Multiscale mathematical modelling of cell systems

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### 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
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

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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**Collaboration with experimentalists**

- Thomas Holstein, Zoology Institute, University of Heidelberg
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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
Concept of pattern generation

Cutting experiment
Concept of pattern generation

Cutting experiment

Observations on the tissue level

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

Hypothesis

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

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Models of pattern formation
Concept of pattern generation

Grafting experiment

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Head formation is correlated with the overexpression of Wnt gene (Holstein 2003)
**Concept of pattern generation**

**Observations on the molecular level**

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

**Model of receptor-ligand dynamics**

- Diffusion of ligands (Wnt) in the intercellular space
- Binding to the receptors (Frizzled) on the cell membranes
- Nonlinear regulatory feedbacks (intracellular signalling)
### Multiscale mathematical models

#### Microscopic models

<table>
<thead>
<tr>
<th>$x$</th>
<th>$\Omega \subset \mathbb{R}^N$</th>
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#### Macroscopic receptor-based models

\[
\begin{align*}
\frac{\partial_t u(x, t)}{} & = f(u(x, t), v(x, t)) \\
\frac{\partial_t v(x, t)}{} & = D \Delta v(x, t) + g(u(x, t), v(x, t)) \\
\end{align*}
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+ zero-flux boundary conditions
+ initial conditions

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

---

**homogenisation**

(rigorous)
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

Anna Marciniak-Czochra | Models of pattern formation
Novel approach: Multiple quasi-steady states

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**Multistability leads to the formation of transition-layer patterns**

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](image)

(laboratory of Thomas Holstein, Guder *et al* 2006)

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Conclusions and future work

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- Proposed models show how the nonlinearities of signalling pathways may result in spatial patterning
- Multistability in the dynamics of the signalling molecules is necessary to explain the transplantation experiments
- Models with multiple steady states seem very promising and lead to mathematical and modelling open problems

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
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