Modeling Cell Migration in a Simulated Bioelectrical Signaling Network for Anatomical Regeneration

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Introduction

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- These tissues could fix a birth defect or induce remodeling of a damaged organ
- This is one of the goals of synthetic biology. A field that aims to design and engineer biologically parts, devices and systems

Model Organism – Planarian Flatworm

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- Note that the shape to which an animal regenerates upon damage can be altered without genetic changes
- For example, it is possible to produce two headed planarian worms
- Genes and proteins involved in regeneration are known, but the exact mechanism of storing and using morphological information for regeneration is still unknown

Computational Model of Morphology Discovery and Repair

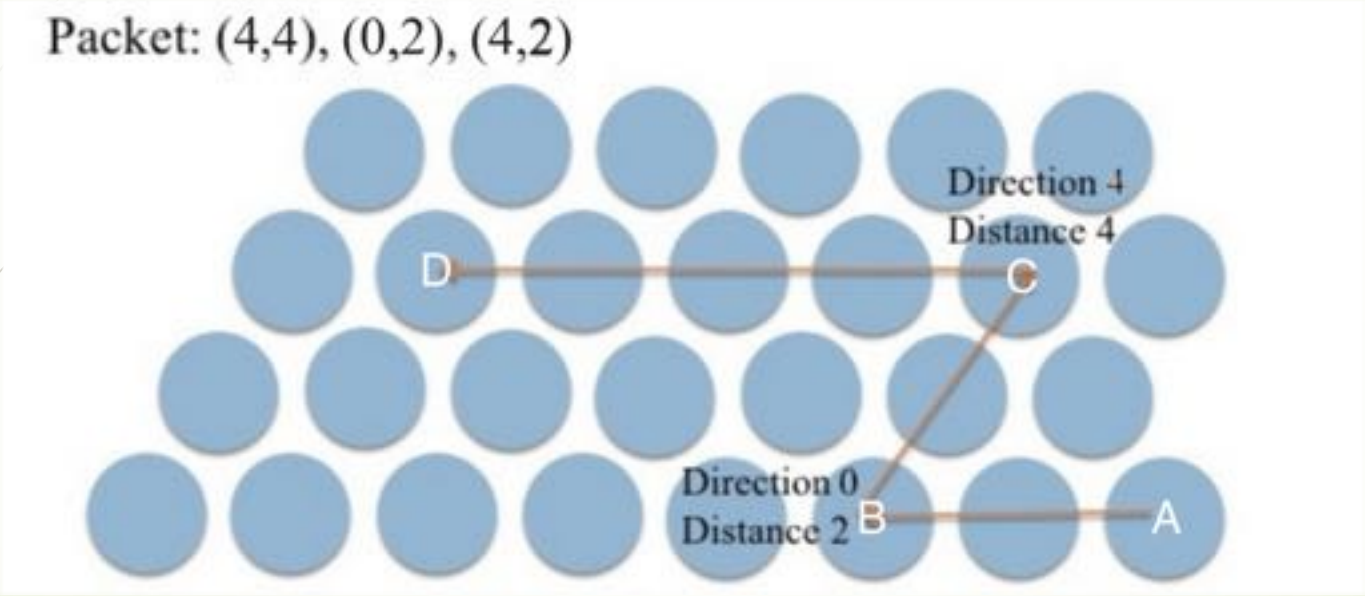
- We previously developed a model that could discover the morphological information of an organism, during a discovery phase
- Later, when the organism was lesioned the dynamic messaging mechanism in the model was able to cause regeneration of the damaged parts
- The model has demonstrated a variety of functional properties of regeneration displayed by Planaria

Features of the model

- Proposed in Ferreira et al. 2016 [1]
- Morphological information is stored in a dynamic distributed fashion across cells
- The genome is hypothesized to encode the computational machinery necessary for carrying out morphological discovery and repair
- A key feature of the model is that it can dynamically learn and maintain new morphologies using the same computational mechanism

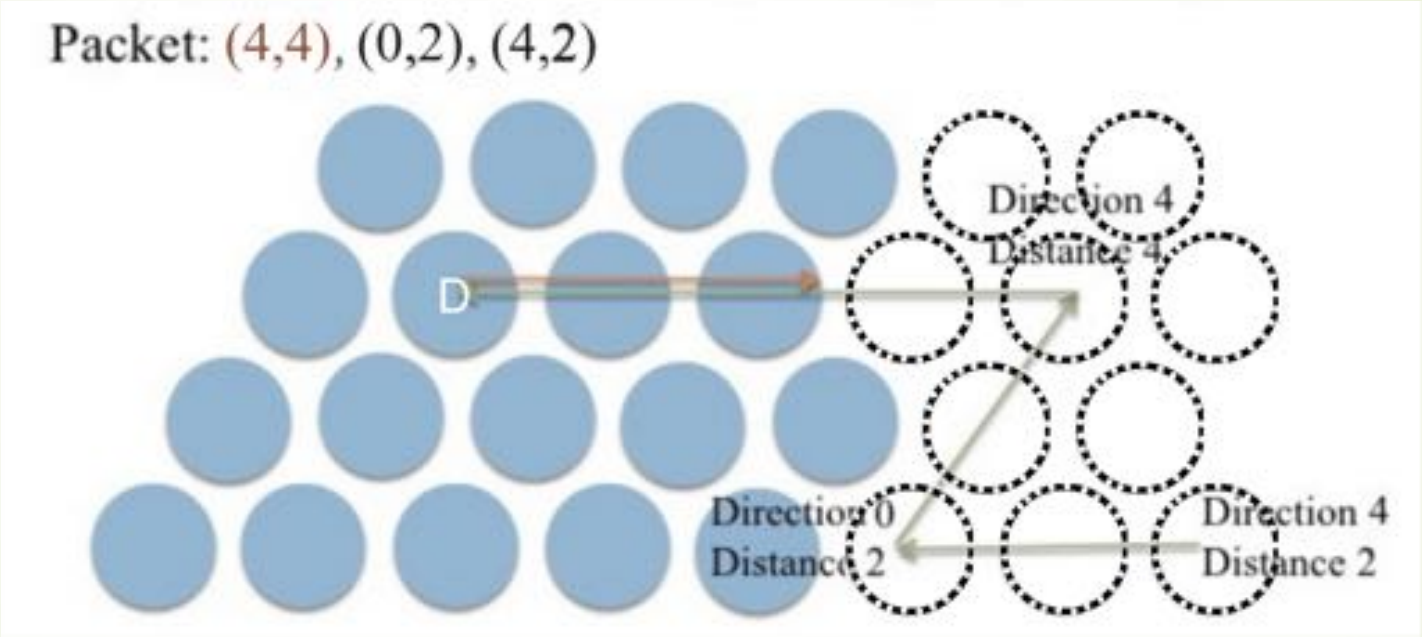
[1] Ferreira, G. B. S., Smiley, M., Scheutz, M., and Levin, M. (2016). Dynamic structure discovery and repair for 3d cell assemblages. In *Proceedings of the Fifteenth International Conference on the Synthesis and Simulation of Living Systems (ALIFEXV)*

Discovery



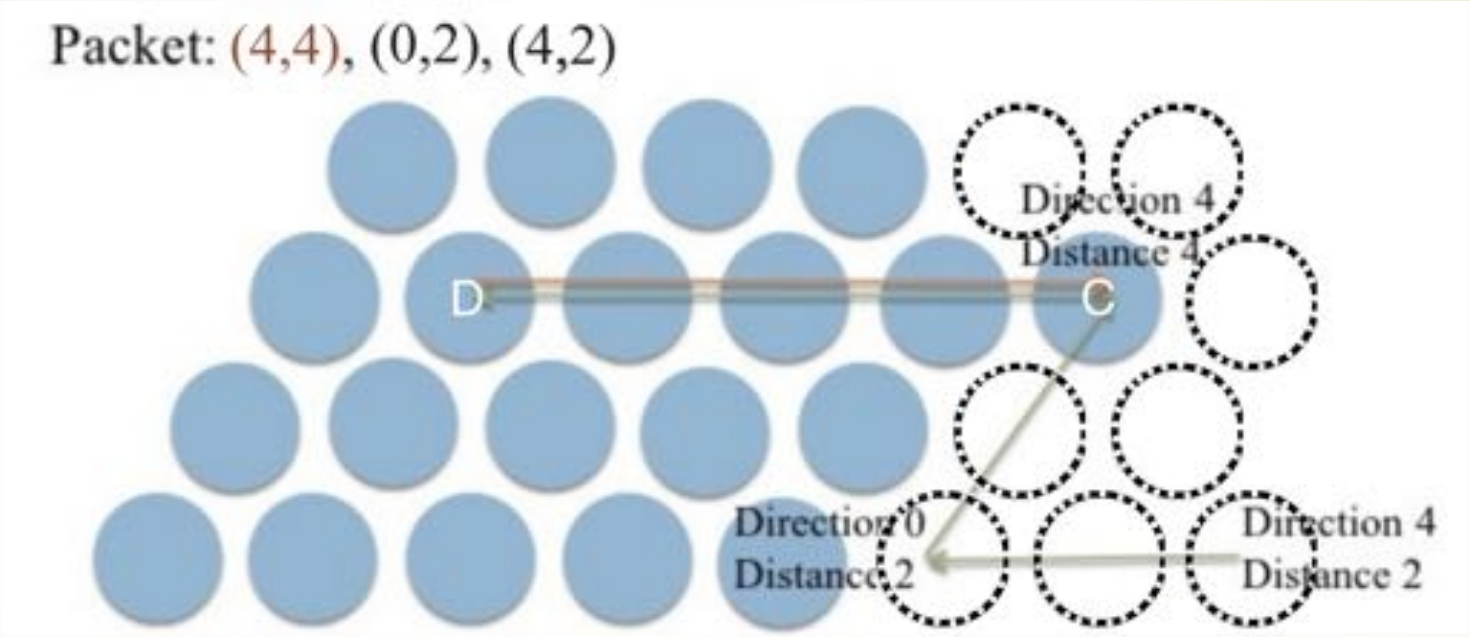
Cells send messages to other cells containing information about the path that those messages traveled.

Regeneration

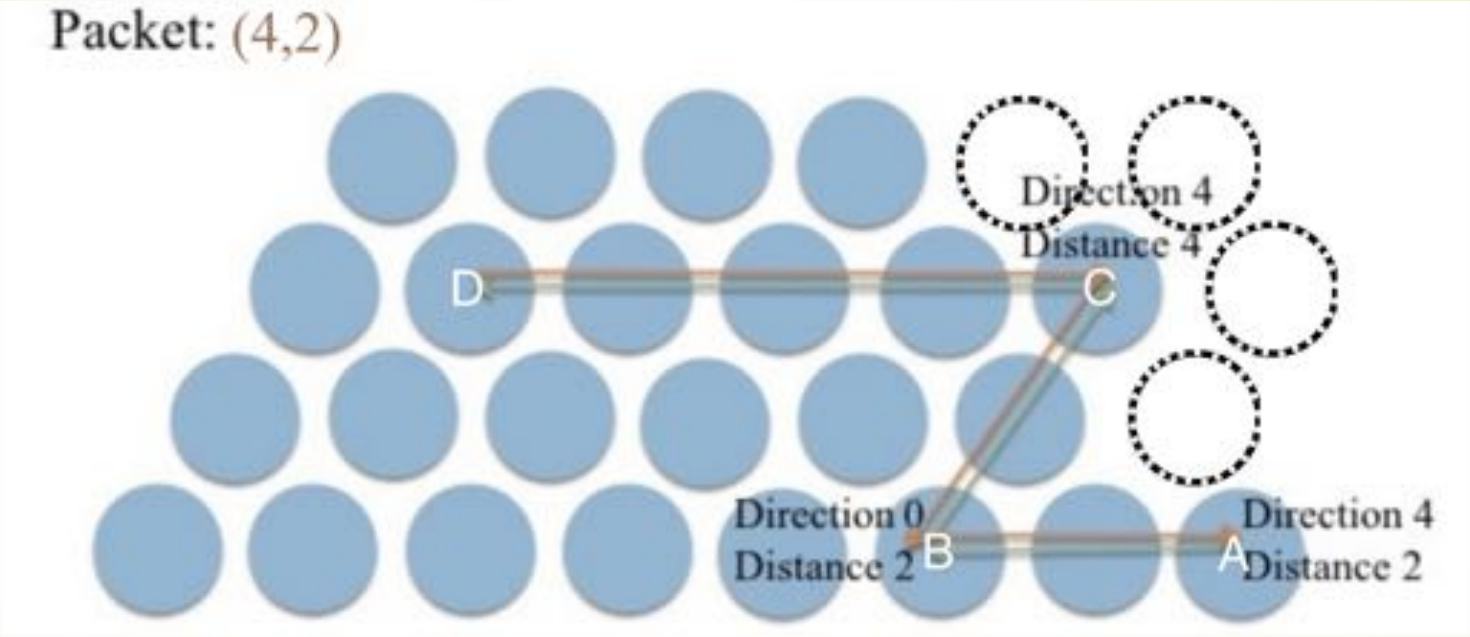


Then those message packets "backtrack" verifying if there exists a missing cell in the previous path, repairing it.

Regeneration



Regeneration



Previous Findings

- In Ferreira et al (2016) [1] we showed that this model was capable of maintaining the structure of the worm indefinitely in the light of random damages happening to parts of it
- However, communication was assumed to be perfect and without losses, which is not realistic in any actual organism
- In Ferreira et al (2017) [2] we investigated our model of dynamic messaging morphology discovery and repair under various conditions of noise and proposed simple extensions to overcome the detrimental effects of noise

[1] Ferreira, G. B. S., Smiley, M., Scheutz, M., and Levin, M. (2016). Dynamic structure discovery and repair for 3d cell assemblages. In *Proceedings of the Fifteenth International Conference on the Synthesis and Simulation of Living Systems (ALIFEXV)*

[2] Ferreira, G. B. S., Smiley, M., Scheutz, M., and Levin, M. (2017). Investigating the Effects of Noise on a Cell-to-Cell Communication Mechanism for Structure Regeneration. In *Proceedings of the 14th European Conference on Artificial Life (ECAL 2017)*

Adult Stem Cells – ”Neoblasts”

- An explanation for Planaria’s regeneration capabilities is the high number of adult stem cells (called ”neoblasts”) that exist in their body
  - Between 20% and 30% of cells in Planaria are neoblasts
  - Neoblasts are the only type of cells capable of dividing and differentiating into any other cell type
  - Worms with no neoblasts lose their regeneration capabilities

Migration of Neoblasts

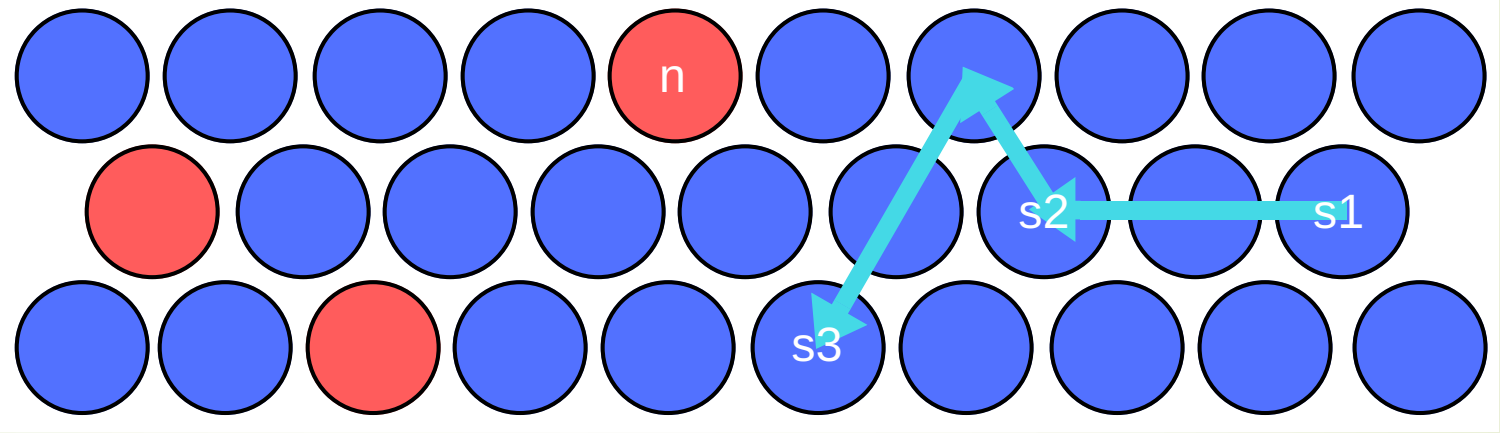
- There is evidence that signals coming from the wound guide neoblasts to the injury site.
- In a partially irradiated worm (e.g., with neoblasts existing only in the posterior part), regeneration does not start immediately following a anterior injury. Instead, it takes up to 4 weeks to create a mass of cells capable of differentiating into a head. [3]
- This suggests that neoblasts can migrate over long distances until they reach the area of the injury.

[3] · Wolff E, Dubois F. 1948. Sur la migration des cellules de régénération chez les planaires. Rev. Swisse Zool. 55:218–27

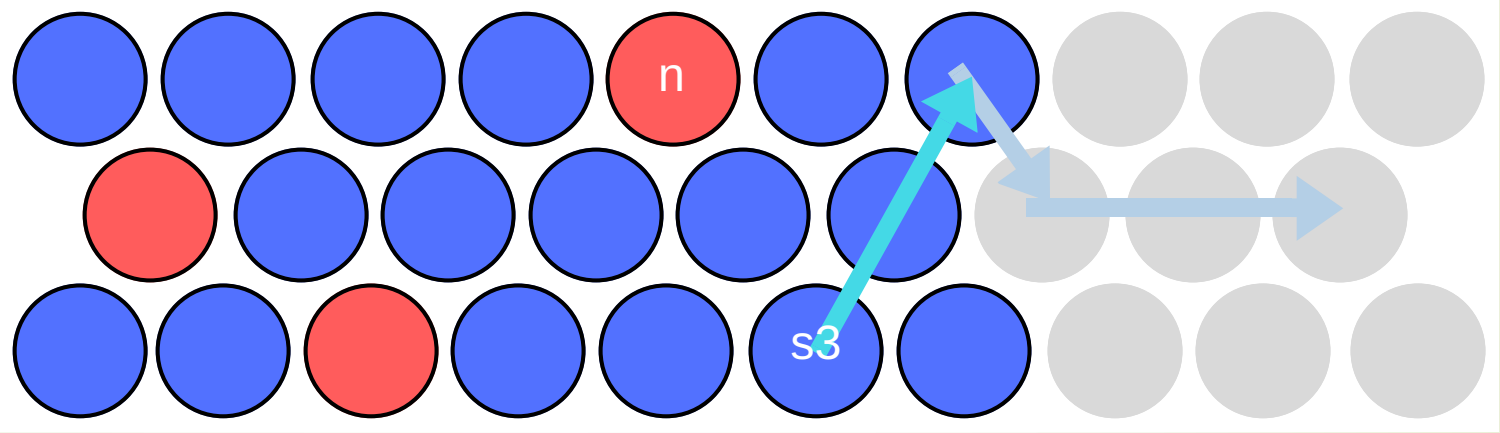
Simulated Neoblasts

- In this work, there exist two cell types: neoblasts and somatic cells
- Only neoblasts are capable of dividing
- Somatic cells create migration messages that guide neoblasts to the injury area
- We want to test whether the worm can recover from an injury that removed half of its tissue

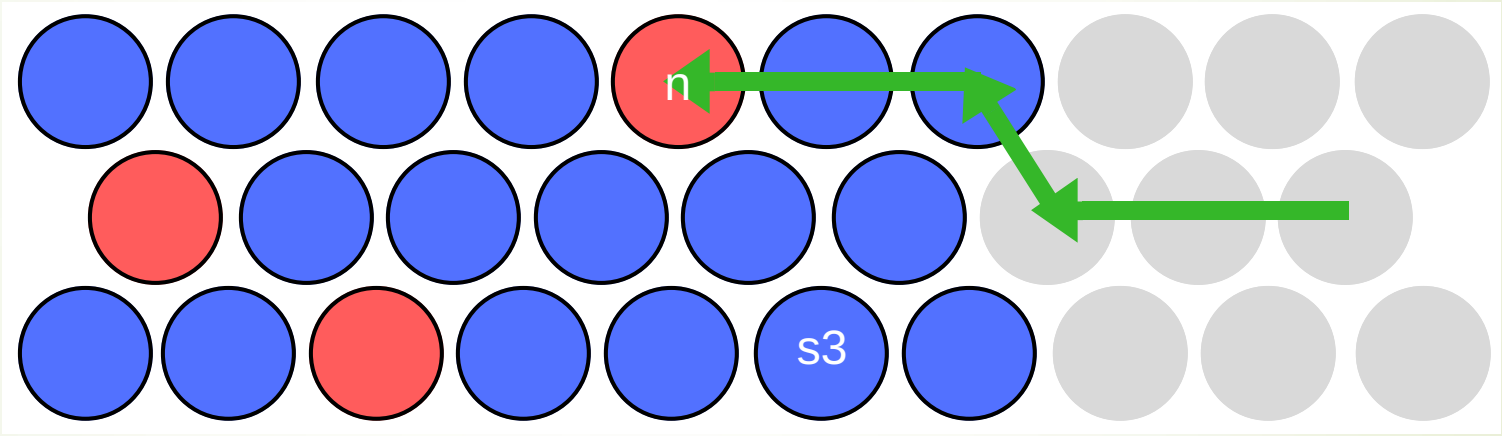
Discovery With Neoblasts



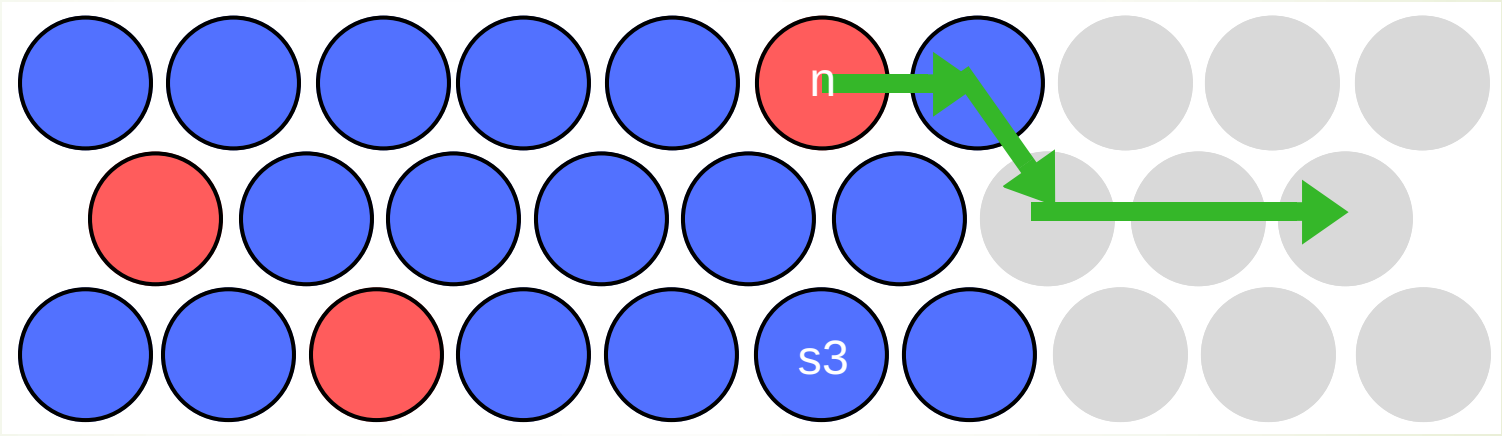
Backtracking



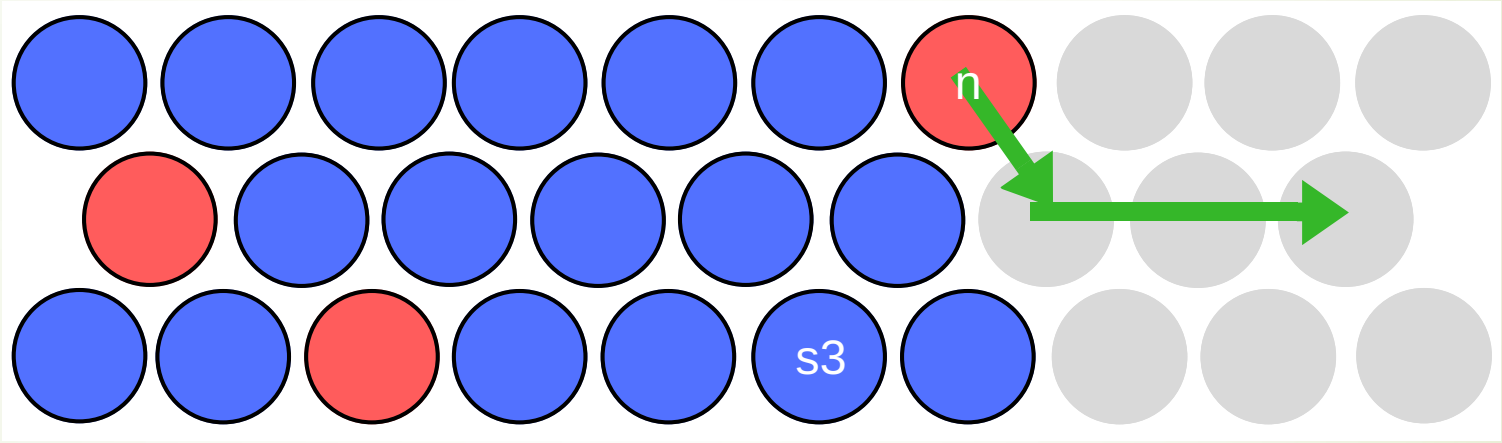
Migration Message



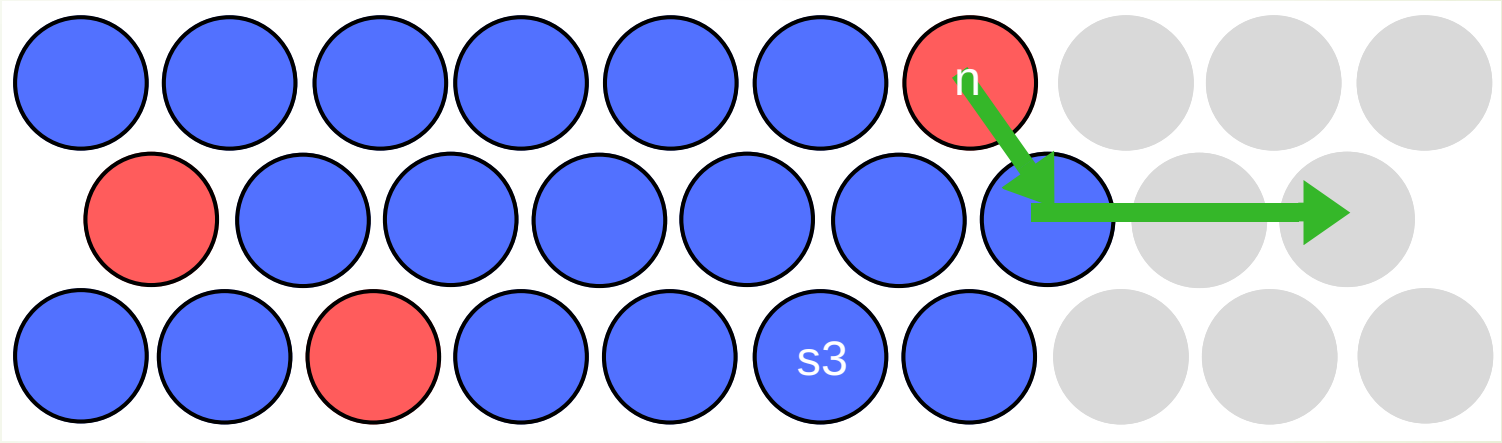
Migration



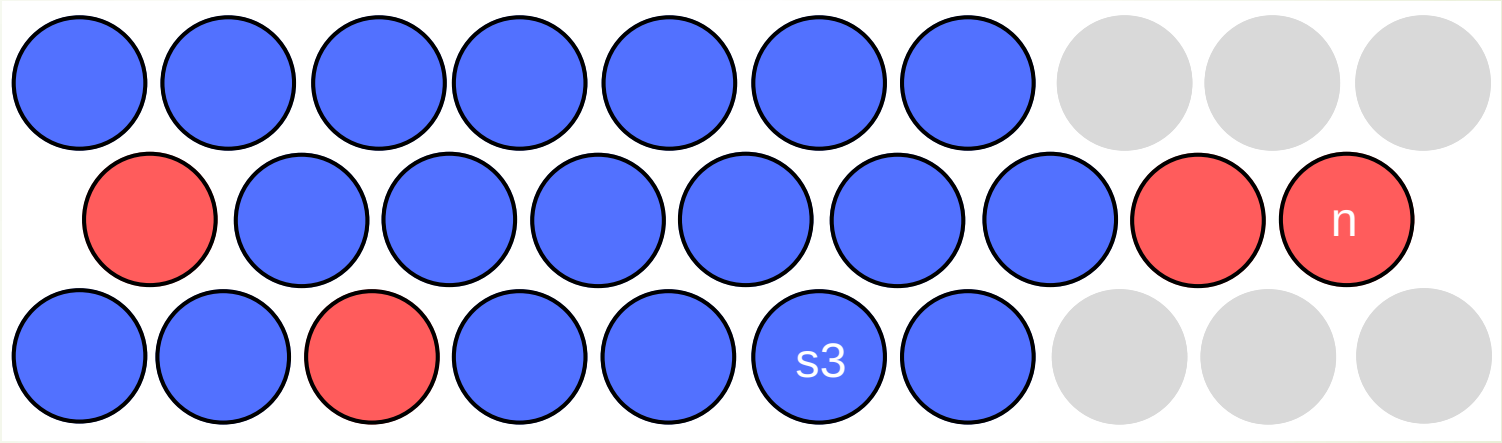
Migration



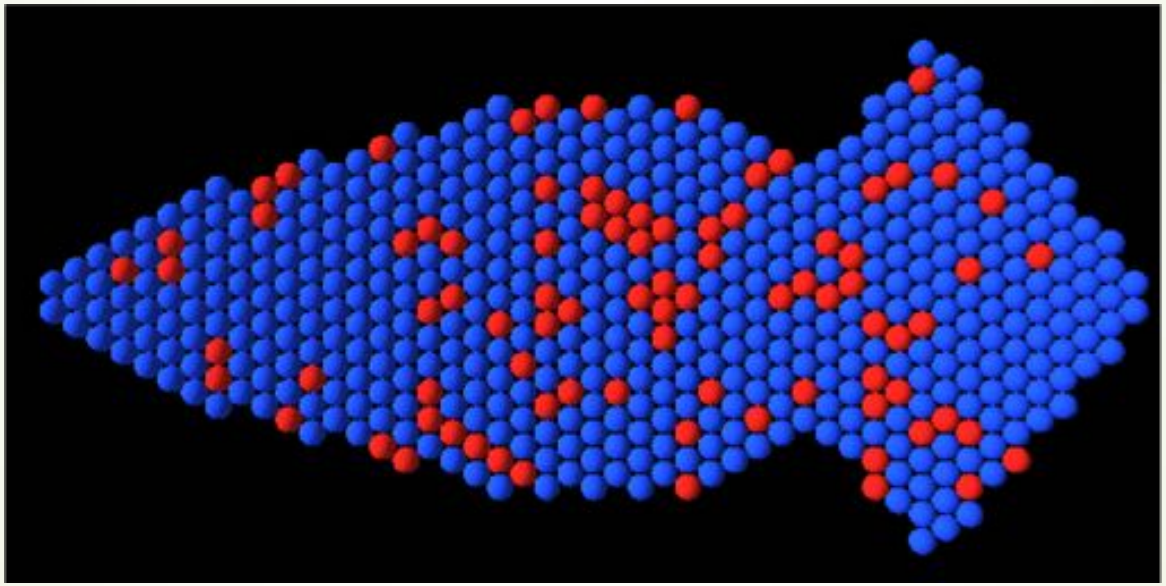
Proliferation



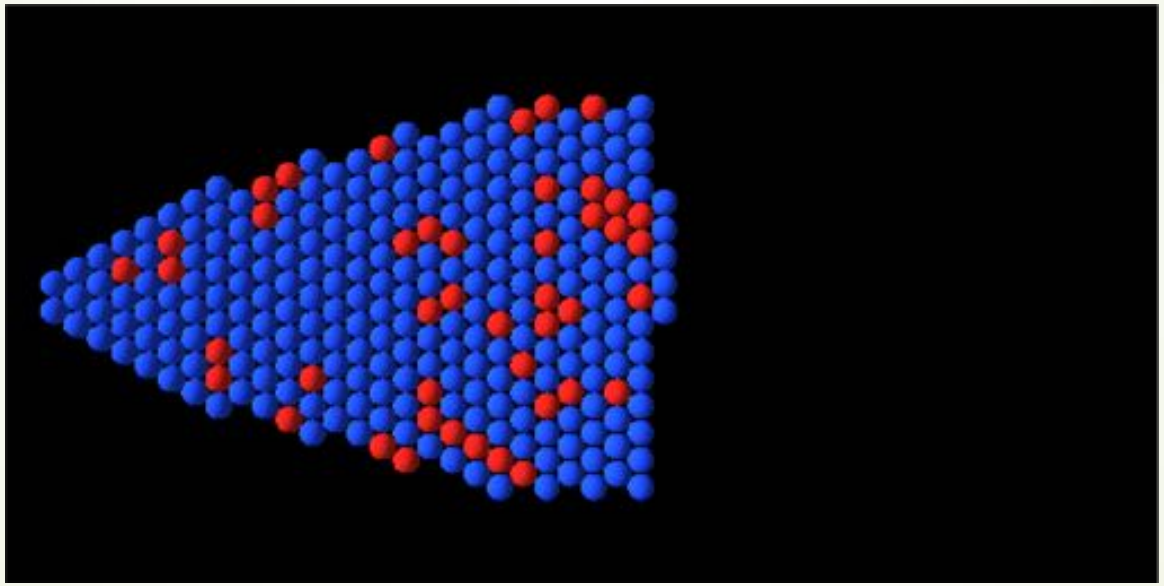
Proliferation



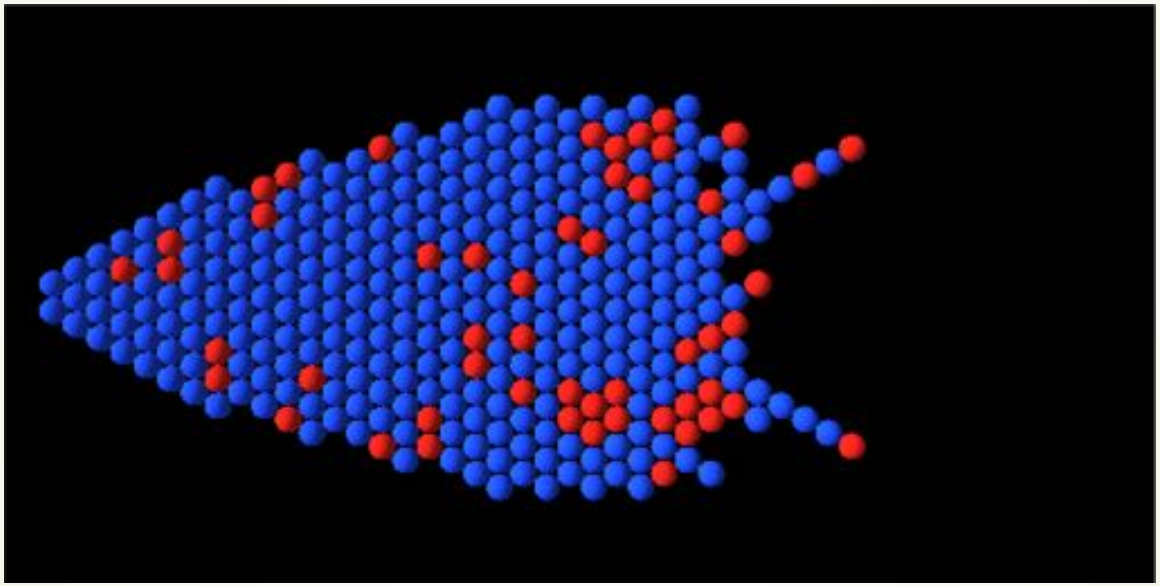
Simulated Morphology



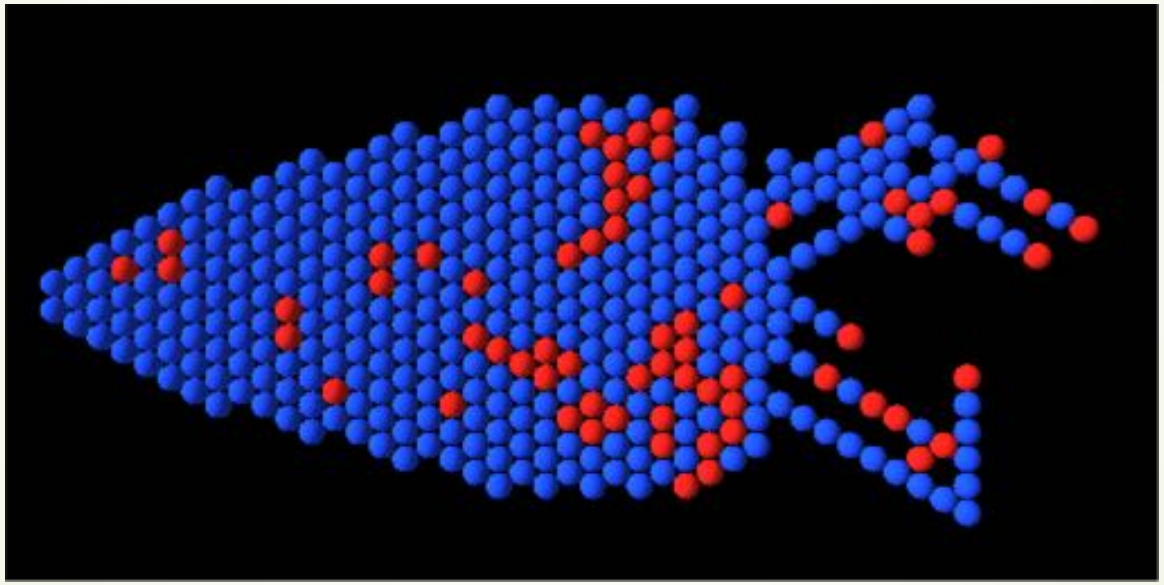
Worm cut – Cycle 50



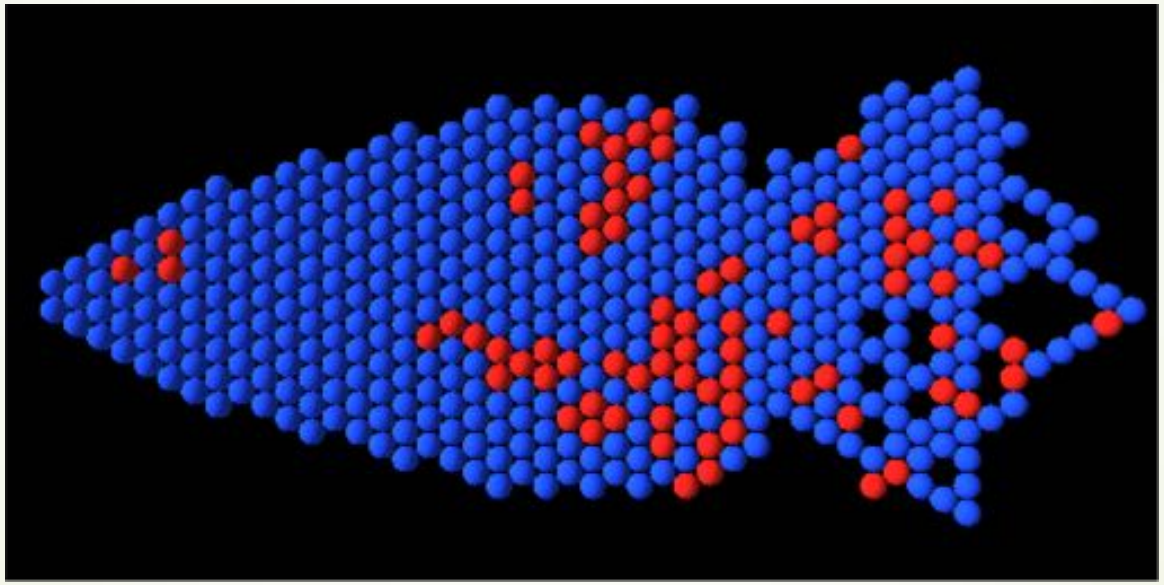
Cycle 60



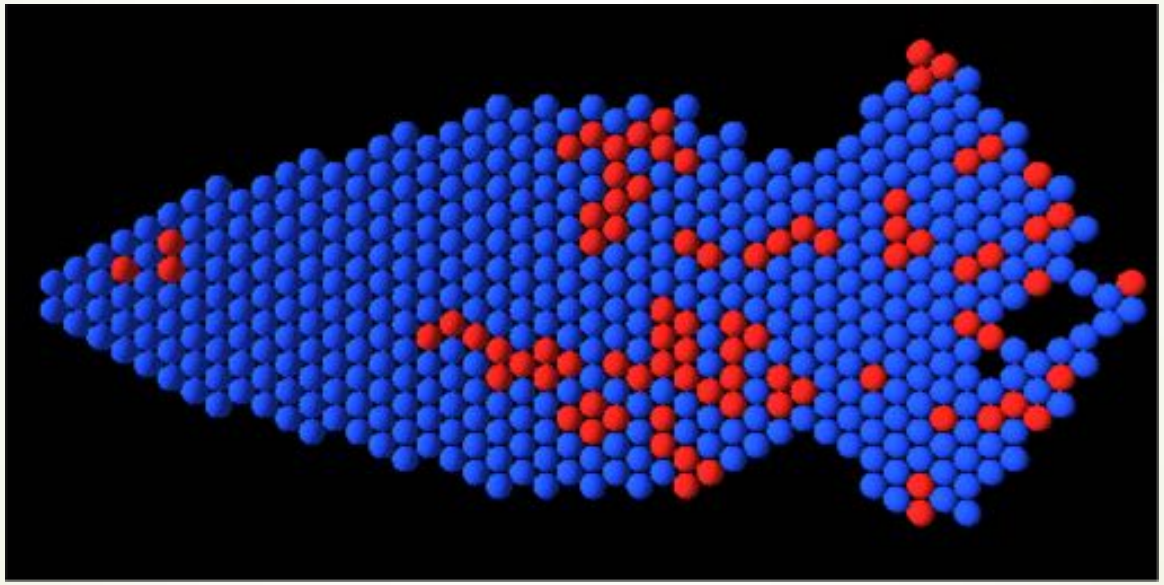
CYCLE 70



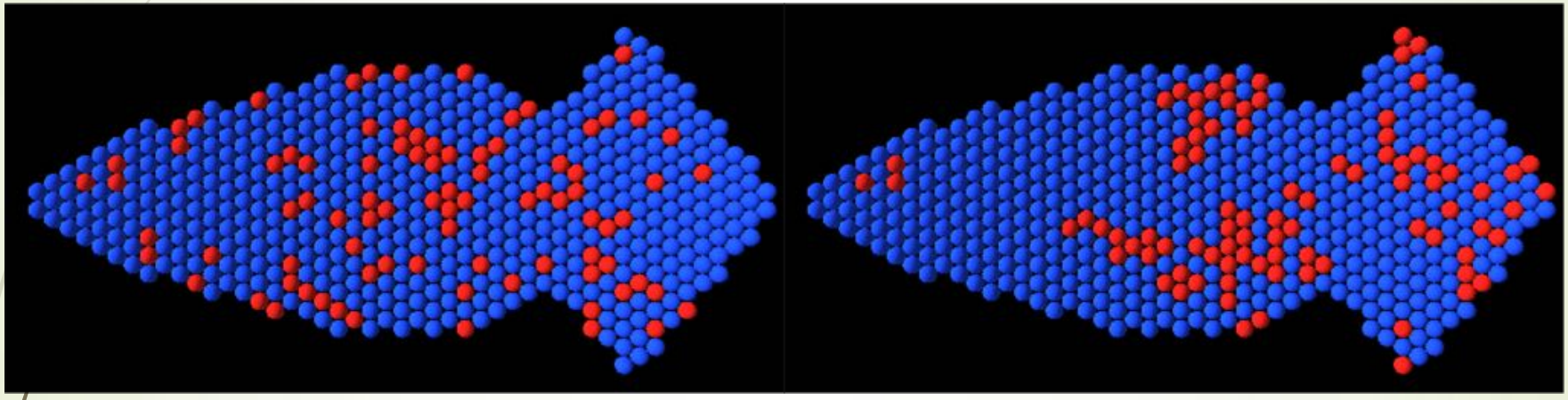
CYCLE 80



CYCLE 90



End of the Regeneration Process



Results – Full Regeneration

- The model completely regenerated the simulated worm in 19.56% (1565 out of 8000) of the parameter space

Epimorphosis vs Morphallaxis

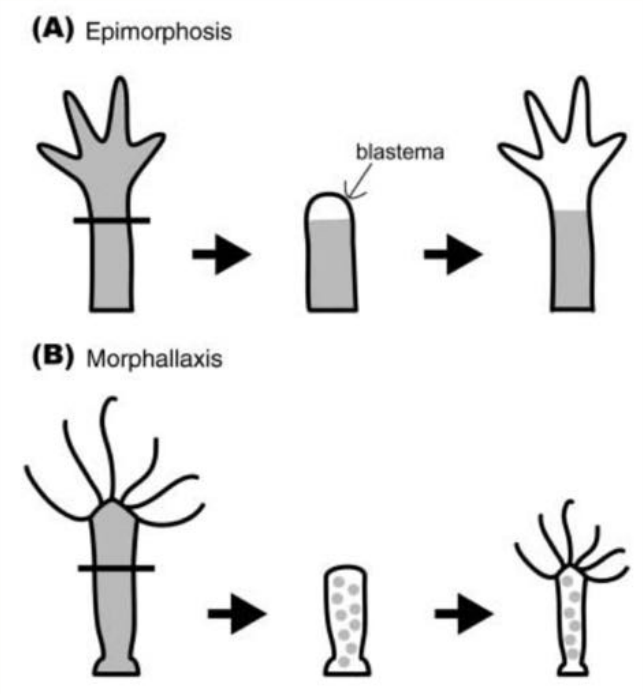


Image taken from: Agata, K., Saito, Y., & Nakajima, E. (2007). Unifying principles of regeneration I: Epimorphosis versus morphallaxis. *Development, growth & differentiation, 49* 2, 73-8.

Conclusion

- In this paper, we expanded the capabilities of our model in two ways:
  - Restricted cell division to adult stem cells (neoblasts);
  - Added stem cell migration as a possible cell behavior
- Large parameter sweeps of the model determined that even for small ratios of neoblasts (10% for instance) the model was able to fully regenerate the original morphology
- As next steps, we want to make the model account for morphallaxis and also to investigate the robustness of the model against mutations.

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