Linkage of several pattern forming reactions to generate complex structures: head, foot and tentacle formation of the freshwater polyp Hydra as an example

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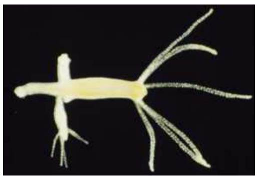
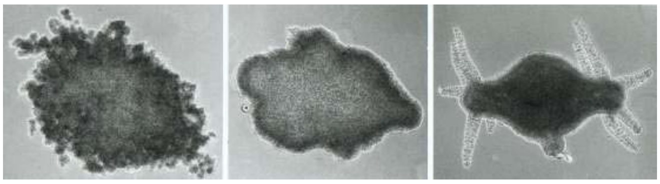
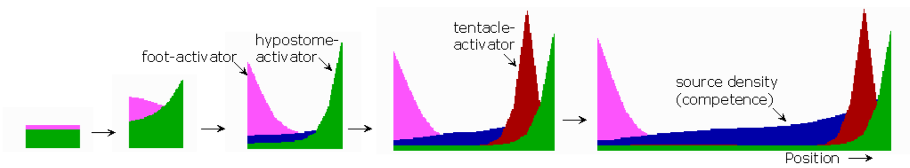
The complexity of patterns in higher organisms requires a hierarchical linkage of many pattern-forming reactions. Basic arrangements are two structures that appear either adjacent to each other or at opposite poles of a field. The freshwater polyp Hydra will be used to illustrate corresponding mechanisms. The hypostome (mouth opening) with the surrounding tentacles is an example for two adjacent structures, the head - foot pattern for different structures at both terminal ends (Meinhardt, 1993).



If hydra tissue is dissociated into individual cells and these cells are allowed to re-aggregate, within 4 days new head and foot structures are formed (Gierer et al., 1972 [PDF]) - a most striking example for the formation of a complex pattern from an initially uniform situation. In the aggregate shown below, first two heads are formed with a single foot in the centre. During further development, both animals separate from each other and are fully viable.

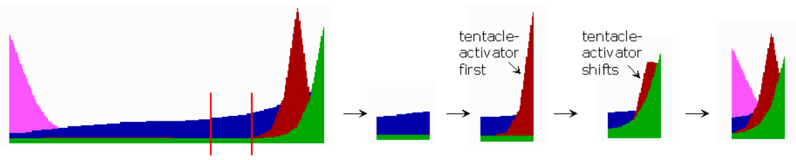


Simulation of hydra patterning: As discussed on the preceding page, the maintenance of a single organizing region in growing fields requires a stabilization by a graded competence (source density, blue in the following simulations). In hydra, evidence exists that this gradient is also used to localize the formation of the tentacles and the foot.

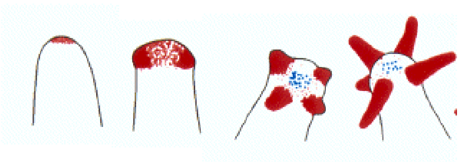


Head and foot formation: two organizing regions at opposite sites of a field: A Hydra is under control of two organizing regions located at opposite ends. This is a common feature of many morphogenetic fields. How can it be achieved that two organizing centres reliably appear at opposite positions? A simple cross-inhibition is not appropriate since in small (young) animals head and foot must appear very close together. At such short distances a direct mutual inhibition between the two systems lead would lead to the suppression of a foot by the nearby head. As mentioned, hydra has a polarity. The head activation appears at the position where the cells are most competent, and the head signal stabilizes this competence in the surroundings. If the foot system has the opposite behavior, i.e., if the foot appears in the region of lowest head-forming competence (lowest source density, blue in the simulation), the foot signal (pink) forms at the maximum distance from the head signal (green) without a direct inhibition. Therefore, in small animals head and foot system can coexist at a close neighborhood. In the simulation further below this is demonstrated by a simulation of regeneration in a small fragment. The graded source density only generates a preference for the terminal positions.

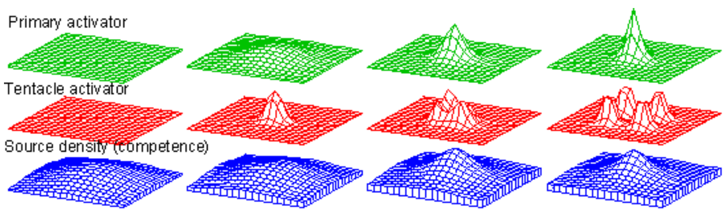
Hypostome and tentacles: formation of structures adjacent to each other: During development many structures emerge close to each other. A controlled neighborhood of structures is enforced if one structure activates the other on long range and excludes it locally (see also segmentation and left-right patterning) In Hydra, the tentacles appear around the opening of the gastric column, the hypostome. Many experiments can be accounted for by the assumption that tentacles are under control of a separate activator-inhibitor system that also depends on the source density. Since the primary head system causes an increase in the source density in a wider area, the head system generates the precondition for tentacle initiation. Locally, however, the head signal suppresses tentacle formation. Thus, tentacle formation (red) occurs next to the head signal. The following simulations show that the model describes not only the generation but also the correct regeneration of these signals:



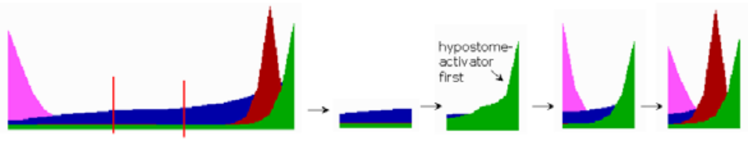
The model correctly describes a strange-appearing observation. With tentacle-specific antibodies, Bode et al. [1] have shown that after head removal, tentacle activation first reappears at the very tip of the gastric column (red in the drawing below). It is only later that this activation becomes shifted towards a more basal position where the tentacles eventually appear:



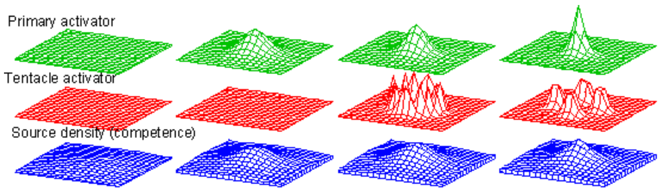
According to the model, since tentacles are formed close together, the tentacle inhibitor needs not to diffuse very far. Thus, the tentacle inhibitor can have a short half-life. After removal of the head and the tentacles, the tentacle inhibitor fades away more rapidly than the head inhibitor. Therefore, the tentacle activator can reappear sooner than the head activator. Since no suppressing head activator is present, this happens at the highest possible source density (blue), i.e., at the apical end of the remaining gastric column. After the trigger of the primary head activation at the same position, tentacle activation becomes shifted to the final location. This shift after the trigger of the head signal (green) is clearly visible in the simulation above. The simulation below approximates the dome-shaped geometry of the hypostome by a flat sheet of cells. The source density is high enough to trigger tentacle formation directly. After the trigger of the head signal (green), the spot-like signal for tentacle formation broadens, the centre becomes de-activated and the resulting ring decays in individual maxima, in agreement with the observation mentioned above.



The prediction was further that the sequence of events is the reverse after cutting closer to the budding region. At larger distances from the original head, the source density is too low to allow a direct trigger of the tentacle signal. However, after the trigger of the head signal, the source density slowly increases until the threshold for tentacle formation is reached. Since the repelling head signal is then already present, the tentacle signal emerges next to the head signal, i.e., at the correct position.



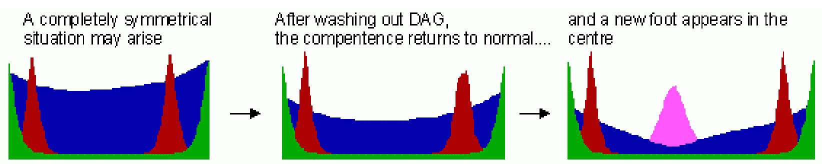
This prediction that has been verified [2]. A corresponding simulation in a two-dimensional field shows first the formation of the hypostome signal (green) that becomes then surrounded by a ring-shaped signal for tentacle formation. Subsequently this ring decays into the individual tentacle signals.



Recent expression studies with a Hydra homologue of the *aristaless* gene [3] have provided further support of this model.

The molecular nature of the graded competence is not yet clear. Known is, however, of how this gradient can be modified. By diacyl-glycerol (DAC) it can be achieved that the tissue of whole animal obtains near-head properties [4]. After foot removal, for instance, a second head regenerates instead of a foot. In the following simulation it is assumed first that the competence (source density, blue) increases due DAG treatment. After foot removal (pink) a head signal regenerates instead.

After washing out of DAG, the competence returns to normal and a new foot appears at in the centre:



However, there is an interesting feature *not* yet described by the model. Before the new foot appears, first buds are formed in the centre [4], indicting that with decreasing competence, first a situation is achieved where buds are allowed.

[Next: Hy-beta-catenin and WNT have properties as expected from the theory
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Further readings:

Meinhardt, H. (1993). A model for pattern-formation of hypostome, tentacles, and foot in hydra: how to form structures close to each other, how to form them at a distance. Dev. Biol. **157**, 321-333
Gierer, A., Berking, S., Bode, H., David, C.N., Flick, K., Hansmann, G., Schaller, H. and Trenkner, E. (1972). Regeneration of hydra from reaggregated cells. Nature New Biology 239, 98-101. [PDF]

[1] Bode, P.M., Awad, T.A., Koizumi, O., Nakashima, Y., Grimmelikhuijzen, C.J.P. and Bode, H.R. (1988). Development of the two-part pattern during regeneration of the head in hydra. Development **102**, 223-235.
[2] Technau, U. and Holstein, T.W. (1995). Head formation in hydra is different at apical and basal levels. Development **121**, 1273-1282.
[3] Smith, K.M., Gee, L. and Bode, H.R. (2000). Hyalx, an aristaless-related gene, is involved in tentacle formation in hydra. Development **127**, 4743-4752.
[4] Müller,W.A. (1989). Diacylglycerol-induced multihead formation in hydra. Development, 105, 309-316

Feedback to: hans.meinhardt@tuebingen.mpg.de