Agent-Based Modeling of Syn-Notch Signaling

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Agent-Based modeling

Fundamentals:

- Model the behavior of a system as a whole from individual elements called agents.[1]
- These agents act autonomously
  - Will read their environment and respond according to their individual logic

Example: NetLogo turtle logic

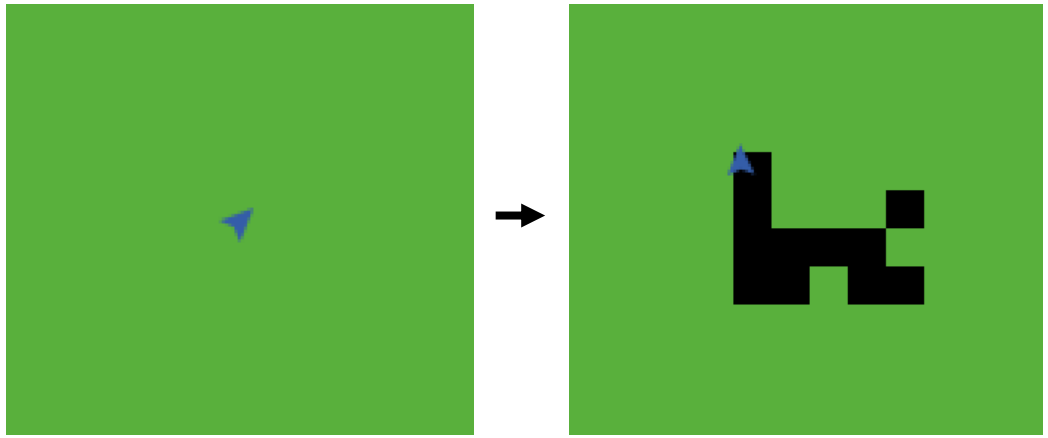


Figure 1: Tutorial in Netlogo, The "turtle" (blue arrow) is in green "patches". The turtle will move randomly, turning green patches it is standing on into black patches.

Advantages and Disadvantages

Key features of Agent-Based models:

- Can give insight into the system as a whole: Emergent Phenomenon [1]
- Allow for integration of data into the agents logic to examine effects.
- Can simplify behavior

Drawbacks still exist within this method

- Computationally expensive
- Complexity

Notable usage

Economic Applications [2]

- Customer migration in grocery stores
- Crowd behavior [1]

Migration Behavior

- Road Traffic [3]

Cell patterning

- Cell patterns emerging from signaling [4]

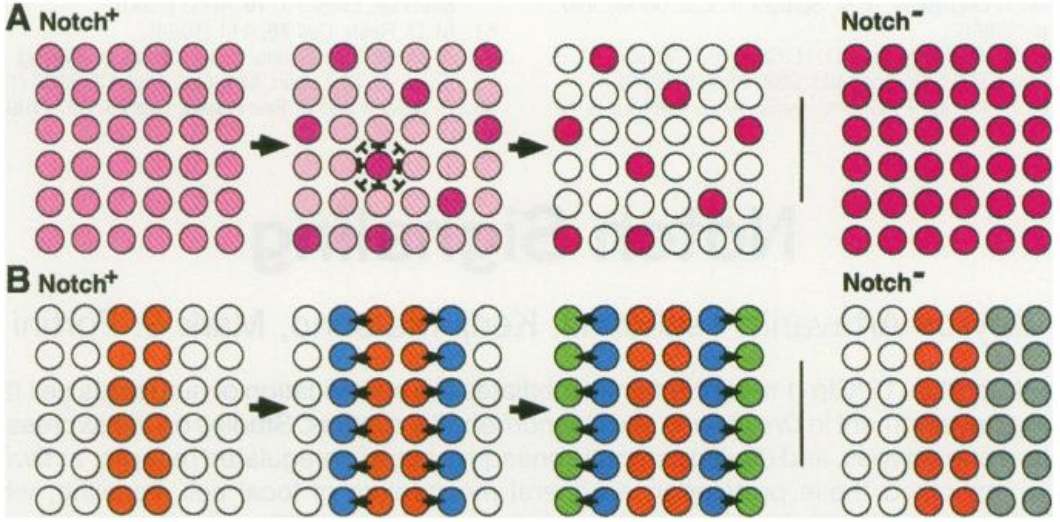


Figure 1: Spatial cell patterning as a result of Syn-Notch signaling [5]

Delta-Notch Signaling

Contact Inhibition Where cells express Notch and Delta [6]

- Notch: Membrane receptor, Delta binding triggers cleavage of internal Notch
- Delta: Membrane ligand, binds to Notch

Notch presence represses Delta

- More Notch on membrane = Less Delta on membrane
- Cleavage of Notch triggers cell fate or response

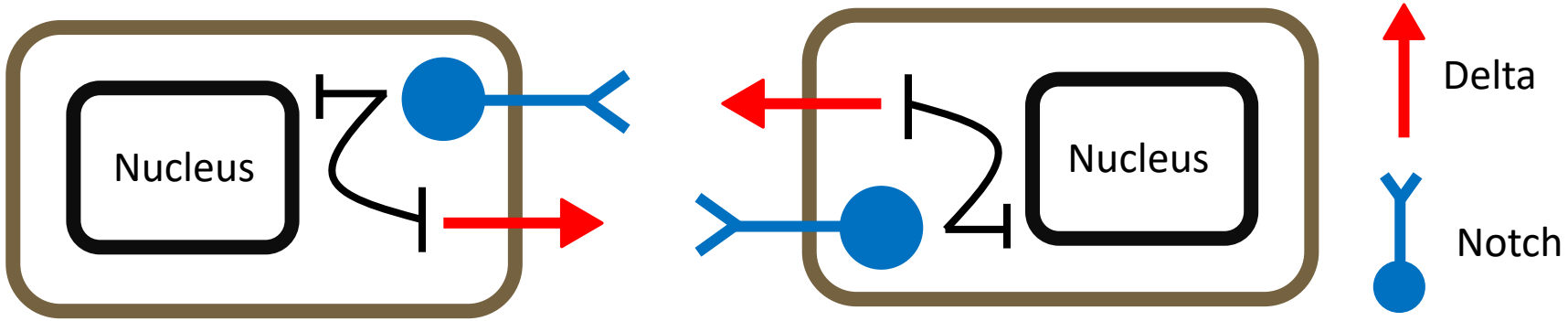


Figure 2: Basic Syn-Notch Circuit. Red arrows are Delta. Blue Y's with bound Spheres are Notch

Syn-Notch Signaling

Use in spatial patterning

- Todo etc al. use syn notch signaling to drive cell fate. A separate gene was activated based on notch signaling that organized the structure after a fate of the cell was selected.[4]

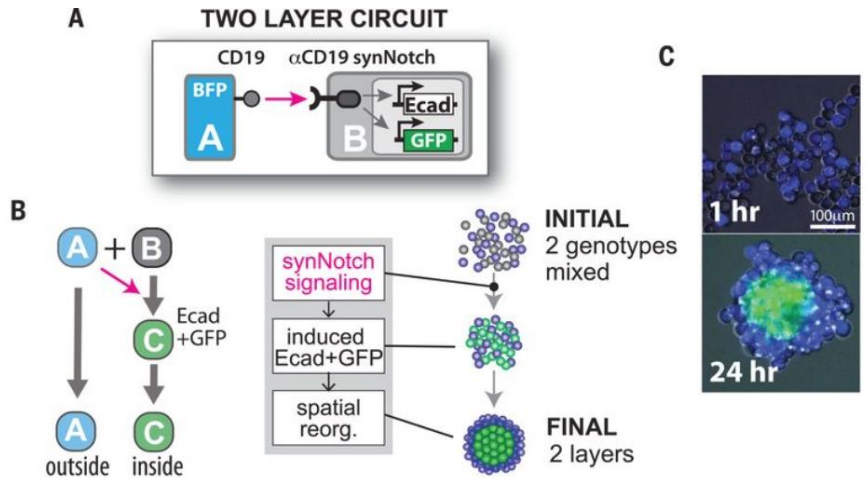


Figure 3: Two layer circuit from Todo etc al. A is the graphic. B describes the pathway. C shows experimental results [4]

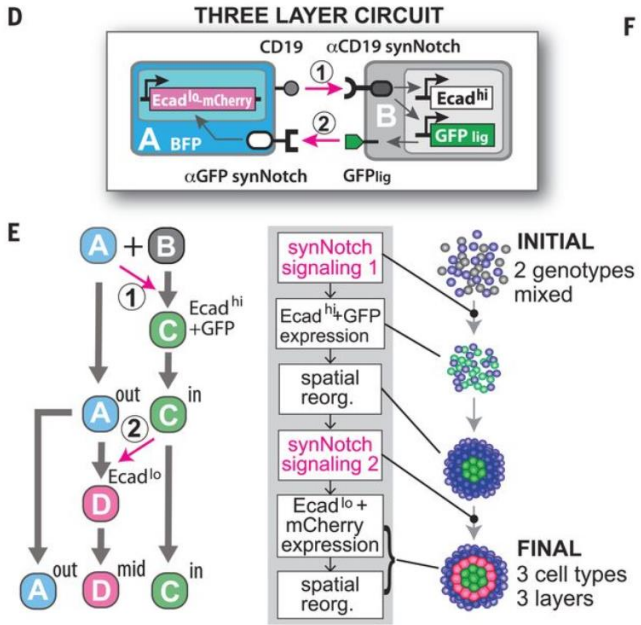


Figure 4: Three layer circuit from Todo etc al. D is the graphic. E describes the pathway. [4]

Agent-Based modeling and Cell fate

Reynolds etc al. paper generated a model of cell fate by Syn-Notch signaling with single genotype cell line.[6]

- Corresponds to Figure 2 Earlier in Todo etc al.

Example of the model results

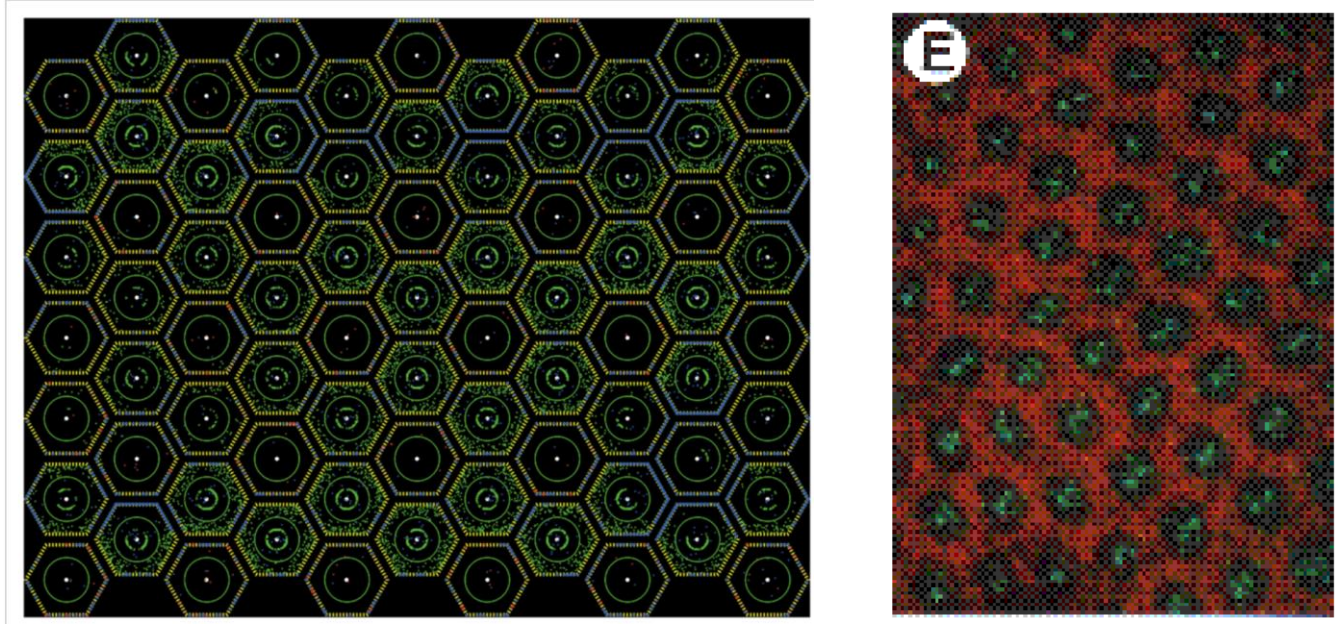


Figure 5: On the left is the Reynolds et al. paper Model of Drosophila fly eye cell pattern. On the right labeled E is experimental results from P.J Kooh etc al. 1993, the motivation of the agent based model from Reynolds [6][7]

Further Extension of the model

First the model was verified to run the single genotype two cell fate contact inhibition.

The model was then extended past the Drosophila eye into circuits proposed by Todo etc al.

- Two layer circuit, two genotype (figure 1)
- Three layer circuit, two genotype (figure 1)

The Single genotype Syn-Notch circuit was expanded to have two Syn-Notch circuits, generating a single genotype three layer circuit resembling the asymmetric three layer circuit by Todo et al.

- Examine if the “Rosette”[6] pattern is retained under the addition of a new cell fate

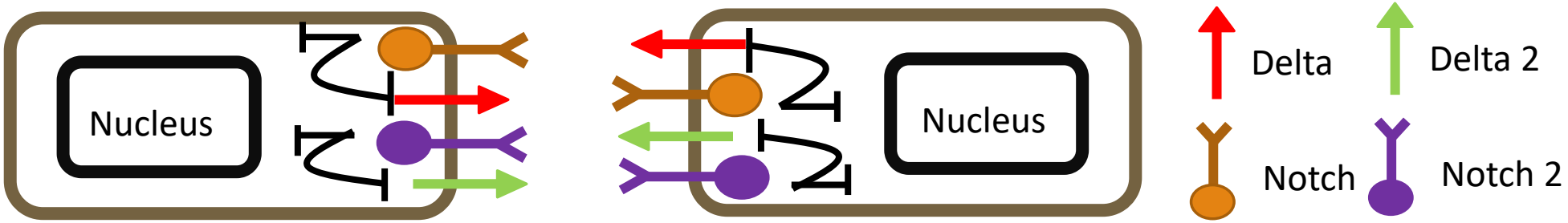
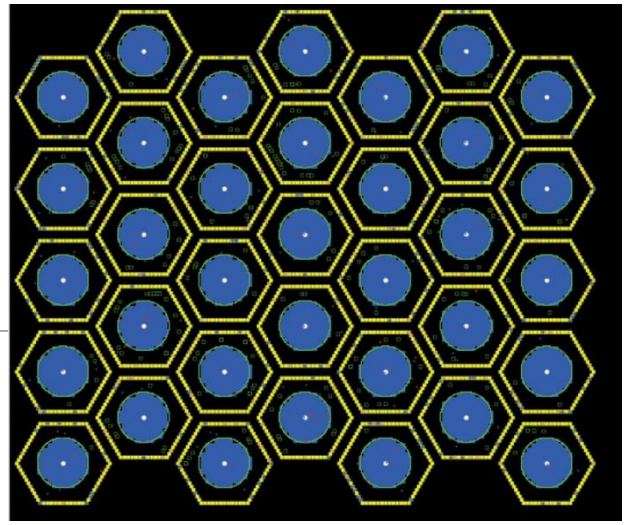


Figure 6: Modification of Todo etc al. Asymmetric Syn-Notch circuit to be single genotype

Verification Contact inhibition



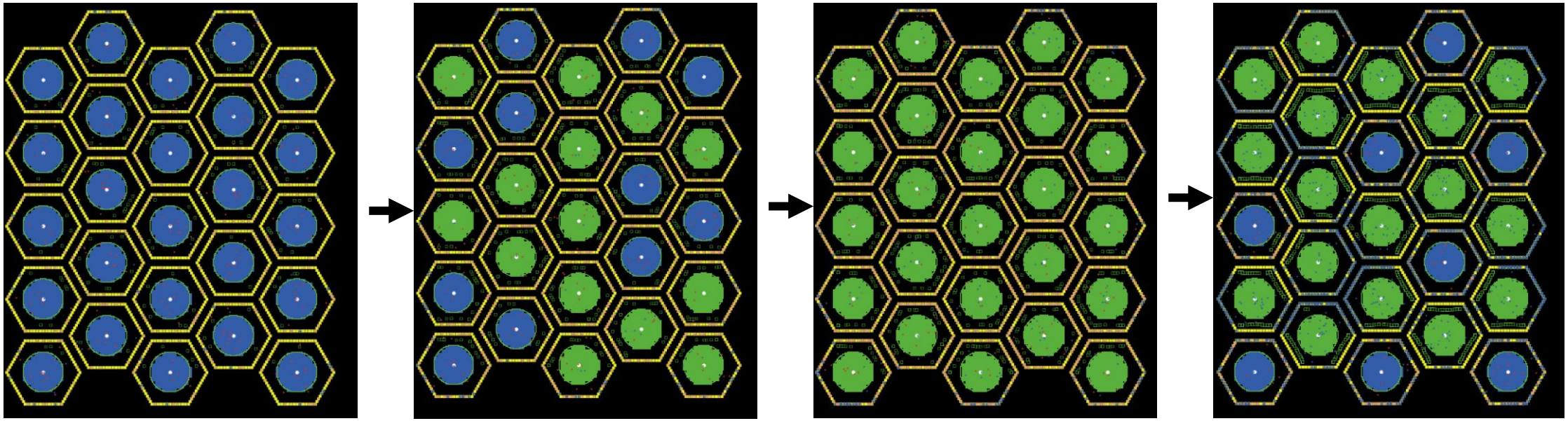
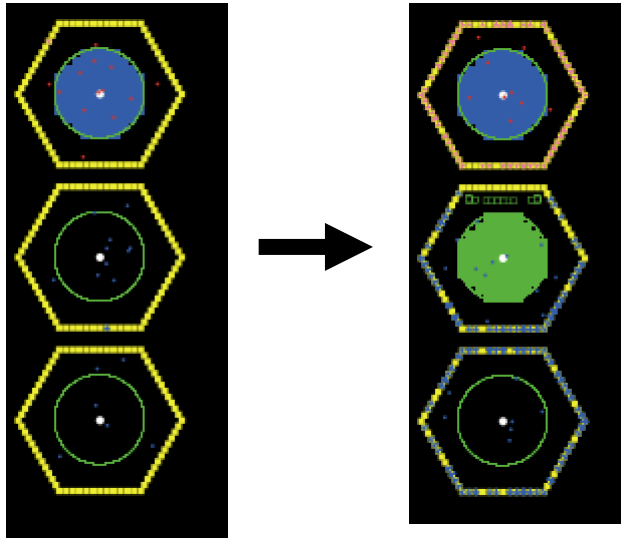


Figure 7: Change in the spatial pattern of Blue “neurons” and green “skin cells”. Development of the “Rosettes” after several periods alternating between cell fates.

Modeling Two layer circuit

Simplest Syn-Notch signaling, Cell A activates Cell B



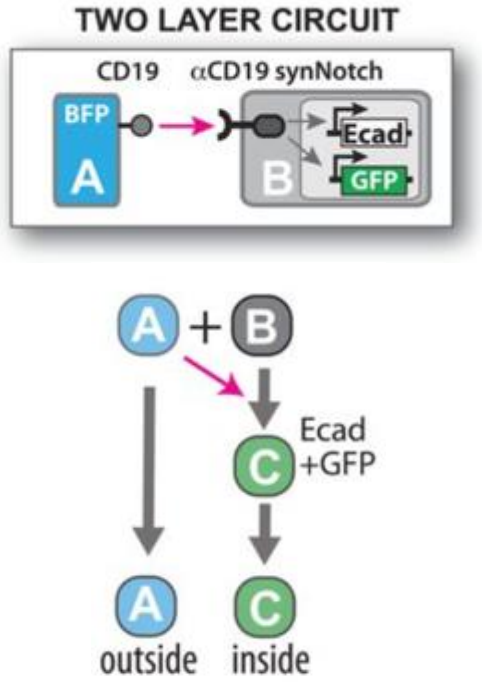
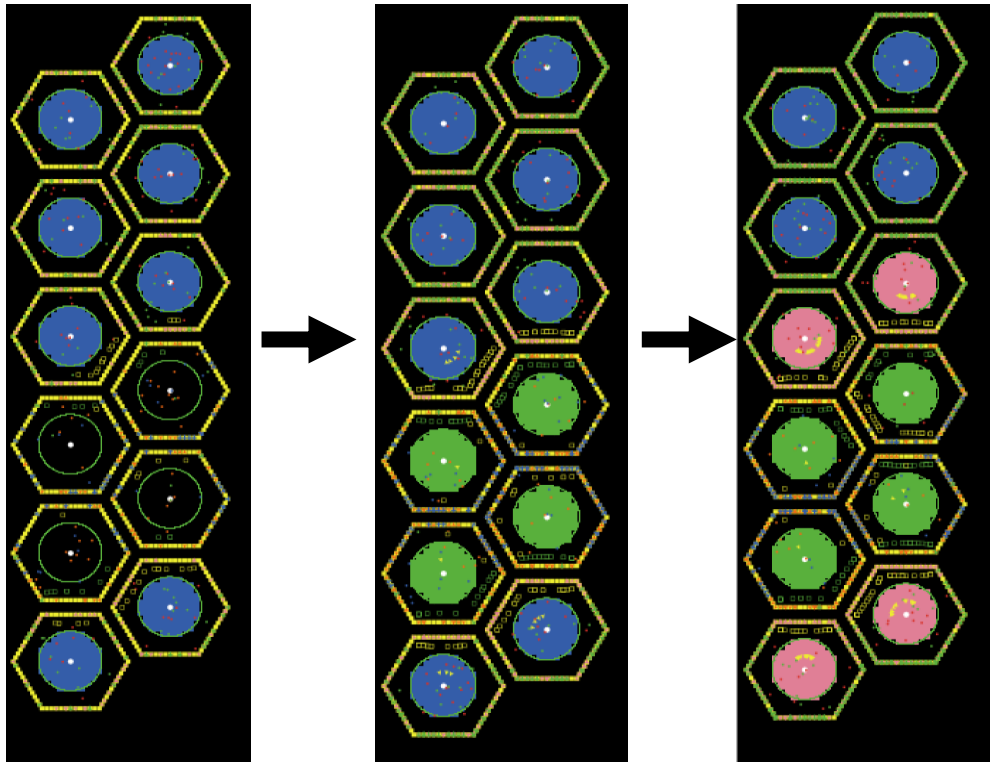
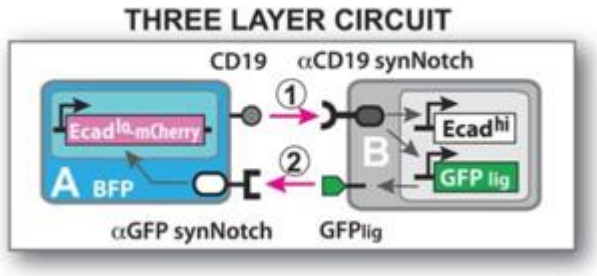


Figure 8: Model of Two layer circuit. Blue is a "neuron" cell and green is a "skin" cell [1].

Three Layer Circuit





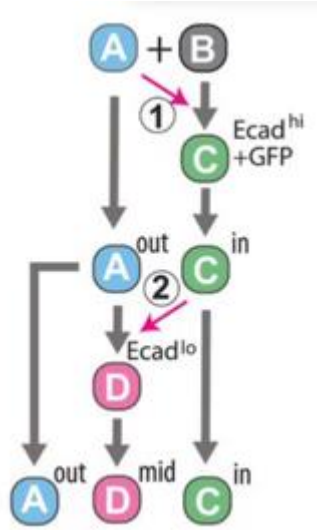


Figure 9: Three layer circuit. Blue cells express delta and Notch2. Delta binds Notch and creates cleaved notch (Black cell turns green). Green cells then express delta2 which binds Notch2 (blue cells turn pink)

Limitation

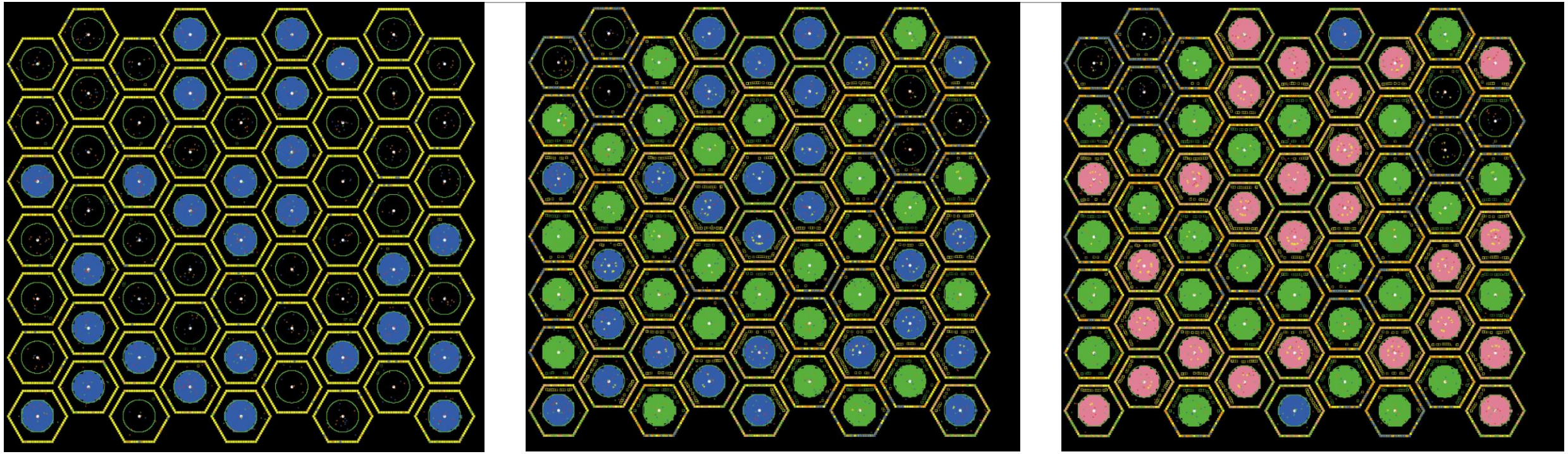


Figure 10: Three layer circuit on cell layer with random selection of starting A (blue) cells. If blue was not shielded by other blue cells its fate would result in a pink cell. Final layout is primarily pink and green.

Single genotype, double Syn-Notch

Extension off of single genotype notch signaling, however now it is a three way tug of war.

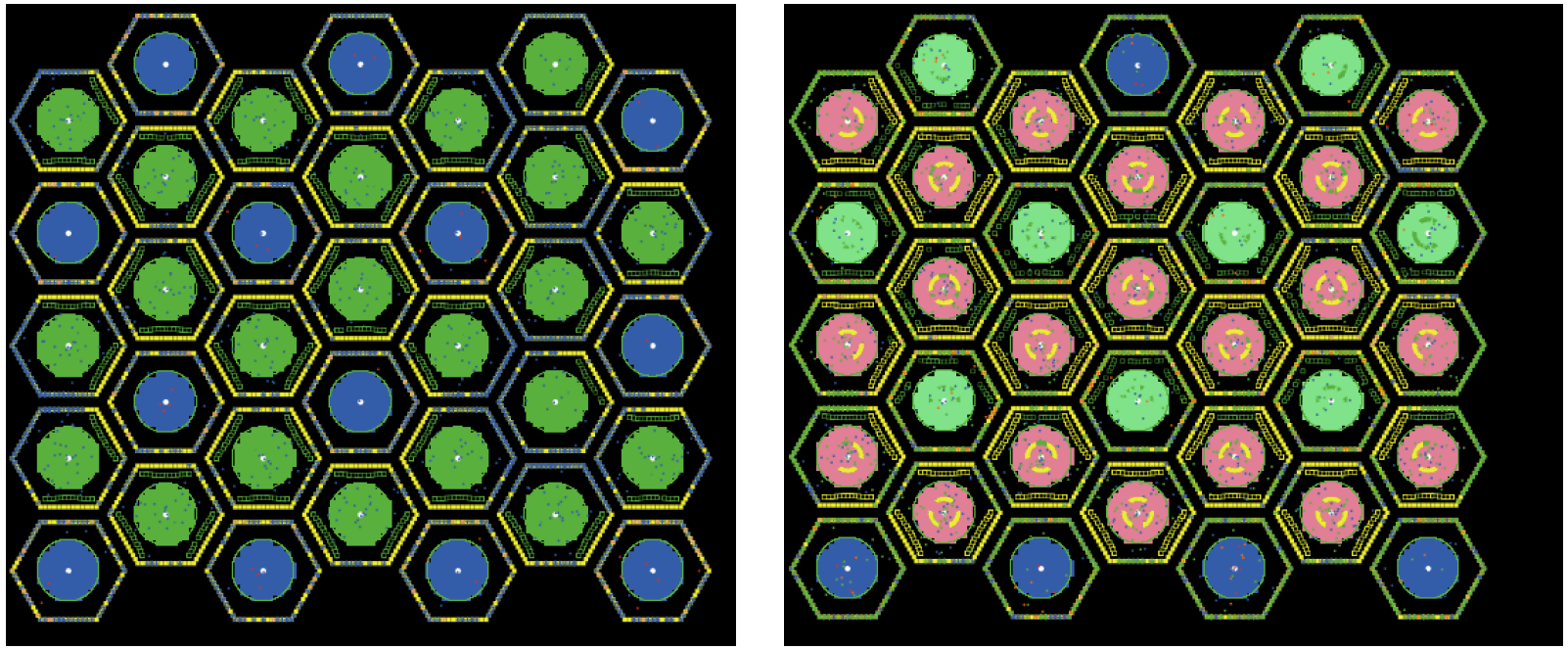


Figure 11: On the right is a Reynolds Drosophila pattern under a single contact inhibition Syn-Notch circuit. On the left is a modified circuit that allows for a third fate to be adopted (pink). The "Rosette" pattern Reynolds observed was retained, however blue cells are replaced by green cells inside some "Rosettes"

Discussion

Extension of the Reynolds model was able to capture some features of the spatial pattering in circuits outside the simple two cell contact inhibition.

- Two Circuit
- Three Circuit

Introducing a third cell fate into the Drosophila model of single genotype Syn-Notch signaling retained the “Rosette” pattern

- however some blue neurons were replaced with green skin cells in the center of the cell sheet.

Severely limited by the immobility of the cells in the cell space.

- Would improve sorting of the cells, a feature explored by Todo et al.

References

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[7] P. J. Kooh, R. G. Fehon, and M. A. Muskavitch, “Implications of dynamic patterns of Delta and Notch expression for cellular interactions during Drosophila development,” *Development*, vol. 117, no. 2, pp. 493–507, Feb. 1993.

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