System biology of development

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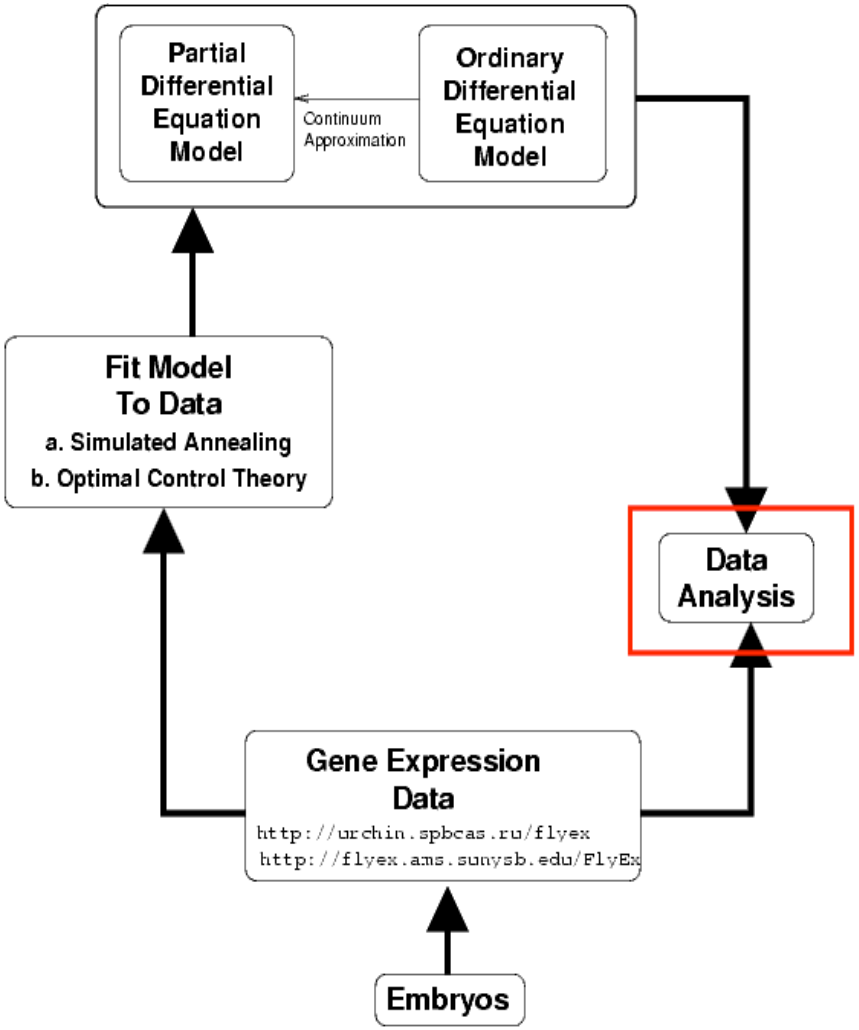
System Biology of Segment Determination



Model Parameters

Cost Functions

Shifts,
Positional Errors,
Strip Asymmetry

Database Records,
Numerical Text Files

Images

Synthesis

$$\frac{dv_i^a}{dt} = R_a g_a \left(\sum_{b=1}^{N} T^{ab} v_i^b + m^a v_i^{bcd} + h_a \right)$$

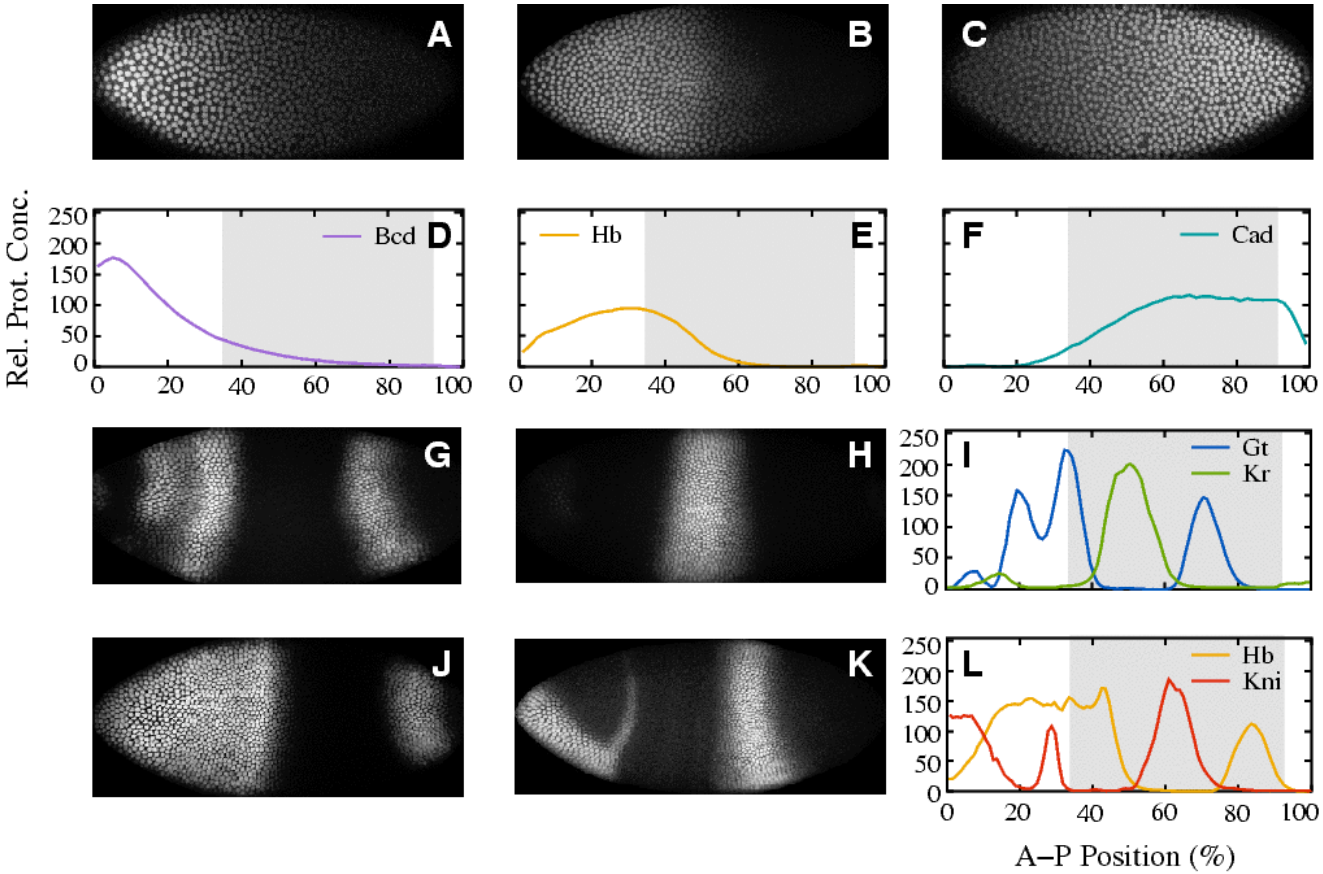
Transport

$$+D^a(n)\left[\left(v_{i-1}^a - v_i^a\right) - \left(v_{i+1}^a - v_i^a\right)\right]$$

Decay

$$-\lambda_a v_i^a$$

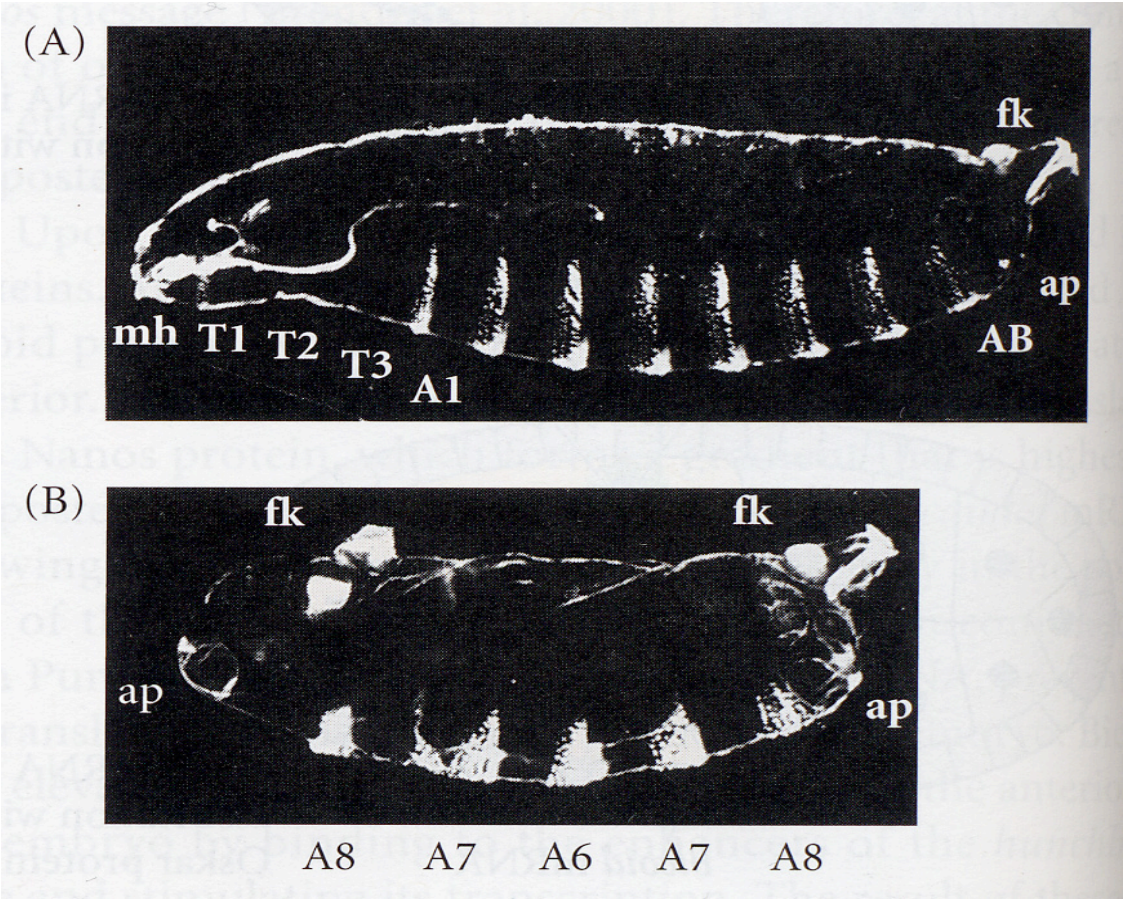
Expression patterns of gap genes



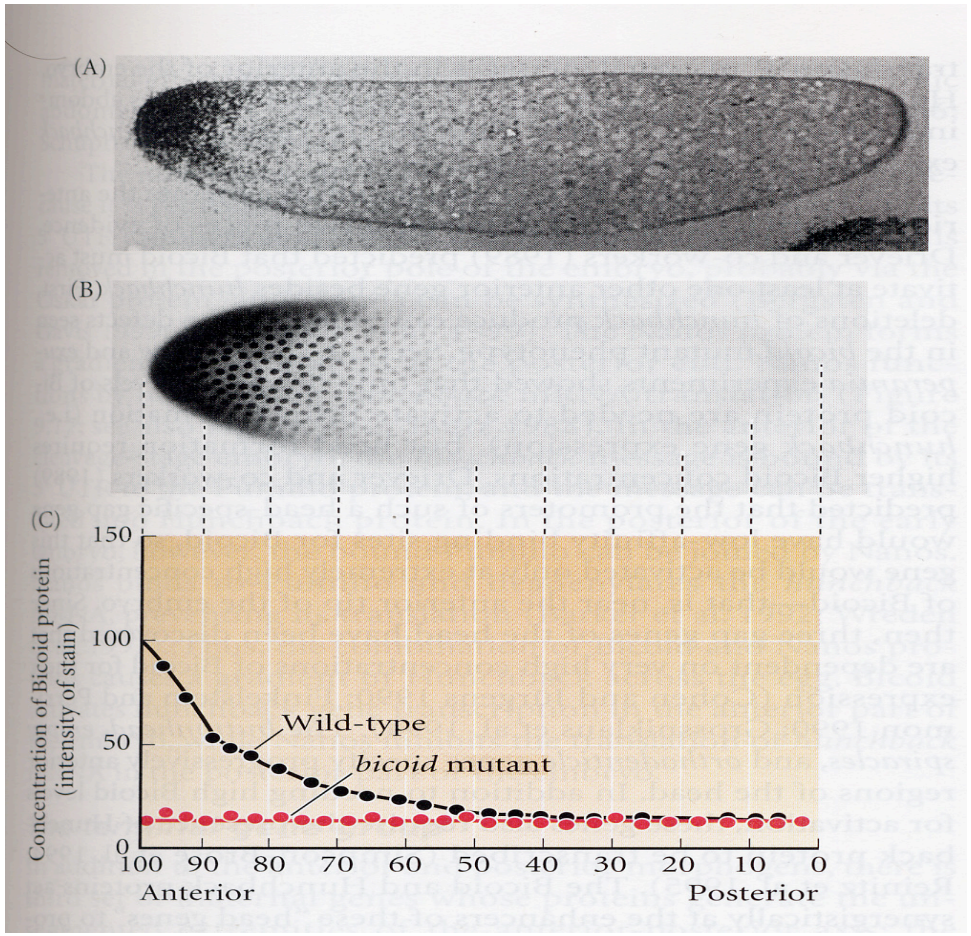
Criteria for morphogen action

- Released from localized source;
- form a concentration gradient over a population of nearby and distant cells that respond to signaling molecule in concentration-dependent way;
- Cells in the pathway of the gradient should show two or more qualitatively different responses;
- Over- and underexpression experiments should change the cell fate in the predicted directions;
- Morphogen action should be direct.

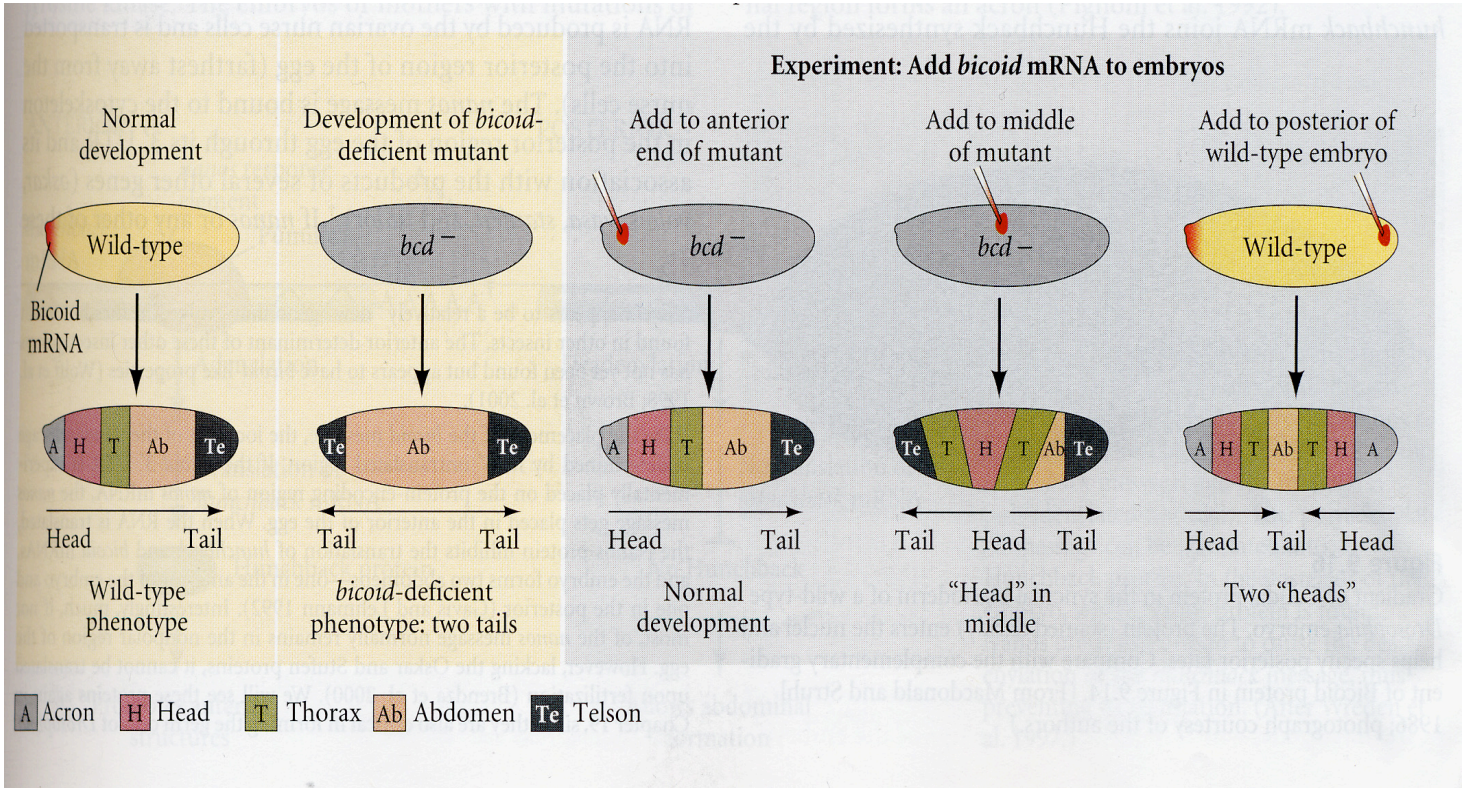
Phenotype of the strongly affected embryo from a female fly deficient in the *bicoid* gene



Gradient of Bicoid protein in the early Drosophila embryo

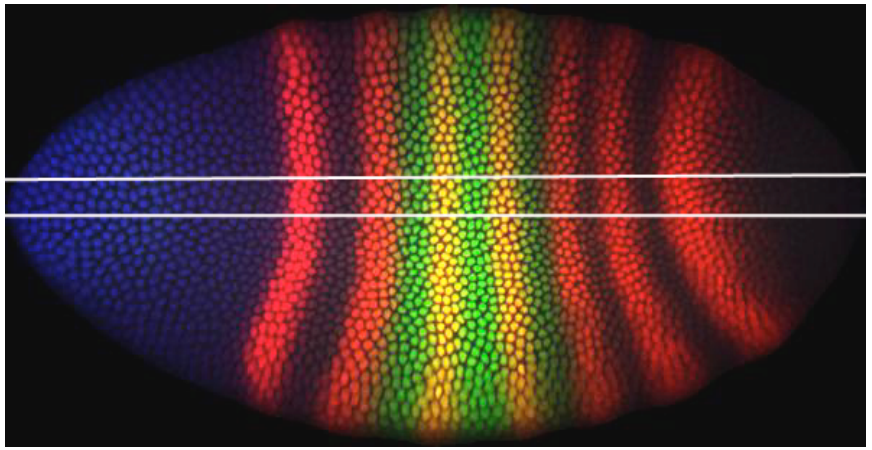


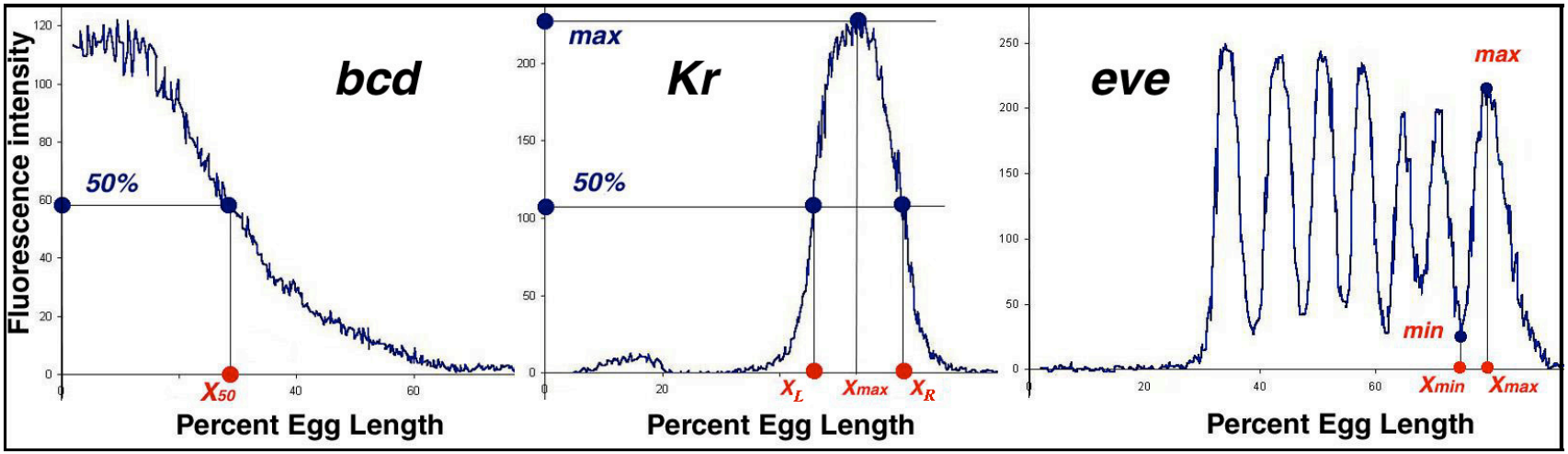
bicoid encodes the morphogen responsible for head structures

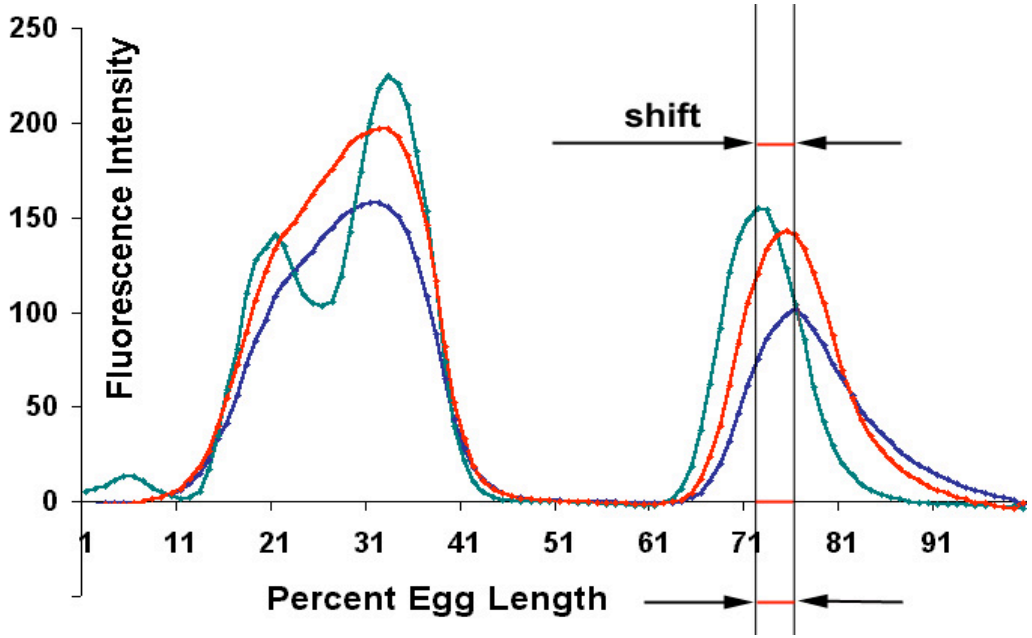


Features used to characterize expression patterns

Embryo stained for expression of *bcd*, *Kr* and *eve*



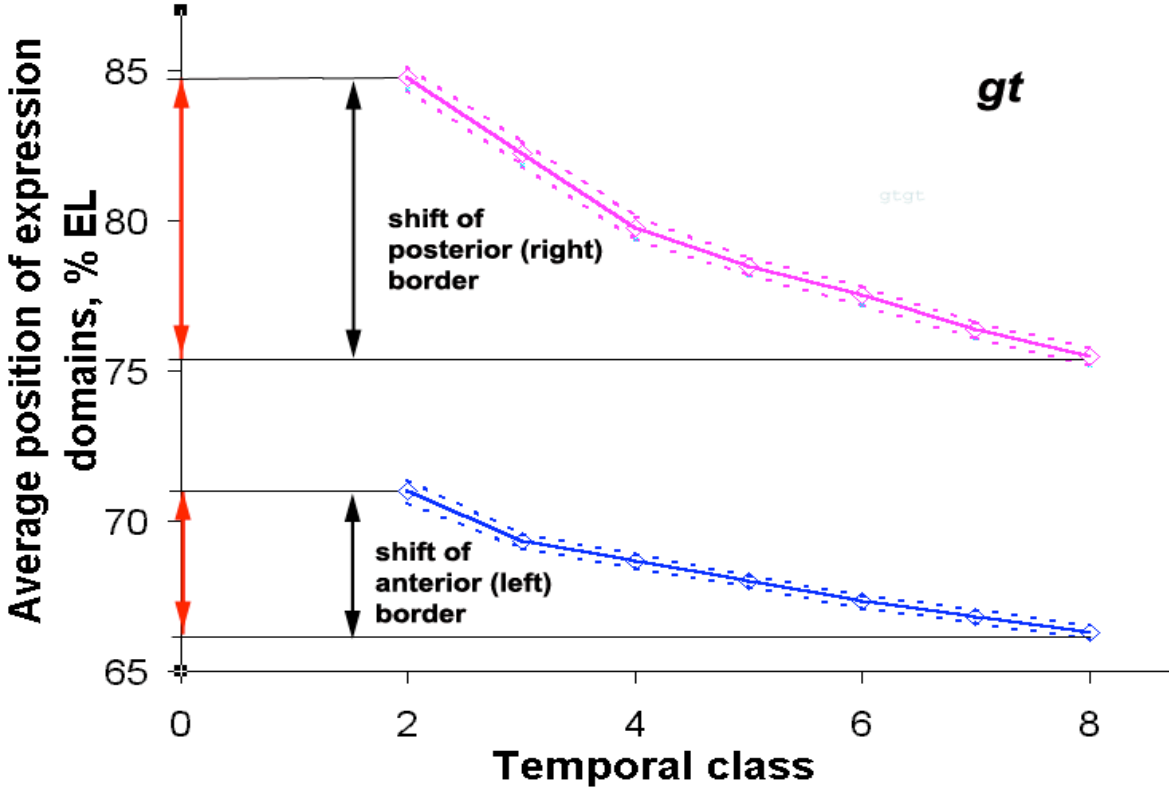




Computation of shifts: the highly dynamic pattern of *gt* as an example

1. Extract characteristic features of expression domain.
2. Calculate the average position of a given characteristic feature over the embryos of each time class.
3. Compute the difference between average positions of the feature in different time classes.

Shifts of domains of gap genes



gene	*Kr* {n=261}		*kni* {n=134}		*gt* {n=137}	
	A-border	P-border	A-border	P-border	A-border	P-border
shift (%EL)	1.02	5.23	1.60	6.32	4.72	11.04

Analysis of the Gap Gene System

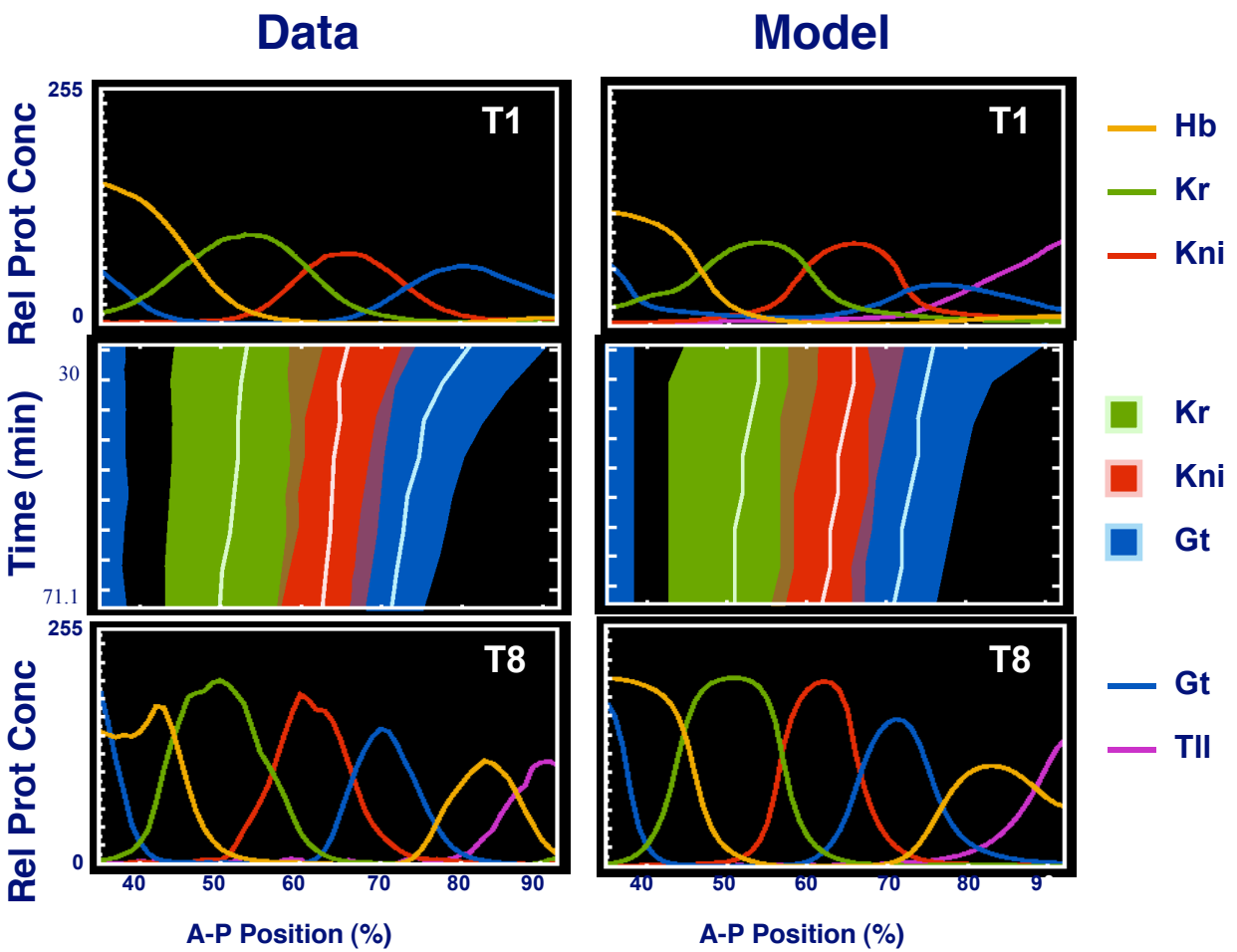
Using the new dataset and the ODE model with nuclear divisions, we ask:

How are gap gene domains maintained and refined?

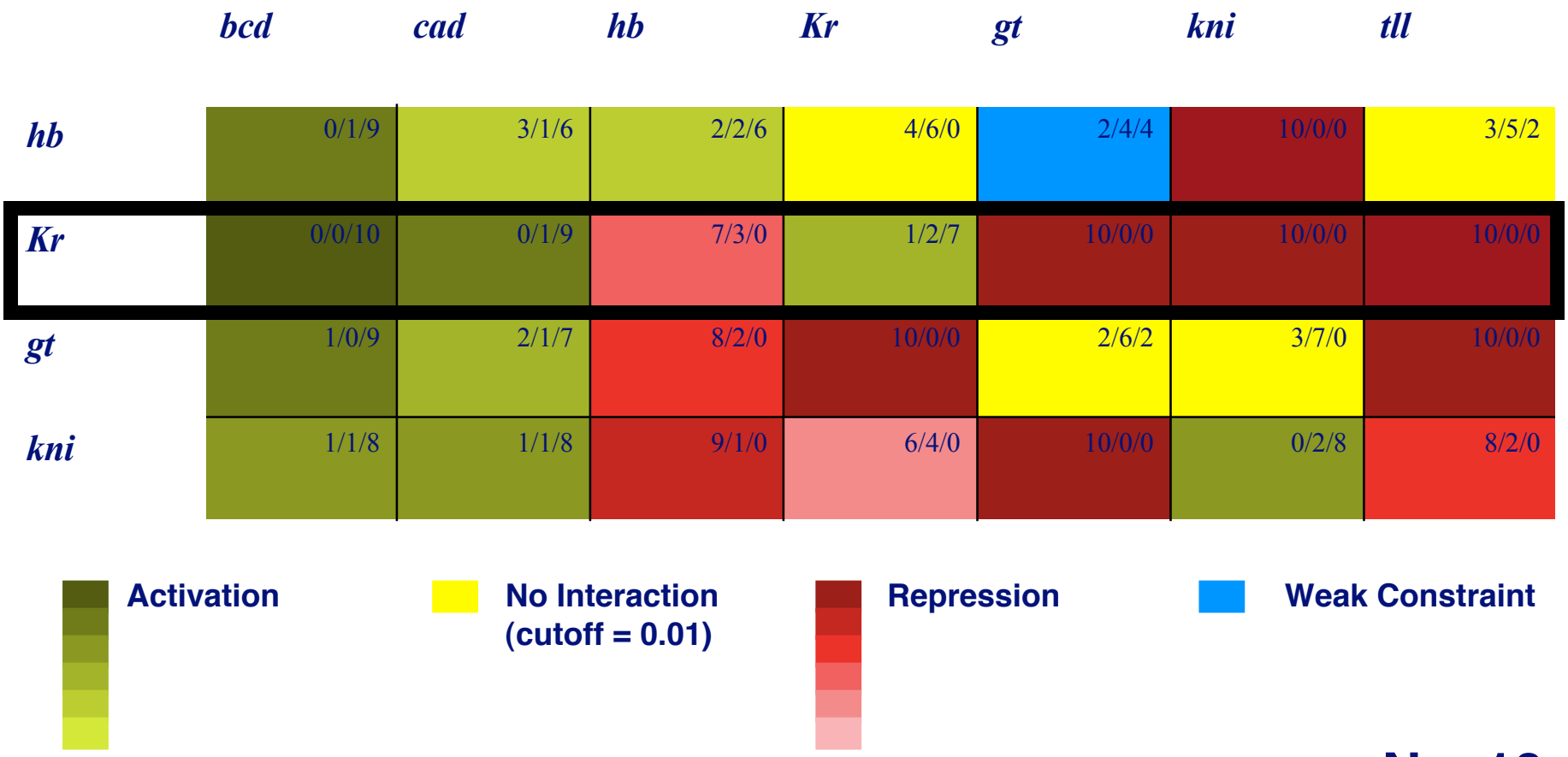
Why do they move?

Is Bcd a morphogen?

Gap Gene Expression



Constraints on the T Matrix



N = 10

Synthesis

$$\frac{dv_i^a}{dt} = R_a g_a \left(\sum_{b=1}^{N} T^{ab} v_i^b + m^a v_i^{bcd} + h_a \right)$$

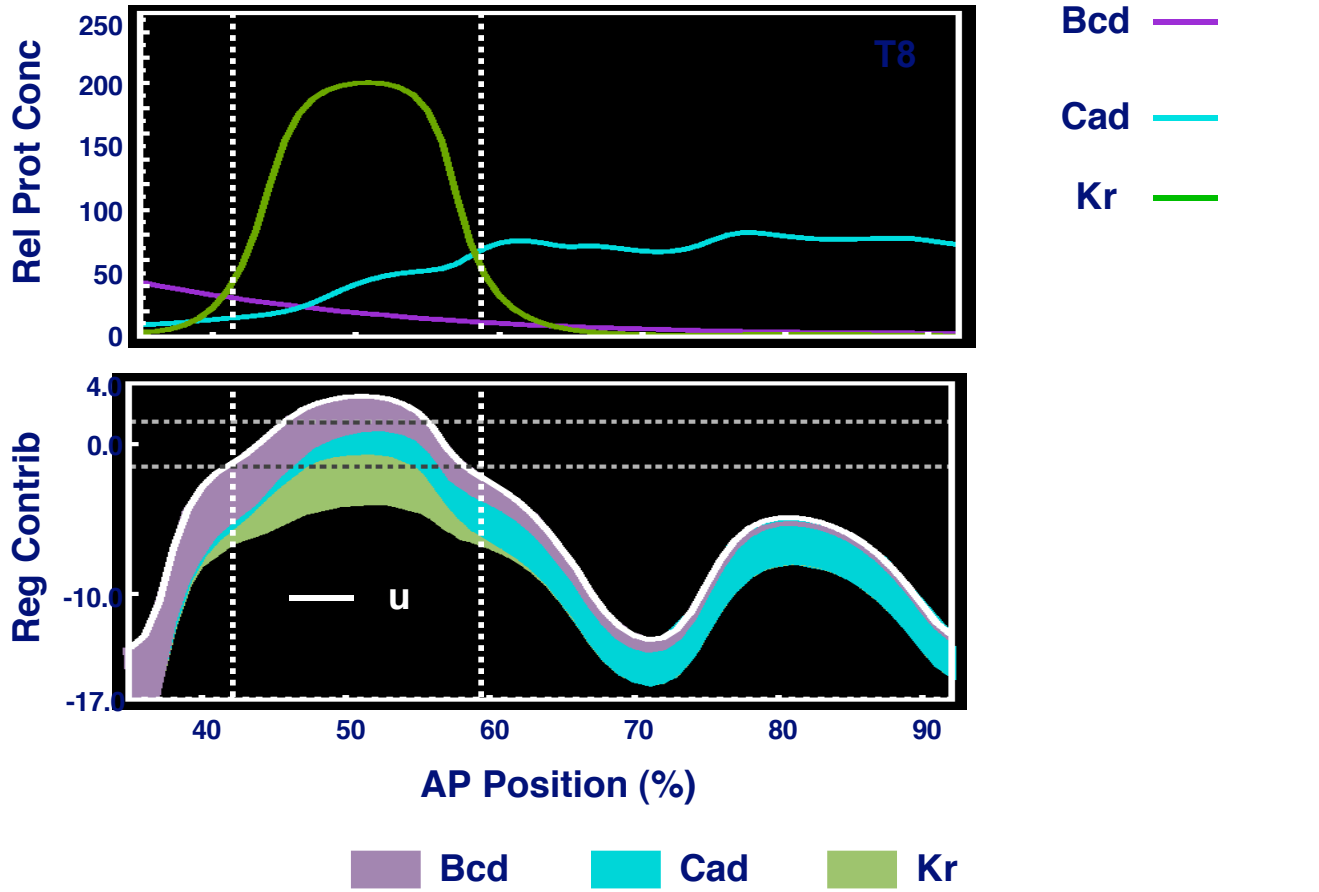
Dynamic dissection:

We can look at individual parts of this sum to 'dissect' the various regulatory contributions on a specific gene.

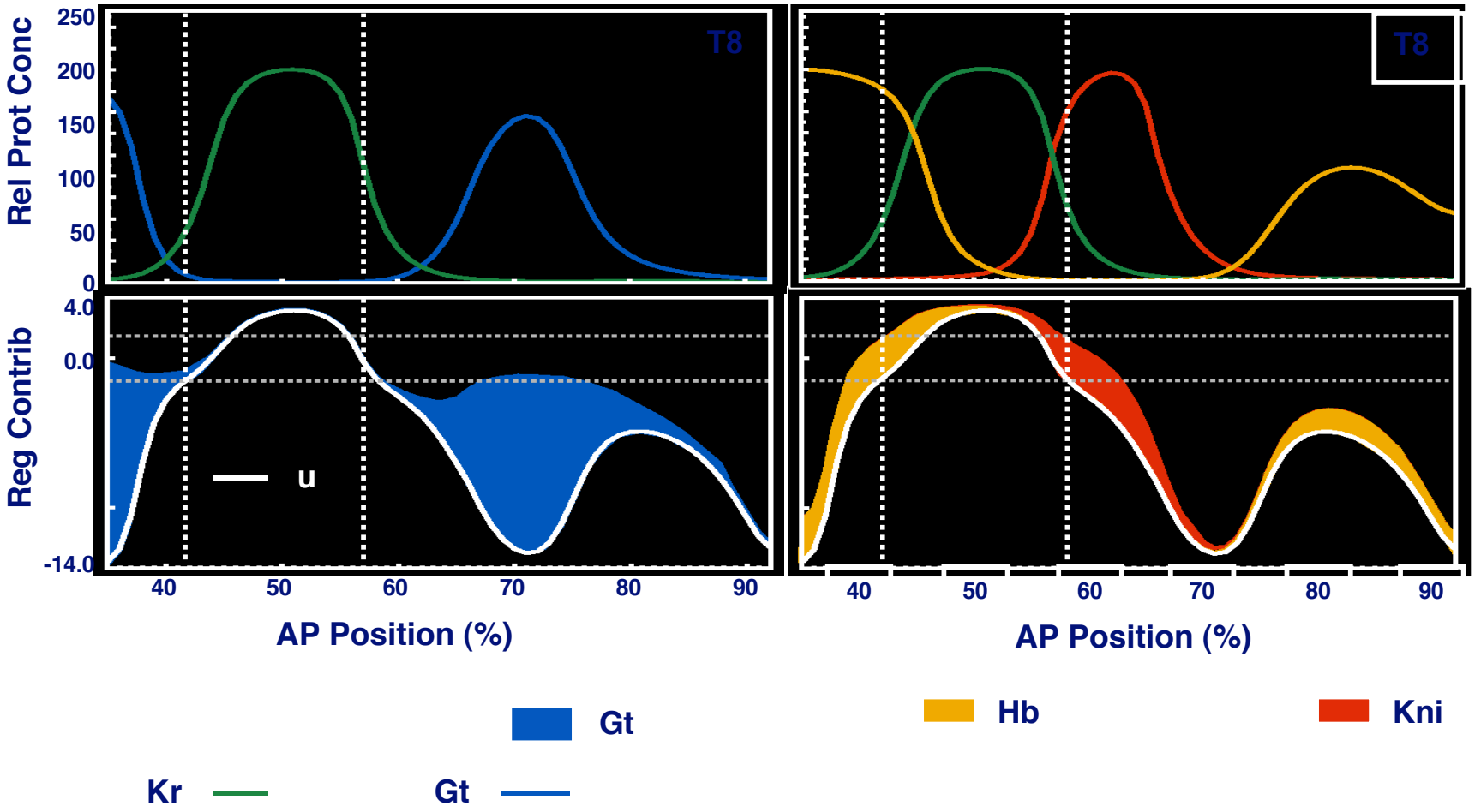
For example:

$T^{Kr->hb}$ v^{Kr} represents Kr's regulatory input on *hb*

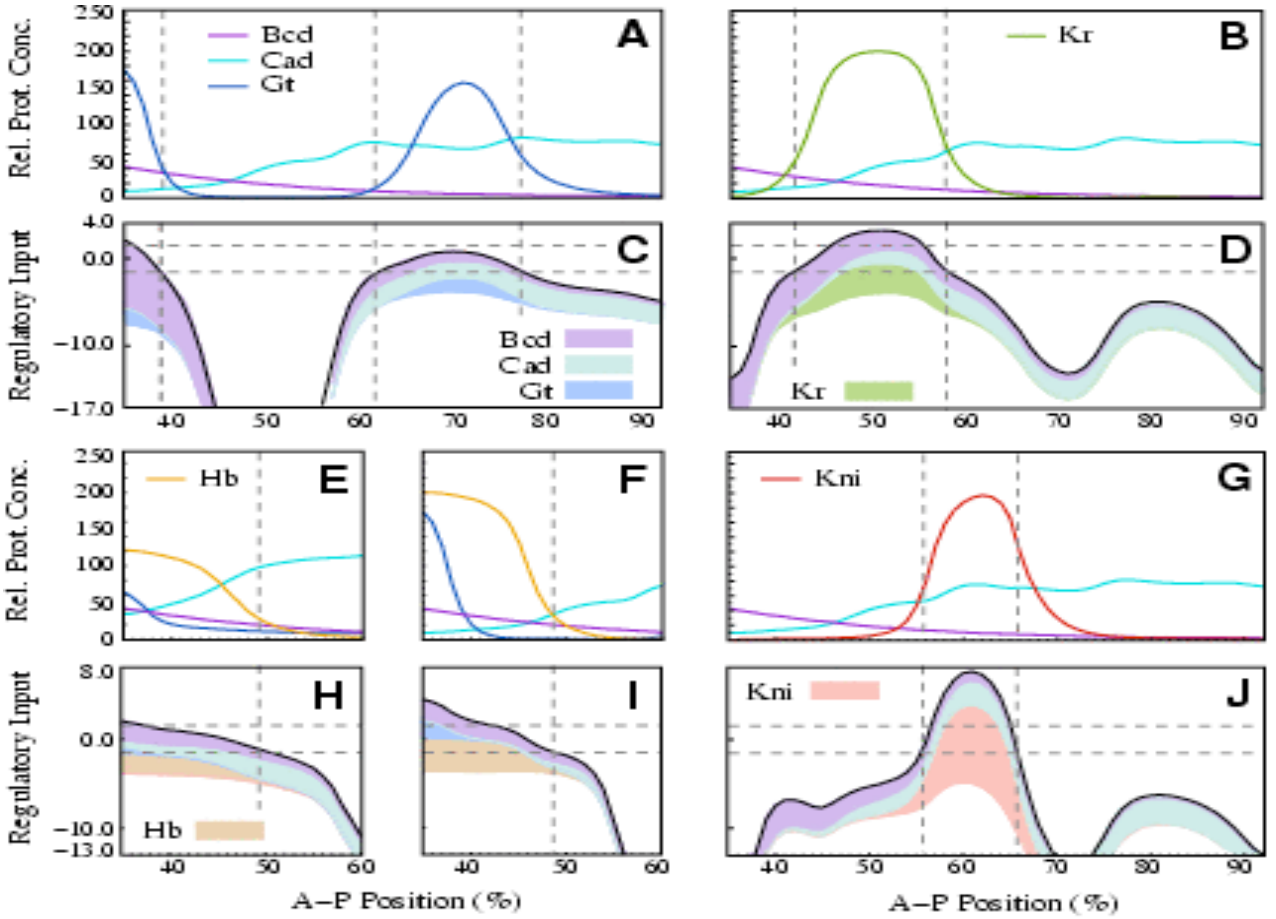
Graphical analysis of gap gene regulation: boundary control by activation



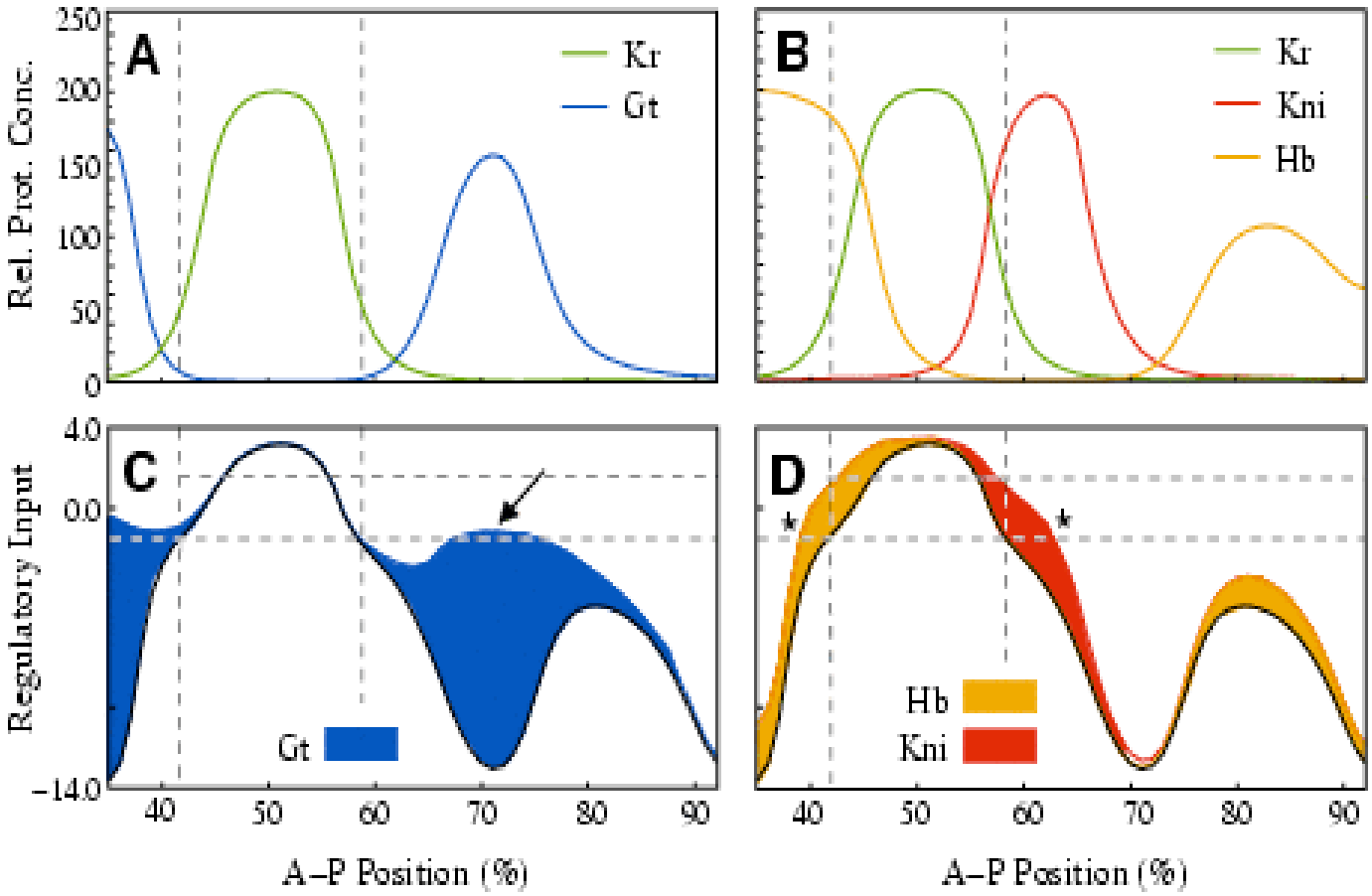
Graphical analysis of gap gene regulation: boundary control by repression



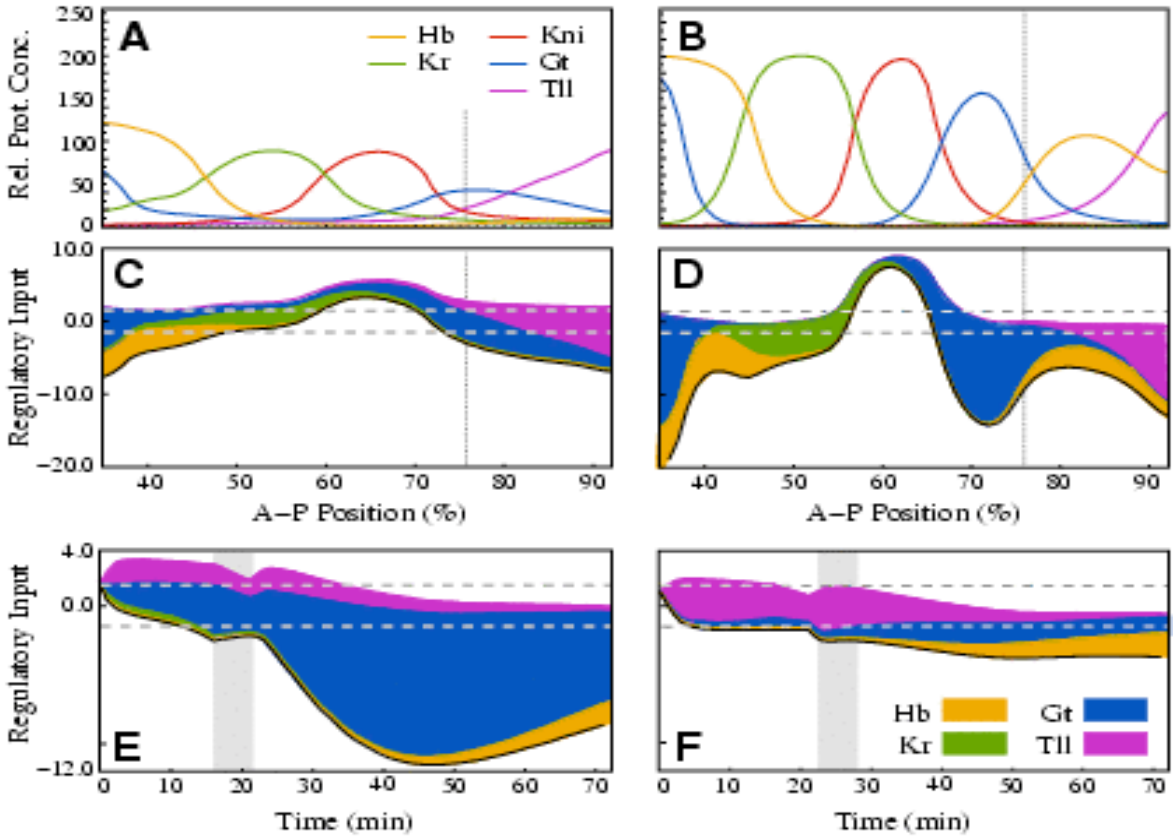
Gap gene activation



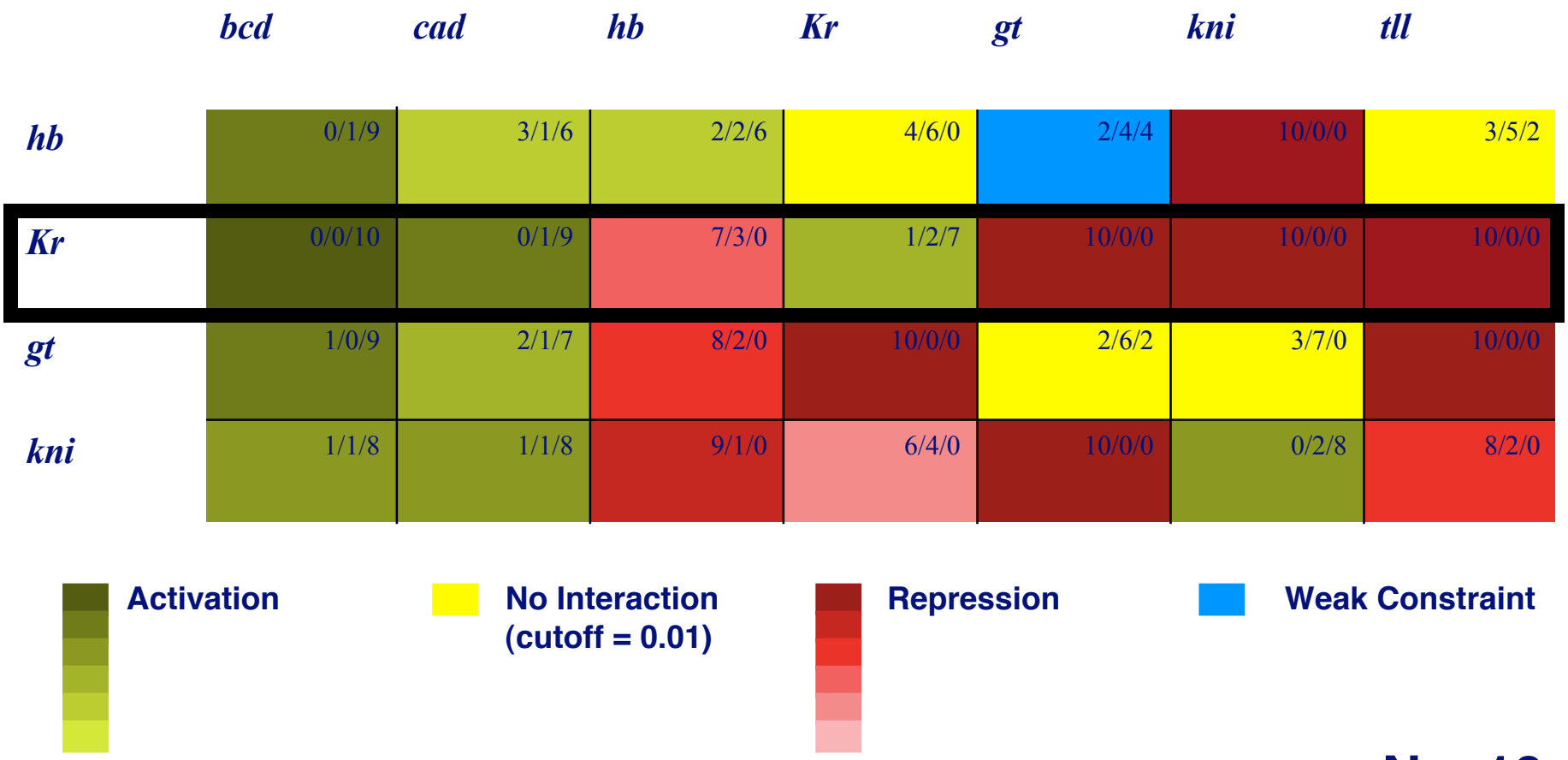
Kr repression



Kni repression

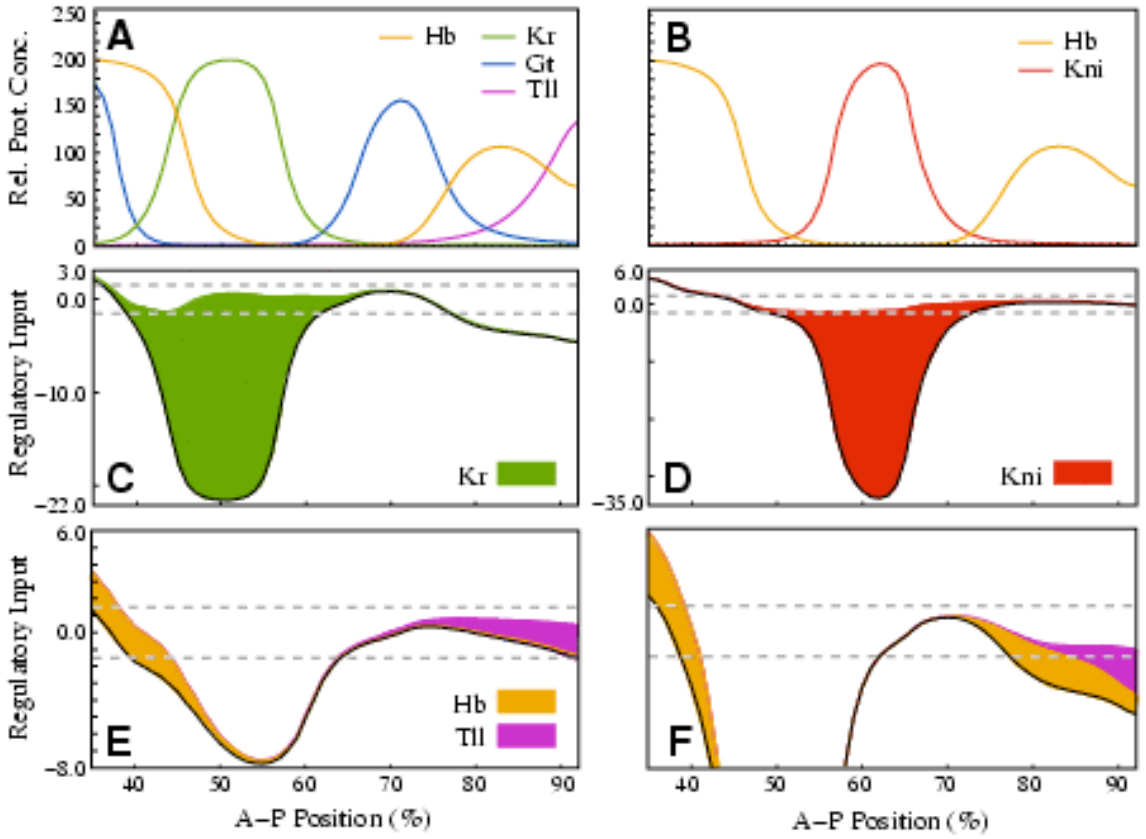


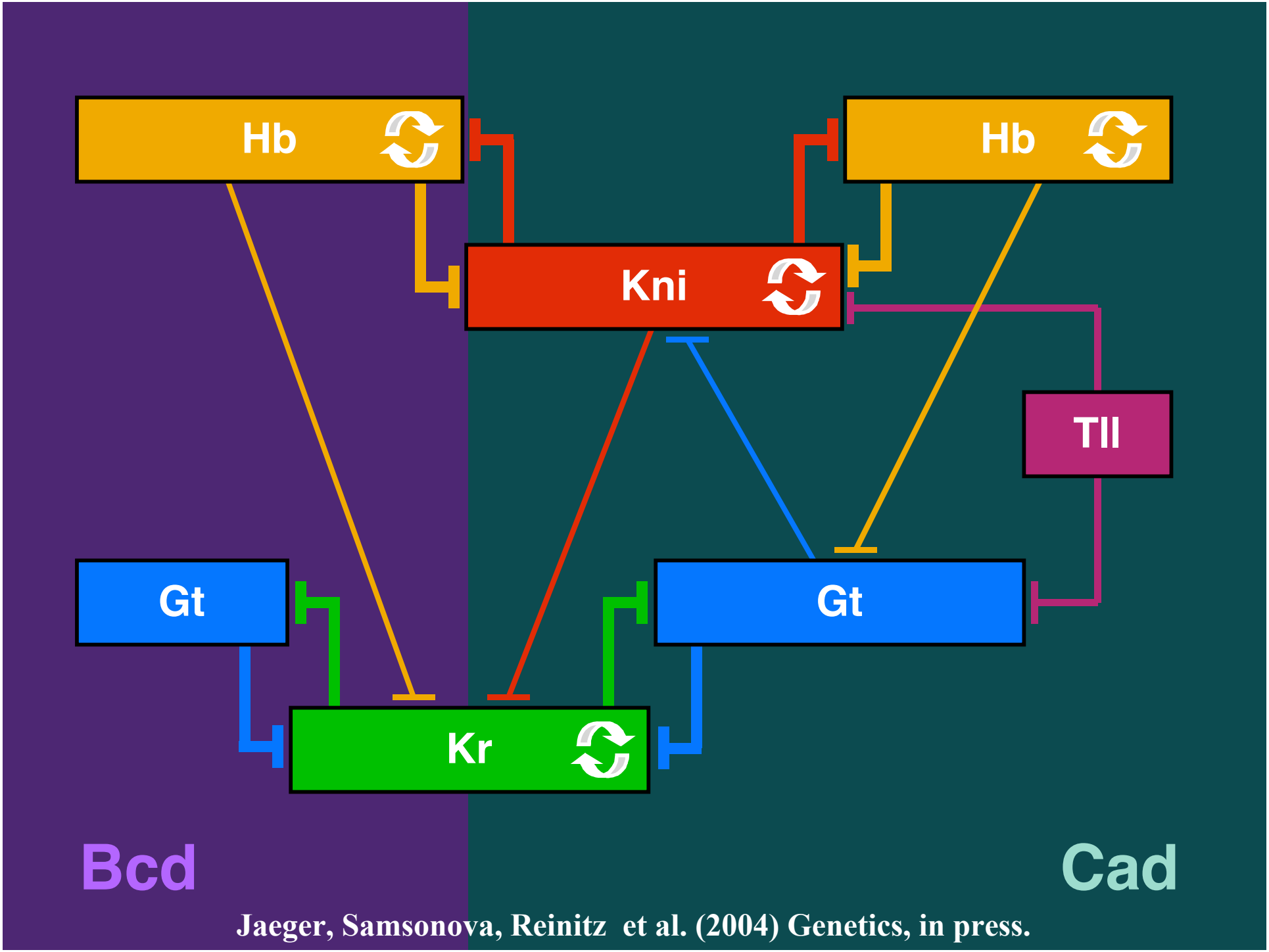
Constraints on the T Matrix



N = 10

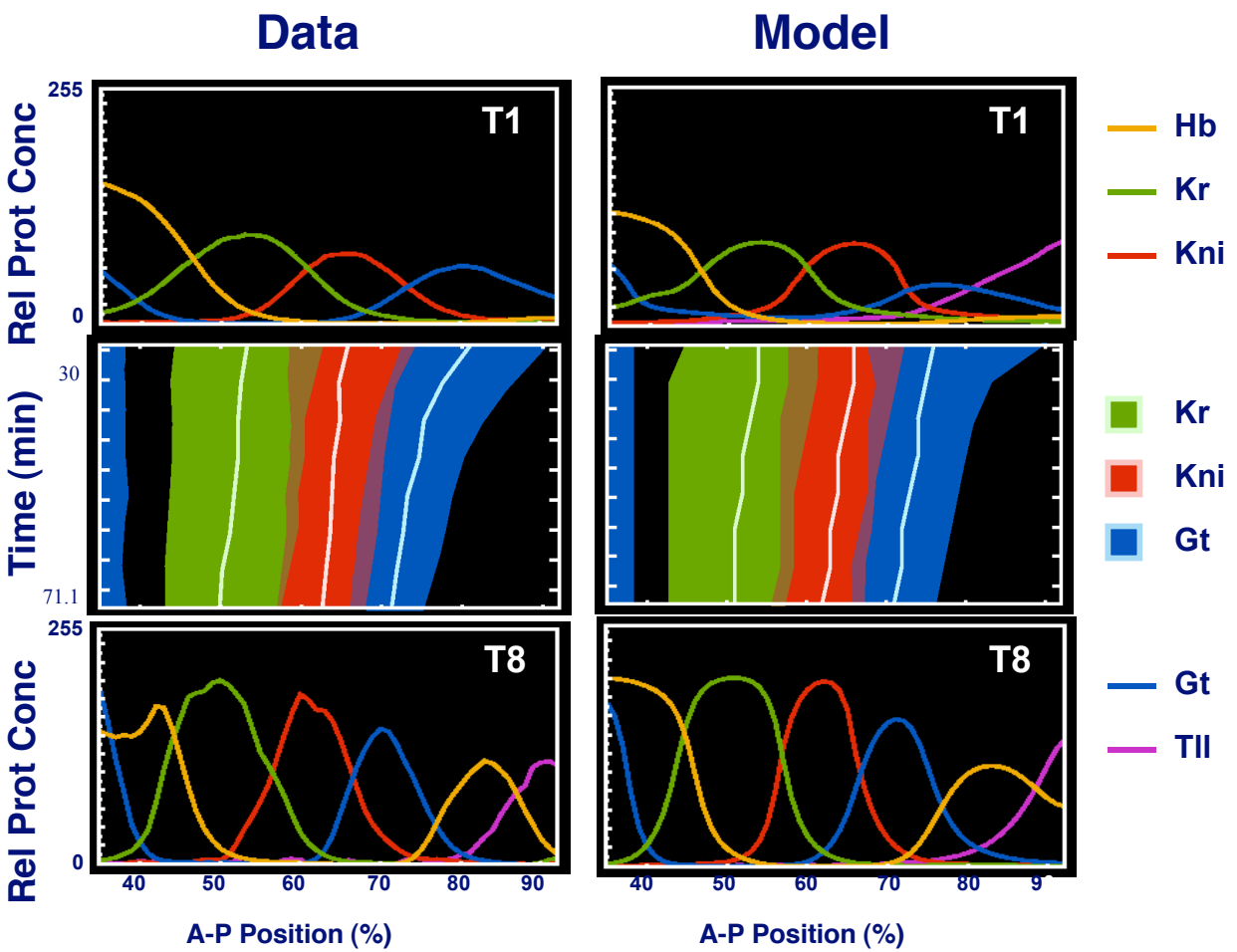
Gt and hb repression



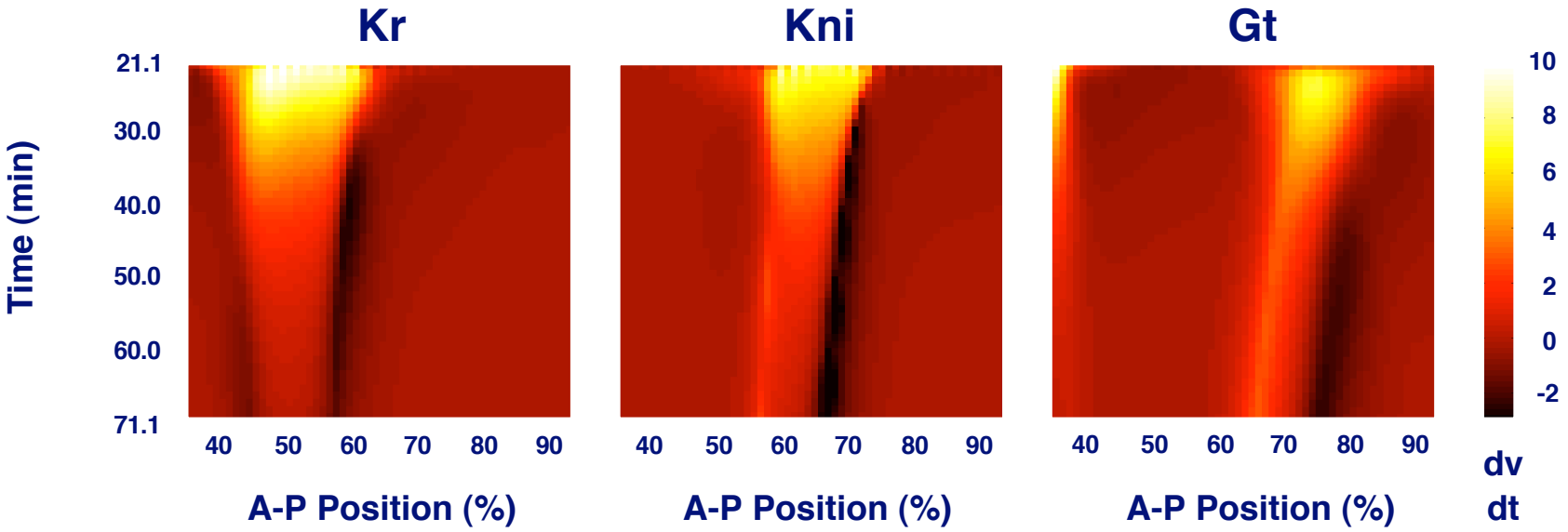


Jaeger, Samsonova, Reinitz et al. (2004) Genetics, in press.

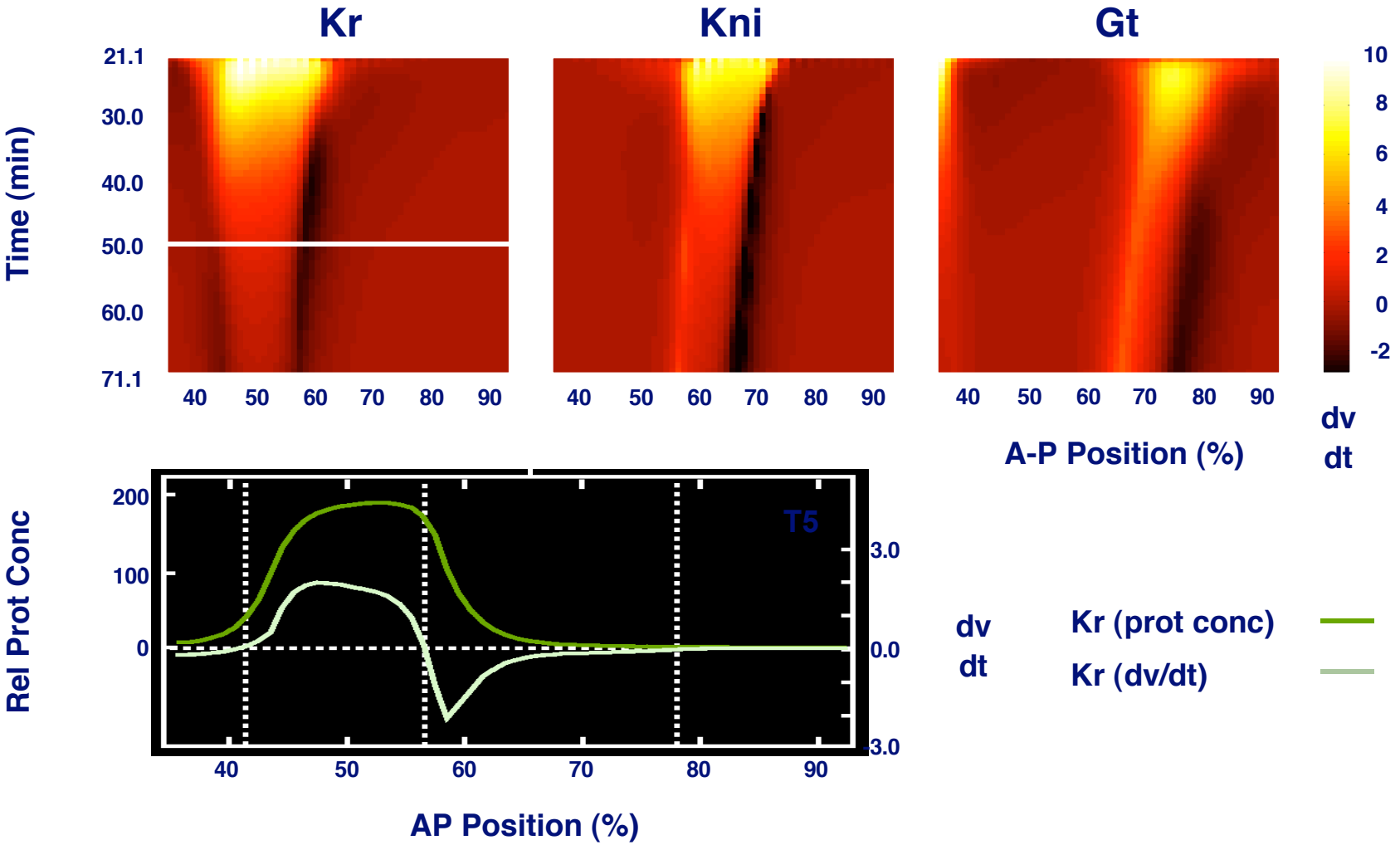
Gap Gene Expression



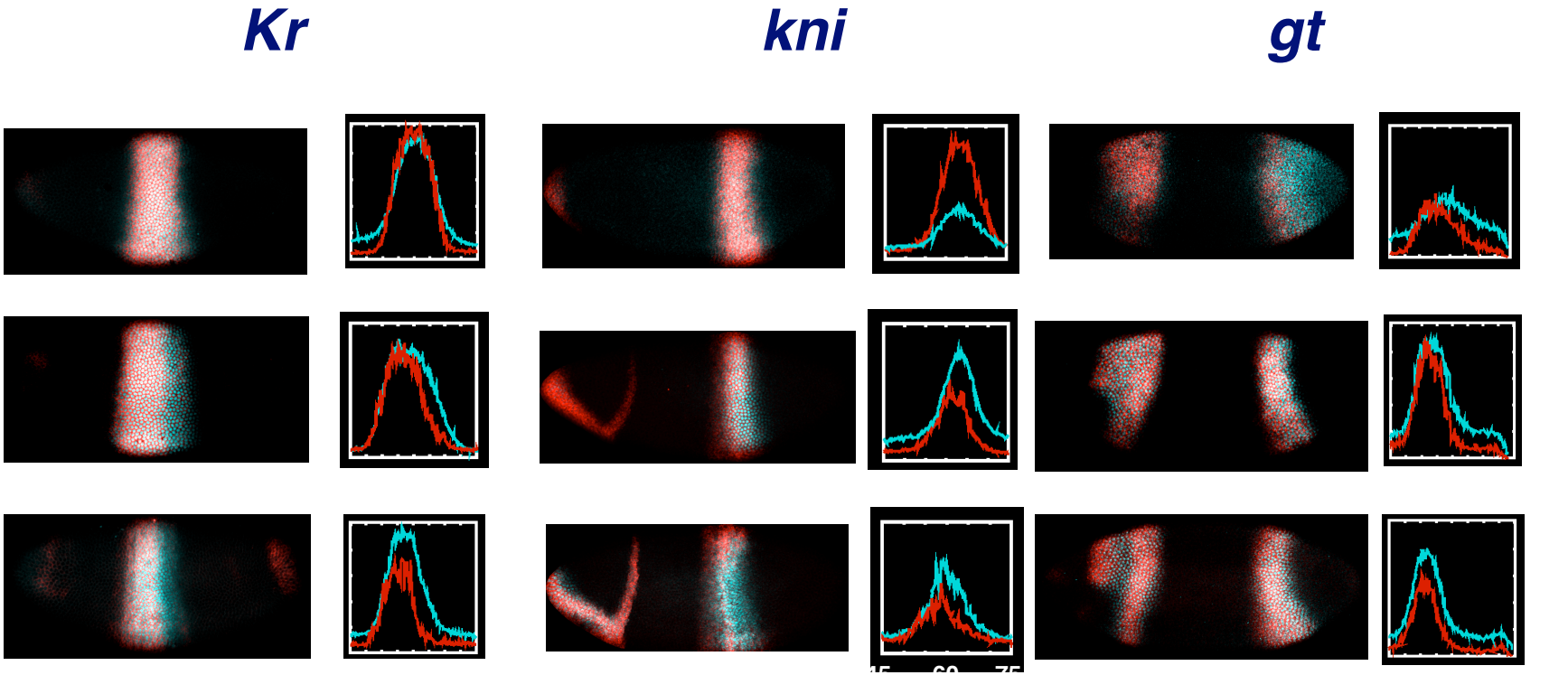
Domain Shifts: Mechanism



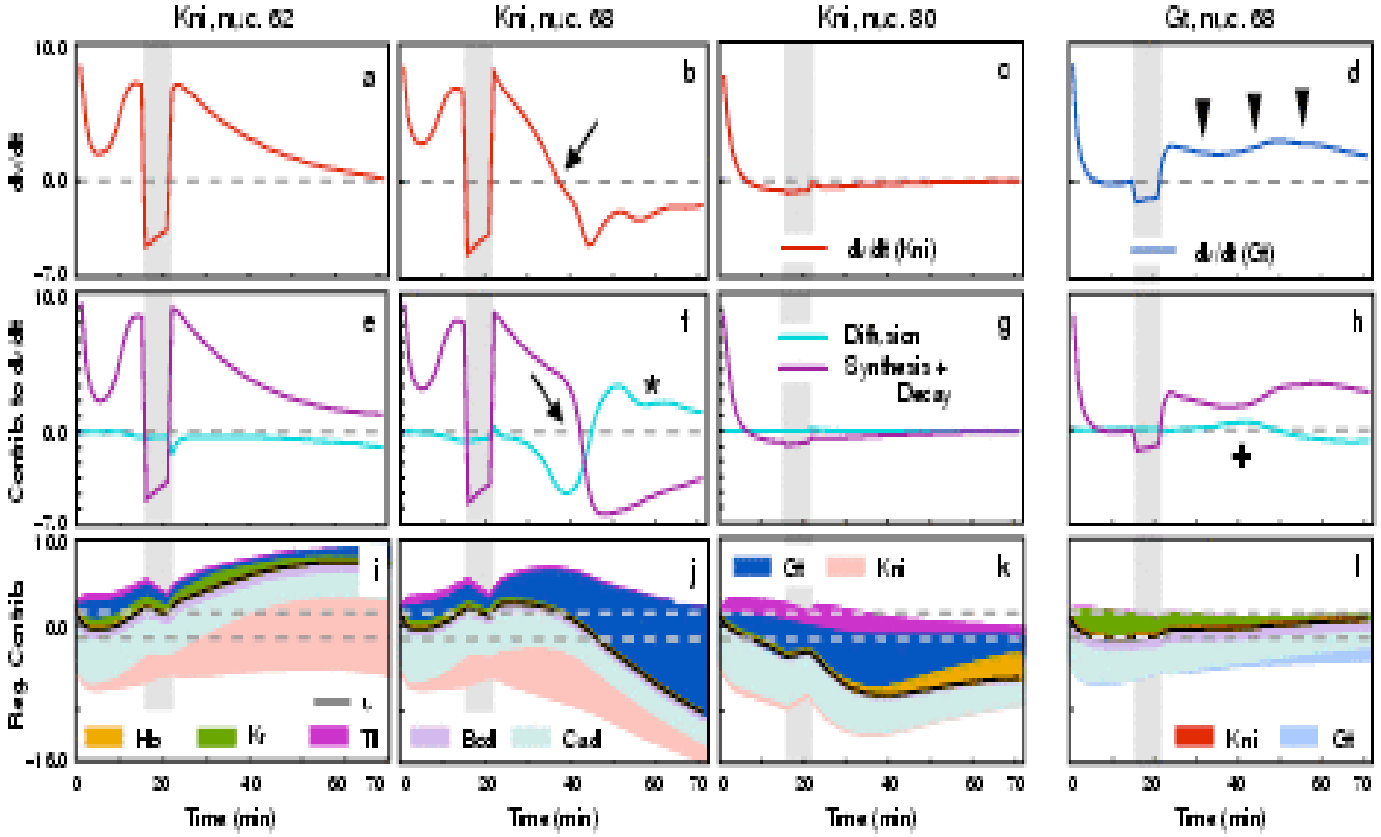
Spatial Dynamics: Domains of Synthesis and Decay



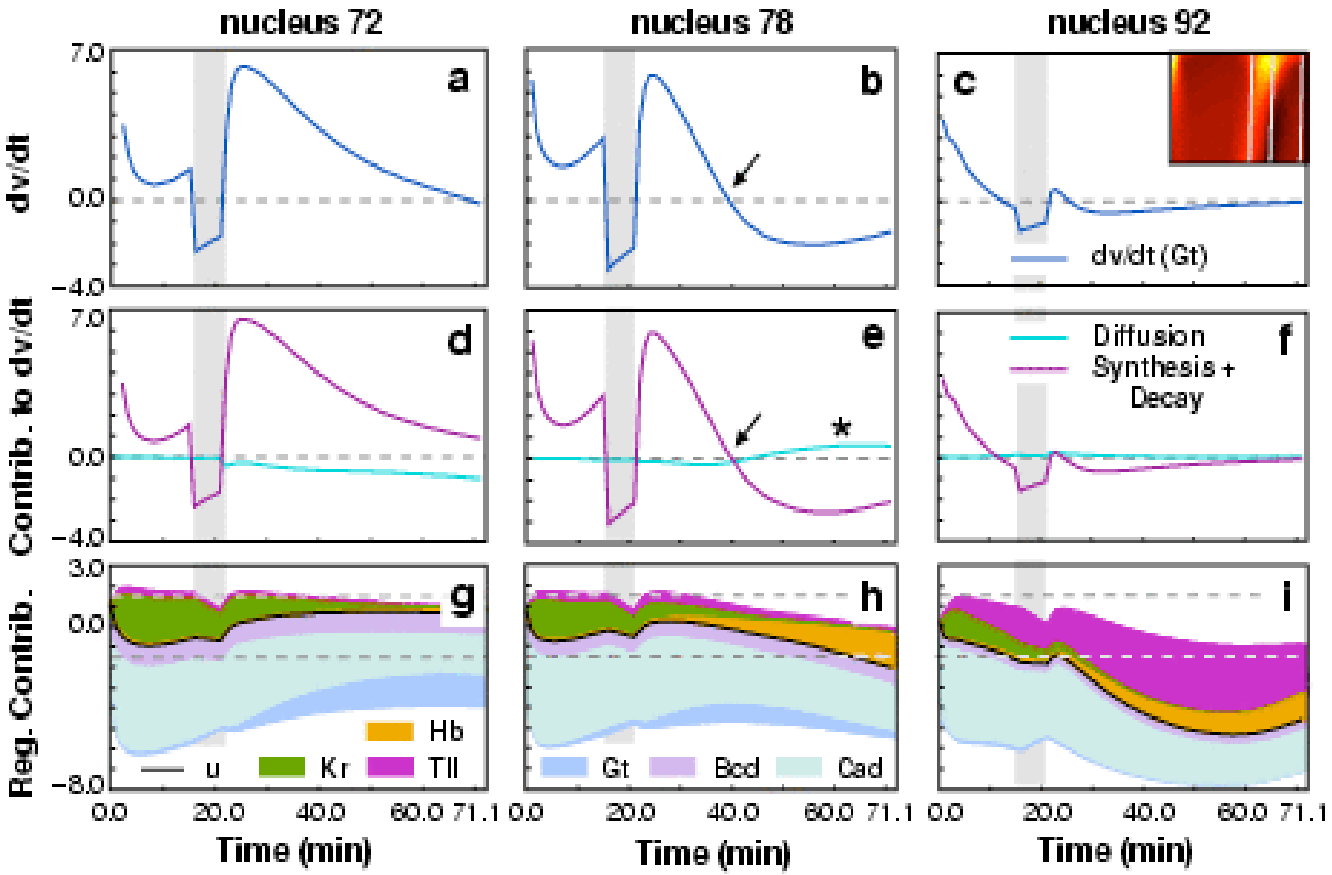
Gap Domains: RNA vs Protein



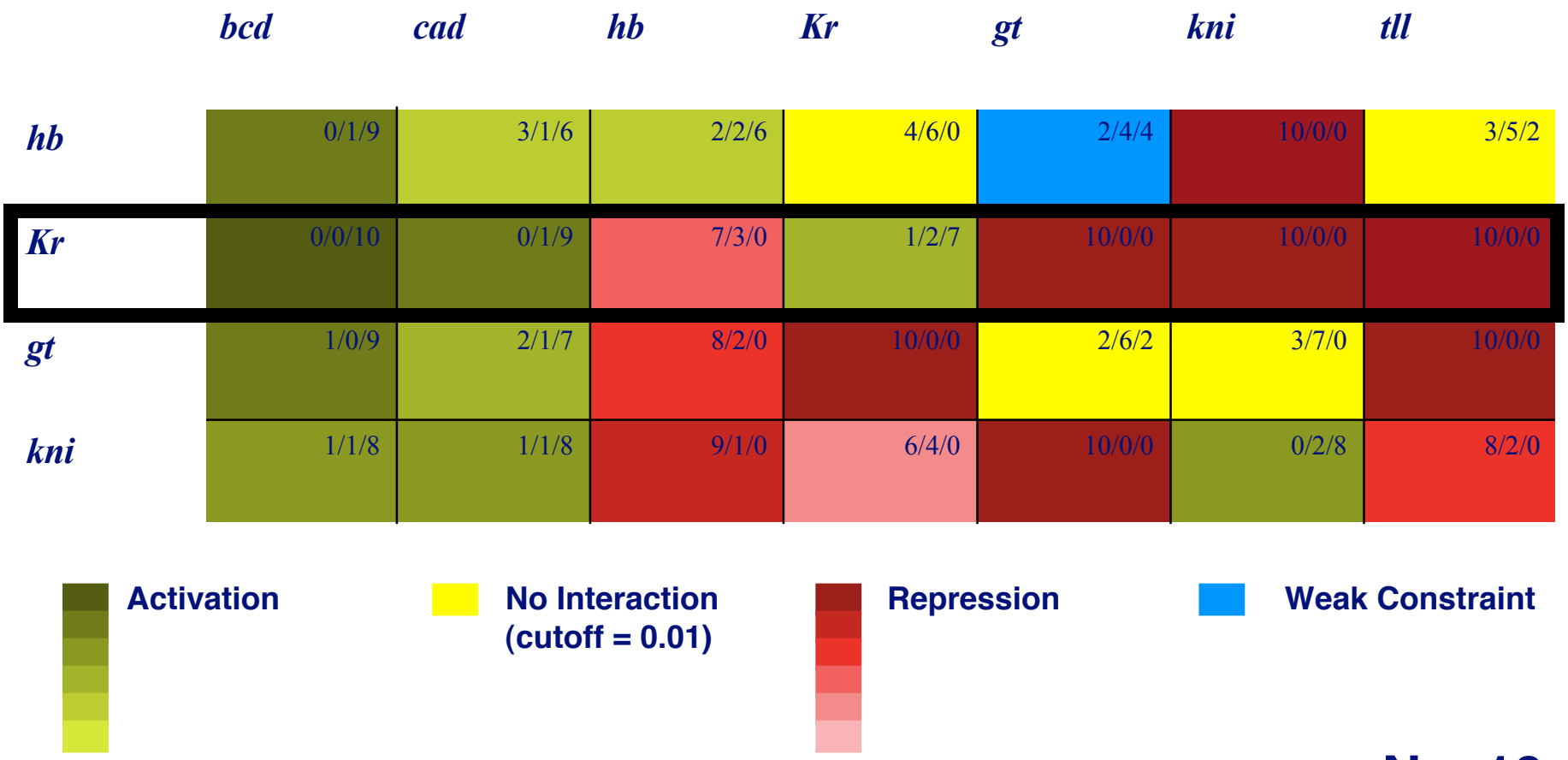
Shift in the posterior *kni* boundary



Shitf in the posterior boundary of the posterior *gt* domain

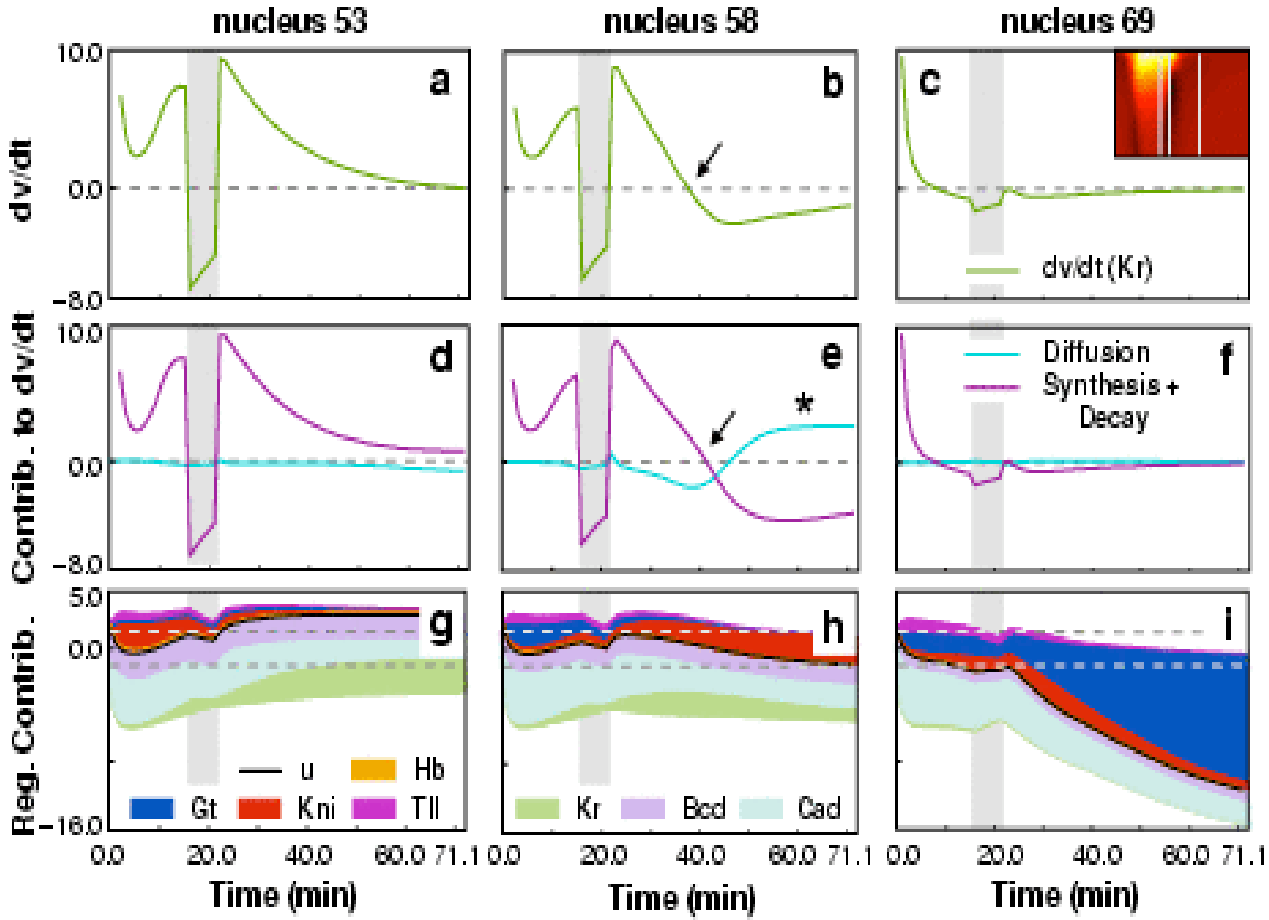


Constraints on the T Matrix

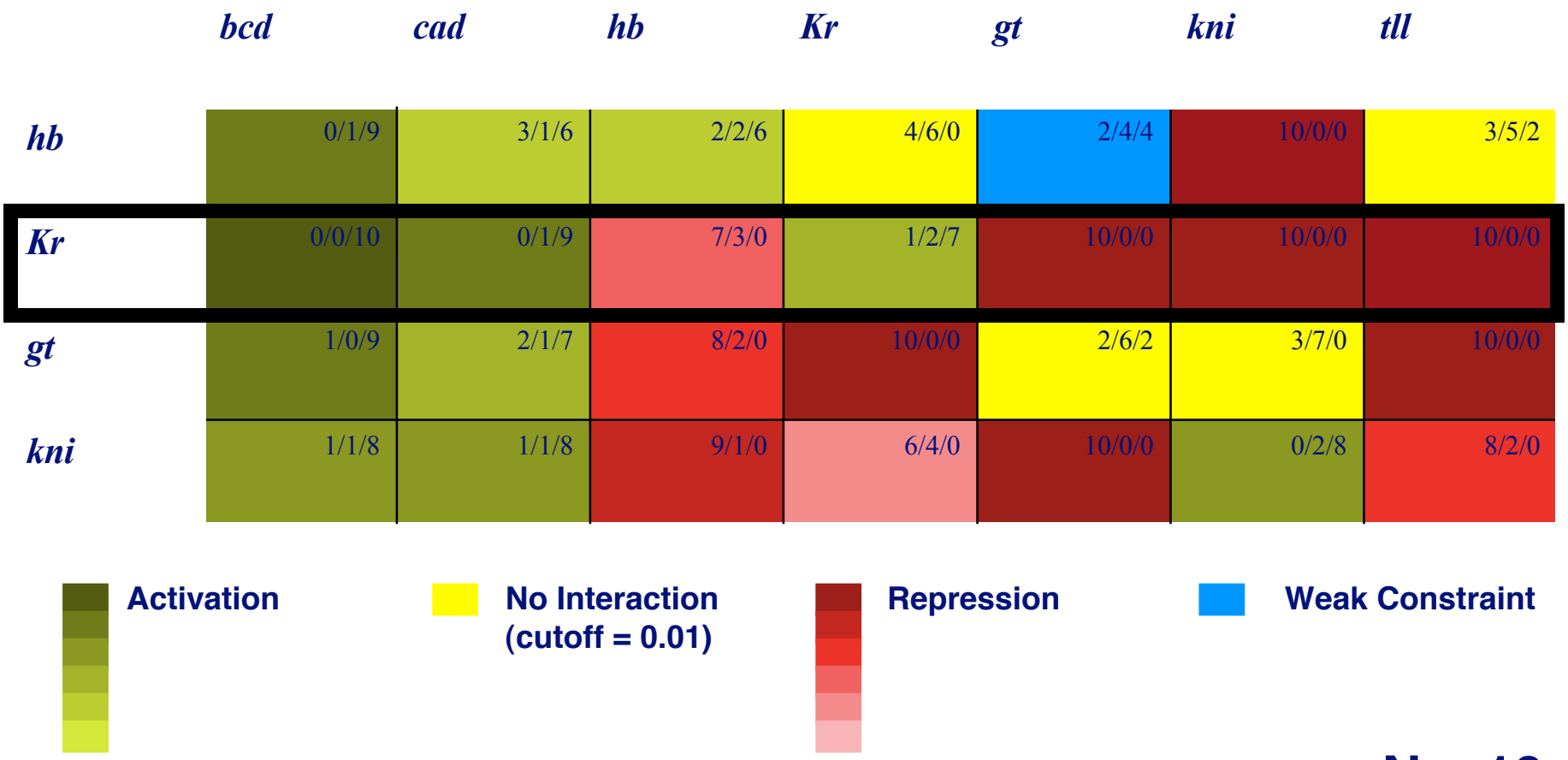


N = 10

Shitf in the posterior Kr boundary

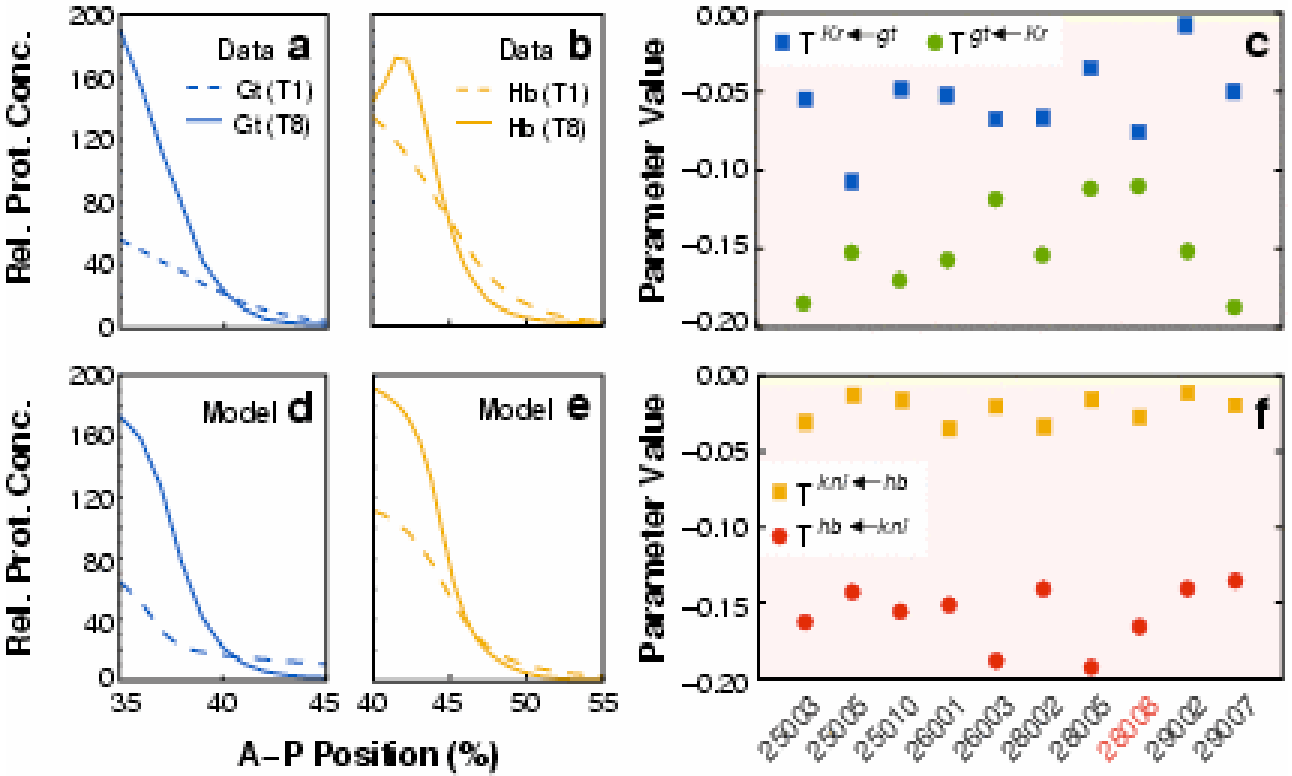


Constraints on the T Matrix

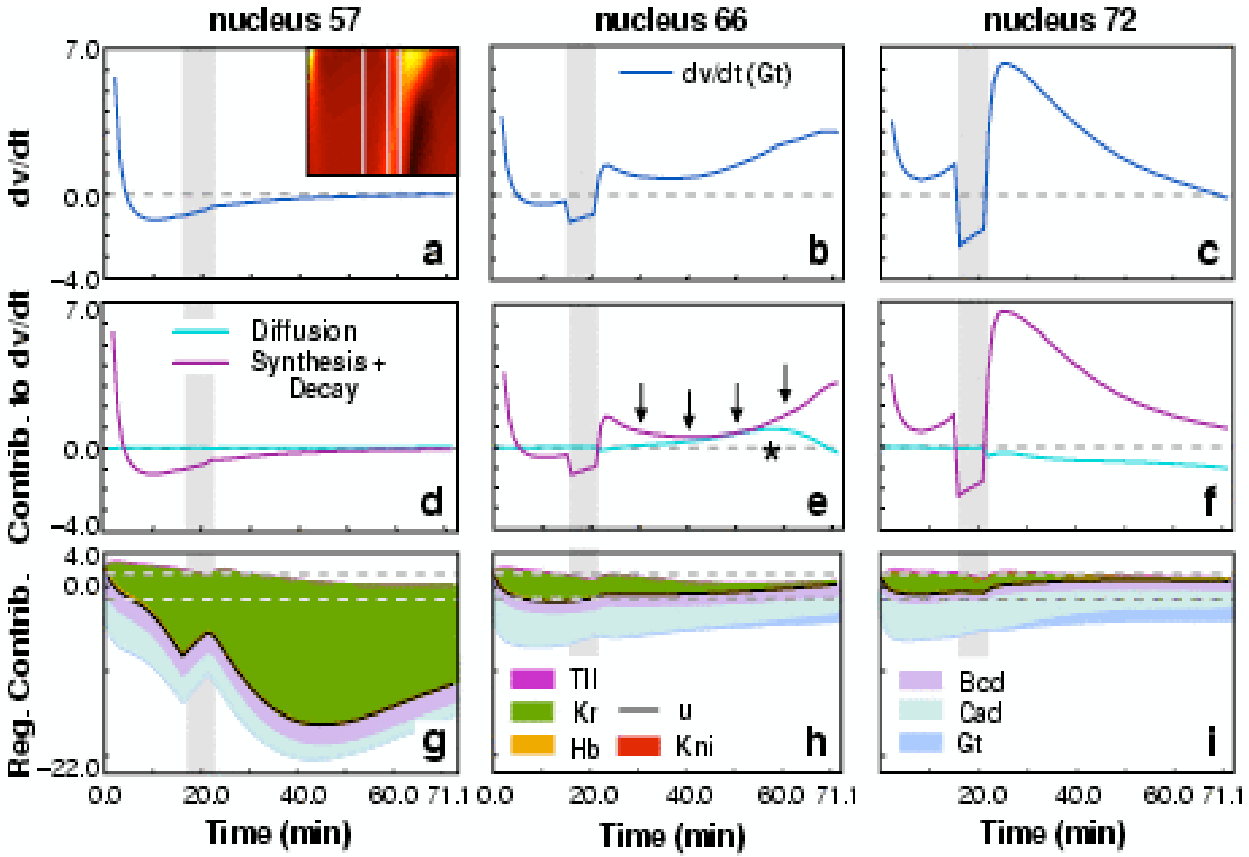


N = 10

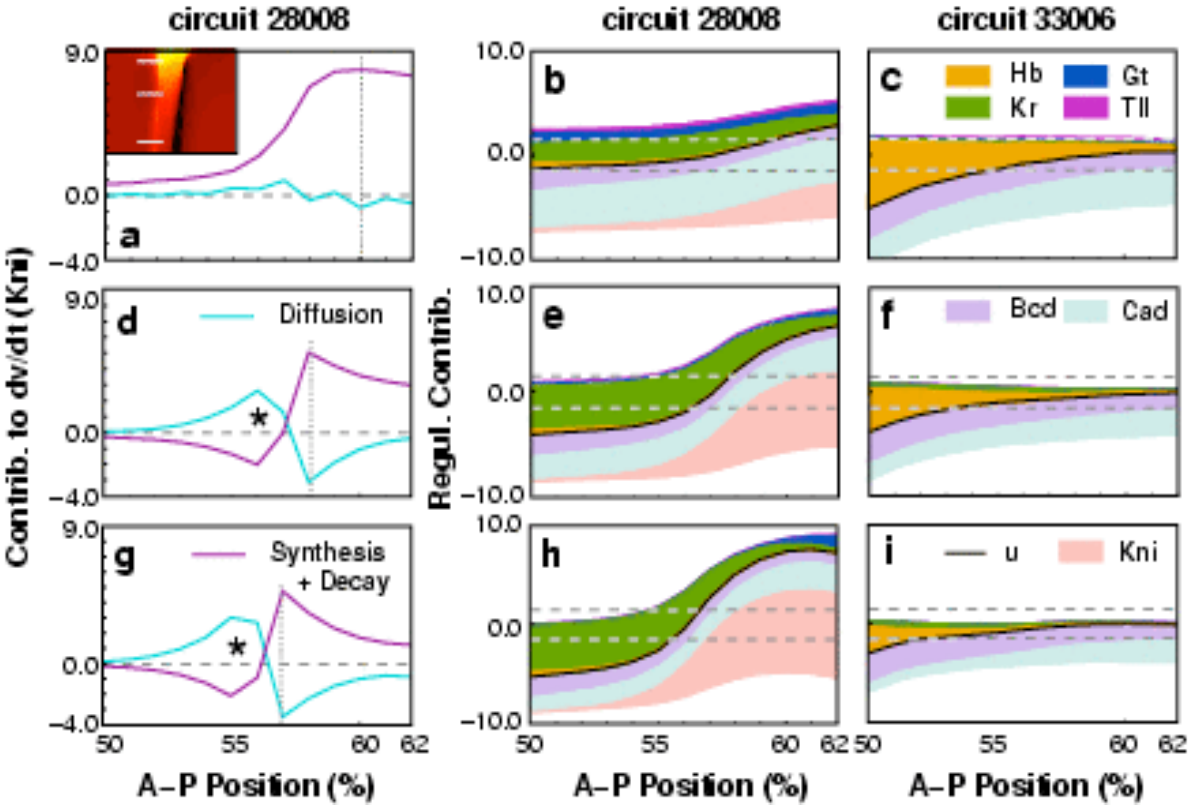
No shifts for the posterior boundaries of gt and hb anterior domains



Shift in the anterior boundary of the posterior *gt* domain



Shift in the anterior boundary of the posterior *kni* domain

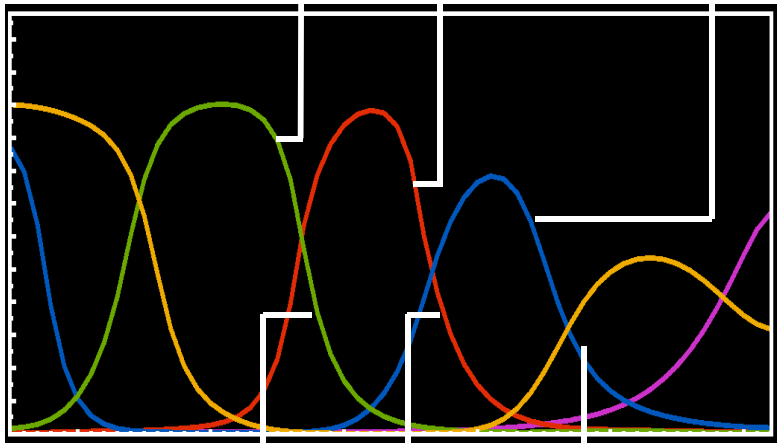


Posterior Boundaries

central *Kr* domain
asymmetric repression by Kni

posterior *kni* domain
asymmetric repression by Gt

posterior *gt* domain
asymmetric repression by Hb



posterior *hb* domain
follows shift of
posterior boundary of posteriorl *kni*

posterior *kni* domain
follows sharpening of
posterior boundary of anterior *hb*

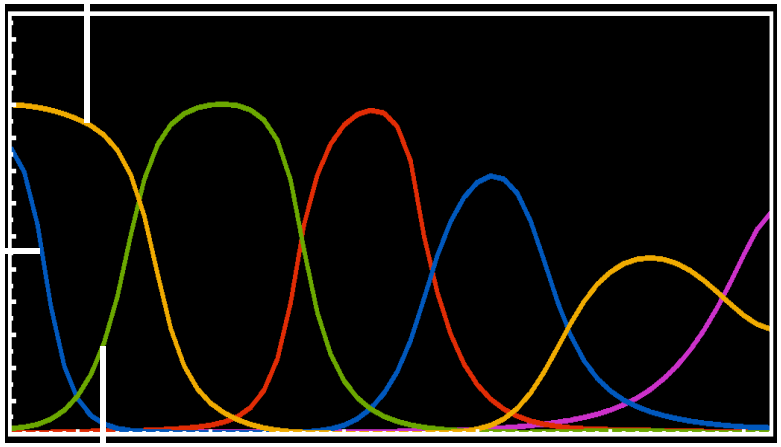
posterior *gt* domain
follows shift of
posterior boundary of central *Kr*

Anterior Boundaries

Posterior Boundaries

anterior *hb* domain
no shift
strong repression by Kni

anterior *gt* domain
no shift
strong repression by Kr



central *Kr* domain
very small shift
diffusion
early insufficient repression by Gt

Anterior Boundaries

Conclusions

- Proper positioning of gap gene domains requires specific regulatory interactions between gap genes.
- Positional information in early embryo is dynamic and can no longer be seen as a static coordinate system imposed on embryo by maternal genes.
- Posterior domains shift because of regulative cross-interactions. Anterior domains form in place under the control of maternal positional information. Thus, a mosaic mode of development prevails in the anterior and a regulative mode in the posterior of an embryo.
- Bcd is a Turing morphogen, not a modern morphogen, since it does not determine different territories of gene expression directly.

Acknowledgments

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