Simulating Organogenesis in COMSOL
Computational advances and challenges.

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OVERVIEW

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

Biological Questions
LUNG BRANCH MODE SELECTION

FGF10

growth

S

P

2 Ptc

SHH

D
BRANCHING IN 3D
Modelling the Limb

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

\[
\dot{X} + \nabla (u \cdot X) = D_x \Delta X + R_x (X, Y, \ldots)
\]

\[
\dot{Y} + \nabla (u \cdot Y) = D_y \Delta Y + R_y (X, Y, \ldots)
\]

\[
\ldots
\]

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

• 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

\[ \sigma = \frac{X^n}{X^n + K^n} \]
\[ \sigma = \frac{K^n}{K^n + X^n} \]
THE GEOMETRY

0.8 mm

Fgf

Rarβ₀, Ptcₜ₀

Ra₀, Rb₀

Ra

Shh, H

0.8 mm
GENERAL FEATURES

Edges

Traveling waves
STABILITY ISSUES

Spikes

• Produced by complex dynamics
• Appearance all over the domain
POTENTIAL TROUBLEMAKERS

- 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

• **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

![Graph showing speedup vs cores for different models.]

- Limb Bud Model
- Growing Lungs 2D
- 3D Lungs with 48K DOF
- 3D Lungs with 96K DOF
- 3D Lungs with 209K DOF

![Images of simulation outputs.]

b)  
c)
ADAPTIVE REMESHING

- Does not improve computing times
- Can produce artificial asymmetries
Large Deformations from Growth

OUTLOOK
**CHALLENGES: IMPLEMENTING GROWTH**

- 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
OUTLOOK

• Going 3D
• Coupling continuum physics and genetics
• Implementing directed cell divisions (via external forces?)
• Using differential surface tension to model adhesion properties
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Everything should be made as simple as possible, but no simpler.
Albert Einstein