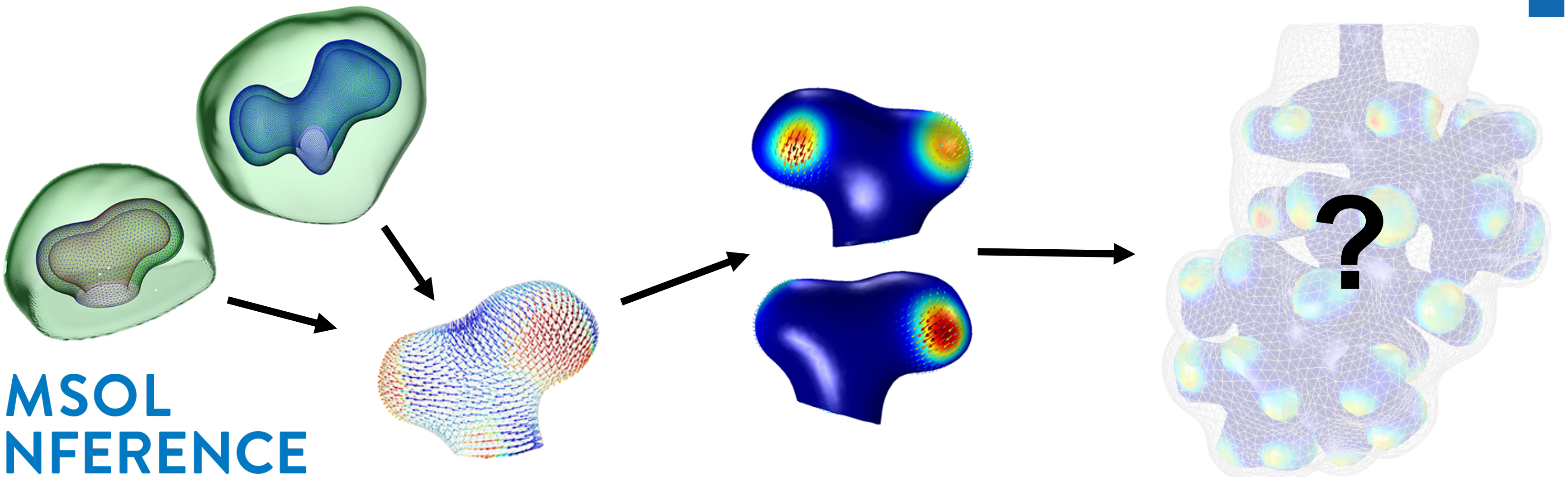
ETH zürich



COMSOL CONFERENCE 2017 ROTTERDAM

Simulating Organogenesis in COMSOL:

Comparison Of Methods For Simulating Branching Morphogenesis

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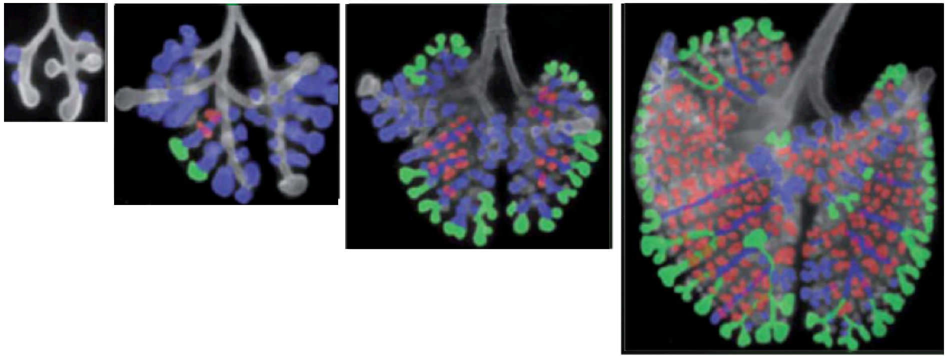
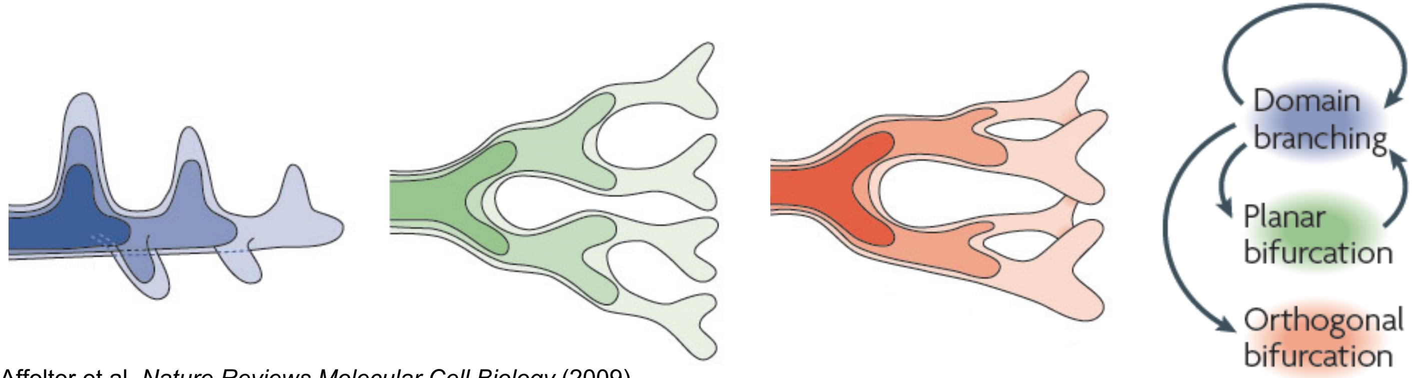
Motivation: Lung Morphogenesis

- 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)



Affolter et al. *Nature Reviews Molecular Cell Biology* (2009)

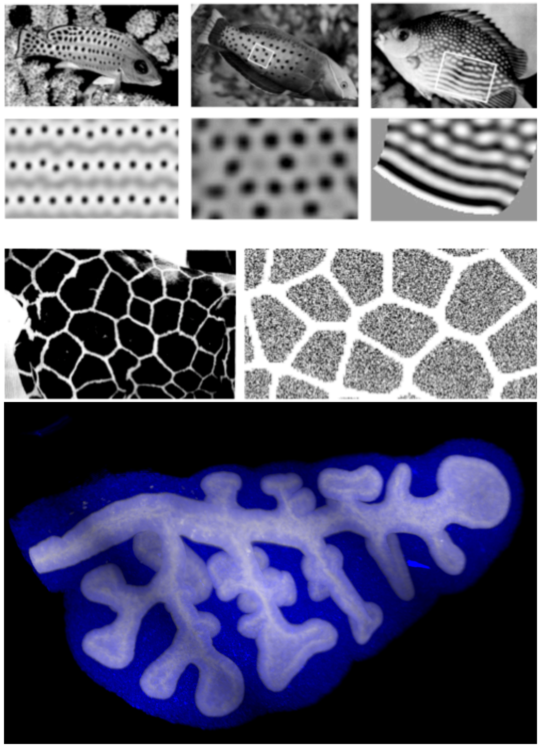
Image-Based Simulations: Mathematical Model

- Receptor-ligand based Turing Model

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

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

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

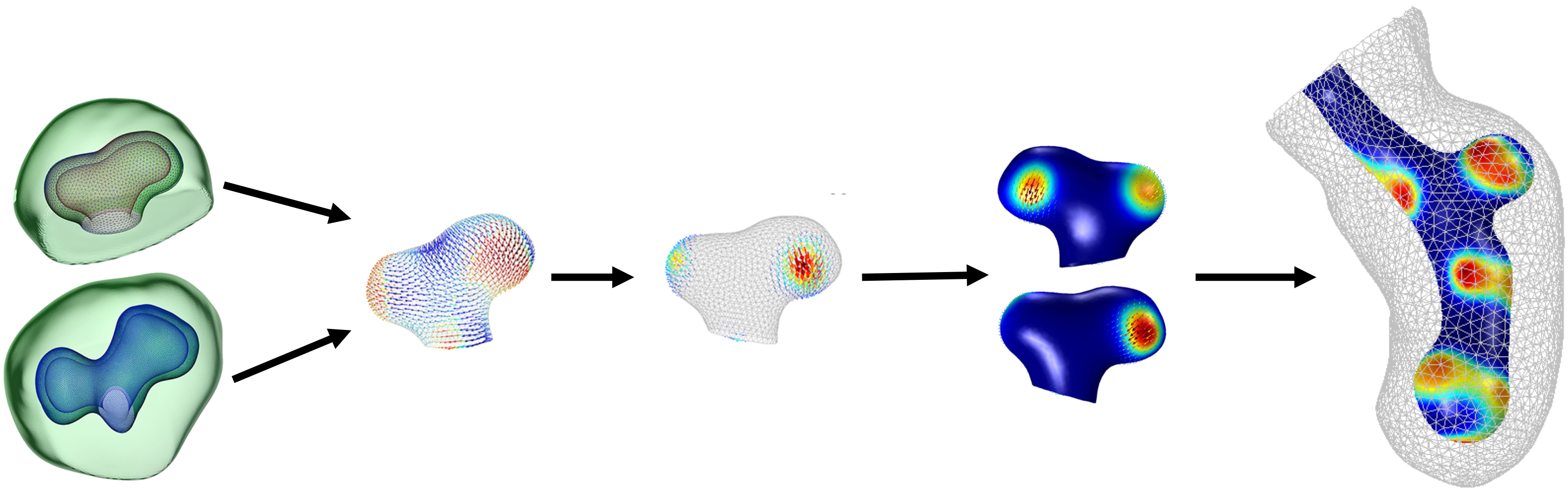


Credit to Conradin Krämer Credit to Lisa Conrad

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

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

Image-Based Simulations: Pipeline



Menshykau et al. *Development* (2014)

Credit to Roberto Croce

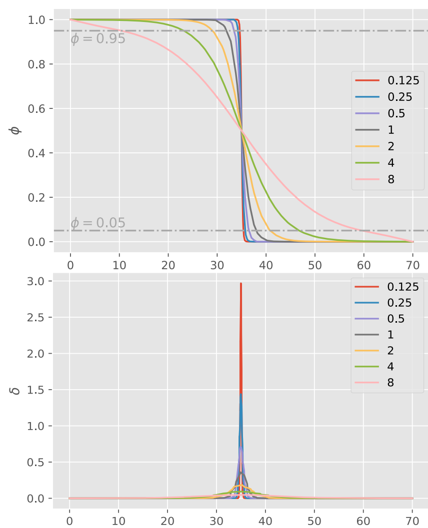
$$\frac{\partial R}{\partial t} = \Delta R + \gamma(a - R + R^2 L)$$

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

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

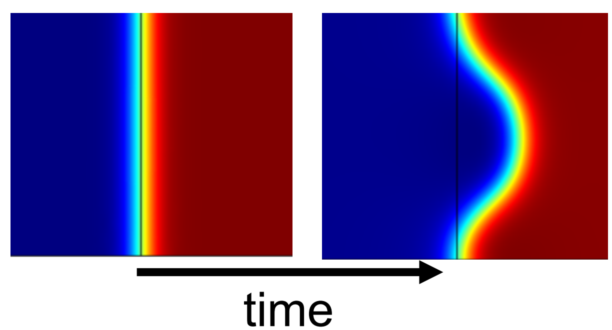
Mathematical Framework: Phase-Field

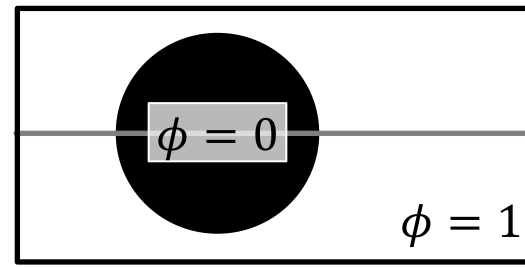
- Phase-Field = Scalar Field ϕ
- Regular mesh on whole domain
- Controllable

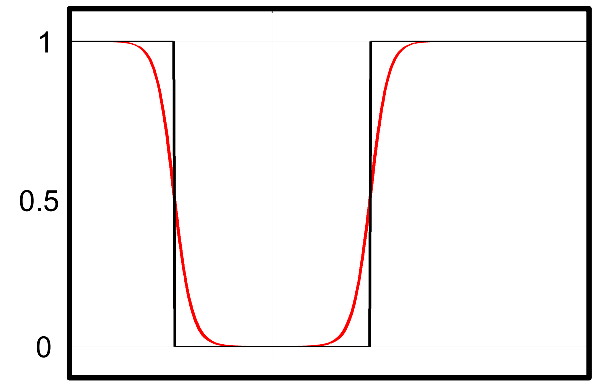


$$\frac{\partial \phi}{\partial t} + \vec{w} \cdot \nabla \phi = f$$

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







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

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Phase-Field Receptor-Ligand Turing Mechanism

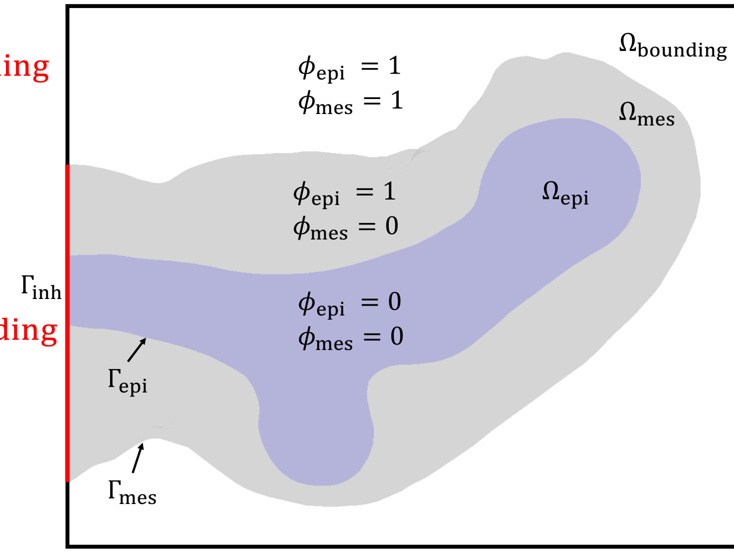
$$\delta_{\mathrm{epi}} \frac{\partial R}{\partial t} = \nabla \cdot (\delta_{\mathrm{epi}} \nabla R) + \gamma \delta_{\mathrm{epi}} (a - R + R^2 L) \qquad in\ \Omega_{\mathrm{bounding}}$$

$$\phi_L \frac{\partial L}{\partial t} = d\ \nabla \cdot (\phi_L \nabla L) + \gamma \phi_L (1 + I^2)^{-1} b - \gamma \delta_{\mathrm{epi}} R^2 L \quad in\ \Omega_{\mathrm{boun}}$$

$$\phi_L \frac{\partial I}{\partial t} = D\ \nabla \cdot (\phi_L \nabla I) - \phi_L k_d I \qquad in\ \Omega_{\mathrm{bounding}}$$

$$D\, \vec{n} \cdot \nabla L = -\gamma R^2 L \qquad on\ \Gamma_{\mathrm{epi}}$$

$$\frac{\partial I}{\partial t} = p_0 \qquad on\ \Gamma_{\mathrm{inh}}$$



- Extending to $\Omega_{\mathrm{bounding}}$:
  - Bulk reactions-terms: Multiply with ϕ
  - Boundary reactions-terms: Multiply with $\delta \approx |\nabla \phi|$

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

$$\phi_L = \phi_{\mathrm{epi}} - \phi_{\mathrm{mes}}$$

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

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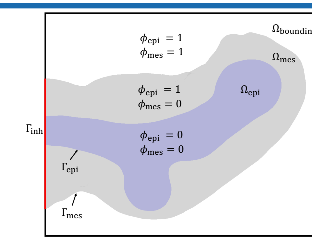
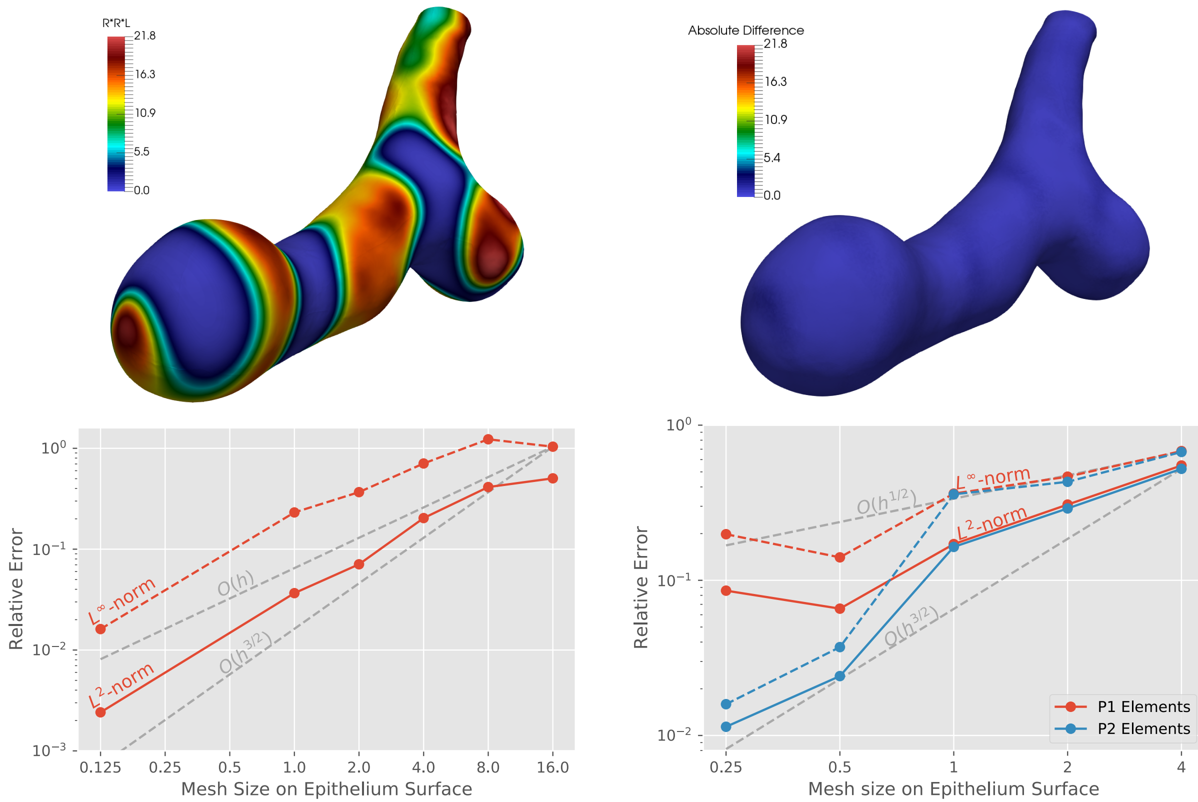
$$\frac{\partial \phi}{\partial t} + \vec{w} \cdot \nabla \phi = f$$

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



Results: Convergence Analysis (stationary)



$$\delta_{\text{epi}} \frac{\partial R}{\partial t} = \nabla \cdot \left(\delta_{\text{epi}} \nabla \mathrm{R}\right) + \gamma \delta_{\text{epi}} (a - R + R^2 L)$$

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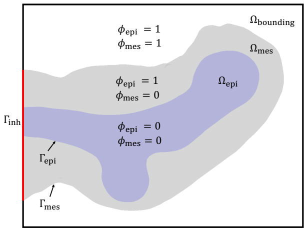

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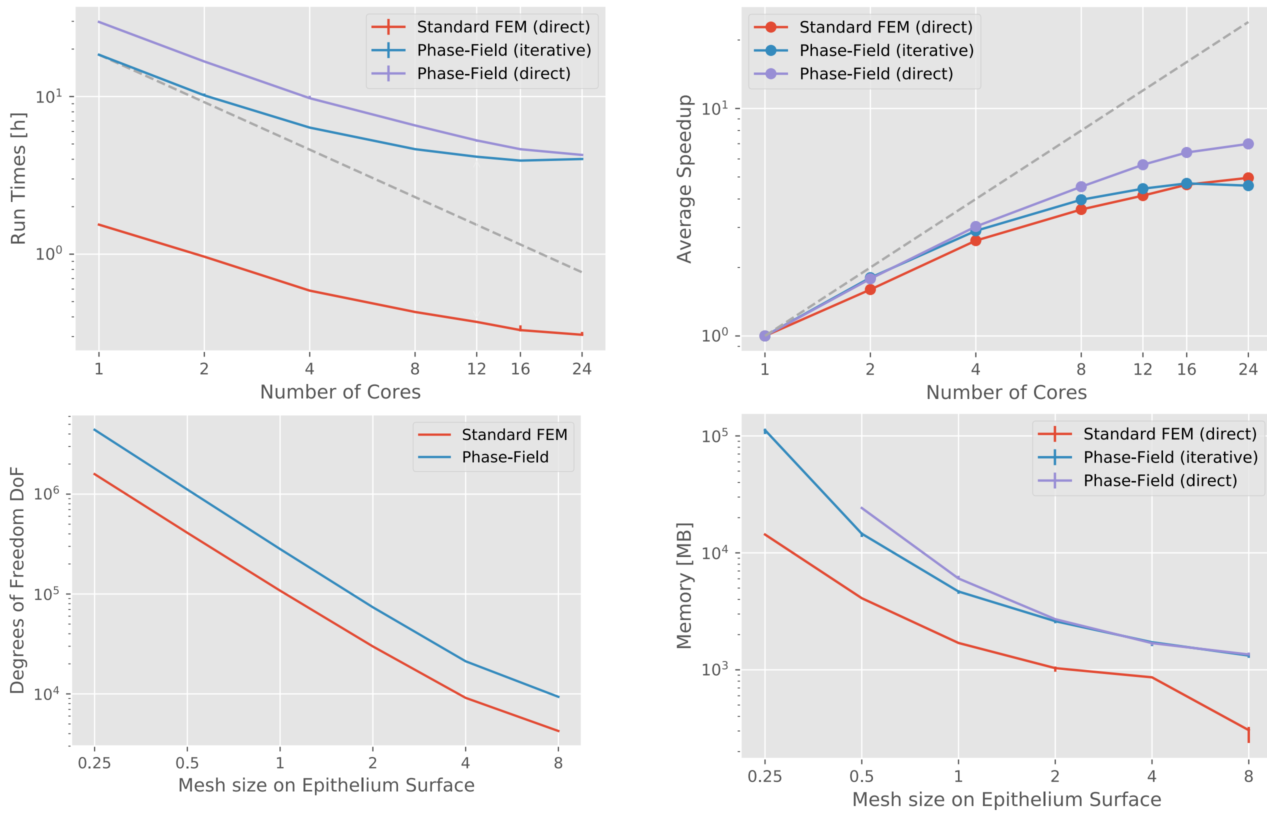
Results: Scaling Analysis (stationary)



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

$$\phi_L\frac{\partial L}{\partial t} = d\,\nabla\cdot(\phi_L\nabla L) + \gamma\phi_L(1+I^2)^{-1}b - \gamma\delta_{epi}R^2 L$$

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

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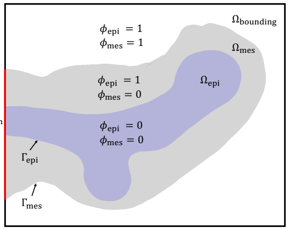
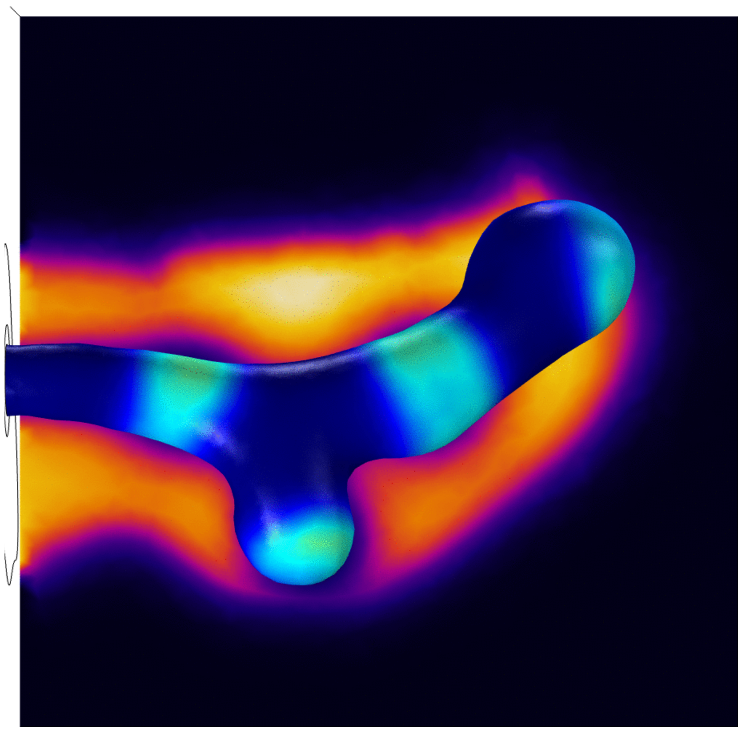
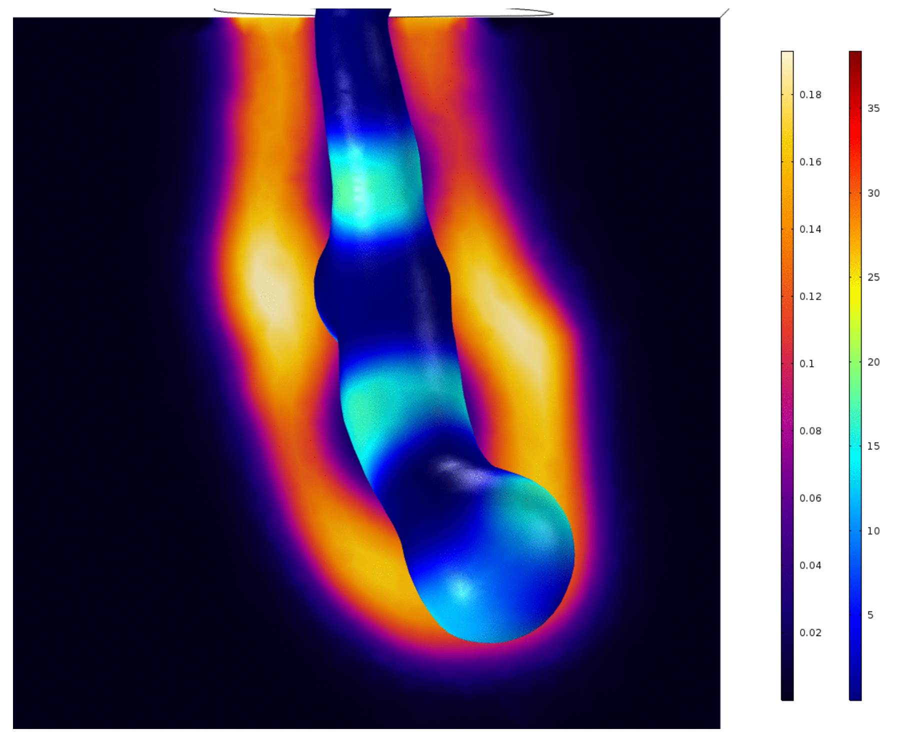


Results: Mesenchymal Growth





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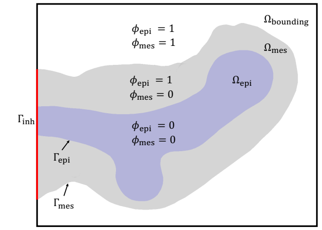
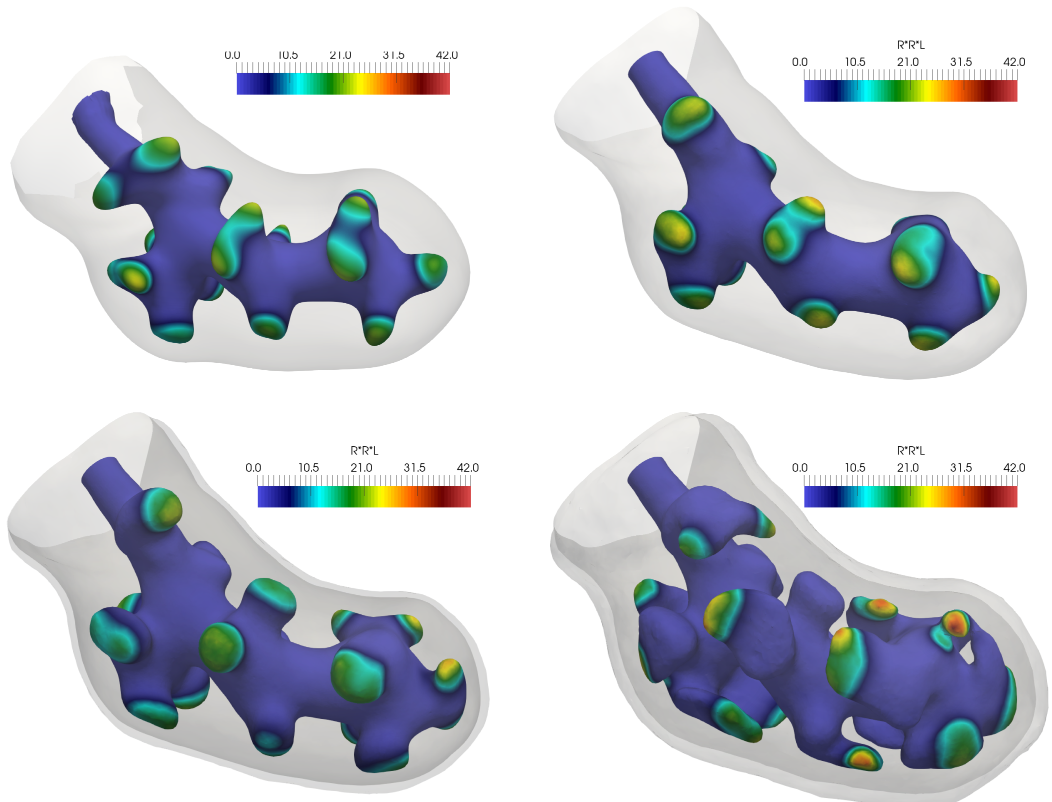


Results: Mesenchymal Growth



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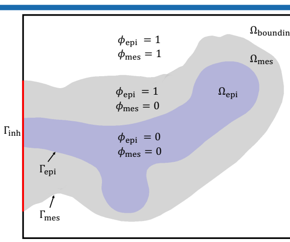
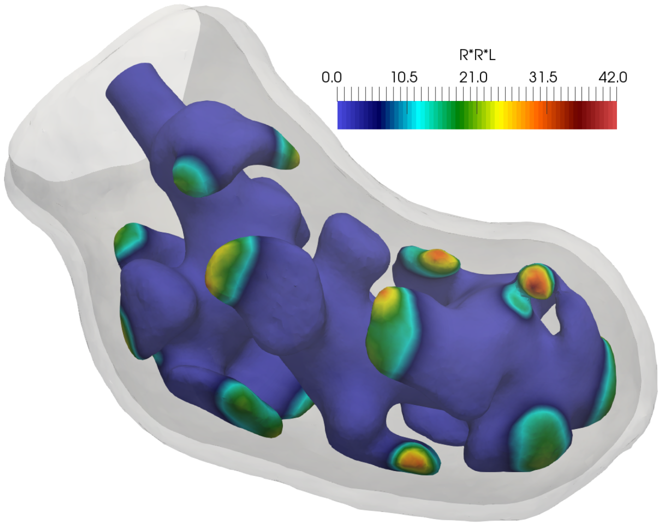


Summary

- Flexible, easy to extend
- Static ALE result reproducible
- Growing ALE result not (yet) reproducible
- Is more stable
- Needs fine mesh on the interface



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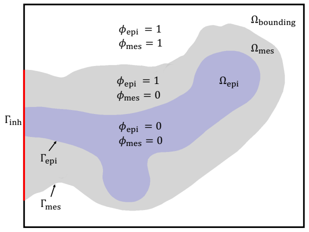

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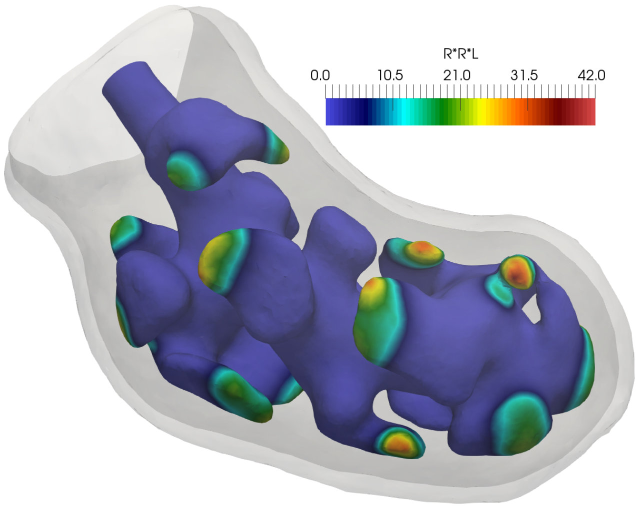

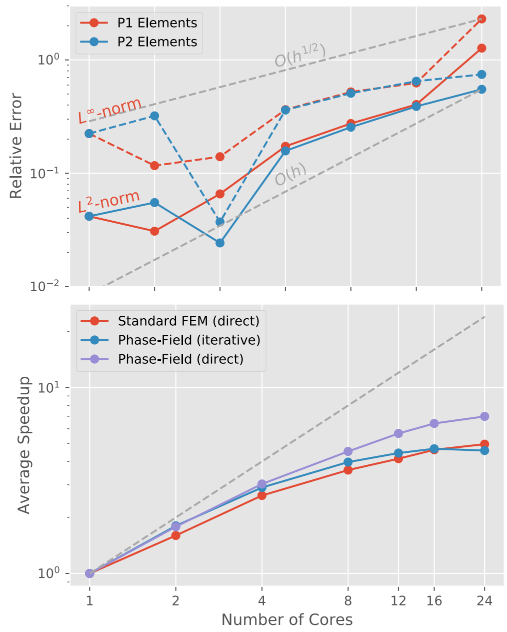

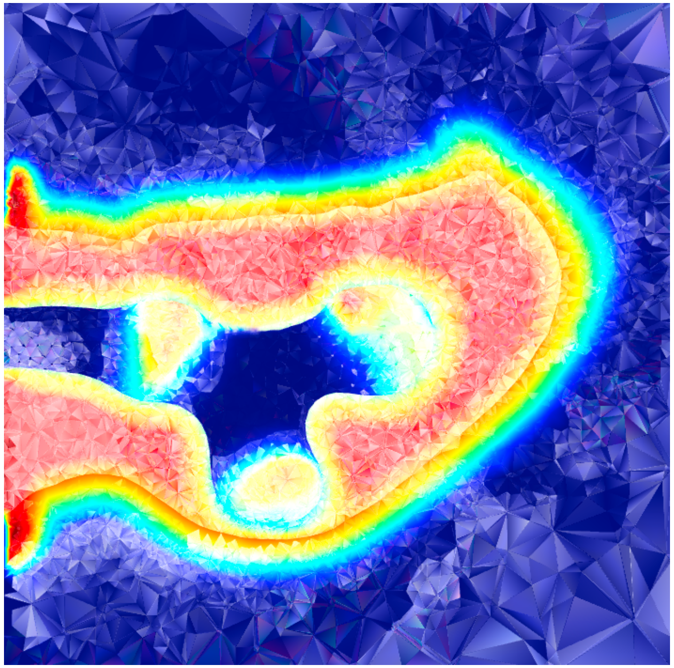

Thank you for your attention!

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