Project Description: Chemical Echolocation  
Lyla Atta

Background:

Mechanisms of motility in prokaryotes and eukaryotes take different forms, but most are governed by the presence of various extracellular cues of interest to the cell. In eukaryotic cells that exhibit functional motility in response to the environment (e.g. macrophages), a gradient of an extracellular species of interest results in differential activation of GPCRs on either side of the cell. GPCR activation can result in either stabilization or destabilization of actin filaments. Increased stability of actin filaments at the leading edge of the cell causes protrusions in the direction of movement, while decreased stability of actin filaments at the trailing edge causes the other side of the cell to retract.

Proposed circuit:

The proposed circuit introduces genes for exogenous expression of an orthogonal GPCR and its corresponding extracellular peptide ligand. Upon binding of the ligand to the GPCR, the GPCR is activated and destabilizes actin filaments in its local environment. This system provides a mechanism for “chemical echolocation,” where the cell can sense and move in response to the location of objects in its environment.

If there is a boundary at one side of the cell, expression and secretion of the ligand will result in the buildup of its concentration on that side of the cell, while it diffuses freely on the other side. This concentration differential across the cell will result in differential activation of GPCRs between the two sides of the cell, with more GPCRs getting activated on the side near the boundary. Since activation of the GPCRs results in destabilization of actin filaments, this differential activation between the two sides of the cell will effectively turn the side near the boundary into a trailing edge (since it has a higher rate of actin degradation, actin filaments retract) and the other side into a leading edge, moving the cell away from the boundary.
Modeling:

The initial model of this system will be one-dimensional. The cell will be modeled as two actin filaments growing in opposite directions at a rate dependent on (A) the concentration of ligand at their outer end and (B) the binding constant of the receptor-ligand interaction. Receptor production/trafficking/degradation will be assumed to be at steady state and thus the number of receptors at the “cell surface” is constant. The concentration of g-actin (the monomer composing actin filaments) will be assumed to be finite and the rate of synthesis of g-actin will be assumed to be zero, such that, in response to no ligand, the filaments do not continue growing infinitely.

The ligand concentration distribution with and without a boundary will be simulated using a random walk approach. Once a molecule is secreted from the cell, it moves a distance X (determined by the diffusion rate) at every time step. It can move either to the left or to the right, with a 0.5 probability of either. If it is less than X away from a boundary, then the probability of it moving away becomes 1.

(*Shouldn’t the probability of moving in either direction be weighted by the concentration on either side?)

Parameter Sensitivity Analysis:

Since movement is entirely dependent on differential activation of the receptors on each side, any factor that affects the ability to establish this difference will affect the cell’s ability to move. For example, if the binding constant between the ligand and the receptor is too high, such that all the receptors are bound, activation will be the same on either side, resulting in no movement. Similarly, if the number of receptors expressed is too low, or if the amount of ligand secreted is too high, all the receptors on either side of the cell will be in complex resulting in no differential activation
and, again, no movement. The system’s sensitivity to such parameters, or ratios of parameters will be analyzed to determine which parameter relationships are most critical.

*Possible Applications of System:*

Being able to engineer cells to detect and respond to the location of objects around them can have applications that extend to bio-manufacturing, tissue culture and tissue engineering. One can imagine coupling obstacle detection to another response circuit, such as a degradation circuit. The system can also be engineered such that cells move towards boundaries, instead of away from them, in which case, cells can be programmed to aggregate to a scaffold. Additionally, systems of cell populations can be programmed to respond in different ways such that they arrange with each other in prearranged patterns.