Modeling Fibroblast Growth Factor Expression in Embryonic Lungs

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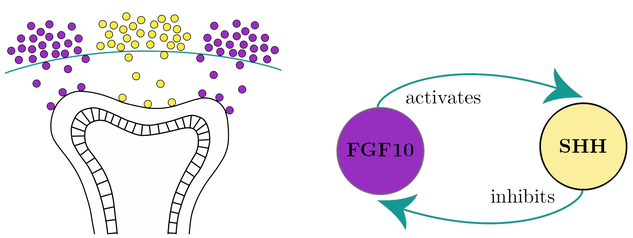
BACKGROUND

The geometry of embryonic lungs is believed to affect the location of Fibroblast Growth Factor 10 (FGF10) and Sonic Hedgehog (SHH) gene expression, which drive epithelial branching. In addition, branching morphogenesis has been observed to resemble Turing-type pattern formation. **We propose that a computational model investigating FGF10 and SSH interactions near the lung periphery and and their diffusion into the lung tissues will provide new insights into the regulation of FGF10 expression**. In view of this, we are currently developing a computational model of the embryonic lungs using the surface finite element method to approximate reaction- diffusion equations of FGF10 and SHH via the C++ program library *deal.ii*.

Right: **Human lung branching stages** (left to right): 4-7 weeks, 5-17 weeks, and 16-27 weeks. The mesenchyme (green) surrounds the epithelial buds (black) [1].



Above left: Proposed mechanism for branch selections: Gene proteins **diffuse from the lung surface**, through the mesenchyme, and onto the epithelial bud to determine branch selection. Above right: FGF10 (blue) stimulates cell growth and activates SHH (yellow), while SHH dampens cell growth and inhibits FGF10 [2]. The two genes form a **feedback loop** that can give rise to patterning.

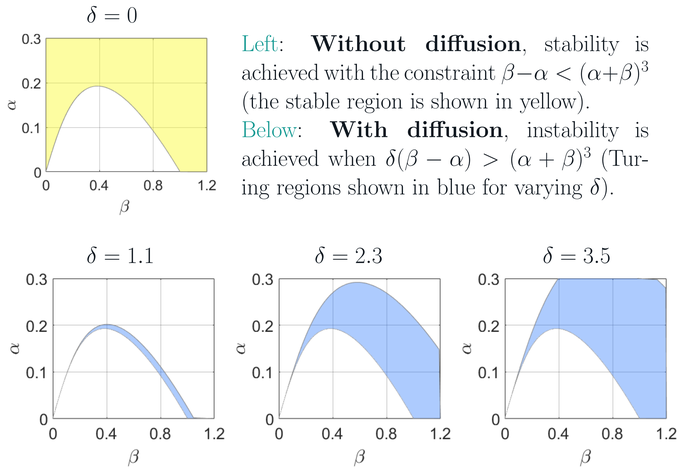
METHODS

The auto-catalytic chemical equation driving FGF10 expression:

$$X \rightleftharpoons \mathrm{F} \qquad 2\mathrm{F}+\mathrm{S} \longrightarrow 3\,\mathrm{F} \qquad Y \longrightarrow \mathrm{S}$$

The Schnakenberg model using the Laplace-Beltrami operator:

$$\textbf{FGF10}: \ \dot{F} = \Delta_\Gamma F + \gamma(\alpha - F + F^2 S)$$
$$\textbf{SHH}: \ \dot{S} = \delta\Delta_\Gamma S + \gamma(\beta - F^2 S)$$



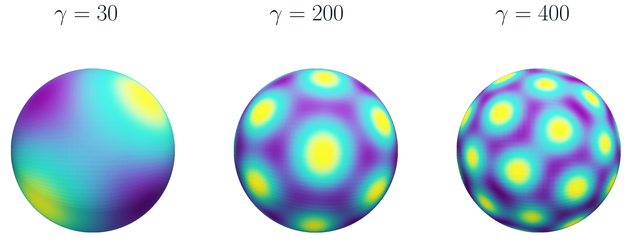
Left: **Without diffusion**, stability is achieved with the constraint $\beta-\alpha < (\alpha+\beta)^3$ (the stable region is shown in yellow).
Below: **With diffusion**, instability is achieved when $\delta(\beta-\alpha) > (\alpha+\beta)^3$ (Turing regions shown in blue for varying δ).

This model can be solved **analytically** by using eigenvalue substitutions for the time derivative and the Laplace-Beltrami operator:

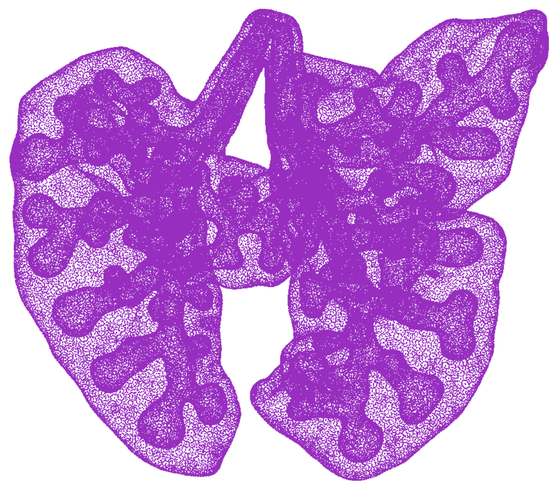
$$\dot{W} = \underbrace{D\Delta_\Gamma W}_{\text{diffusion}} + \underbrace{\gamma J W}_{\text{expansion}} \quad \text{substitute} \rightarrow \quad \dot{W} = \lambda W \ \text{ and } \ \Delta_\Gamma W = k^2 W$$

Solution on unit sphere: $$W(\phi,\theta,t) = \sum_{m=0}^{\infty}\sum_{n_k \geq m}^{n_{\max}} A_{mn_k} e^{\lambda t} Y_{n_k}^m(\phi,\theta)$$

RESULTS



FUTURE WORK: The eigenvalue solution will be compared with numerical solutions, then **solved on the lung surface**. Varying the parameter γ mimics the effects of a growing domain.
Below: MRI images were used to create a lung mesh. Some modifications still remain before using as a numerical domain.



Results from this study can offer new insights into embryonic lung development, and the techniques used in this study could be extended to examine other branching organs like the kidney or mammary glands. Particularly, there are some possible applications for treating **Congenital Diaphragmatic Hernias**.