Modeling and simulation of mechano-chemical pattern formation processes

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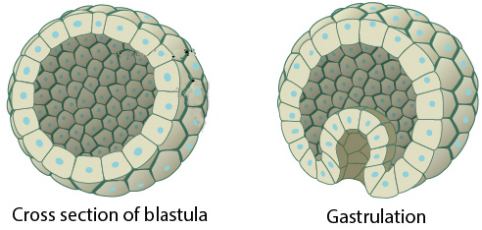
- Motivation
- Modeling
- Numerics & Results



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Theories explaining pattern formation processes

1. A sequence of successive chemical patterns form. This would rule out spontaneous self-organized processes, as they are observed in dissociated and re-aggregated cells.

2. Chemical patterns can form spontaneously by an interplay of mutual interaction of diffusing morphogens by the *Turing mechanism*. While the *Turing mechanism* creates many relevant patterns, experiments usually do not find morphogens with requires diffusion and reaction rates.

Turing: *The chemical basis of morphogenesis*, **Phil. Trans. R. Soc. London, 1953**
Meinhardt & Gierer: *Pattern formation by local self-activation and lateral inhibition*, **Bioessays, 2000**

- Both theories say, that mechanical patterns are *blind end results* of chemical pre-patterns. Recent studies however show, that mechanical patterns play an *active role*.

Brouzes & Farge: *Interplay of mechanical deformation and patterned gene expression in developing embryos*, **Curr. Opin. Genet. Dev., 2004**

Mechanics

$$-\operatorname{div}\left(\mathbf{F}\boldsymbol{\Sigma}\right) = 0 \text{ in V},$$

assuming a St. Venant Kirchhoff material

$$\boldsymbol{\Sigma} = 2\mu\mathbf{E} + \lambda\operatorname{tr}(\mathbf{E})I, \quad \mathbf{E} = \frac{1}{2}(\mathbf{F}^T\mathbf{F} - I), \quad \mathbf{F} = I + \nabla\mathbf{u}$$

With

$$\mathbf{u} = 0 \text{ on } \Gamma_D, \quad \mathbf{F}\boldsymbol{\Sigma}\mathbf{n} = g \text{ on } \Gamma_N$$

We assume, that growth is very slow compared to elastic dynamics such that the mechanical system is always in a stationary limit

(Bio-)Chemistry

System of reaction diffusion equations (in Lagrangian coordinates)

$$J\partial_t c_i - \operatorname{div}\left(J\mathbf{F}^{-1}D\mathbf{F}^{-T}\nabla c_i\right) - JR_i(c_1,\dots,c_n) = 0 \text{ in } V \text{ for } i = 1,\dots,n$$

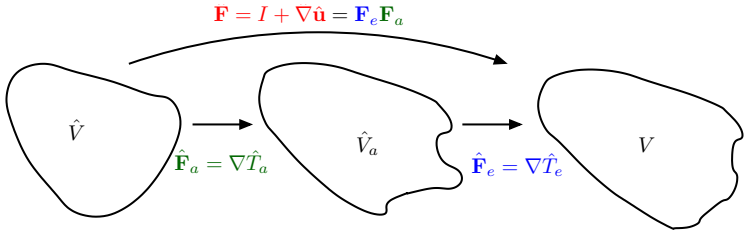
with initial and boundary conditions

$$c_i = c_i^0 \text{ for } t = 0 \text{ and } J\mathbf{F}^{-1}D\mathbf{F}^{-T}\nabla c_i\mathbf{n} = 0 \text{ on } \Gamma$$

- Intermediate configuration

$$\hat{V} \xrightarrow{\hat{T}_a} \hat{V}_a \xrightarrow{\hat{T}_e} V$$

- Active deformation $\hat{T}_a$ and elastic deformation $\hat{T}_e$



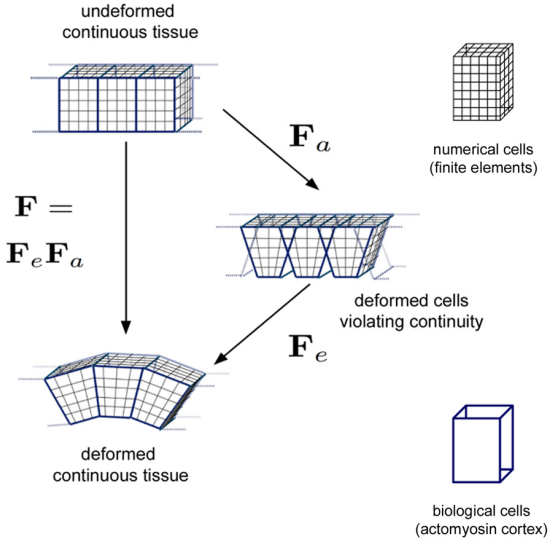
Elasticity takes place between V_a and V

$$\mathbf{\Sigma} = \mathbf{\Sigma}(\mathbf{F}_e) = \mathbf{\Sigma}(\mathbf{F}\mathbf{F}_a^{-1})$$

For the St. Venant Kirchhoff material

$$\mathbf{\Sigma} = J_a\mathbf{F}_a^{-1}\mathbf{\Sigma}_e\mathbf{F}_a^{-T}, \quad \mathbf{\Sigma}_e = 2\mu\mathbf{E}_e + \lambda\,\mathrm{tr}(\mathbf{E}_e)I, \quad \mathbf{E}_a = \frac{1}{2}(\mathbf{F}_e^T\mathbf{F}_e - I) = \frac{1}{2}(\mathbf{F}_a^{-T}\mathbf{F}^T\mathbf{F}\mathbf{F}_a^{-1} - I).$$

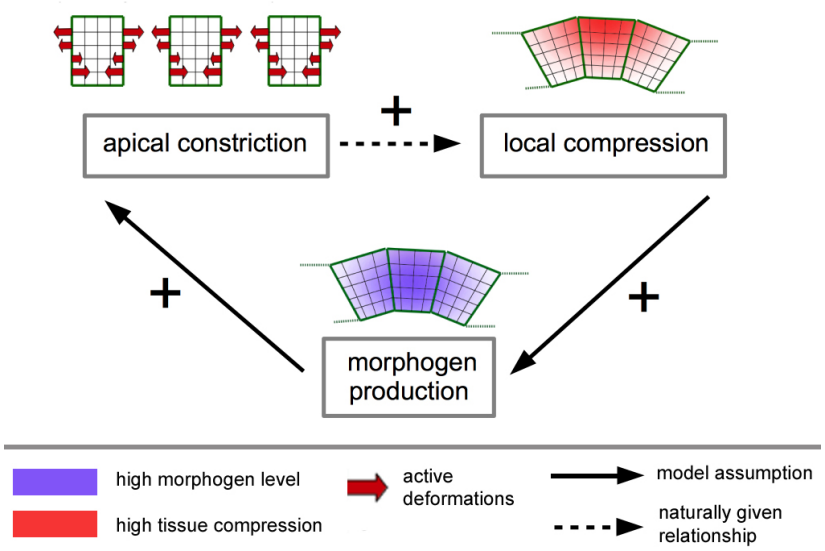
Rodriguez, Hoger & McCulloch: *Stress-depedent finite growth in soft elastic tissues*, **J. BioMech. 1994**
Ambrosi & Mollica: *On the mechanics of a growing tumor*, **IJ Eng. Science 2002**



- Active deformation (here apical constriction) depends on one chemical concentration c

$$\hat{\mathbf{F}}_a(x,y,z,c)\Big|_M = \begin{pmatrix} 1+\kappa c\hat{z} & 0 & \kappa c\hat{x} \\ 0 & 1+\kappa c\hat{z} & \kappa c\hat{y} \\ 0 & 0 & 1 \end{pmatrix}, \quad \begin{pmatrix} \hat{x} \\ \hat{y} \\ \hat{z} \end{pmatrix} = \begin{pmatrix} x - x_M \\ y - y_M \\ z - z_M \end{pmatrix} \text{ rel. to midpoint of cell } M$$

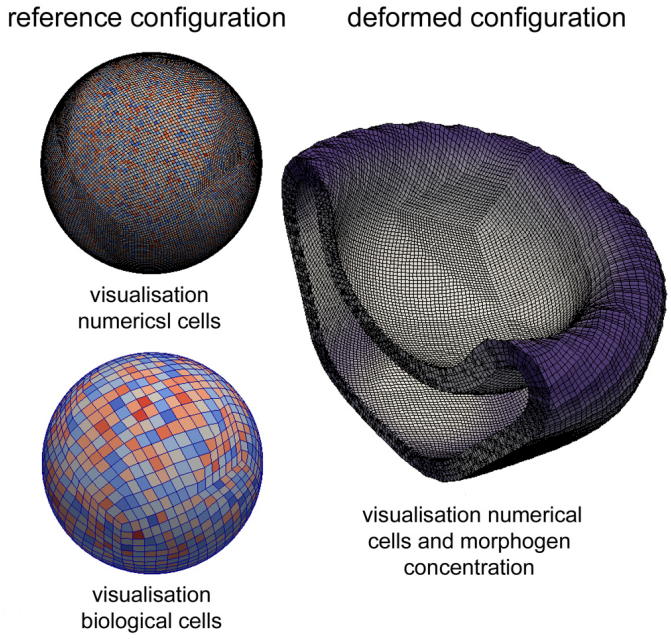
- (Simplified, as we first have to rotate every biological cell to a reference orientation)



- High morphogen level causes apical constriction $\mathbf{F}_a = \mathbf{F}_a(c)$
- Apical constriction causes elastic feedback with local compression $\boldsymbol{\Sigma}_e = \boldsymbol{\Sigma}(\mathbf{F}\mathbf{F}_a^{-1})$
- Local compression triggers morphogen production (Michaelis-Menten kinetics)

$$R(c, \mathbf{F}) = \kappa_1 \frac{\max\{\det \mathbf{F}, 0\}}{\kappa_3 + \max\{\det \mathbf{F}, 0\}} - \kappa_2 c, \quad \kappa_1, \kappa_2, \kappa_3 > 0$$

- We consider a layer of biological cells. The (adaptive) finite element discretization is much finer
- Overall very large active and elastic deformation appears



Monolithic Model

$$U = \{\mathbf{u}, c\} \in \mathcal{X}: \quad A(U)(\Phi) = 0 \qquad \forall \Phi \in \mathcal{X}$$

The variational formulation is given by

$$\begin{aligned} A(U)(\Phi) = &\left(\mathbf{F} J_a \mathbf{F}_a^{-1} \boldsymbol{\Sigma}_e \mathbf{F}_a^{-T}, \nabla\phi\right) \\ &+ \left(J\partial_t c, \psi\right) + \left(J\mathbf{F}^{-1} D\mathbf{F}^{-T} \nabla c, \nabla\psi\right) - \left(JR(c,\mathbf{F}), \psi\right) \end{aligned}$$

with

- Growth model

$$\hat{\mathbf{F}}_a\Big|_M = \begin{pmatrix} 1+\kappa c\hat{z} & 0 & \kappa c\hat{x} \\ 0 & 1+\kappa c\hat{z} & \kappa c\hat{y} \\ 0 & 0 & 1 \end{pmatrix}$$

- Reaction feedback

$$R(c,\mathbf{F}) = \kappa_1 \frac{\max\{\det \mathbf{F}, 0\}}{\kappa_3 + \max\{\det \mathbf{F}, 0\}} - \kappa_2 c$$

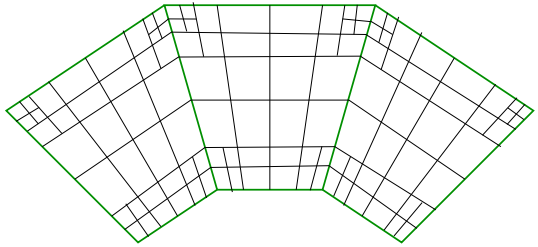
- Stress model with growth-splitting

$$\Sigma_e = 2\mu \mathbf{E}_e + \lambda \operatorname{tr}(\mathbf{E}_e), \quad \mathbf{E}_e = \frac{1}{2}(\mathbf{F}_a^{-T}\mathbf{F}^T\mathbf{F}\mathbf{F}_a^{-1} - I),$$
$$\mathbf{F} = I + \nabla\mathbf{u}$$

- Quadratic finite elements (3 deformation variables + 1 concentration)

$$X_h \subset \mathcal{X}, \quad X_h := \{\phi \in C(\bar{\Omega})^{3+1},\ \phi\big|_K \in Q^2(K)^4\ \forall K \in \Omega_h\}$$

- Adaptive Meshes to efficiently resolve biological cells (there are jumps in the active growth model $\mathbf{F}_a$ at the biological cell boundaries)



- Monolithic coupled approach

$$\text{Find } U_h = (\mathbf{u}_h, c_h) \in X_h : \quad A(U_h)(\Phi_h) = 0 \quad \forall \Phi_h \in X_h$$

- Time stepping with the implicit Euler method. We found, that temporal accuracy is of lesser important (compared to spatial accuracy and stability problems)

Nonlinear Solver

Linearization with Newton's method

$$A'(U_h^{(i)})(W_h^{(i)}, \Phi_h) = F(\Phi_h) - A(U_h^{(i)})(\Phi_h) \quad \forall \Phi_h \in X_h, \quad U_h^{(i+1)} = U_h^{(i)} + \omega W_h^{(i)}$$

Analytic computation of the monolithic Jacobian

- Large and ill-structure linear system of equations (couplings to elasticity $\mathbf{A}$ to growth $\mathbf{A}_G$ chemistry transport $\mathbf{M}$, diffusion $\mathbf{A}_d$, reaction $\mathbf{A}_R$ and mapping to Lagrangian coordinates $\mathbf{A}_E$

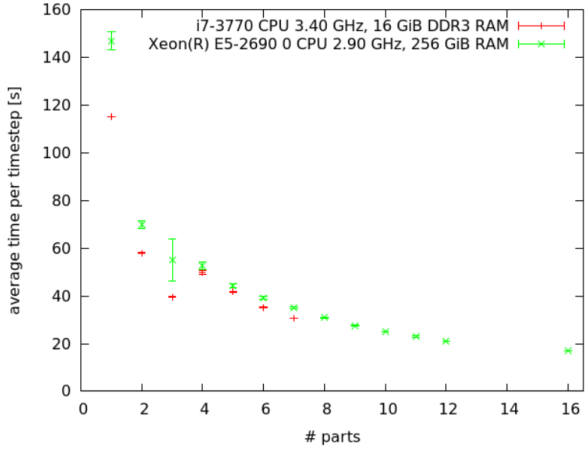
$$\begin{pmatrix} \mathbf{A} & \mathbf{A}_G \\ \mathbf{A}_R + \mathbf{A}_E & k^{-1}M + \mathbf{A}_d \end{pmatrix} \begin{pmatrix} \delta\mathbf{u} \\ \delta c \end{pmatrix} = \begin{pmatrix} \mathbf{b}_\mathbf{u} \\ \mathbf{b}_c \end{pmatrix}$$

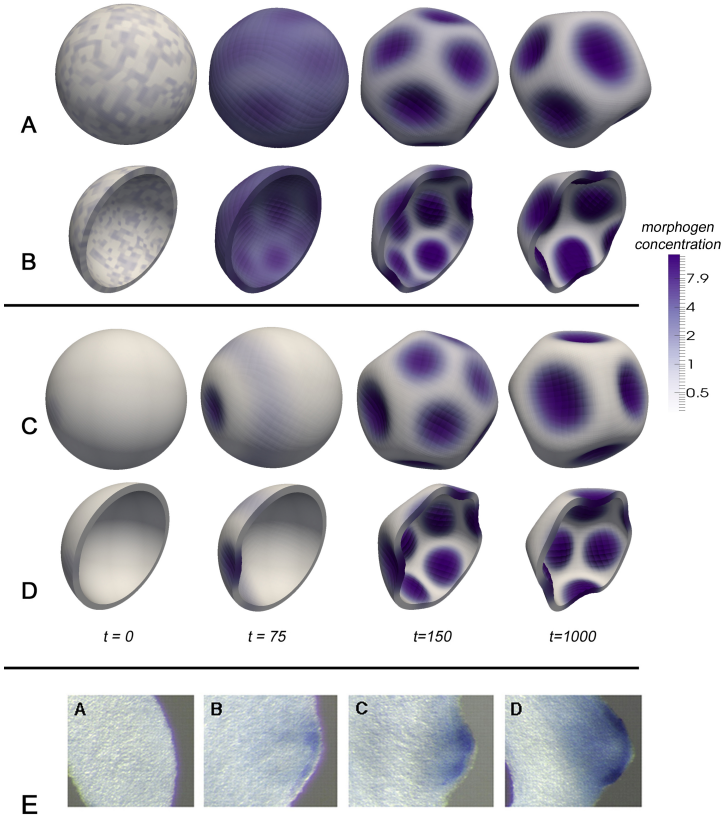
- Multigrid solver for the linear systems

$$\mathbf{A}\mathbf{x} = \mathbf{b}$$

- Parallelization of the multigrid solver by a *domain decomposition smoother*

- Highly complex simulations (nonlinearity and ill-structured linear systems)
- Fine meshes are required
- About 20 seconds per time-step
- Total simulation time in 3d about 10 days



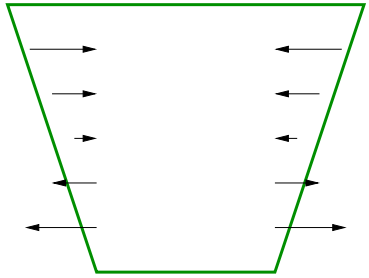


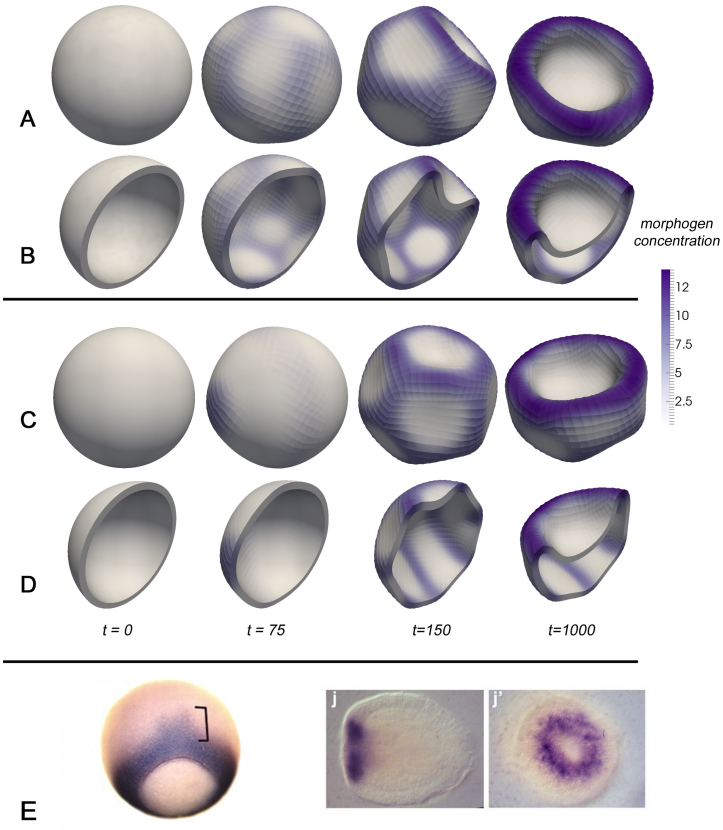
Feedback Mechanism:

- Apical constriction
- Morphogen production by compression

Results:

- The process is stable in the following sense: different initial morphogen concentrations give the same stationary mechanical pattern
- Similar patterns are observed in *Hydra development*



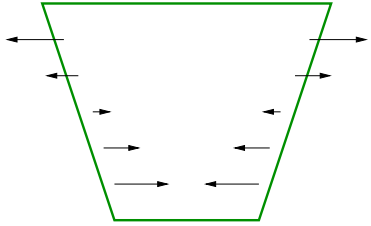


Feedback Mechanism:

- Basal constriction
- Morphogen production by compression

Results:

- Again, stable process
- Similar results are found in *Nematostella* and *Xenopus gastrulation*.



- **Numerical Simulation**
  We identify possible feedback-loops and mechanisms
  - What is the trigger for morphogen production?
    Cell-size or shape $\mathbf{F}$, elastic stress $\mathbf{\Sigma}_e$, strain $\mathbf{E}_e$ or $\mathbf{E}$?
  - How does the biological cell react?
    Compression, apical or basal constriction, shear, ...

- **Biological verification**
  Currently, experimentalists run experiments that are based on our simulations:
  - Can we trigger morphogen-production by a mechanical stimulus?
  - Can we produce a mechanical reaction by a injecting morphogens?

- **Mathematical Analysis**
  Is the coupled mechano-chemical system of partial differential equations well-posed?
  - Stability estimates for the long-term simulations. Control of the chemical concentration and elastic stresses
  - Design of robust and efficient solvers

Summary

- Novel numerical model that is able to show spontaneous pattern formation processes based on an interplay of mechanics and bio-chemistry
- Robust high-performance framework for mechano-chemical coupled simulations

All computations done with GASCOIGNE 3D

Upcoming thesis:

Felix Brinkmann: *Mathematical models and numerical simulation of mechanochemical pattern formation in biological tissues*, **Dissertation, University of Heidelberg, 2017**

Y. Yang & T.R. & W. Jäger & M. Neuss-Radu: *An ALE approach to mechano-chemical processes in fluid-structure interactions*, **Int. J. Numer. Meth. Fluids, 2017**

M. Mercker & F. Brinkmann & A. Marcinbia-Czochra & T.R.: *Beyond Turing: Mechano-chemical pattern formation in biological tissues*, **Biology Direct, 2016**

T.R.: *Fluid-structure Interactions.*, **Lecture Notes in Computational Science and Engineering 118, November 2017**