Cancer evolution model based on Moran processes

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1 Introduction

Neoplasia is a phenomenon involving the excessive and abnormal growth of tissue. Neoplasm are usually classified as "benign", "potentially malignant", or "malignant" (cancer). A single tumor is presumed to be a clonal population of cells, deriving from a unique clone. However this population of cells is often heterogeneous, containing different types of cells. In this context, genetic and epigenetic differences may confer selective advantages to a given individual, enabling it to expand. The dynamics of the populations of mutant clones are tailored by **natural selection** and **drift**, and the fitness of a clone often depends on the interaction with other cells, and its environment. Generally, the dynamics of the **clonal selection** leads to phenomena such as invasion, metastasis and therapeutic resistance. The importance of the evolutionary dynamics of the neoplasm clones, has leaded recently to an increasing interest in research, as reported for instance in [2, 3, 1]. Most of the works in this field, used stochastic process to model the evolutionary dynamics of the clones population. For instance, in [4], the authors use Moran processes to model the evolution of cancer cells.

In this project, we will focus on the genetic instability phenomenon, and its impact on the emergence of resistance to treatments. We refer the reader to [2] (Figure 2a)[1], for a graphical representation (Muller plot) of the frequency of clones in the population, and further explanations.

2 Methodology

In this work, we use a Moran process based model, in order to study the impact of genetic instability in the development of cancer, and its impact on the emergence of resistance to treatments. The major points of the model are detailed hereafter:

[1] https://www.researchgate.net/profile/John_Pepper3/publication/6688835_Cancer_as_an_evolutionary_and_ecological_process/links/00b4952aafdf67a39d000000/Cancer-as-an-evolutionary-and-ecological-process.pdf

- Constant population of size $N = 1000$.
- Two major types of cells coexist: normal cells and cancer cells.
- Among cancer cells, different clones may coexist.
- Each cancer clone type is labeled as $c \in \{1, \ldots, C\}$, where C defines the number of clone types that appeared so far. Each clone type is characterized by its fitness f_c, its frequency n_c and its mutation rate μ_c.
- Normal cells have a fitness $f_n = 1$, a frequency $N - \sum_c n_c$, and a mutation rate $\mu_n = 0.001$.

The steps of the process are described hereafter:

- Select an individual with a probability proportional to the fitness f_i of its cell type i.
- With a probability μ the new individual gives birth to a new cancer clone $c' = C + 1$, with a fitness $f_{c'}$ and a mutation rate $\mu_{c'}$. In this case, the number of clone types is updated accordingly $C \leftarrow C + 1$.
- Otherwise, simply increment the frequency of the cell type of the individual that was selected.
- Choose a random individual and kill it.
- The cancer is detected as soon as $\sum_c n_c > \omega N$, with $\omega \in]0, 1]$.
- Then treatment against a chosen cancer clone c can be injected. This treatment reduced the fitness f_c, by multiplying it by α, during t generations, with $\alpha \in [0, 1]$.
- The experiments ends when $\sum_c n_c = 0$ (recovery) or $N - \sum_c n_c = 0$ (death) or $t = T_{death}$ (natural death reached).

For the sake of simplicity we consider that $\forall c$, $\mu_c = \mu$ and $f_c = f$. At the beginning of the simulation, only a small number of cancer cells of type $c = 1$ exist.

3 Questions

3.1 Individual based simulation

- Build a simulator for this model.
- Make a function that computes the diversity in the population, by means of the Shannon diversity index: $H = -\sum_{i=1} p_i \ln p_i$ where $p_i = \frac{n_i}{N}$.
- Set up an experimental protocol that could help you to grasp the impact of the genetic instability in the development of cancer, and the efficiency of the treatment, justify your choice of methodology.
- Execute your experiment(s).
- Analyze your results.

References

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