Multiscale mathematical modelling of cell systems

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Biological motivation and objectives

Developmental processes

- Differentiation programs based on positional information
- Information delivered by extracellular signalling molecules
- Processes conserved in all metazoans including humans
- The same processes involved in various diseases

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Objectives

- Role of cell-to-cell communication and regulatory feedbacks in cell growth and differentiation
- Mechanisms of pattern formation during development
- New mathematical models and methods

Test organism - a fresh-water polyp *Hydra*

- One of the oldest and simplest multicellular organisms
- Can be treated as a model for axis formation in higher organisms
- Frontiers in stem cells research

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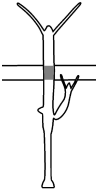
Objectives

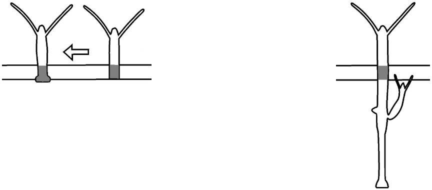
- To understand mechanism of head formation and regeneration
- To bridge the gap between observations at the tissue level and at the cellular and subcellular level

Cutting experiment



Concept of pattern generation

Cutting experiment



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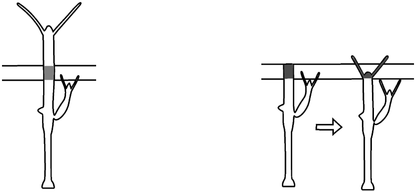
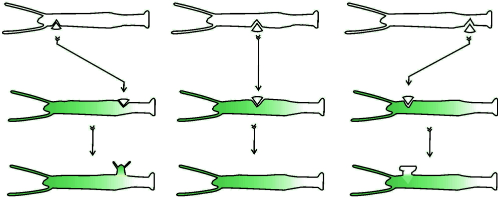


Concept of pattern generation

Grafting experiment



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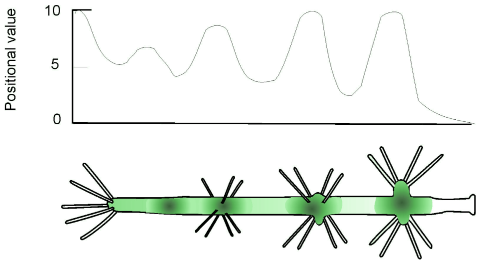
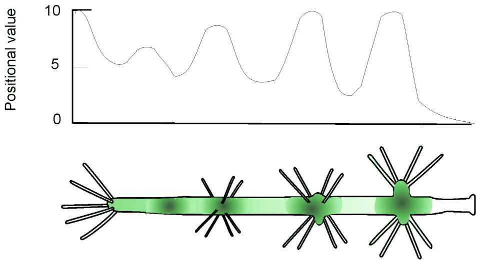


Observations on the tissue level

- Cells differentiate according their position along the body axis ("positional value", Wolpert 1972)

Concept of pattern generation



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Hypothesis

- Differentiation is determined by the density of bound receptors (Sherrat, Maini, Jäger and Müller 1995)

Concept of pattern generation

Observations on the molecular level

- Head formation is correlated with the overexpression of Wnt gene (Holstein 2003)

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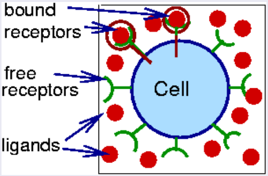
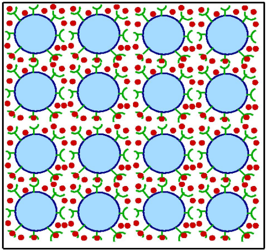
Model of receptor-ligand dynamics



- Diffusion of ligands (Wnt) in the intercellular space
- Binding to the receptors (Frizzled) on the cell membranes
- Nonlinear regulatory feebacks (intracellular signalling)

Multiscale mathematical models

Microscopic models

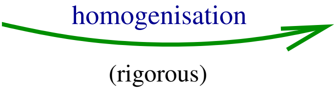


Macroscopic receptor-based models

$$\begin{aligned} \partial_t u(x,t) &= f(u(x,t), v(x,t)) \\ \partial_t v(x,t) &= D\Delta v(x,t) + g(u(x,t), v(x,t)) \end{aligned}$$

+ zero-flux boundary conditions
+ initial conditions

$x \in \Omega \subset \mathbb{R}^N, \quad t \in \mathbb{R}^+$



Receptor-based models

$$
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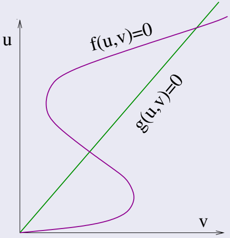
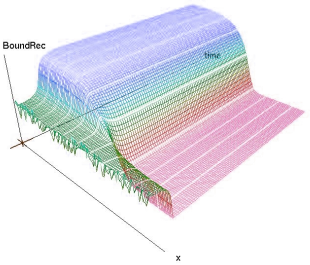


Mechanisms of pattern formation

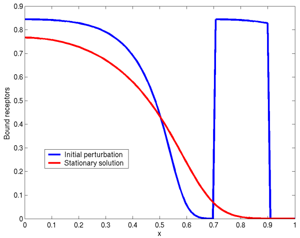
- Diffusion-driven instabilities (DDI)
- Existence of multiple quasi-steady states (hysteresis)

Models with diffusion-driven instability

- Spatially uniform initial data evolves into a gradient pattern
- Models with DDI cannot explain the outcome of transplantation experiments



Stable gradient-like pattern

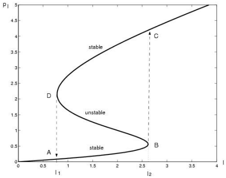


Grafting experiment

- Initial data corresponding to the head transplantation
- Final distribution showing the transplant disappearance

Novel approach: Multiple quasi-steady states

- New model: bistability in signalling pathway



$$\frac{\partial}{\partial t} p_l = -\delta_l \frac{p_l}{1+p_l^2} + \frac{m_2 l r_b}{(1+\sigma_l p_l^2 - \beta_l p_l)(1+\alpha_l r_b)}$$

p_l	-	rate of ligand synthesis
l	-	ligands
r_b	-	receptors

- Multistability leads to the formation of transition-layer patterns

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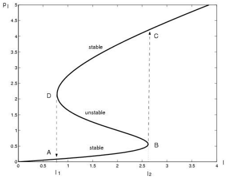

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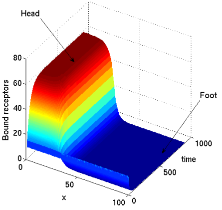
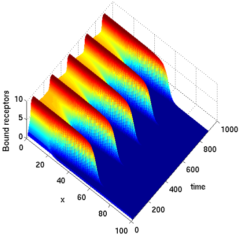
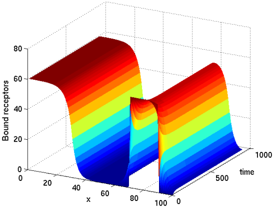


Stationary patterns



Spatio-temporal patterns



Grafting experiments

Experimental verification

- How is differentiation initiated?
  - Critical number of cells (size of domain), above which the spatially homogeneous attractor loses stability, which leads to "spontaneous" spatial patterning
  - External inducing signal, which drives the system into a new, spatially inhomogeneous state

- Evidence of bistability in Wnt dynamics in Drosophila (Krueger *et al* 2004)

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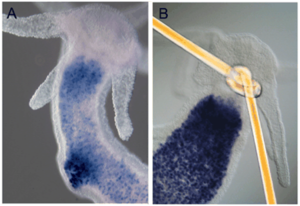

Experimental evidence of injury stimulus (laboratory of Thomas Holstein, Guder *et al* 2006)

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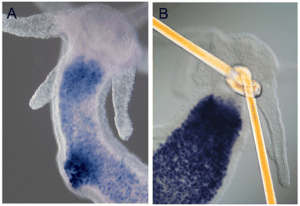

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Conclusions and future work

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- Multistability in the dynamics of the signalling molecules is necessary to explain the transplantation experiments
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Future work

- Include key regulatory processes of Wnt signalling
- Explain the role of Dickkopf-Wnt interactions
- Model serial and overlapping expression patterns of different Wnt proteins in a sea anemone *Nematostella vectensis*