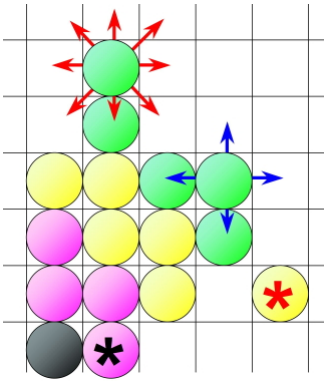
Computer Lab Session on Tumor Growth

Instructor: Kasia Rejniak, Moffitt

INTRODUCTION

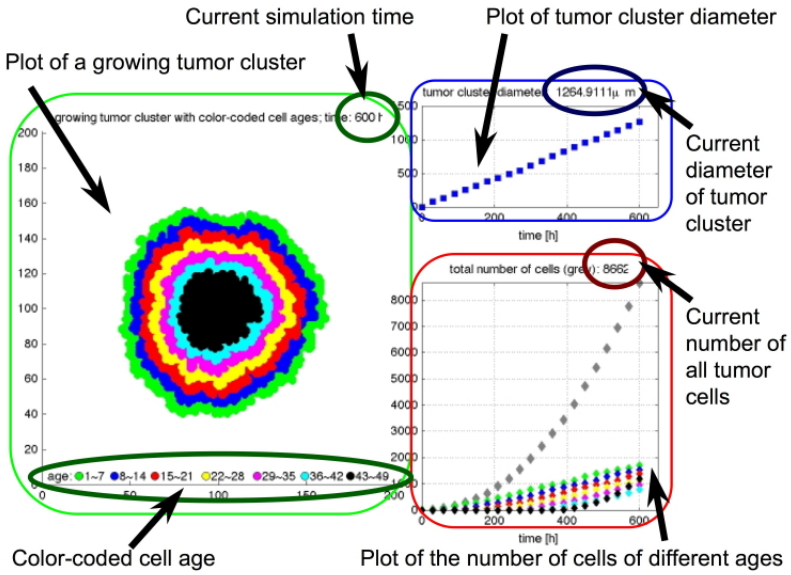
We will use an agent-based model defined on a regular square (in 2D) or cubic (in 3D) grid. Each grid site may be occupied by at most one cell (an agent) of individually specified properties that collectively will form a tumor cluster.



Tumor cell description:

- cell age will be color coded: (green, blue, red, yellow, magenta, cyan, black; with black being the oldest);
- cell can divide and produce a daughter cell if it reaches its doubling time (i.e., 6, 12, ..., 36 hours) and if there is free space around;
- a daughter cell can be placed in one of the 4 neighboring sites (blue arrows), if they are empty; if more than one site is empty the daughter cell location will be chosen at random;
- a cell can move along one of the 8 directions (red arrows) at the distance defined by cell "motility speed" (1, 2 or 3), if the indicated grid site is empty; if more than one site is empty the direction will be chosen at random;
- a cell can move towards higher concentration of nutrients (if present), i.e. it will be relocated to a neighboring grid site (red arrows) that is empty and contains the highest amount of nutrients;
- a cell can acquire one of the metabolic states: viable (alive, ready to proliferate or move; colored green), quiescent (not enough nutrients to grow, but can migrate; red), or necrotic (starving, not able to grow and move; black) depending on a level of nutrients in its environment;
- a cell may acquire a mutation (indicated by a star) and thus can gain some proliferative or migratory advantage over other cells.

A typical simulation screen will show a (2D or 3D) growing cluster of tumor cells that are color-coded either to show their age structure or to show their metabolic status, together with plots showing quantitative data, such as a tumor diameter or counts of cells of certain characteristics (age or metabolism).



EXERCISE 1: Tumor Growth

Different cell lines when grown in different conditions duplicate with different frequency. Here we examine how growth of the whole tumor cluster depends on individual cell doubling time.

call program `Ex1` from the Matlab command line, i.e. `>> Ex1`

1. Choose cell doubling time between 6 and 36 hours (time after which a mother cell will produce an offspring, if there is space around).
2. Observe the development of a whole tumor cluster; individual cells are color-coded depending on their age; the diameter of the whole tumor cluster and the number of cells are shown over the time of 600 hours.
3. Run program for each doubling time indicated below and note the final number of tumor cells and tumor diameter in each case (we will use this in the next exercise for comparison); note a layered age structure.

doubling time	6 hours	18 hours	30 hours
cell number			
cluster diameter in μm			

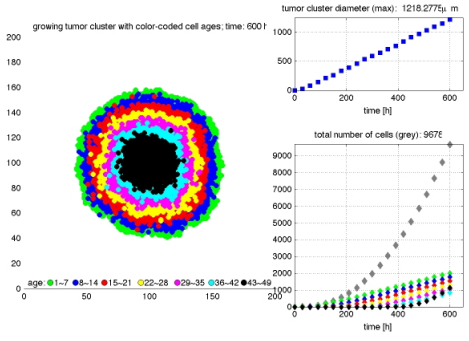
EXERCISE 2: Go or Grow

We assume here that each cell has a chance (with a probability that you define) to chose between moving away or growing, provided of course that the cell reaches a doubling time (defined by you), and there is space for the cells to either move or grow.

Which tumors will be larger (both in terms of the number of cells and the area they cover), those in which each cell can divide very often or those in which the cell will rather move away than divide? We can check this here.

call program `Ex2` from the Matlab command line, i.e. `>> Ex2`

1. Choose three following parameters:
   - cell doubling time between 6 and 36 hours;
   - cell speed mode: 1, 2 or 3, that corresponds to cell speed of 1.5, 3 and 4.5 microns per hour, respectively;
   - probability (between 0% and 100%) of cell choosing to "go" rather than to "grow".



You should see a figure similar to that in Ex1, however, note that cell of different ages do not form nice layers anymore (unless you've chosen probability=0, which means that cells are not motile as in Ex1).

EXERCISE 2 (cont.)

2. Run program for each doubling time, cell speed and "go" probability indicated below and compare the final numbers of tumor cells and tumor diameters with the results in Ex1.

cell number / tumor cluster diameter					
6 hours; speed 1; probability 50%		18 hours; speed 1; probability 50%		30 hours; speed 3; probability 50%	
6 hours; speed 1; probability 95%		18 hours; speed 3; probability 50%		30 hours; speed 3; probability 95%	

Note the difference in tumor size and cell number in each pair of simulations that differ in only one parameter (either doubling time, or cell speed, or "go probability).

Let us try to analyze how the size of the tumor cluster depends on cell doubling time and cell motility. Run all required simulation and record the total number of tumor cells at the end of each simulation (NOTE: use data from the previous table, if possible. The 6 hrs, speed 3, 50% "go" simulation may take a long time to run).

probability= 5%	6 hours	18 hours	30 hours
speed 1			
speed 2			

probability=50%	6 hours	18 hours	30 hours
speed 1			
speed 3			

probability=95%	6 hours	18 hours	30 hours
speed 1			
speed 3			

call program `ParamSpace` from the Matlab command line, i.e. `>> ParamSpace`.

This program will create a 3D model parameter space that shows classification of your results into 4 color-coded categories depending on tumor size. This method allows for a better visualization of multi-dimensional results.

EXERCISE 3: Cell Metabolism

Tumor cells are usually exposed to various environmental factors that may influence their life cycle and behavior. We consider here one such factor, let's say nutrients, that will be supplied at three locations (you may think about them as three veins bringing oxygen or glucose to the tissue). We assume that upon division the daughter cell will be placed randomly in a near-by grid site (as previously), but when the cell is moving its migration is directed toward grid sites with higher nutrient contents. For this exercise we fix cell doubling time to 18 hours, cell migration speed to $2(\times 1.5\mu m/h)$, and cell "go" probability to 90%.

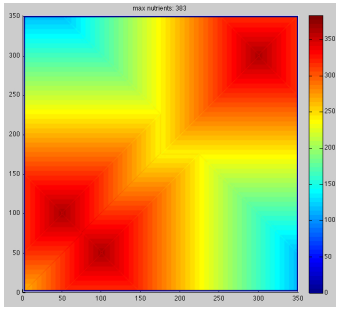
call program `Ex3` from the Matlab command line, i.e. `>> Ex3`

1. Choose three following parameters:

   - cell growth threshold (between 10 and 300); the cell will try to grow and divide only if the nutrient level at the cell location is larger than the chosen threshold;
   - cell death threshold (between 5 and 100); the cell become necrotic when the nutrient level at the cell location is lower that this threshold;
   - nutrient uptake threshold (between 5 and 50); each cell which is alive will consume this amount of nutrient during each simulation step.

   Note, that the cell is viable (colored green) if the nutrient level at its location is larger than the growth threshold; cell is quiescent (colored red), if the nutrient level is between the death and growth thresholds; and the cell is dying (necrotic, colored black) if the nutrient level is below the death threshold.

2. Choose three locations for the sources of nutrients. Use your mouse to choose these three points. The pattern shown on the right was created by choosing points: (50,100), (100,50) and (300,300). The chosen spots will have the highest concentrations of nutrients that will spread through the whole domain to form an irregular gradient.



3. The first tumor cell will be located in the middle of the domain. The shape, structure and locations of the emerging tumor cluster will depend on chosen parameters and nutrient gradient, and will be traced for 600 hours of simulated time.

4. Run 3-4 simulations with different combinations of metabolic properties but try to keep the same nutrient pattern (for example: (growth,death,uptake)=(100,40,30), (200,40,30), (200,60,30) for the pattern above).

5. Run a few simulations with the same combinations of metabolic parameters but change nutrient pattern.

NOTE: all final results of your simulations are saved on the hard drive as JPEG pictures (look for filenames like `Ex3_100g_50d_25u.jpg`})to compare results from different simulation runs.

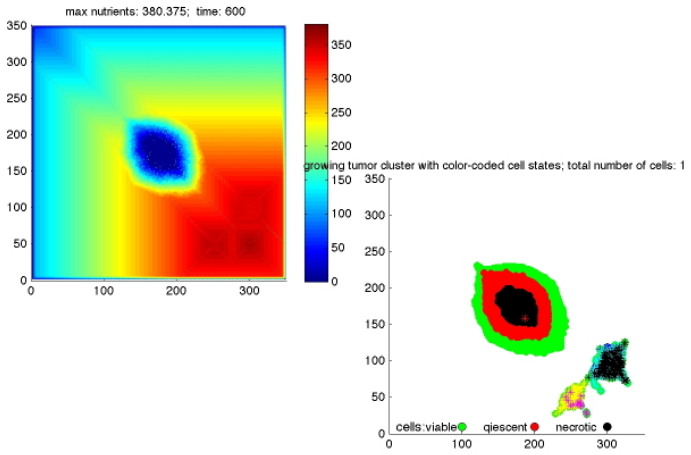
EXERCISE 4: Cell Mutations

Since tumor cells proliferate very often, they are prone to mutations. Here we examine the difference in evolution between the base tumor line and 6 clones of mutated cells with the properties that you define.

call program `Ex4` from the Matlab command line, i.e. `>> Ex4`

1. Define five properties of mutated clones. Make them different than the properties of the tumor base line, which are:
   - doubling time of 36 hours;
   - cell motility speed: 1;
   - cell "go" probability: 50;%
   - cell growth nutrient threshold: 150;
   - cell death nutrient threshold: 5.

2. The following set of parameters should produce pattern similar to that shown on the right (it will not be identical, since there is a strong randomness involved in cell doubling and motility).
   - doubling time of **6** hours;
   - cell motility speed: **3**;
   - cell "go" probability: **90%**;
   - cell growth nutrient threshold: **250**;
   - cell death nutrient threshold: **45**;



and place the three nutrient sources in one corner of the domain to see different behavior of the base tumor cell line and the 6 mutated clones.

3. Chose your own parameters.

EXERCISE 5: All-in-one

In this routine you can combine all features discussed previously and define all properties for a tumor cell base line and the mutants.

call program `Ex5` from the Matlab command line, i.e. `>> Ex5`

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EXERCISE 6: Three-dimensional Tumor Growth
The same algorithms can be applied in a three-dimensional case, however computations will take much longer.

call program `Ex6` from the Matlab command line, i.e. `>> Ex6`

1. Choose cell parameters as before;

2. This routine will:
– produce a 3D cluster of tumor cells,
– rotate it,
– draw seven horizontal z-sections through the cluster,
– draw the final tumor cluster with cell age structure represented by different colors,
– the quarter of the cluster will be cut off for illustration;

3. Two examples below were created for the following parameters:
– top: doubling time: **6** hrs; speed: **1**; "go" probability: **0%**,
– bottom: doubling time: **6** hrs; speed: **1**; "go" probability: **50%**.