

Spatio-Temporal Dynamic Model in *Drosophila* Early Development via Protein Data and Microarray Data

Cheng-Wei Li and Bor-Sen Chen

Extended Abstract

Before segmentation determination, the embryo is not yet separated by membranes and macromolecules such as transcription factors (TFs), which are translated by maternal and zygotic mRNA and diffuse freely and regulate downstream target genes in neighbor nucleus. By a series of concentration thresholds and high/low affinity bindings, downstream genes are dictated to express in different space. In past several decades, the spatio-temporal expressions of the early development-related genes (*bicoid*, *caudal*, *hunchback*, *giant*, *knirps*, *kruppel*, *tailless*, *even-skipped(eve)*, *fushi-tarazu(ftz)*, *hairy*, *odd-skipped(odd)*, *paired*, *runt* and *sloppy-paired(slp)*) have been long-term studied at early developmental stages of *Drosophila melanogaster*. In this study, we incorporate the proposed 3-dimensional (3-D) spatio-temporal expression data and mRNA 3-D spatio-temporal expression data to construct the diffusion and transcription regulation mechanisms of early embryogenesis based on our dynamic model from a more reality point of view.

In this study, both protein and mRNA expression data are used to construct a spatio-temporal dynamic model for early embryogenesis. Five basic mechanisms are incorporated in our model for the interplaying dynamics of genes and proteins: (1) protein synthesis, (2) protein decay, (3) mRNA decay, (4) protein diffusion, (5) transcription regulations. For distinction between mRNA and protein expressions, we define two state variables X_i and Y_i to represent the 3-D spatio-temporal profiles of the mRNA of the i th target gene and its TF, respectively. Based on the transcription regulation model proposed in previous studies (Chang, et al., 2005; Chen, et al., 2004; Jaeger, et al., 2004; Perkins, et al., 2006), the 3-DEST model for target gene i and its regulatory TFs is proposed as follows:

$$\begin{aligned} \frac{\partial X_i(t, x_i, y_i)}{\partial t} &= -\alpha_i(x_i, y_i)X_i(t, x_i, y_i) + \sum_{j=1}^{14} \beta_{ij}(x_i, y_i)Y_j(t, x_i, y_i) + \nu_i(t, x_i, y_i) \\ \frac{\partial Y_i(t, x_i, y_i)}{\partial t} &= \alpha_i(x_i, y_i)X_i(t, x_i, y_i) - \lambda_i(x_i, y_i)Y_i(t, x_i, y_i) \\ &+ \gamma_i(x_i, y_i) \frac{\partial^2 Y_i(t, x_i, y_i)}{\partial x_i \partial y_i} + \zeta_i(t, x_i, y_i) \end{aligned} \quad , \quad i=1, \dots, 14 \quad (1)$$

These partial differential equations construct a spatio-temporal gene transcriptional regulatory network through TFs in the early development of *Drosophila*. Based on the maximum likelihood parameter estimation method, the dynamic model in *Drosophila* early development is constructed. Then, we incorporate AIC into our identification process to prune the insignificant parameters in the model from the most parsimonious perspective. This allows us to pick up the TFs, which may be the most possible regulators to control the downstream genes in the early development of *Drosophila*. The simulation results of the system model based on maximum likelihood estimation method and AIC are shown in Figure 1(b,d) compared with the original data in Figure 1(a,c).

Furthermore, we want to find which TFs directly affect each eve stripe border's formation by the diffusion parameter γ_i of eq.(1). We summarize the changed signs (CS) of the γ_i in eq.(1) on the borders of two neighboring stripes by assuming that a stripe border should be affected by the TFs which have the CS in this border. The total number of CS of a TF is less than or equal to 3 in one of the eve stripe borders. The TFs with more CS are considered with more possibility to affect the border formation of eve stripes. By our model, we can not only find the transcription regulations of *eve* but also infer what TFs could affect the border formation of eve stripes, which could be also confirmed by previous studies.

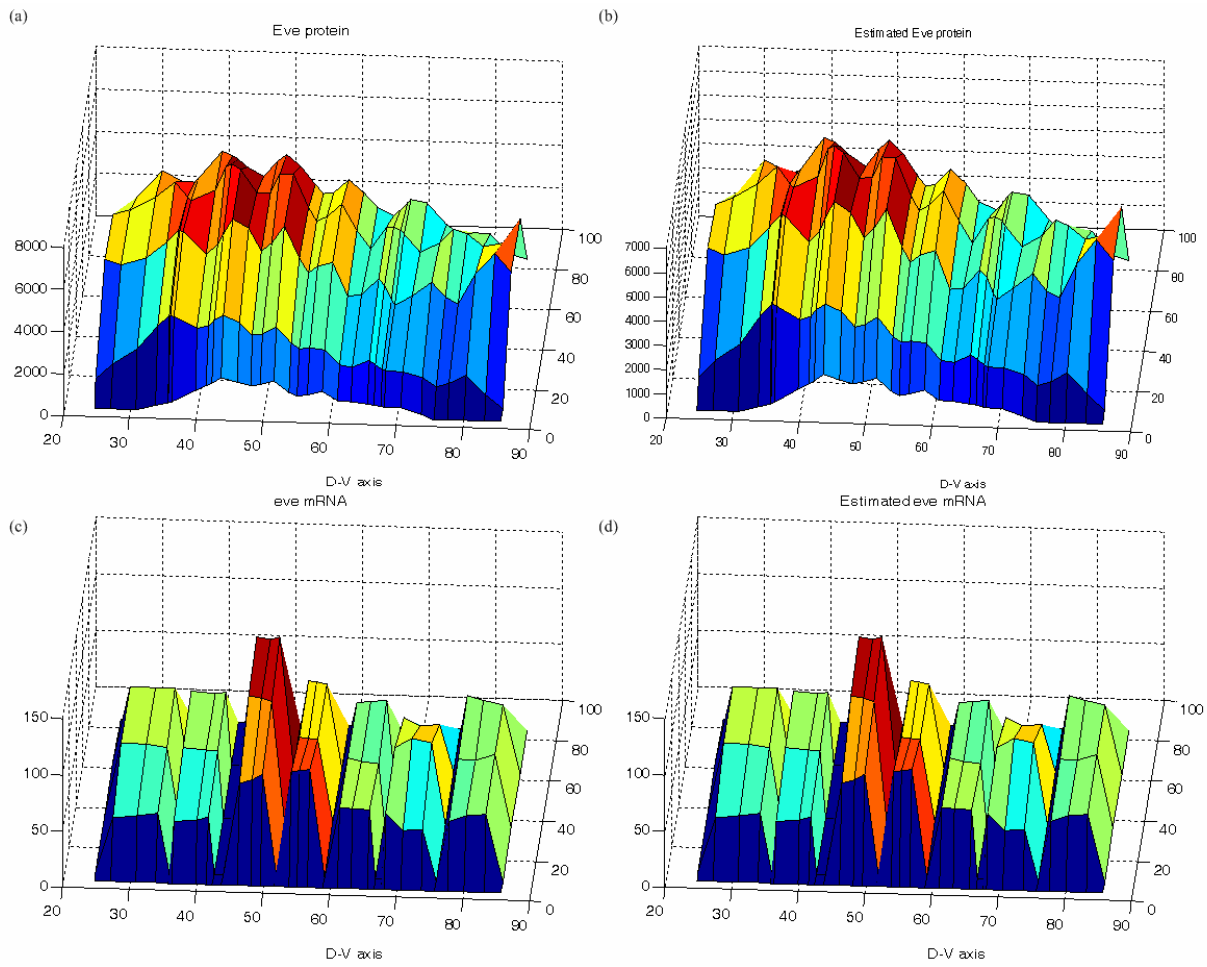


Figure 1: Original data and estimated results by our proposed dynamic model

The original *eve* protein and mRNA spatio data at cleavage cycle 14A temporal class 8 are shown in (a) and (c), respectively, and the estimated *eve* protein and mRNA spatio concentration by the proposed dynamic 3-DEST model are shown in (b) and (d), respectively.

Category	TFs	Eve stripe borders		Literature evidence
		CS \geq 2	CS=1	
maternal genes	Bicoid	3-4 5-6	1-2 2-3 4-5	(Kraut and Levine, 1991; Small, et al., 1996)
	Caudal	1-2 4-5 6-7	2-3 3-4	
maternal/ gap gene	Hunchback	1-2 2-3 4-5	6-7	(Frasch and Levine, 1987; Kraut and Levine, 1991; Small, et al., 1996)
gap genes	Giant	1-2 3-4	4-5 6-7	(Frasch and Levine, 1987; Small, et al., 1996; Wu, et al., 1998)
	Knirps	2-3 3-4 4-5 5-6 6-7	1-2	(Frasch and Levine, 1987; Kraut and Levine, 1991; Small, et al., 1996)
	Kruppel	1-2 5-6 6-7	2-3	(Frasch and Levine, 1987; Kraut and Levine, 1991; Small, et al., 1996)
	Tailless	2-3 3-4 4-5 5-6 6-7		(Frasch and Levine, 1987; Kraut and Levine, 1991)
pair-rule genes	Eve	all		(Carroll and Vavra, 1989)
	Ftz	all		(Yu and Pick, 1995)
	Hairy	1-2 2-3	3-4 4-5 5-6 6-7	(Carroll and Vavra, 1989; Frasch and Levine, 1987)
	Odd	1-2 2-3 3-4	5-6 6-7	(Fujioka, et al., 1996)
	Paired	1-2 2-3 3-4	4-5 5-6 6-7	
	Runt	3-4 5-6 6-7	2-3 4-5	(Carroll and Vavra, 1989; Frasch and Levine, 1987)
	Slp	all		(Cadigan, et al., 1994)

Table 1: Summary of TFs action on eve stripe borders

CS denotes the total number of the changed signs of the parameter γ_i in eq.(1) on the borders of neighbor two stripes. The doublets ($a-b$) represent border between the posterior of eve stripe a and the anterior of eve stripe b .

Reference

- Cadigan, K.M., Grossniklaus, U. and Gehring, W.J. (1994) Localized expression of sloppy paired protein maintains the polarity of Drosophila parasegments, *Genes & development*, **8**, 899-913.
- Carroll, S.B. and Vavra, S.H. (1989) The zygotic control of Drosophila pair-rule gene expression. II. Spatial repression by gap and pair-rule gene products, *Development (Cambridge, England)*, **107**, 673-683.
- Chang, W.-C., Li, C.-W. and Chen, B.-S. (2005) Quantitative inference of dynamic regulatory pathways via microarray data, *BMC bioinformatics*, **6**, 44.
- Chen, H.C., Lee, H.C., Lin, T.Y., Li, W.H. and Chen, B.S. (2004) Quantitative characterization of the transcriptional regulatory network in the yeast cell cycle, *Bioinformatics*, **20**, 1914 - 1927.
- Frasch, M. and Levine, M. (1987) Complementary patterns of even-skipped and fushi tarazu expression involve their differential regulation by a common set of segmentation genes in Drosophila, *Genes & development*, **1**, 981-995.
- Fujioka, M., Miskiewicz, P., Raj, L., Gullledge, A.A., Weir, M. and Goto, T. (1996) Drosophila Paired regulates late even-skipped expression through a composite binding site for the paired domain and the homeodomain, *Development (Cambridge, England)*, **122**, 2697-2707.
- Jaeger, J., Surkova, S., Blagov, M., Janssens, H., Kosman, D., Kozlov, K.N., Manu, Myasnikova, E., Vanario-Alonso, C.E., Samsonova, M., Sharp, D.H. and Reinitz, J. (2004) Dynamic control of positional information in the early Drosophila embryo, *Nature*, **430**, 368-371.
- Kraut, R. and Levine, M. (1991) Spatial regulation of the gap gene giant during Drosophila development, *Development*, **111**, 601-609.
- Perkins, T.J., Jaeger, J., Reinitz, J. and Glass, L. (2006) Reverse engineering the gap gene network of Drosophila melanogaster, *PLoS Comput Biol*, **2**, e51.
- Yu, Y. and Pick, L. (1995) Non-periodic cues generate seven ftz stripes in the Drosophila embryo, *Mech Dev*, **50**, 163-175.