Mathematical Modeling of Pituitary Organogenesis

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Introduction

The organogenesis of the mammalian pituitary gland occurs in early embryonic development, as differentiated cells emerge in an indeterminant manner from ectodermal cells with definite influence from several hormonal and other proliferative indicators. We have built upon cellular dynamics models and 2D simulations of deformable polygons to construct a new class of models aimed at capturing the pituitary gland development. We use collected data on the pituitary gland ontogeny to found and guide the formulation of mathematical models governing the movement and interactions of cellular bodies, simulating the processes of cellular growth, division, and chemical & physical communication. In addition, the analysis of these data is used to determine the magnitude to which each of the proliferative and peripatetic signals acts upon the cells in order to yield movement and specialized development from an early unordered mass of stem cells into a specialized arrangement of differentiated cells. Once fully developed, our models will have the ability to empirically predict the effects of experimentation upon pituitary development, and to better understand how certain developmental disorders affect the pituitary's summative development.

Methodology

An initial configuration of 28 cells was constructed representing each developing stem cell as a quasi-circular polygon with a variable number of vertices defining the perimeter. Multiple forces act upon each cell to mimic the physical intercellular, chemical intercellular, and chemical intracellular signals which promote cellular growth, influence movement, and maintain independent cellular membranes [1]. Only 24 cells are used in the initial configuration in the interest of computational efficiency; each cell goes through an average of five mitotic divisions, yielding approximately 768 differentiated cells after the global proliferative stage.

$$U = \frac{k_a}{2}\sum_{m=1}^{N}(a_m - a_0)^2 + \frac{k_b N_v}{2}\sum_{m=1}^{N}\sum_{i=1}^{N_v}(l_{m,i} - l_0)^2 + U^{EV}$$

$$F_{r_i} = -\nabla U = -\frac{\partial U}{\partial r_i} \quad | \quad r_i(t+\Delta t) = r_i(t) + \frac{\Delta t}{\zeta} + F_{r_i}$$

Figure 1:
These equations show the general formula used in our simulation to define the energy of the system, U, with a generic definition for force, F_r and for the new position of any given vertex, r_i

These forces are represented as spring forces with unique equilibrium lengths and spring constants, with values determined from a temporally linked parameter space analysis between our continuous simulation data and static data collected in Dr. Shannon Davis' lab studying pituitary organogenesis in embryonic mice [Figure 1] [Figure 2]. These forces act upon our simulation via a Euler discretization in the interest of computational efficiency. Each force is either unique to the cell such that all vertices within one cell are affected to the same magnitude or is unique to the vertices themselves such that every vertex receives a force whose magnitude and direction is not necessarily congruent to that assigned to other vertices within the same cell.

In representing our simulation with respect to the true orientation and environment of the developing pituitary gland in mammalian life, the first quadrant of our cartesian plane maps to the ventral posterior lobe in a cross section along the middle of the pituitary gland, with the second quadrant mapping to the dorsal posterior lobe [Figure 3].

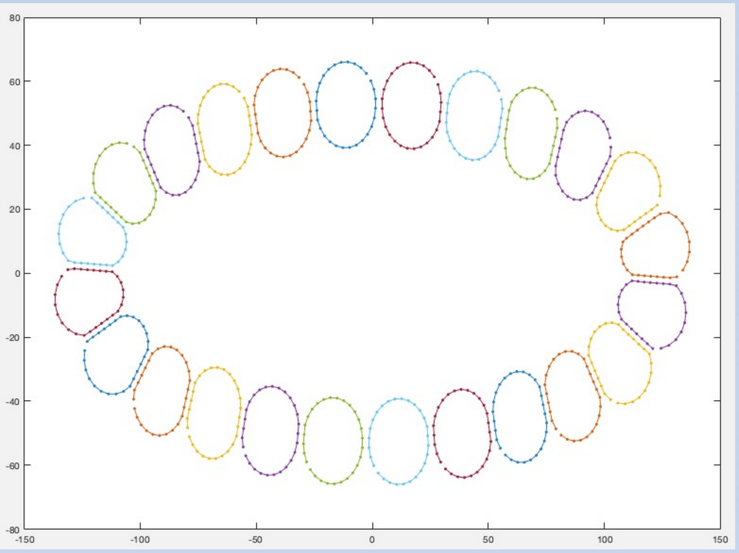


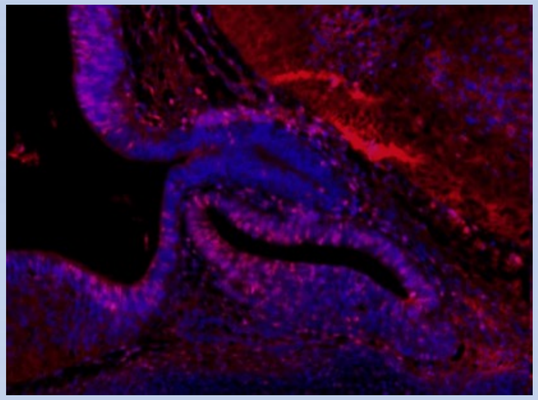
Figure 2:
This is a cartesian plane showing the configuration of the 24 initial cells currently used in the simulation. Each closed polygon consists of multiple vectors which define the perimeter of the cell. The scale of the simulation is shown, though the units are arbitrary in this stage and the size and position of each is only relative to the other factors in the simulation.

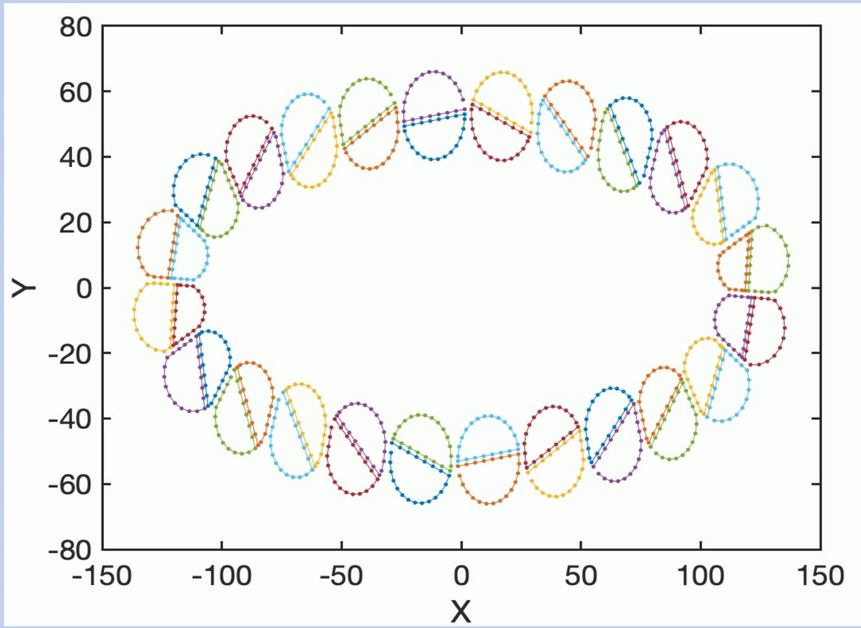
Results and Discussion

The model has been run multiple times to success, with all cellular processes correctly simulated. These initial stages of research were focused on creating the model and balancing all parameters to allow all modeled cells to interact with each other and to grow and proliferate without obstruction or interference. Figure 4 shows a simple simulation being run with all elementary interactive and intra-active forces contributing to the movement of the simulation. There are no locomotive forces accounted for, nor are cells differentiated at any point due to any factors. Proliferative signals aren't accounted for in order to explicit areas of greater mitosis, as is suggested by Dr. Davis' data. The region in the ventral anterior lobe does not form into Rathke's pouch in this version of the simulation, as is known to be true of all mammalian pituitary glands.

Figure 4 (right):
This video shows a simulation being run with generally balanced parameters. The cells divide at normally distributed times, are initially uniformly distributed, and grow without respect to other cells.

Figure 3 (Bottom):
This is an example of the data collected by Dr. Davis. This image shows a forming pituitary gland at 12.5 days post fertilization.





Conclusions

This empirical analysis of the pituitary organogenesis is sufficient evidence to reject the null hypothesis that the physical movement and interactions of the proliferative and differentiated cells, as well as their transition from the former to the latter, are stochastic in nature. These results, while seemingly intuitive, are necessary to continue to progress our model and to assert empirical reasoning for the implementation of proliferative, locomotive, and differentiating hormones in future research.

New Work

Ultimately, this model needs to be built out to account for more mitotic promoting factors, as well as to account for cellular differentiation based on variable and yet undetermined factors. We are working on developing this model further to include the known information of these effects to determine to what magnitude these variables affect organogenesis.

References

[1] Boromand, A., Signoriello, A., Ye, F., O'Hern, C. S., Shattuck, M. D. (2018). Jamming of Deformable Polygons. *Physical Review Letters, 121* (24). https://doi.org/10.1103/physrevlett.121.248003