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Pre-steady and stable morphogen gradients: can they coexist?

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In our recent paper (de Lachapelle and Bergmann, 2010), we studied two systems properties of early *Drosophila* embryo development: using staining images for three gap genes and the pair-rule gene Eve that were produced in an earlier study (Bergmann *et al*, 2007), we investigated precision and scaling of their expression domains. These images were taken not only for wild-type embryos, but also for embryos with single and quadruple dosage of maternal bicoid mRNA, inducing shifted expression domains. Interestingly, our careful quantification of precision and scaling indicates that these features are position-dependent more than gene-dependent. Indeed, when expression domains are shifted due to altered bicoid dosage, their precision and scaling properties seem to change according to their new position. In our view, this suggests that precision and scaling are, at least in part, already achieved at the level of the Bicoid gradient itself and then passed on to its target genes. Investigating models that can reproduce the position-dependent signatures of precision and scaling at the gradient level, we identify two necessary ingredients: it is essential to include nuclear trapping and an external pre-steady-state morpohogen gradient to achieve both maximal precision at mid-embryo and almost perfect scaling away from the source.

In his correspondence, Johannes Jaeger (Jaeger, 2010) raises concerns about the validity of our study. He questions whether measuring the target gene properties at cycle 14 can teach us anything about the morphogen gradient, which provides positional information to the target genes much earlier. He consequently argues that the conclusions from our modeling approach are invalid, declaring pre-steady state as 'incorrect' for the Bcd gradient.

There is indeed evidence that the initial gene expression pattern continues to evolve due to gap–gene interactions, which contribute to the robustness of the final pattern (Jaeger *et al*, 2004, 2007; Manu *et al*, 2009). Our measurements of the target genes therefore provide indirect information on the properties of the Bicoid gradient. To account for this, we assessed statistically the possible impact of such drifts using the data from Surkova *et al* (2008) for the maximal drift within cycle 14 (Supplementary Text S1 and Figure S4 in the study by de Lachapelle and Bergmann, 2010). As our images were mostly taken during the earlier time classes, we likely overestimated the effect of these drifts. Nevertheless, we cautioned that there is a chance of about one in five ($P<0.2$) that the decrease of precision toward the posterior pole is an artifact. Yet, we find it very unlikely that this is also the case for the observed decrease toward the anterior pole ($P<0.002$). Importantly, within our modeling framework, this alone favors that the external Bicoid gradient is at pre-steady state at the decoding time, as we could only reproduce this result with a pre-steady-state gradient and assuming noise in either the production or nuclear trapping rates.

The other argument in favor of the validity of our indirect measurements of precision is that the observed positional profile for the different downstream genes (for varying bicoid dosage) is similar to that measured directly for the Bicoid gradient (Gregor *et al*, 2007a). Thus, there is a clear need for models that give rise to maximal precision at mid-embryo.

Any modeling approach needs to make simplifications and thus provides at best an approximate description of the real system with all its complexities. Modeling of the gap gene dynamics so far has used additive models for Bicoid activation and gap genes mutual repression, and requires fitting many parameters (Jaeger *et al*, 2004; Manu *et al*, 2009). These and other simplifications may be the reason why these models still have difficulties in explaining some observations, such as the shifts of the gap gene expression domains induced by altered bicoid dosage (Bergmann *et al*, 2007). We thus believe that it is legitimate to model only the gradient evolution and assume a simple French-flag decoding when trying to qualitatively reproduce systems properties, such as the position-dependent behavior of precision and scaling. At the same time, we agree that our proposed model should be tested using positional expression data from earlier embryos and further quantification of the Bicoid gradient. For this end, it would be very useful to make publicly available the raw image data, as we have done in our study. In particular, this is necessary to validate our observation that domain positions retain their proportions across embryos of different lengths (except for the most anterior part of the embryo). Our proposed position-dependent measure of scaling would in fact also allow to assess the scaling behavior of the Bicoid gradient itself when applied to a sufficient number of unnormalized expression profiles.

Our search for models was guided by simplicity, but also took into account the results from Gregor *et al* (2007b) who showed that nuclear Bicoid concentrations remain constant from cycle 10 on. Yet, as we argued previously (Bergmann *et al*,

2008), this is fully consistent with, and actually requires, an evolving external gradient. Thus, nuclear trapping slows down the evolution of the external gradient, which remains longer at pre-steady state, while the divisions and changing sizes of the nuclei effectively stabilize the nuclear concentrations. Interestingly, this intriguing combination might actually yield an increase in overall pattern robustness, as the external super-exponentially decaying profile is more robust to fluctuations in the production, degradation and nuclear trapping rates (Bergmann *et al*, 2007; de Lachapelle and Bergmann, 2010), while stabilized nuclear concentrations allow for longer averaging times, thus reducing read-out stochastic noise (Saunders and Howard, 2009). Coexistence of an external pre-steady-state gradient and stabilized nuclear concentrations might therefore be the start to robust patterning in *Drosophila* early embryo development.

Conflict of interest

The authors declare that they have no conflict of interest.

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