Genetic Patterning in Lung Development

AMS Fall Western Sectional Meeting

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Applied Mathematics

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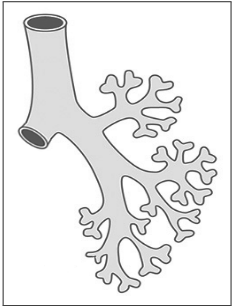
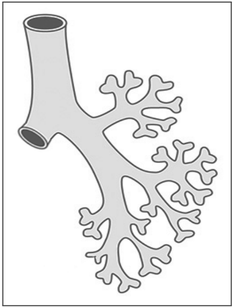
The Developing Lung

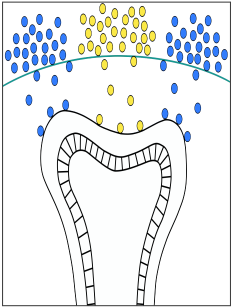


(a) Branching at the pseudoglandular stage

The Developing Lung



(d) Branching at the pseudoglandular stage



(e) Gene proteins diffuse from lung surface

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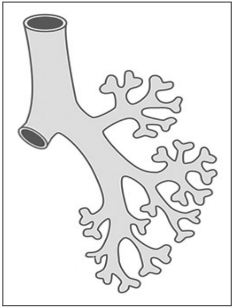

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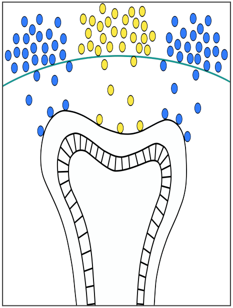
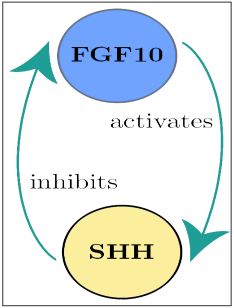


(h) Gene proteins diffuse from lung surface



(i) Feedback loop between FGF10 and SHH genes

Research Motivation

Applications to lung regeneration and disease research:

Congenital Diaphragmatic Hernias (CDH) causes hypoplastic lung development in the fetus. There is currently no treatment to encourage continued branching growth postpartum.

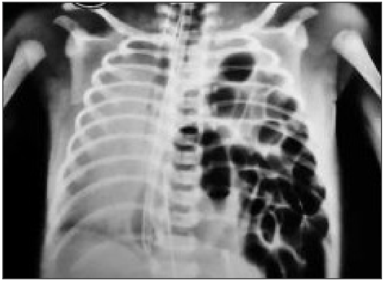


Figure: Left-sided CDH in infant

Reaction-Diffusion Equations

Auto-catalytic Reaction Model

$$\mathrm{X} \underset{\mathrm{k_2}}{\overset{\mathrm{k_1}}{\rightleftharpoons}} \mathrm{F} \qquad 2\,\mathrm{F} + \mathrm{S} \xrightarrow{\mathrm{k_3}} 3\,\mathrm{F} \qquad \mathrm{Y} \xrightarrow{\mathrm{k_4}} \mathrm{S}$$

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Laplace-Beltrami Operator

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=

Schnakenberg Equations on Surface

$$\dot{F} = \Delta_\Gamma F + \gamma\left(\alpha - F + F^2 S\right)$$

$$\dot{S} = \delta \Delta_\Gamma S + \gamma\left(\beta - F^2 S\right)$$

Stability Without Diffusion

$$\left.\begin{aligned} \dot{F} &= \gamma\left(\alpha - F + F^2 S\right) \\ \dot{S} &= \gamma\left(\beta - F^2 S\right) \end{aligned}\right\} \xrightarrow{\text{Taylor Expansion}} \dot{W} = \gamma\, J_* W$$

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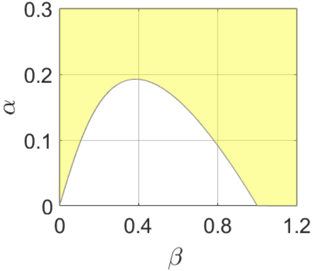
Equilibrium point:
$$\left(\alpha+\beta, \frac{\beta}{(\alpha+\beta)^2}\right)$$

Stable parameters:
$$\beta - \alpha < (\alpha+\beta)^3$$



(b) Stability region for α and β

Analytic Solution

$$\left.\begin{aligned}\dot{F} &= \Delta_\Gamma F \gamma\left(\alpha - F + F^2 S\right)\\ \dot{S} &= \delta \Delta_\Gamma S \gamma\left(\beta - F^2 S\right)\end{aligned}\right\} \xrightarrow{\text{T.E.}} \dot{W} = D\Delta_\Gamma W + \gamma J_* W$$

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Eigenvalue Problem: $\dot{W} = \lambda W$ and $\Delta_\Gamma W = -k^2 W$

$$W(\phi,\theta,t) = \sum_{m=0}^{\infty} \sum_{n_k^- \geq m}^{n_k^+} A_{mn} \cdot e^{\lambda t} \cdot Y_n^m(\phi,\theta)$$

with $$A_{mn} = \frac{\int_0^\pi \int_{-\pi}^{\pi} W_* Y_n^m(\phi,\theta) \sin\phi \, d\theta d\phi}{\int_0^\pi \int_{-\pi}^{\pi} [Y_n^m(\phi,\theta)]^2 \sin\phi \, d\theta d\phi}$$

Instability with Diffusion

$$\lambda W = -k^2 W + \gamma J_* W \quad \longrightarrow \quad \det(-Dk^2 + \gamma J - \lambda I) = 0$$

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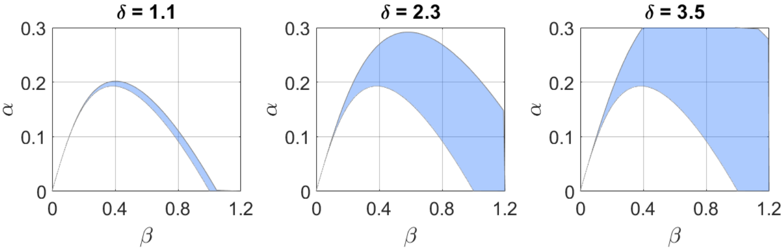

(e) Delta regions for α and β constraints to induce instability

Eigenvalue Solutions

Isolate single k_c^2 such that $k_-^2 < k_c^2 = n(n+1) < k_+^2$

$$k^2 = \frac{\delta(\beta-\alpha)-(\alpha+\beta)^3 \pm \sqrt{[\delta(\beta-\alpha)-(\alpha+\beta)^3]^2 - 4\delta(\alpha+\beta)^4}}{2\delta(\alpha+\beta)}$$

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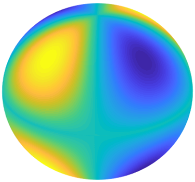
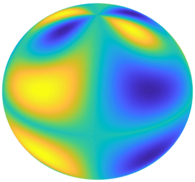
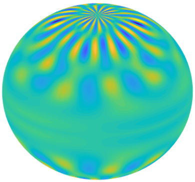


(i) n = 2



(j) n = 4



(k) n = 20

Spacial Discretization

$$\dot{F} - \Delta_\Gamma F = \gamma\left(\alpha - F + F^2 S\right)$$

Spacial Discretization

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Multiply by test function, put into weak form:

$$\int_\Omega \left[(\dot{F} - \Delta_\Gamma F)\varphi_i \right] = \gamma \int_\Omega \left[\left(\alpha - F + F^2 S \right) \varphi_i \right]$$

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Integrate by parts, sum over domain:

$$\sum \left(\dot{f}\varphi_j, \varphi_i\right) + \sum \left(f \nabla\varphi_j, \nabla\varphi_i\right) =$$
$$\gamma \left[\alpha \sum(\varphi_i, 1) - \sum(f\varphi_j, \varphi_i) + \sum(f^2 s\varphi_j, \varphi_i)\right]$$

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$$\mathbf{M} = \sum (\varphi_i, \varphi_j) \quad \mathbf{A} = \sum (\nabla \varphi_i, \nabla \varphi_j) \quad \mathbf{C} = \sum (\varphi_i, 1)$$

Time Discretization

$$\mathbf{M}\dot{f} + \mathbf{A}f = \gamma \left[\alpha \mathbf{C} - \mathbf{M}f + \mathbf{M}f^2 s\right]$$

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IMEX scheme, first order backward Euler:

$$\frac{\mathbf{M}(f_{n+1} - f_n)}{\Delta t} + \mathbf{A}f_{n+1} = \gamma\left(\alpha\mathbf{C} - \mathbf{M}f_{n+1} + \mathbf{M}f_n^2 s_n\right)$$

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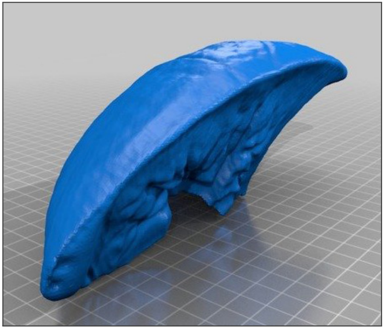
Solve the linear system Ax=b:

$$\left[(1 + \gamma\Delta t)\mathbf{M} + \Delta t\mathbf{A}\right] f_{n+1} = \gamma\Delta t\left(\alpha\mathbf{C} + \mathbf{M}f_n^2 s_n\right)$$

Future Work



(l) 3D model of left lung

- Code mode isolation algorithm

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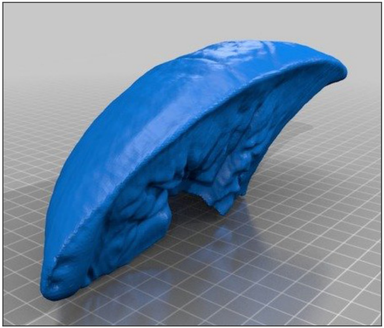

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- Code mode isolation algorithm
- Use second order temporal discretization scheme

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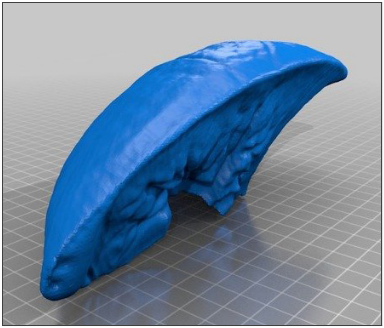

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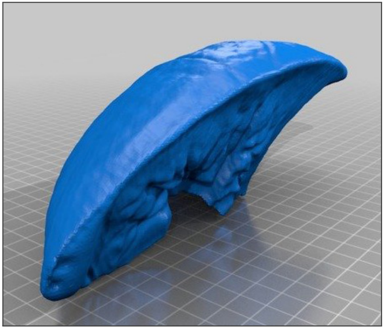

(l) 3D model of left lung

- Code mode isolation algorithm
- Use second order temporal discretization scheme
- Examine model on the mesh of a human lung
- Solve on growing domain of developing lung

Further Reading

- A. Madzvamuse, "Time-stepping schemes for moving grid finite elements applied to reaction-diffusion systems on fixed and growing domains," *Journal of Computational Physics*, vol. 214, no. 1, pp. 239–263, 2006.
- L. Murphy, C. Venkataraman, and A. Madzvamuse, "A Computational approach for Mode Isolation for Reaction-Diffusion Systems on Arbitraty Geometries," p. 26, 2016.
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- J. Schnakenberg, "Simple Chemical Reaction Systems With Limit Cycle Behavior," *Institute for Theoretical Physics*, vol. 81, no. 3, pp. 389–400, 1979.
- A. M. Turing, "The Chemical Basis of Morphogenesis," *Philosophical Transactions of the Royal Society of London*, vol. 237, no. 641, pp. 37–72, 1952.

Thank You!

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