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Project #2: an expert system and cellular automata environment for testing and discovery of the mechanisms of tissue regeneration in flatworms

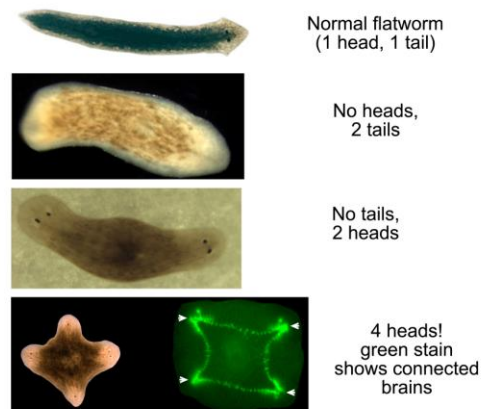
Currently, bioinformatics approaches focus almost entirely on gene sequences. The most exciting and necessary next step is to understand the 3-dimensional structure of complex organisms - applying computer informatics tools to the final shape, not just the underlying genetics, of complex biological structures. One of the most interesting aspects of the biological system is its ability to repair damage. Living organisms know what shape they need to be, detect damage, perform repairs, and stop when the target shape is complete. My lab seeks to understand the molecular mechanisms and information processing that is required for a pattern to be created, maintained, and restored. This work has applications not only for regenerative medicine (e.g., re-growing damaged limbs or eyes in a biomedical setting) and repair of birth defects, but also has implications for the design of robots that self-repair.

Flatworms known as "planaria" are a remarkable illustration of this mechanism. A worm (which has a central nervous system, a true brain, eyes, etc.) can be cut into 200 pieces, each of which will give rise to a tiny worm. Worms grow when you feed them, and shrink when you starve them, allometrically adjusting their proportions to cell number (re-specifying existing tissue). When you cut off their heads, they re-grow a new head. If cut in half, one end of the cut makes a head, and the other makes a tail, resulting in 2 normal worms - each and every time. Our lab has uncovered bioelectrical signals by means of which the correct head/tail identity of regenerating tissue is maintained. Please see attached figure as an example of what happens when we manipulate these signals - we can control the pattern and make worms with 0, 1, 2, 3, or even 4 heads!

What we propose for a software project is a system to formalize the rules of regeneration such that specific models for this control system can be discovered and tested. The project has the following components:

(1) There exists a mountain of data on what happens when you cut worms and treat the pieces in various ways; these experiments need to be formalized into an expert system so that a user can ask "what happens when I do this kind of cut/treatment" and if the answer is known, it will tell them. The expert system needs to be able to accommodate new results (add them to the database). We will provide the list of known data. This component will provide a much-needed repository of data on worm regeneration.

(2) A simple "language" needs to be implemented, whose primitives are basic types of cell behavior (divide, move, die, become a different type of cell, etc.) and basic signals that cells can send to each other. We will provide that list. A set of sentences in this language constitutes a model of cell behavior. An example: "if signal A is received, divide; if signal B is received from at least 2 neighboring cells, become a nerve cell". Each such set of rules can be implemented as a cellular automata system in 2D. This



component will provide a basic formalization of cell behavior during development and regeneration.

(3) A modeling system needs to be implemented to take a set of sentences like the above, and "run them" as a cellular automaton to see what kind of patterning system they describe. Such a patterning system may or may not turn out to match the rules in the known database (#1 above). If it does not match, then it's a bad model. If it matches some or all, then it's a good model to explain how it works. For example, if I come up with a list of 5 rules that every cell carries out, and the simulation is able to restore pattern when the organism it makes is cut in half, that's a great model of how the real thing might work. This component will provide a way for the user to see if his ideas of how individual cells behave actually adds up to a system that can repair damage (cells artificially removed).

(4) Ultimately, we will use genetic programming (simulated evolution of randomly-altered rule sets) to find rule sets that best explain the observed regeneration behavior of worm pieces. This will allow us to uncover new and powerful models of regeneration beyond what biologists can come up with by simple intuition.

This is a challenging and interesting project. I look forward to hearing from any students interested in biology, applications of artificial intelligence to bioinformatics, cellular automata, etc. Please contact me at michael.levin@tufts.edu and see my lab at <http://www.drmihaellevin.org>