Simulating Organogenesis in COMSOL

Cell-based Signaling Models

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Understanding Developmental Processes

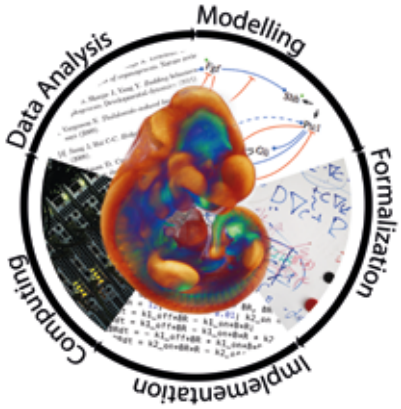

Fig. 1: A sketch summarizing our approach to organogenesis.

During organogenesis tissue layers differentiate into functionally organized units. We use COMSOL to build models for the development of various organs. These models are used to identify and analyse the key mechanism controlling these highly complex processes.

Modeling Organogesis on Growing Domains

Our models are based on systems of coupled reaction-diffusion equations for concentration C, following

$$\dot{C} + C\nabla \cdot u + u\nabla C = D\triangle C + R$$

where D is the diffusion coefficient, u the velocity of growth and R the reaction terms. As the size of the tissue changes dramatically during organogesis, these equations are solved on growing and deforming domains using the Moving Boundaries interface in COMSOL.

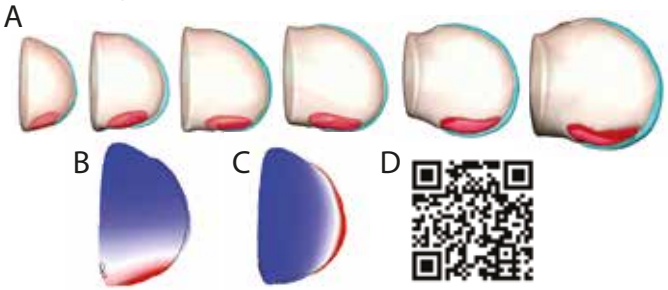

Fig. 2: (A) 3D data of the growing limb bud, showing the dramatic change in size (Red: ZPA, Blue: AER). (B, C) Simulations showing production of (B) SHH and (C) AER-FGFs . (D) QR-code to a movie demonstrating morphing of the limb bud domains.

Cell-based Models - A Motivation

Most models of biological pattern formation, including our own, are simulated on continuous domains, even though cells are discrete objects that provide internal boundaries to the diffusion of regulatory components. Various processes, including Notch-Delta signaling, have been described, for which models with cell resolution would be necessary.

Therefore, we present first steps here how to implement signaling models at cellular resolution with subcellular compartments in COMSOL Multiphysics.

Implementation of Surface Reactions

One key requirement for cell-based models is the ability to include surface reactions like the binding of a ligand to a membrane-bound receptor. Modeling the membrane as a boundary and coupling of the compartments using flux boundary conditions was identified to be the most accuarate and efficient implementation.

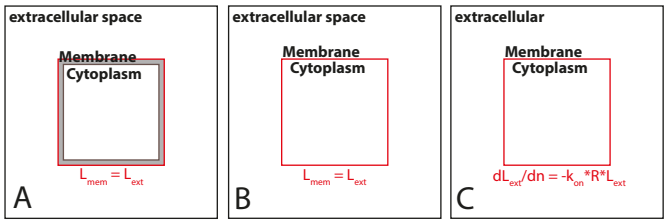

Fig 3: Different implementations of surface reactions tested within this work. (A) Membrane implemented as separate compartment. (B,C) Membrane implemented as boundary and coupled using (B) concentration BCs or (C) via flux BCs

A 3D cell-based signaling model

An model of a signaling cascade at subcellular resolution was implemented in COMSOL to test the performance of coupling compartments and of the implementation of surface reactions. The simulation described accurately the time course of the concentrations of the species.

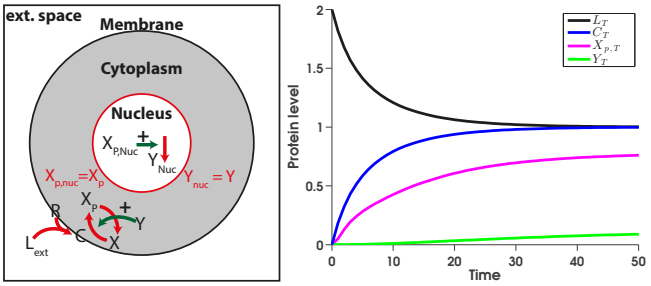

Fig 4: Scheme of the signaling cascade implemented in comsol and the resulting time courses. The scheme is shown as a cut plane through the 3D model geometry.

Limitations of COMSOL Multiphysics®

- **Computationally efficiency and parallelization:** to couple hundreds to thousands of cells

- **Cell division:** be able to solve reaction-diffusion equations on freely deforming domains (e.g. using the level set method)

- **Handling of stiff reactions**

Vollmer J, Menshykau D, and Iber D, Simulating Organogenesis in COMSOL: Cell-based Signaling Models. Proceedings of COMSOL Conference 2013, Rotterdam

P. Germann, D. Menshykau, S. Tanaka, and D. Iber, Simulating Organogenesis in COMSOL, Proceedings of COMSOL Conference 2011, Stuttgart

Excerpt from the Proceedings of the 2013 COMSOL Conference in Rotterdam