# IMO 1 Exam 1

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October 14th, 2022

Tumor growth can be modeled using different techniques and different levels of detail. Continuous ordinary differential equations (ODE) may describe the change in tumor volume over time without the resolution of single cell dynamics. Agent-based models (ABM) can simulate the dynamics of individual cells based on internal decision points and extracellular conditions.

## 1 Question 1

Describe exponential tumor growth from 1 cell to a population of 10,000 cells with a growth rate equivalent to cells dividing once per day using an ODE. Develop a flow diagram that describes the above biological system. (30%)

### 1.1 Solution

Normal cells grow, divide, and die. In contrast, cancer cells avoid cell death and sustain proliferation. These two scenarios are depicted in figure 1, where $\alpha$ and $\beta$ are the growth rates (cell cycle speeds) of the normal and cancer cells, respectively; and $\delta$ is the normal cells' death rate.

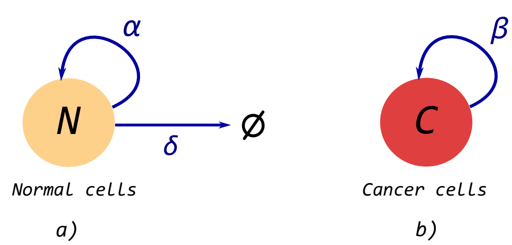


Figure 1: Flow diagram for a) normal cells with $\alpha$ as proliferation rate and $\delta$ as death rate, and b) cancer cells with proliferation rate of $\beta$. $N$ and $C$ represent the number of normal and cancer cells, respectively.

Figure 2 shows the schematic representation of the division of cancer cells from 1 to 8 cells, with a growth rate equivalent to cells dividing once per day; and considering symmetric division, where a parent cell divides to produce two identical daughter cells. If $t$ is in days, then the number of cancer cells -indicated by $C$- follows the exponential growth law $C(t) = 2^t$, since the number of cells doubles each time. Therefore, to obtain 10,000 cells the number of days that should pass must be $log_2(10,000) \approx 13.2877$ days.

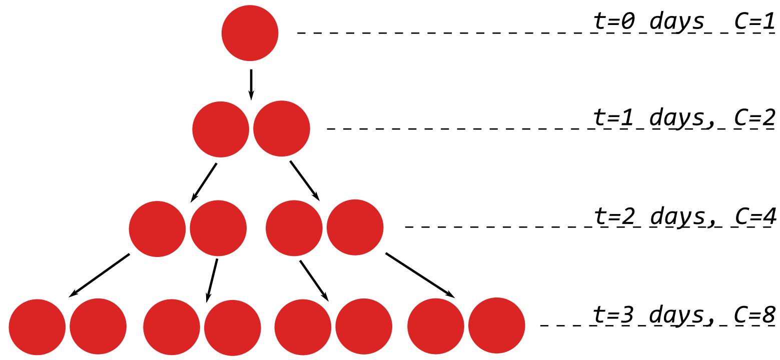


Figure 2: Cell growth graphical description. Cells are duplicated once per day.

# 2 Question 2

Translate the verbal description and flow diagram of the above biological system into a system of differential equations. Analyze and simulate. Denote variables with capital Roman letters and parameters with small Greek letters.(30%)

## 2.1 Solution

Since I defined symmetric cell division previously, with all daughter cells identical to their progenitor. The system of differential equations that describe this system is:

$$\frac{dC(t)}{dt} = \beta C(t) \tag{1}$$

with the initial condition:

$$C(0) = 1 \tag{2}$$

The analytical solution to equation 1 can be found by separation of variables, taking into account that $\beta$ is a constant. Then it follows:

$$C(t) = C(0)e^{\beta t} \tag{3}$$

Using the initial condition:

$$C(t) = e^{\beta t} \tag{4}$$

This result is an exponential growth in which the rate $\beta$ can be determined with knowledge of the time it takes for a cell to divide. In this case, cells divide once per day, which means $C(t = 1day) = 2$:

$$2 = e^{\beta(1)}$$

$$\beta = ln(2) \tag{5}$$

In general, $\beta$ corresponds to the cell cycle speed, $ln(2)/T$ where $T$ is the duration of the cell cycle.

$$C(t) = e^{ln(2)t} \tag{6}$$

Now, using the rules of logarithms, the equation 6 is equivalent as the first expression in the solution of Question 1. That is:

$$C(t) = 2^t$$

Figure 3 shows the numerical ODE solution. Fitting the data with an exponential function gives parameters near to the ones in equation 6. See section 4 for the implemented code.

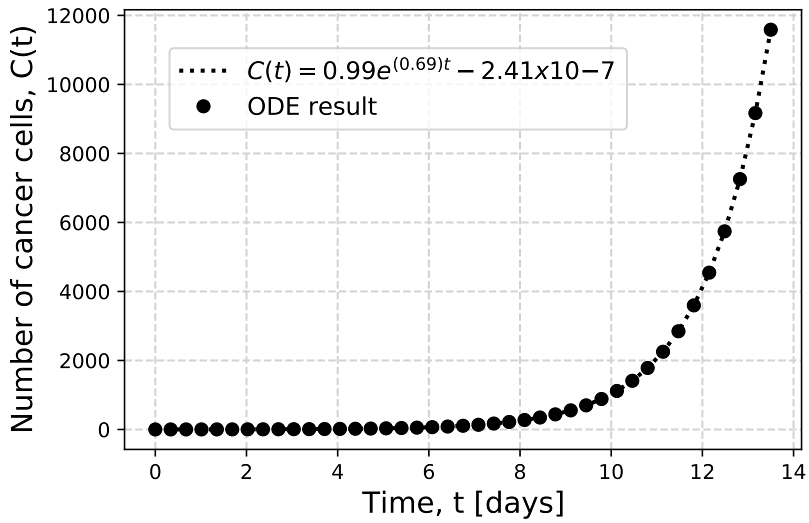


Figure 3: ODE solution for tumor growth. Black dots correspond to the solution data, and the dotted line corresponds to the exponential fit.

# 3 Question 3

Identify ABM rules (cell intrinsic and cell extrinsic) that yield tumor cell numbers over time that are analogous to the ODE solution. Implement and run ABM. (40%)

## 3.1 Solution

**ABM rules:**

- **Cell intrinsic:**
  1. All agents have the same cycle speed at every time (even after division). So, each time step (1 day, cell cycle speed) all agents try to divide, duplicate.
  2. No agents die.
- **Cell extrinsic:**
  1. If the number of neighbors is less than 8, the cell can divide. A new cell is placed on an unoccupied grid in the neighborhood.
  2. If the number of neighbors is equal to 8, the cell doesn't divide as if by contact inhibition.

To implement the ABM, I used the Moore neighborhood. Here, the neighbors of $ij$ ($i$=row,$j$=column) are:

- $(i-1, j)$ : Up.
- $(i+1, j)$ : Down.
- $(i, j+1)$ : Right.
- $(i, j-1)$ : Left.
- $(i-1, j+1)$ : Upper right (diagonal).
- $(i+1, j+1)$ : Lower right (diagonal).
- $(i-1, j-1)$ : Upper left (diagonal).
- $(i+1, j-1)$ : Lower left (diagonal).

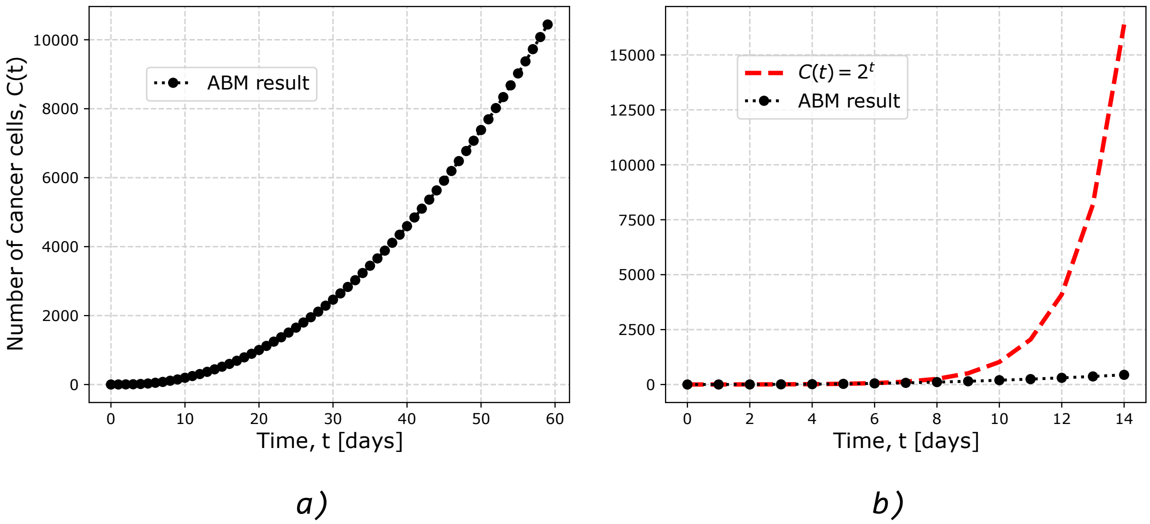


Figure 4: Tumor growth simulation. a) Solution of the ABM, b) comparison between the ODE analytic solution (red dashed line) and the ABM solution.

Figure 4 shows the solution of the ABM which uses the rules stated above. The time to obtain a number of cancer cells $\approx 10,000$ is between 58 and 59 days, which is significantly more than 100% of error compared to the analytical solution (see section 1.1 and red dashed line in panel b).

The same figure also shows, for the ABM solution, an initial exponential growth behavior for at least the first 8 days; then the behavior does not appear to be exponential. This is due to the fact that not all cells divide always. Cells can stop proliferating if the maximum number of neighbors (8 in this case) is achieved. This is contrary to the exponential growth described in section 2.1, where all cells divide always at the same time.

The code in section 4 includes more figures to visualize tumor growth from 1 cell to more than 10,000 cells.

# 4 Code

The code for questions 2 and 3 is attached together with this document. Or can be found at: `https://colab.research.google.com/drive/1MYidmiHYLN1Rs94yp3c5g3WWgp8LZFnM?usp=sharing`