Using PDE models to describe *m*RNA expression pattern dynamics

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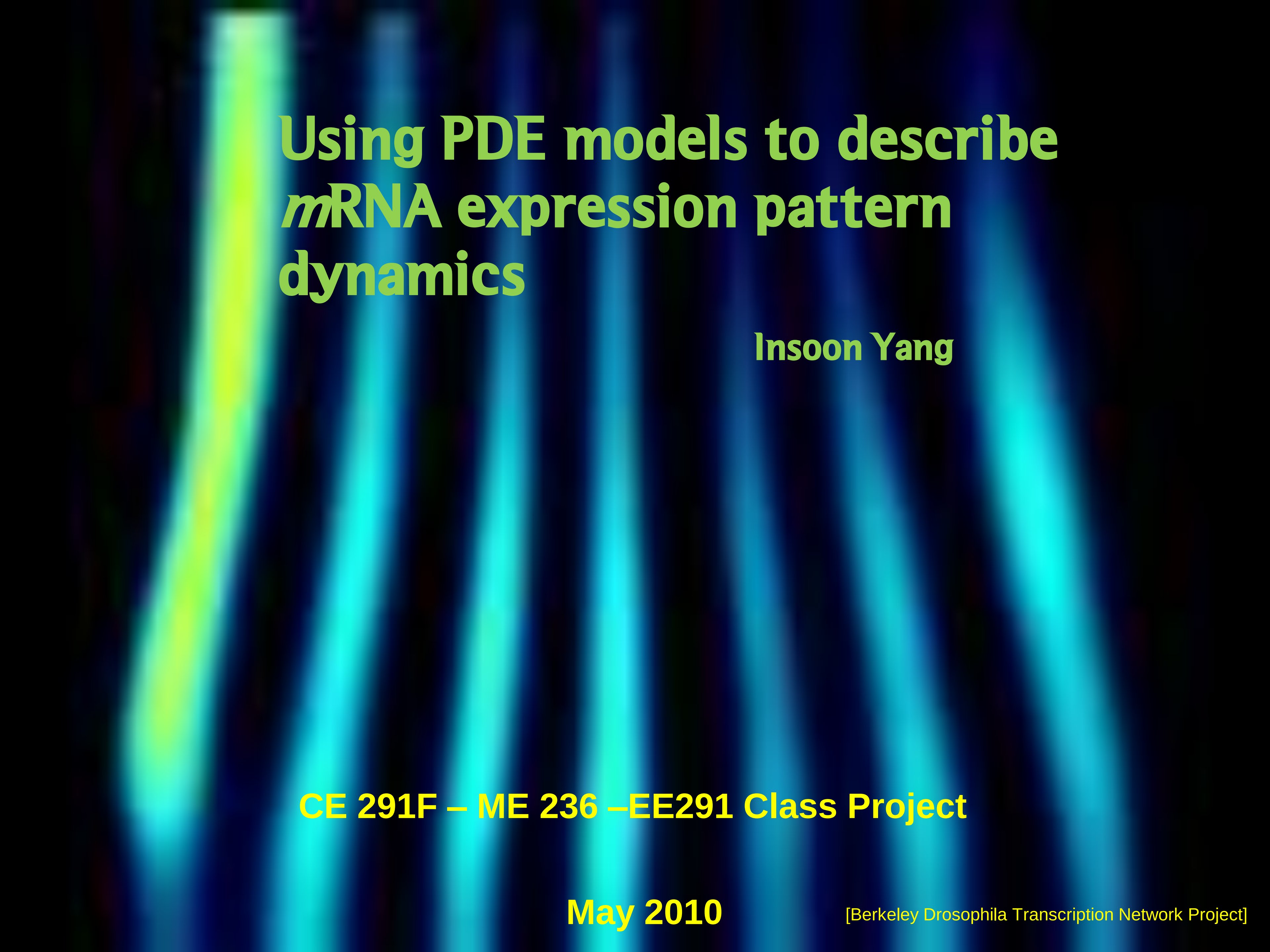
CE 291F – ME 236 –EE291 Class Project

May 2010



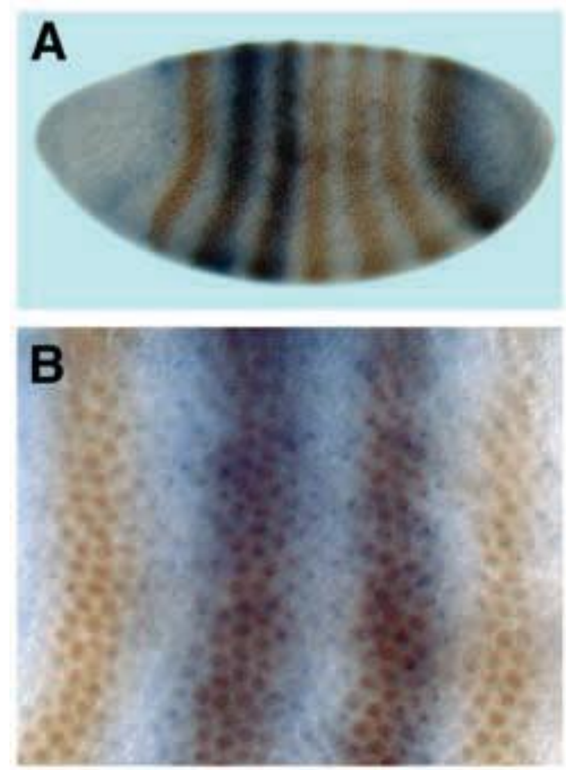
[Berkeley Drosophila Transcription Network Project]

*m*RNA transcription in *Drosophila* Embryo

[Muhammad Mahdi Karim]

Drosophila

Embryo with *eve* stripes



[Ludwig et al., *Development* 125, 949-958, 1998]

Transcription factors **activate** **or** **repress** ***m*RNA transcription**

⇩

Pattern generation
(*m*RNA concentration gradient)

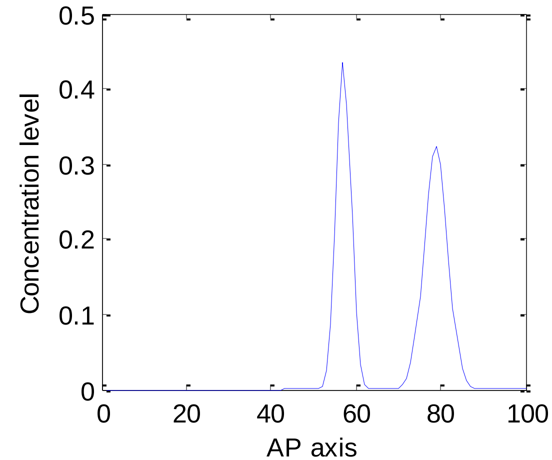
[Levine et al., *PNAS* 102, 14, 4936-4942, 2005]

Problem formulation

Error

$u(x,t)$

Solution



Concentration of *eve*

:experimental data

Transcription factors

bound to DNA

Configuration (c)

: control input

[Segal, et al., *Nature* 451, 535-541, 2008]

Spatiotemporal model

(PDE w/ distributed controller ϕ)

Parameters are unknown

Parameter estimation of a diffusion PDE

$$
\begin{aligned}
u_t &= D\Delta u + g \\
&= \underline{D}\Delta u - \underline{d}u + \phi
\end{aligned}
$$

u: concentration of *eve* *m*RNA

g: rate of increase of *eve* *m*RNA per volume

ϕ: transcription rate

D: mass diffusivity

d: feedback gain

Estimate Parameters using an *adjoint-based* method.

Describe the dynamic propagation of *eve* mRNA expression pattern.

Q) How can we model ϕ?

Nuclei: Distributed over an embryo

Input:

- configuration (c)

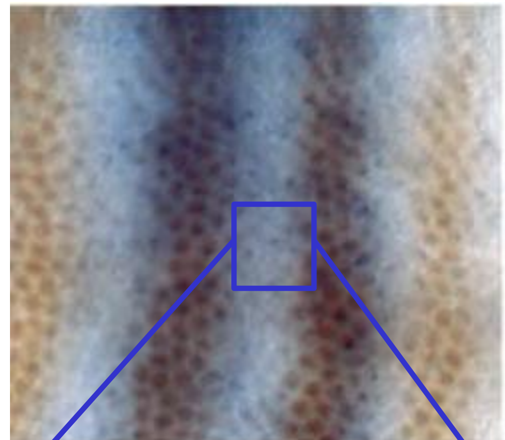
⇩

Controller ϕ
(a nucleus at (x, t))

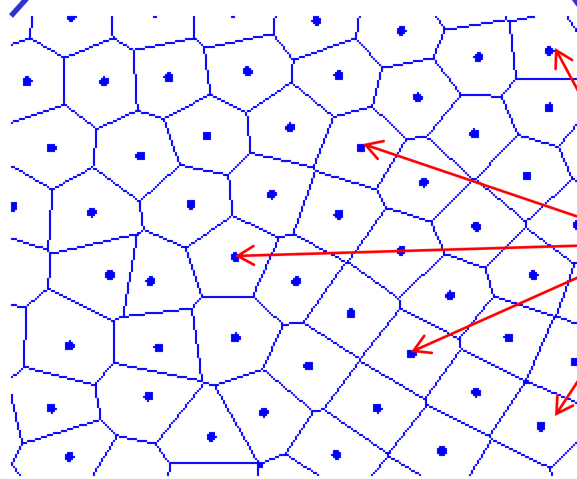
⇩

Output:

- *eve m*RNA transcription rate at (x, t)



[Ludwig, et al., *Development* 125, 949-958, 1998]



Embryo
: domain

Nuclei
: distributed machines with a controller

Combinatorial controller modeling

$$\phi = eP(E \mid x,t)$$
$$= e\sum_{c \in C} P(E \mid c,x,t)P(c \mid x,t)$$

Configuration (c): **control input**

$$P(E \mid c,x,t) = \sigma\left(w_0 + \frac{1000}{|s|} \sum_{i=1}^{l(c)} w_{\tau_i} \right) = \sigma\left(\underline{w_0} + \frac{1000}{|s|} \sum_{\tau=1}^{m} \underline{z_\tau}(c)\underline{w_\tau} \right)$$

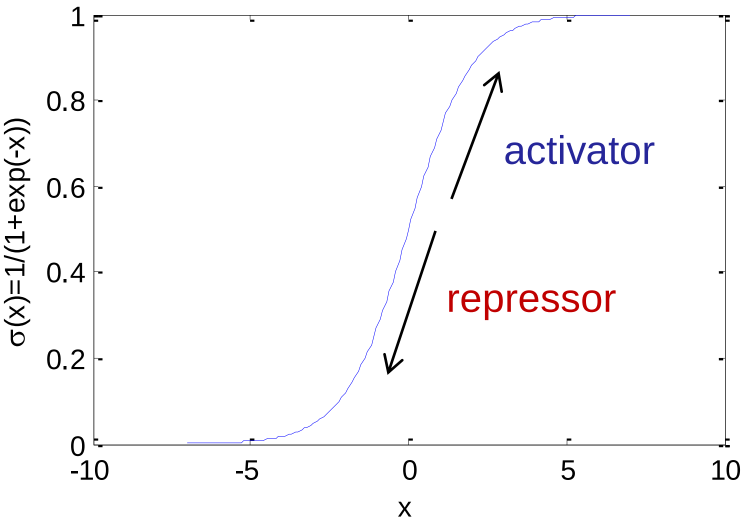
Transcription contribution

# of TF$_\tau$ in c

TFτ: **activator** $\Leftrightarrow w_\tau > 0$

TFτ: **repressor** $\Leftrightarrow w_\tau < 0$

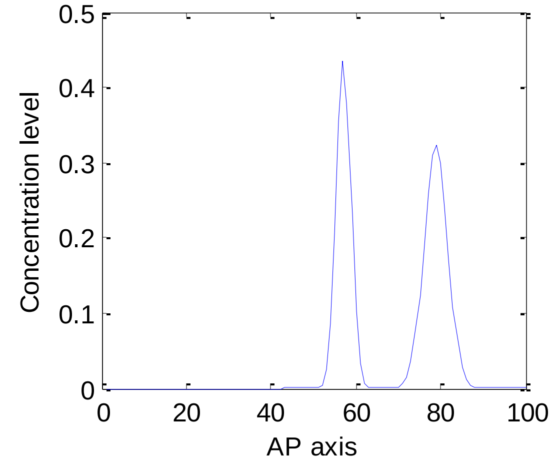
σ(*x*): *logistic function*



[Segal, et al., *Nature* 451, 535-541, 2008]

Model development

Error



Concentration of *eve*
:experimental data

$$\boxed{u(x,t)}$$

Solution

$$\boxed{u_t = Du_{xx} - du + \phi}$$

$$\boxed{\phi}$$

Transcription rate

Configuration(c): control input

Adjoint-based parameter estimation

minimize: $$J = \frac{1}{2}\int_\Omega \sum_{i=1}^{T} \left\| u(x,t_i) - o(x,t_i) \right\|_2^2 dx$$

subject to:
$$u_t = Q(u,\theta) + S(\theta)\Delta u$$
$$\nabla_x u_j(x,t)\cdot n = 0 \qquad \forall x \in \partial\Omega \qquad j = 1,2,\cdots d_u$$
$$u(x,t_0) = o(x,t_0) \qquad \forall x \in \Omega$$

Equation of first variation:

$$\hat{u}_t = \frac{\delta Q(u,\theta)}{\delta u}\hat{u} + S(\theta)\Delta\hat{u} + \frac{\partial Q(u,\theta)}{\partial\theta}\hat{\theta} + V(u,\theta)\hat{\theta}$$

where $$V(u,\theta) = \begin{bmatrix} \sum_{j=1}^{d_u} \frac{\partial S_{1j}}{\partial\theta}\Delta u_j \\ \vdots \\ \sum_{j=1}^{d_u} \frac{\partial S_{d_u j}}{\partial\theta}\Delta u_j \end{bmatrix}$$

Adjoint-based parameter estimation

Adjoint PDEs:

$$-\mu_t = \frac{\delta Q(u,\theta)}{\delta u}^T \mu + S^T(\theta)\Delta\mu \quad \text{on } (t_{i-1}, t_i] \text{ for } i = 1, \cdots, T$$

$$\nabla_x \mu_j(x,t)\cdot n = 0 \quad \forall x \in \partial\Omega \quad j = 1, 2, \cdots d_u$$

with terminal conditions:

$$\mu(x,t_T) = u(x,t_T) - o(x,t_T)$$

$$\mu(x,t_i) = \mu(x,t_i^+) + u(x,t_i) - o(x,t_i) \quad \text{for } i = 1, \cdots, T-1$$

Adjoint-based parameter estimation

Gateaux derivative (in the direction $\hat{u}$):

$$dJ(\theta;\hat{\theta}) = \lim_{h\to 0}\frac{J(\theta+h\hat{\theta})-J(\theta)}{h} = \int_\Omega \sum_{i=1}^{T}(u(x,t_i)-o(x,t_i))^T\,\hat{u}dx$$

$$= \int_\Omega \sum_{i=1}^{T}\int_{t_{i-1}}^{t_i}\mu^T\left(\frac{\partial Q(u,\theta)}{\partial\theta}+V(u,\theta)\right)\hat{\theta}dtdx$$

Gradient:

$$\nabla_\theta J = \int_\Omega \sum_{i=1}^{T}\int_{t_{i-1}}^{t_i}\left(\frac{\partial Q(u,\theta)}{\partial\theta}+V(u,\theta)\right)^T\mu dtdx$$

Adjoint-based method algorithm

Step 1. Guess (initial) parameter θ

Step 2. Solve PDE numerically $\Rightarrow$ $u(x,t)$

Step 3. Solve Adjoint PDE numerically $\Rightarrow$ $\mu(x,t)$

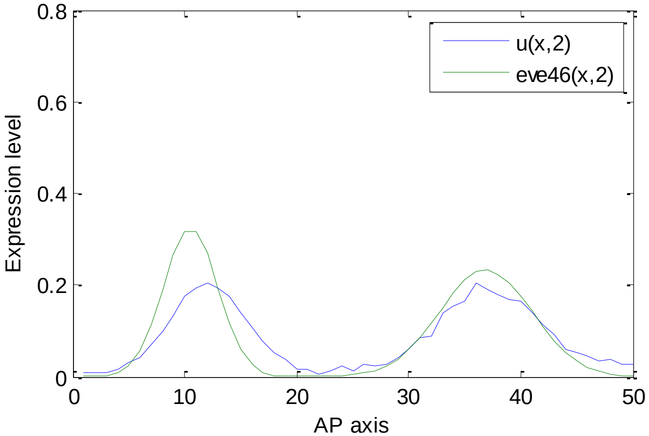
Step 4. Update parameter: $\theta = \theta - \alpha \nabla_\theta J$

where

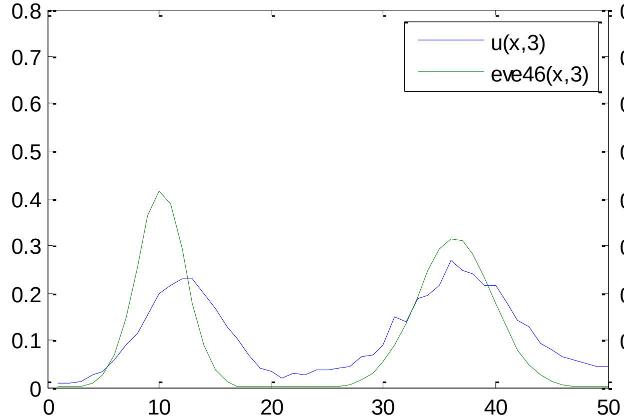
$$\nabla_\theta J = \int_\Omega \sum_{i=1}^{T} \int_{t_{i-1}}^{t_i} \left(\frac{\partial Q(u,\theta)}{\partial \theta} + V(u,\theta) \right)^T \mu \, dt dx$$

Parameter estimation results

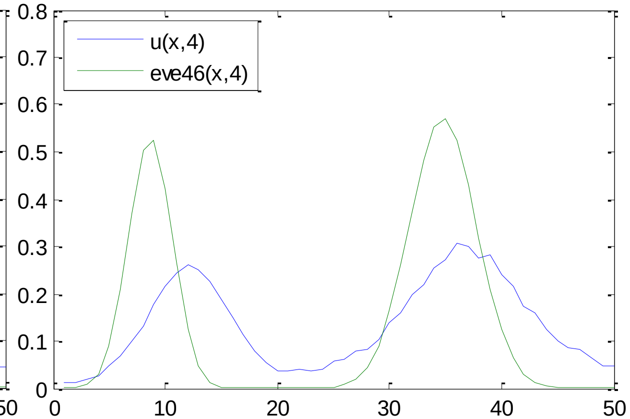
Time 2



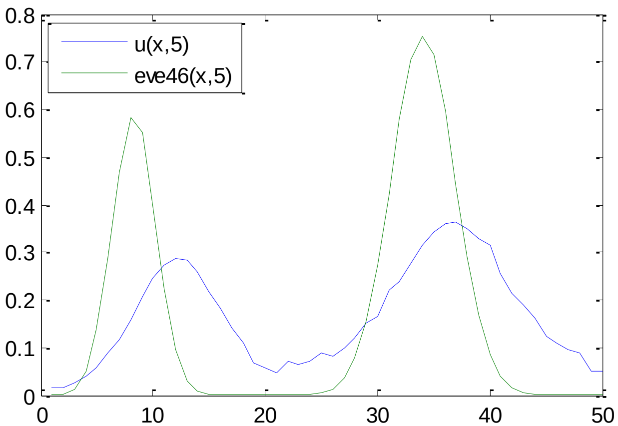
Time 3



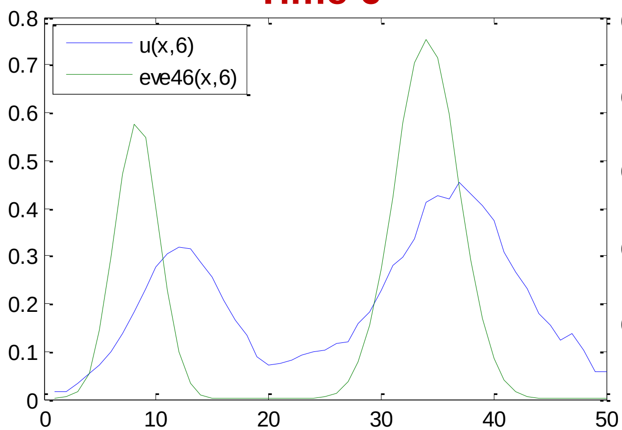
Time 4

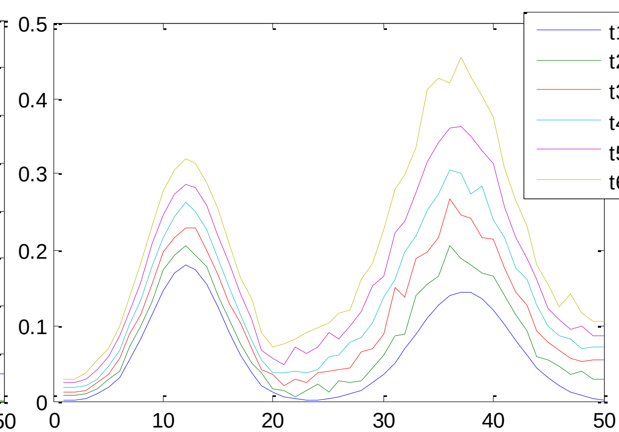


Time 5



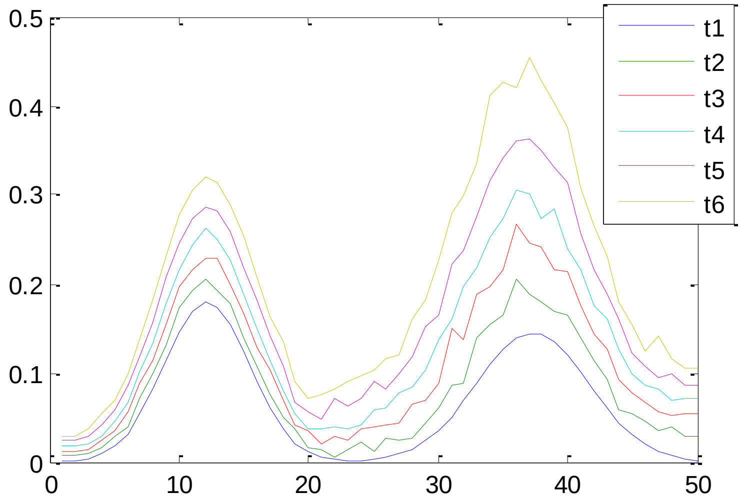
Time 6





$$\theta = (0.3210, -0.1298, -1.5619, 9.1793, -3.8370, -1.4426)$$

Conclusions and future goals



+ Describe fast enhancement of the right stripe

– Cannot describe late stage of pattern dynamics

Future Work (in summer):

- 2D PDE
- More transcription factors & *m*RNAs
- Study algebra
  : find a group structure of configuration

Thank you!

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[Berkeley Drosophila Transcription Network Project]