

Investigating the Role of Collagen Stiffness in Epithelial Ductal Branching Using Optimal Transport Theory



Mammary gland development involves the formation of ductal branches necessary for milk production and delivery. The network primarily develops during puberty and is composed of four key epithelial cells types. Research shows that the interactions between the epithelial cells and collagen in the surrounding extracellular matrix (ECM) is crucial for ductal formation. However, understanding this process in situ is often complicated and must be done in vitro. By simulating this process with an agent-based model (ABM), we can conduct a wider range of in silico experiments on ductal formation. In particular, we aim to determine if ductal formation is determined by collagen stiffness throughout the gland.

The ABM will simulate the dynamics of epithelial cells, collagen fibers, and their interactions. To model movement through collagen, we introduce a novel approach that utilizes optimal transport theory to determine the optimal path for ductal formation using an elastic modulus, a matrix of collagen stiffness measurements. The elastic modulus is transformed about a goldilocks stiffness, an ideal stiffness for ductal growth. The ductal formation will utilize a hypothetical subtype of outer epithelial cells, called leader cells, to direct movement towards the optimal path. Preliminary results show the ABM is able to model a bifurcating duct, a process necessary for complex ductal networks.

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A

$$\text{Elastic Modulus } (E) = \frac{\text{stress}}{\text{strain}} = \frac{\sigma}{\gamma}$$

σ - a function of displacement, average crosslinker length, crosslinker, count, and collagen count in a given region

γ - displacement and average cross linker length

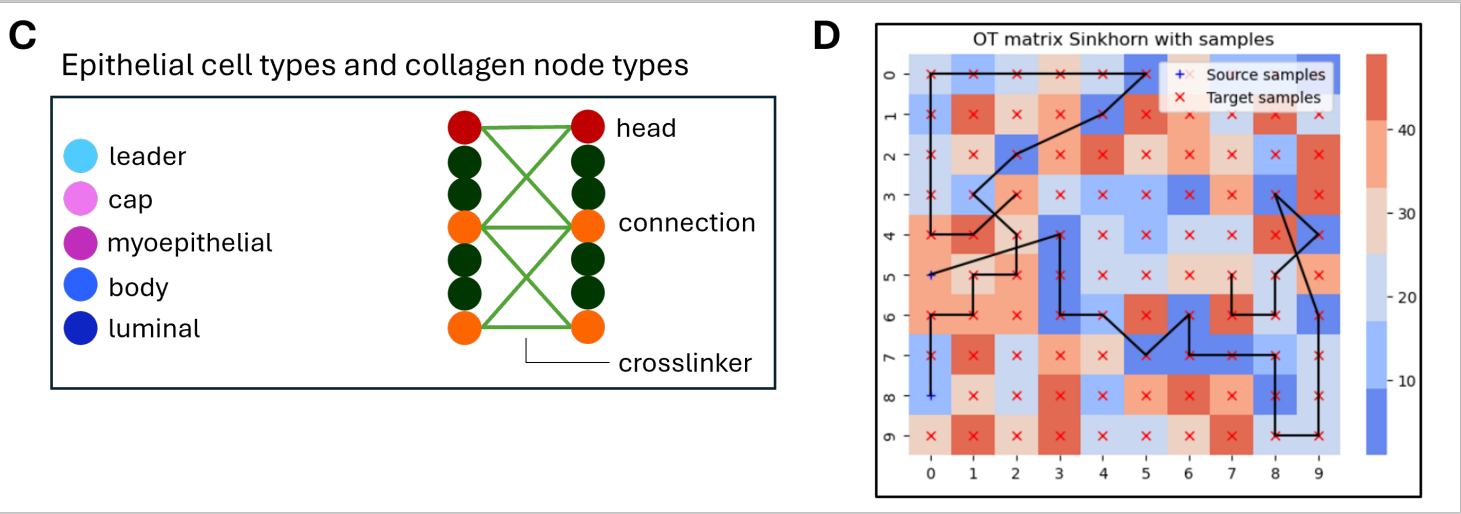
B

$$\text{Cost } (M) = ||xs - xt||^2 \Delta E$$

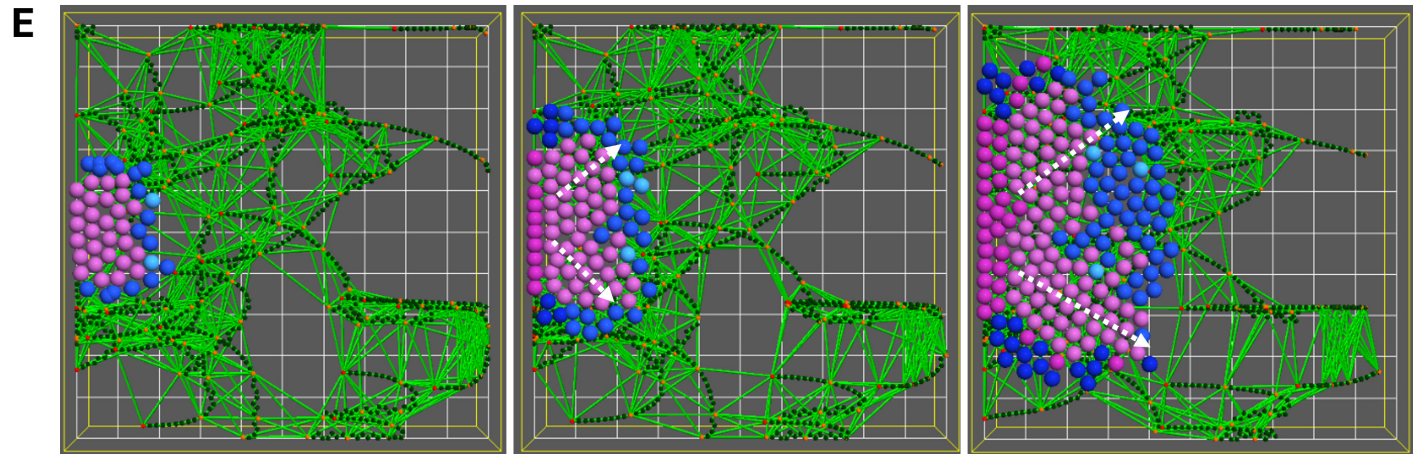
$$\gamma = \arg \min_{\gamma} \langle \gamma, M \rangle_F + \text{reg} \cdot \Omega(\gamma)$$

s.t. $\gamma = a$
 $\gamma^T = b$

Equations A) The elastic modulus is calculated by measuring the proportion of collagen and crosslinkers, the connections between collagen. E is calculated in equal intervals throughout the ECM. B) Optimal transport (OT) is used to find the optimal path through the ECM. xs is the position of leader cells, xt is the center of all intervals in which E is calculated. ΔE is the difference between E and the goldilock stiffness.



Implementation C) The epithelial cell types (left) and collagen node types (right) are all agents in the model with individual dynamics. D) OT using test ΔE values where smaller values are closer to the goldilocks stiffness. The test uses two leader cell positions as source samples and all interval centers as the target samples.



Preliminary results E) Three stages of the agent-based model can be seen above. With two leader cells (seen in **C**), we see the early formation of a bifurcation, which is a parent ductal branch splitting into two daughter ductal branches.