Precision in a rush: *hunchback* pattern formation in a limited time

Huy Tran[12], Carmina A Perez[3], Jonathan Desponds[5], Mathieu Coppey[14], Cecile Fradin[3], Nathalie Dostatni[14] and Aleksandra M. Walczak[24]

Fly development amazes us by the precision and reproducibility of gene expression, especially since the initial expression patterns are established during very short nuclear cycles. Recent live imaging of *hunchback* promoter dynamics shows a stable sharp binary expression pattern established within the 3 minute interphase of nuclear cycle 11. Considering expression models of different complexity we show how a limited readout time imposed by short developmental cycles affects the ability of the gene to read positional information and express reliably. Comparing our theoretical results to real-time monitoring of the *hunchback* transcription dynamics in live flies we discuss possible regulatory strategies.

***Keywords* — Drosophila melanogaster, hunchback, gene expression regulation, positional sensing**

I. Introduction

The *hunchback* pattern formation in *Drosophila melanogaster* has been extensively studied as a model to understand how cell identity is established reliably at the correct time, correct location in space [1-2]. In this system, the *hunchback* gene extracts the positional information from transcription factor gradients, including Bicoid, and forms a sharp binary-like expression pattern that is key for the development of properly proportioned individuals. Driven by recent real-time monitoring of the *hunchback* transcription activity in live fly embryos [3-4] using the MCP-GFP system [5], we explore the constraints that a limited readout time coming from the short developmental nuclear cycles (3-10 mins in cycle 11-13) imposes on the ability of the gene network to readout positional information.

II. Results

Using a theoretical model of gene expression regulation at the molecular level [6], we show that the steep expression pattern can emerge from the cooperative interactions between transcription factors and the operator sites of the *hunchback* promoter. However, this cooperativity comes at the cost of a long pattern formation time and an increased heterogeneity of gene expression at the pattern boundary. The identified trade-off has an impact on the system's "positional resolution", which corresponds to the minimum morphogen concentration difference at the expression boundary that neighboring nuclei are able to detect. We find that the kinetic parameters controlling gene expression yielding the highest positional resolution depend on the nuclear cycle duration (Fig. 1).

Our results show that if transcription regulation is done by a single transcription factor (e.g. Bicoid) via the operator sites of the *hunchback* promoter alone, the *hunchback* readout is likely to adopt a pattern of moderate steepness, much less than the experimentally observed steepness in flies [7]. We hypothesize that multiple transcription factors are required to cooperate with one another to achieve such high steepness while ensuring that future cell identity can be correctly encoded in the *hunchback* readout.

Finally, we present our first attempts to validate the hypothesis experimentally using synthetic promoters derived from the *hunchback* promoter, where the operator sites of known transcription factors (Bicoid, Hunchback, Caudal, Zelda) are present/absent.

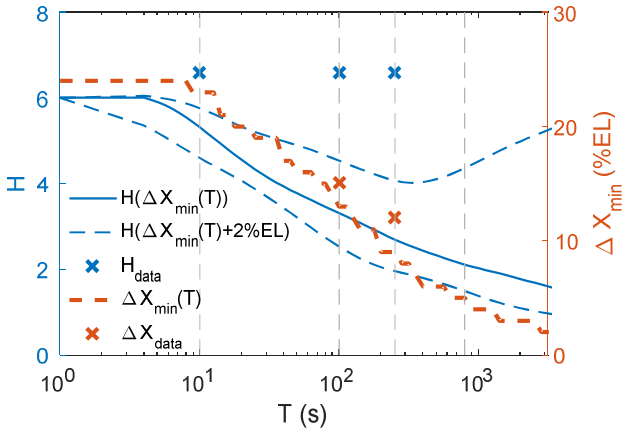

Figure 1. Optimal Hill coefficient H (solid blue line) yielding the best positional resolution (ΔX) (dashed orange line) for the varying readout time T, along with the confidence interval (blue dashed) with 2% EL (embryo length) tolerance. Also shown are the observed Hill coefficient (blue crosses) and positional resolution (orange crosses) in live flies.

References

[1] Driever W and Nusslein-Volhard C (1988). The Bicoid protein determines position in the *Drosophila* embryo in a concentration-dependent manner, *Cell* **54** 95-104

[2] Porcher A and Dostatni N (2010) The Bicoid morphogen system, *Current Biology* **20**, 249-254

[3] Lucas T *et al*. (2013) Live imaging of Bicoid-dependent transcription in Drosophila embryos, *Current Biology* **23(11)**, 2135-2139

[4] Garcia H *et al.* (2013) Quantitative imaging of transcription in living Drosophila embryos links polymerase activity to patterning, *Current Biology* **23(11)** 2140-2145

[5] Bertrand E *et al.* (1998) Localization of ASH1 mRNA particles in living yeast, *Molecular Cell* **2(4)**, 437-445

[6] Estrada J *et al.* (2016) Information integration and energy expenditure in gene regulation, *Cell* **166(1)** 234-244

[7] Xu H *et al.* (2015) Combining protein and mRNA quantification to decipher transcriptional regulation, *Nature Methods* **12(8)**, 739-742

Email: huy.tran@lpt.ens.fr
[1]Institut Curie, Paris, France
[2]École Normale Supérieur, Paris, France
[3]McMaster University, Hamilton, Canada
[4]CNRS, Paris, France
[5]UC San Diego, CA, US