

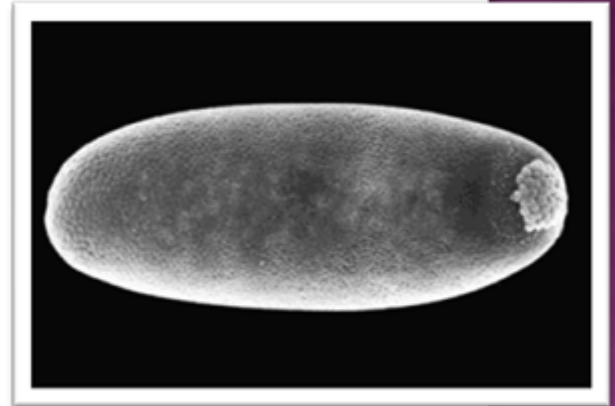
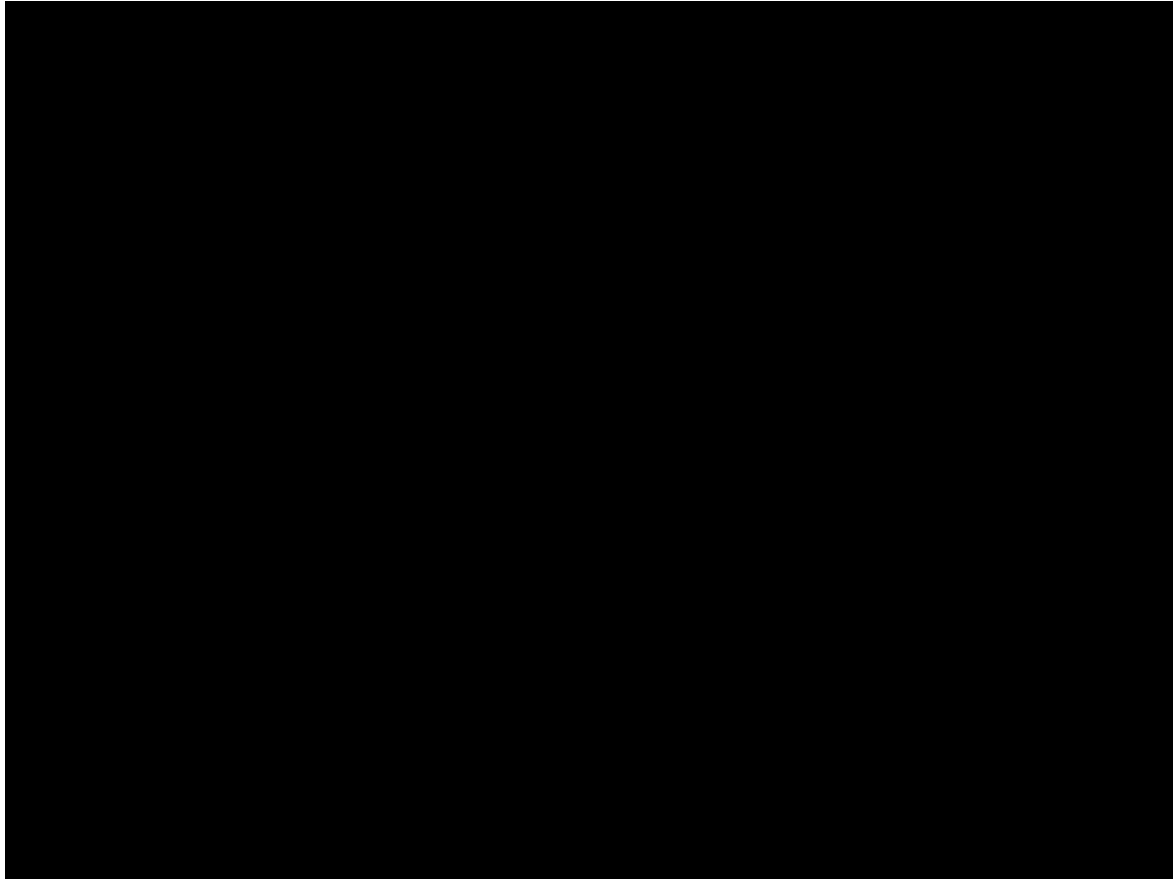
# Deterministic and Stochastic Models of Bicoid Protein Gradient Formation in *Drosophila* Embryos

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*Learning and Inference in Computational Systems Biology 2010*

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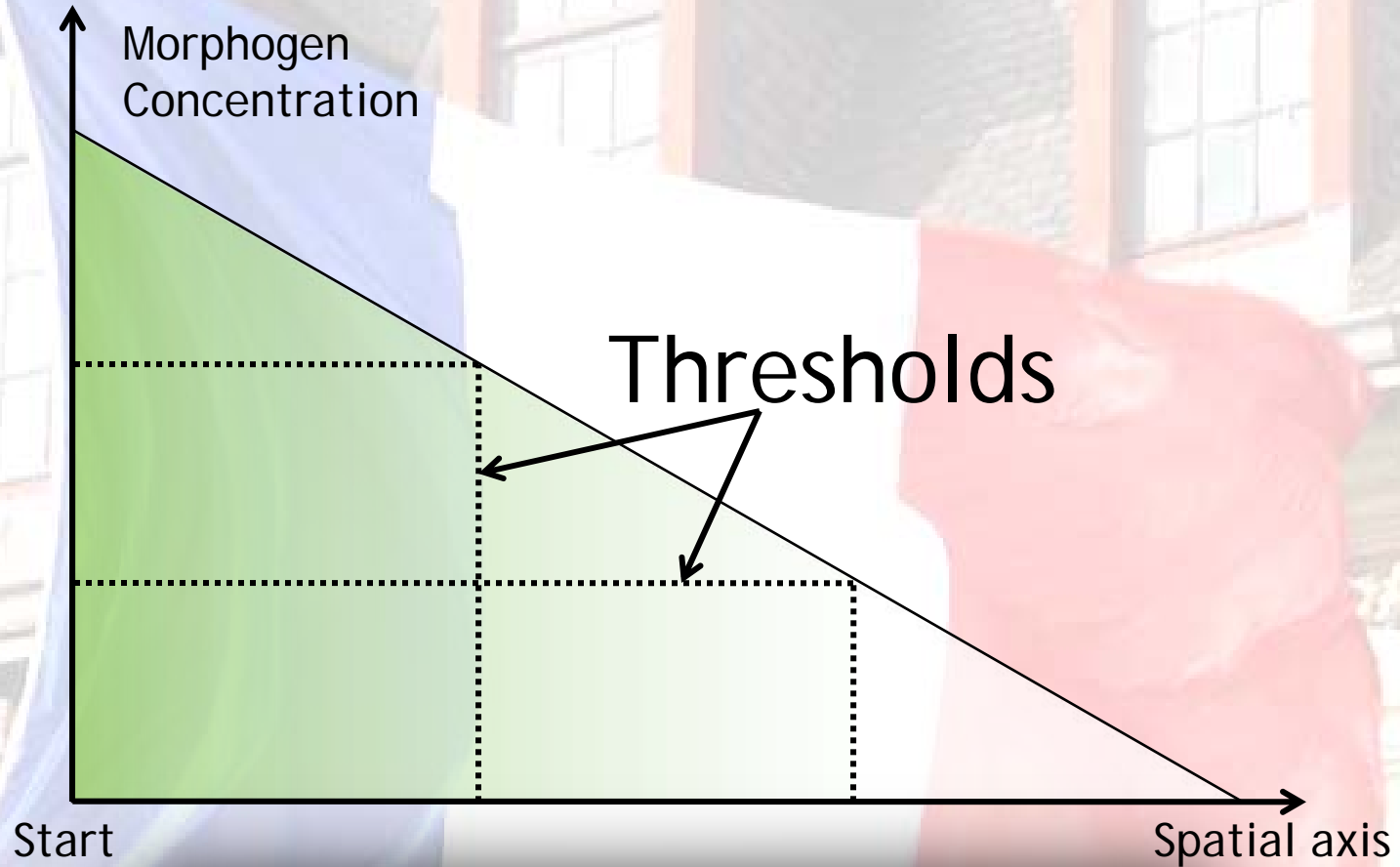
# Drosophila



Essential Cell Biology, 3<sup>rd</sup> Edition, 2009

By Bruce Alberts, Dennis Bray, Karen Hopkin, Alexander Johnson,  
Julian Lewis, Martin Raff, Keith Roberts, Peter Walter

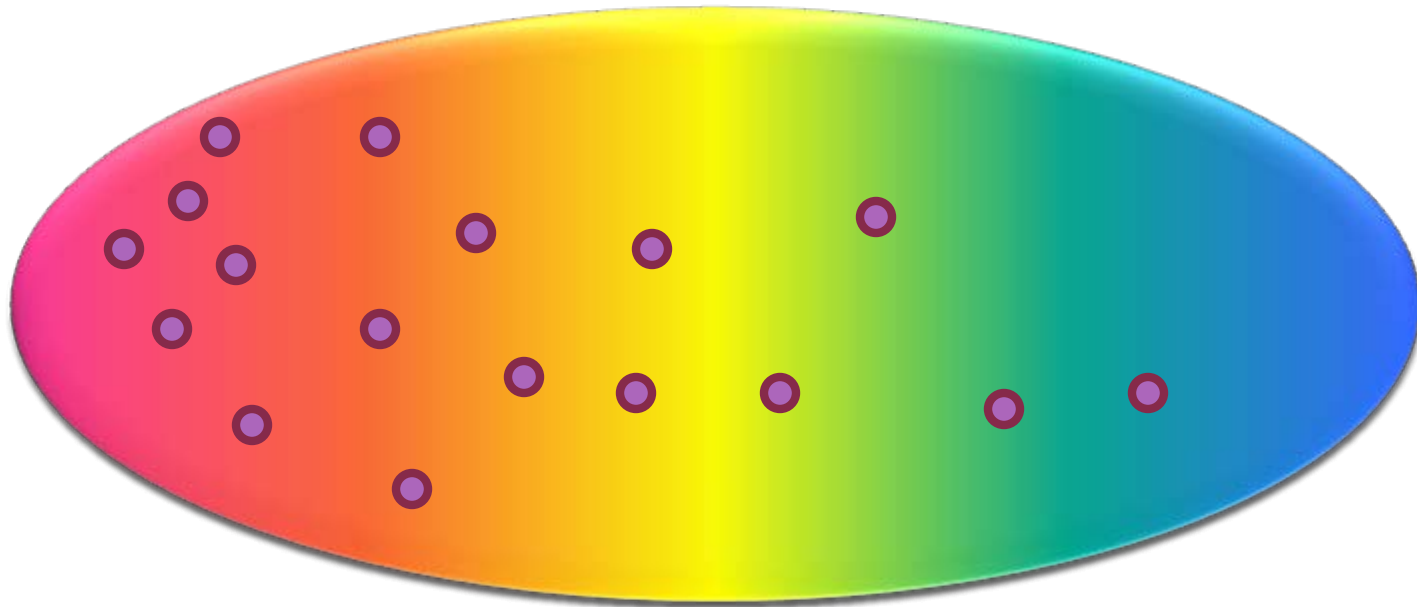
# French Flag



# Bicoid Morphogen

- ◉ Drosophila body plan and position information.
- ◉ Providing the concentration mechanism to activate other gap genes in Drosophila embryo
- ◉ Contributing to set up the anterior-posterior axis.
- ◉ Controlling cell fate along 70% of this axis.

# Bicoid Morphogen Concentration



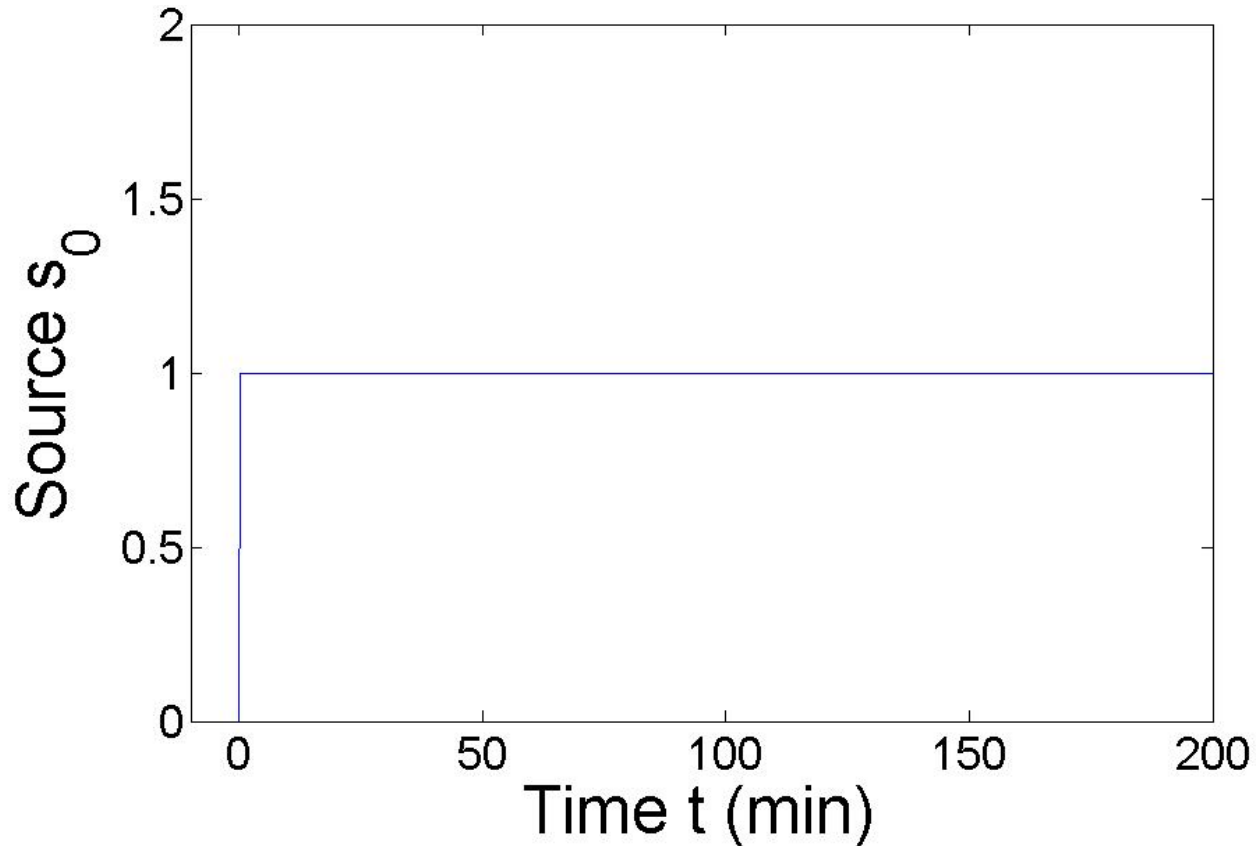
**Anterior part**

**Posterior part**

# Constant Source

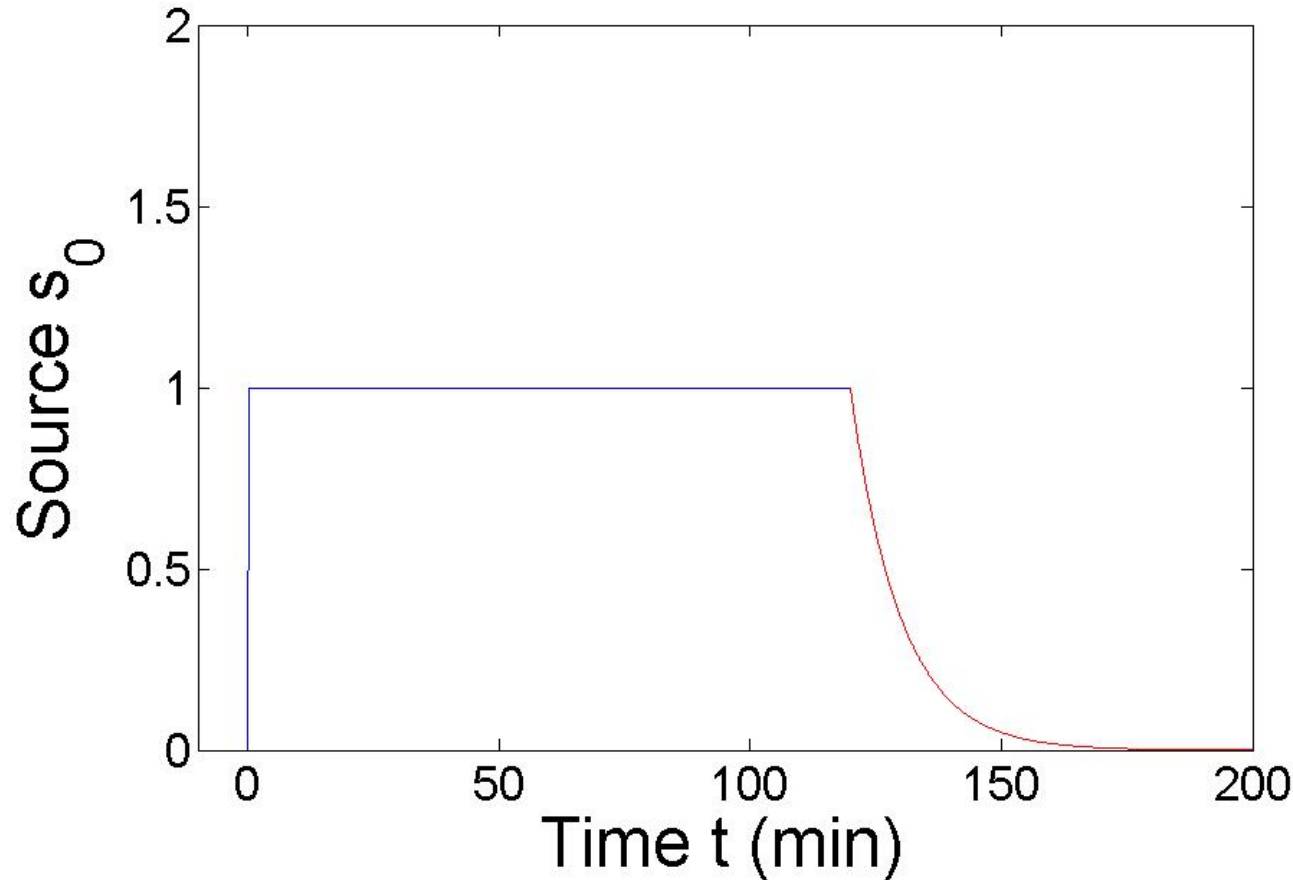
- ◉ Usual assumption

$$S_{con}(x, t) = S_0 \delta(x) \Theta(t)$$



# New Source Model

$$S_{com} = S_0 \delta(x) (\Theta(t) - \Theta(t - t_0)) + S_0 \delta(x) \Theta(t - t_0) \exp\left\{-\frac{t - t_0}{\tau_m}\right\}$$



Surdej, P., Jacobs-Lorena, M.: *Developmental regulation of bicoid mRNA stability is mediated by the first 43 nucleotides of the 3' untranslated region*. Molecular and Cellular Biology 18(5) (1998) 2892-2900

# Reaction Diffusion Equation

- The reaction-diffusion equation of single-morphogen concentration system is below:

$$\frac{\partial}{\partial t} M(x, t) = D \frac{\partial^2}{\partial x^2} M(x, t) - \tau_p^{-1} M(x, t) + S(x, t)$$

- $M(x, t)$  is morphogen concentration
- $S(x, t)$  is a general source term at the anterior pole
- $D$  is diffusion constant
- $\tau_p$  is half-life of the morphogen protein

Turing, A.: *The chemical basis of morphogenesis*. (1952)

Bergmann, S : *Pre-Steady-State Decoding of the Bicoid Morphogen Gradient*. (2007)



# Reaction Diffusion Equation in Flow model

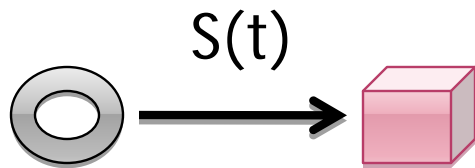
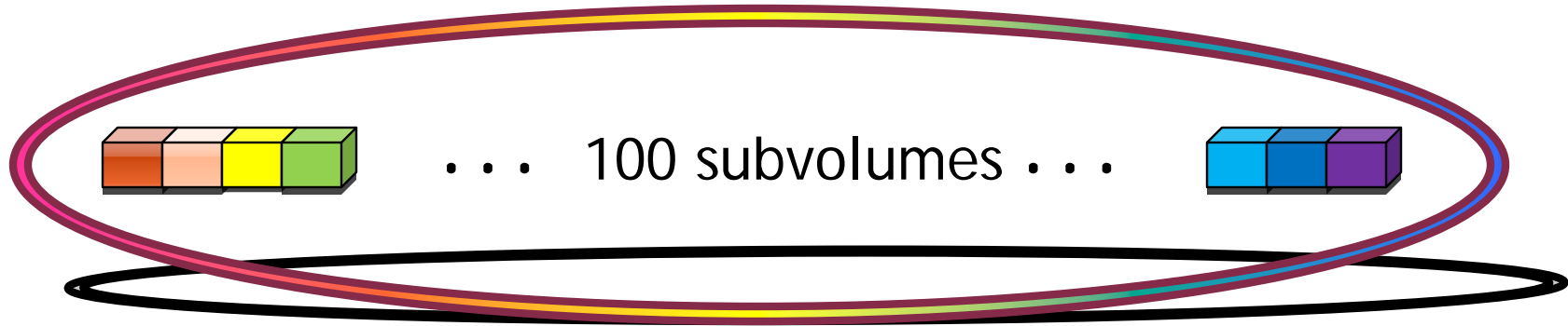
- The reaction-diffusion equation of single-morphogen concentration system with cytoplasmic flow:

$$\frac{\partial}{\partial t} M(x, t) = D \frac{\partial^2}{\partial x^2} M(x, t) - \tau_p^{-1} M(x, t) - v \frac{\partial}{\partial x} M(x, t) + S(x, t)$$

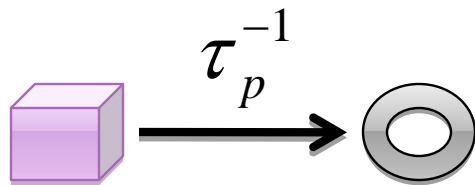
- $M(x, t)$  is morphogen concentration
- $S(x, t)$  is a general source term at the anterior pole
- $D$  is diffusion constant
- $\tau_p$  is half-life of the morphogen protein
- $v$  is flow velocity

# Stochastic Model

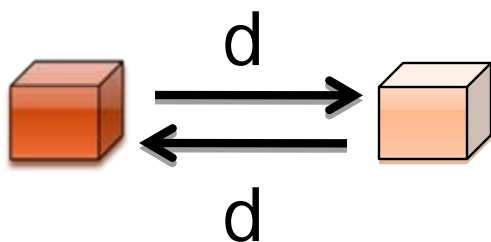
- Bicoid proteins chemical reaction diffusion



Bicoid proteins production

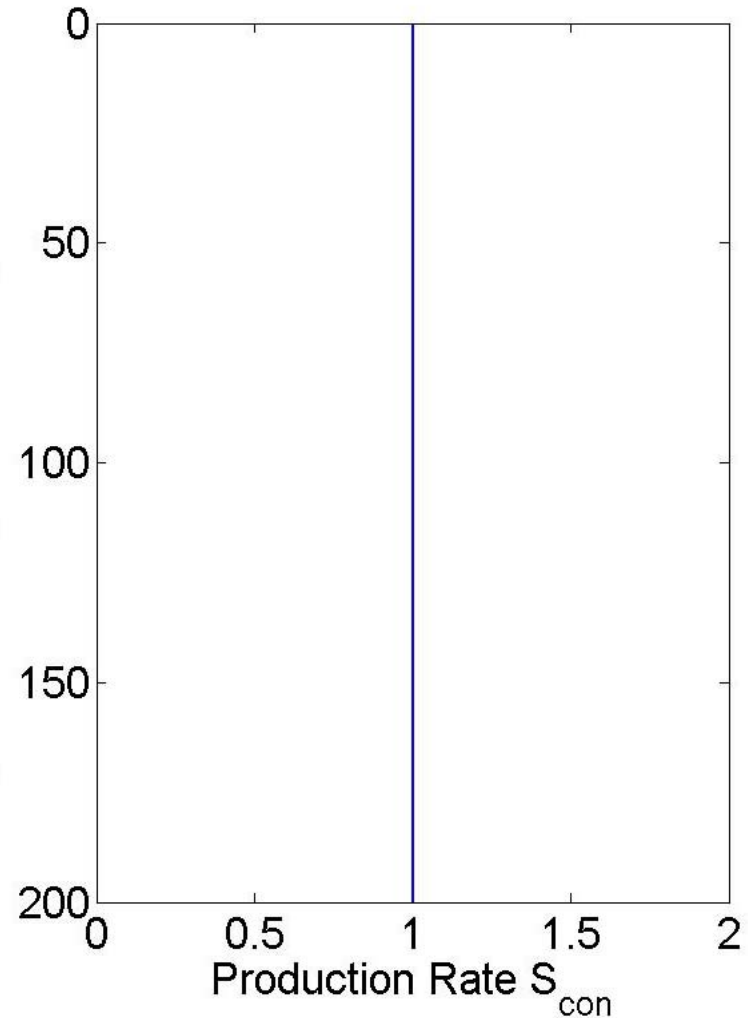
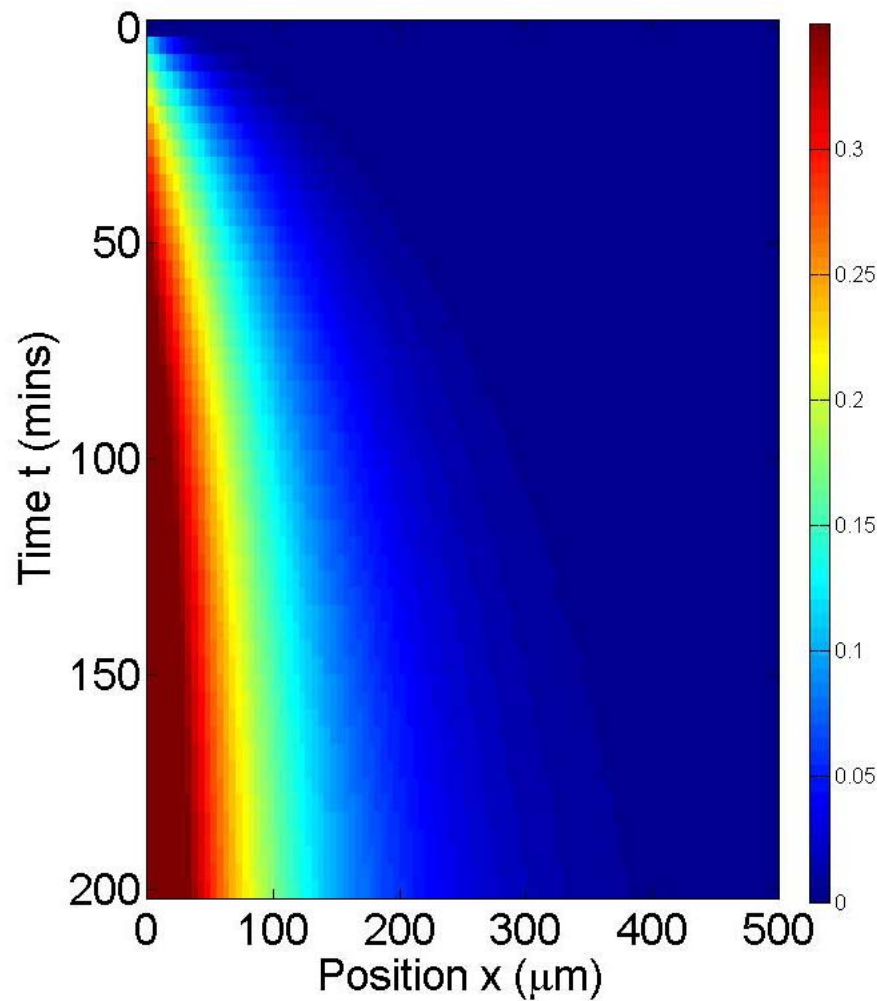


Bicoid proteins degradation

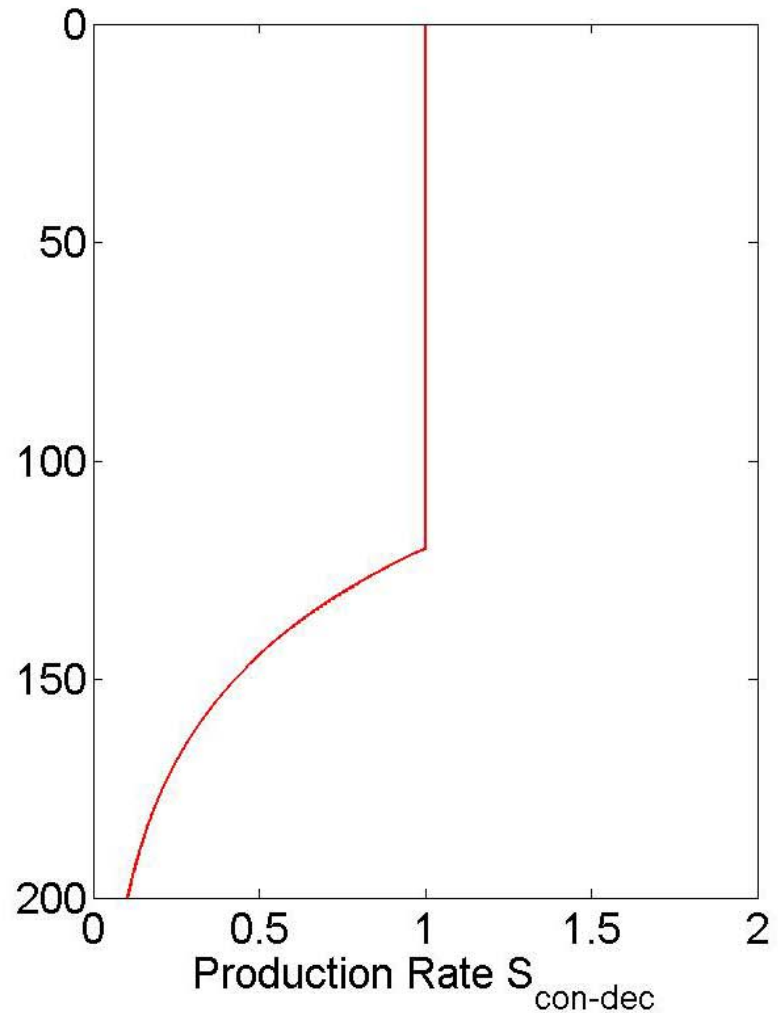
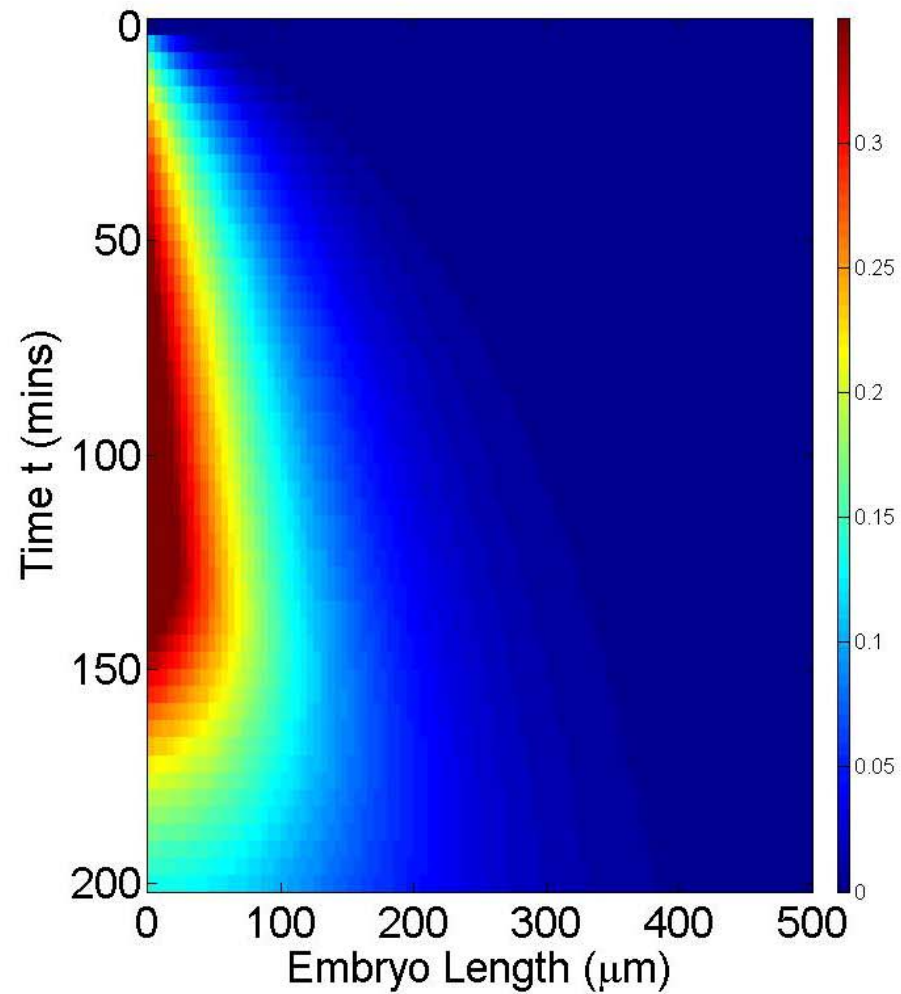


Bicoid proteins diffusion

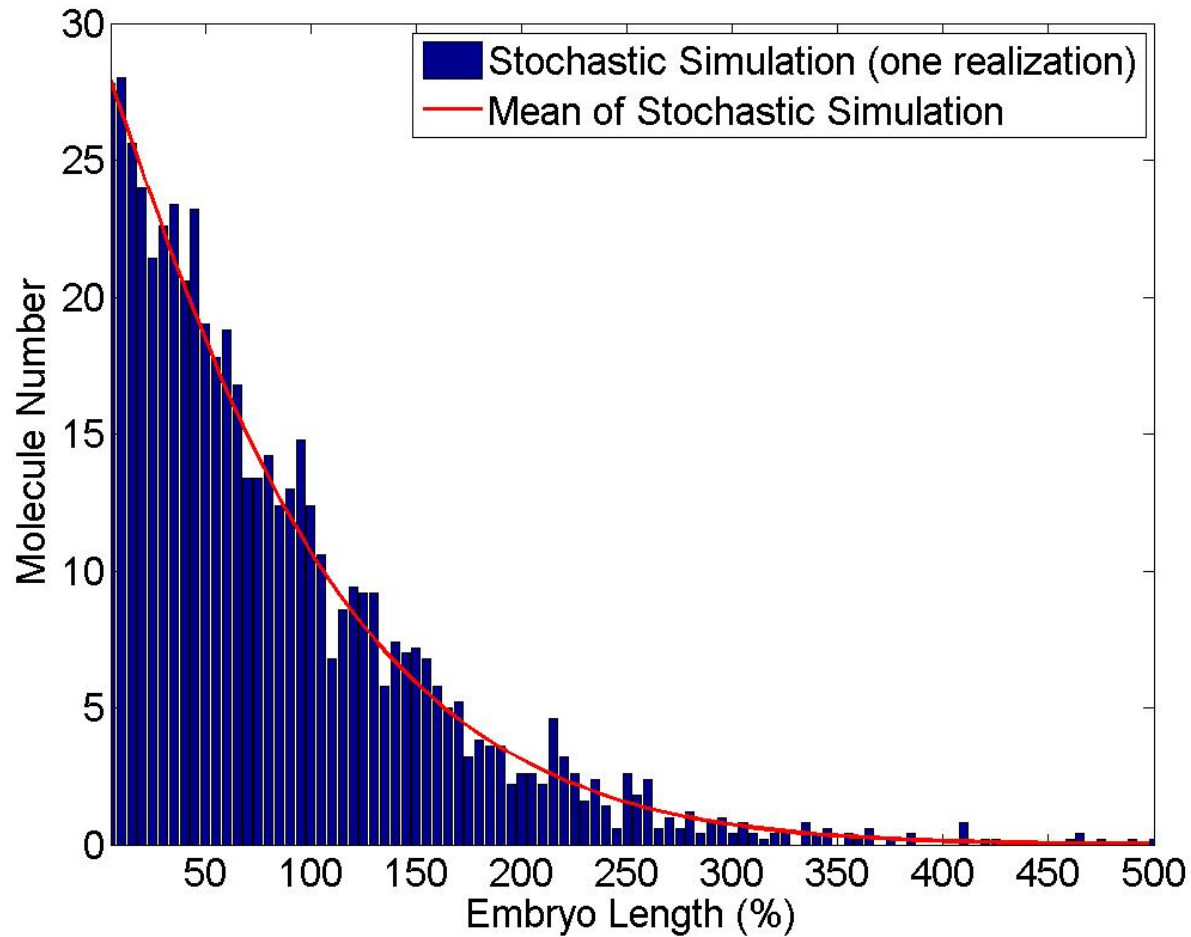
# Solution to Model with Constant Source



# Solution to Model with Combined Source



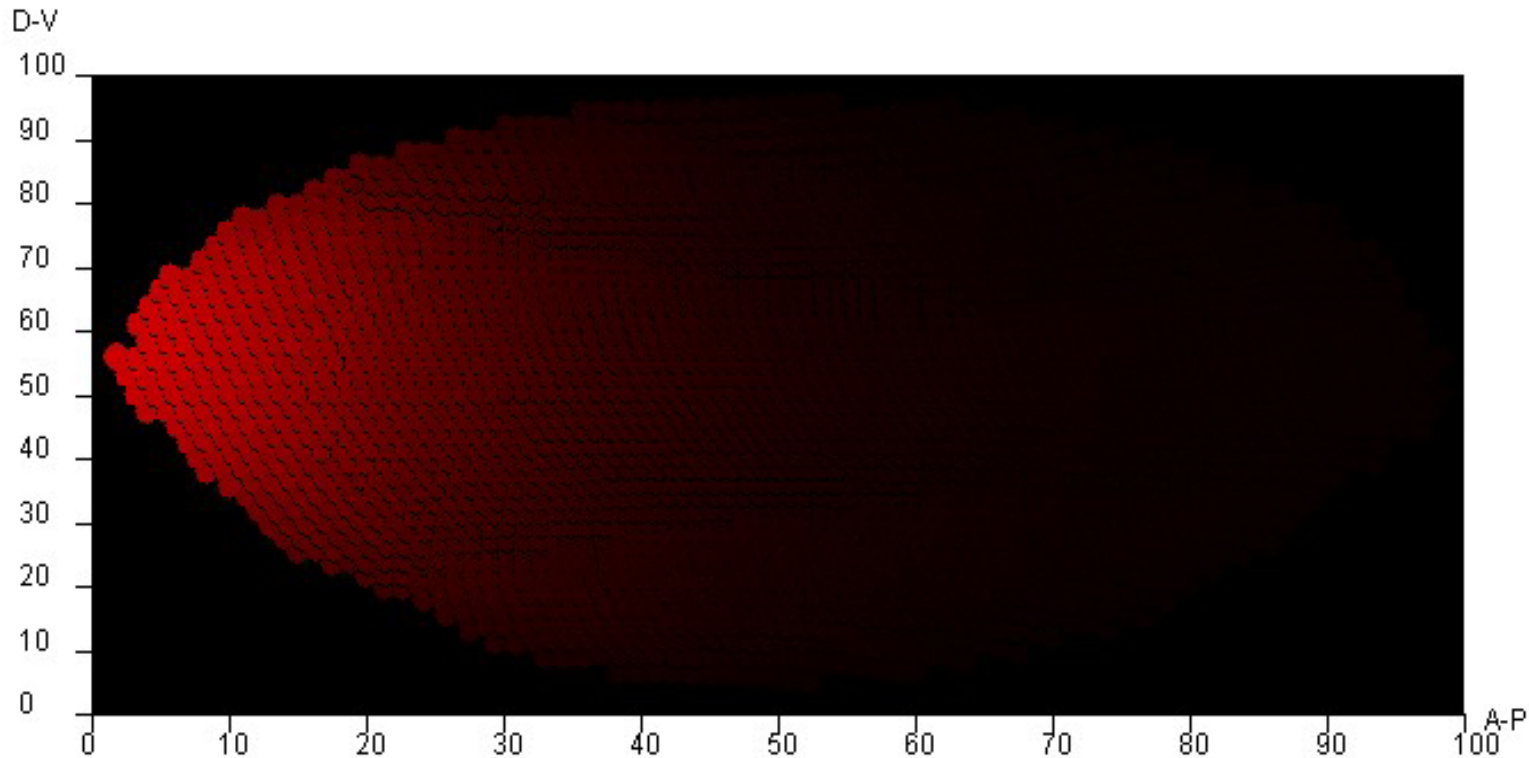
# Solution to Stochastic model



# Measured Data



- Integrated 2D patterns - reconstructed image  
14A-2

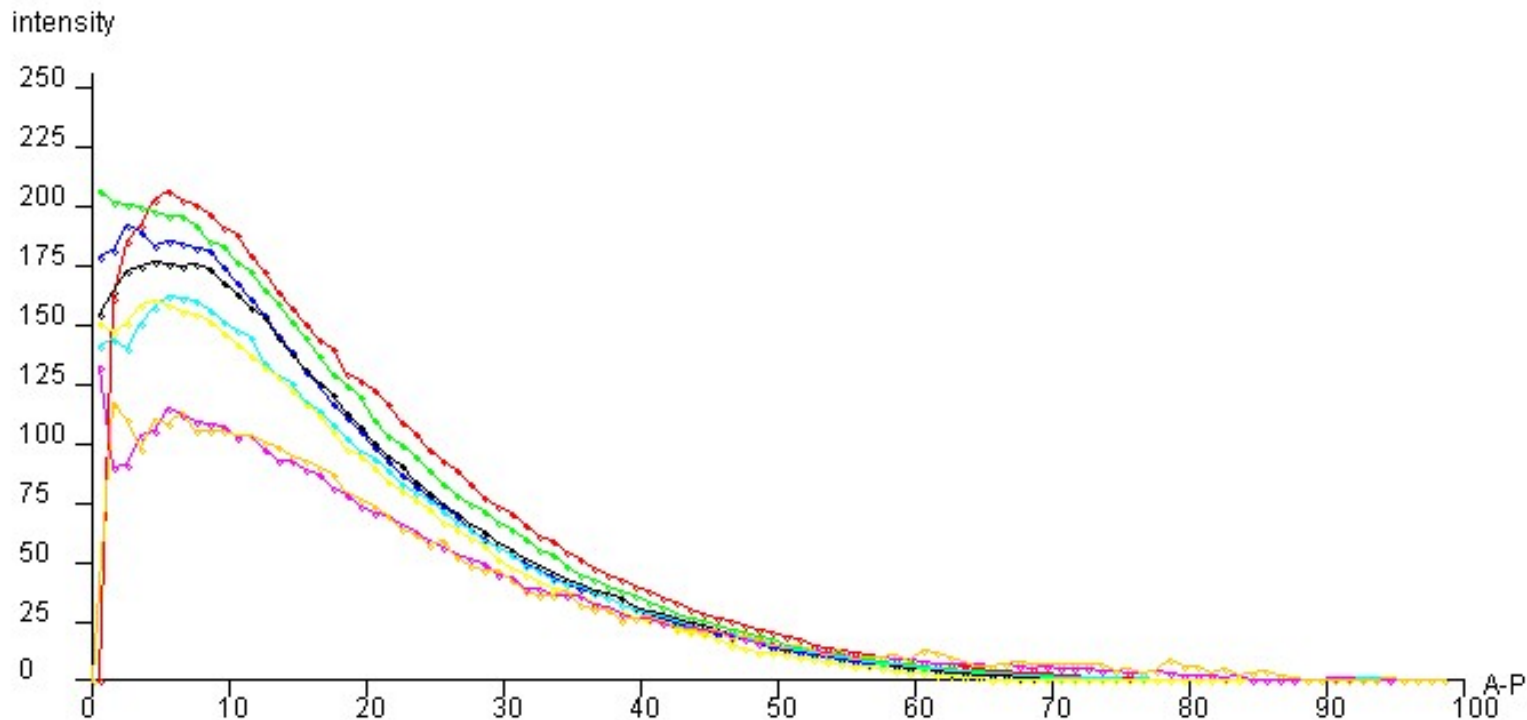


# Measured Data

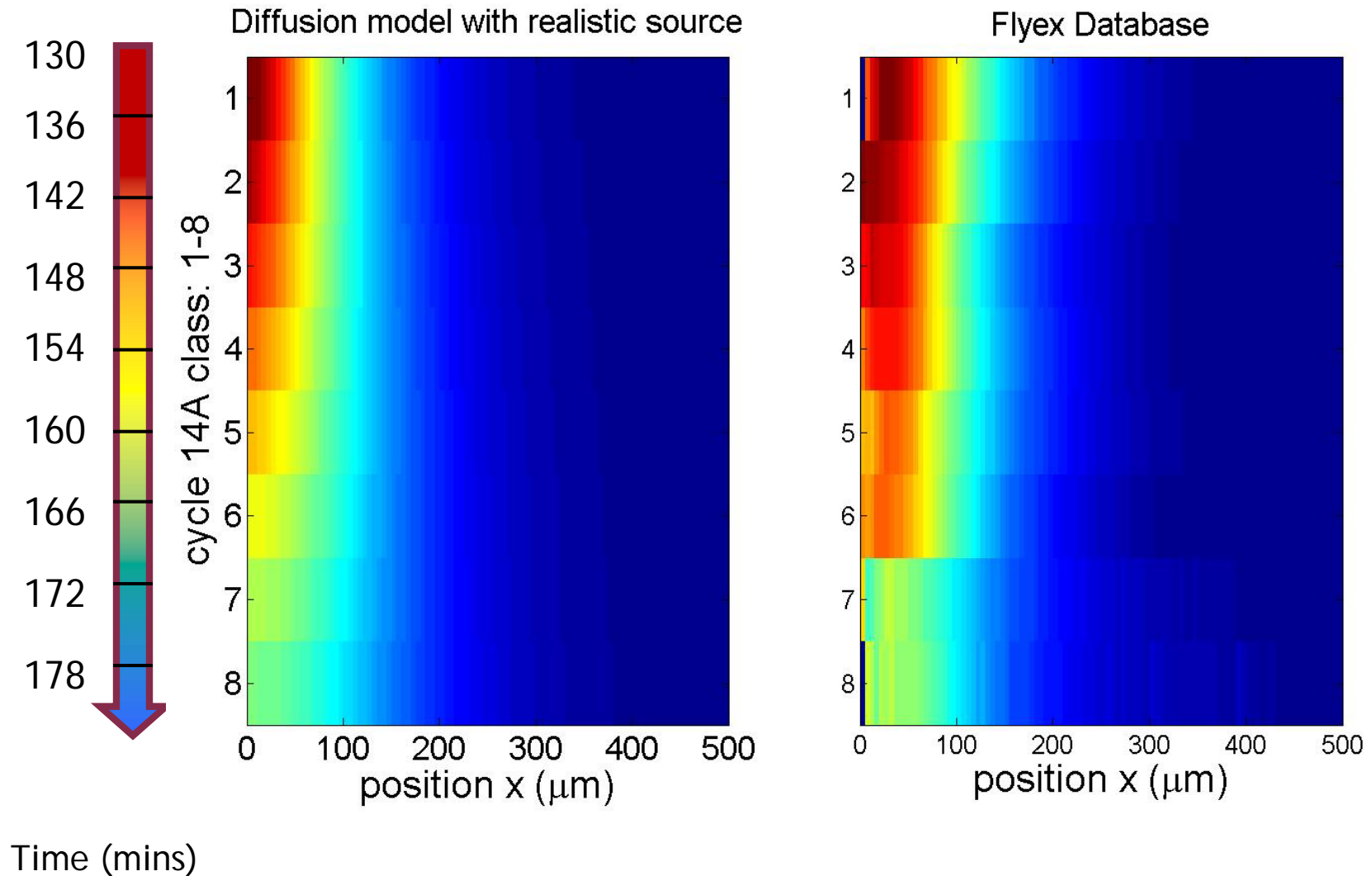


- 1D integrated data - cycle 14A (1-8 classes)

1)  2)  3)  4)  5)  6)  7)  8)

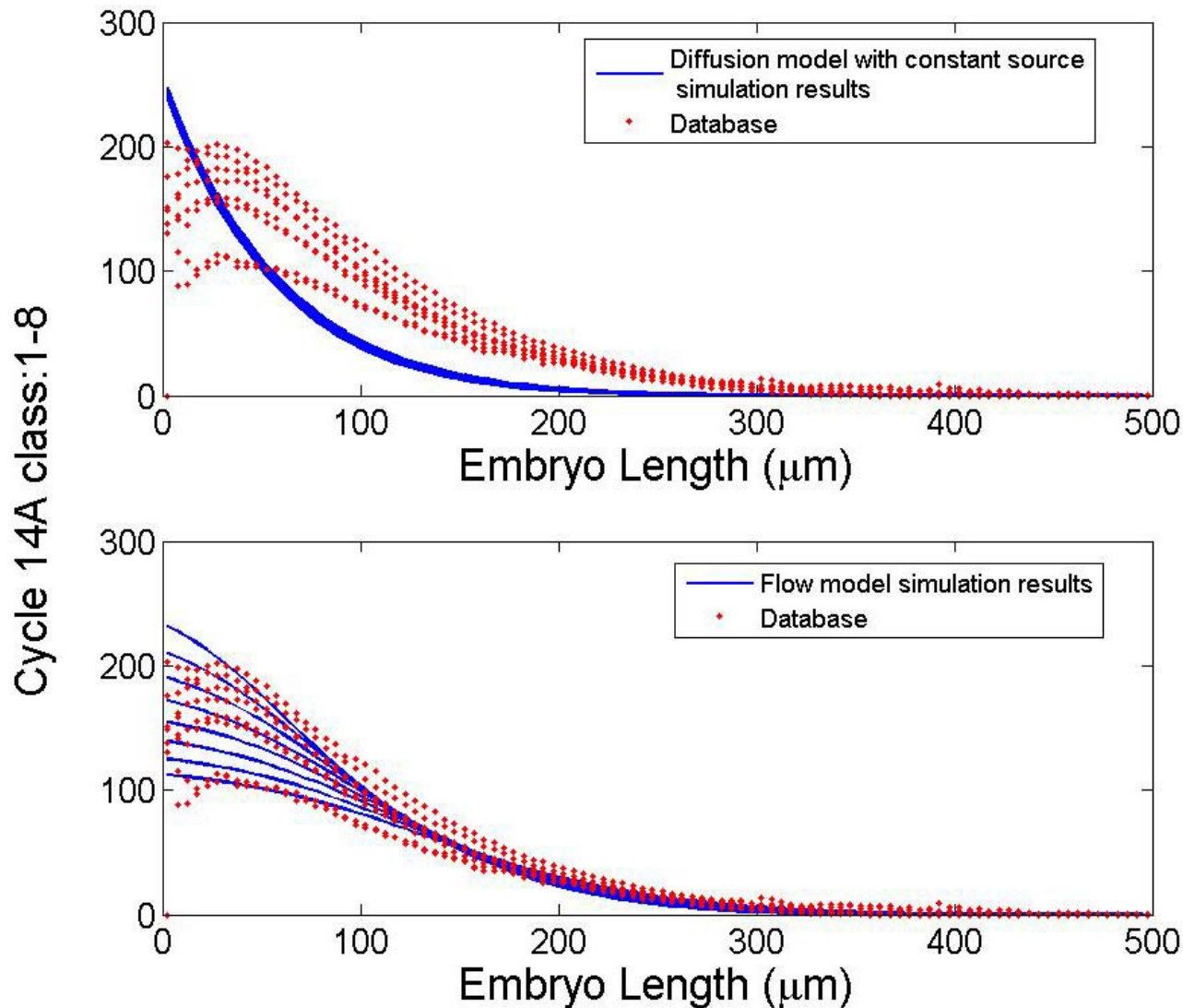


# Matching Models to Data

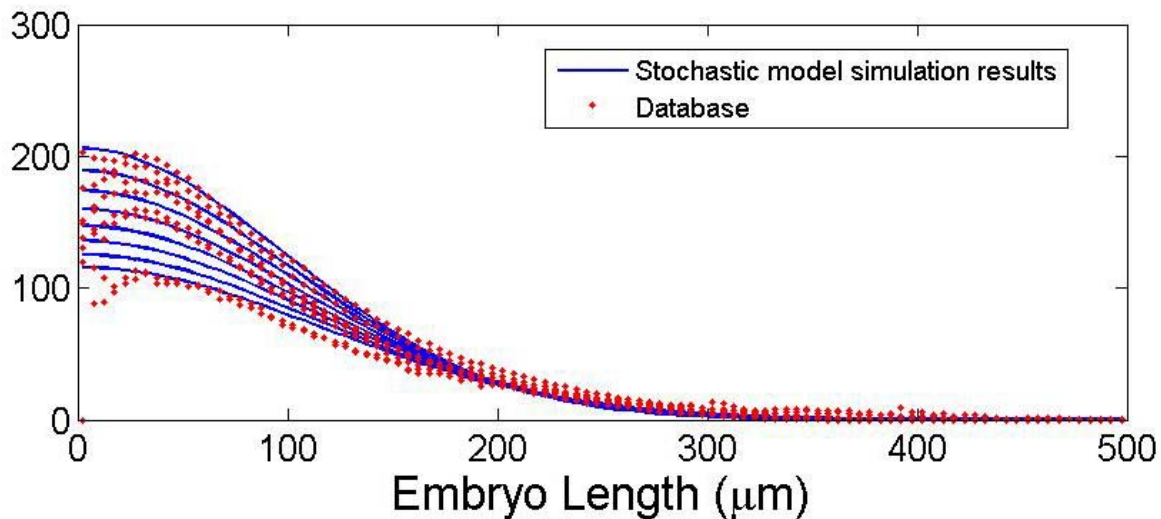
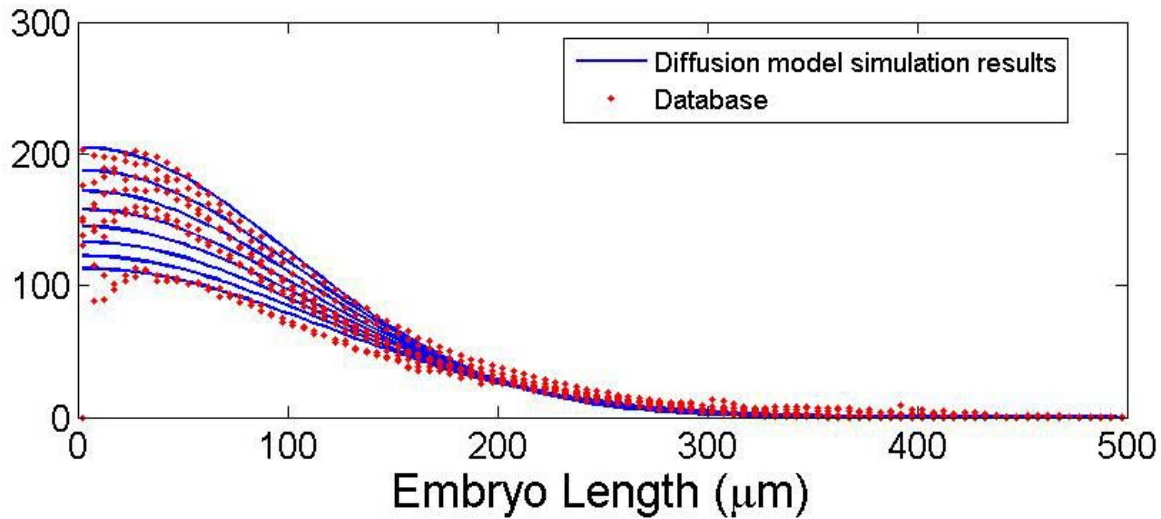




# Comparison Between Model Output and Database in Cycle14A with 8 Classes



# Comparison Between Model Output and Database in Cycle14A with 8 Classes



# Estimating Parameter Values

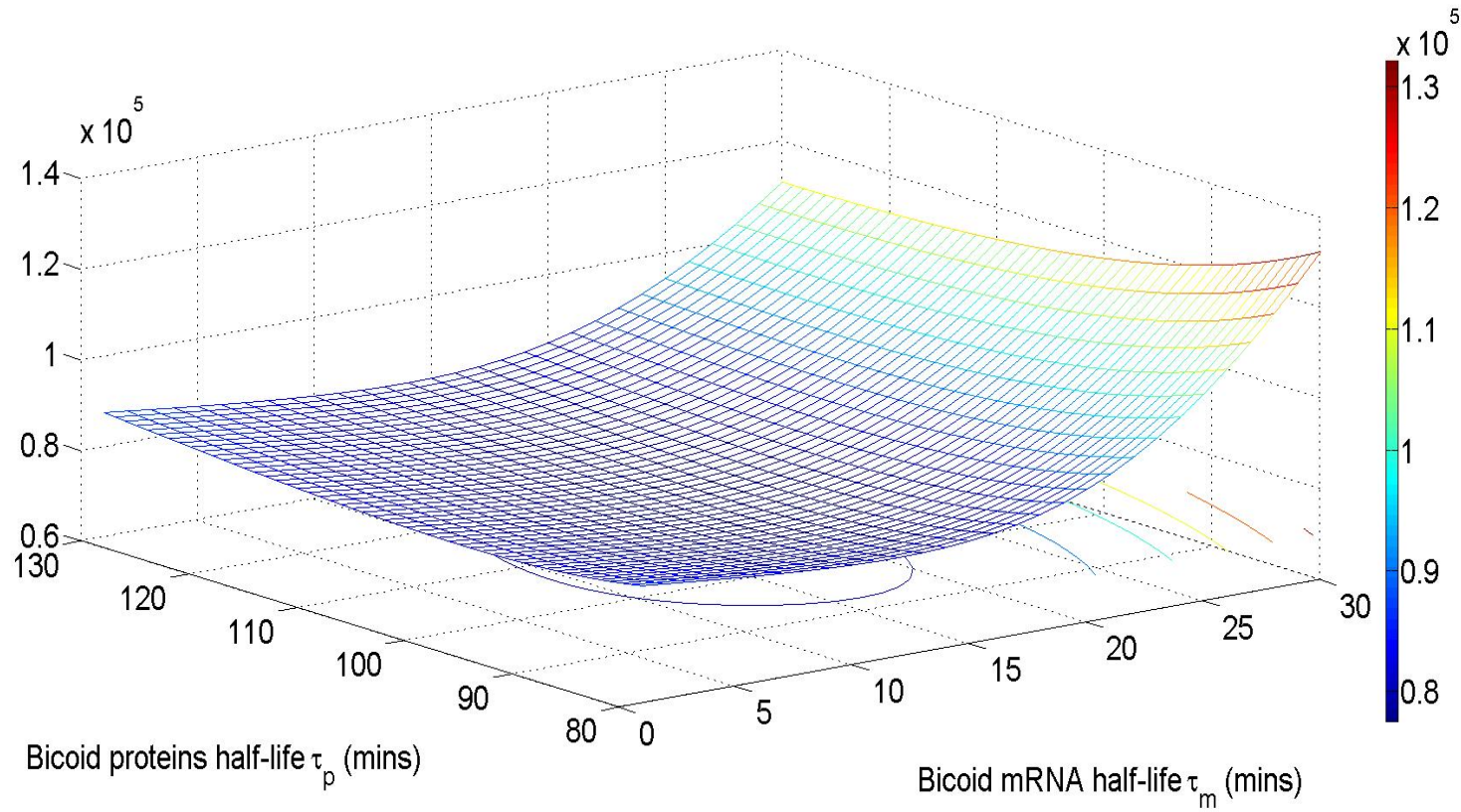
- Squared error between model output and measured intensities to evaluate error.

$$E = \sum_{t=T_1}^{T_2} \sum_{x=1}^L \{M(x, t) - M_d(x, t)\}^2$$

- Parameters estimation:
  - Diffusion constant  $D = 1.8 \mu m^2 / s$ ,
  - The time mRNA starts to decay  $t_0 = 118$  mins,
  - mRNA half-life  $\tau_m = 29$  mins
  - Bicoid protein half-life  $\tau_p = 120$  mins.

# Matching Parameter Values to Data

- The errors in the joint space of diffusion constant and maternal mRNA decay onset time.



# Conclusion

- ◉ Widely used model with a constant source is unrealistic.
- ◉ Three models with realistic source.
- ◉ Matching models output to database.
  
- ◉ Developing data driven model for embryo spatio-temporal data i.e. Kriged Kalman Filter

THANKS !

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## Dynamic control of positional information in the early *Drosophila* embryo

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