Lung Development & Pattern Formation

Math 638 Final Presentation

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Applied Mathematics

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OVERVIEW

The Developing Lung

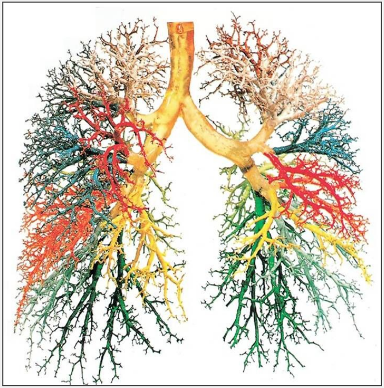
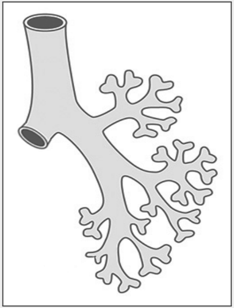


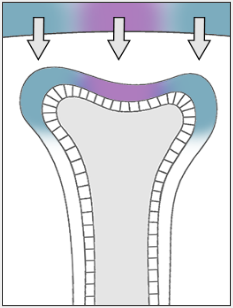
Figure: Human bronchial tree of adult male, color coded.

This research examines the pseudoglandular stage of vertebrate lung development and the role of two gene proteins in branching morphogenesis: Fibroblast Growth Factor 10 **FGF10** and Sonic Hedgehog gene **SHH**. These proteins form a feedback loop.[1]

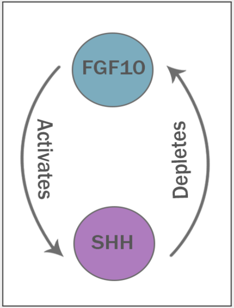
The Developing Lung



(a) Branching at the pseudoglandular stage



(b) Gene proteins diffuse from lung surface



(c) Feedback loop between FGF10 and SHH genes

The Developing Lung

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.[2]

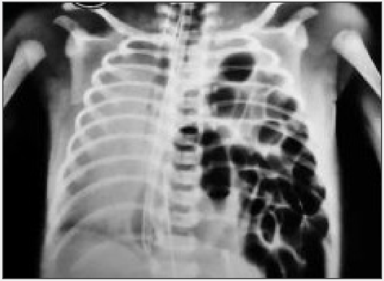


Figure: Left-sided CDH in infant

Analysis Approach

Reaction-Diffusion Equations

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

+

Turing Instability Regions

The system is **stable** *without* the diffusion terms.
The system is **unstable** *with* the diffusion terms.

=

Pattern Formation Model

The deviation from homogeneity yielding a domain with nonuniform concentrations of morphogens[3]

Analysis Approach

Schnakenberg[4] considered a simple kinetic model for a reaction-diffusion system that emphasized the activator-depletion relationship between two morphogens:

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

$F(r, \phi, \theta, t)$ is the activator concentration for the FGF10 gene.
$S(r, \phi, \theta, t)$ is for depletion substrate, or the SHH gene.

And X and Y are precursor substrate concentrations.

Analysis Approach

This analysis will replace the diffusion term in the classic reaction-diffusion model with the surface Laplacian Δ_Γ, defined:

$$\Delta_\Gamma u = \nabla_\Gamma \cdot \nabla_\Gamma u \quad \text{with} \quad \nabla_\Gamma u = \nabla u - (\nabla u \cdot \vec{n})\vec{n}$$

The resulting hybrid model of a reaction-diffusion system on the surface of a sphere is given by:

$$\dot{F} = D_F \Delta_\Gamma F + k_1 - k_2 F + k_3 F^2 S$$

$$\dot{S} = D_S \Delta_\Gamma S + k_4 - k_3 F^2 S$$

Analysis Approach

$$
\begin{aligned}
\dot{F} &= \overbrace{D_F \Delta_\Gamma F}^{\text{diffusion}} + \overbrace{k_1}^{\text{rate constant}} - \overbrace{k_2 F}^{\text{degradation}} + \overbrace{k_3 F^2 S}^{\text{autocatalysis}} \\
\dot{S} &= \underbrace{D_S \Delta_\Gamma S}_{\text{diffusion}} + \underbrace{k_4}_{\text{rate constant}} - \underbrace{k_3 F^2 S}_{\text{autocatalysis}}
\end{aligned}
$$

Diffusion Net movement of substrates

Rate Constant Precursor substrate production of FGF10 and SHH

Degradation FGF10 is catalyzed to a precursor substrate

Autocatalysis FGF10 uses SHH for self-production

Stability Without Diffusion

Using scaling substitutions, we get:

$$\alpha = \frac{k_1}{k_2}\sqrt{\frac{k_3}{k_2}} \qquad \beta = \frac{k_4}{k_2}\sqrt{\frac{k_3}{k_2}} \qquad \delta = \frac{D_S}{D_F} \qquad \text{and} \qquad \gamma = k_2$$

$$\begin{aligned} \dot{F} &= \Delta_\Gamma F + \gamma\left(\alpha - F + F^2 S\right) &&= \Delta_\Gamma F + \gamma\, f(F,S) \\ \dot{S} &= \delta\Delta_\Gamma S + \gamma\left(\beta - F^2 S\right) &&= \delta\Delta_\Gamma S + \gamma\, s(F,S) \end{aligned}$$

Eliminating the diffusion terms, the fixed points are:

$$(F^*, S^*) = \left(\alpha + \beta, \frac{\beta}{(\alpha+\beta)^2}\right)$$

Stability Without Diffusion

To determine stability a perturbation is made:

$$F = F^* + \varepsilon \tilde{F} \quad \longrightarrow \quad \dot{F} = \varepsilon \tilde{F}_t = \gamma f(F^* + \varepsilon \tilde{F})$$
$$S = S^* + \varepsilon \tilde{S} \quad \longrightarrow \quad \dot{S} = \varepsilon \tilde{S}_t = \gamma s(S^* + \varepsilon \tilde{S})$$

With some substitutions and a Taylor expansion:

$$\begin{pmatrix} \tilde{F}_t \\ \tilde{S}_t \end{pmatrix} = \gamma \begin{pmatrix} f_F(F^*, S^*) & f_S(F^*, S^*) \\ s_F(F^*, S^*) & s_S(F^*, S^*) \end{pmatrix} \cdot \begin{pmatrix} \tilde{F} \\ \tilde{S} \end{pmatrix} + \mathcal{O}(\varepsilon^2)$$

Or more simply:

$$\dot{W} = \gamma J^* W$$

Stability Without Diffusion

The Jacobian is evaluated to be:

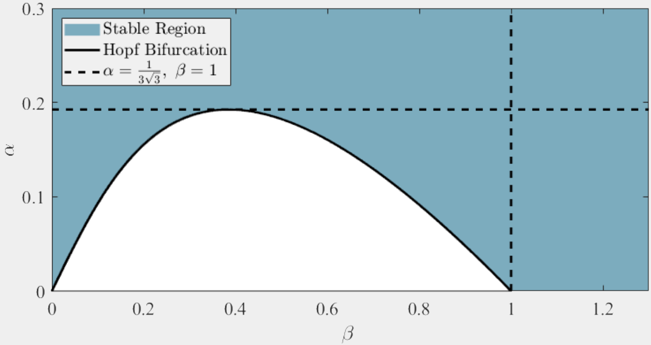
$$J^* = \begin{pmatrix} -1 + \dfrac{2\beta}{\alpha+\beta} & (\alpha+\beta)^2 \\ -\dfrac{2\beta}{\alpha+\beta} & -(\alpha+\beta)^2 \end{pmatrix}$$

Yielding the eigenvalues:

$$\lambda = \frac{\gamma}{2}\left(\frac{\beta-\alpha}{(\alpha+\beta)} - (\alpha+\beta)^2 \pm \sqrt{\left(\frac{\alpha-\beta}{\alpha+\beta} + (\alpha+\beta)^2\right)^2 - 4(\alpha+\beta)^2}\right)$$

Stability Without Diffusion

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



(a) Stability region for α and β values

The Eigenvalue Problem

Without diffusion, there was $\dot{W} = \gamma\, J^* W$. With diffusion:

$$\dot{W} = D\Delta_\Gamma W + \gamma\, J^* W$$

To turn this into a linear system:

$$\dot{W} = \lambda W \quad \text{and} \quad \Delta_\Gamma W = -k^2 W$$

This yields the eigenfunctions for W:

$$e^{\lambda t}, \quad P_n^m(\cos\phi), \quad \text{and} \quad e^{im\theta} \quad \text{with} \quad m = 0, 1, 2, \ldots \quad \text{and} \quad n \geq m$$

Leaving the linear system:

$$\lambda W = -Dk^2 W + \gamma J^* W$$

Instability with Diffusion

The parameter constraints for **instability** with diffusion are:

$$\det(-Dk^2 + \gamma J^* - \lambda I) = 0 \quad \text{and} \quad \exists \, \mathrm{Re}[\lambda(k^2)] > 0$$

Which gives the characteristic equation:

$$\lambda^2 - \lambda[\gamma\,(f_F + s_S) - k^2(1+\delta)] + h(k^2) = 0$$

$$\text{Where} \;\; h(k^2) = \delta k^4 - \gamma\,(\delta f_F + s_S)k^2 + \gamma \det(J^*)$$

For instability:

$$\mathrm{Re}[\lambda(k^2)] > 0 \quad \longrightarrow \quad \gamma\,(\delta f_F + s_S)k^2 > \delta k^4 + \gamma \det(J^*)$$

Instability with Diffusion

$$\delta > 1$$

Therefore, SHH must diffuse faster than FGF10

Analytical Solution

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

With

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

Surface Diffusion Patterns

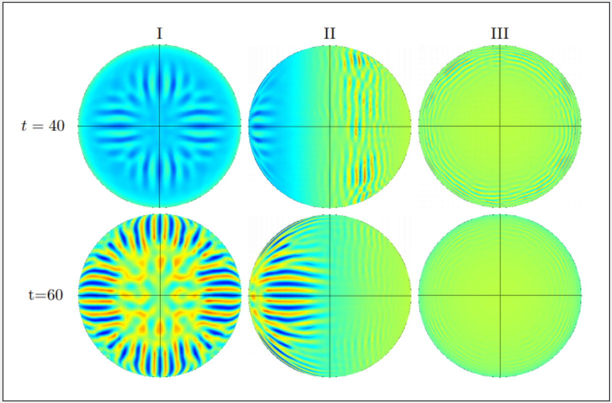


Figure: R=100, $\alpha = 0.1$, $\beta = 0.9$, $\delta = 10$, $\gamma = 4$[5]

Surface Diffusion Patterns

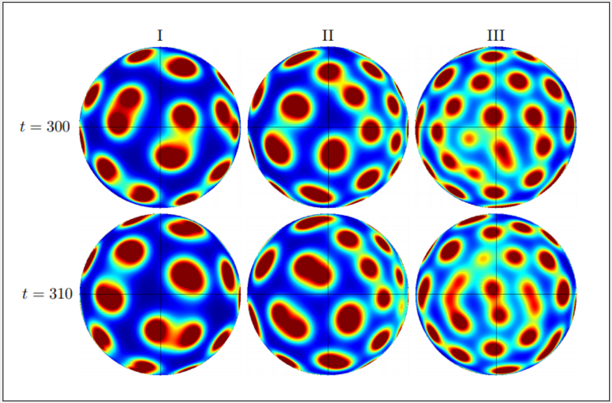


Figure: r=20, $\alpha = 0.1$, $\beta = 0.9$, $\delta = 20$, $\gamma = 0.5$[5]

Surface Diffusion Patterns

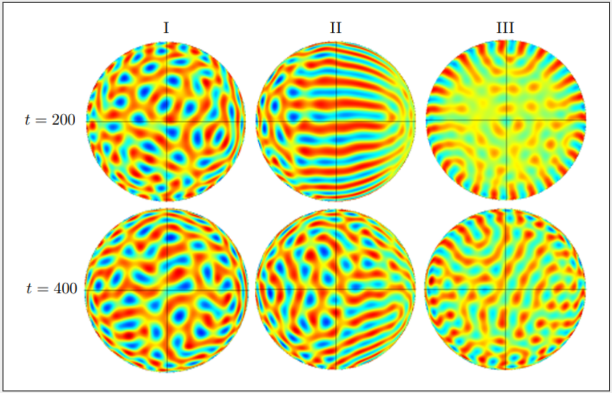


Figure: r=40, $\alpha = 0.01$, $\beta = 1.2$, $\delta = 10$, $\gamma = 0.1$[5]

Next Steps and Future Work

Thesis Goals:

- Examine model on the mesh of a human lung
- Use surface finite element method for numerical solutions
- Solve on growing domain

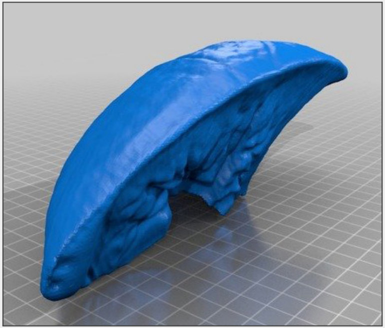


Figure: 3D model of left lung

References

- L. S. Prince, "Fgf10 and human lung disease across the life spectrum," *Frontiers in Genetics*, vol. 9, no. 517, pp. 1–6, 2018.
- R. Pearse, R. Vieira, and J. Rankin, "Factors influencing survival of infants with isolated, left-sided congenital diaphragmatic hernia: a systematic review," *BJOG-An International Journal of Obstetrics and Gynaecology*, vol. 125, 4 2018.
- A. M. Turing, "The Chemical Basis of Morphogenesis," *Philosophical Transactions of the Royal Society of London*, vol. 237, no. 641, pp. 37–72, 1952.
- J. Schnakenberg, "Simple Chemical Reaction Systems With Limit Cycle Behavior," *Institute for Theoretical Physics*, vol. 81, no. 3, pp. 389–400, 1979.
- A. L. Krause, A. M. Burton, N. T. Fadai, and R. A. Van Gorder, "Emergent Structures in Reaction-Advection-Diffusion Systems On a Sphere," tech. rep., 2018.

Thank You!