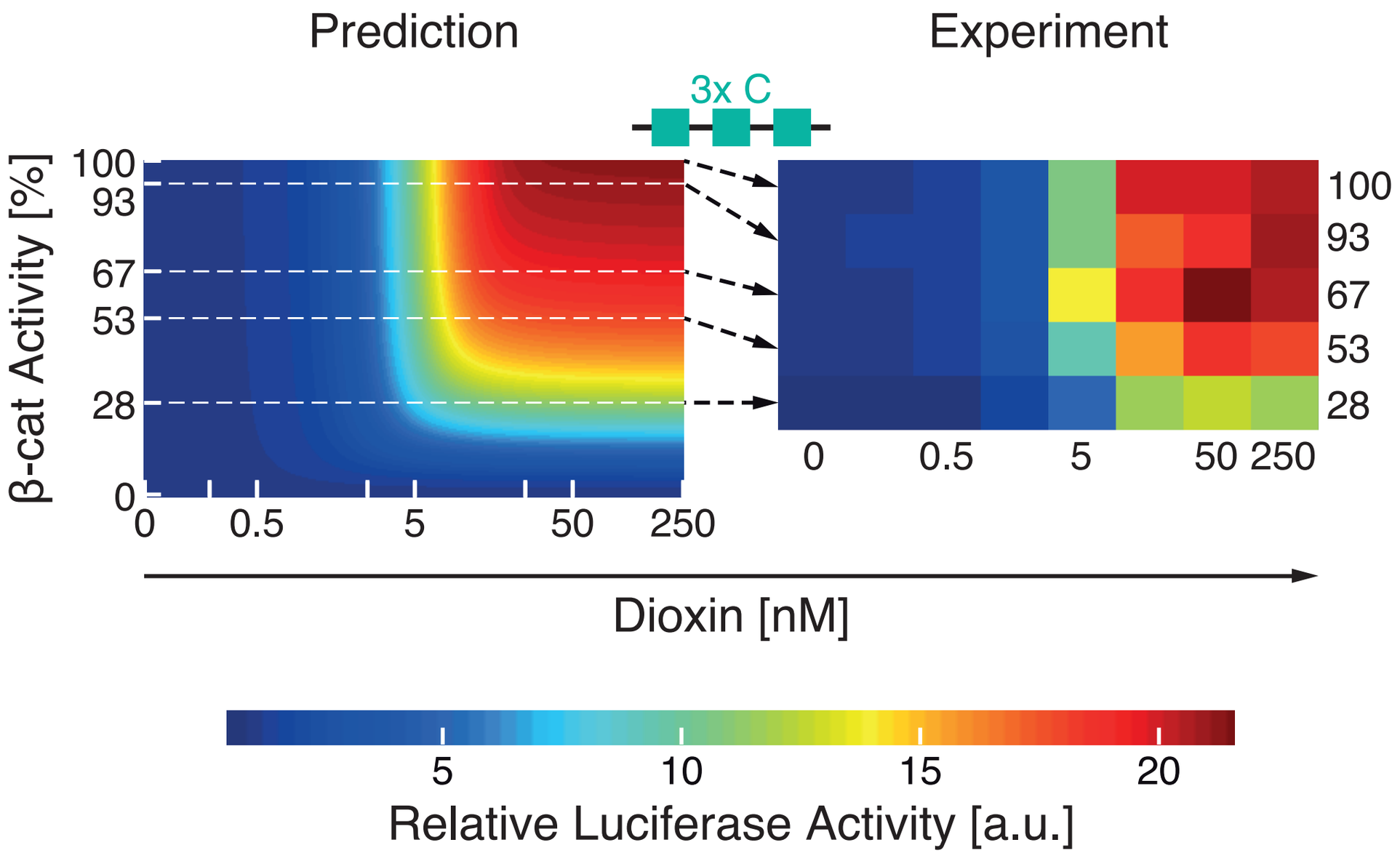
Prediction of dioxin and β-catenin signaling integration



Prediction of dioxin and β-catenin signaling integration



Prediction of dioxin and β-catenin signaling integration



Integration of the two signals follows AND gate logic

Conclusion for synthetic promoter

How do binding sites cooperate?

How are the two signaling pathways integrated?

Conclusion for synthetic promoter

How do binding sites cooperate?

- only first binding site interacts with polymerase
- only nearby binding sites cooperate

How are the two signaling pathways integrated?

Conclusion for synthetic promoter

How do binding sites cooperate?

- only first binding site interacts with polymerase
- only nearby binding sites cooperate

How are the two signaling pathways integrated?

- integration follows an AND gate logic

Does the same hold true for the

wild-type *CYP1A1* promoter?

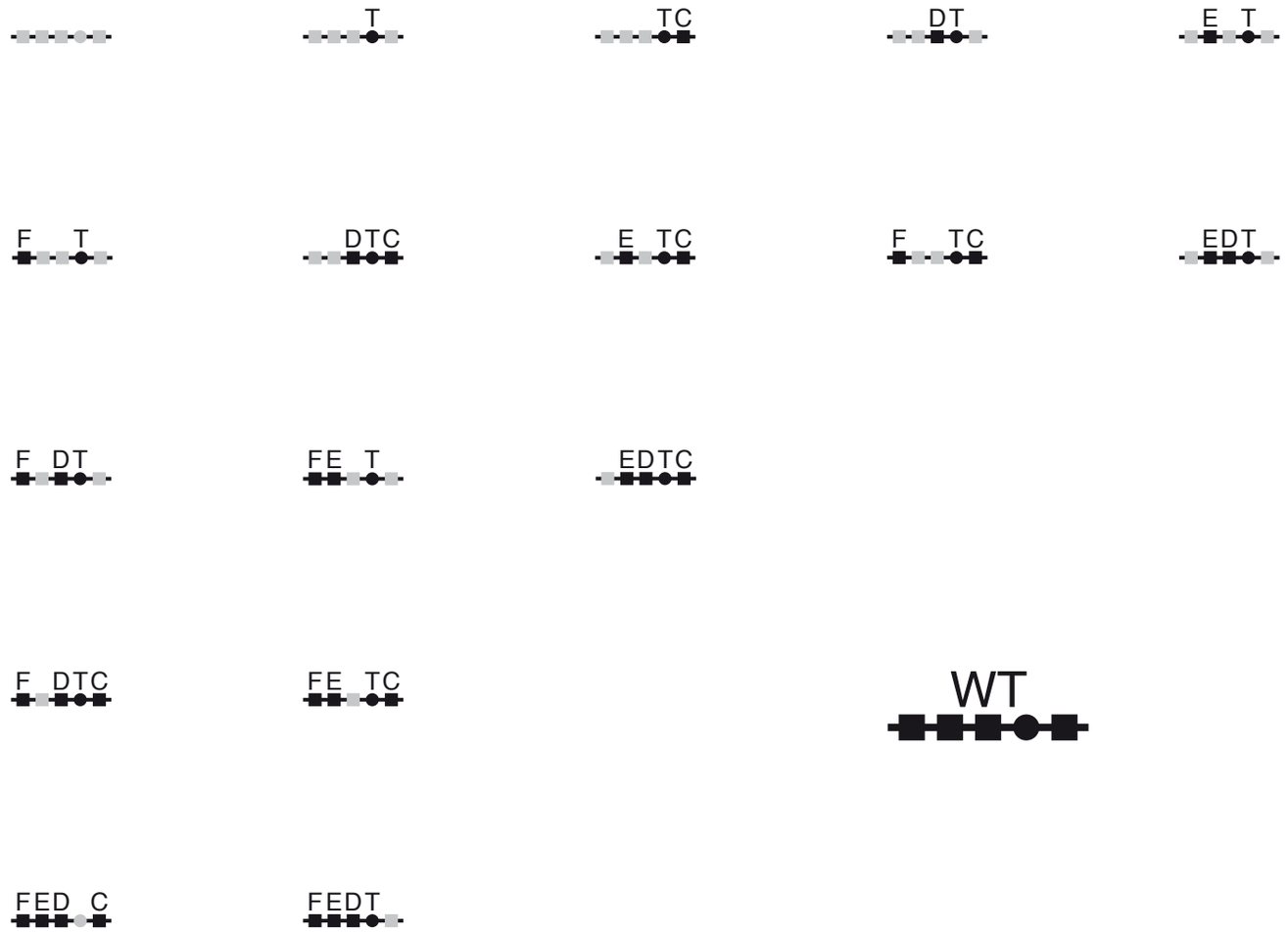
Outline

1. Introduction of the modeling framework

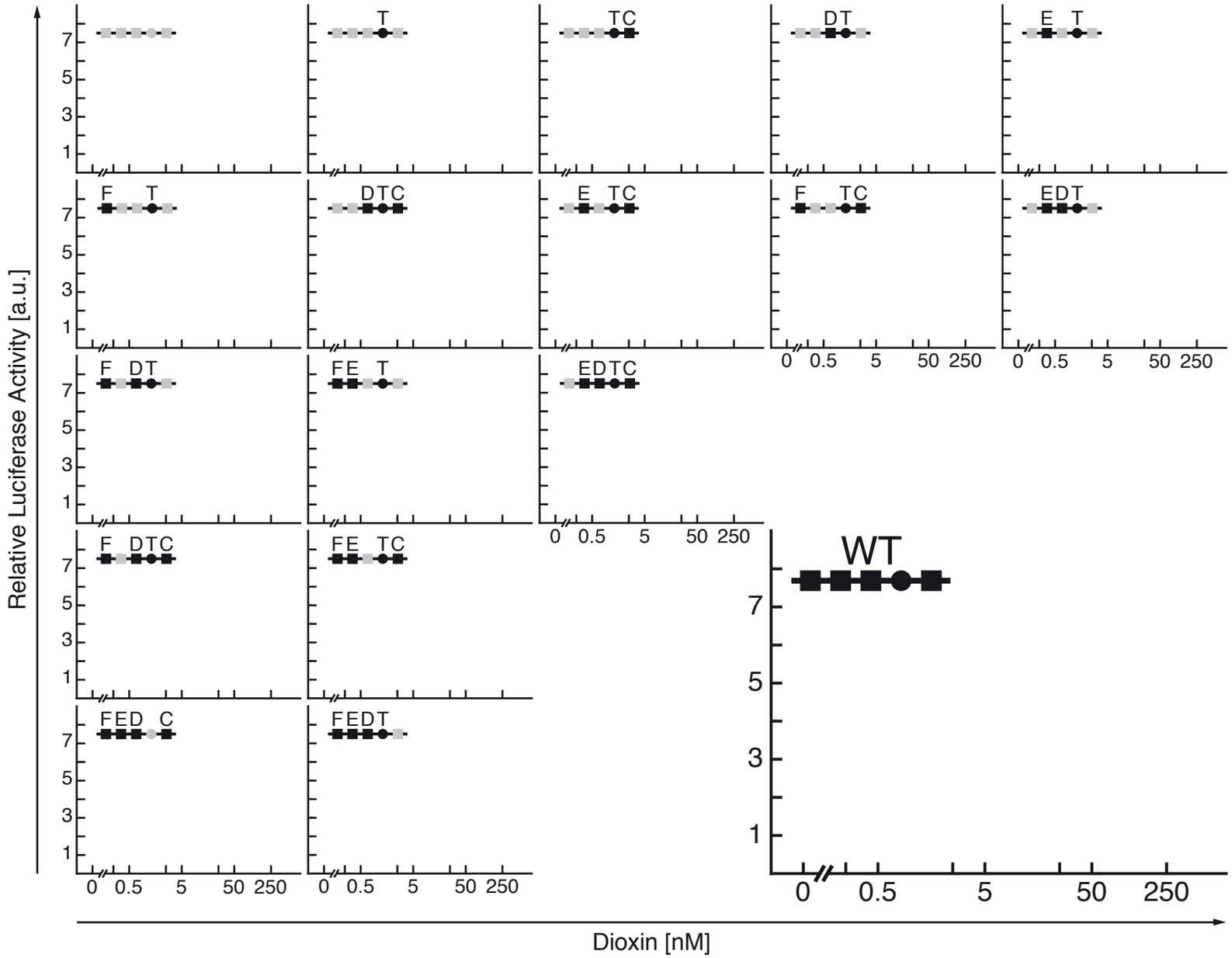
2. Model of synthetic promoter

3. Model of wild-type *CYP1A1* promoter

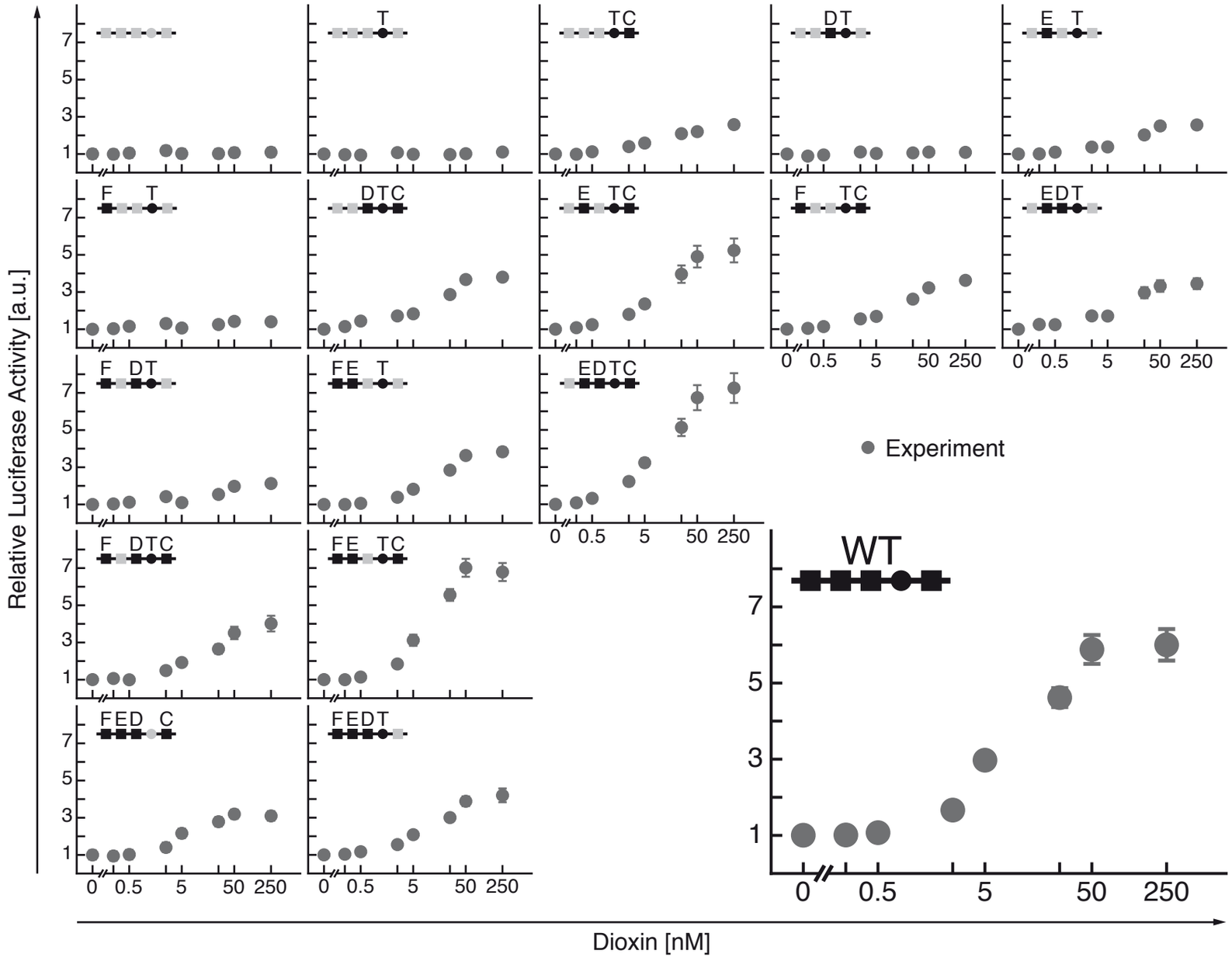
Model of wild-type *CYP1A1* promoter



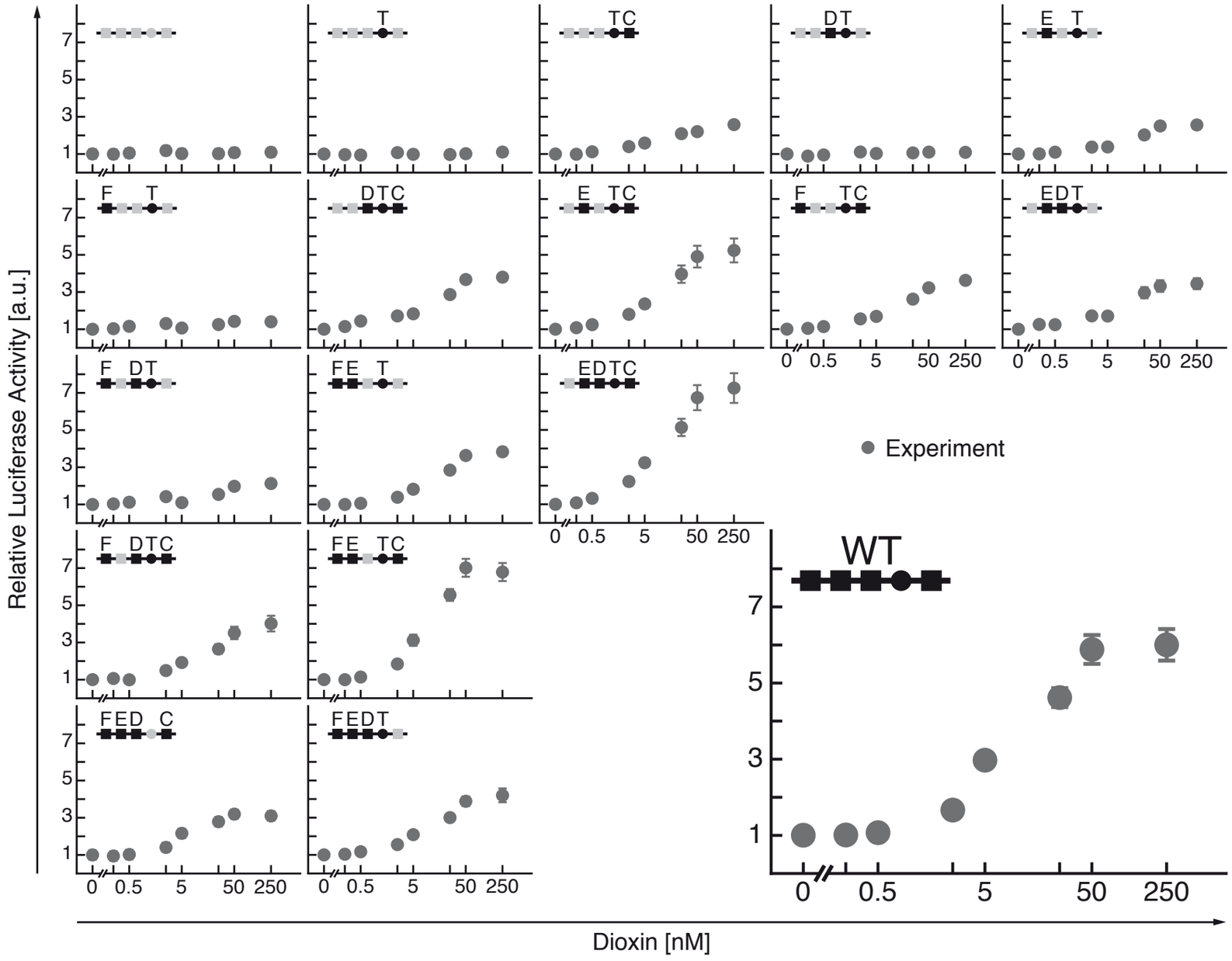
Model of wild-type *CYP1A1* promoter



Model of wild-type *CYP1A1* promoter

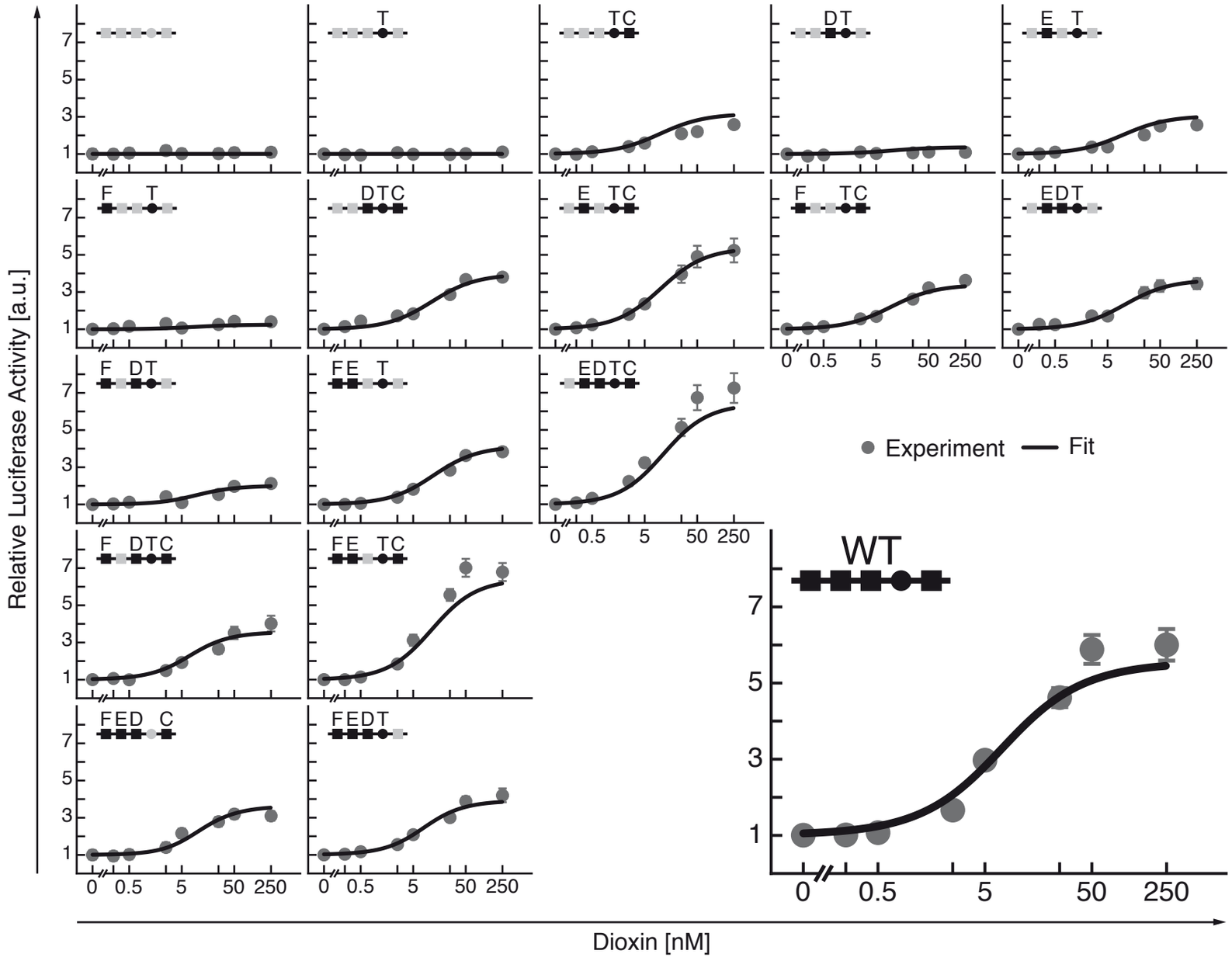


Model of wild-type *CYP1A1* promoter



model	parameters
signaling	3
thermodynamic	16 (21)

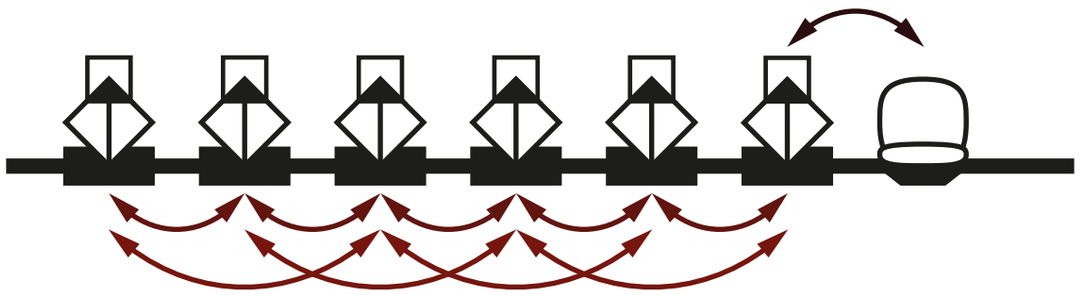
Model of wild-type *CYP1A1* promoter

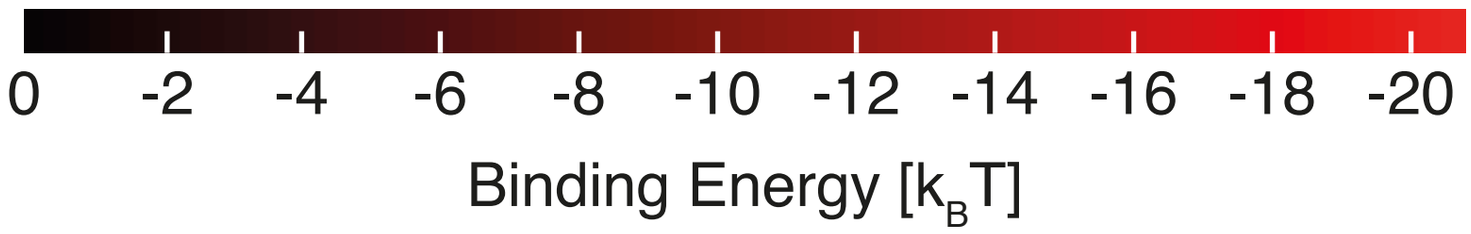


model	parameters
signaling	3
thermodynamic	16 (21)

Model parameters unravel TF interactions

synthetic promoter

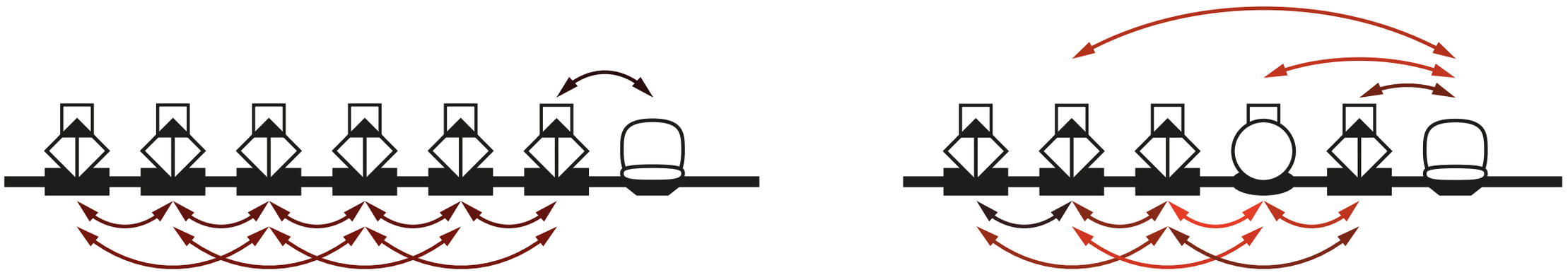


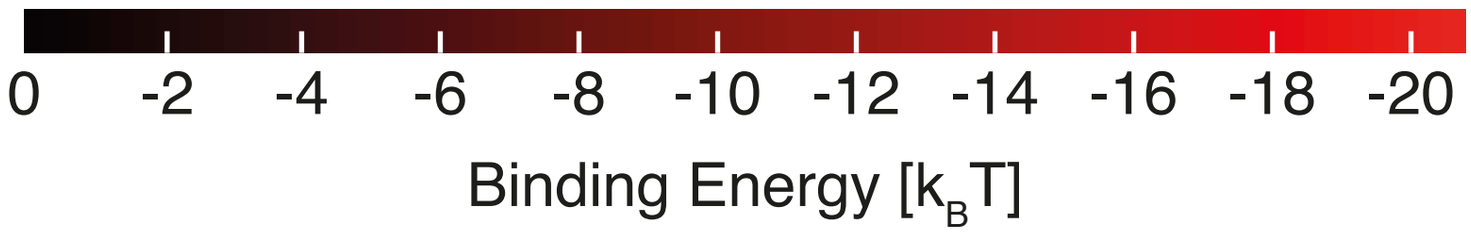


Model parameters unravel TF interactions

synthetic promoter

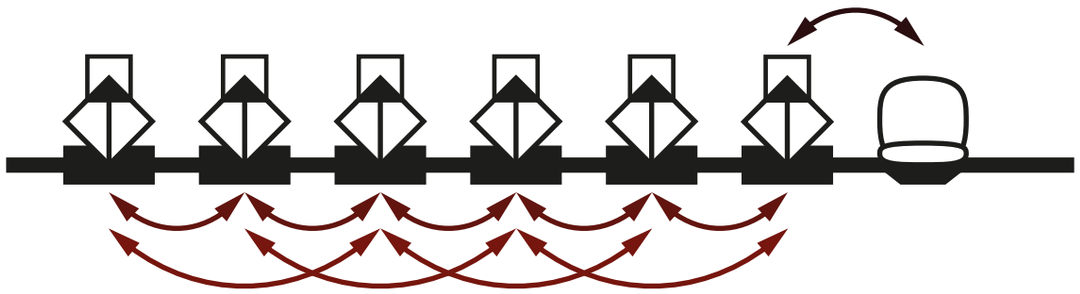
wild-type *CYP1A1* promoter



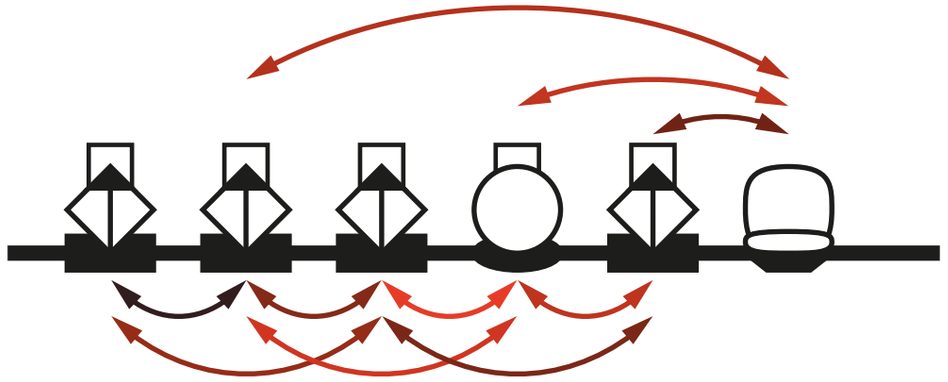


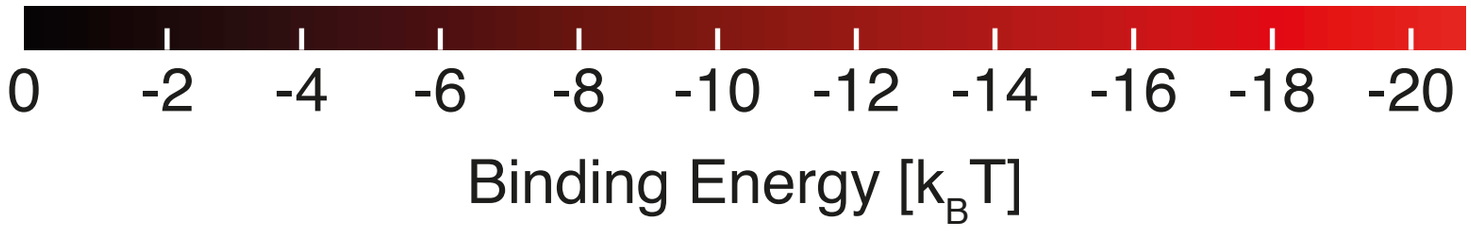
Model parameters unravel TF interactions

synthetic promoter



wild-type *CYP1A1* promoter

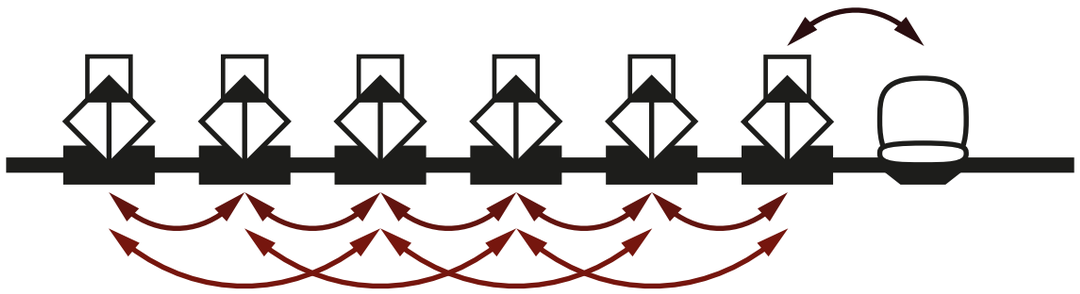




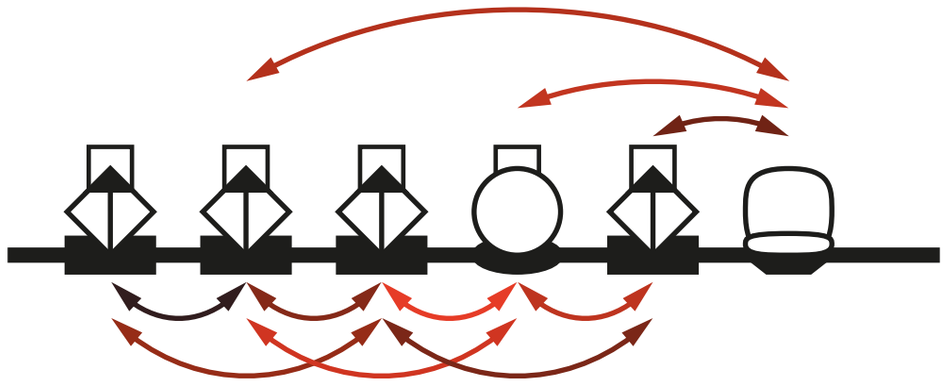
More and stronger TF-RNAP interactions

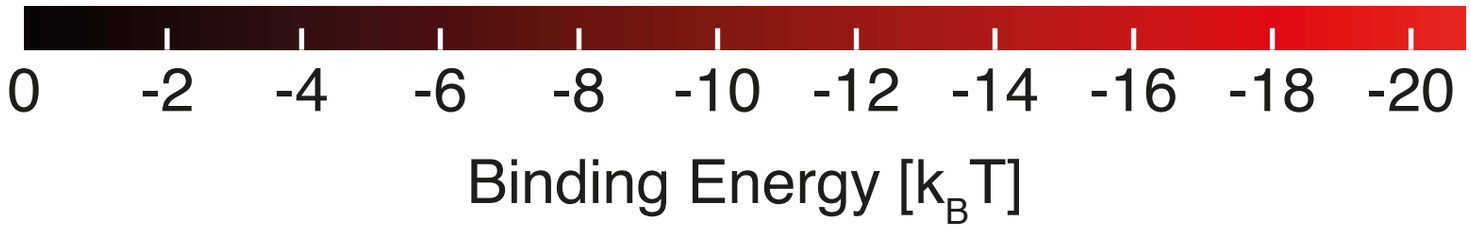
Model parameters unravel TF interactions

synthetic promoter



wild-type *CYP1A1* promoter

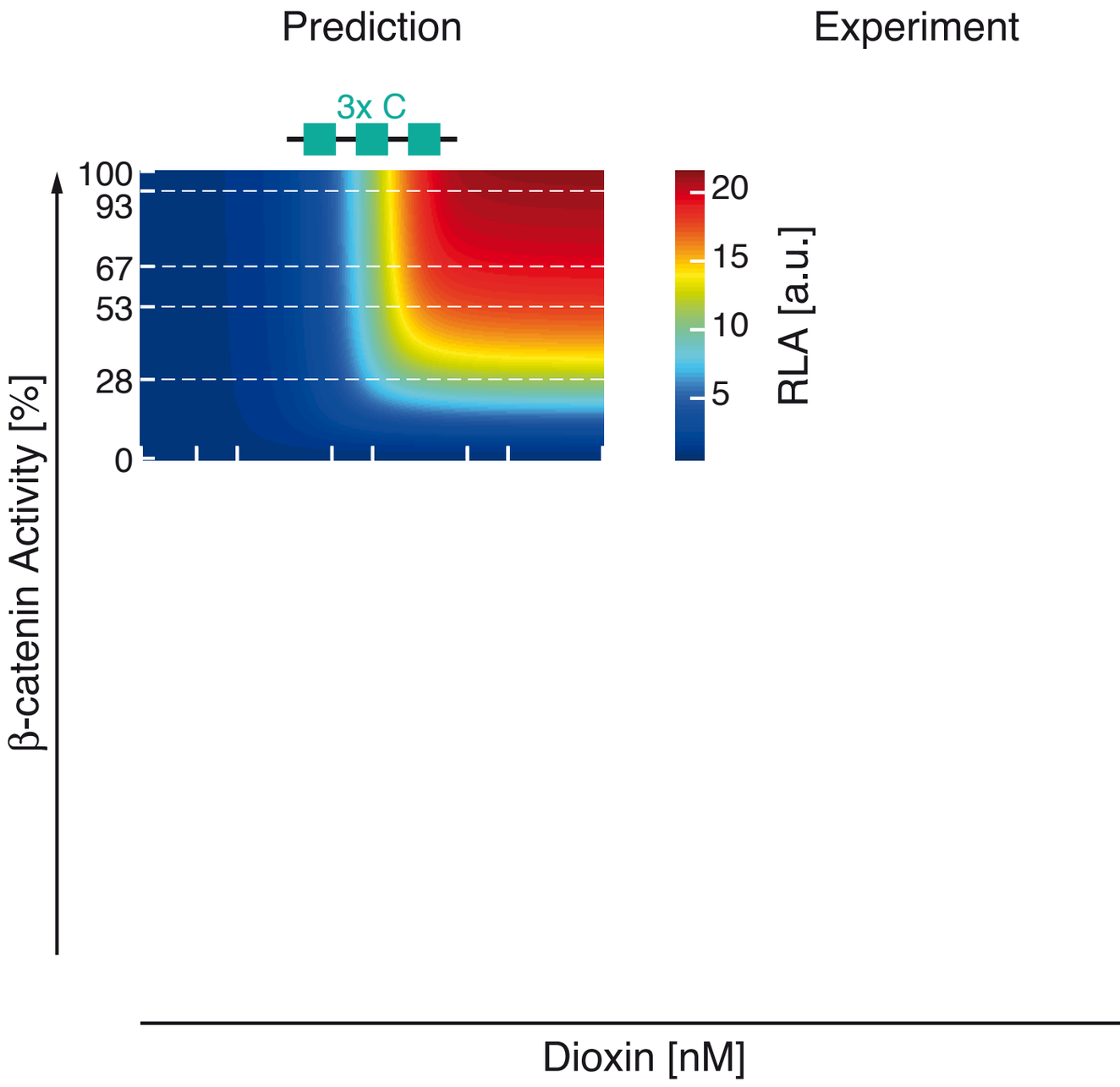




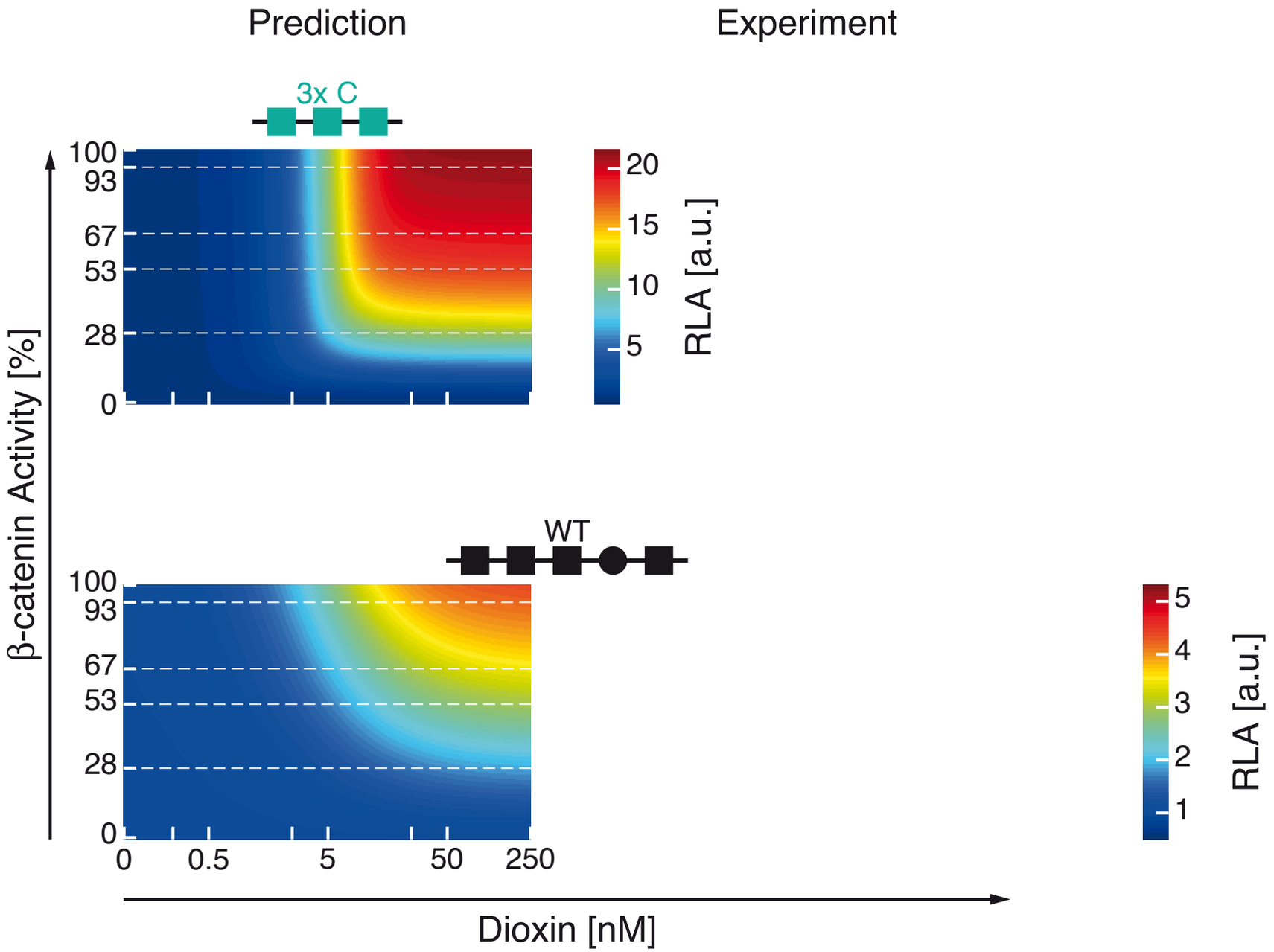
More and stronger TF-RNAP interactions

β-catenin is important interaction partner

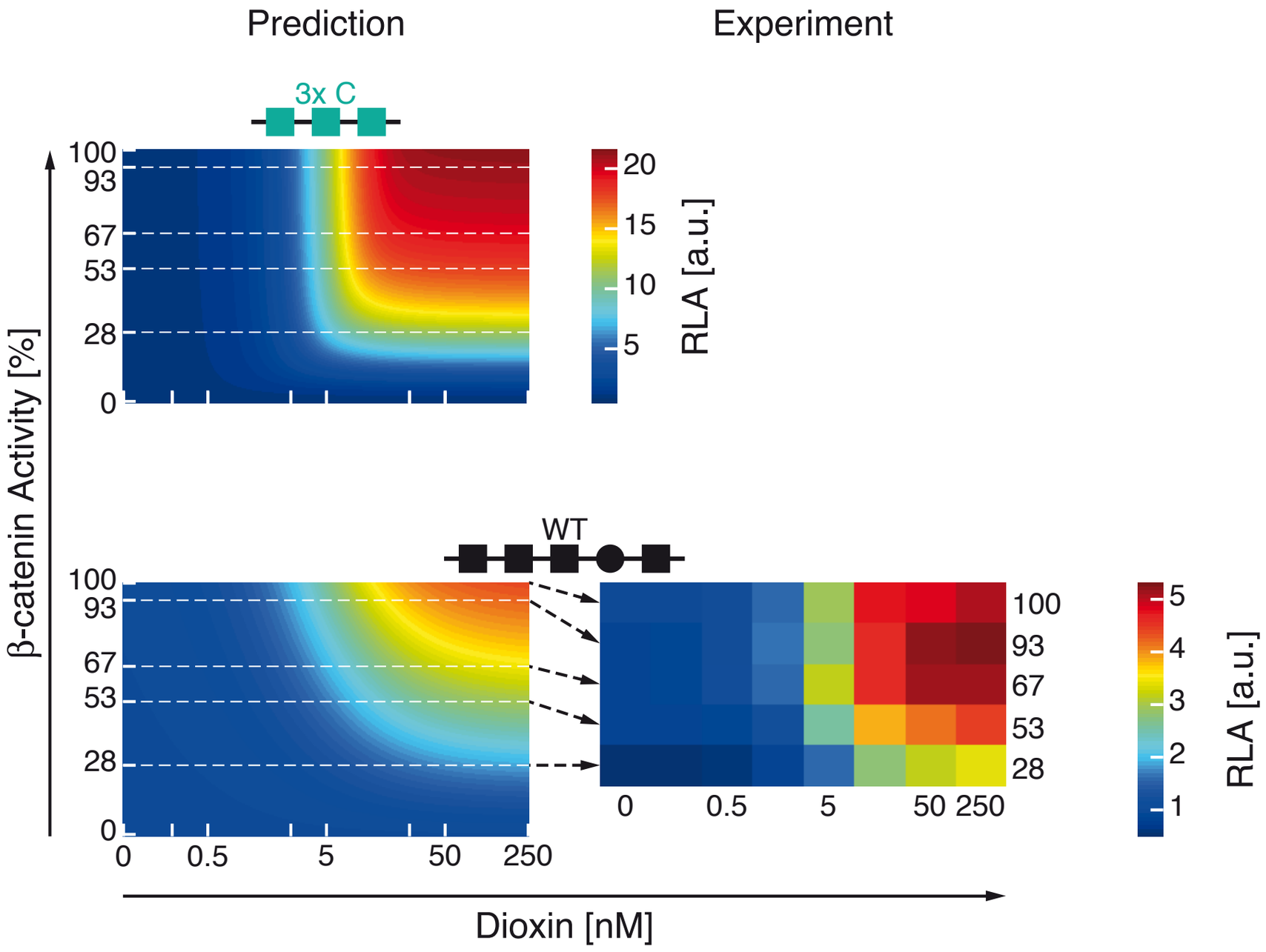
Prediction of dioxin and β-catenin signaling integration



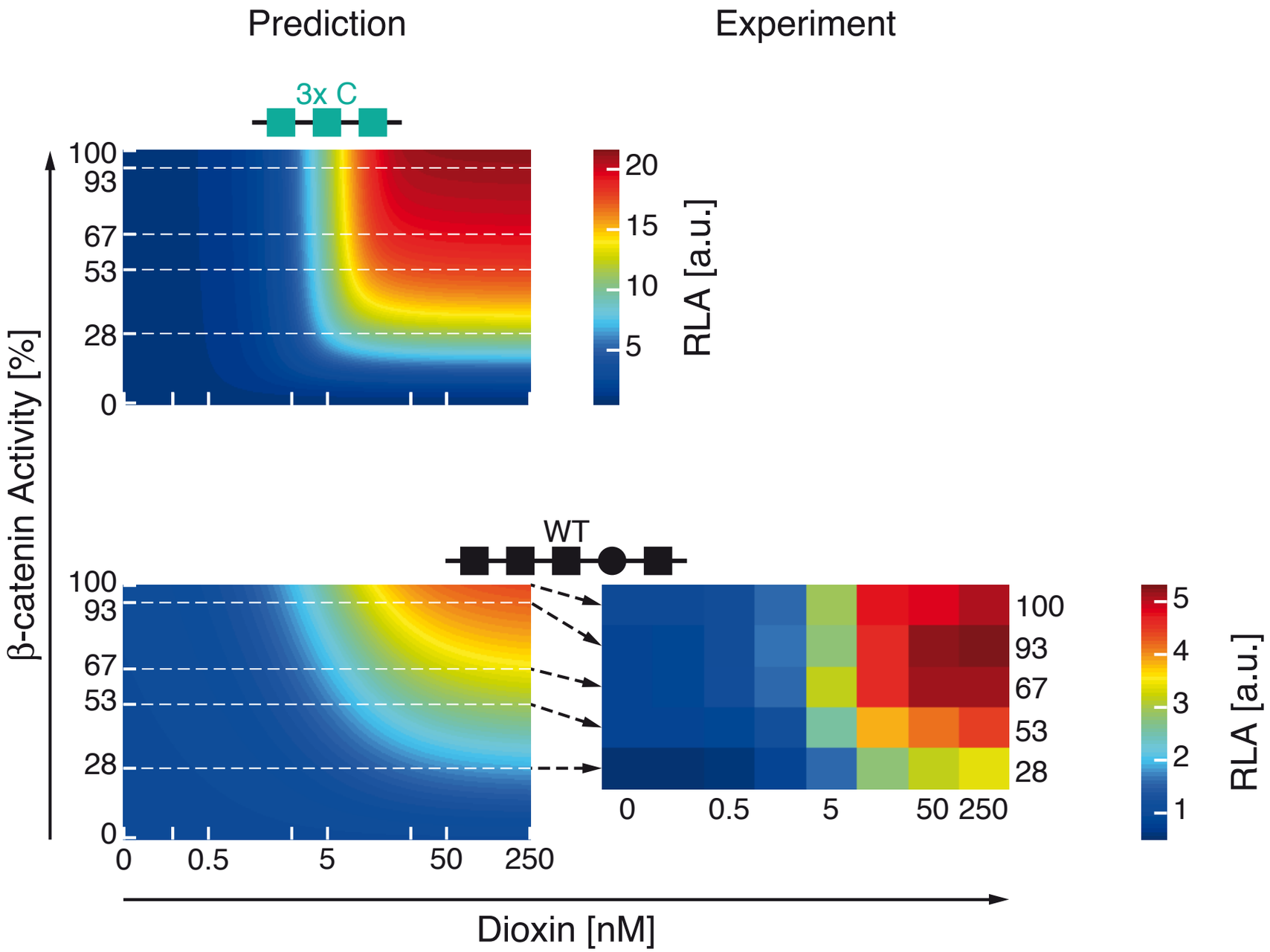
Prediction of dioxin and β-catenin signaling integration



Prediction of dioxin and β-catenin signaling integration



Prediction of dioxin and β-catenin signaling integration



Gradual AND gate enables finer regulation

Conclusion for wild-type *CYP1A1* promoter

How do binding sites cooperate?

How are the two signaling pathways integrated?

Conclusion for wild-type *CYP1A1* promoter

How do binding sites <u>cooperate</u>?

- more complex interaction patterns
- increased importance of TF-RNAP interactions
- β-catenin is an important interaction partner

How are the two signaling pathways <u>integrated</u>?

Conclusion for wild-type *CYP1A1* promoter

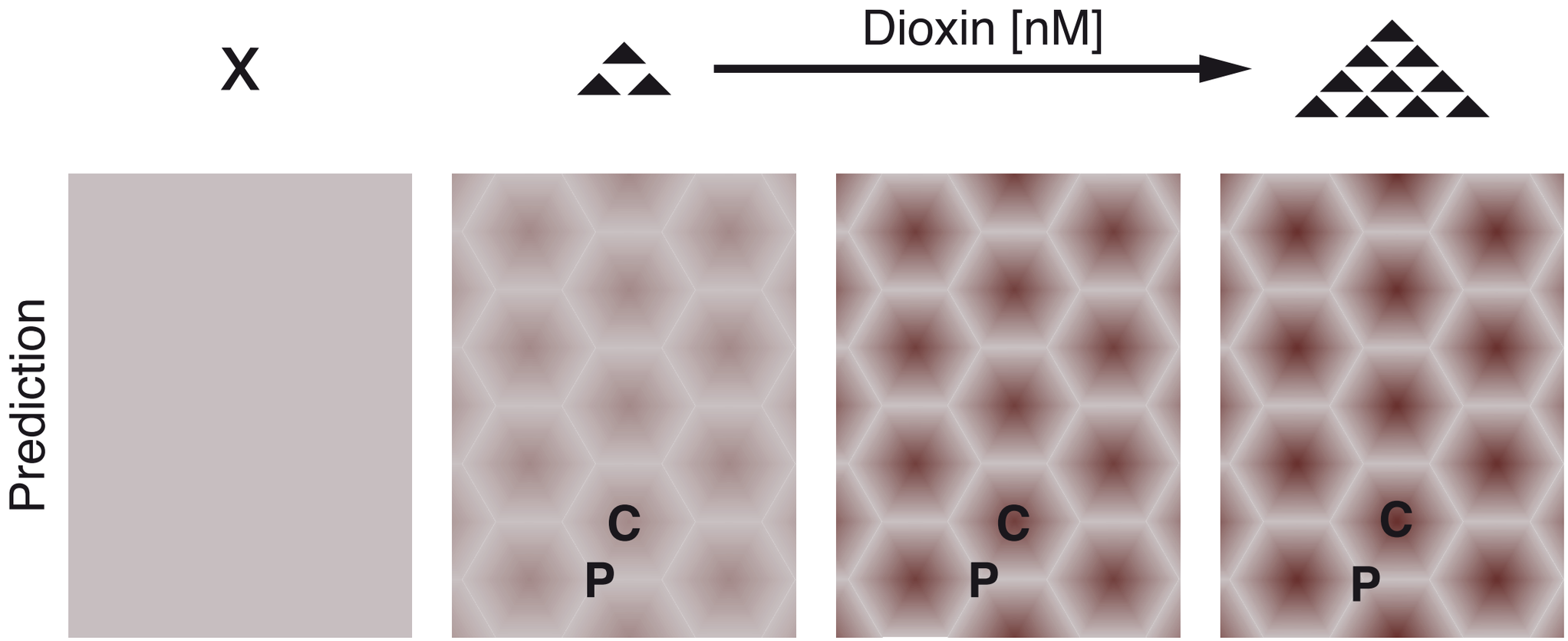
How do binding sites <u>cooperate</u>?

- more complex interaction patterns
- increased importance of TF-RNAP interactions
- β-catenin is an important interaction partner

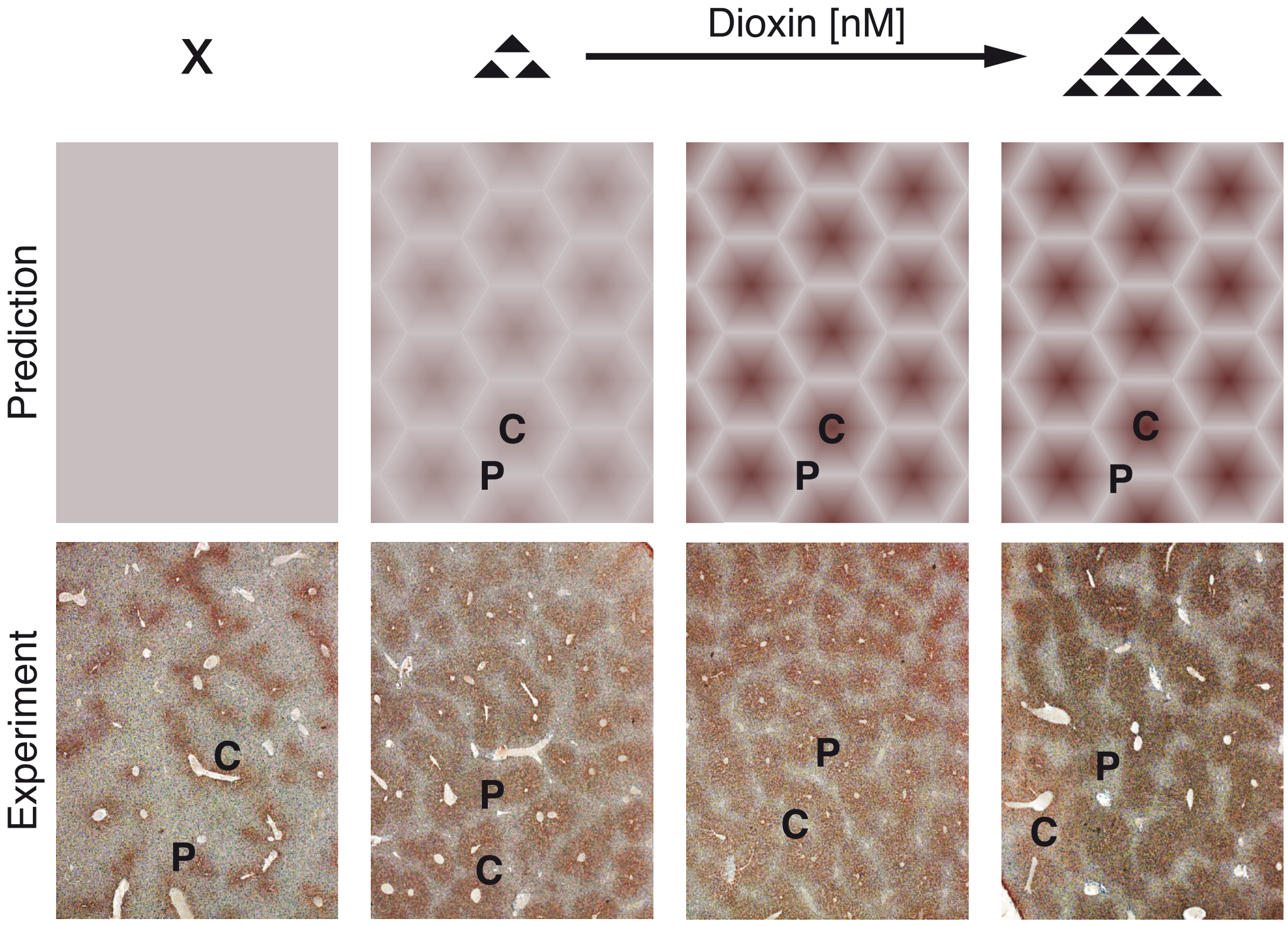
How are the two signaling pathways <u>integrated</u>?

- integration follows an AND gate logic
- gradual signal integration enables a finer regulation of promoter response

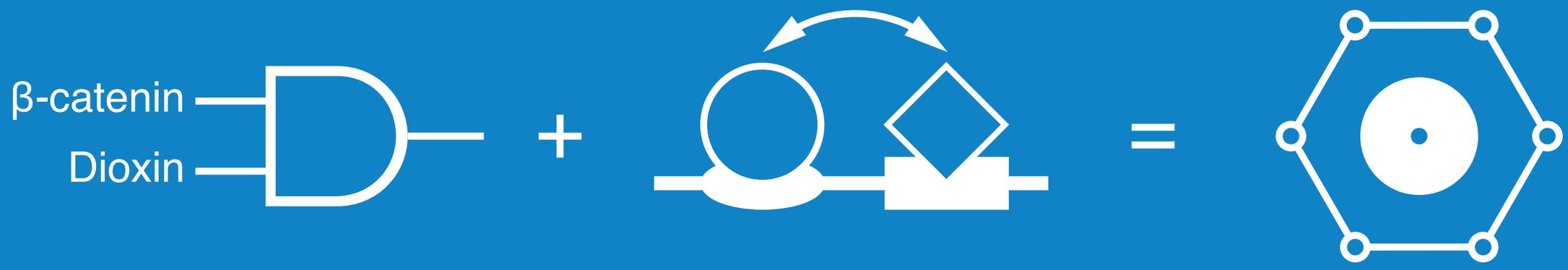
Model qualitatively predicts hepatic zonation



Model qualitatively predicts hepatic zonation



Conclusion



The interactions at the **signaling** level, together with the TF **cooperativity** in the *CYP1A1* promoter enable the **spatial expression** pattern observed *in vivo*.

Schulthess P, et al. (2015) Signal integration by the *CYP1A1* promoter - a quantitative study. *Nucleic Acids Research* 43(11):5318–5330.

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