



## Cancer: Modeling evolution and natural selection, the „Mitosis Game“

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Submitted: 3. March 2016  
Published: 3. March 2016  
Volume: 3  
Issue: 1  
Keywords: cancer, cancer progression, evolution, population genetics, probabilistic graphical models, cancer genetics, microenvironment, cancer therapy, computational biology and bioinformatics, genetics, simulation, real time imaging, in silico  
DOI: 10.17160/josha.3.1.100

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## Cancer: Modeling evolution and natural selection, the „Mitosis Game“

Maximilian Georg, Roland Mertelsmann

### Background

We have previously analyzed and discussed the importance of cellular evolution for oncogenesis and the clinical course of malignant disease.

In view of the complexity of the genetic phenomena and the effects of environment and chance, we have designed a tool to both, better understand and to facilitate studying evolution in silico.

After review of the literature and of evolutionary algorithms (see Reading List in pdf document) we have developed a conceptual framework for describing, understanding and modeling evolutionary processes. As a result, we have identified ten key intrinsic parameters of cells, which we would like to call “The Hallmarks of Evolution”.

### The Hallmarks of Evolution: Ten key cellular parameters

**Reproduction:** Intrinsic ability of the cell to divide

**Regeneration:** Ability of the cell to recover from environmental damages

**Energy Store:** Ability to store energy

**Absorption:** Uptake of substrates to generate energy

**Agility:** Ability to move

**Interaction:** Ability to interact with other cells

**Attack:** Ability to destroy competing cells

**Defense:** Ability to resist attacks by competing cells

**Lifetime:** Survival probability (dependent on adaptation to environmental conditions)

**Receptor Sensitivity:** Ability of cells to recognize environmental signals (sensitivity subject to evolution, not shown in the descriptive texts in the game, but indicated by the spectral color violet)

In the Mitosis Model, each hallmark is assigned a specific spectral color. The resulting color of each cells is thus a combination of the expression as well as the extent of expression of each hallmark property. In addition, the expression of these properties by each cell can be expressed in arbitrary units (numbers).

In order to study evolutionary processes and to play the game, the investigator and player can set certain environmental parameters, to which cells have to adapt by evolution to achieve the ultimate goal, “survival of the fittest”.

### Six Key external (environmental) parameters

These parameters can be set and modified by the user. These parameters are used as paradigmatic examples of environmental factors.

**O<sub>2</sub>:** Optimal Oxygen concentration for cell survival

**pH:** Optimal Acid/base balance for cell survival

**Temperature:** Optimal temperature for cell survival

**Nutrition:** Local concentration of nutrition, that cells are able to use

**Mutation Rate:** Effects the evolutionary rate (symbolized as radiation dose by the radiation symbol), any other mutagen would have similar effects

**Cytokines:** („pheromones“) stimulating either proliferation or interaction, indicated by the symbol



In view of the infinite number of possible variations, in silico experiments might help to better understand the principles of evolution governing e.g. carcinogenesis and the clinical course of malignant disease. While in silico experiments allow nearly unlimited numbers of experiments, wet lab experiments would of course be required to validate any in silico results.

Its design as a game will hopefully make it attractive to a wide group of investigators and students in educational and academic settings.

## The Mitosis Game

The game about evolution and natural selection, Mitosis is your evolutionary sandbox. Mitosis brings machine learning into an exciting strategy game. The simulation is based on evolutionary algorithms which are normally used to solve complex problems. Due to our technology the evolution in mitosis is real evolution, no creationism or scripted process. Learn about basic principles that drive nature, experience the power of chance.

In Mitosis you can become a cell biologist and use different tools to grow a cell population and change its environment. Through modifications of the environment the conditions of survival change, the cells having to adapt to their new surroundings. Unlike similar games you cannot change the cell`s genome directly but only influence the chances of survival for cells carrying certain mutations. This is what evolution is about: Random mutation and natural selection, “survival of the fittest”.

Play through the campaign or set up your own experiments!

Check your skills and increase your understanding by playing the Mitosis game!

**If you like to see more or want to play the Mitosis game, check the following links:**

### Trailer

<https://www.youtube.com/watch?v=FB7y0pudL0I>

### Steam Greenlight

<http://steamcommunity.com/sharedfiles/filedetails/?id=632876718>

Discussion Forum for Computer Games including Mitosis (comments only available to registered Steam users)

### Download Game

<https://www.dropbox.com/s/wpjavooh9nv3ajl/Mitosis.zip?dl=0>

## Acknowledgements

We would like to express our thanks to the Mitosis Team:

Idea: Prof. Dr. Drs. h.c. Roland Mertelsmann, Dr. Sascha Lange

Development Team: Jona Boeddinghaus, David Canela, Rolf Cöster, Maximilian Georg, Jan-Hendrik Kegel, Dr. Sascha Lange, Alexander Mertelsmann, Prof. Dr. Drs. h.c. Roland Mertelsmann, Alexander Pierschel

(Pikomi), Adam is a Girl, Prof. Dr. Martin Riedmiller, Linus Schaub, Artur Susdorf, Radik Yusupov

## References and Reading List

### Cancer: A Story of Stem Cells and Evolution

Roland Mertelsmann

JOSHA Journal Volume 2, Issue 2 - 26. February 2015

DOI: 10.17160/josha.2.2.20

<http://josha-journal.org/en/categories/medicine/articles/cancer-a-story-of-stem-cells-and-evolution>

**Abstract:** Cancer is an acquired genetic disease of clonal origin. Carcinogenesis and its subsequent development follow the principles of evolution, starting with a single cell with stem cell properties and a proliferative advantage, leading to clonal expansion, clonal evolution and subsequent demise by killing the host: “Evolution gone awry”. Evolution can be divided into three essential steps: 1. “Chance” or random movement of molecules allows structures to interact. 2. Molecular affinity, “Necessity” (J. Monod, Chance and Necessity: Essay on the Natural Philosophy of Modern Biology, 1970), leads to a new structure providing novel properties and function. The 3rd step of the evolutionary processes, for which I would propose the term “Synclipse”, occurs, if the new constellation provides a biochemical and biological survival advantage, “survival of the fittest”, in a given environmental context.

### A spatial model predicts that dispersal and cell turnover limit intratumour heterogeneity

Bartłomiej Waclaw, Ivana Bozic, Meredith E. Pittman, Ralph H. Hruban, Bert Vogelstein and Martin A. Nowak

Nature 525, 261-264 (10 September 2015)

DOI: 10.1038/nature14971

<http://www.nature.com/nature/journal/v525/n7568/full/nature14971.html>

**Abstract:** Most cancers in humans are large, measuring centimetres in diameter, and composed of many billions of cells. An equivalent mass of normal cells would be highly heterogeneous as a result of the mutations that occur during each cell division. What is remarkable about cancers is that virtually every neoplastic cell within a large tumour often contains the same core set of genetic alterations, with heterogeneity confined to mutations that emerge late during tumour growth. How such alterations expand within the spatially constrained three-dimensional architecture of a tumour, and come to dominate a large, pre-existing lesion, has been unclear. Here we describe a model for tumour evolution that shows how short-range dispersal and cell turnover can account for rapid cell mixing inside the tumour. We show that even a small selective advantage of a single cell within a large tumour allows the descendants of that cell to replace the precursor mass in a clinically relevant time frame. We also demonstrate that the same mechanisms can be responsible for the rapid onset of resistance to chemotherapy. Our model not only provides insights into spatial and temporal aspects of tumour growth, but also suggests that targeting short-range cellular migratory activity could have marked effects on tumour growth rates.

## Cancer evolution: mathematical models and computational inference.

Beerenwinkel N, Schwarz RE, Gerstung M, Markowitz F

Syst Biol. 2015 Jan;64(1):e1-25.

DOI: 10.1093/sysbio/syu081. Epub 2014 Oct 7

<http://www.ncbi.nlm.nih.gov/pubmed/25293804>

**Abstract:** Cancer is a somatic evolutionary process characterized by the accumulation of mutations, which contribute to tumor growth, clinical progression, immune escape, and drug resistance development. Evolutionary theory can be used to analyze the dynamics of tumor cell populations and to make inference about the evolutionary history of a tumor from molecular data. We review recent approaches to modeling the evolution of cancer, including population dynamics models of tumor initiation and progression, phylogenetic methods to model the evolutionary relationship between tumor subclones, and probabilistic graphical models to describe dependencies among mutations. Evolutionary modeling helps to understand how tumors arise and will also play an increasingly important prognostic role in predicting disease progression and the outcome of medical interventions, such as targeted therapy.

## The mathematics of cancer: integrating quantitative models

Philipp M. Altrock, Lin L. Liu and Franziska Michor

Nature Reviews Cancer 15,730-745 (2015)

DOI: 10.1038/nrc4029

<http://www.nature.com/nrc/journal/v15/n12/full/nrc4029.html>

**Abstract:** Mathematical modelling approaches have become increasingly abundant in cancer research. The complexity of cancer is well suited to quantitative approaches as it provides challenges and opportunities for new developments. In turn, mathematical modelling contributes to cancer research by helping to elucidate mechanisms and by providing quantitative predictions that can be validated. The recent expansion of quantitative models addresses many questions regarding tumour initiation, progression and metastases as well as intra-tumour heterogeneity, treatment responses and resistance. Mathematical models can complement experimental and clinical studies, but also challenge current paradigms, redefine our understanding of mechanisms driving tumorigenesis and shape future research in cancer biology.

## Identification of neutral tumor evolution across cancer types

MJ Williams, B Werner, CP Barnes, TA Graham?

Nature Genetics 48, 238-244 (2016)

doi:10.1038/ng.3489

<http://www.nature.com/ng/journal/v48/n3/full/ng.3489.html>

**Abstract:** Despite extraordinary efforts to profile cancer genomes, interpreting the vast amount of genomic data in the light of cancer evolution remains challenging. Here we demonstrate that neutral tumor evolution results in a power-law distribution of the mutant allele frequencies reported by next-generation sequencing of tumor bulk samples. We find that the neutral power law fits with high precision 323 of 904 cancers from 14 types and from different cohorts. In malignancies identified as evolving neutrally, all clonal selection seemingly occurred before the onset of cancer growth and not in later-arising subclones, resulting in numerous passenger mutations that are responsible for intratumoral heterogeneity. Reanalyzing cancer sequencing data within the neutral framework allowed the measurement, in each patient, of both the *in vivo* mutation rate and the order and timing of mutations. This result provides a new way to interpret existing cancer genomic data and to discriminate between functional and non-functional intratumoral heterogeneity.

### Online Evolution for Multi-Action Adversarial Games

N Justesen, T Mahlmann, J Togelius

Evostar 2016 In: Applications of Evolutionary Computation 2016

<https://lup.lub.lu.se/search/publication/8569733>

**Abstract:** We present Online Evolution, a novel method for playing turn-based multi-action adversarial games. Such games, which include most strategy games, have extremely high branching factors due to each turn having multiple actions. In Online Evolution, an evolutionary algorithm is used to evolve the combination of atomic actions that make up a single move, with a state evaluation function used for fitness. We implement Online Evolution for the turn-based multi-action game Hero Academy and compare it with a standard Monte Carlo Tree Search implementation as well as two types of greedy algorithms. Online Evolution is shown to outperform these methods by a large margin. This shows that evolutionary planning on the level of a single move can be very effective for this sort of problems.

### Not Just a Theory—The Utility of Mathematical Models in Evolutionary Biology

Maria R. Servedio, Yaniv Brandvain, Sumit Dhole, Courtney L. Fitzpatrick, Emma E. Goldberg, Caitlin A. Stern, Jeremy Van Cleve, et al.

PLoS Biology Published: December 9, 2014

DOI: 10.1371/journal.pbio.1002017

<http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1002017>

**Summary:** Progress in science often begins with verbal hypotheses meant to explain why certain biological phenomena exist. An important purpose of mathematical models in evolutionary research, as in many other fields, is to act as “proof-of-concept” tests of the logic in verbal explanations, paralleling the way in which empirical data are used to test hypotheses. Because not all subfields of biology use mathematics for this purpose, misunderstandings of the function of

proof-of-concept modeling are common. In the hope of facilitating communication, we discuss the role of proof-of-concept modeling in evolutionary biology.

### In silico experimental evolution: a tool to test evolutionary scenarios

B erence Batut, David P Parsons, Stephan Fischer, Guillaume Beslon and Carole Knibbe

BMC Bioinformatics 2013, 14 (Suppl 15):S11

DOI: 10.1186/1471-2105-14-S15-S11

<http://bmcbioinformatics.biomedcentral.com/articles/10.1186/1471-2105-14-S15-S11>

#### Abstract

Comparative genomics has revealed that some species have exceptional genomes, compared to their closest relatives. For instance, some species have undergone a strong reduction of their genome with a drastic reduction of their genic repertoire. Deciphering the causes of these atypical trajectories can be very difficult because of the many phenomena that are intertwined during their evolution (e.g. changes of population size, environment structure and dynamics, selection strength, mutation rates...). Here we propose a methodology based on synthetic experiments to test the individual effect of these phenomena on a population of simulated organisms. We developed an evolutionary model - aevol - in which evolutionary conditions can be changed one at a time to test their effects on genome size and organization (e.g. coding ratio). To illustrate the proposed approach, we used aevol to test the effects of a strong reduction in the selection strength on a population of (simulated) bacteria. Our results show that this reduction of selection strength leads to a genome reduction of ~35% with a slight loss of coding sequences (~15% of the genes are lost - mainly those for which the contribution to fitness is the lowest). More surprisingly, under a low selection strength, genomes undergo a strong reduction of the noncoding compartment (~55% of the noncoding sequences being lost). These results are consistent with what is observed in reduced *Prochlorococcus* strains (marine cyanobacteria) when compared to close relatives.

### Introduction to evolutionary computing

A.E. Eiben, J.E. Smith

Springer Berlin Heidelberg New York 2007, 300 pages