ETH
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

SIB
Swiss Institute of Bioinformatics

D-BSSE
Department of Biosystems Science and Engineering

Simulating Organogenesis in COMSOL

Computational advances and challenges.

Computational Biology Group (CoBi)

D-BSSE

ETH Zurich

OVERVIEW

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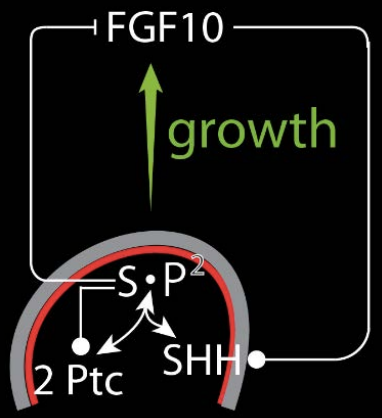
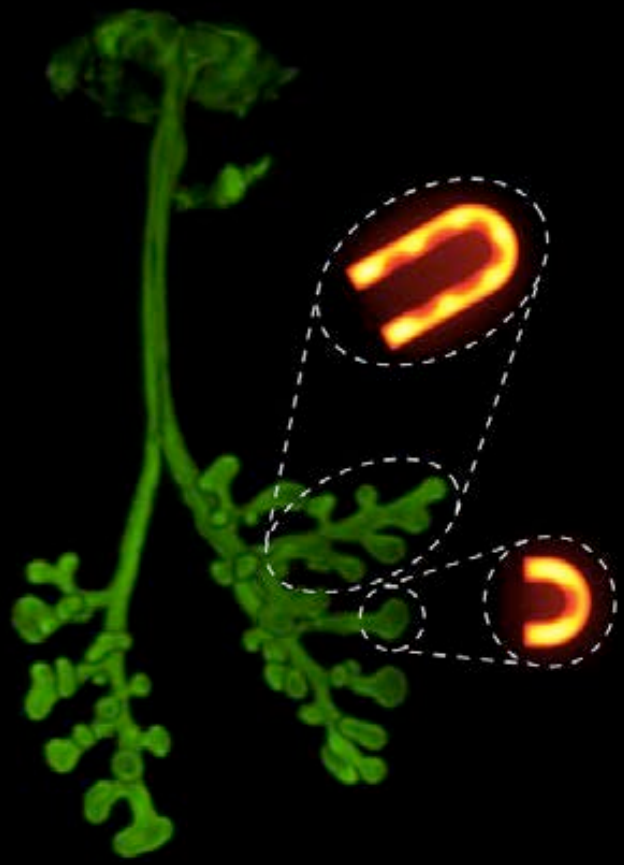
- **Motivation**: Biological Questions
- **Example**: Modeling the Limb Bud
- **Results**: Optimizing this Model
- **Outlook**: Large Deformations

Biological Questions

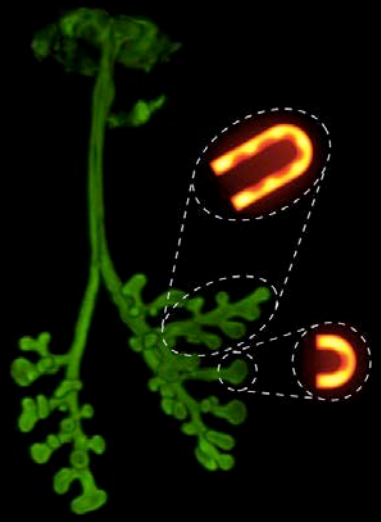
MOTIVATION

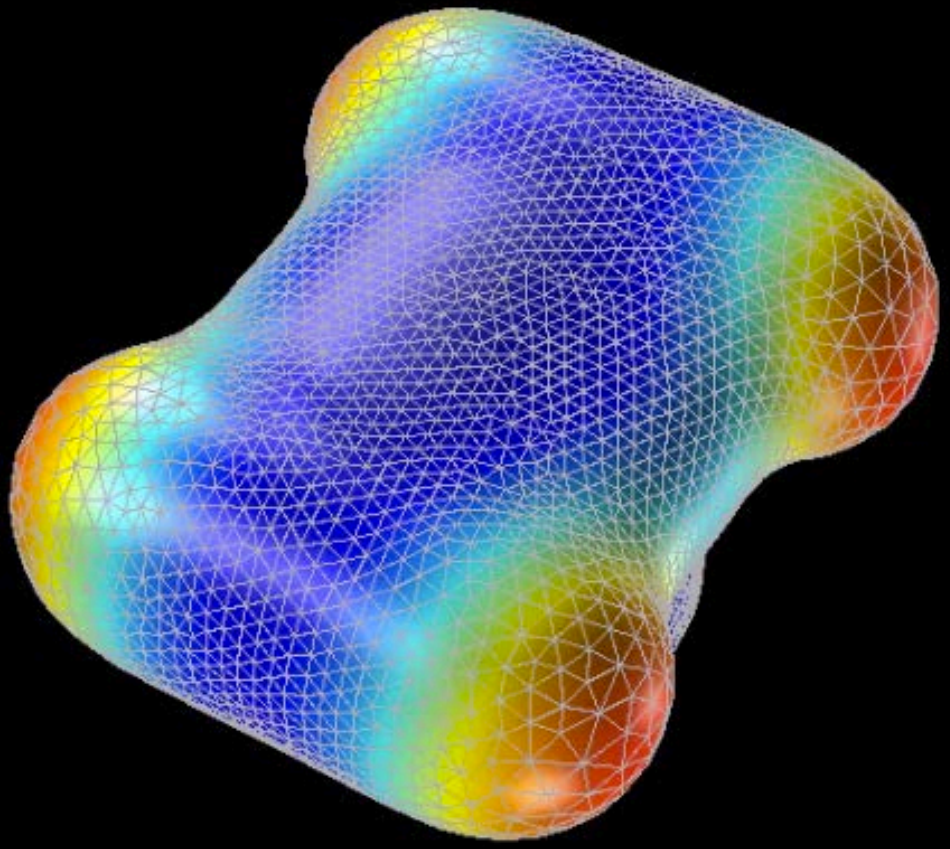
LUNG BRANCH MODE SELECTION





BRANCHING IN 3D





Modelling the Limb

EXAMPLE

REACTION DIFFUSION EQUATION

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- We use systems of reaction diffusion equations on a growing domain

$$\dot{X} + \vec{\nabla}(u \cdot X) = D_X \Delta X + R_X(X, Y, \ldots)$$

$$\dot{Y} + \vec{\nabla}(u \cdot Y) = D_Y \Delta Y + R_Y(X, Y, \ldots)$$

$$\ldots$$

- Typically we have 3-15 of these equations, non linearly coupled via the reactions R_X
- Speed u might be given (e.g. zero or constant) or a function of reactions (e.g. on the boundary proportional to the normal and some concentration)

TYPICAL REACTIONS

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- A simple reaction is decay

$$R_X = -\delta X$$

- Often we have complex formation

$$R_L = -\rho_{LR} \cdot L \cdot R$$

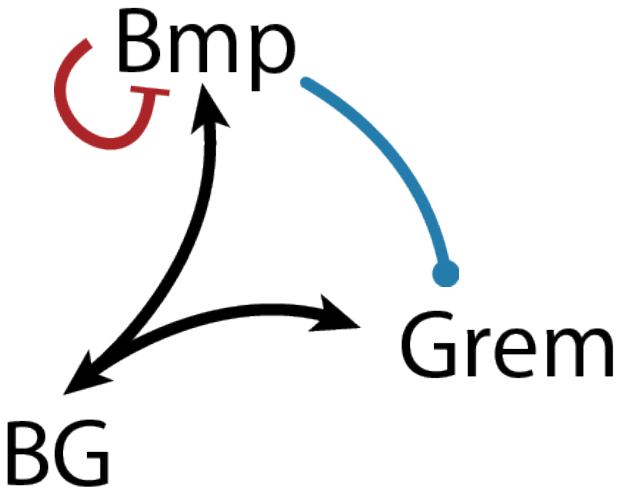
$$R_R = -\rho_{LR} \cdot L \cdot R$$

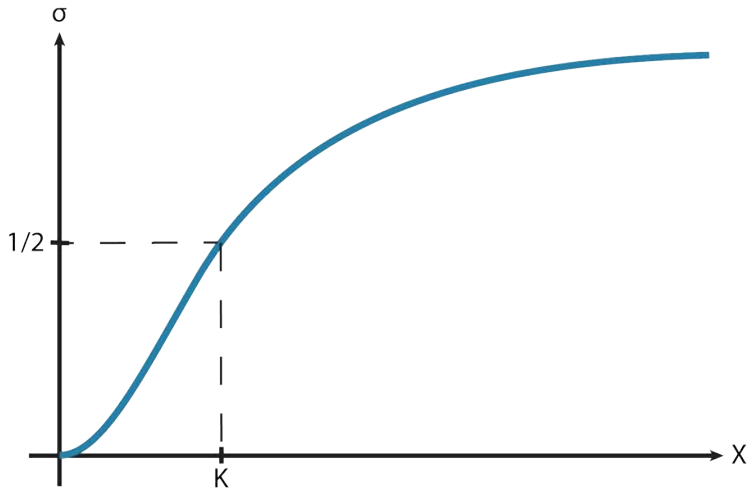
$$R_{LR} = \rho_{LR} \cdot L \cdot R$$

- Or activation and inhibition respectively

$$\sigma = \frac{X^n}{X^n + K^n}$$

$$\bar{\sigma} = \frac{K^n}{K^n + X^n}$$





SIGNALING NETWORK LIMB

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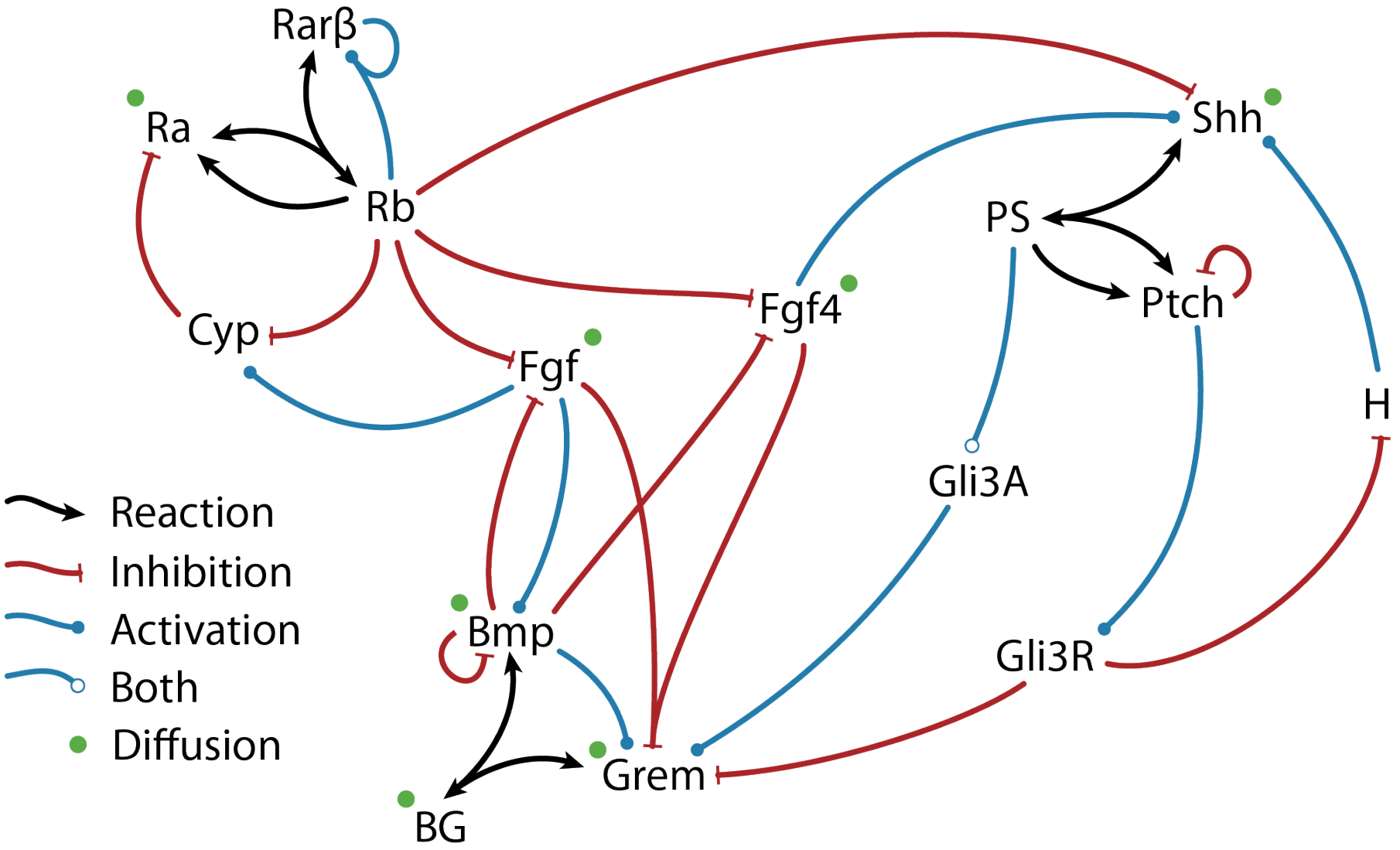

THE GEOMETRY

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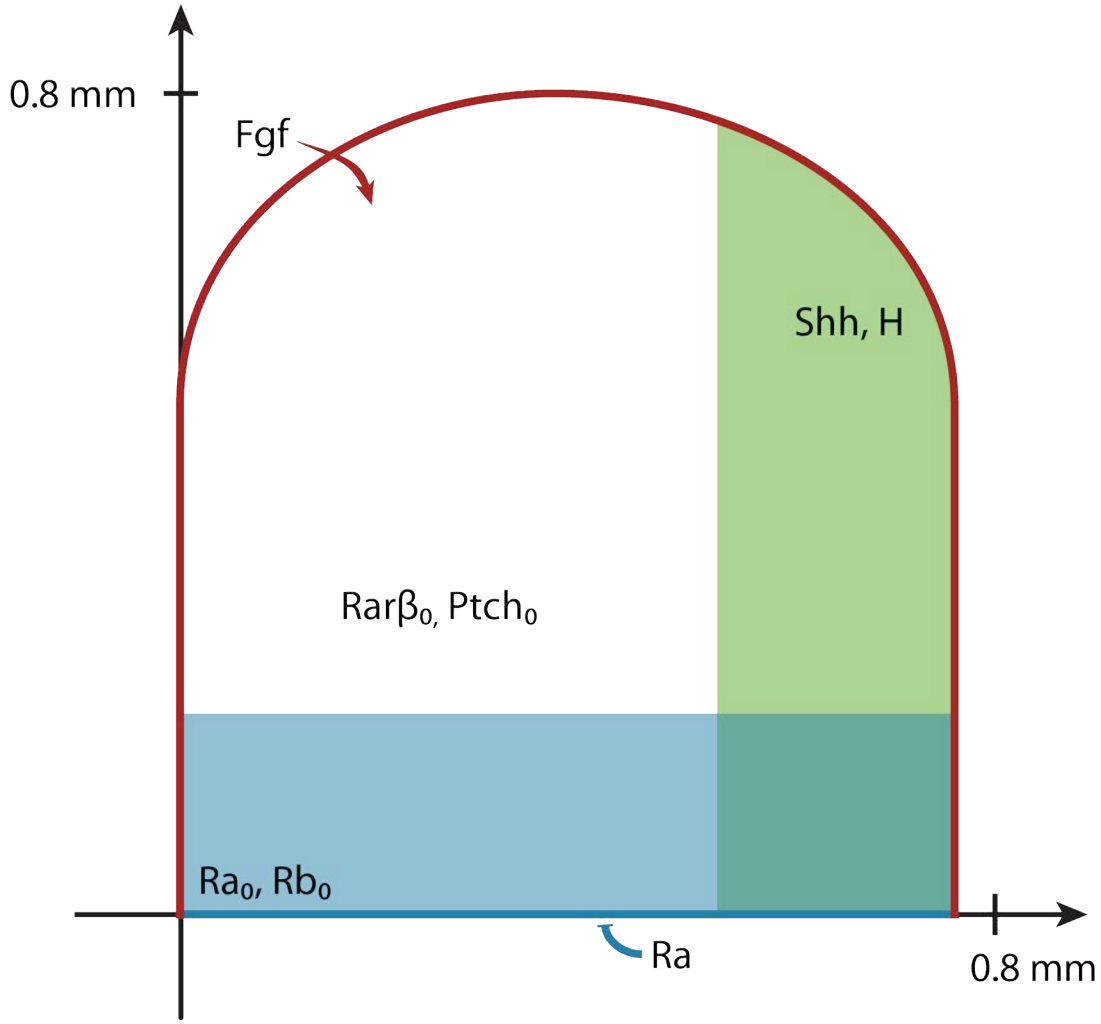

GENERAL FEATURES

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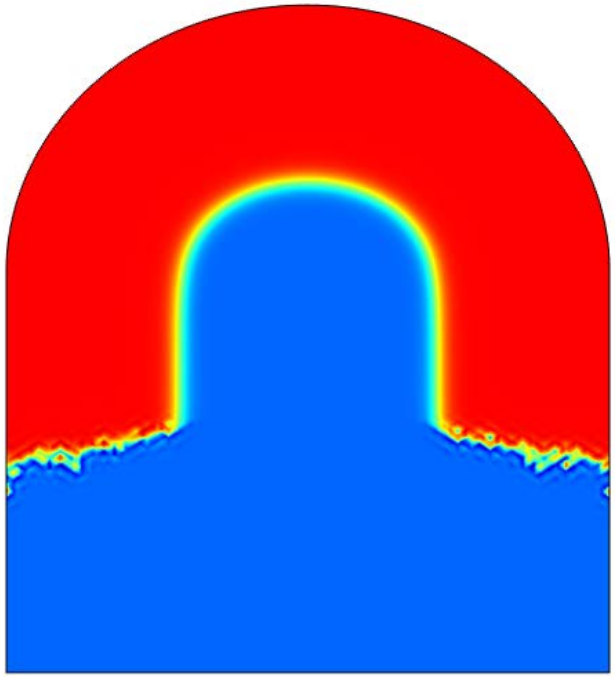
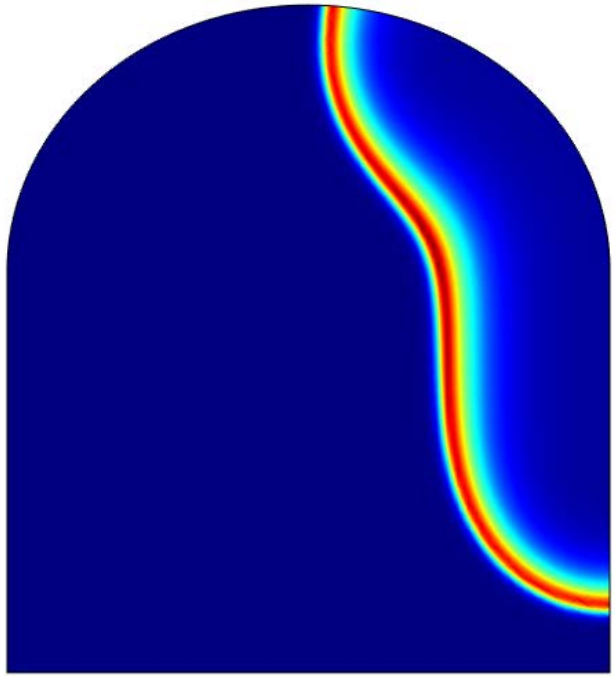
Edges



Traveling waves



STABILITY ISSUES

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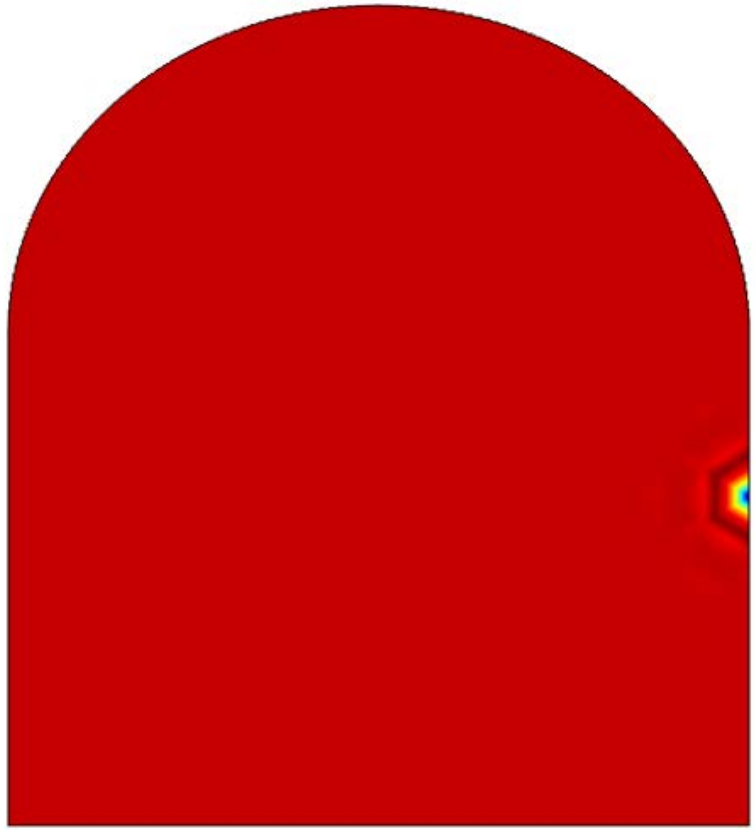
Spikes

- Produced by complex dynamics
- Appearance all over the domain



POTENTIAL TROUBLEMAKERS

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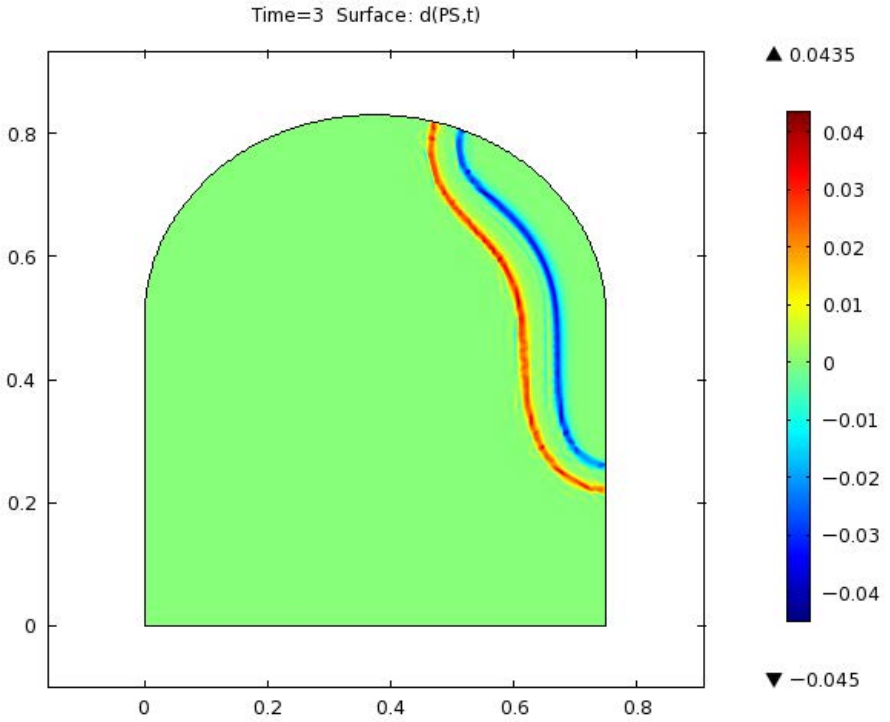
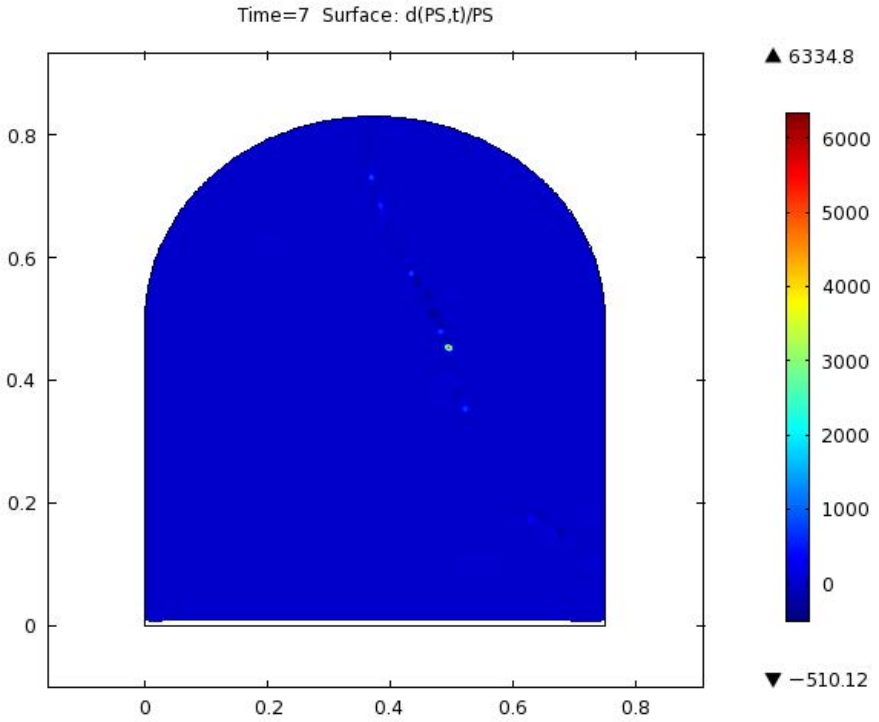
- Three complexes on different time scales
- The involved diffusion constants range from 0.02 to 0.0002, some species do not diffuse at all
- Maximal species concentrations range from order 0.0001 up to order 100
- Stiffness?





Optimising the Limb Model

RESULTS

ADVANCES: OPTIMIZING MODELS

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- **36 h** using Sledgehammer method (smaller relative error, limited timesteps & Jacobian update at each iteration)

➢ **Not acceptable for finding parameters and testing ideas efficiently**

- **9 h** removing discontinuities in production terms and initial conditions and relaxing solver settings
- **< 3 h** using cubic Lagrange elements (instead of quadratic) on a coarser grid
- **30 minutes** using manual scaling for the error estimation, allowing for quadratic elements on coarser grids
- **5 minutes** segregating the delicate complex formations from the rest

➢ Keep ALE & 3D in mind!

PARALLELIZATION

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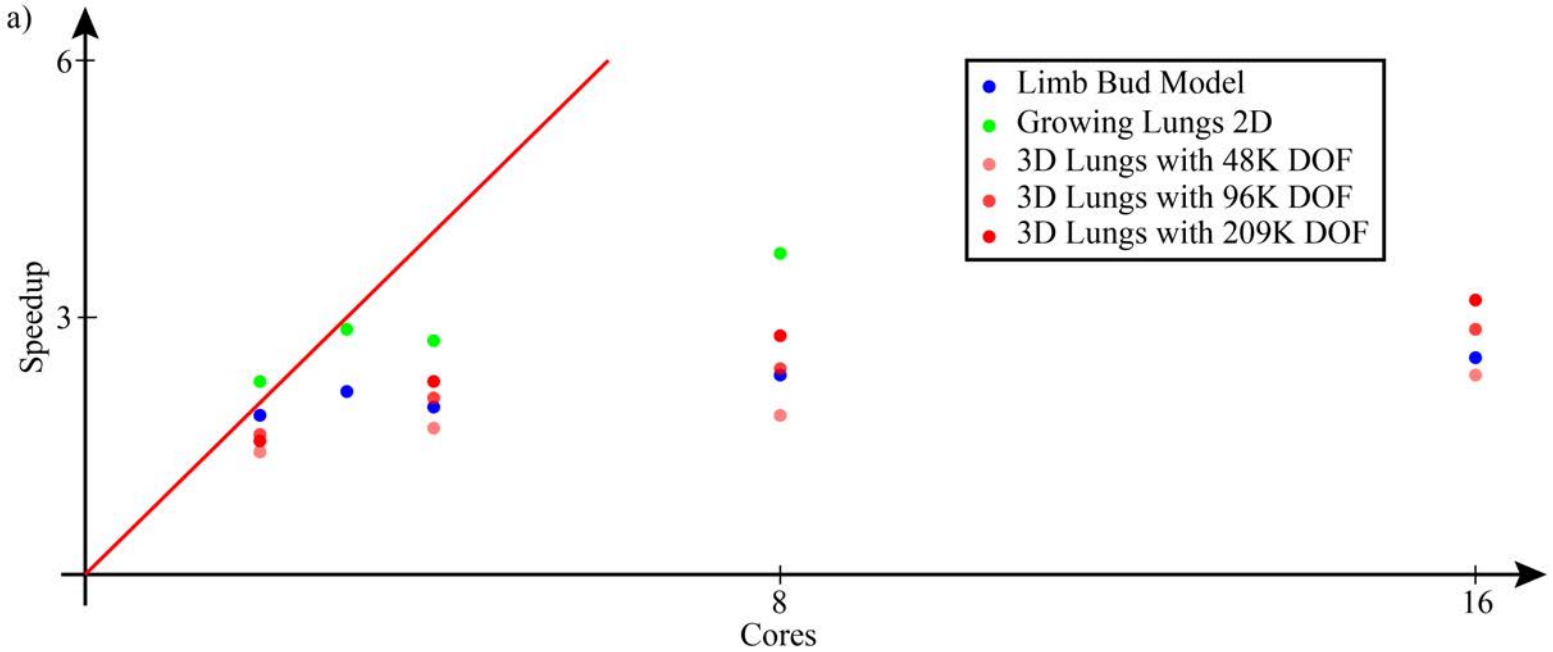

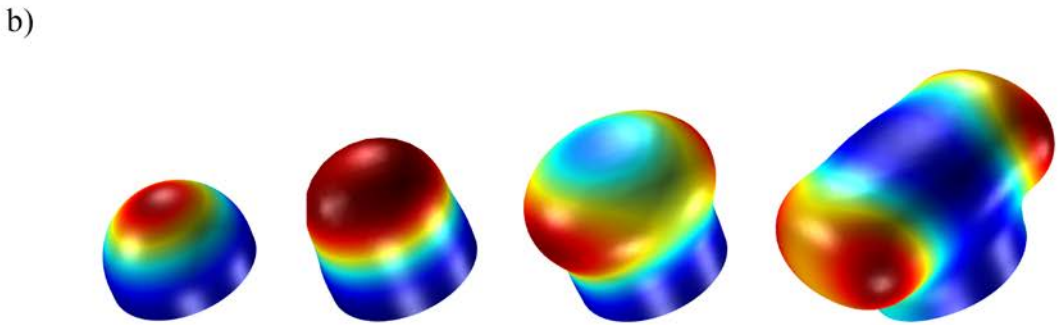

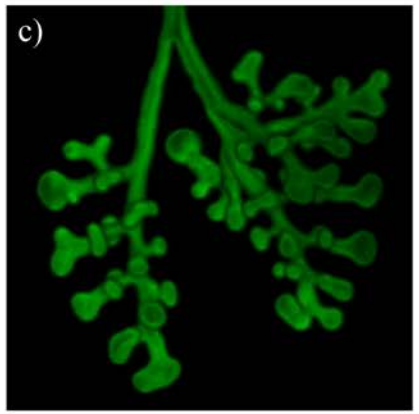

ADAPTIVE REMESHING

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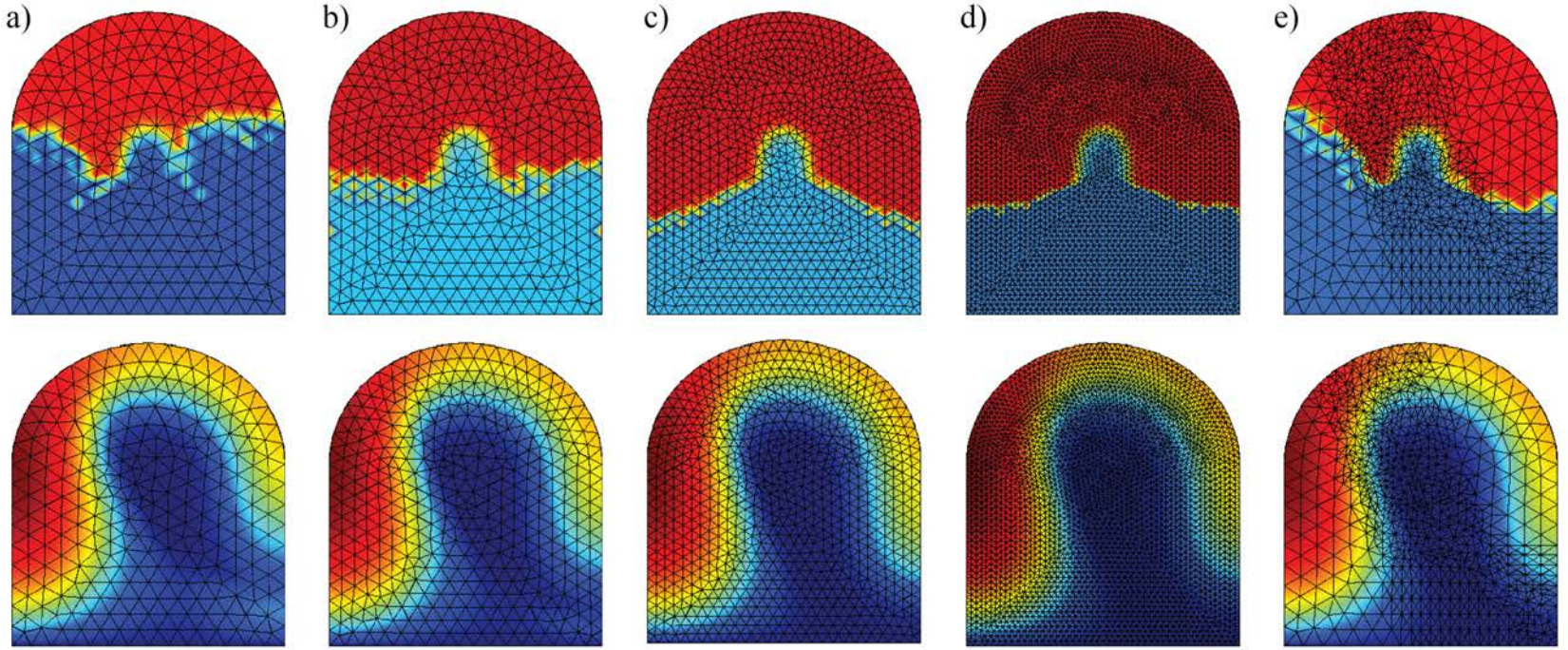
- Does not improve computing times
- Can produce artificial asymmetries



Large Deformations from Growth

OUTLOOK

CHALLENGES: IMPLEMENTING GROWTH

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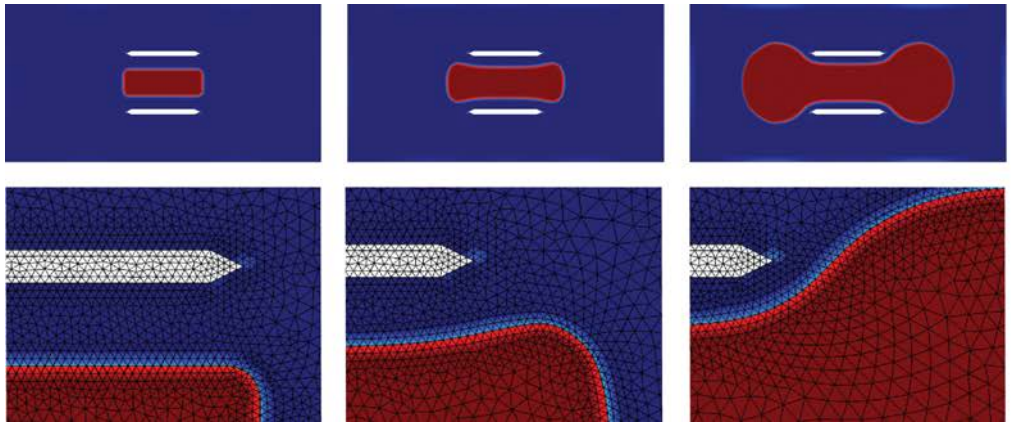
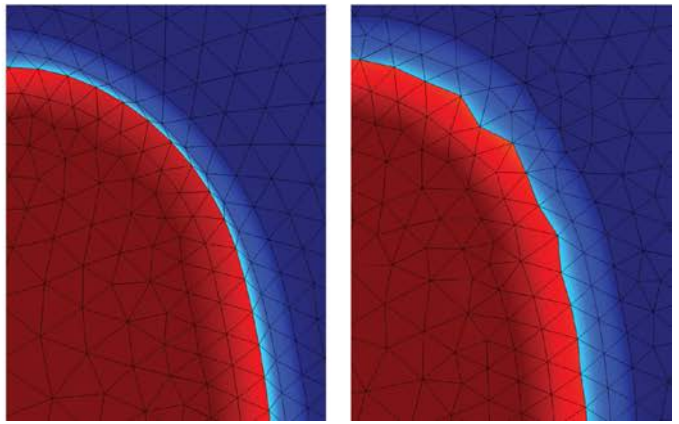
- Coupling to solid state or fluid mechanics equations
- Morphogens influence cell divisions and adhesion
- Similar strategies help avoid problems with automatic remeshing in COMSOL
- Linear shape order & Laplacian smoothing works in our experience best





STABILITY ISSUES

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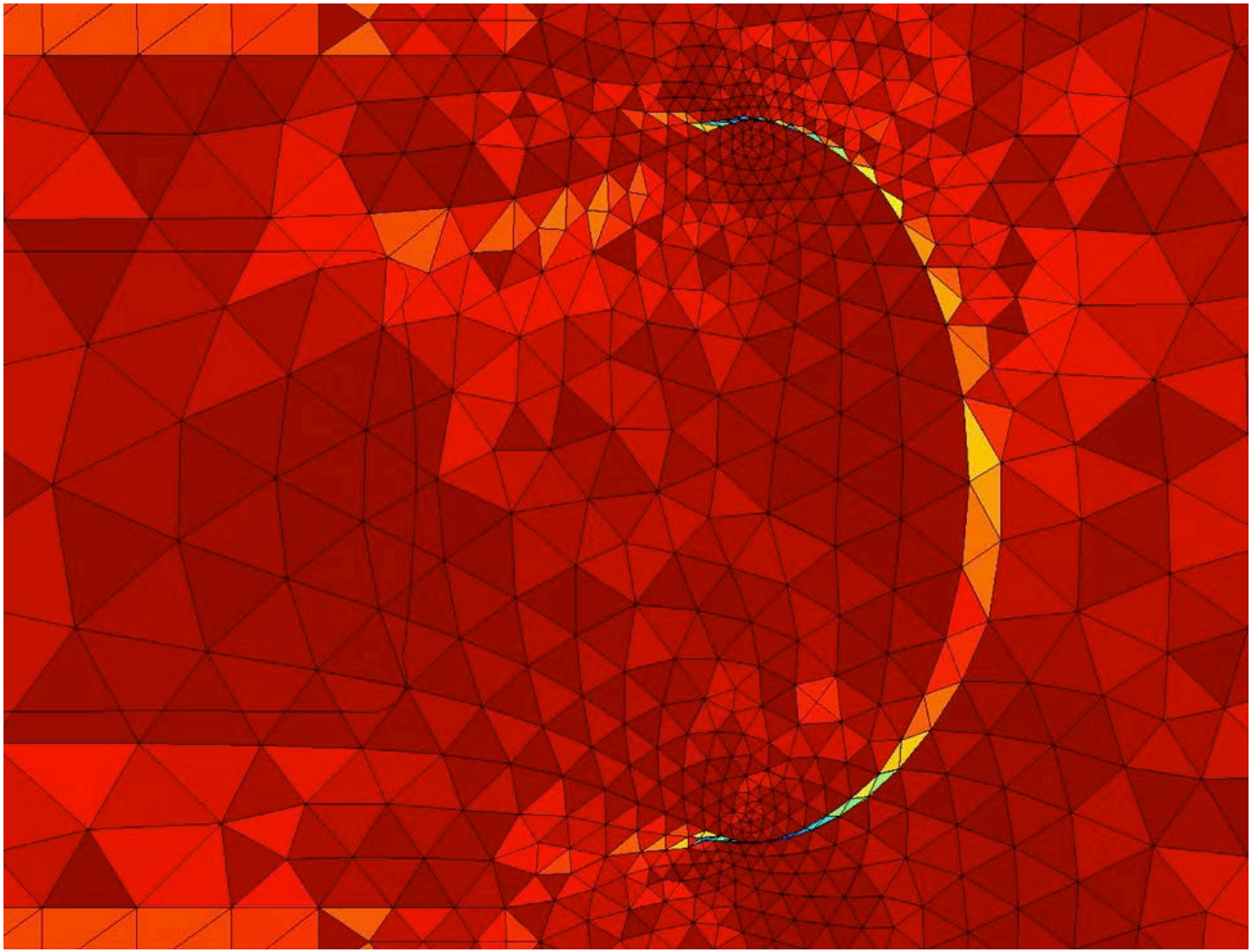

OUTLOOK

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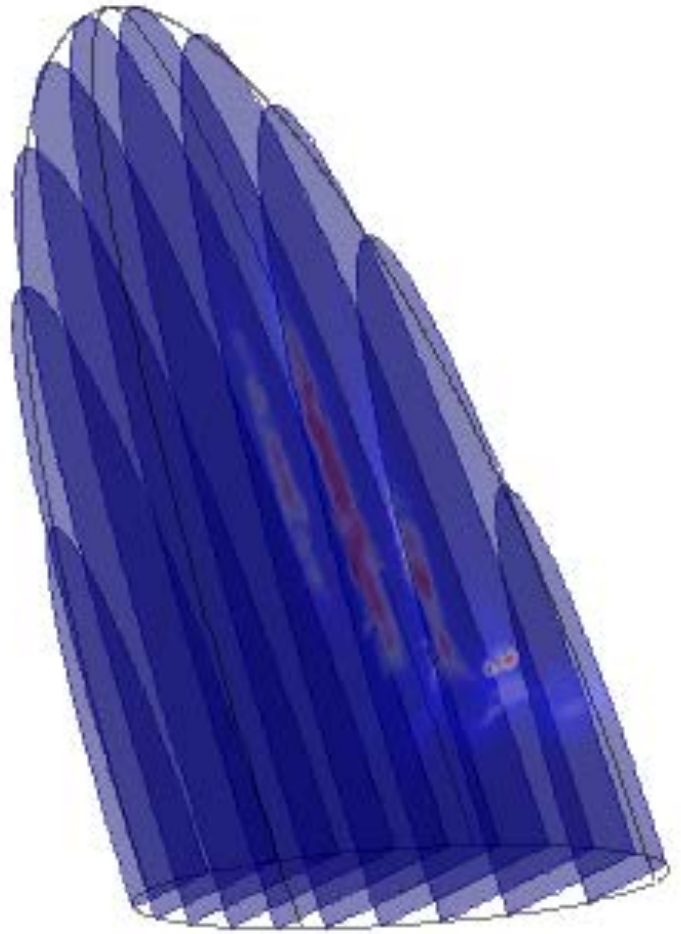
- Going 3D
- Coupling continuum physics and genetics
- Implementing directed cell divisions (via external forces?)
- Using differential surface tension to model adhesion properties



AKNOWLEDGEMENTS

Everything should be made as simple as possible, but no simpler.
Albert Einstein

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