MSc GBE Course:
Genes: from sequence to function

Brief Introduction to Systems Biology

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Modeling Crash course

Pre-Steady-State Decoding of the Bicoid Morphogen Gradient

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Pre-Steady-State Decoding of the Bicoid Morphogen Gradient

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Morphogen gradients are established by the localized production and subsequent diffusion of signaling molecules. It is generally assumed that cell fates are induced only after morphogen profiles have reached their steady state. Yet, patterning processes during early development occur rapidly, and tissue patterning may precede the convergence of the gradient to its steady state. Here we consider the implications of pre-steady-state decoding of the Bicoid morphogen gradient for patterning of the anterior–posterior axis of the *Drosophila* embryo. Quantitative analysis of the shift in the expression domains of several Bicoid targets (gap genes) upon alteration of *bcd* dosage, as well as a temporal analysis of a reporter for Bicoid activity, suggest that a transient decoding mechanism is employed in this setting. We show that decoding the pre-steady-state morphogen profile can reduce patterning errors caused by fluctuations in the rate of morphogen production. This can explain the surprisingly small shifts in gap and pair-rule gene expression domains observed in response to alterations in *bcd* dosage.

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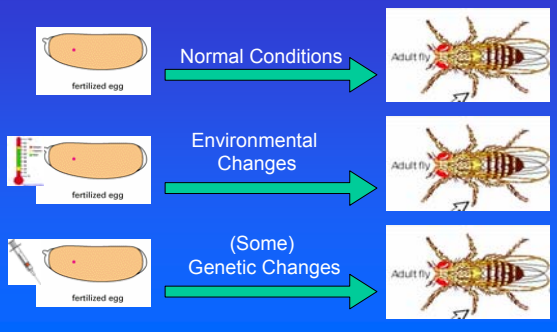
Drosophila as model for Development

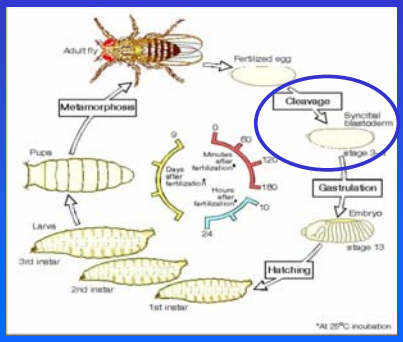
Development is a precise process



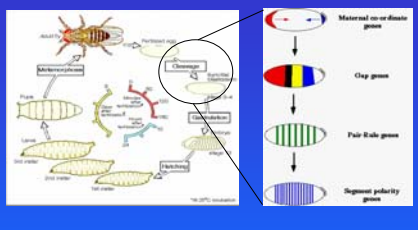
How to ensure buffering when patterning proceeds rapidly?

Genetic buffering mechanisms are hard to establish in fast development!

The Life Cycle of *Drosophila*

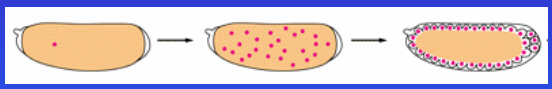


Drosophila development



- Maternal *bicoid* mRNA is localized at anterior pole
- Diffusion of the bicoid protein establishes gradient (defining anterior-posterior axis)
- Cascade of gene regulation refines segments of bodyplan (that will determine shape of adult fly)

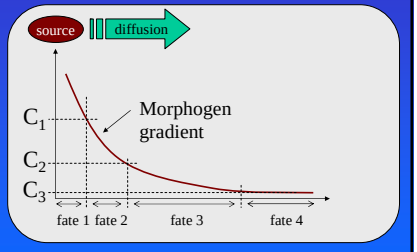
Syncytial Blastoderm Stage



Nuclei divide, but no intercellular membranes yet

Free diffusion
of developmentally important factors between the nuclei of the syncytium!

Morphogen Gradients are used for translating cellular position into cell-fate

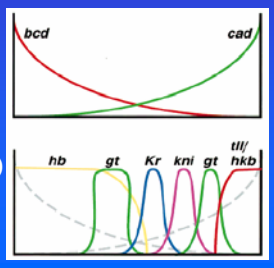


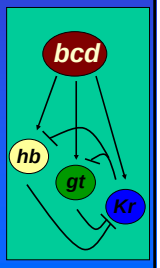
Cell fates are determined according to the concentration of the morphogen

The maternal and zygotic segmentation genes form a hierarchical network of sequential transcriptional regulation

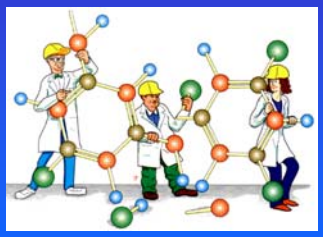
Maternal genes:
Bicoid (bcd)
Caudal (cad)

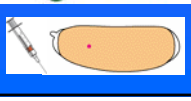
Zygotic genes:
Hunchback (hb)
Giant (gt)
Kruppel (Kr)
Knirps (kni)
…



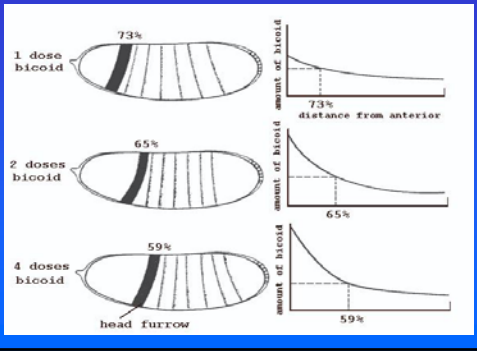


What happens when perturbing the system?

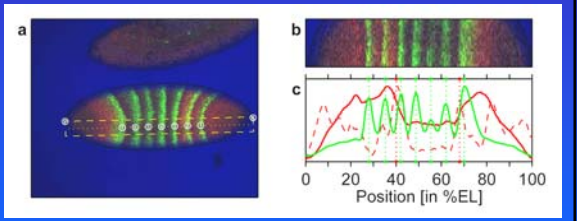




Changes in bicoid mRNA dosage lead to shifts in expression domain of downstream genes:

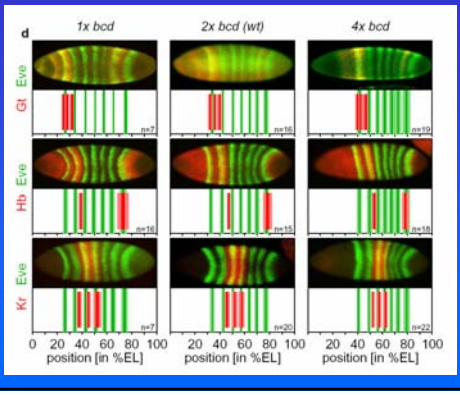


Quantitative Study using Automated Image Processing

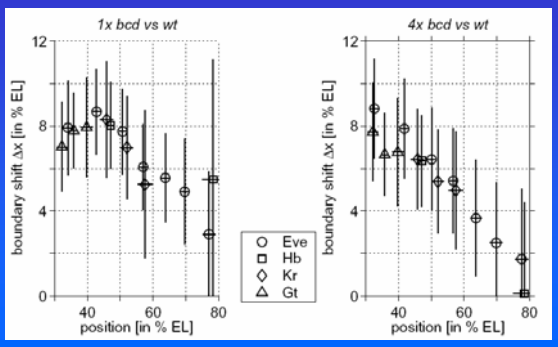


a: mark anterior and posterior pole, first and last eve-stripe
b: extract region around dorsal midline
c: semi-automatic determination of stripes/boundaries

:Our Experimental Results



Shifts are small and position-dependent!



A bit of Theory…

The morphogen density $M(x,t)$ can be modeled by a differential equation (reaction diffusion equation):

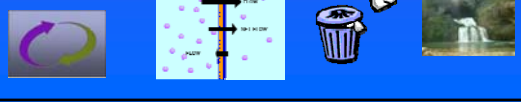
$$\frac{\partial}{\partial t}M(x,t) = D\frac{\partial^2}{\partial x^2}M(x,t) - \alpha M(x,t) + s(x,t)$$

Change in concentration of the morphogen at position x, time t

Diffusion D: diffusion const.

Degradation α: decay rate

Source



The Canonical Model

Steady state:

$\partial M(x,t)/\partial t = 0$ (no change in time)

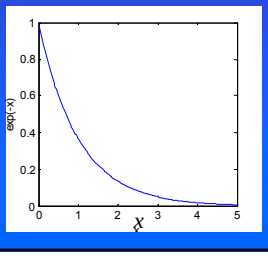
Solution:

$M(x) = M_0 \exp(-x/\lambda)$

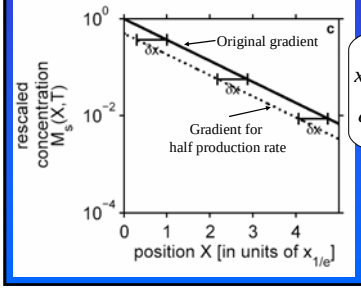
Length scale:

$\lambda = \sqrt{D/\alpha} = \sqrt{D\tau}$

decay time



In steady-state induced shifts are <u>independent</u> of position:



$$x = \lambda \cdot log[M(0)/M(x)]$$

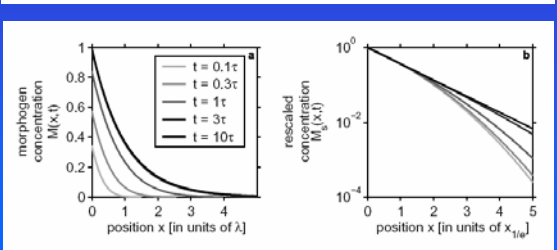
$$\delta x = \lambda \cdot log\, 2 \approx 12\% EL$$

What if the profile has *not* reached its steady state yet?

- **Steady state assumption is *ad-hoc***
- **Early patterning processes are very rapid**
- **Consistent with typical values for diffusion**

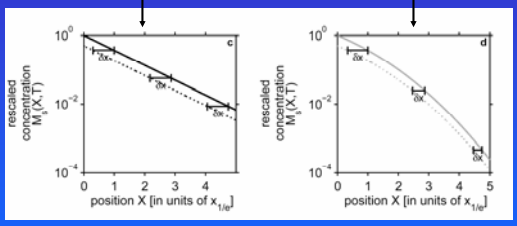
Modeling the morphogen (Bcd) by a time-dependent PDE:

$$\frac{\partial}{\partial t}M(x,t) = D\frac{\partial^2}{\partial x^2}M(x,t) - \alpha M(x,t) + s(x,t)$$



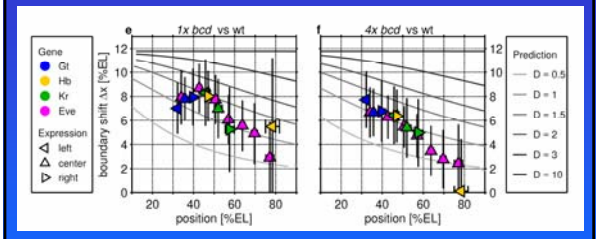
Shifts induced by altered *bcd* dosage:

<u>steady-state</u> vs <u>transient profile</u>



Decoding the transient profile:
- **Position-dependent shifts**
- **Smaller shifts towards the posterior pole**

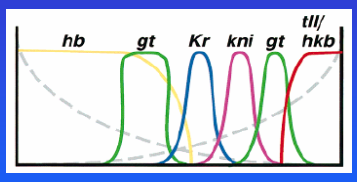
Model vs Data

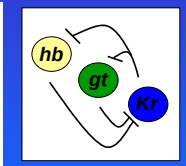


Prediction: Bcd diffusion is relatively small!

$$D \sim 1\mu m^2 / sec$$

Pattern Fixation





Can mutual suppression of gap genes fixate their expression domains after initial pattern is established?

Simulating the system

Model using partial differential equations:

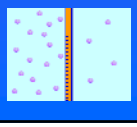
$$\frac{\partial}{\partial t}C_i(x,t) = D_i\frac{\partial^2}{\partial x^2}C_i(x,t) - \alpha_i C_i(x,t) + s_i(t)$$

Change in concentration of gene i=Bcd, Gt, Hb, … at position *x*, time *t*

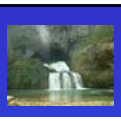
Diffusion D_i: diffusion const.

Degradation α_i: decay rate

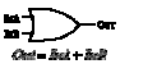
Source

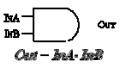


Source term encodes gene-interactions

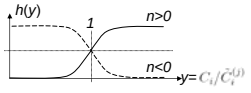


$$s_i(t) = \underbrace{\Theta(t-t_i)p_i}_{\text{Start at time } t_i} \cdot \underbrace{\sum_{j\in A_i} h(C_i/\tilde{C}_i^{(j)}, n_i^{(j)})}_{\text{Sum over activators: OR}} \cdot \underbrace{\prod_{j\in S_i} h(C_i/\tilde{C}_i^{(j)}, n_i^{(j)})}_{\text{Multiply suppressors: AND}}$$

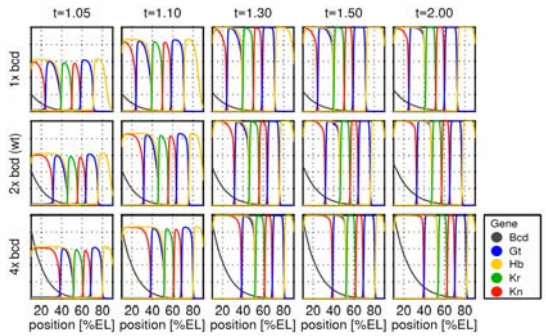




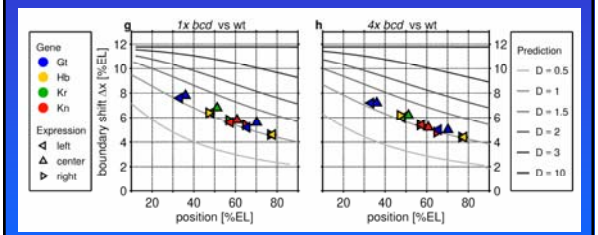
Hill-function: $h(y,n) \equiv \frac{y^n}{1+y^n}$



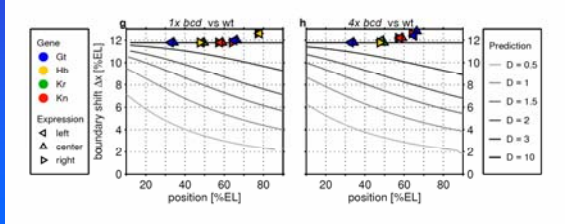
Gradient evolution in time



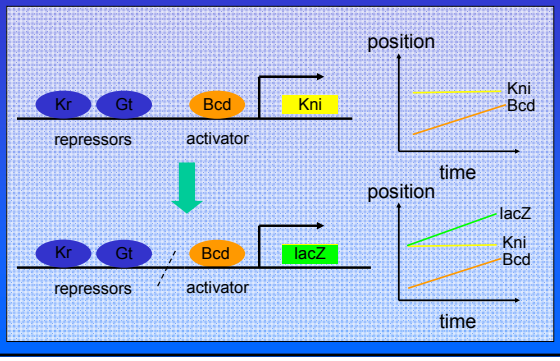
Simulations agree with naïve model

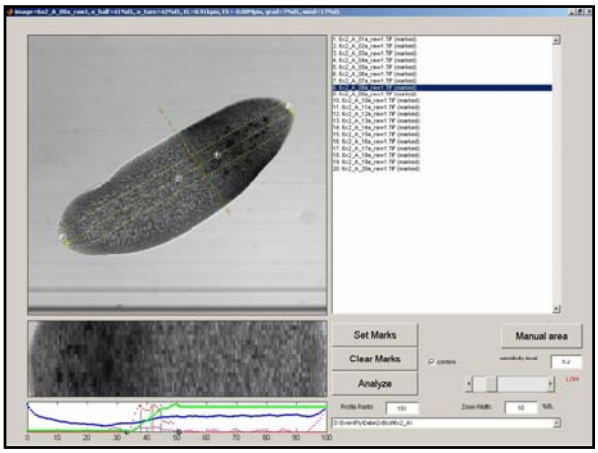


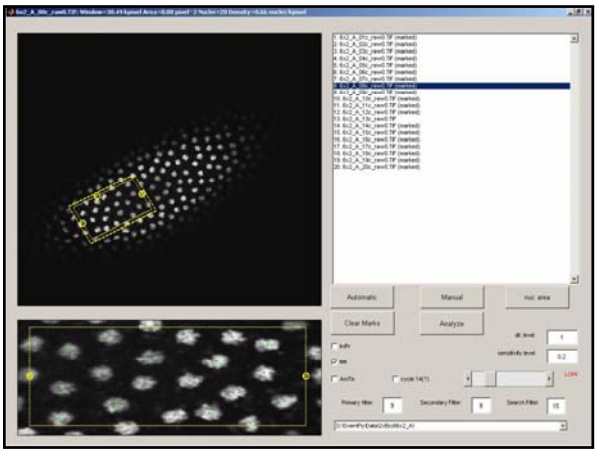
Buffering is lost when patterning occurs after Bcd has reached steady state (t_{init} >> τ)!



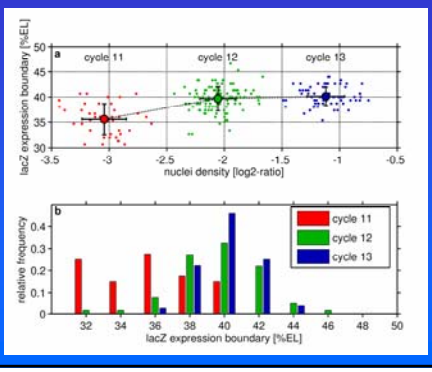
"Nail down" experiment







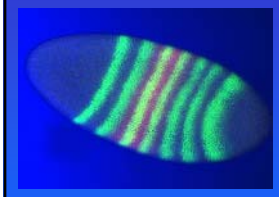
lacZ reporter indicates that Bcd has not reached steady state during patterning

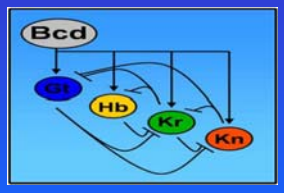


Conclusion:

Systems approach to the gap-gene network reveals that *dynamic* decoding of *pre-steady state* morphogen gradient is consistent with experimental data from the anterior-posterior patterning in early *Drosophila* embryos

Acknowledgements





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Gregor et al., 2007