Pattern formation and morphogen gradients: A causality dilemma

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***Short Abstract* — The development of multicellular organisms depends on pattern formation – the spatial organization of cell types. This, in turn, depends on the ability of cells to acquire positional information. A longstanding paradigm for the establishment of positional information in tissues is through the concentration gradients of "morphogens". Our studies of the *Drosophila* wing suggest that patterns feed back onto the shape of the morphogen gradients that produce them. This suggests a degree of self-organization in morphogen-dependent pattern formation that departs from the common view that patterns are formed strictly "downstream" of morphogens.**

***Keywords* — pattern formation, morphogen gradients, Dpp,**

I. Background

Morphogens are signaling factors that are secreted from specific regions of a developing tissue, and whose decreasing concentrations over space provide positional information to cells; i.e., a cell can use the local concentration of a morphogen in order to determine its distance from the morphogen's source.

The shape of a morphogen concentration gradient is important in determining how positional information is communicated in a tissue, as well as how that information is affected by perturbations. The concentration gradient of a morphogen that experiences no consumption, except at a boundary far from its source, will be linear. Such "source-sink" gradients have desirable adaptive properties (e.g., automatic scaling in differently sized tissues), and were originally proposed to underlie pattern formation [1]. However, it is now known that most morphogens are consumed throughout the tissues in which they diffuse, usually through receptor-mediated endocytosis (via the same cell-surface receptors used to sense morphogen concentration). A morphogen experiencing uniform consumption will exhibit a decaying exponential gradient, the steepness of which can be described by a constant decay length (which depends on the consumption rate and diffusivity of the morphogen).

II. Results

One of the best-understood morphogen gradient systems is the Decapentaplegic (Dpp; an orthologue of the vertebrate BMP2/4) gradient that patterns the wing primordium (wing disc) of the fruit fly *Drosophila melanogaster* (reviewed in [2]). Many studies have shown that the overall shape of the Dpp gradient is well-fit by a decaying exponential. Our measurements support this view broadly, but when we examine sub-regions of the gradient more carefully, we conclude that the gradient's shape is closer to linear up to the boundary of a specific pattern element, the location where the Dpp target gene *Spalt* switches from being on to off (this boundary is important in determining the placement of adult wing veins [2]). This conclusion is supported by the presence of reproducible trends in the residuals from exponential fits across many wing discs. From solutions to reaction diffusion equations with spatially varying decay lengths, we know that a necessary and sufficient condition for the observed trends in fitting-residuals is for the morphogen gradient to have a long (intrinsic) decay length proximal to the pattern boundary, and a short one distal to it (this would make this distal region act as a "sink" for the proximal region, thus causing the gradient to fall linearly in the proximal region). By "intrinsic" decay length, here, we mean the decay length that would be observed without any distal "sink".

The possibility that *Spalt* itself is responsible for the change in decay length at the *Spalt* boundary is supported by the observation that the Dpp gradient is much steeper in *Spalt*-mutant wing discs. One possible explanation for these results is that *Spalt* downregulates the expression of Dpp's cell-surface receptor, a phenomenon we confirm using clonal loss-of-function experiments.

III. Conclusions

Although many feedback loops have been identified in morphogen gradient systems, this is, to our knowledge, the first example where what has been identified as a downstream pattern element feeds back onto the shape of a morphogen gradient. This suggests that morphogen gradients do not just passively provide positional information, that their shapes may be modified by patterns in the course of pattern formation.

Rferences

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