

Computer Simulation of Motors and Microtubules in a Cell

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Introduction

Inside a cell, **motor proteins** (or simply **motors**), such as kinesins and dyneins, walk along structures called microtubules and transport cargo such as vesicles. **Microtubules** (or **MTs** for short), which are long, hollow, cylindrical structures, serve as a support for the shape of a cell and as roads for transportation inside the cell. They also make up strands of spindle fibre which pull chromosomes apart during mitosis. A microtubule is attached to a centrosome at its negative end, and its positive end grows or shrinks. It can switch between growing and shrinking states through events called catastrophe (transition from growth to shrinkage) and rescue (transition from shrinkage to growth).

This project was motivated by the biological finding that cell division requires delivery of substances that cause contraction at the cell equator, which may be related to significant concentration of motors in this region. The goal of this project was to investigate which parameter values would lead to such concentration of motors. I built an interactive Java simulation with graphical user interface simulating the system of motors and microtubules in a cell to explore the effects different parameter values have on their behaviour. The simulation can be found on <https://dl.dropbox.com/u/3479481/walkersontracks2012/index.html>.

Implementation

MICROTUBULES

Microtubules are implemented as line segments that can increase or decrease in length. When new microtubules are created, they spawn from one of two centrosomes. On the other hand, if a microtubule's length becomes 0, it disappears. A microtubule can be either growing or shrinking, and either bound (one or more motor is attached near the positive tip of the MT) or unbound. Switching between growing and shrinking states depends on rates $f_{c,u}$, $f_{c,b}$, $f_{r,u}$, and $f_{r,b}$ (see the Parameters section below for details). Also, the speed at which the MT tip grows or shrinks depends on the parameters v_g and v_s , respectively.

In real cells, microtubules have been observed to bend when they are near the centre of the cell between the two centrosomes, although the mechanism is unknown. There is an option in the simulation to make the microtubules bend. If the positive tip of a microtubule is within a certain distance (1/20 of the width of the cell) from the vertical centre line, it has some probability of bending, and as it nears the centre line, this probability increases. When it reaches the centre line, the microtubule bends.

MOTORS

Motors can either be free or attached to a microtubule. The rate of detachment, f_{detach} , is proportional to the number of attached motors. The rate of attachment of a free motor, f_{attach} , is proportional to the number of current microtubules, the number of free motors, and a spatially non-uniform motor density of the cell defined as a Gaussian function. This function reflects the activation of motors close to the cell centre resulting from some localized activation, and is given by the equation $M(x,y) = e^{-(x/\sigma_x)^2} * e^{-(y/\sigma_y)^2}$. It is assumed that this background motor density does not change over time, and as such, the function M is independent of time, allowing for the omission of a computation of actual diffusion.

Attached motors are implemented as dots that move along microtubules. There are two types of attached motors: kinesins, which walk towards the positive tip of the microtubule (away from centrosome) and dyneins, which walk towards the negative tip of the microtubule (towards centrosome). These types do not change, and when the motors reach either end of the microtubule, they stay there.

CELL AND CENTROSOMES

The cell cortex is drawn as an ellipse whose width and height are adjustable. There are two centrosomes in the cell, each of which is a circle with specific position (x and y components). The distance between the centres of the centrosomes is 3/10 of the width of the cell.

THE SIMULATION

The simulation is stochastic. In other words, even if two runs of the simulation are run with identical initial conditions and inputs from the user, the results would be different. This is due to some randomness in the system, such as those in the list below.

- The time when a new microtubule spawns is random, although the frequency is proportional to one of the parameters.
- When a microtubule is created, the centrosome that it should attach to gets decided randomly.
- When a microtubule spawns, it spawns at a random angle around its centrosome.
- In each time step, each microtubule has only a probability of switching between growing and shrinking states that is proportional to one of $f_{c,u}$, $f_{c,b}$, $f_{r,u}$, and $f_{r,b}$.

- The type of motor, and thus its direction of movement, is chosen randomly when it attaches to a microtubule.
- The number of motors that attach/detach is random, although proportional to f_{attach} and f_{detach} .
- Motors attach to random microtubules, although they are more likely to attach where the background motor density function is high.
- In each time step, the motors that detach from microtubules are chosen randomly.
- The velocity of a motor at a particular point in time during the simulation is the sum of two different velocities which get re-calculated each 'second' in the simulation as specified below.
 - Velocity of biased motion: The magnitude (in $\mu\text{m/s}$) is a random integer in the interval $[0, x]$ where x is an adjustable parameter, and the direction is the direction of motion of the motor on the microtubule (towards positive end for kinesin, towards negative end for dynein).
 - Velocity of random motion (in $\mu\text{m/s}$) is a random integer in the interval $[-y, y]$, where y is an adjustable parameter.

Parameters

In the simulation, lengths are measured in μm (microns), time in seconds, and velocities in $\mu\text{m/s}$. There are many parameters used in the simulation. Below is a list of those related to the microtubule dynamics (growing and shrinking of microtubules).

Parameter	Meaning	Units
$f_{c,u}$	Catastrophe rate of an unbound MT tip	/s
$f_{c,b}$	Catastrophe rate of a bound MT tip	/s
$f_{r,u}$	Rescue rate of an unbound MT tip	/s
$f_{r,b}$	Rescue rate of a bound MT tip	/s
v_g	Velocity of a growing MT tip	$\mu\text{m/s}$
v_s	Velocity of a shrinking MT tip	$\mu\text{m/s}$

Observations

When microtubules bend between the two centrosomes, motors accumulate at the cell equator under a few different combinations of parameter values for $f_{c,u}$, $f_{c,b}$, $f_{r,u}$, and $f_{r,b}$. When both catastrophe rate parameters are small and at least one of the rescue parameters is large, and when $f_{c,u}$ is small with $f_{c,b}$ and $f_{r,u}$ are large, many microtubules reach the cell cortex with their tips concentrated at the cell equator. For all other combinations of parameter values, microtubules have been found to be too short to reach the cell cortex, due to the large amount of shrinking compared to the amount of growth.

An interesting observation is that near the beginning of the simulation, as microtubules have been growing for only a short while, long MT tips are focused near the left and right ends of the cell. As

time progresses, however, the tips of microtubules also accumulate close to the cell equator and MT tips are focused near these 3 regions: left and right ends of the cell as well as the cell equator. Finally, over time, the accumulation of MT tips at the cell equator overtakes microtubules near the left and right ends, leading to a distinct peak of concentration of motors at the cell equator. This seems to be because when MTs reach the cell cortex, those that bend are longer and therefore take a longer time to reach the cell cortex.

On the other hand, if the microtubules do not bend, no combination of parameter values that lead to such accumulation of motors have been found. Future goals will be to explore which parameters can change this behavior and how.