A guide for the perplexed: Systems biology, transcriptional modeling, and the Drosophila embryo

David Arnosti

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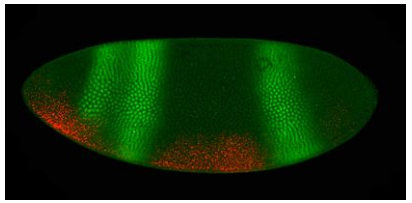
Michigan State University



What is systems biology?

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- Biological theory of everything

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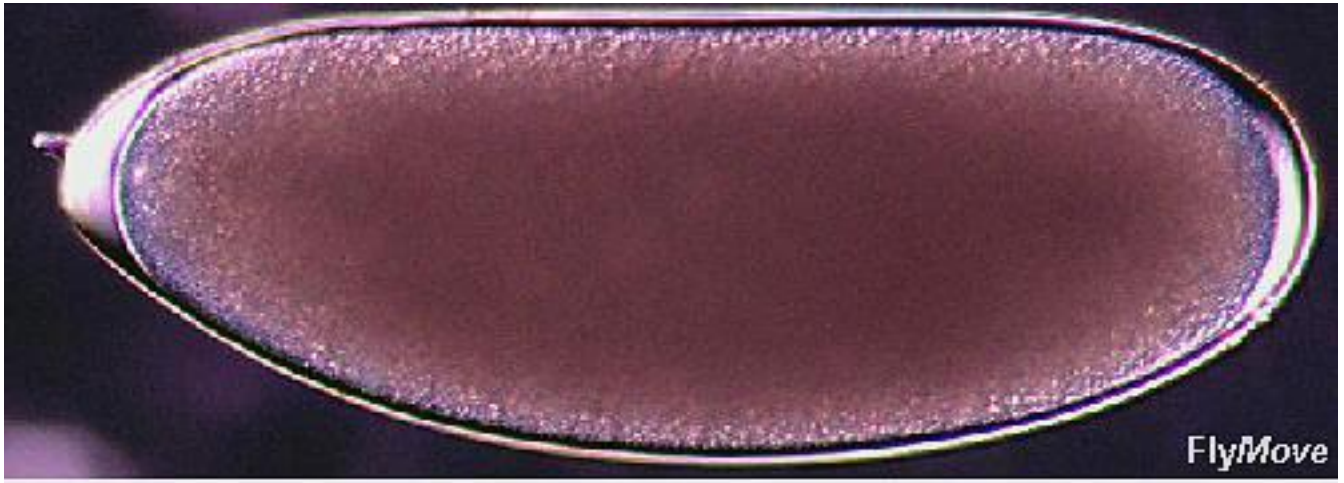
What is systems biology?

- Biological theory of everything
- Excuse not to think before doing experiments
- Way to glean good insights from bad data
- Integration of quantitative tools and large-scale datasets to bring us to the next level of understanding of systems

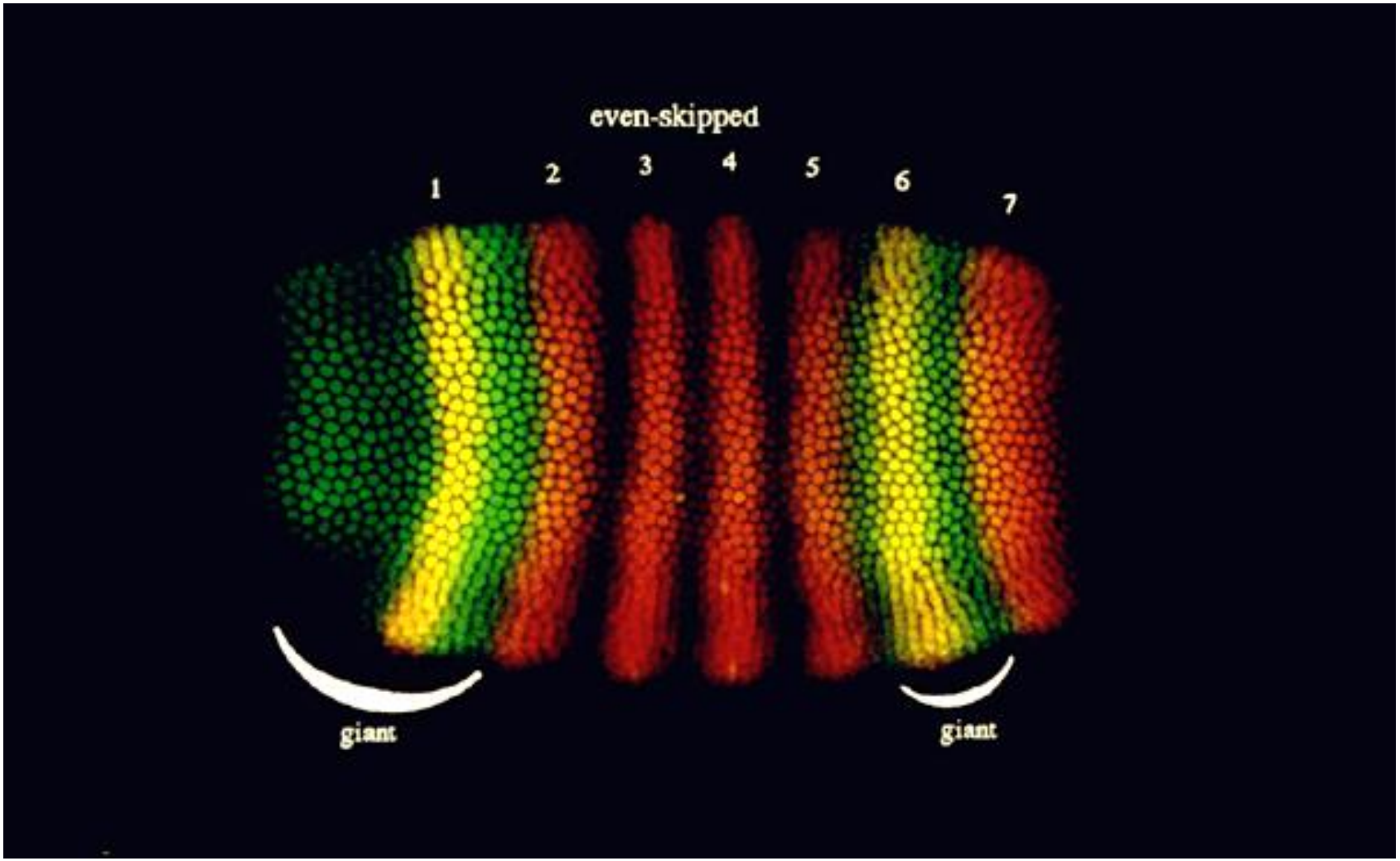


stage 2 Nuclear division Number: **5**

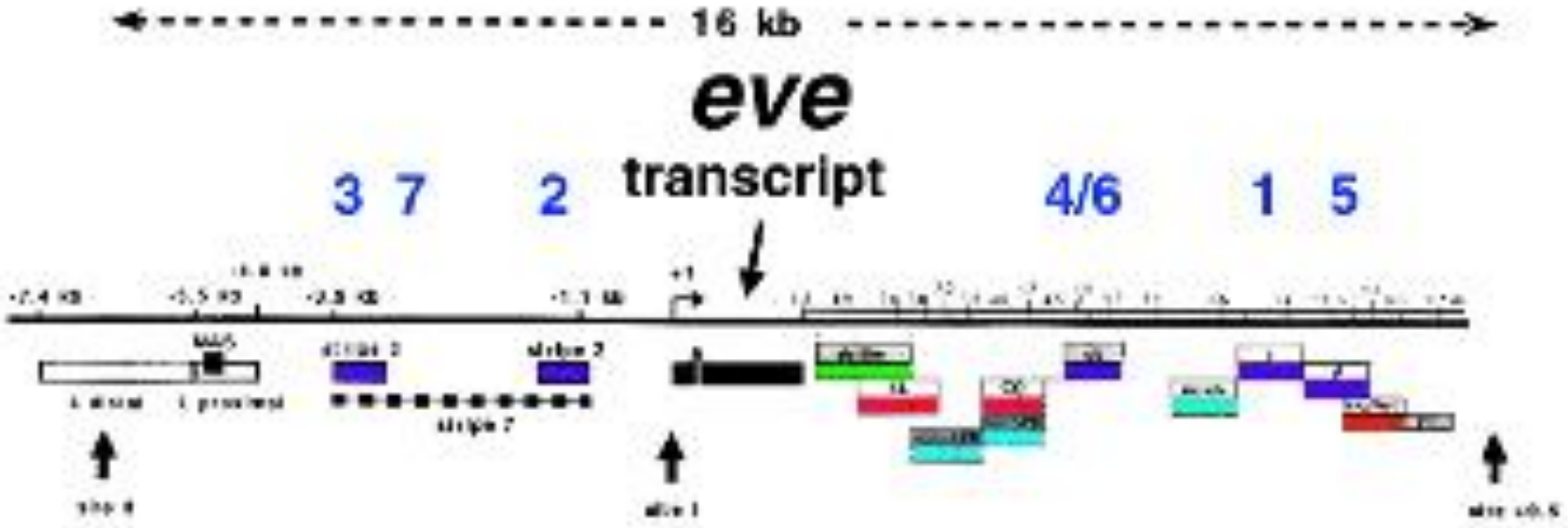
I wonder how that works…

Development starts with a few ordered manifoldnesses; but the manifoldnesses create, by interactions, new manifoldnesses, and these are able, by acting back on the original ones, to provoke new differences, and so on. With each new response, a new cause is immediately provided, and a new specific reactivity for further specific responses.

Hans Driesch (1894) *Analytische Theorie der organischen Entwicklung*
(http://7e.devbio.com/article.php?ch=10&id=110)

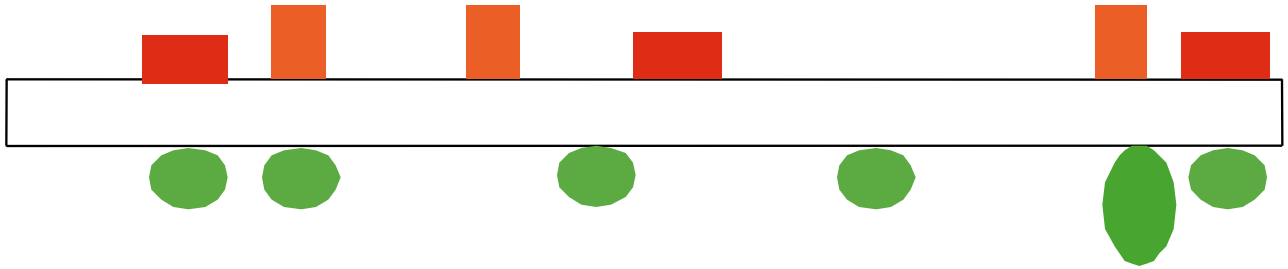


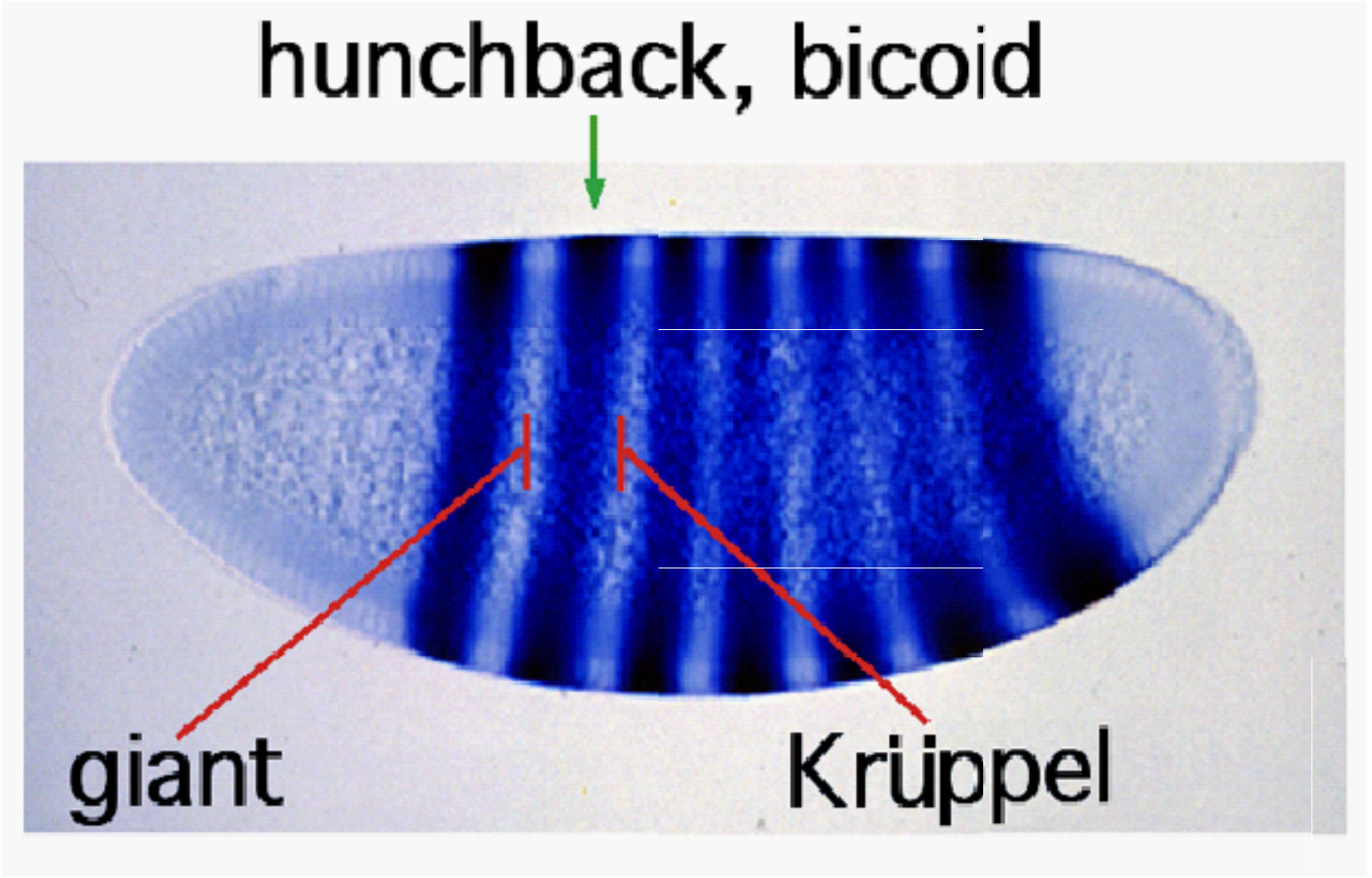
Wieschaus & Nusslein-Volhard, Levine and others:
We need to know something about transcription



Fujioka et al. (1999) Development 12:2827 and Sackerson et al. (1999) Dev. Biol.211: 39.

eve **stripe 2 enhancer**





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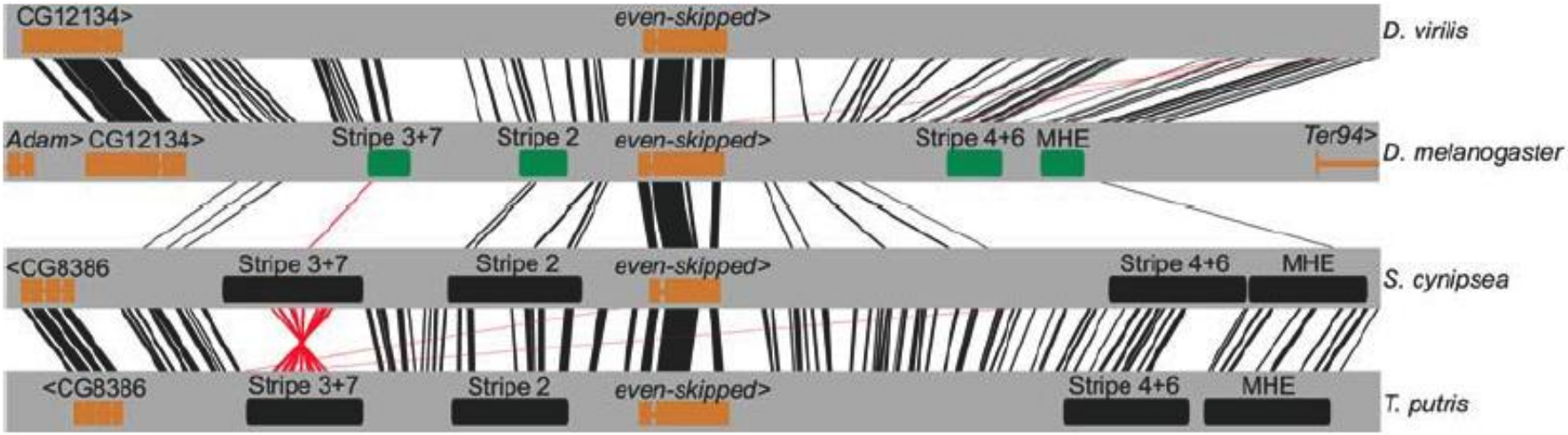
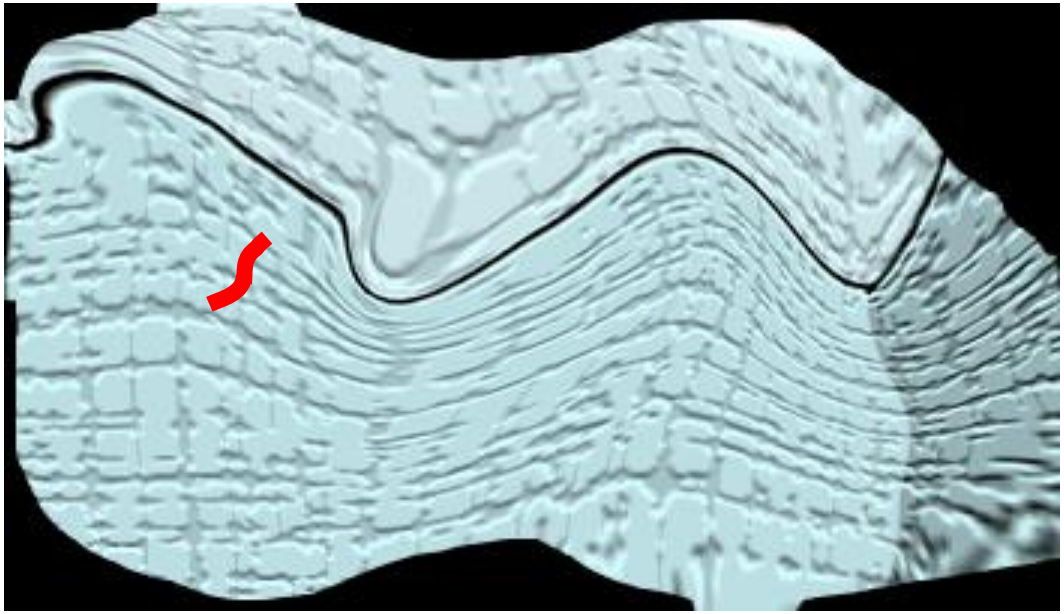
PLoS GENETICS

Sepsid *even-skipped* Enhancers Are Functionally Conserved in *Drosophila* Despite Lack of Sequence Conservation

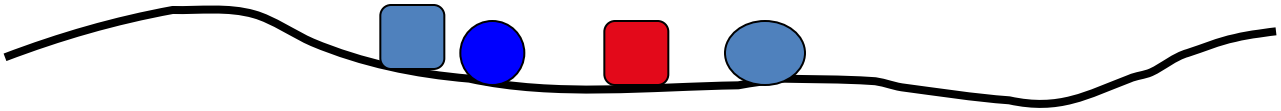
Emily E. Hare[1☯], Brant K. Peterson[1,2☯], Venky N. Iyer[1], Rudolf Meier[3], Michael B. Eisen[1,2,4,5*]



Kreitman, Eisen, and others – we need to know something about evolution

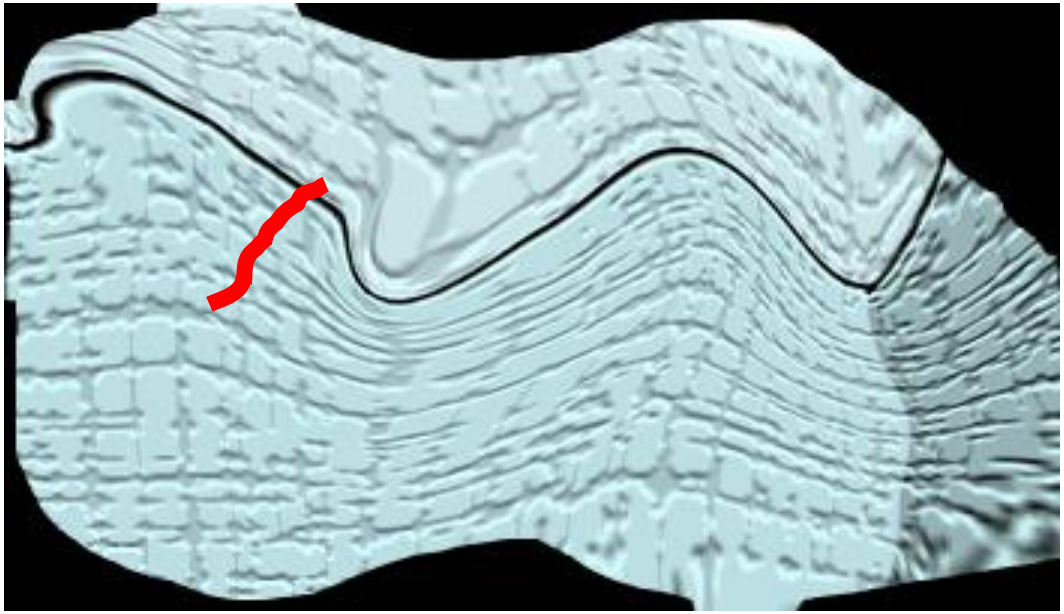


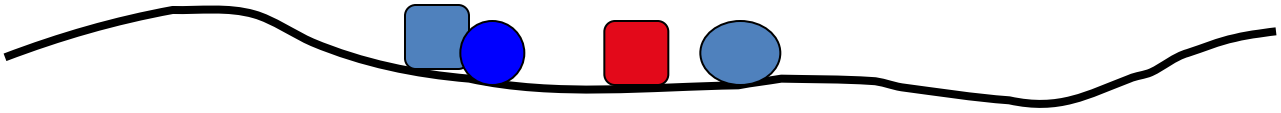
Functional Output Fitness Landscape

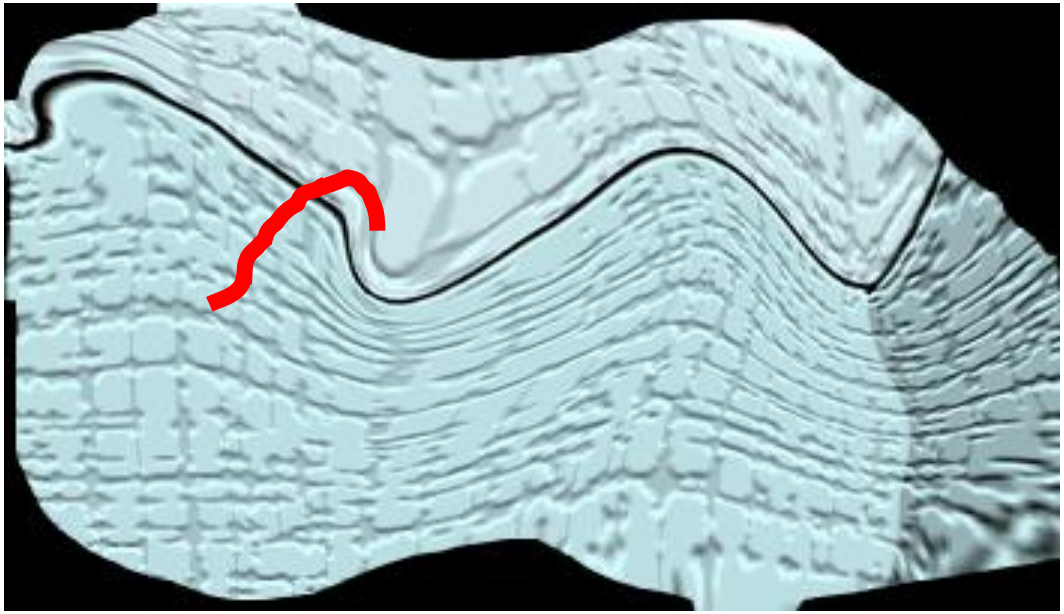


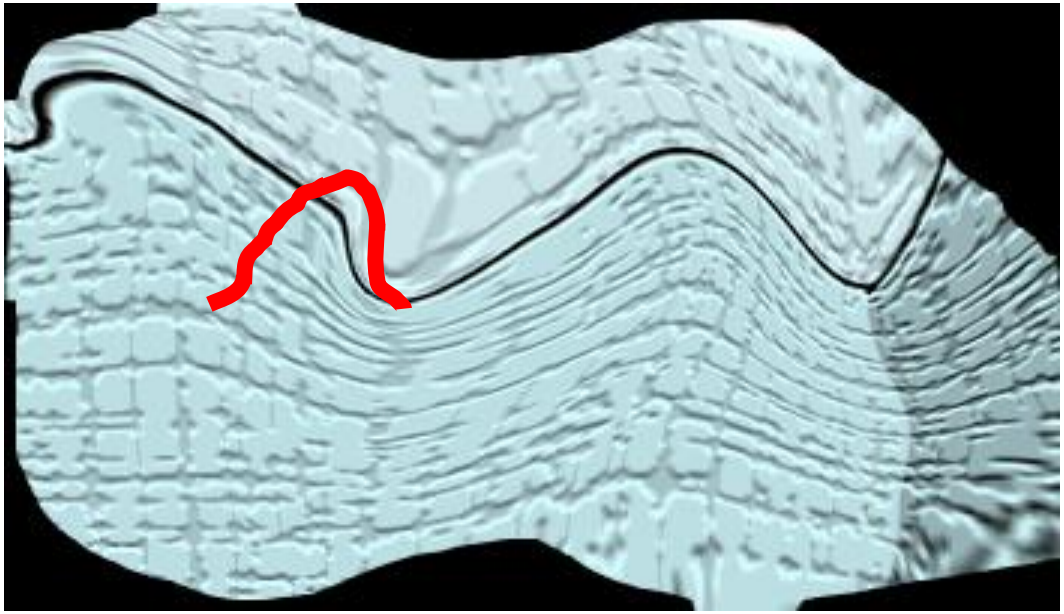
“Billboard” Enhancer Model

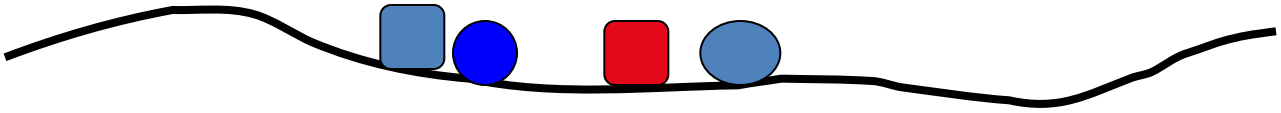
Arnosti and Kulkarni, 2005

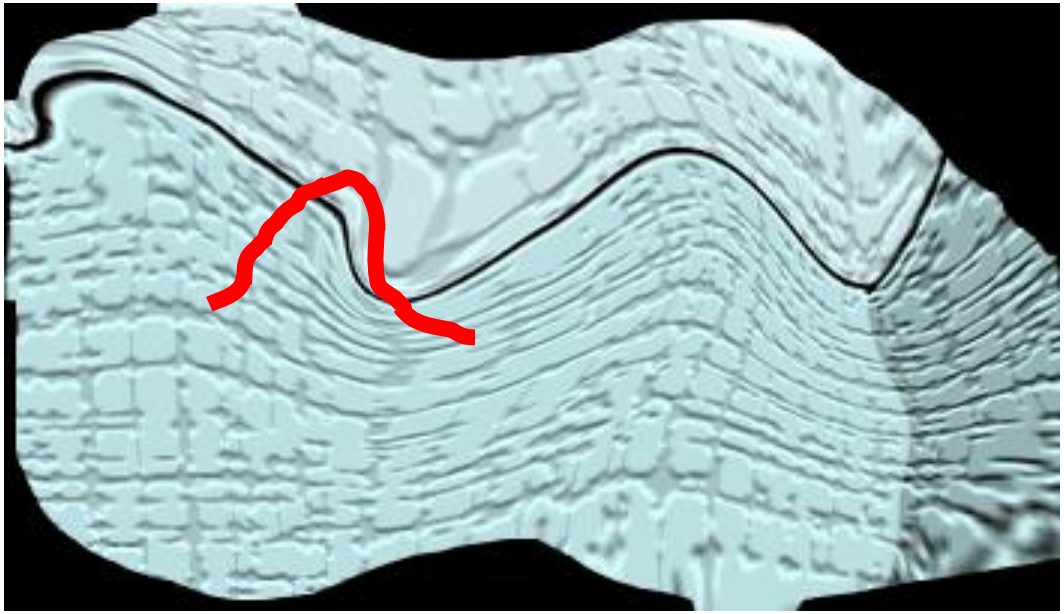


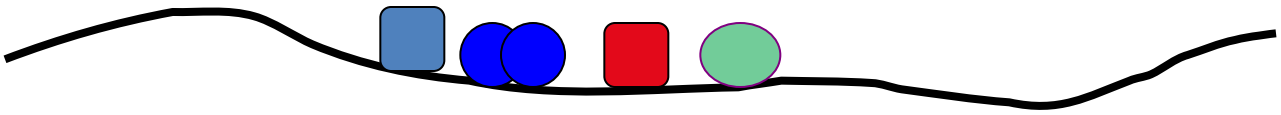


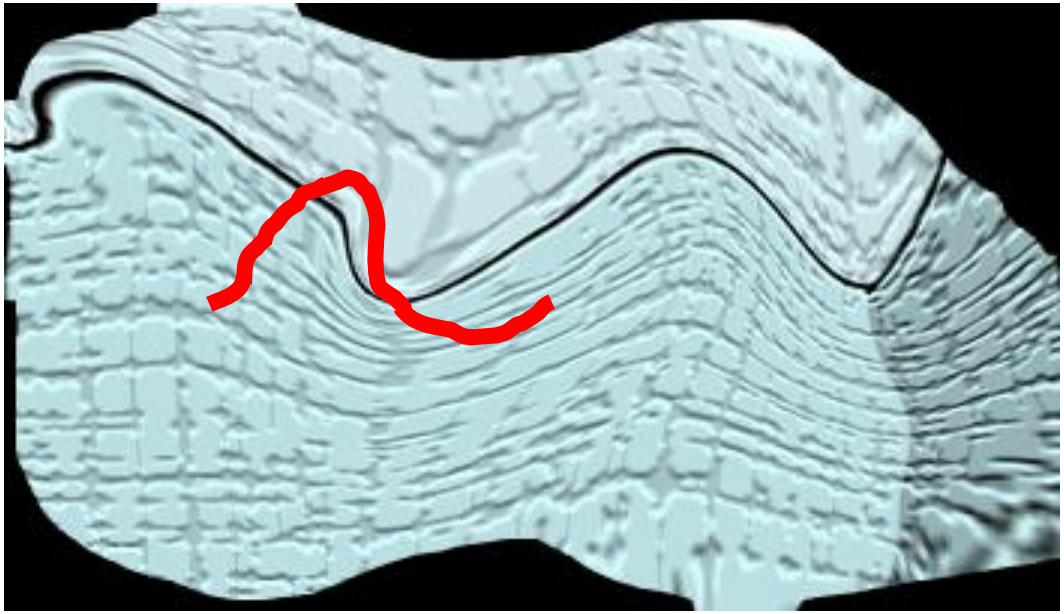


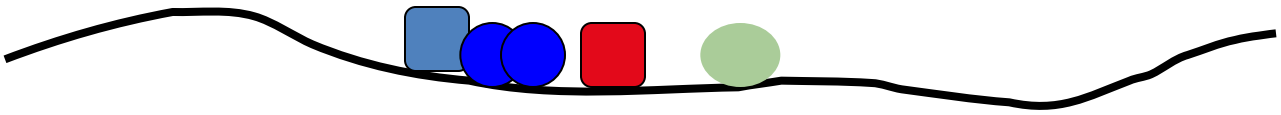


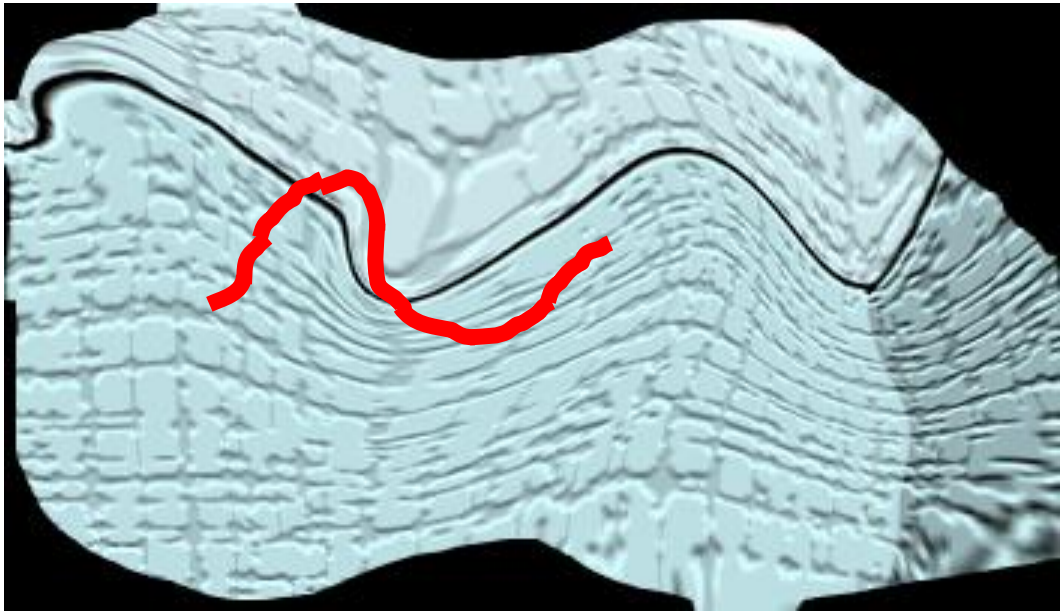


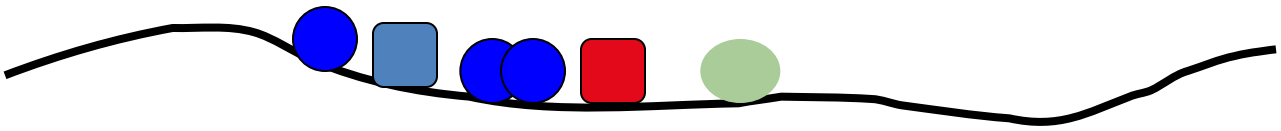












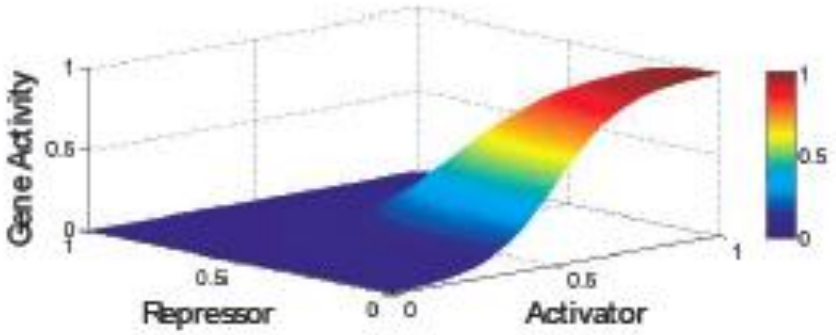
Empirical identification of a cis regulatory element “grammar” – what matters for enhancer output?

- ***Spacing (cooperativity, quenching)***
- ***Activator/repressor stoichiometry***
- ***Site arrangement***
- ***Binding site affinity***
- ***Abundance of factors***

Application of a Predictive Model

A

B



C

D

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REVIEW ARTICLE

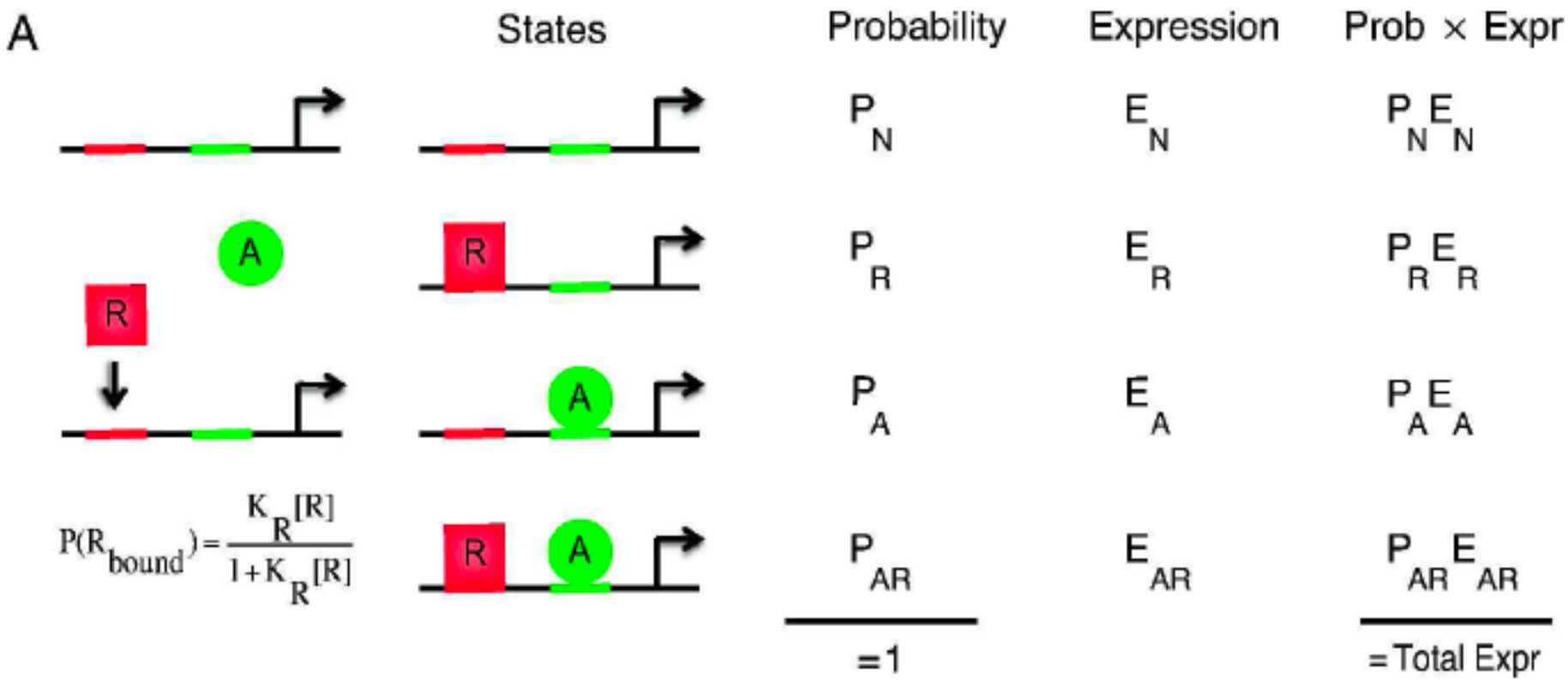
Mathematical modeling of gene expression: a guide for the perplexed biologist

Ahmet Ay[1,2] and David N. Arnosti[3]

[1]*Department of Biology, Colgate University, Hamilton, NY, USA,* [2]*Department of Mathematics, Colgate University, Hamilton, NY, USA, and* [3]*Department of Biochemistry and Molecular Biology, Michigan State University, East Lansing, MI, USA*

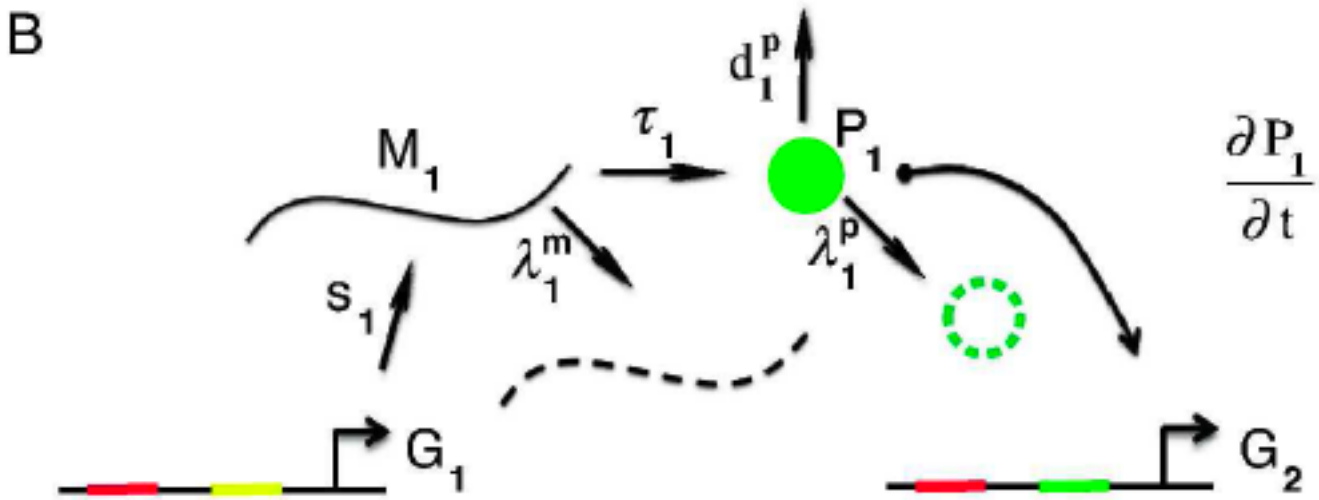
Some approaches involving modeling…

“Thermodynamic” model



- Uses DNA sequence information
- Subtle modifications – spacing, affinity, overlaps
- Snapshot – equilibrium situation

Differential Equation model

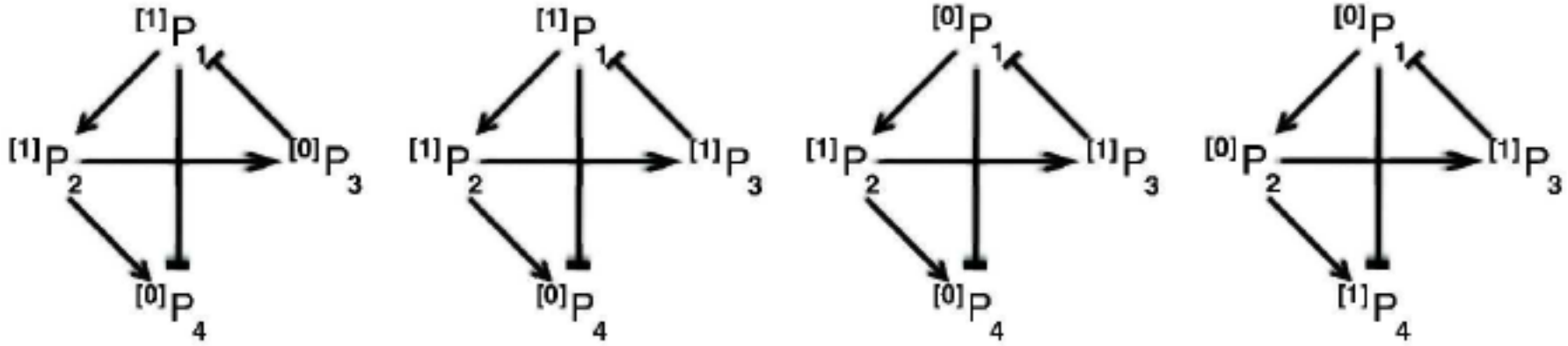


$$\frac{\partial P_1}{\partial t} = \tau_1 M_1 - \lambda_1^p P_1 + d_1^p \Delta P_1$$

- Promoter treated as black box
- Incorporates post-transcriptional processes
- Movie – provides dynamic pictures

Boolean model

C



- Promoter - black box
- Post-transcriptional processes
- Movie
- Interactions simplified to +/-
- Computations simpler, output coarser

1. **For DNA-level modeling,**
   thermodynamic approaches are especially apt

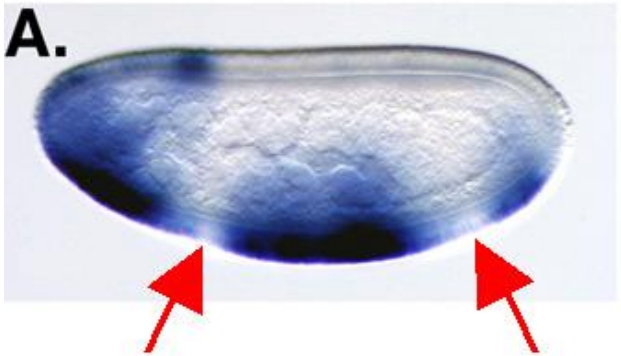
2. **If you are fastidious,**
   you must collect your own data

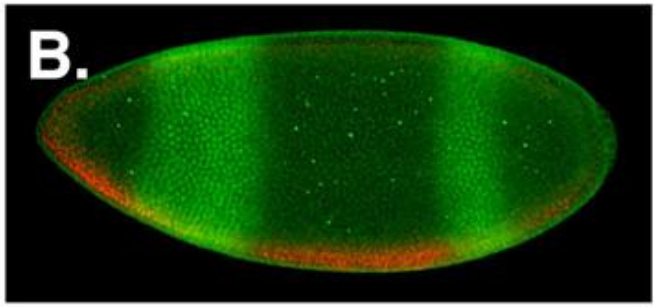
Quantitative and predictive model of transcriptional control of the *Drosophila melanogaster even skipped* gene

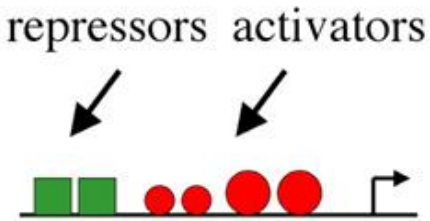
Hilde Janssens[1], Shuling Hou[2], Johannes Jaeger[1], Ah-Ram Kim[1], Ekaterina Myasnikova[3], David Sharp[4] & John Reinitz[1]

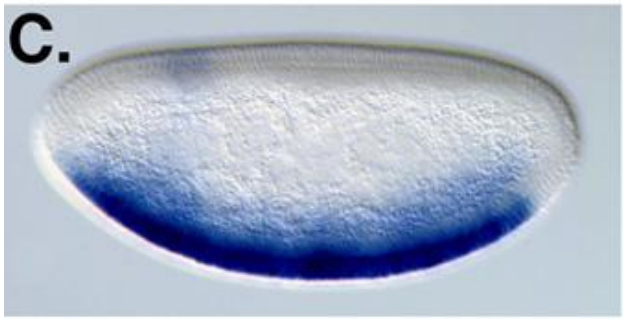
Nature Genetics 38: 1159 (2006)

Focusing specifically on properties of short-range transcriptional repressors:

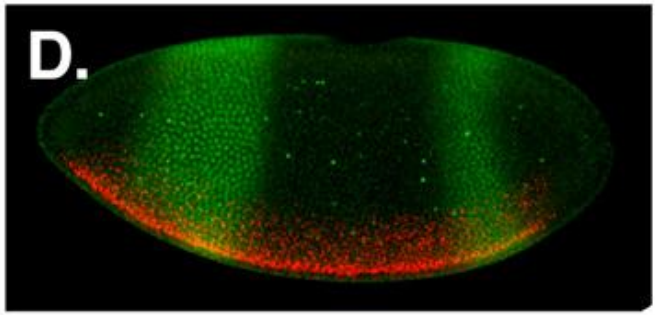




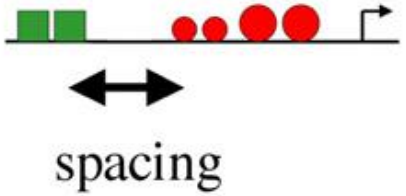




Qualitative

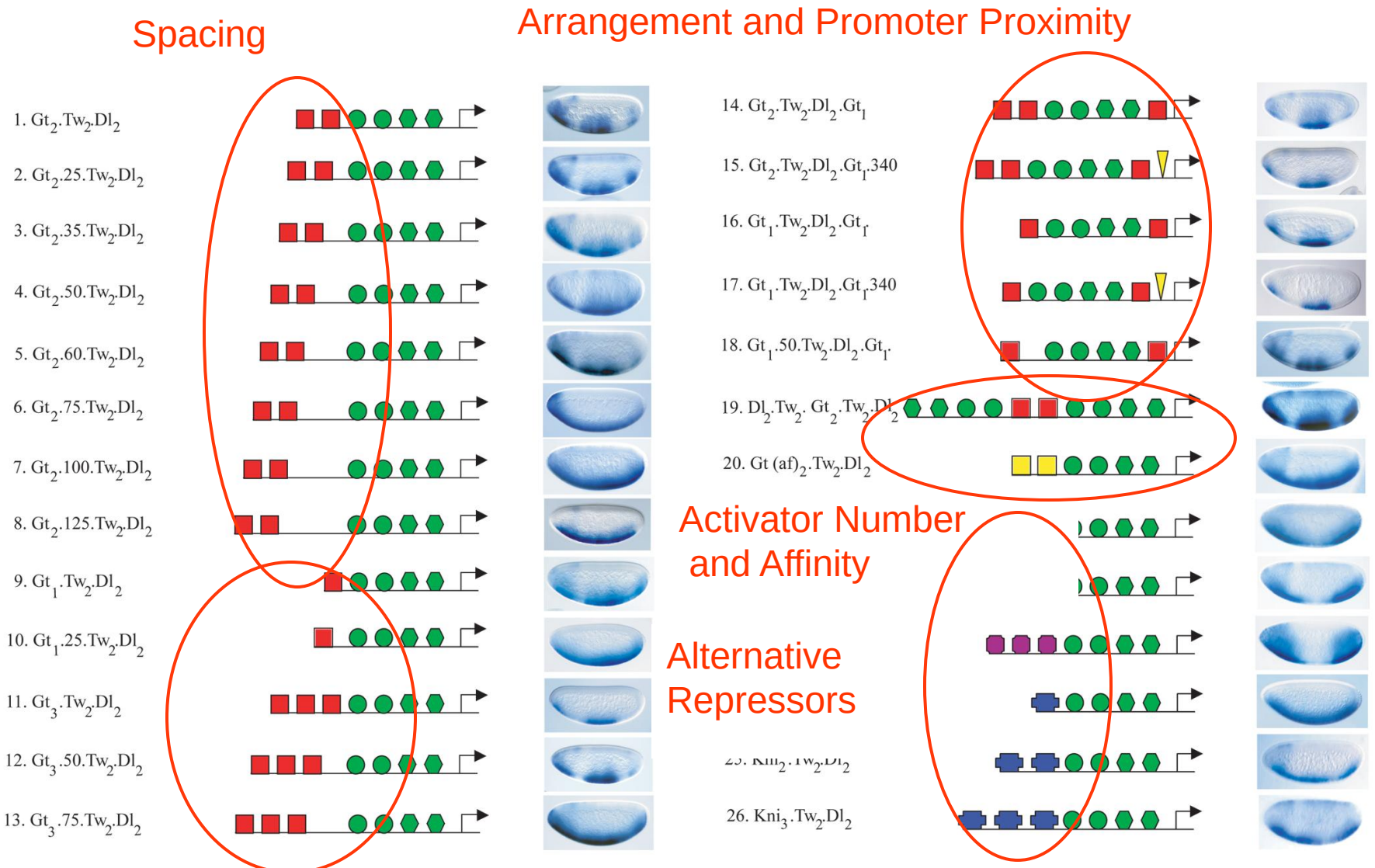


Quantitative



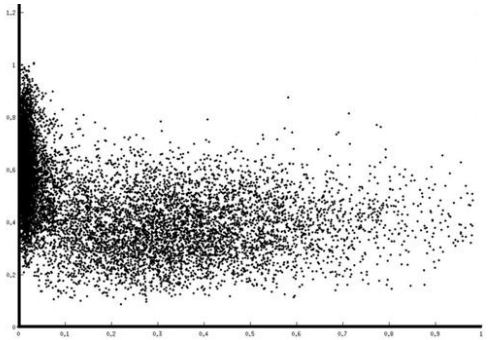
Walid Fakhouri

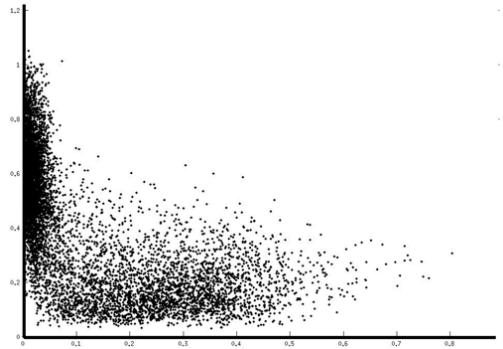
Empirical Testing of Transcriptional Grammar

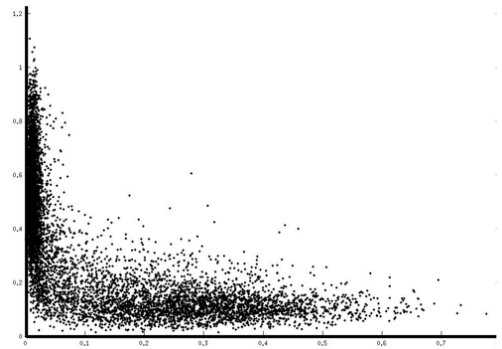


Walid Fakhouri and Rupinder Sayal

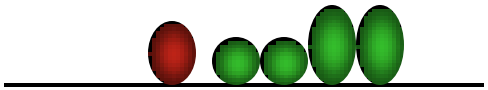
Gene expression as a function of [Giant]

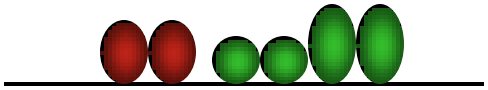


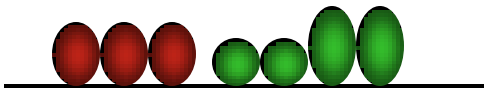




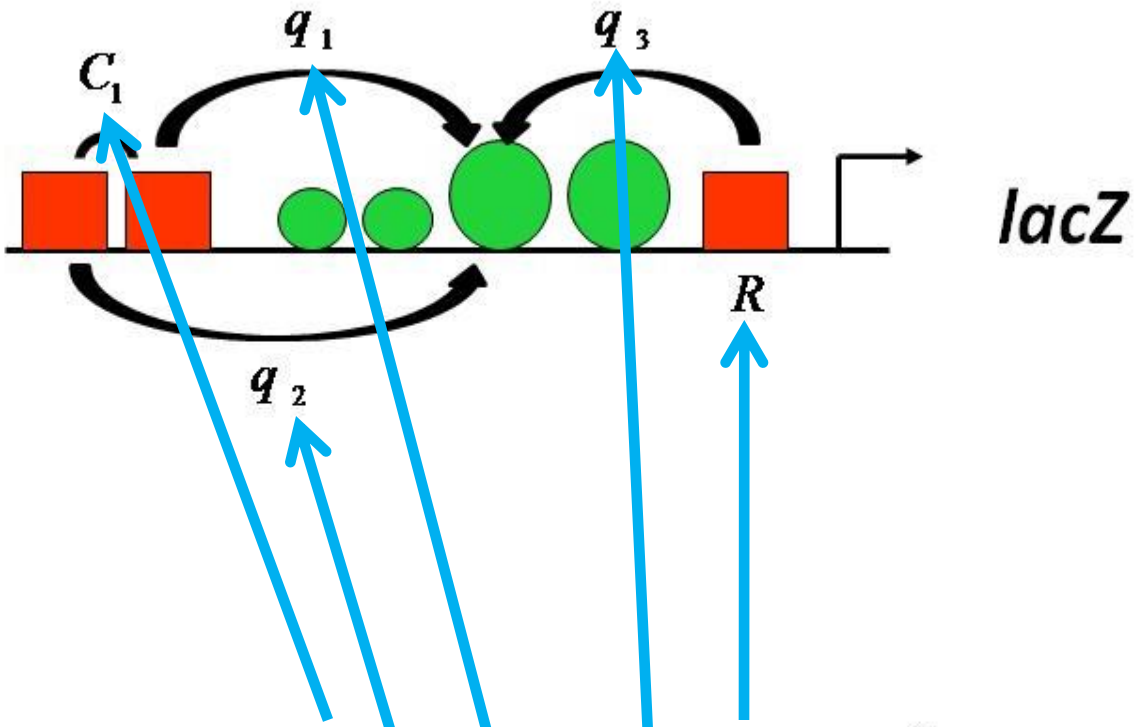
[Giant]





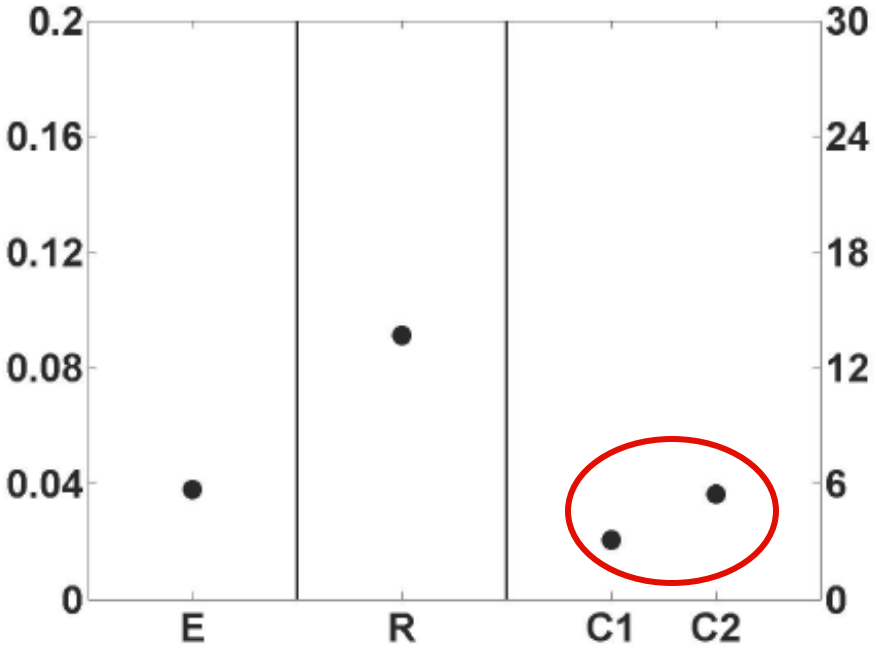


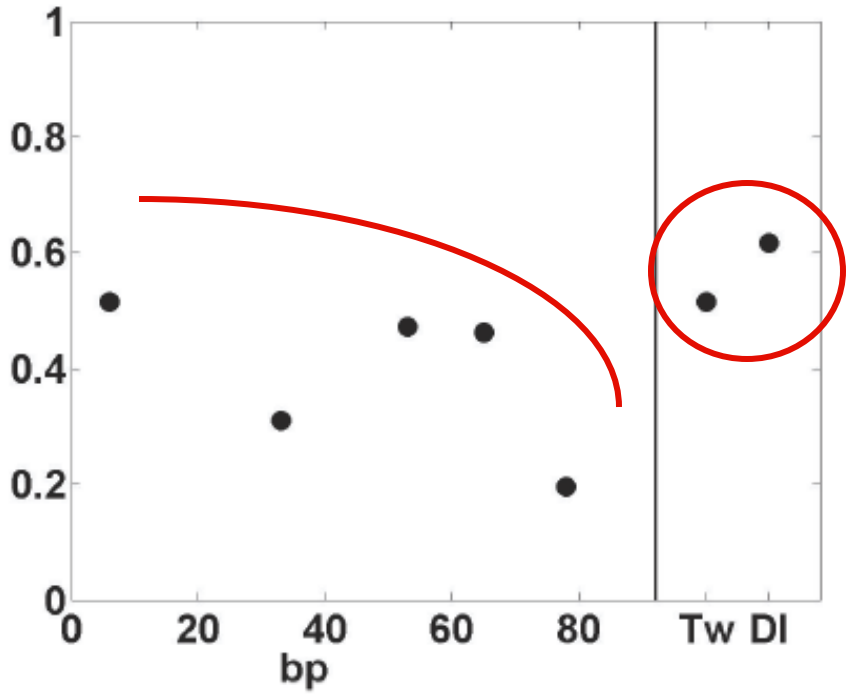
Example of modeling for one construct



$$\frac{K_A[A]}{1+K_A[A]} \times \frac{1+\{q_1+q_2+q_3\}RK_{Gt}[Gt]+\{C_1q_1q_2+q_1q_3+q_2q_3\}(RK_{Gt}[Gt])^2+C_1q_1q_2q_3(RK_{Gt}[Gt])^3}{1+3RK_{Gt}[Gt]+\{C_1+1+1\}(RK_{Gt}[Gt])^2+C_1(RK_{Gt}[Gt])^3}$$

C : Cooperativity, R : Repressor Scaling Factor, q : Quenching Efficiency





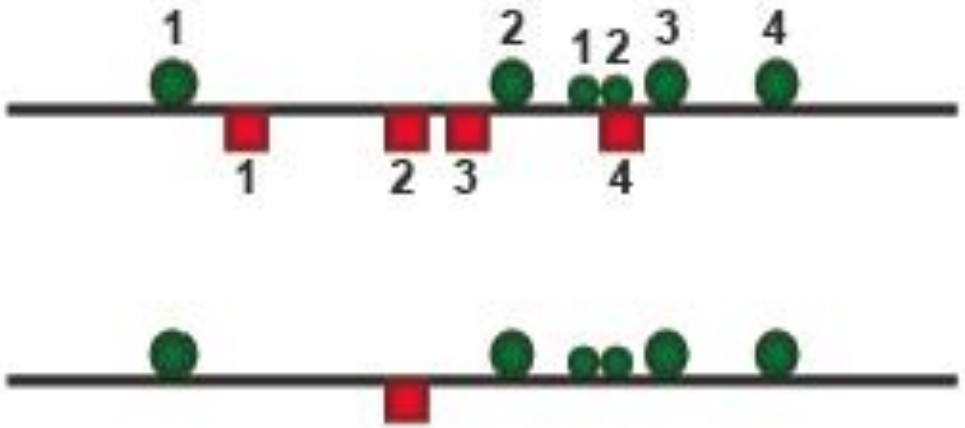
Repressor Scaling Factor

Quenching

Activator specificity

Root mean square error

Giant-Giant cooperativity



Mesodermal Expression

0.16% ± 0.01%

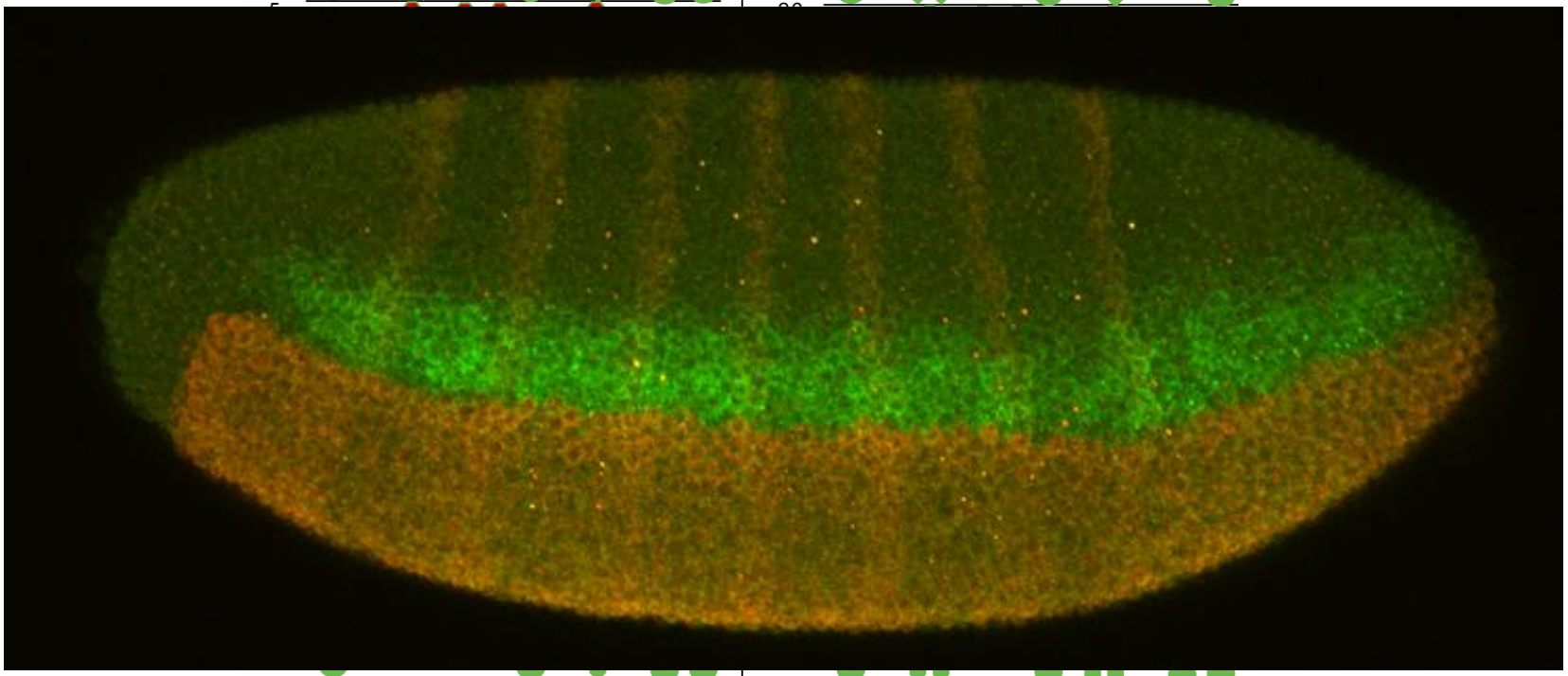
11% ± 0.9%

Parameters

Scaling Factors
Dorsal : 1.2 ± 0.13
Twist : 75 ± 18
Snail : 54 ± 6.5

Cooperativity
Dorsal2-Twist1 : 7 ± 1.3
Dorsal3-Twist2 : 74 ± 16
Twist1-Twist2 : 69 ± 22
Snail2-Snail3 : 65 ± 20

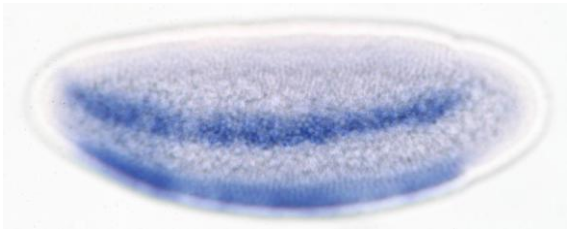
Ip, Gray and Levine



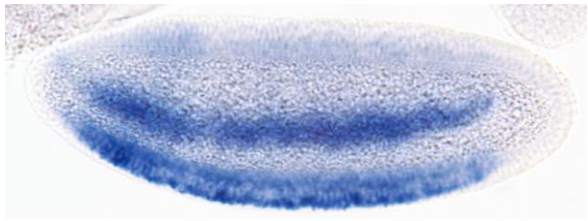
Rupinder Sayal

Enhancer robustness

Wild-Type



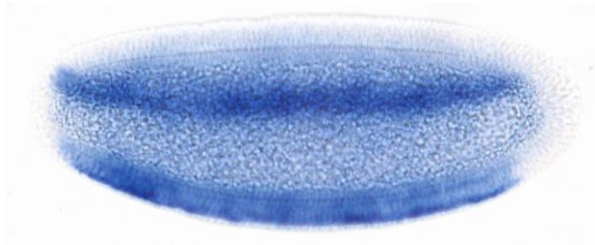
Dl3



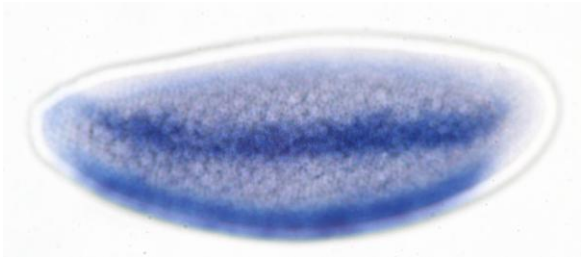
Twi1

Dl1

Dl4



Twi2

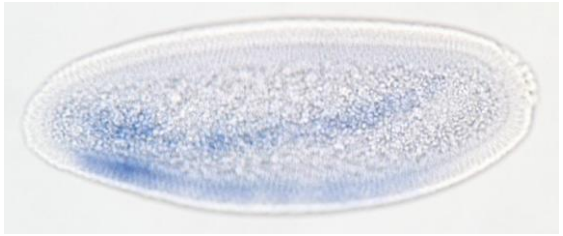


Dl2

bHLH duo

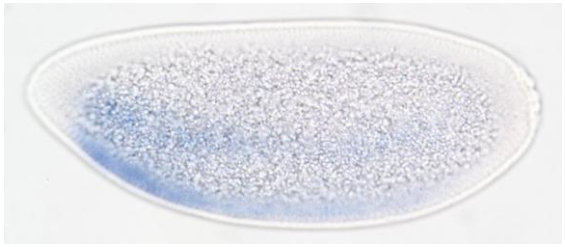
Probing the limits to enhancer robustness

Wild-Type



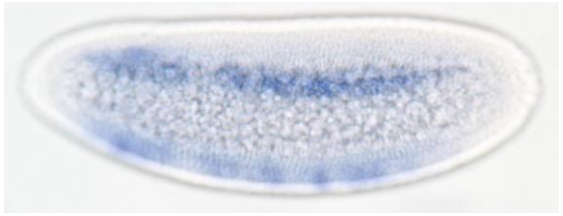
Dl1, Twi2

Dl2, Twi2

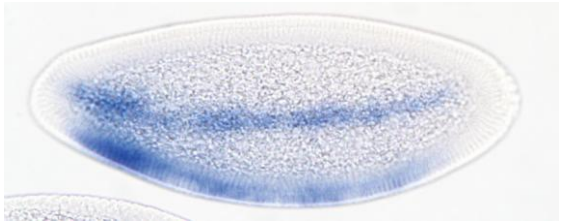


Dl1, Dl2

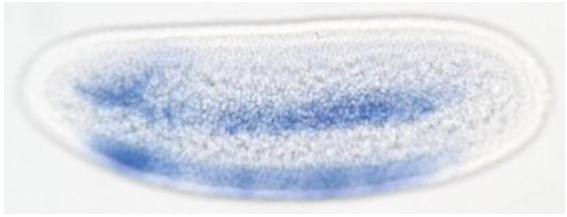
Dl2, Dl3



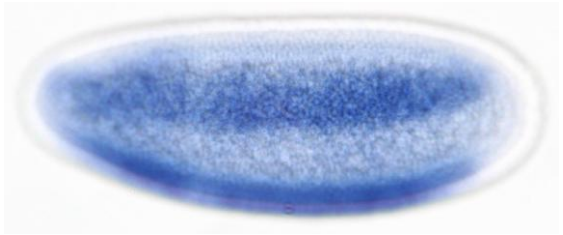
Dl3, Twi2



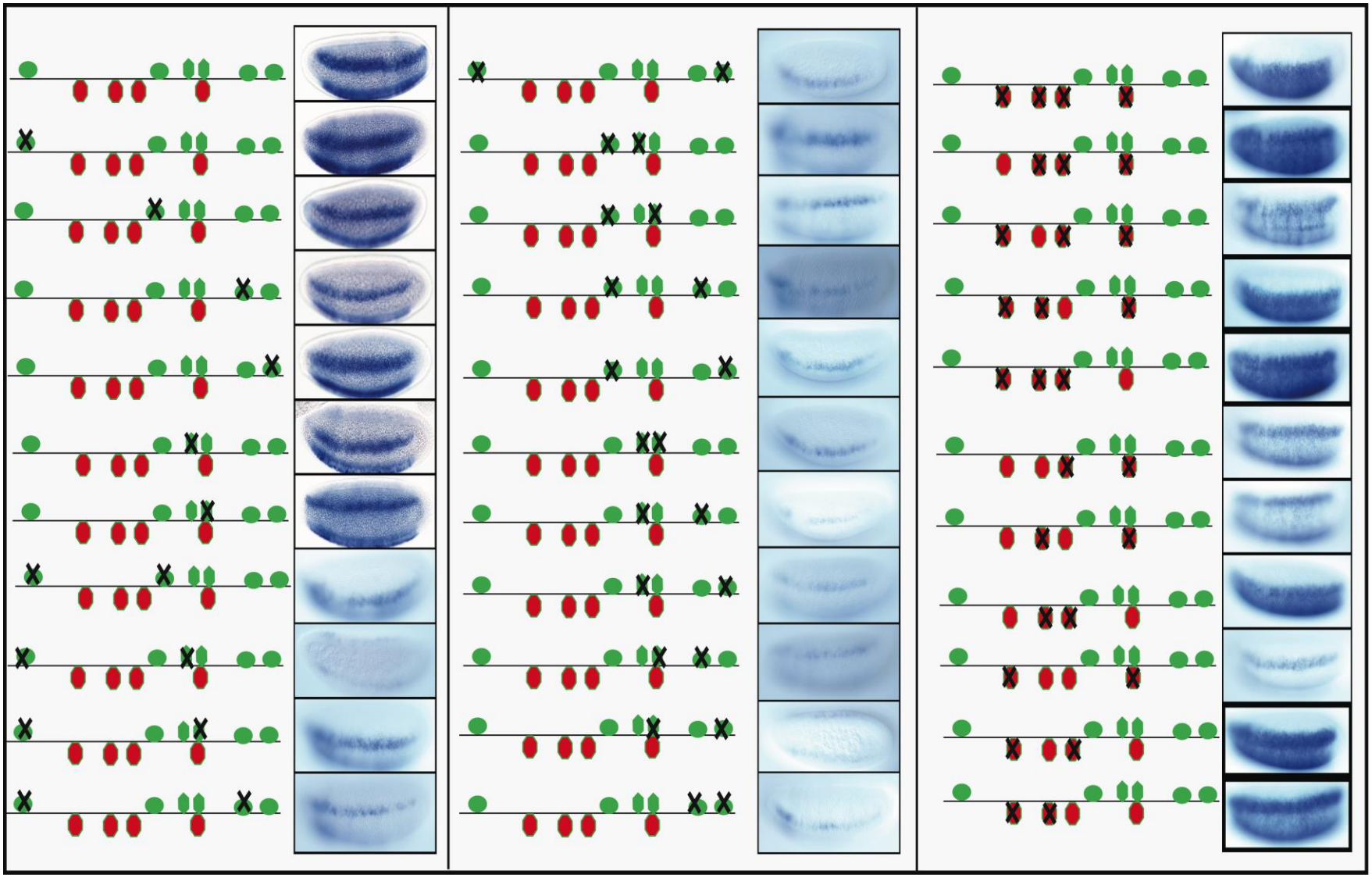
Dl1, Dl3

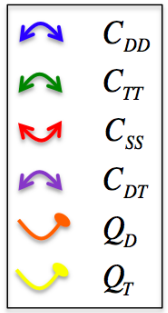


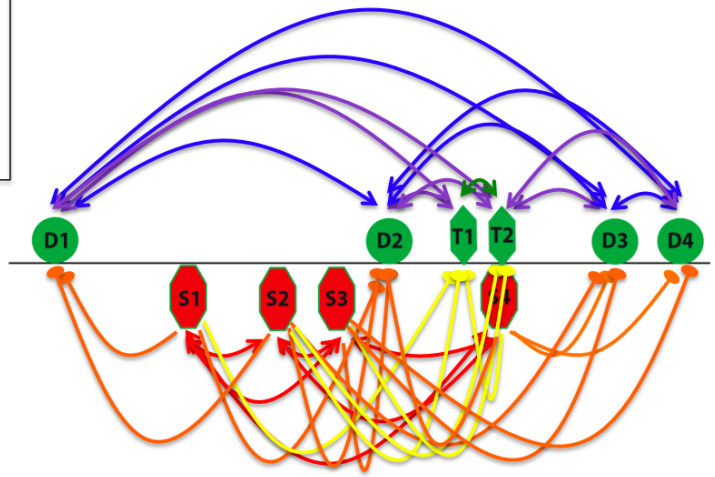
Dl2, Twi1



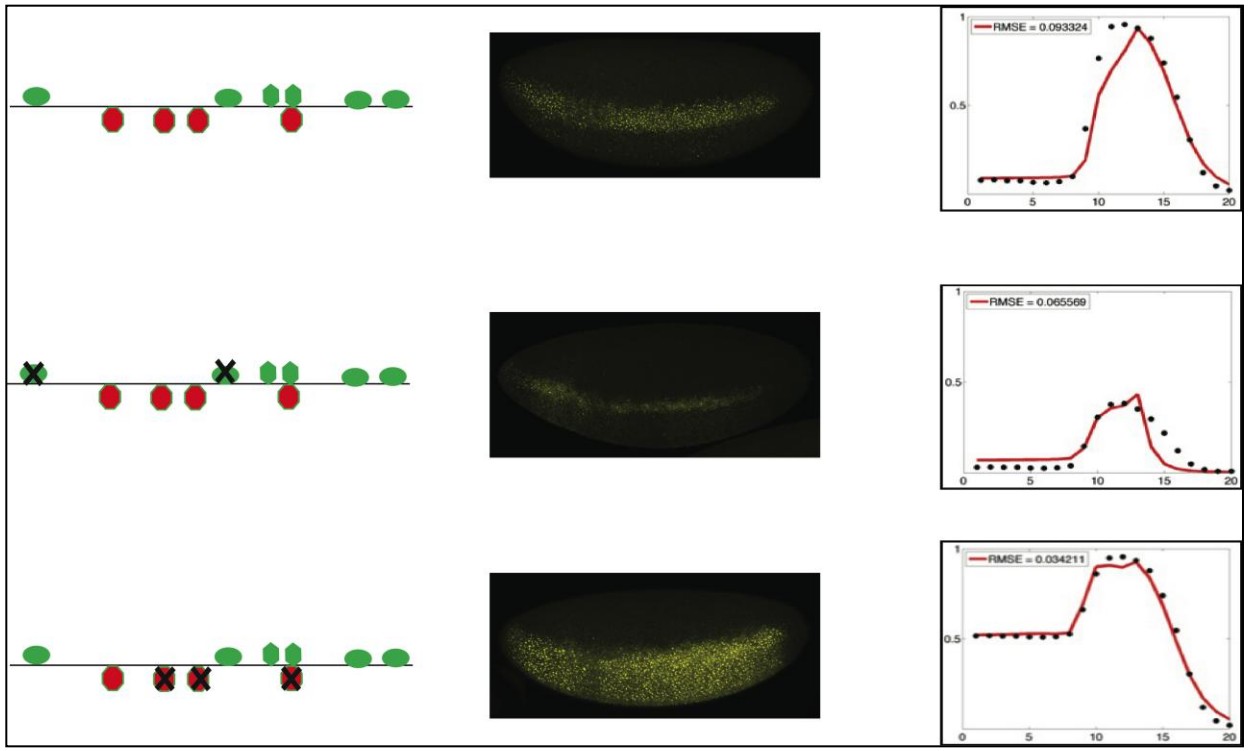
Dl1, bHLH Duo







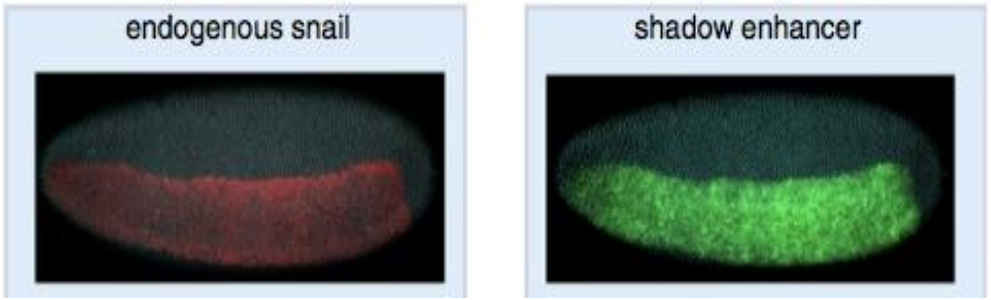
Test specific hypotheses about protein interactions on the enhancer

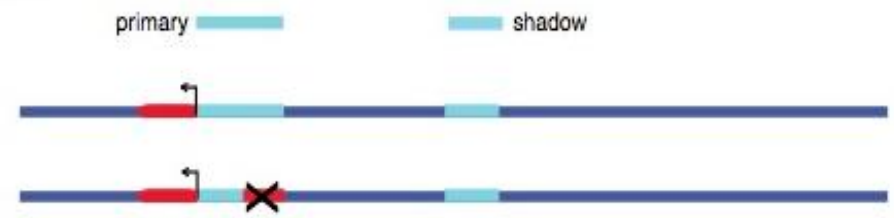


Two-layer model to incorporate *cis*-regulatory and temporal information

How does variation in *cis*-regulatory information affect development?

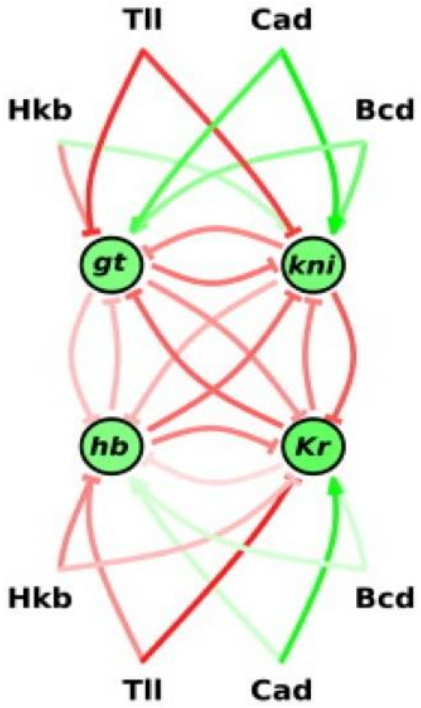
Jacqueline Dresch





Perry et al, *Current Biology* 2010

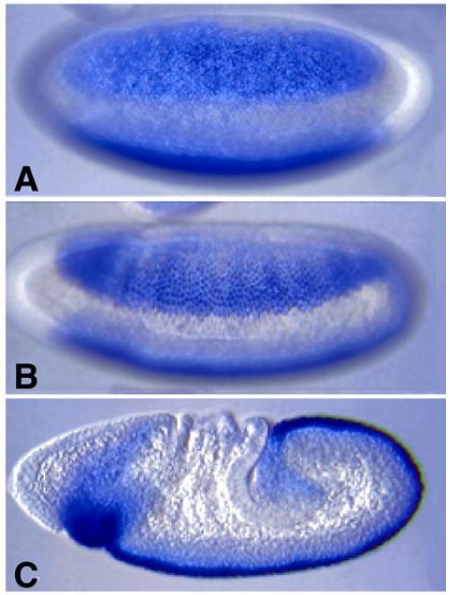
Comprehensively incorporate *cis*-regulatory information



Bieler et al, *Biophysical Journal* 2011

Comprehensively incorporate *cis*-regulatory information

Incorporate GRNs and protein interactions

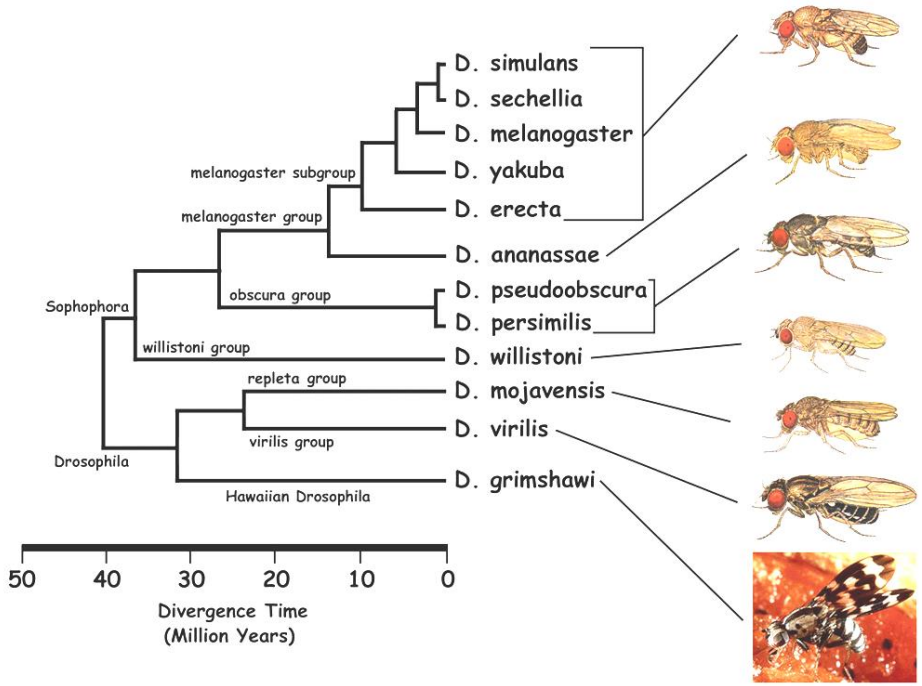


Markstein et al, *PNAS* 2002

Comprehensively incorporate *cis*-regulatory information

Incorporate GRNs and protein interactions

Predict changes through time



http://insects.eugenes.org/DroSpeGe/

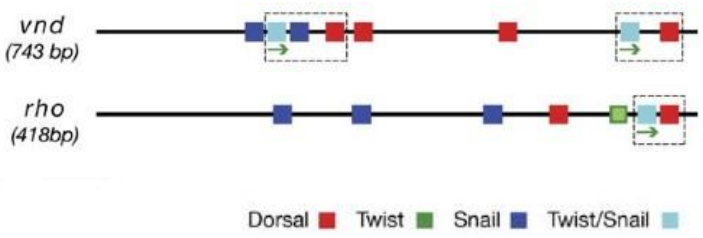
Comprehensively incorporate *cis*-regulatory information

Incorporate GRNs and protein interactions

Predict changes through time

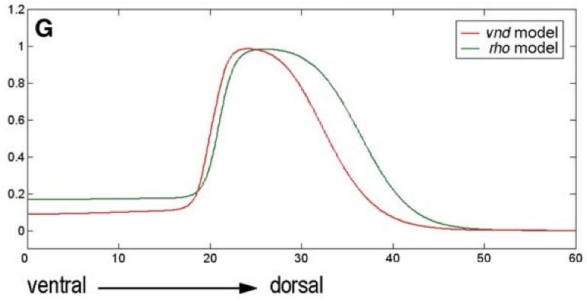
Understand the impact of evolution on gene expression

1.



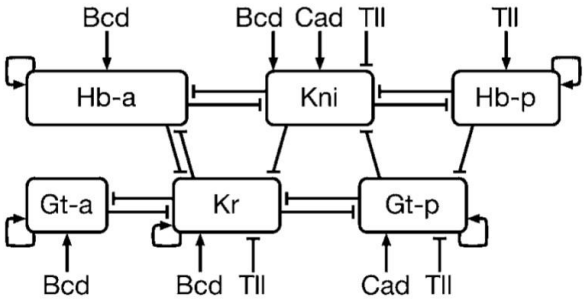
Thermodynamic

Model



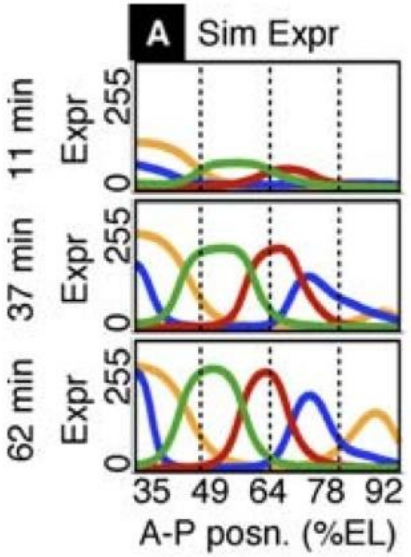
Zinzen et al, *Current Biology* 2006

2.



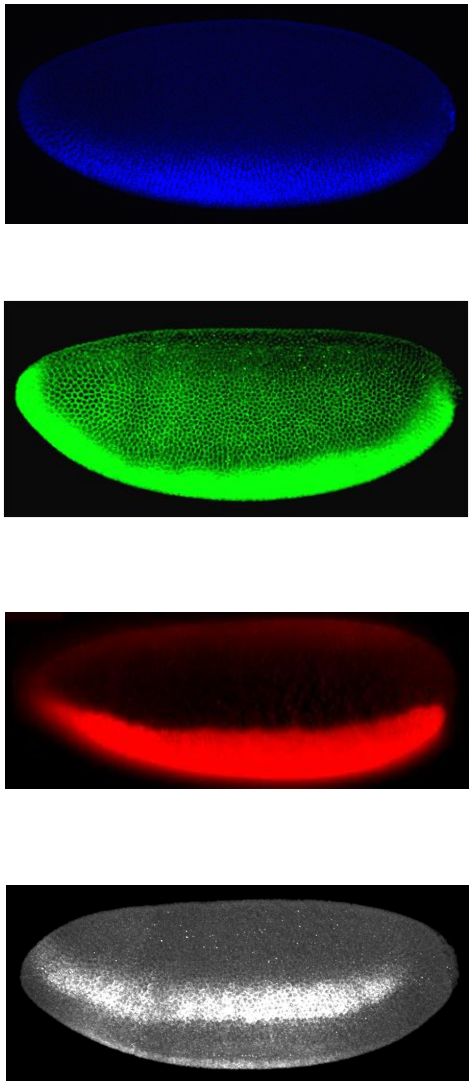
Differential Equation

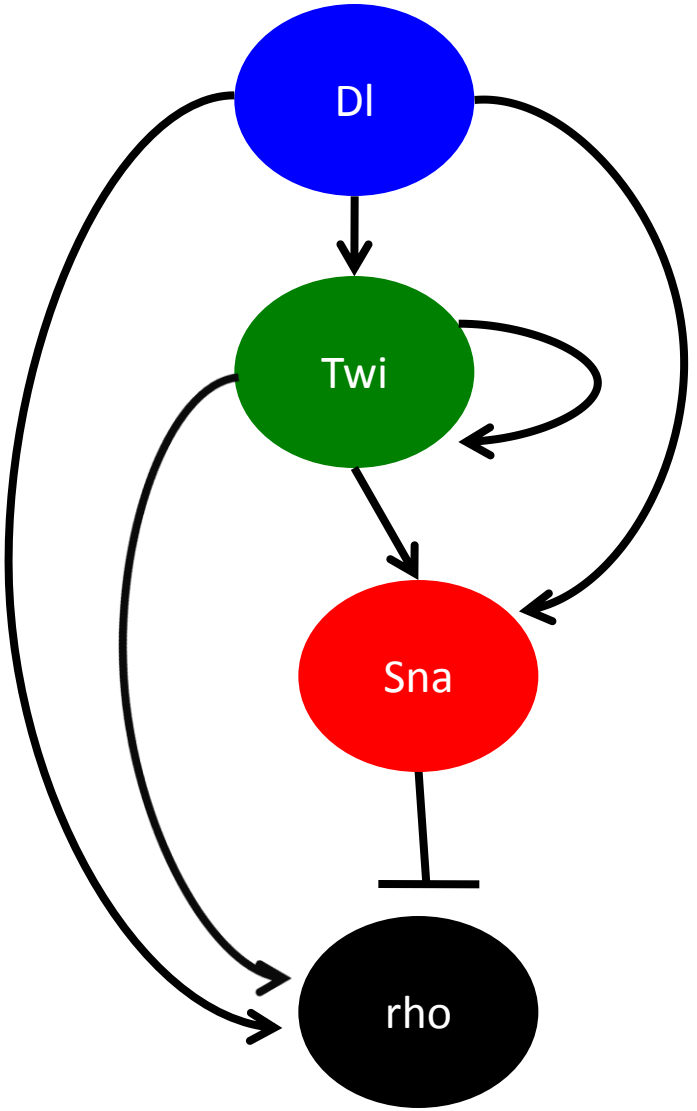
Model



Perkins et al, *PLoS Comp Bio* 2006

Simple Gene Network:





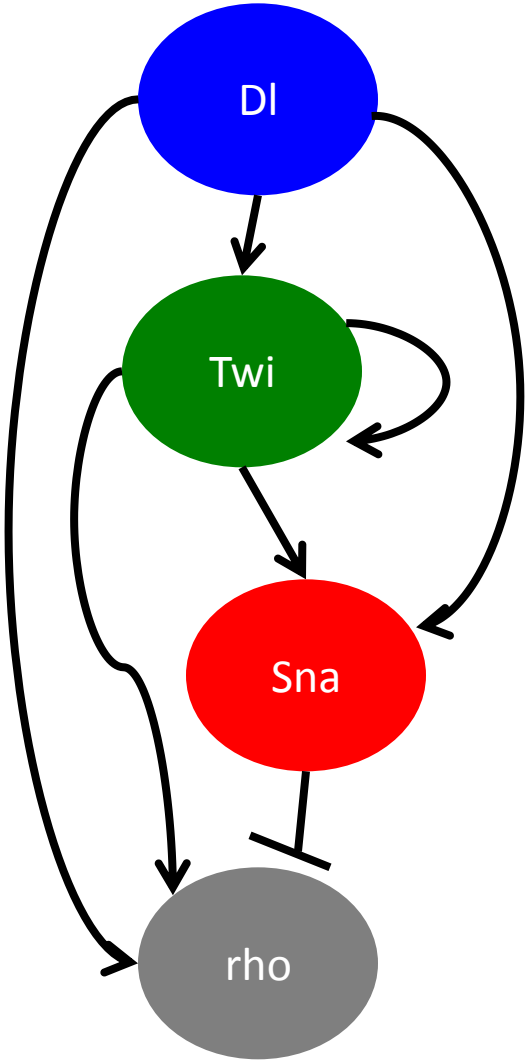
Dorsal, twist, snail, and *rhomboid*

\+ + − (target)

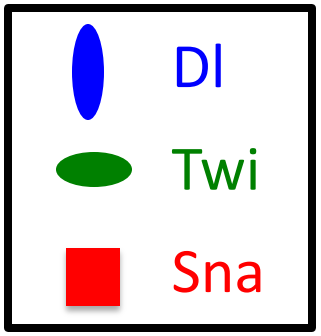
Dorsal levels relatively invariant during modeled interval

Feedback loop

Coherent and incoherent feed-forward loops



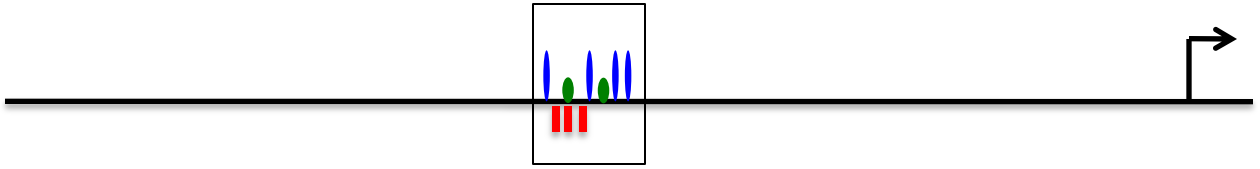
Predicted binding sites on each enhancer



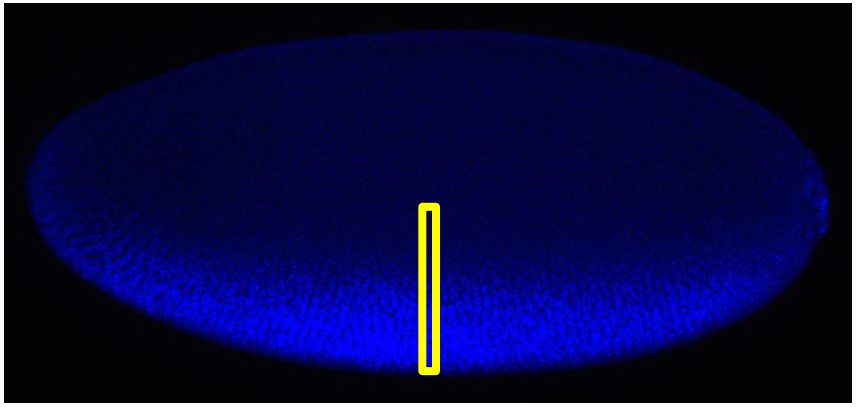
twi

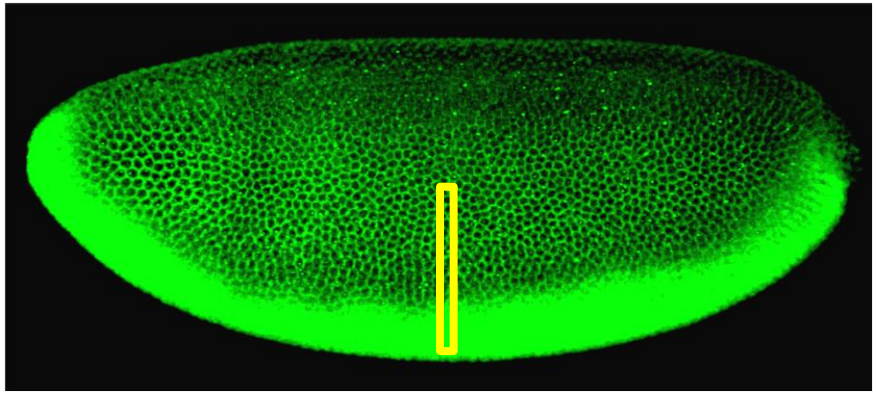
sna

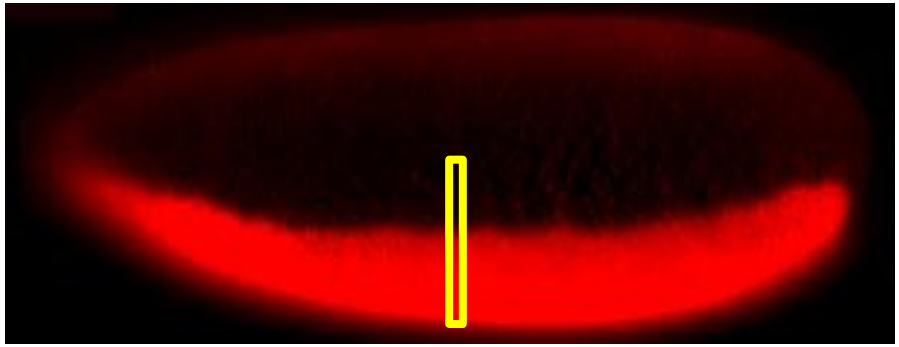
rho

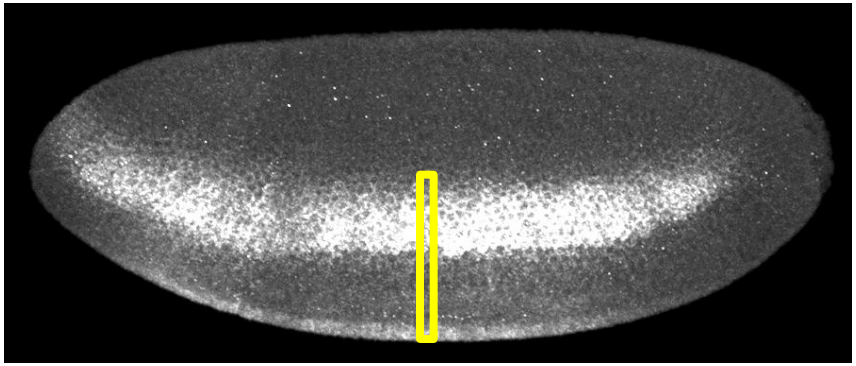


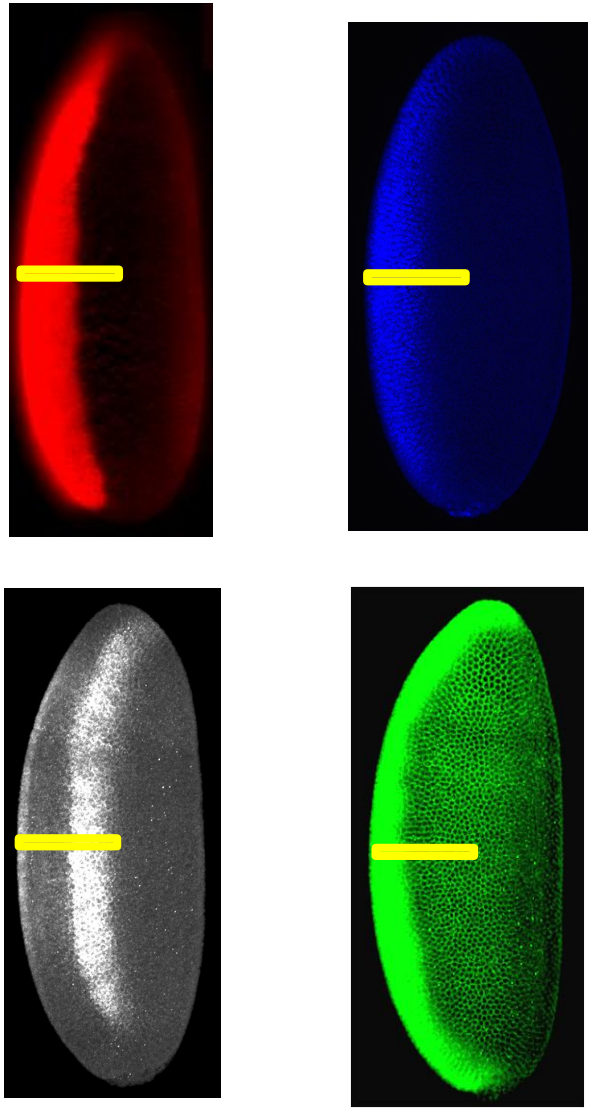
Expression Profiles

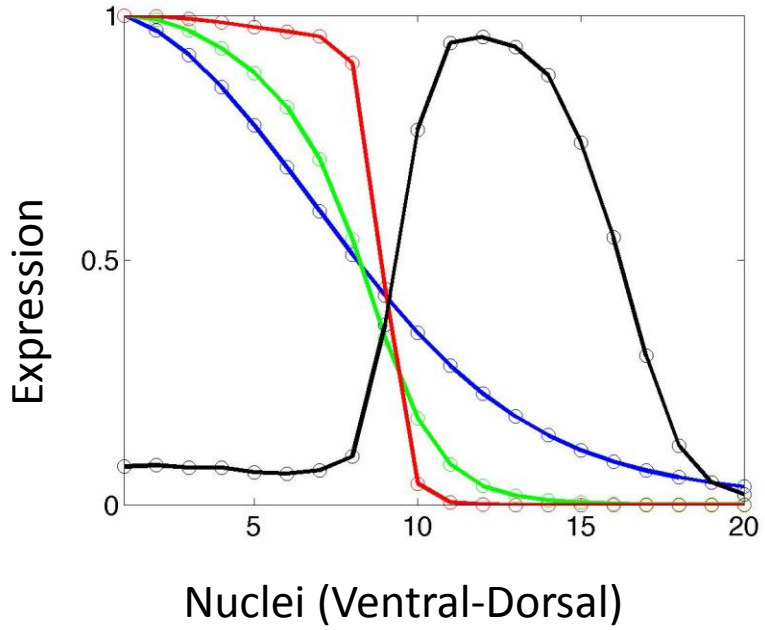











Expression
1
0.5
0
5
10
15
20
Nuclei (Ventral-Dorsal)

Two-Layer Model…

mRNA rate of change

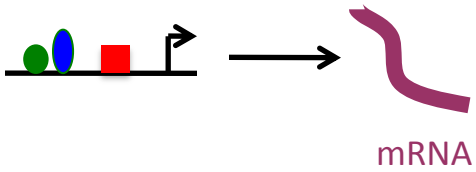
$$\frac{\partial m_i^a}{\partial t} = S^a(p_i) + D^{m,a}\left[\left(m_{i-1}^a - m_i^a\right) + \left(m_{i+1}^a - m_i^a\right)\right] - \lambda^{m,a} m_i^a$$

$$\frac{\partial p_i^a}{\partial t} = T^a m_i + D^{p,a}\left[\left(p_{i-1}^a - p_i^a\right) + \left(p_{i+1}^a - p_i^a\right)\right] - \lambda^{p,a} p_i^a$$

protein rate of change

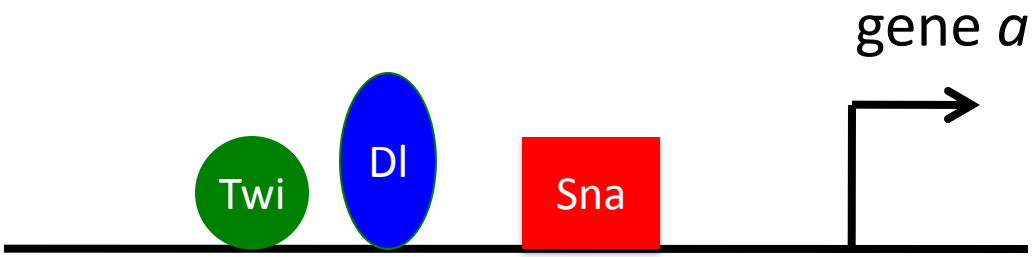
$$\frac{\partial m_i^a}{\partial t} = S^a(p_i) + D^{m,a}\left[\left(m_{i-1}^a - m_i^a\right) + \left(m_{i+1}^a - m_i^a\right)\right] - \lambda^{m,a} m_i^a$$

Thermo Model

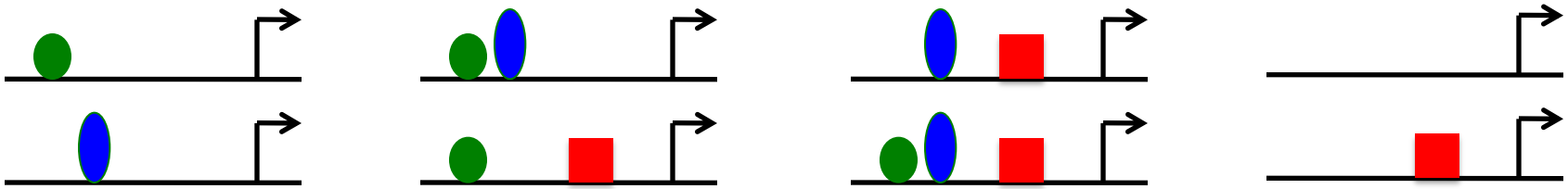


Thermodynamic synthesis term

(similar to those of Fakhouri & Ay 2010 and Janssens 2006)



$$S^a(p_i) = \frac{\text{successful states}}{\text{all possible states}}$$

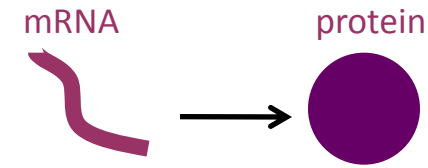


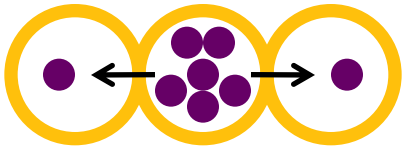
$$S^a(p_i) = \frac{K_T[T] + K_D[D] + CK_TK_D[T][D] + Q_TK_TK_S[T][S] + Q_DK_DK_S[D][S] + CQ_DK_TK_DK_S[T][D][S]}{1 + K_T[T] + K_D[D] + K_S[S] + CK_TK_D[T][D] + K_TK_S[T][S] + K_DK_S[D][S] + K_TK_DK_S[T][D][S]}$$

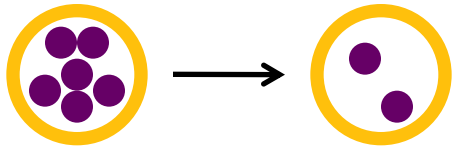
$$\frac{\partial m_i^a}{\partial t} = S^a(p_i) + D^{m,a}\left[\left(m_{i-1}^a - m_i^a\right) + \left(m_{i+1}^a - m_i^a\right)\right] - \lambda^{m,a} m_i^a$$

mRNA Diffusion rate

mRNA Decay rate







Translation rate

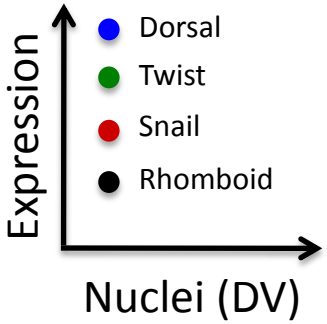
protein Diffusion rate

protein Decay rate

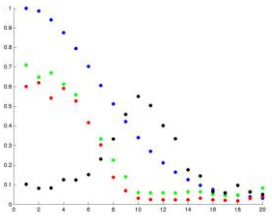
$$\frac{\partial p_i^a}{\partial t} = T^a m_i + D^{p,a}\left[\left(p_{i-1}^a - p_i^a\right) + \left(p_{i+1}^a - p_i^a\right)\right] - \lambda^{p,a} p_i^a$$

Preliminary Results

Data Used for Fitting:
(from BDTNP)



Predictions after Fitting: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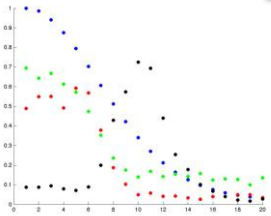
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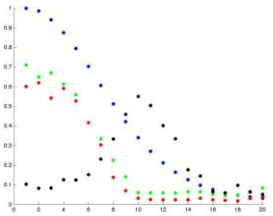
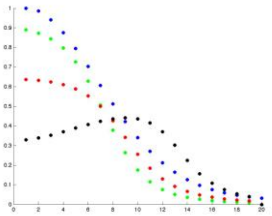

t = 0 min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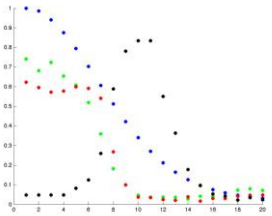
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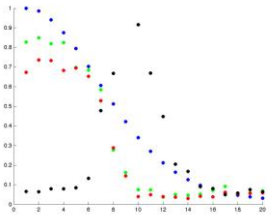
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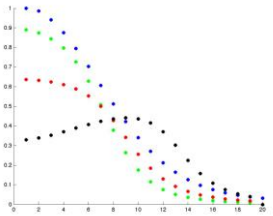
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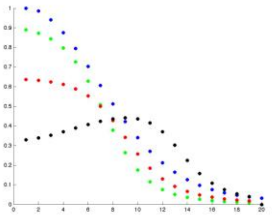
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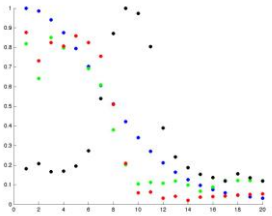
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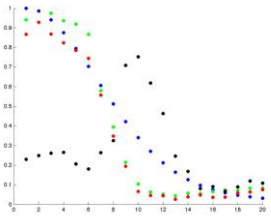
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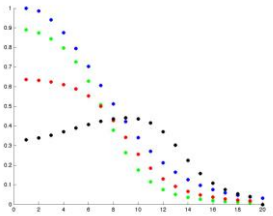
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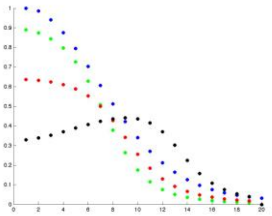

t = 50 min

Sensitivity analysis of biological models:

(How much model output changes as particular parameters are tweaked)

OPEN ACCESS Freely available online

PLoS COMPUTATIONAL BIOLOGY

Universally Sloppy Parameter Sensitivities in Systems Biology Models

Ryan N. Gutenkunst[1*], Joshua J. Waterfall[2], Fergal P. Casey[3], Kevin S. Brown[4], Christopher R. Myers[5], James P. Sethna[1]

Thermodynamic transcription models have not been similarly analyzed…

Jackie Dresch, Xiaozhou Liu, Ahmet Ay

Dresch *et al. BMC Systems Biology* 2010, **4**:142
http://www.biomedcentral.com/1752-0509/4/142

BMC
Systems Biology

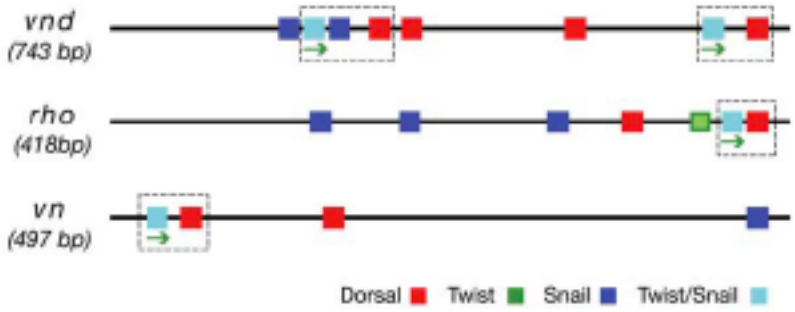
RESEARCH ARTICLE Open Access

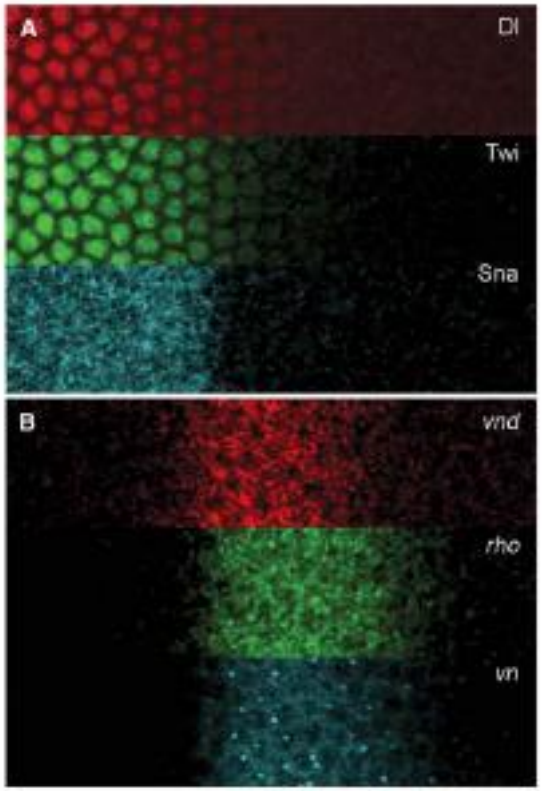
Thermodynamic modeling of transcription: sensitivity analysis differentiates biological mechanism from mathematical model-induced effects

Jacqueline M Dresch[1], Xiaozhou Liu[2], David N Arnosti[2*], Ahmet Ay[3,4*]

Computational Models for Neurogenic Gene Expression in the *Drosophila* Embryo

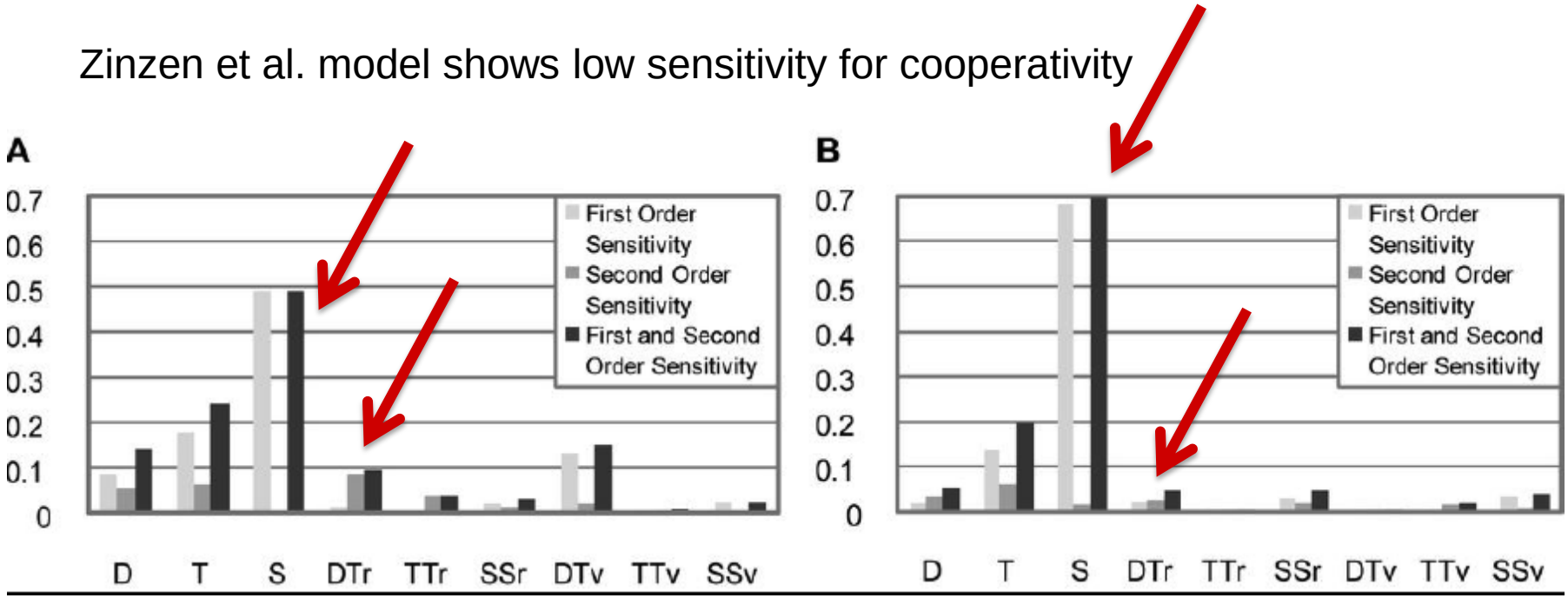
Robert P. Zinzen,[1] Kate Senger,[1] Mike Levine,[1,*] and Dmitri Papatsenko[1]
[1] Center for Integrative Genomics
Department of Molecular and Cell Biology
University of California, Berkeley
Berkeley, California 94720-3204



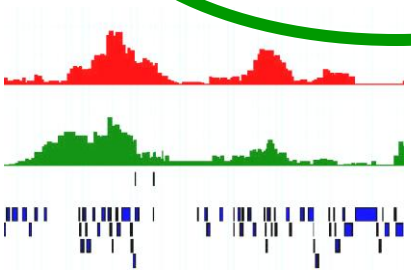


C
u
r
r

Zinzen et al. model shows low sensitivity for cooperativity



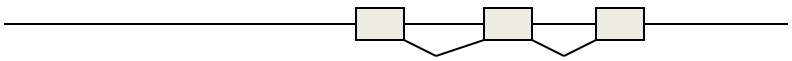
global bioinformatic analysis/ChIP data



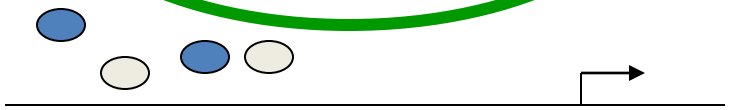
phylogenetic comparisons

Cis regulatory grammar

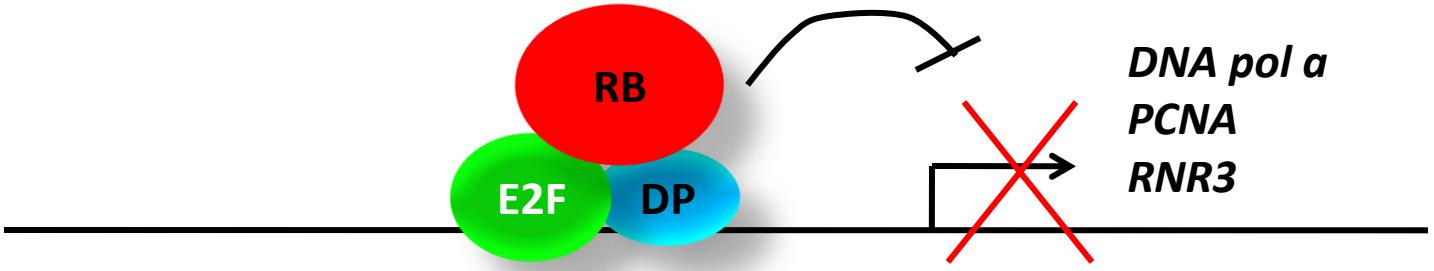
expression patterns

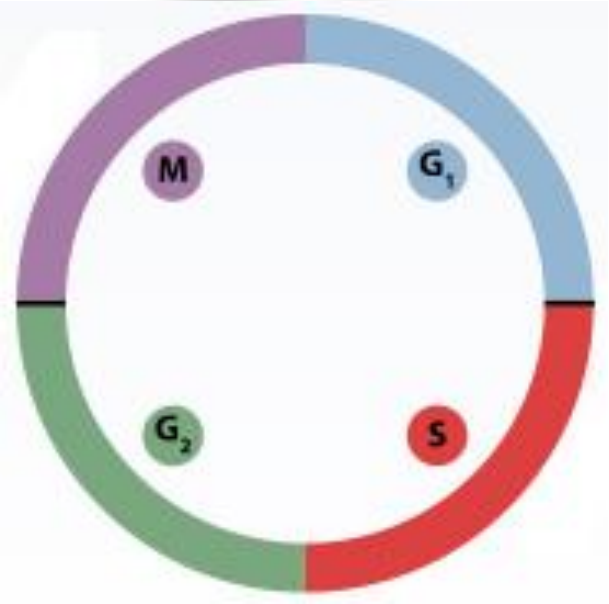


trans-acting factors

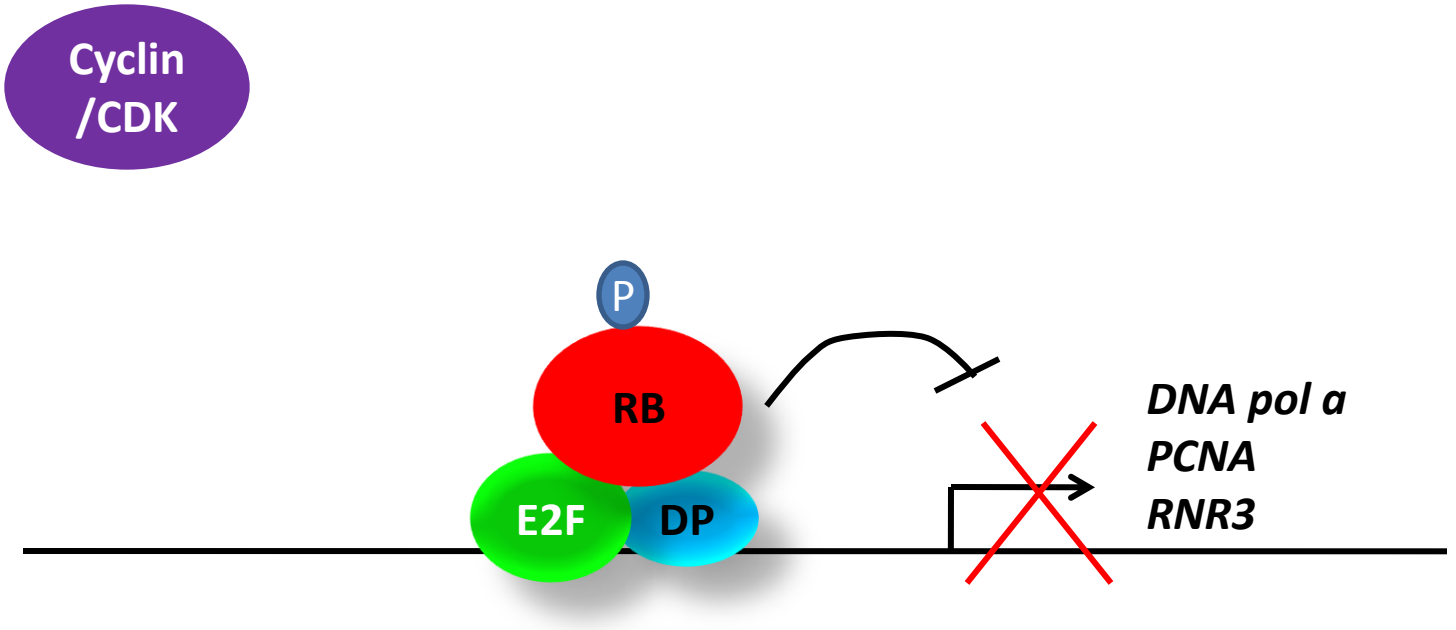


Retinoblastoma (RB) corepressors

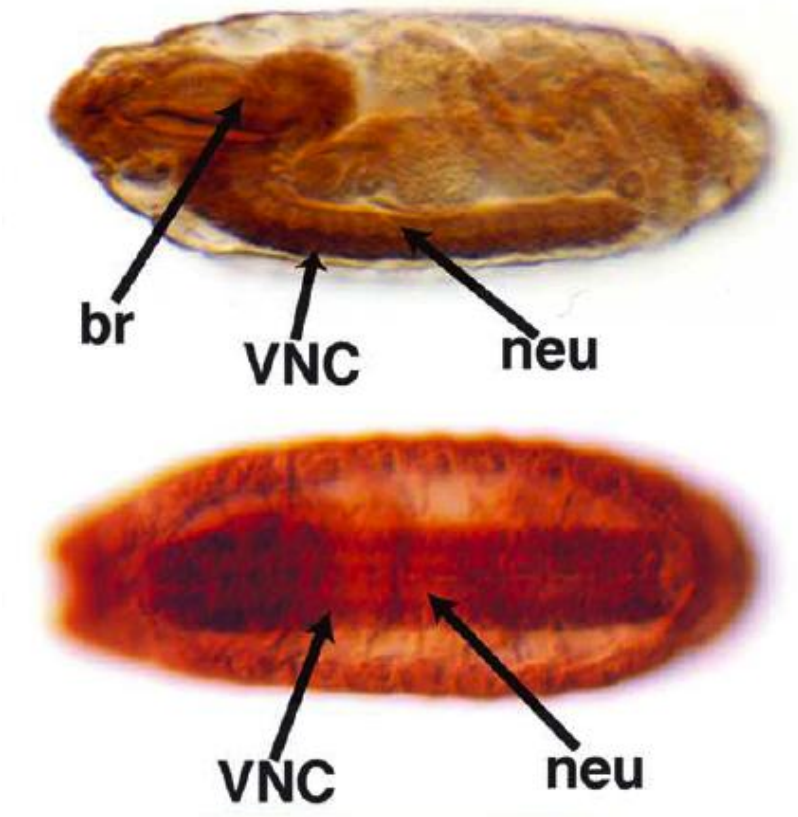


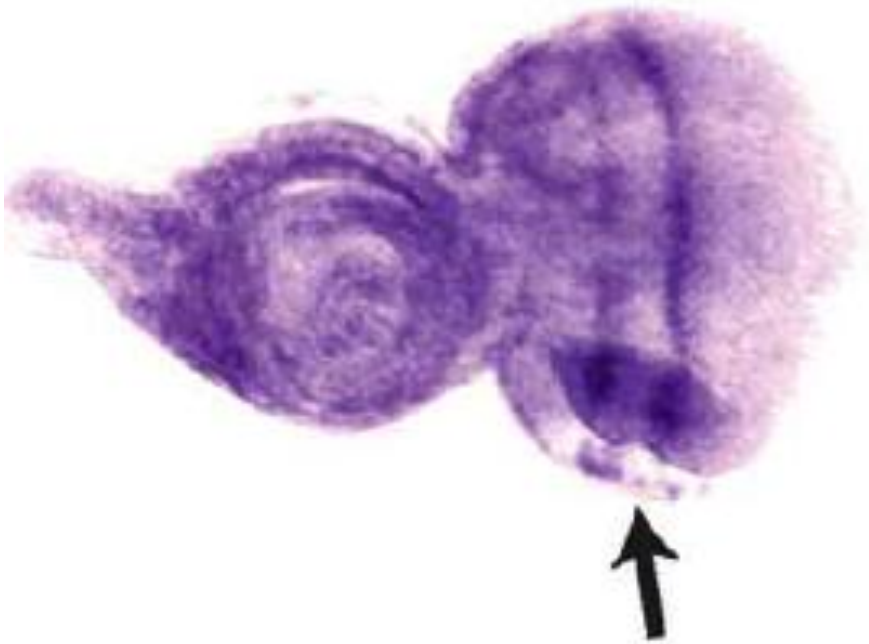


RB regulation by phosphorylation



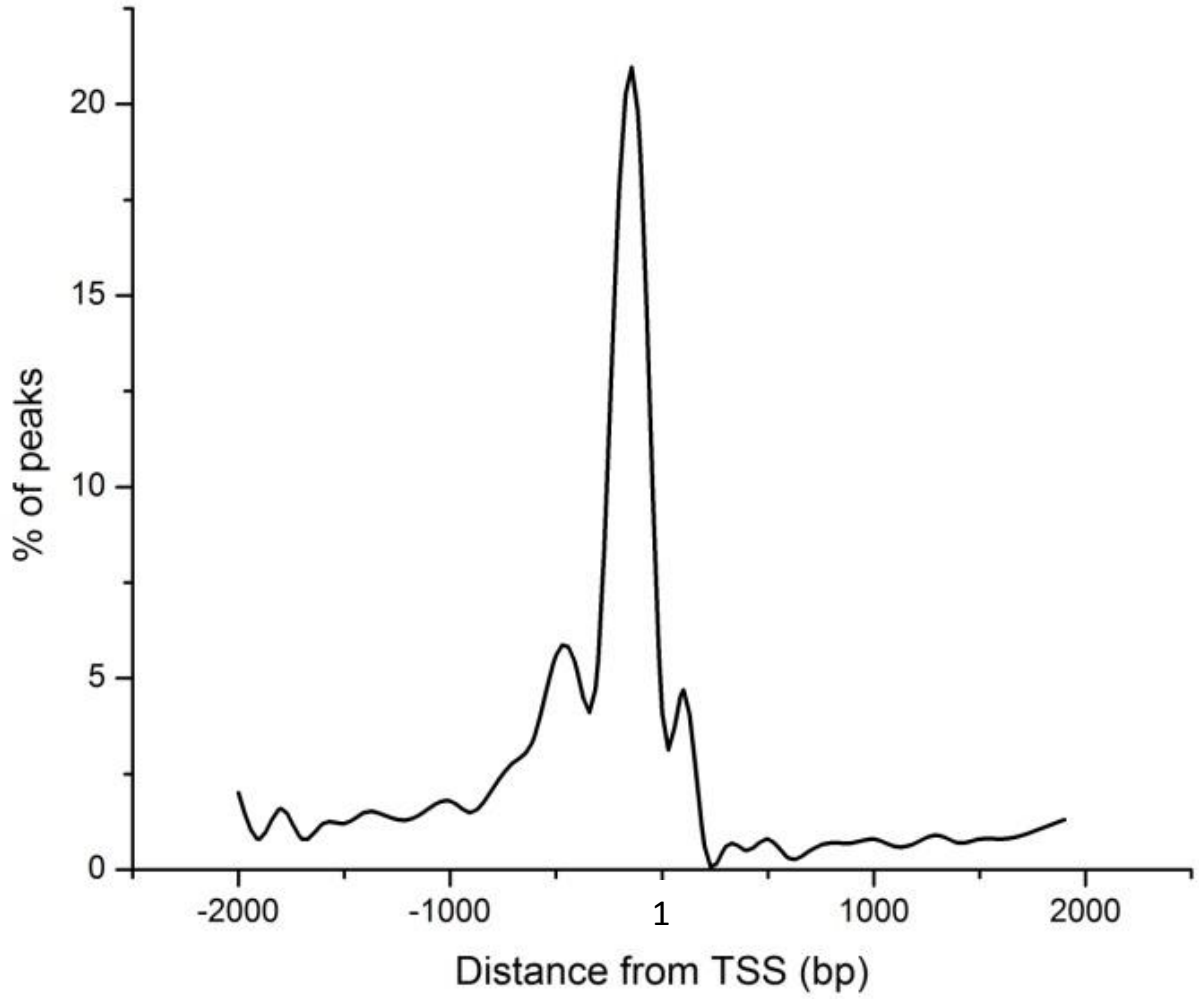
Developmental- and tissue-specific expression of Rbf1

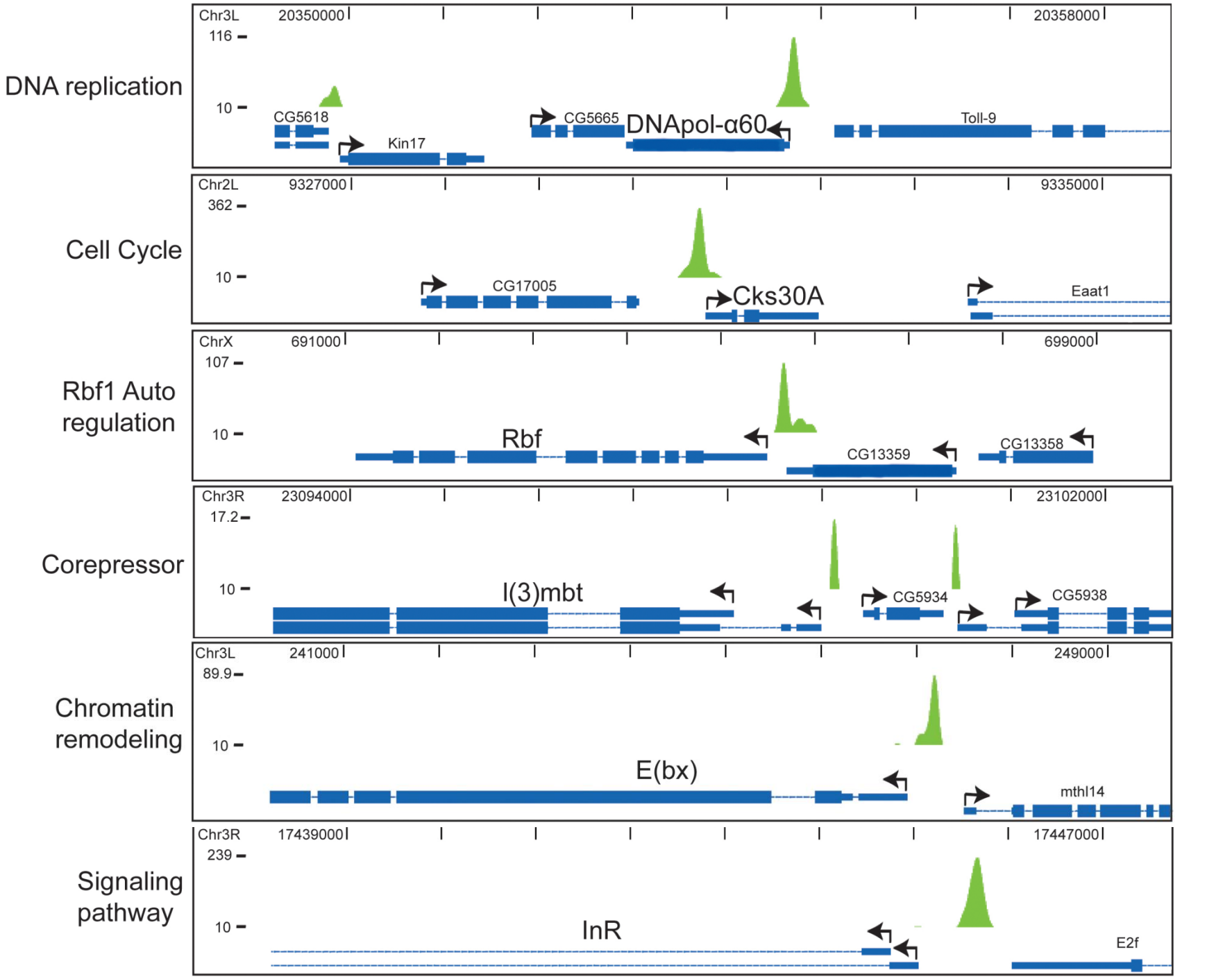


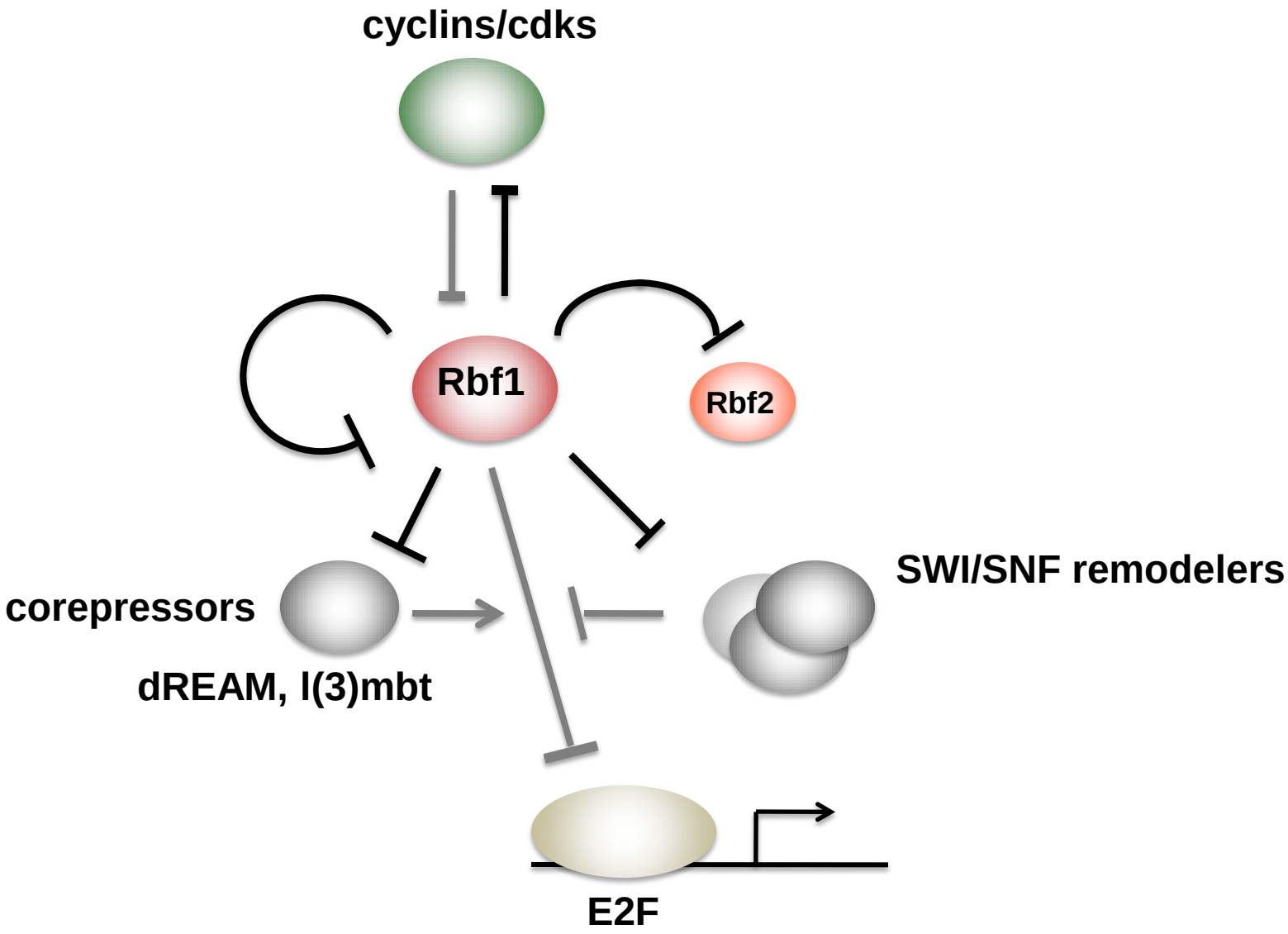


Keller et al. (2004)

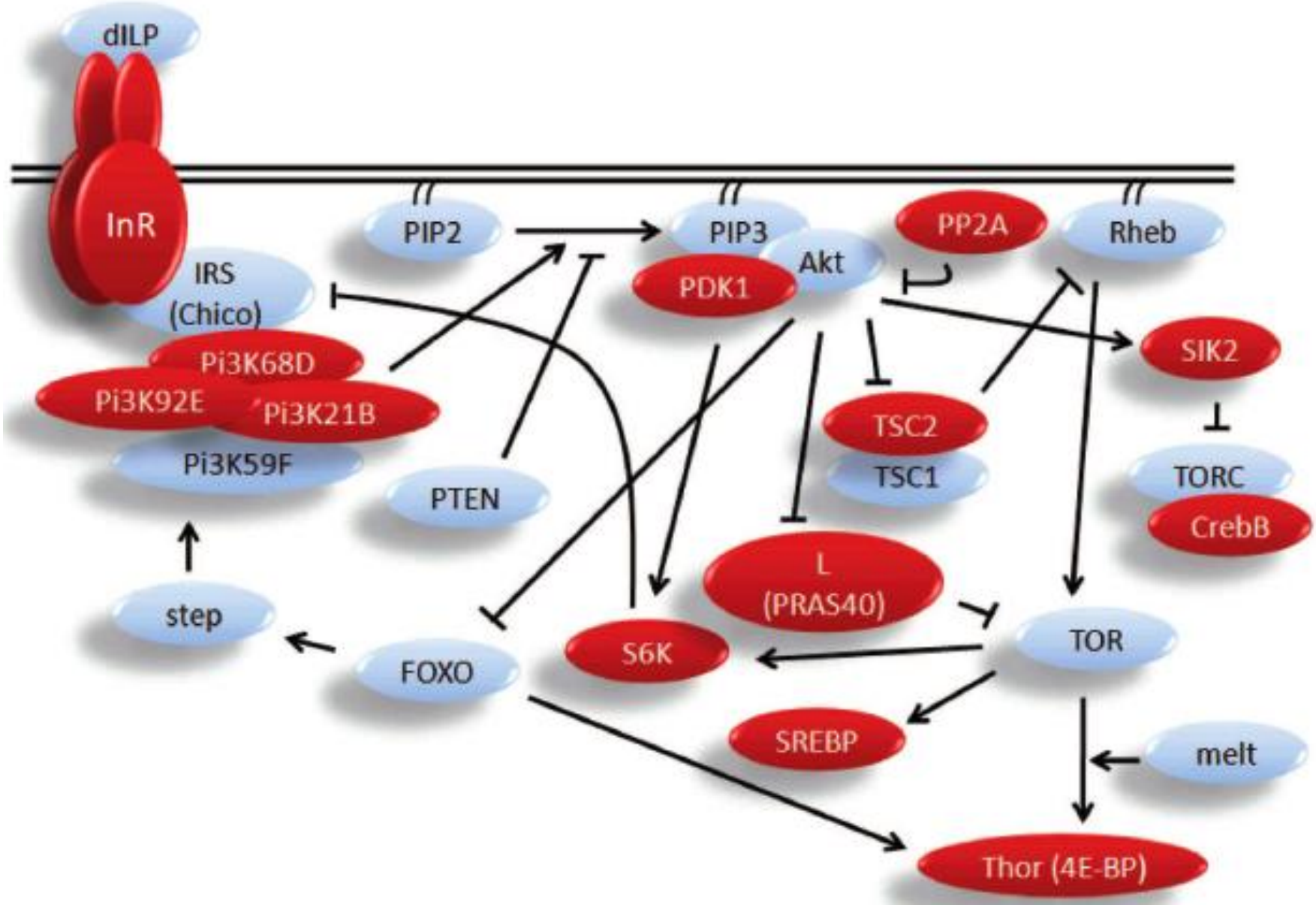
Rbf1 binds close to transcriptional start sites



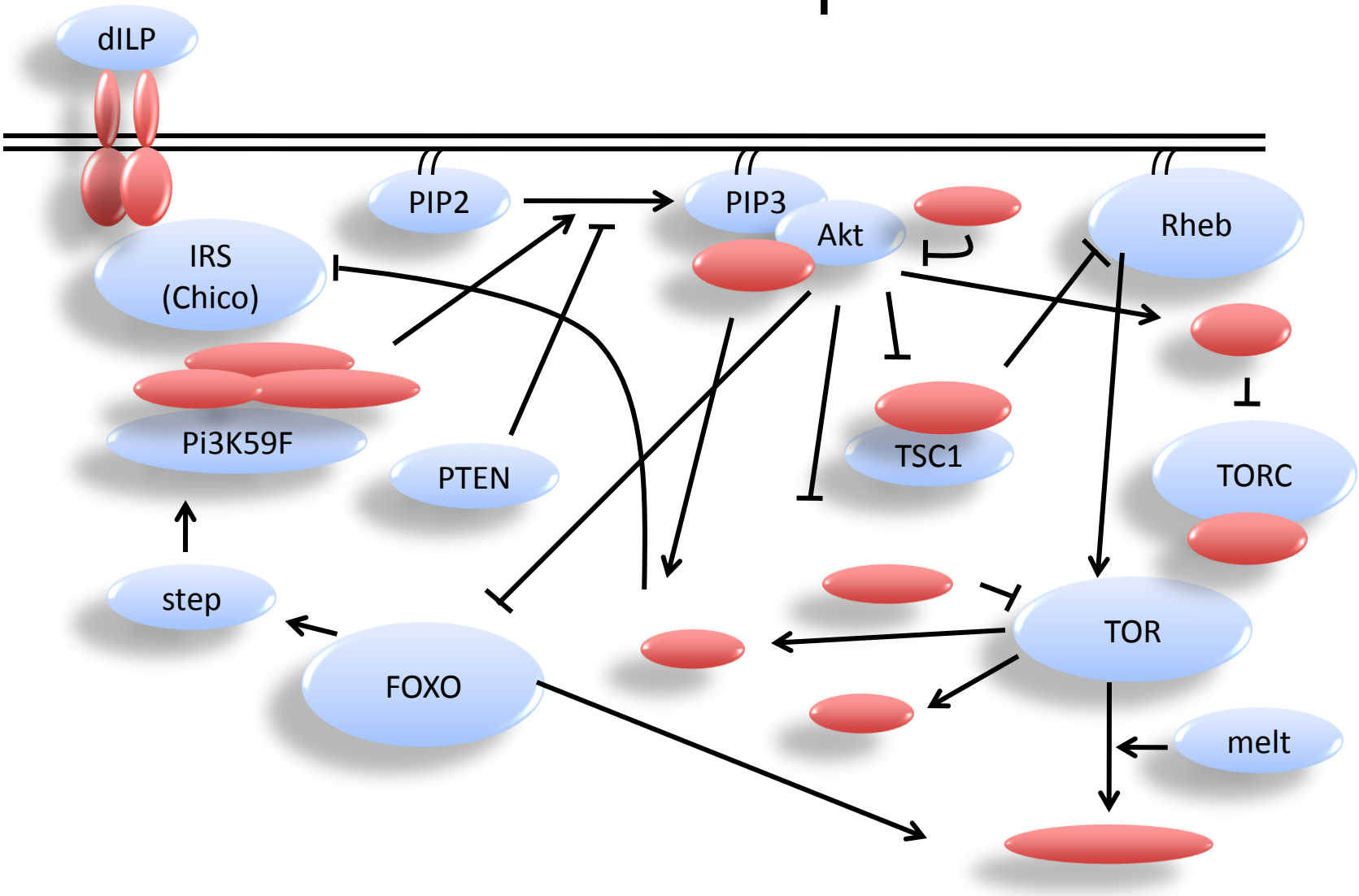

DNA replication
Chr3L
20350000
20358000
116
10
CG5618
Kin17
CG5665
DNApol-α60
Toll-9
Cell Cycle
Chr2L
9327000
9335000
362
10
CG17005
Cks30A
Eaat1
Rbf1 Auto regulation
ChrX
691000
699000
107
10
Rbf
CG13359
CG13358
Corepressor
Chr3R
23094000
23102000
17.2
10
l(3)mbt
CG5934
CG5938
Chromatin remodeling
Chr3L
241000
249000
89.9
10
E(bx)
mthl14
Signaling pathway
Chr3R
17439000
17447000
239
10
InR
E2f


cyclins/cdks
Rbf1
Rbf2
corepressors
dREAM, l(3)mbt
SWI/SNF remodelers
E2F

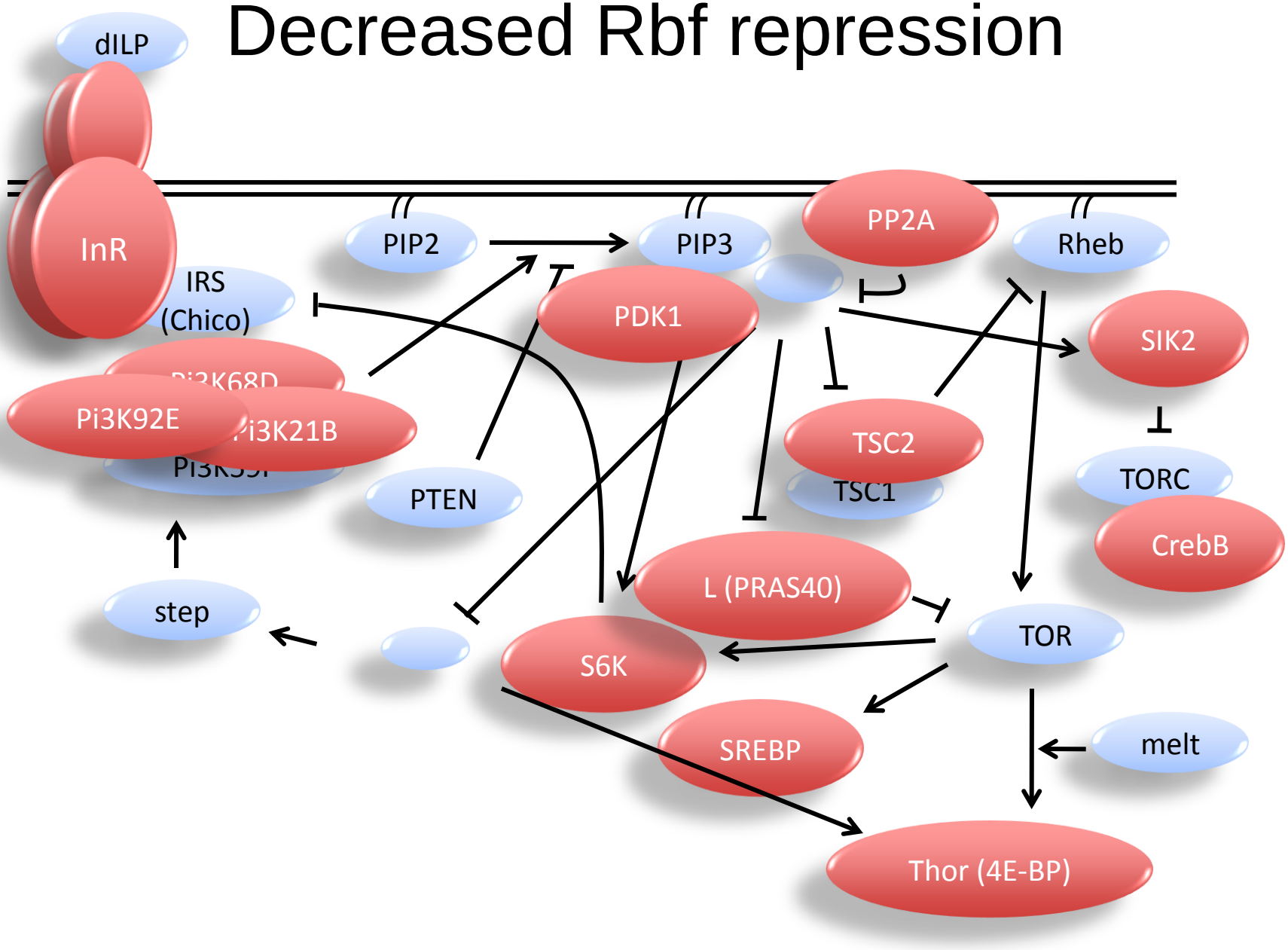
Insulin Pathway

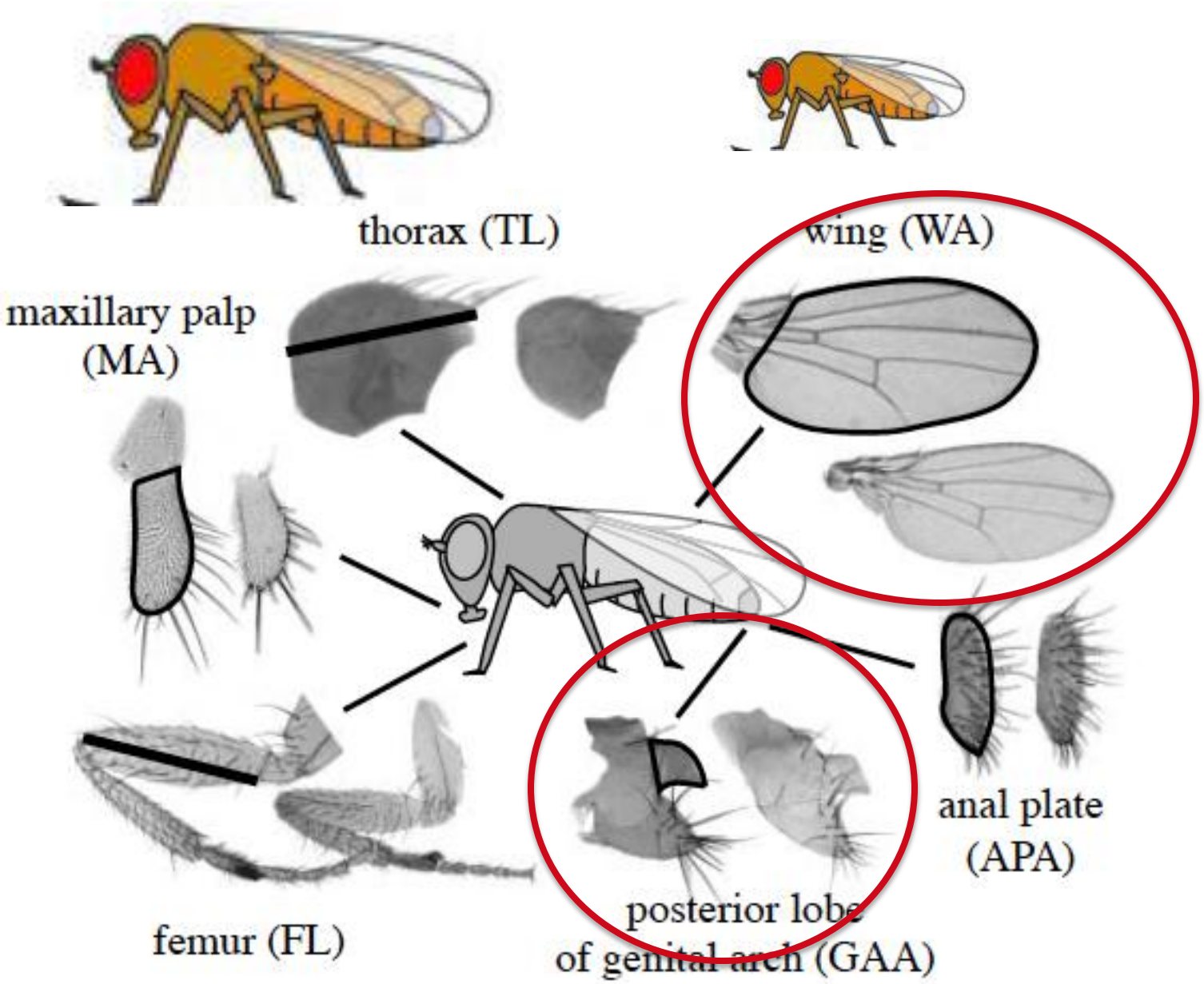


Increased Rbf repression



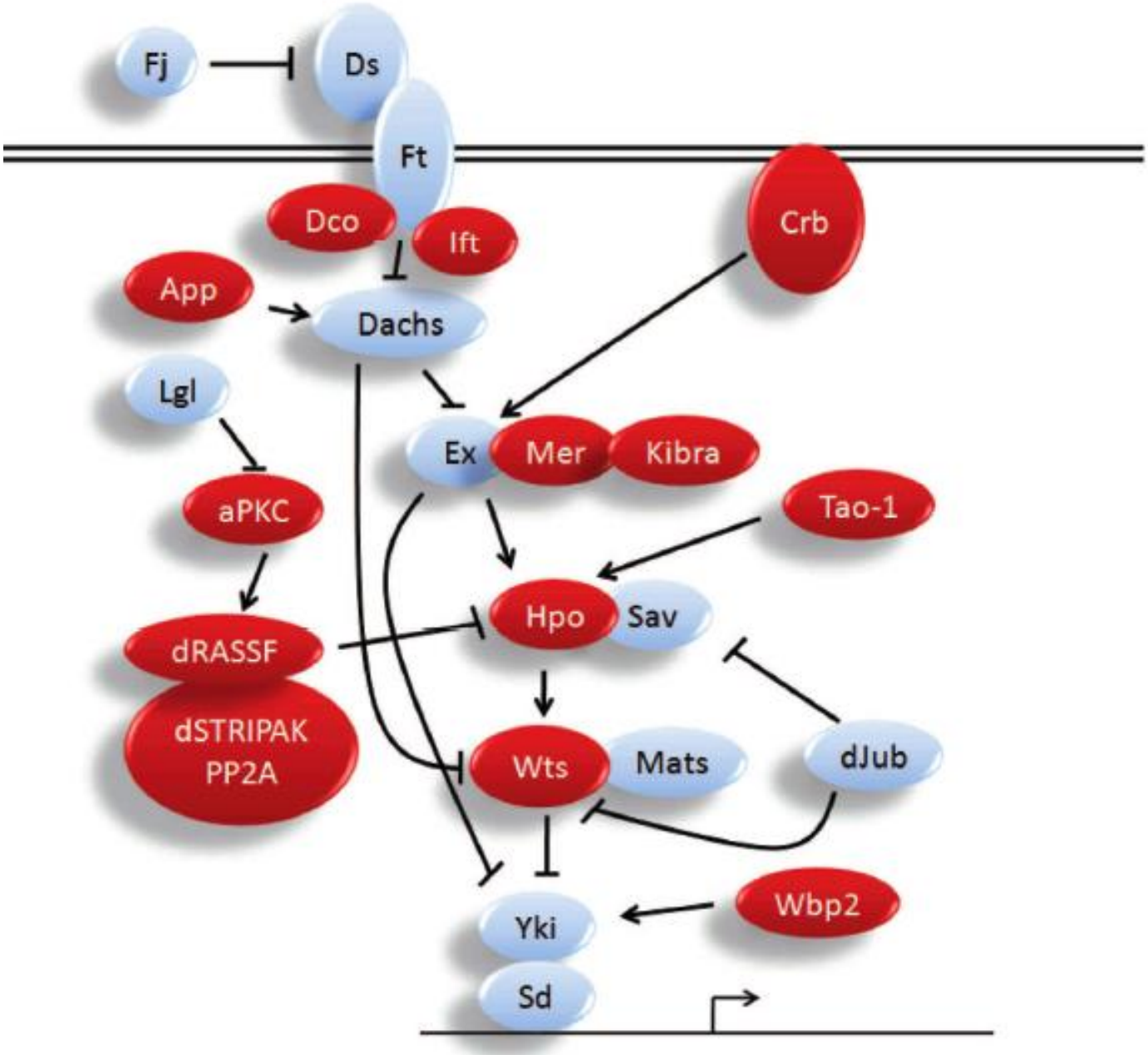
Decreased Rbf repression



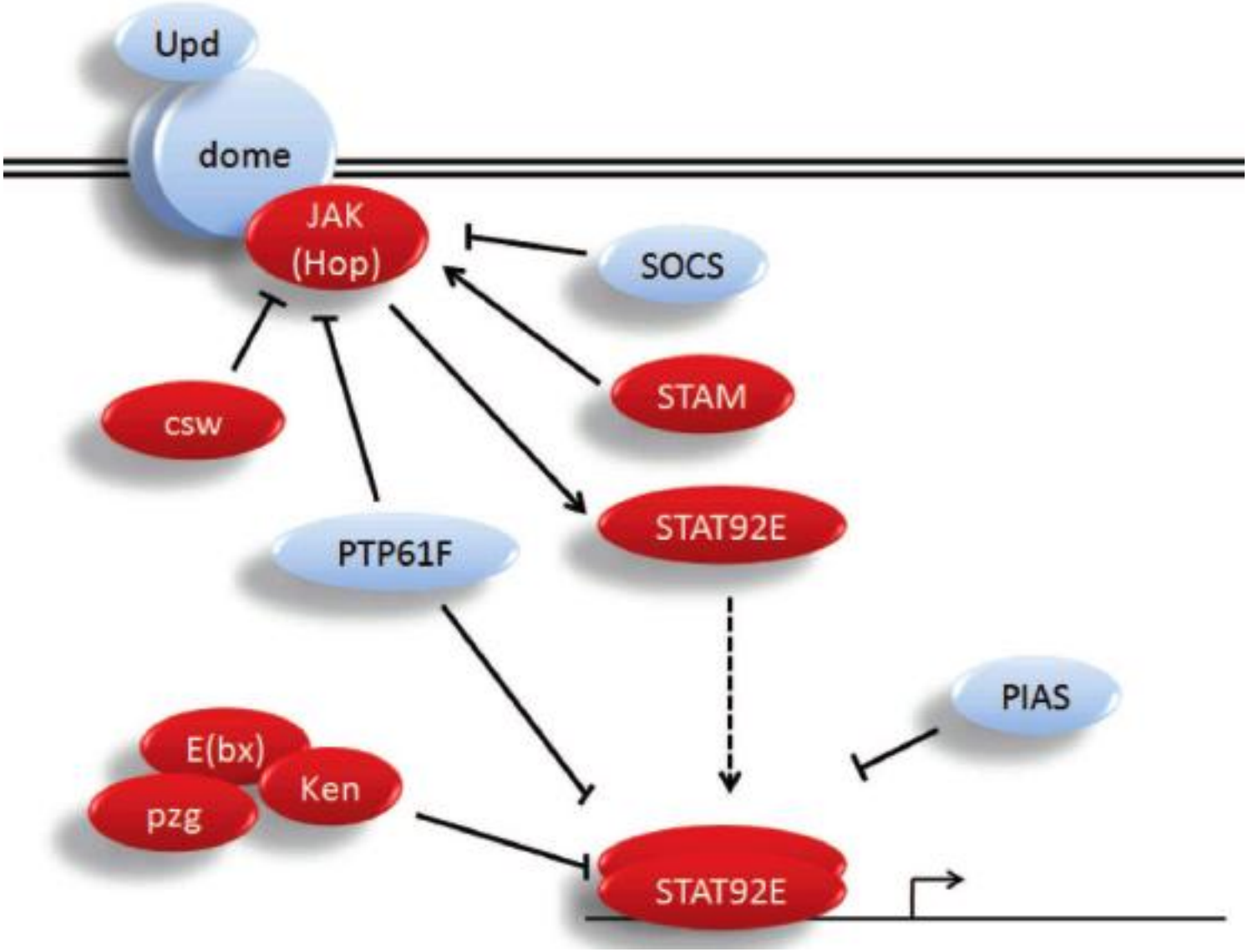


Shingleton et al. (2009) Proc Biol Sci 276:2625.

Hippo Pathway



JAK / STAT Pathway



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