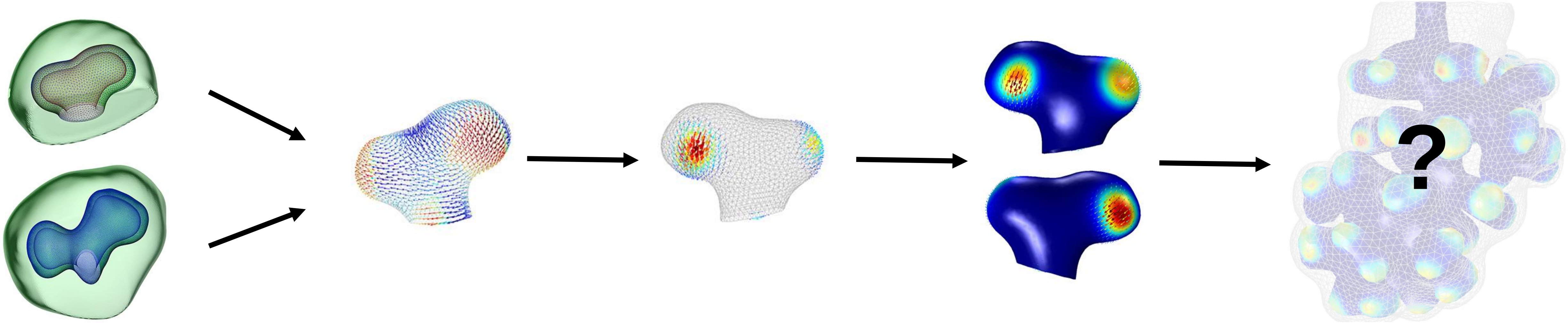

Simulating Organogenesis in COMSOL:
Phase-Field Based Simulations of Embryonic Lung Branching Morphogenesis

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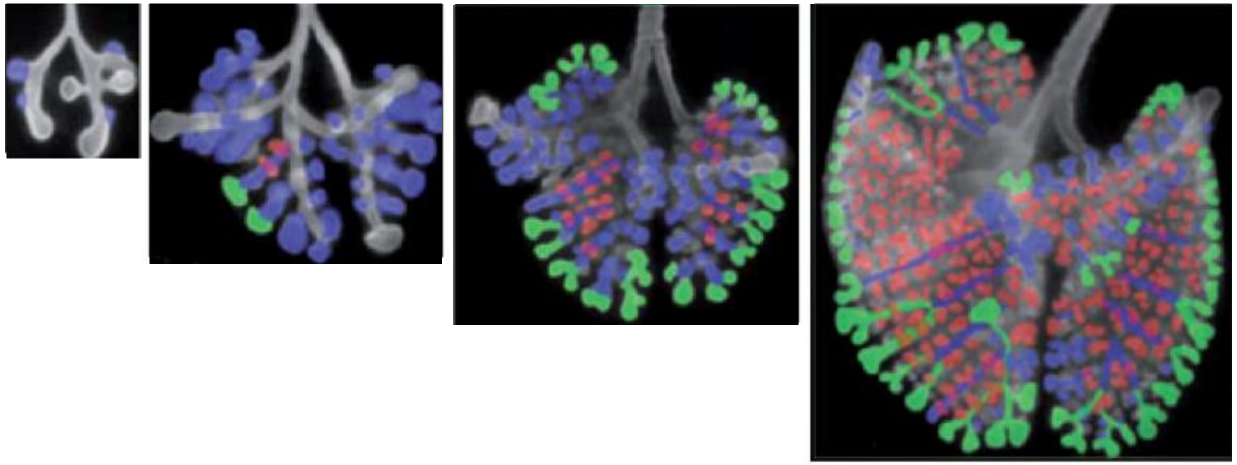
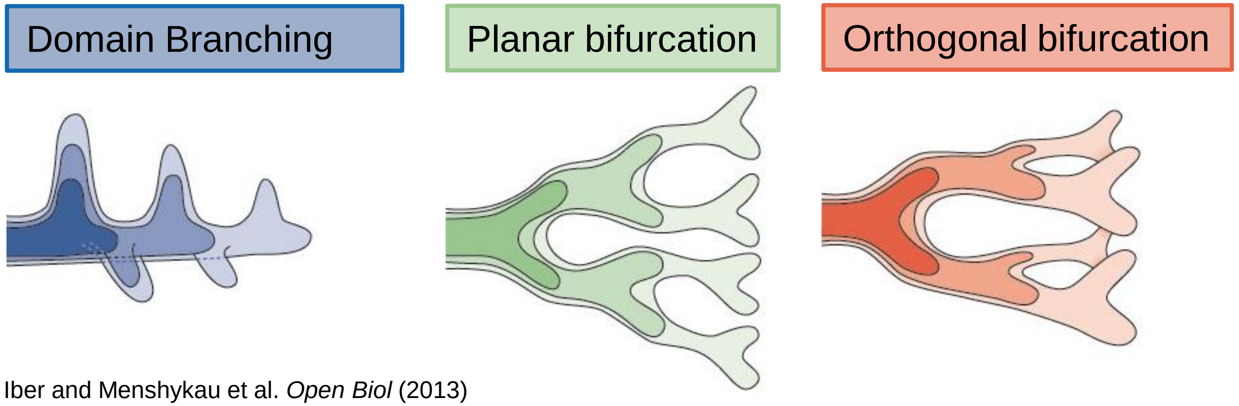
Motivation: Lung Morphogenesis

- Morphogenesis:
  Creation of Shape
- Lung Branching:
  - High Surface : Volume Ratio
  - Surface of half a tennis court
  - Highly stereotyped
- How is this achieved *in vivo*?



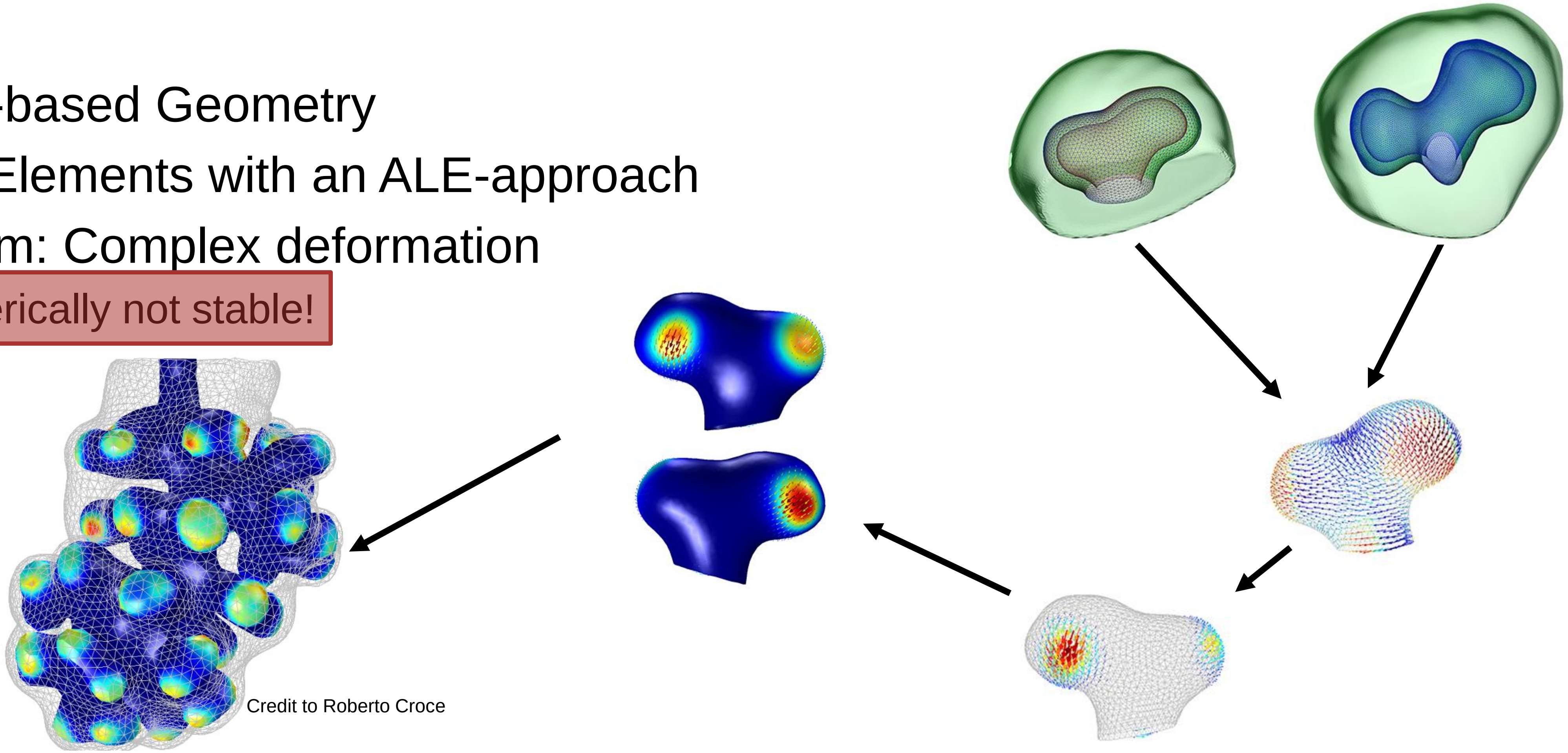
Metzger et al. *Nature* (2008)



Iber and Menshykau et al. *Open Biol* (2013)

Image-Based Simulations

- Image-based Geometry
- Finite Elements with an ALE-approach
- Problem: Complex deformation
  - Numerically not stable!



Credit to Roberto Croce

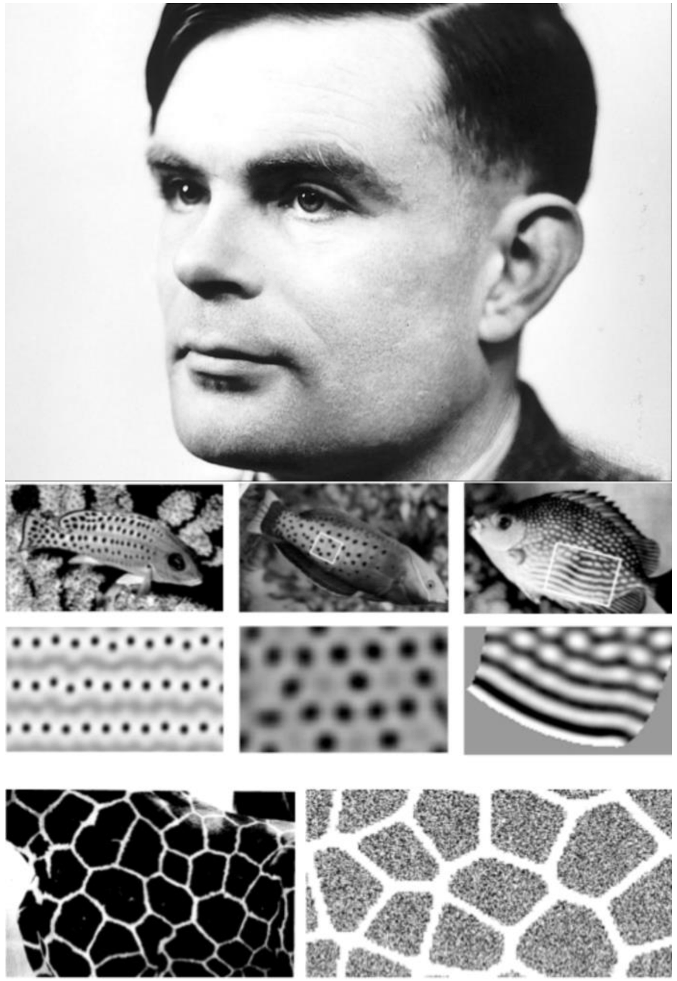
Blanc et al. *PLoS One* (2012), Menshykau et al. *Development* (2014)

Image-Based Simulations: Mathematical Model

- Turing Patterns
  - First described by Alan Turing, 1952
  - Dynamic system with two "morphogens"

$$\frac{\partial u}{\partial t} = D_1 \Delta u + f(u,v)$$
$$\frac{\partial v}{\partial t} = D_2 \Delta v + g(u,v)$$

  - Stable in the absence of diffusion
  - Unstable in the presence of diffusion
- Describes stable patterns observable in nature



http://www.kvarkadabra.net/ Credit to Dagmar

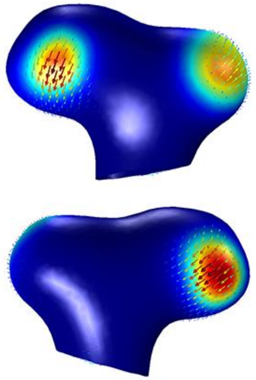
Image-Based Simulations: Mathematical Model

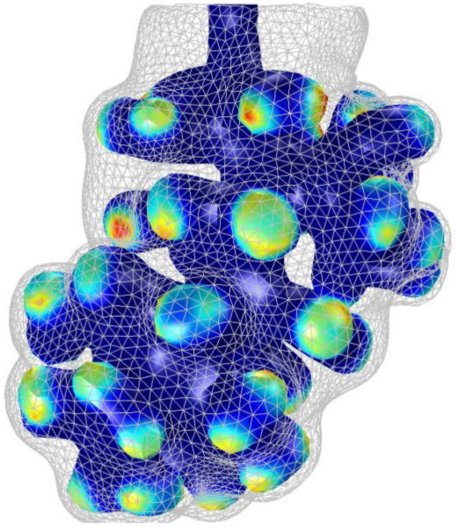
- Receptor-ligand based Turing Models

$$\frac{\partial R}{\partial t} = \Delta R + \gamma(a - R + R^2 L)$$
$$\frac{\partial L}{\partial t} = d\,\Delta L + \gamma(b - R^2 L)$$

  - Receptor R on the lung epithelium
  - Ligand L in the mesenchyme
- Growth velocity field depends on R^2L

$$\vec{v} \approx R^2 L \cdot \vec{n}$$





Menshykau et al. *Development* (2014) Credit to Roberto Croce

Eqs. to solve

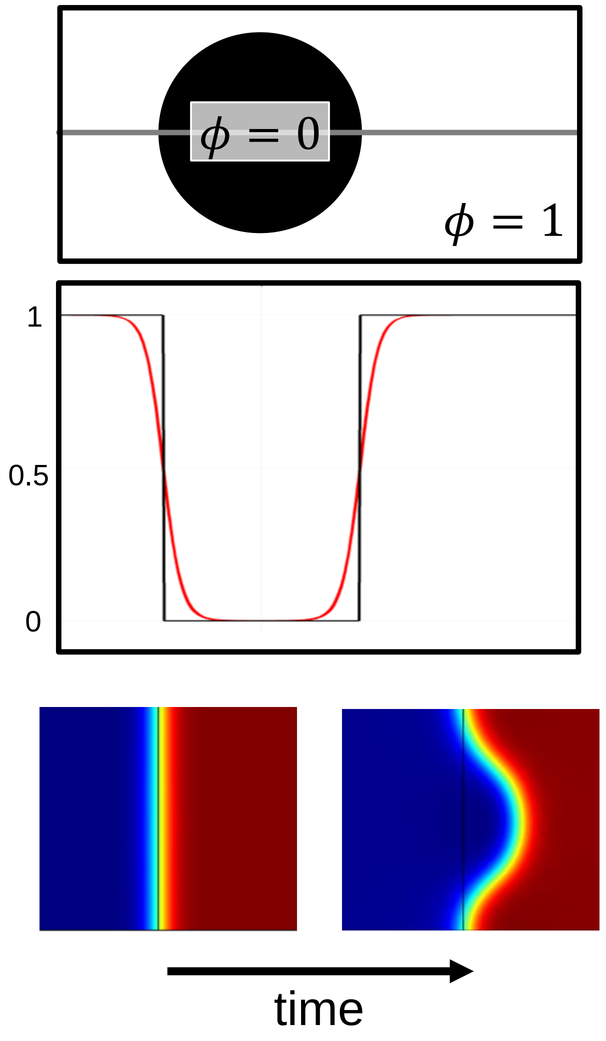
$$\frac{\partial R}{\partial t} = \Delta R + \gamma(a - R + R^2 L)$$
$$\frac{\partial L}{\partial t} = d\,\Delta L + \gamma(b - R^2 L)$$

Growth

$$\vec{v} \approx R^2 L \cdot \vec{n}$$

Mathematical Framework: Phase-Field

- Problem: Complex deformation
- Phase-Field = Scalar Field ϕ
  - Whole domain
  - Continuous
  - Constant in the bulks
  - Differentiable and steep across the diffuse front
- Regular mesh on whole domain
- Controllable
  - Interface thickness ε
  - Interface evolution through velocity field



Eqs. to solve

$$\frac{\partial R}{\partial t} = \Delta R + \gamma(a - R + R^2 L)$$
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Growth

$$\vec{v} \approx R^2 L \cdot \vec{n}$$

Mathematical Framework: Phase-Fields in COMSOL

Phase-Field Module

$$\frac{\partial\phi}{\partial t} + \vec{v}\cdot\nabla\phi = g$$

$$g = \nabla\cdot\frac{\gamma\lambda}{\varepsilon^2}\nabla\left(-\nabla\cdot\varepsilon^2\nabla\phi + (\phi^2-1)\phi + \frac{\varepsilon^2}{\lambda}\frac{\partial f}{\partial\phi}\right)$$

$$\gamma = \frac{3\epsilon\sigma}{\sqrt{8}}$$

Parameters

- Surface tension coefficient σ
- Interface thickness ϵ
- Mobility γ

Drawback

- Curvature minimizing self-dynamics

Level-Set Module

$$\frac{\partial\phi}{\partial t} + \vec{v}\cdot\nabla\phi = f$$

$$f = \gamma\nabla\phi\cdot\left(\epsilon - \phi(1-\phi)\frac{\nabla\phi}{|\nabla\phi|}\right)$$

- Interface thickness ϵ
- Re-initialisation parameter γ

- Computationally more expensive

Eqs. to solve

$$\frac{\partial R}{\partial t} = \Delta R + \gamma(a - R + R^2L)$$

$$\frac{\partial L}{\partial t} = d\,\Delta L + \gamma(b - R^2L)$$

Growth

$$\vec{v} \approx R^2L\cdot\vec{n}$$

Phase-Field Eq.

$$\frac{\partial\phi}{\partial t} + \vec{v}\cdot\nabla\phi = f$$

$$f = \gamma\nabla\phi\cdot(\epsilon - \phi(1-\phi)\frac{\nabla\phi}{|\nabla\phi|})$$

Phase-Field with Reaction-Diffusion Mechanism and Growth

- R exists on the interface only
  - Multiply with the Dirac delta function $\delta \approx |\nabla\phi|$

$$\delta \frac{\partial R}{\partial t} = \nabla \cdot (\delta \nabla R) + \gamma\delta(a - R + R^2 L)$$

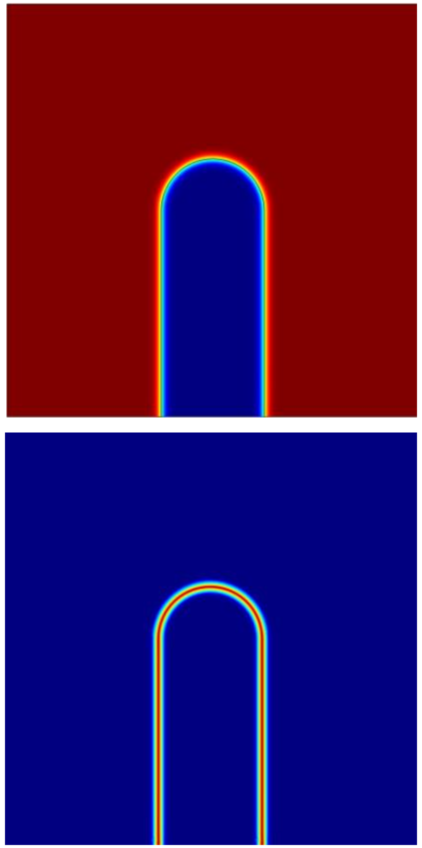
- L exists in the mesenchyme only
  - Multiply with ϕ
  - Interaction occurs only on the interface

$$\phi \frac{\partial L}{\partial t} = D\,\nabla \cdot (\phi \nabla L) + \phi\gamma b - \gamma\delta R^2 L$$

- Growth in normal direction

$$\vec{v} \approx R^2 L \cdot \vec{n}\, \frac{\nabla\phi}{|\nabla\phi|}$$

- And numerical stabilisation terms



Eqs. to solve

$$\delta \frac{\partial R}{\partial t} = \nabla \cdot (\delta \nabla R) + \gamma\delta(a - R + R^2 L)$$

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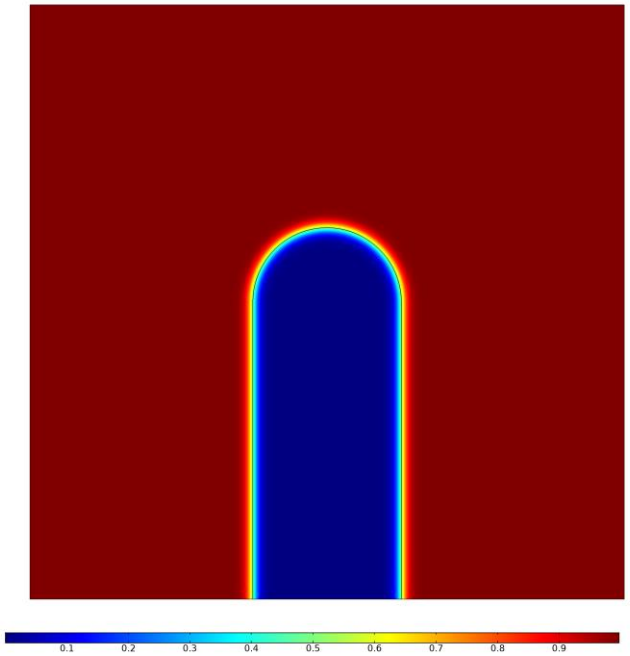
2D Results

Phase Field



R^2L

Eqs. to solve

$$\delta \frac{\partial R}{\partial t} = \nabla \cdot (\delta \nabla \mathrm{R}) + \gamma \delta (a - R + R^2 L)$$

$$\phi \frac{\partial L}{\partial t} = D\, \nabla \cdot (\phi \nabla L) + \phi \gamma b - \gamma \delta R^2 L$$

Growth

$$\vec{v} \approx R^2 L \cdot \delta \frac{\nabla \phi}{|\nabla \phi|}$$

Phase-Field Eq.

$$\frac{\partial \phi}{\partial t} + \vec{v} \cdot \nabla \phi = f$$

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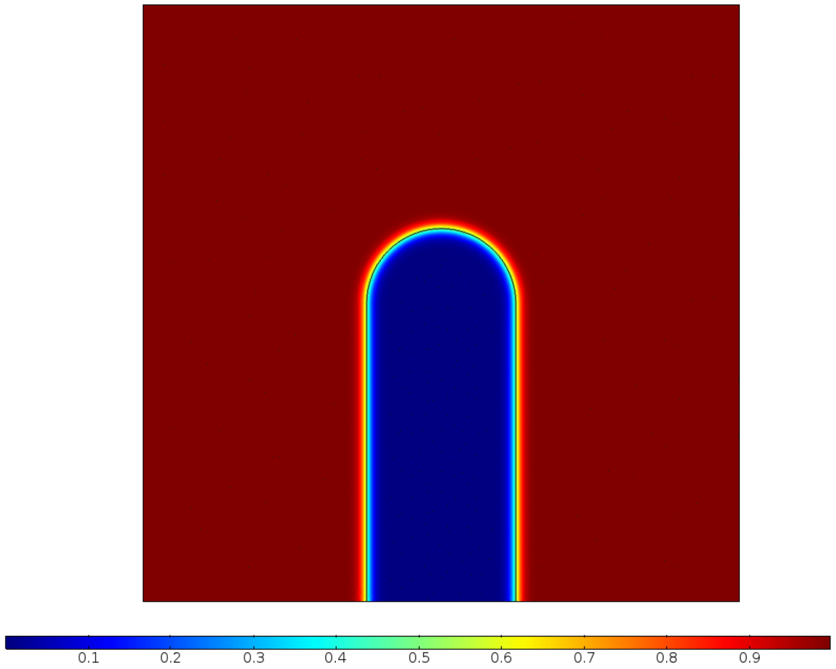
2D Results

Phase Field



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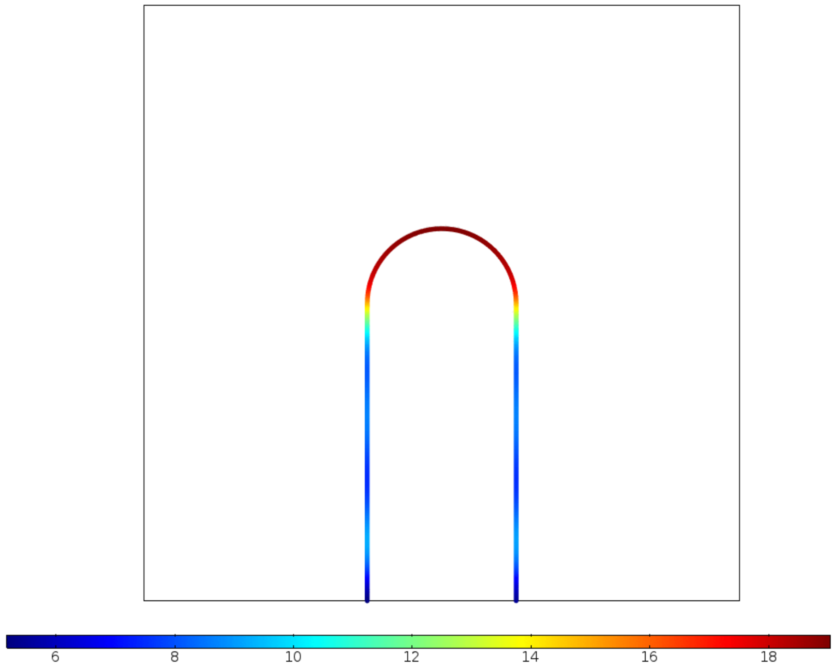

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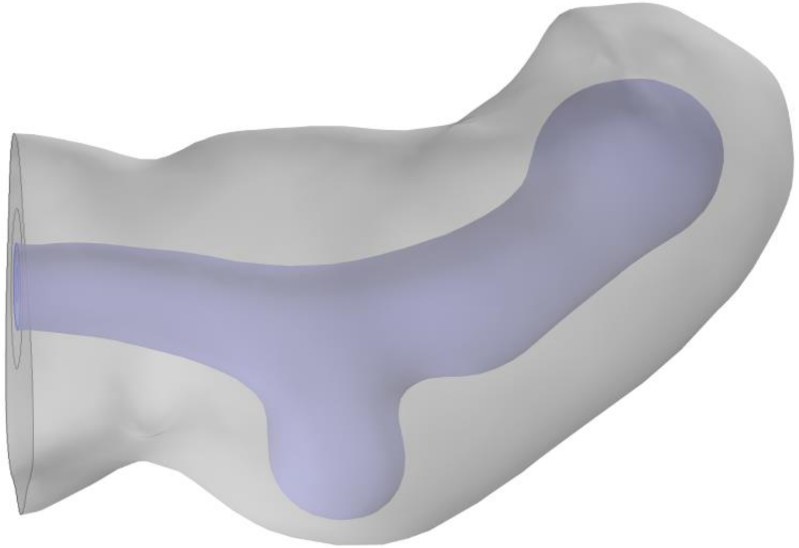
3D Results

Geometry



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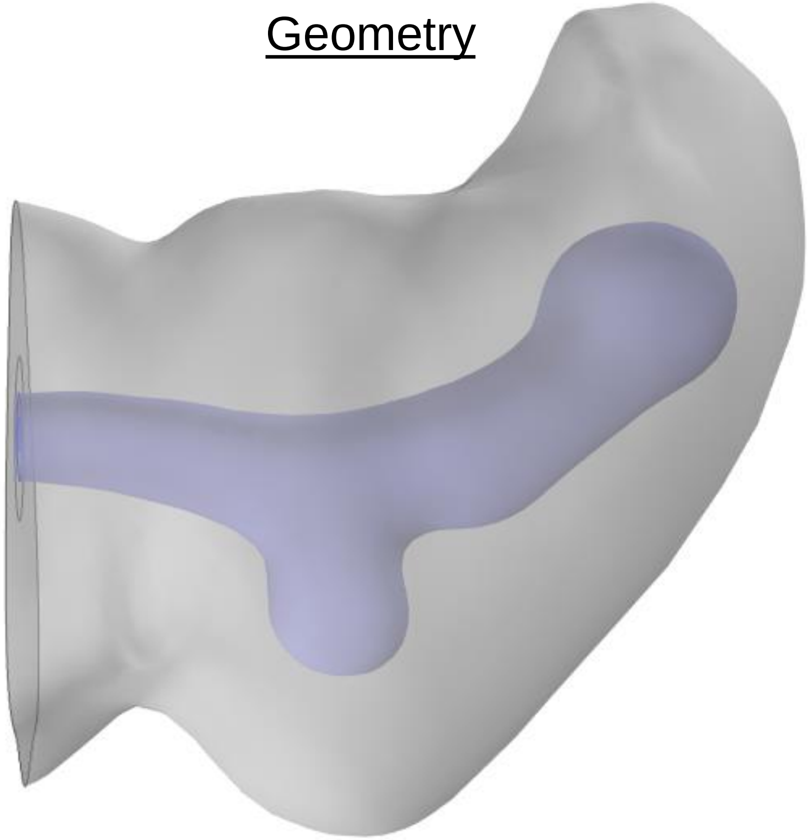
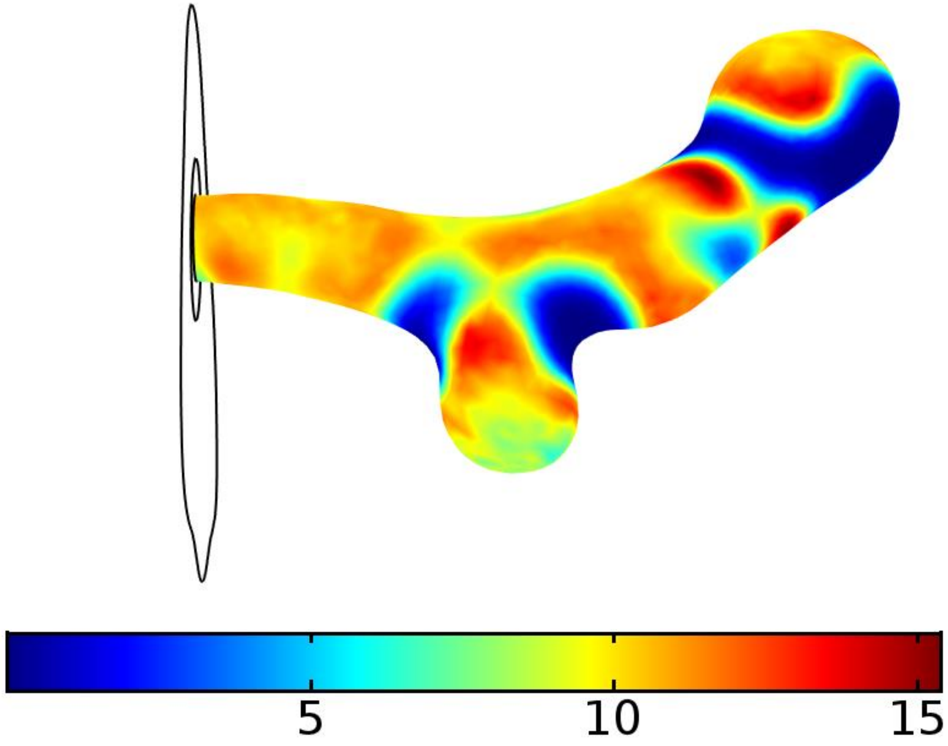
3D Results

Geometry



R²L



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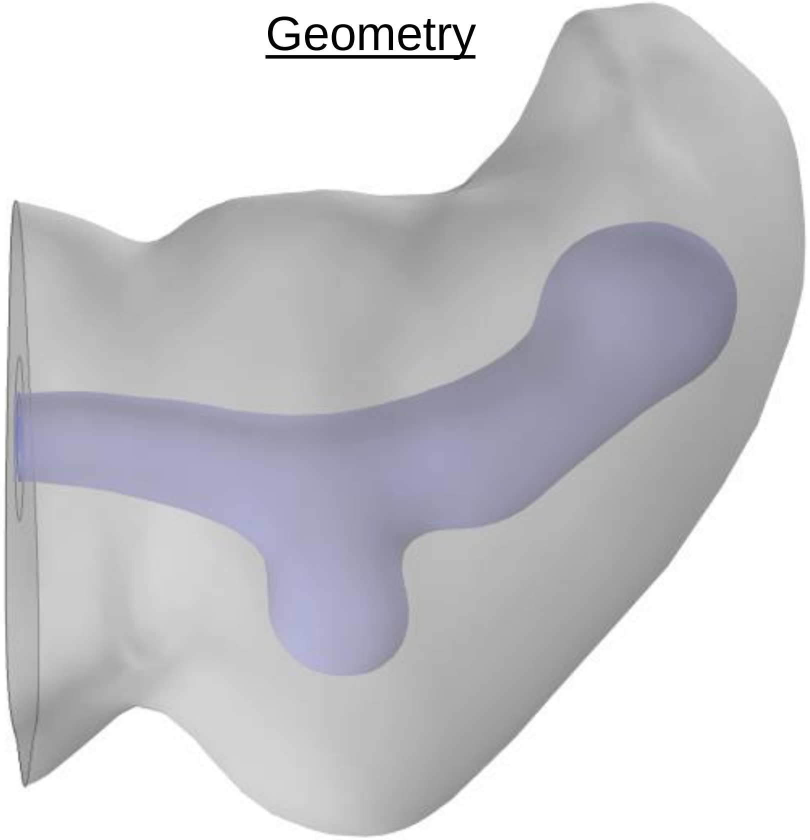
3D Results

Geometry



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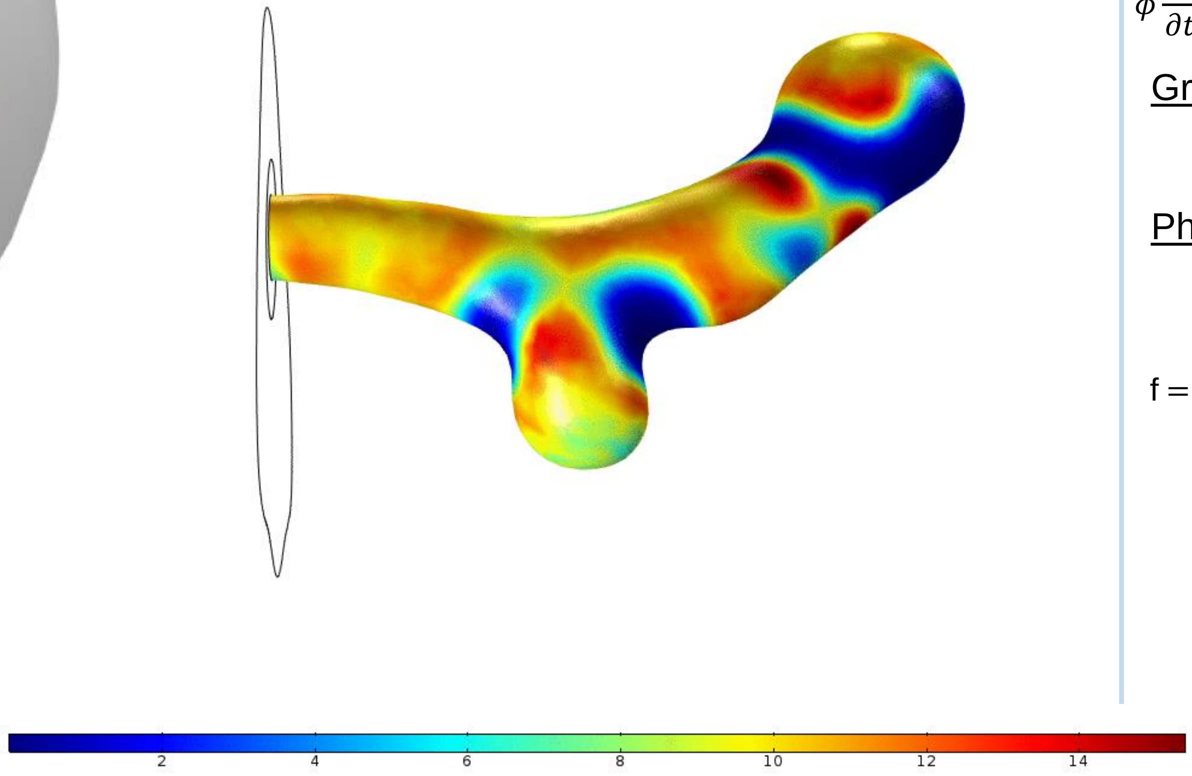

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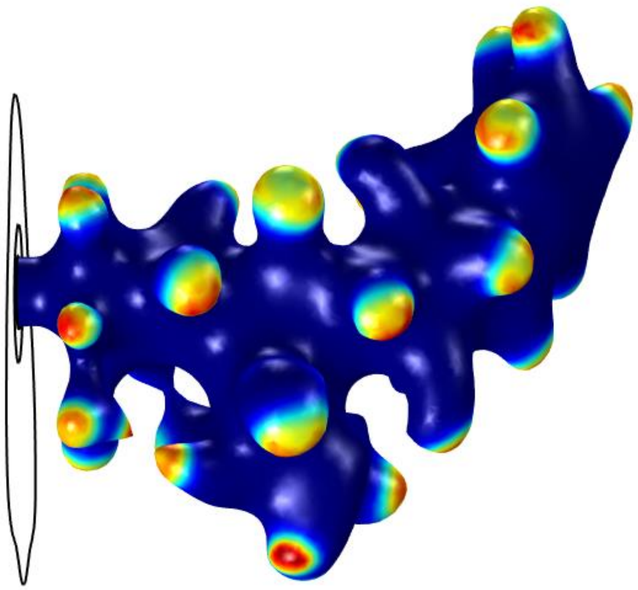
Summary & Conclusions

- Solving Reaction-Diffusion equations on diffuse boundaries with COMSOL is possible
- Complex geometries and displacements can be handled
- Outlook:
  - Make use of adaptive mesh refinement
  - Fine-tune parameters to get similar results as in the ALE-implementation
    - At the moment there is no secondary branching
  - Grow the mesenchyme, too



Acknowledgments

CoBi group

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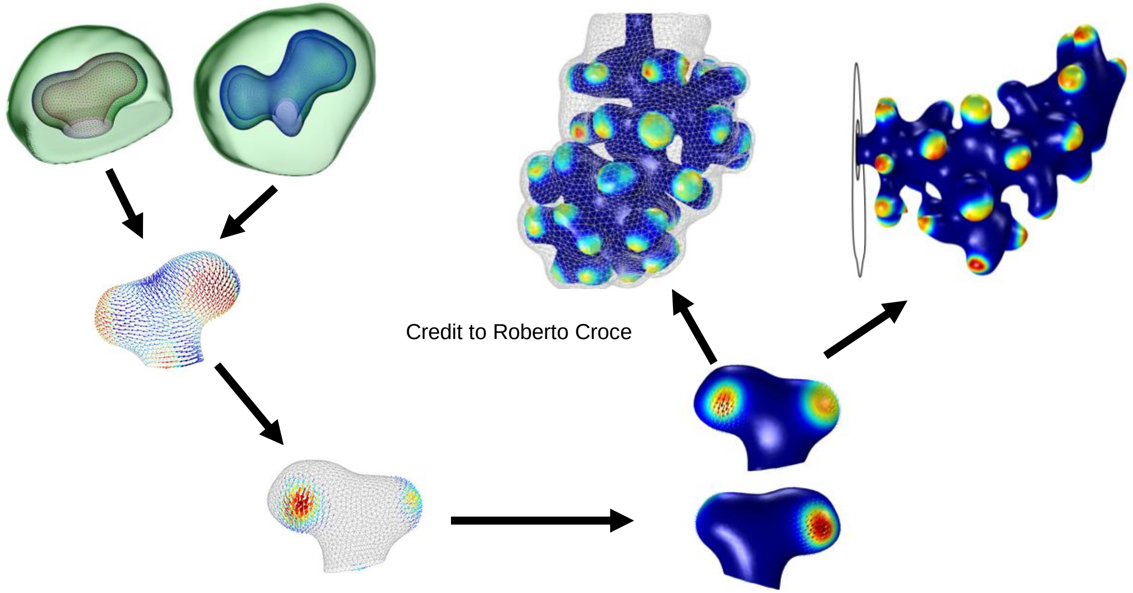
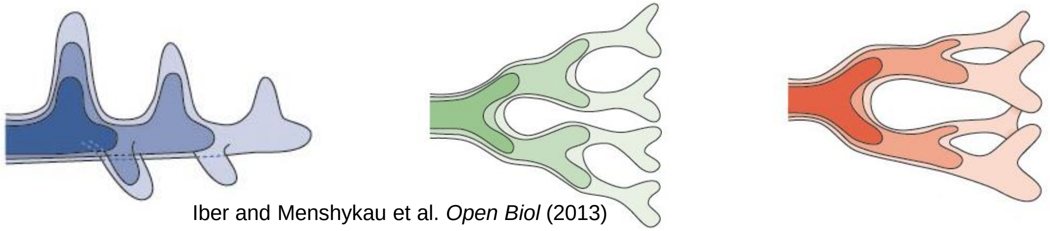
Roberto Croce



Credit to Roberto Croce

Blanc et al. *PLoS One (*2012), Menshykau et al. *Development* (2014)



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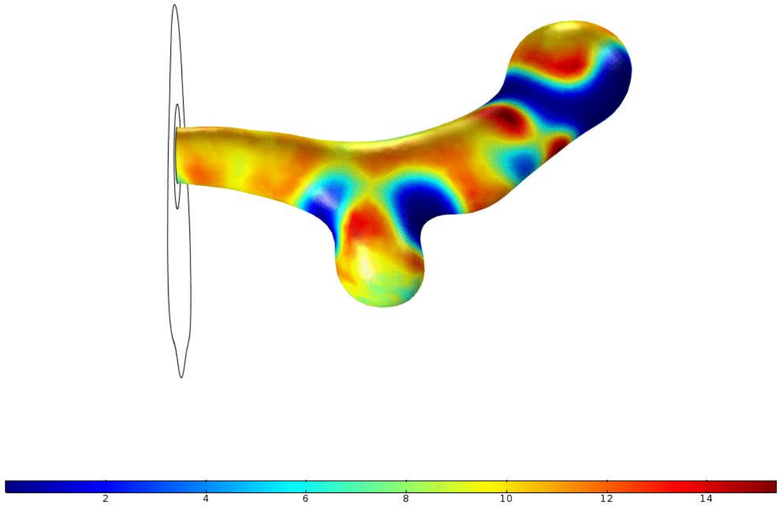


Thank you for your attention!

Phase-Field with Reaction-Diffusion Mechanism and Growth

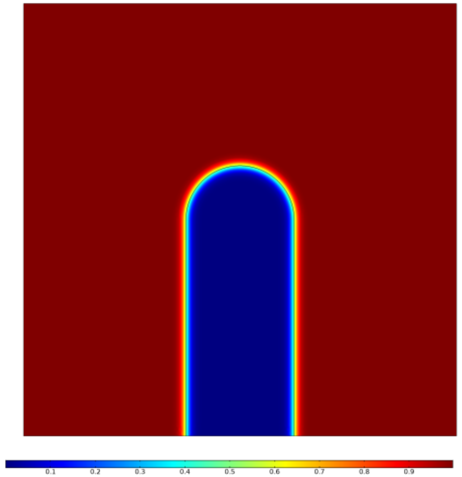
- Equations

$$\frac{\partial R}{\partial t} = \Delta R + \gamma(a - R + R^2 L) \qquad on\ \Gamma_\Omega$$
$$\frac{\partial L}{\partial t} = d\,\Delta L + \gamma b \qquad on\ \Omega$$
$$D\,\vec{n} \cdot \nabla L = -\gamma R^2 L \qquad on\ \Gamma_\Omega$$

- Phase-Field Approach

$$\delta \frac{\partial R}{\partial t} = \nabla \cdot (\delta \nabla \mathrm{R}) + \gamma\delta(a - R + \chi(\phi) R^2 L) + D_n \nabla \cdot (\delta \vec{n}\,\vec{n} \cdot \nabla R)$$

$$\phi \frac{\partial L}{\partial t} = D\,\nabla \cdot (\phi \nabla L) + \phi\gamma b - \gamma\delta R^2 L \qquad \chi(\phi) = \begin{cases} 1 & \chi_{low} < \phi < \chi_{up} \\ 0 & elsewhere. \end{cases}$$



Eqs. to solve

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Growth

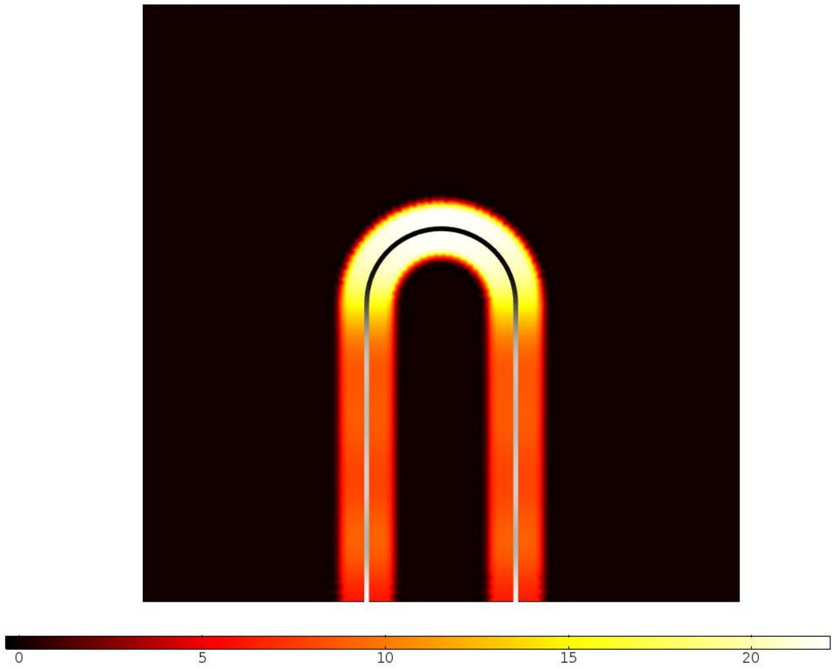
$$\vec{v} \approx R^2 L \cdot \delta \frac{\nabla \phi}{|\nabla \phi|}$$

Phase-Field Eq.

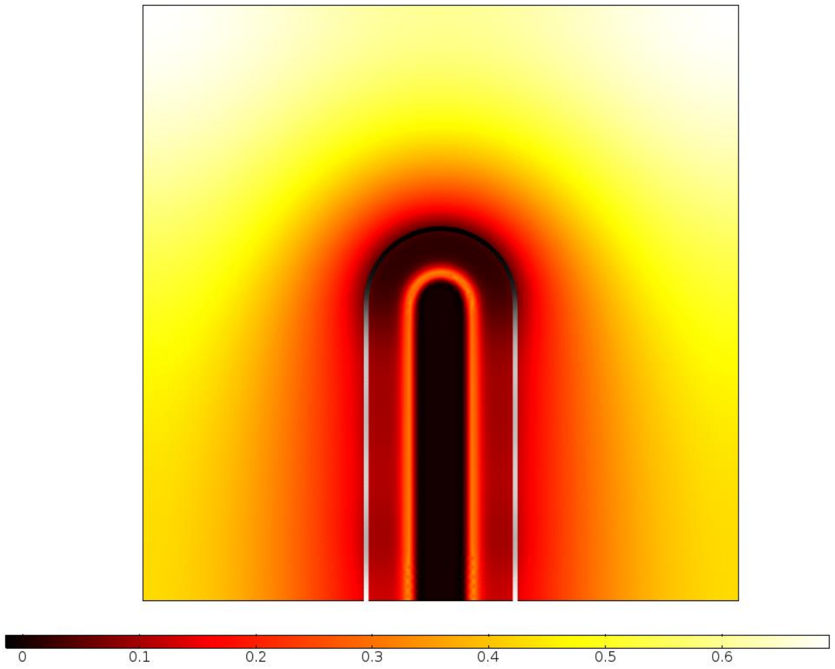
$$\frac{\partial \phi}{\partial t} + \vec{v} \cdot \nabla \phi = f$$
$$\mathrm{f} = \gamma \nabla \phi \cdot \left(\epsilon - \phi(1 - \phi) \frac{\nabla \phi}{|\nabla \phi|}\right)$$

2D Results: Concentrations of R and L

R



L



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