Modelling the Role of Aneuploidy in Tumour Evolution

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Abstract

The role of aneuploidy (the cellular state of having an abnormal number of chromosomes) in cancer is not well understood. A recent theory suggests that aneuploidy may be an initial step towards the generation of variation in cancer. This theory however is very difficult to test in biological experiments. To address this theory and explore the role that aneuploidy has on the development of cancer, a computational model of cancer evolution has been developed. Results show that, depending on the arrangement of tumour suppressors, proto-oncogenes and regulators of chromosome segregation in the genome, aneuploidy induces distinct pathways for the generation of novel genotypes leading to emergent cancer-like behaviour.

1 Introduction

Cancer is a disease through which a group of cells proliferate beyond the normal limits of division, destroying adjacent tissue and sometimes spreading to other locations in the body. Tumours evolve in the body behaving almost like infecting pathogens with the cells undergoing a sequence of genetic mutations until they are able to proliferate almost without limit. Cancer affects people of all ages and ethnicities, with risk increasing with age. Cancer is one of the leading causes of death worldwide, with cancer deaths projected to continue rising (Parkin et al. 2005). To tackle this disease, efforts are being made to generate knowledge about the causes of cancer and the management of the disease. Cancer research, a field ranging from molecular bioscience to clinical trials, seeks to increase our understanding of the fundamental principles of cancer. Through this kind of research, we have been able to identify many of the key factors that influence cancer and the development of treatments and prevention strategies. Because of the complexity of cancer development, which involves the evolution of somatic clones with increasingly aggressive behaviour that eventually undergo metastasis, computational modelling has become a very valuable tool for refuting or supporting theories that explain the underlying individual cell behaviour in tumours (Nagl et al. 2007).

In the field of Artificial Life, efforts are being made to simulate and understand the properties of cancer systems. These contributions are an important part in the development of a more general theory of cancer (Abbott et al. 2006). They have inspired new ways of thinking and revolutionized the way we explore, describe and explain complex biological phenomena. One such phenomenon, aneuploidy, has recently gained much interest in the cancer community.

In the absence of sexual recombination, the path to cellular evolution is through mutation, the generation of chromosome aberrations and aneuploidy– the cellular state of having an abnormal number of chromosomes. Evolutionary pressure selects for genetic changes that enable cells to avoid death and over proliferate. This can be achieved by the overexpression of growth signals, adaptation to hypoxia and evasion of reproductive limits amongst others (Gibbs 2003). Unfortunately it is extremely difficult to devise biological experiments to isolate the effects of aneuploidy in cancer (Weaver and Cleveland 2007). Because of the extreme difficulties encountered when trying to devise this kind of biological experiment, in this work we propose a computational model to address some of the fundamental questions of tumour formation and help further guide experiment and theory.

The aim of this work is investigate the role of aneuploidy and its effect on the dynamics in cancer. By making abstractions of current biological knowledge, data and theories that describe the behaviour of cancer, a computational model that addresses this theory is presented. The model explores the role

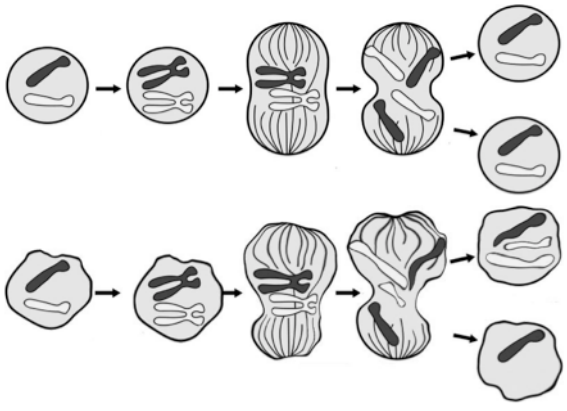

Figure 1- Schematic of normal cell division (top) and the missegregation of chromosomes during mitosis (bottom).

that aneuploidy plays as a main driver for the origin and the subsequent stages of cancer. It is an individual-based evolutionary model, similar to models used in ALife work for other population-based simulation studies (Gras et al. 2009).

In the next section, the essential theories of the origins of cancer are summarised. Section 3 presents the details of the computational model. Section 4 continues with a discussion of the different simulations carried out. Conclusions and future work are provided in the final section.

2 Background

What we currently consider to be cancer includes, in reality, a very broad spectrum of diseases known as malignant neoplasms. Biological systems are complex, and cancer in particular may be best described as an emergent behaviour of a complex system (Nagl et al. 2007). Because it is very difficult to understand a complex system by examining only its components, the exact mechanisms by which cancer can arise are a matter of heated debate (Basanta and Deutsch 2008).

There are two predominant theories regarding the origins of cancer. The first theory suggests that DNA damage over decades leads to many thousands of random mutations in the cell's genome that confers on the cell new proliferative capabilities (Chin et al. 2006). Chemical carcinogens such as ionizing radiation (x-rays, etc) may cause chromosomal breaks and translocations that contribute to cancer development. This kind of damage is largely stochastic and raises the question of how can such a comprehensive genome reprogramming be carried out so consistently for the development of a cancer genotype by means of random mutations.

The second theory suggests that damage to a few "cancer genes", such as those depicted in Table 1, would activate pathways that would lead to tumourigenesis by means of accumulative changes (Hanahan and Weinberg 2000). This theory suggests that the accumulation of very particular alterations (also known as "gate-keeper" mutations) in proto-oncogenes (genes that contribute to cancer because of their increased expression) and tumour suppressor genes (genes that contribute to cancer when its function is reduced) could be a main driver for many cancers (Gatenby et al. 2007). This theory does not directly address the underlying evolutionary and selective forces that play an important role in cancer development, nor the interaction with a particular microenvironment in which phenotype selection takes place.

A third theory, proposes that an abnormal number of chromosomes, or aneuploidy (described in Figure 1), in a cell may be a first step towards generating malignant genotypes (Gibbs 2003). This theory (as first proposed by Boveri in 1914) has recently gained support due to many recent articles that describe the presence of aneuploidy and chromosomal instability in many types of cancers (Rajagopalan and Lengauer 2004). More significantly, mutations leading to chromosome instability lead to a genetic predisposition to cancer (Hanks et al. 2004). The high number of different cellular states that are considered as aneuploid and the different behaviours and interactions that these cells may exhibit make it difficult to trace an evolutionary pathway through this complex system. Because of a lack of a clear pathway, the contribution of aneuploidy as a cause or a consequence of malignant transformation, remains unknown (Holland and Cleveland 2009).

3 The Model

In order to investigate the theory of aneuploidy as a driver for the development of malignant cancer, a model was created. The computational model consists of individual agents that are abstractions of individual cells, incorporating a set of biologically-inspired features dealing with cell division and more specifically chromosome segregation.

The model abstracts biological behaviour at the genetic level, and studies the behaviour at a tissue level that emerges through the interaction of the individual cells under diverse conditions. In the model, abstractions of genes known to play a relevant role in tissue homeostasis are considered. This kind of model could not only provide us with an insight as to the origins and the evolution of cancer, but also with a new tool for developing new cancer therapies.

Gene	Role in Cancer	Biological Function
BUB1	**Aneuploidy**	Chromosome segregation
MYC	**Proto-oncogene**	Promotes growth
PTEN	**Tumour suppressor**	Inhibits growth
RAS	**Proto-oncogene**	Promotes growth, cell cycle progression
RB1	**Tumour suppressor**	Inhibits cell cycle progression
P53	**Tumour suppressor**	Promotes cell death
NF2	**Tumour suppressor**	Regulates contact inhibition

Table 1- Known human cancer genes considered. The function of the genes as given is a broad summary and approximation of their true behaviour, which is still the subject of research.

3.1 Biological Abstractions

In order to develop a computational model to study the biological phenomenon of aneuploidy, it was decided to investigate the behaviour of a few known cancer genes (Futreal et al. 2004), as seen in Table 1. Although alterations in these cancer genes may account for specific cellular misbehaviours, the genetic evolutionary pathway that cells follow when they become cancerous remains unknown. To address this question, behaviour was abstracted from genes that regulate cell death, proliferation, and fidelity during chromosome segregation.

The core of the model is an abstraction of individual cells and their genomes. Each simulated genome is composed of 3 types of genes in diploid chromosomes (pairs of chromosomes, the chromosomes of each pair having identical genes) as the normal state within cells, as seen in Figure 2. The collection of individual cells comprises a simulated tissue, whose population size is determined for each

experiment through an *allocated space* parameter, whose dynamics are determined by the gene expression of the individual cells across time. Although the effects of differences in chromosome number on gene expression patterns in biological systems are only beginning to be assessed (Huettel et al. 2008), the model assumes the up and down regulation of behaviour to be proportional to the number of copies of genes available. Each of the three genes code for corresponding actions at a cellular level, inspired by biological systems. The genes present and their functions, described below, are:

- *Tumour Suppressors- Apoptosis Regulatory Genes (A)*
- *Proto-oncogenes- Cell Division Regulatory Genes (D)*
- *Aneuploidy- Chromosome Segregation Regulatory Genes (S)*

Apoptosis regulatory genes are an abstraction of tumour suppressor genes that regulate cell death by mechanisms such as contact inhibition. Contact inhibition is the natural process by which, when two or more cells come into contact with each other, there is an arrest of the cell growth and division, which is used by the system to maintain homeostasis. (Zeng and Hong 2008). The abstracted genes are used to compare a measurement of the overall number of cells and, if this number exceeds the *carrying capacity* of the tissue (predefined by the initial conditions of the simulation), it stops proliferation and raises the probability of cell death. Malignant cells usually have lost this important homeostatic property (Carmona-Fontaine et al. 2008). Although based on global cell counts, this model is not spatially explicit, but rather of the "well-stirred" kind, akin to the more abstract theoretical models used to describe artificial chemistries (Dittrich et al. 2001).

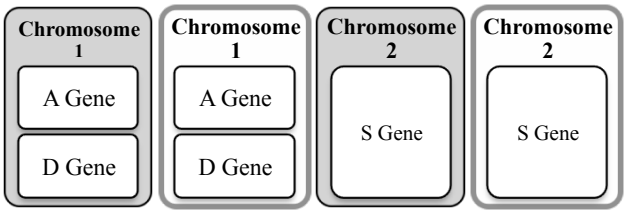

Figure 2- Abstracted Genes in Diploid Chromosomes for Gene Configuration A.

To balance cellular death and maintain homeostasis, *cell division regulatory genes* provide an abstraction of proto-oncogenes that promote growth and progression through the cell cycle. *Apoptosis regulatory genes* and *cell division regulatory genes* together maintain a constant population of cells close to the carrying capacity of the simulated tissue (homeostasis).

The inclusion of the concept of aneuploidy generates variation amongst the cell population (no other form of mutation is modelled in the system). Inspired by genes that limit chromosome missegregation events, *chromosome segregation regulatory genes,* when up regulated, help maintain homeostatic conditions for a prolonged period of time. The role that the up or down regulation of these kinds of genes has in cancer progression is currently unknown (Rajagopalan and Lengauer 2004).

The model contains a population of individual cells, where each cell is initialized with 2 copies of each gene, within diploid chromosomes, as shown in Figure 2. When dividing, the genome of each cell is duplicated and one set of genes then segregated into a daughter cell. It is during this stage that chromosome missegregation events can occur. The behaviour generated by the gene expression is dependent on the number of copies of a given gene within the genome of each individual cell. The algorithm is described in the following section.

3.2 The Algorithm

Inspired by the processes in biological cellular behaviour through which homeostasis is maintained in organisms, the algorithm is as follows:

1. An initial population of 100 cells is created, each with diploid chromosomes, each chromosome with 1 copy of each type of gene (Figure 2). The normal carrying capacity of the tissue is fixed at 200 cells.
2. For each time step, the total number of cells is measured and is not updated until the next time step.
3. For each cell during each time step, if the cell has less than 2 chromosomes in its entire genome, the cell dies.
4. If the cell has not died and if the measurement of the number of cells is greater than the predefined tissue's *carrying capacity*, then the probability of cell death is calculated. The probability of death is dependent on the number of available copies of the *apoptosis regulatory genes*, N_A, within each cell's genome. The probability of apoptosis, P_A, is determined by:
$$P_A = N_A / r_A$$
Where r_A is a parameter for the rate of apoptosis. The cell is then killed with a probability of P_A.
5. If the cell has not died, it has a chance to divide. The probability of division depends on the number of available copies of the *division regulatory genes*, N_D, and a parameter that determines the rate of division, r_D. The probability that a cell divides, P_D, is:
$$P_D = N_D / r_D$$
6. If dividing, the probability of chromosome missegregation is calculated. The probability of chromosome missegregation, P_S, in the model is:
$$P_S = r_S / (N_S + 1)$$
Where N_S is the number copies of the *chromosome segregation regulatory genes* within the cell's genome, and r_S is a parameter for the rate of chromosome missegregation.

If there is no chromosome missegregation, the genome is duplicated and copied with fidelity, thus generating two identical daughter cells. Otherwise, one chromosome chosen at random is misseggregated during cell division. As the mother cell divides into two daughter cells, this results in two daughter cells with a different number of chromosomes, as seen in Figure 1.

4 Experiments

To investigate the properties and the dynamics of the system, and specifically the role that chromosome segregation regulatory genes have, three genome configurations were considered. The parameter settings were determined through a series of preliminary experiments, in order to ensure that the behaviour of the system was both biologically plausible and computationally feasible. Simulations were carried out with the following initial parameters:

- Initial population: 100 cells
- Carrying capacity of the tissue: 200 cells
- Number of time steps: 100
- $r_A = 10$, $r_D = 10$, $r_S = 0.03$

For the analysis of the simulations, the emergent genotypes were assessed. By quantifying the number of chromosomes that a cell has at a given time, a genotype state G_T is defined as:

$$G_T=(N_A, N_D, N_S)$$

Where N_A, N_D *and* N_S are the number of copies of *Apoptosis Regulatory Genes, Cell Division Regulatory Genes* and *Chromosome Segregation Regulatory Genes* respectively. The initial genotype consists of two functional copies of each chromosome: genotype state (2, 2, 2).

Three different gene configurations (Figure 2, 5 and 7), 20 simulations were investigated for each experiment. As will be shown, although the systems tended to converge on similar results, the evolutionary trajectories were usually different. For this reason a representative simulation for each configuration is given in the results sections rather than an average. Future work will investigate an appropriate statistical analysis of the distribution of evolutionary pathways across simulations.

4.1 Gene Configuration A

4.1.1.Objective and Setup

To investigate the role of the *chromosome segregation regulatory genes*, the following configuration was used:

- Chromosome 1: *apoptosis regulatory genes (A)* and *cell-division regulatory genes* (D)
- Chromosome 2: *chromosome segregation regulatory genes (S)*

This gene configuration, as seen in Figure 2, isolates the effects of the loss or gain of Chromosome 2 to those caused by the loss or gain of the *chromosome segregation regulatory genes*.

4.1.2.Results

Homeostatic behaviour can be observed in Figure 3. In normal conditions this kind of homeostatic behaviour provides the tissue with robustness if there were a sudden loss of cells (wound-healing capabilities), maintaining the total number of cells close to that of the carrying capacity of the tissue (200 cells). For 20 simulations of Configuration A, the average

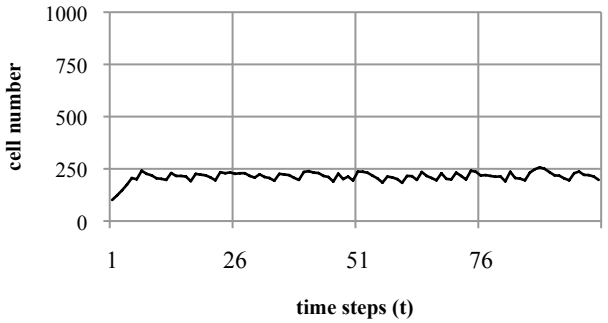

Figure 3- Total number of cells in a 100-time step simulation with Gene Configuration A.

total number of cells at the last time step (t=100) was 210 cells, with a standard deviation of 17.

4.1.3 Analysis

As expected, a comparison of the plot of the total number of cells across the simulations of Configuration A reveals the high variability of the simulation outcomes, as seen in Figure 4. Thus, it is difficult to distil meaningful information with traditional statistical methods. Despite the stochastic nature of the final cell number across experiments, an invariant qualitative behaviour can be observed for each configuration. Although the actual evolutionary pathway exhibits a high degree of variation, a representative simulation captures qualitatively the kind of evolutionary pathway that most of the simulations follow.

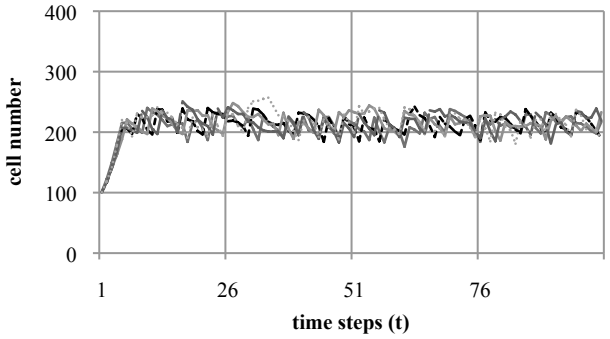

Figure 4- Distribution of the total amount of cells of 5 100-time step simulations with Gene Configuration A. Variability across experiments can be observed.

The initial genotype, genotype state (2, 2, 2), contains 2 functional copies of each gene. For there to be cancer-like behaviour, oncogenes need to have their function reduced and tumour suppressor genes in turn must have an increase in their expression. Because the abstracted genes that model the role of oncogenes and tumour suppressor genes are found in the same chromosome, they become self-regulated. As the system evolves however, novel genotypes emerge but, because of the self-regulation of the cancer genes, the overall behaviour generated by the new genotypes is not dissimilar to that of the

original cell population, as depicted in Figure 9a. This leads to a micro diversity of homeostatic genotypes. However, it is of interest that the more successful genotypes naturally acquire more resistance against chromosome missegregation. In this representative simulation, genotype state (2, 2, 3) accounts for more than 30% of the population at the last time step (t=100), as seen in a quantification of the distribution of genotypes (Table 2).

Genotype	t=0 (%)	t=25 (%)	t=50 (%)	t=75 (%)	t=100 (%)
(2, 2, 2)	**100**	**93.56**	**79.90**	**70.76**	**58.88**
(2, 2, 3)	0	1.72	**8.76**	**20.34**	**31.47**
(3, 3, 2)	0	0	4.12	4.66	0.51
(1, 1, 2)	0	0.43	3.09	2.97	5.58
(2, 2, 1)	0	3.00	2.06	0	0.51
(1, 1, 1)	0	0.43	1.55	0.42	1.02
(2, 2, >3)	0	0	0.52	0.85	1.02
(1, 1, 3)	0	0.86	0	0	0
(>3, >3, 2)	0	0	0	0	1.02

Table 2- Distribution of genotypes at 4 time intervals (0, 25, 50, 75 and 100) for a representative simulation of Gene Configuration A.

4.2 Gene Configuration B

4.2.1.Objective and Setup
To better understand the role of the distribution of the genes in the chromosomes, the initial configuration was modified to:

- Chromosome 1: *apoptosis regulatory genes* (A)
- Chromosome 2: *cell-division regulatory genes (D) and chromosome segregation regulatory genes* (S)

This gene distribution is depicted in Figure 5.

4.2.2.Results
During the 100-time step experiment, a stable homeostatic behaviour can be observed for a period of time. After that homeostatic period however, an uncontrolled proliferative behaviour follows. The total number of cells increases exponentially, reaching the values of the order of thousands in a very short period of time, as shown in Figure 6. This kind of behaviour is obtained across simulations. For 20 simulations of Configuration A, the average total number of cells across simulations at the last time step (t=100) was 59,388 cells, with an expected high standard deviation of 87,215. The

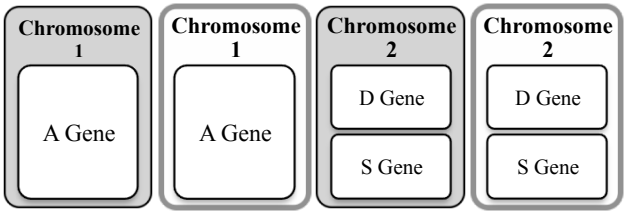

Figure 5- Distribution of Genes in Gene Configuration B

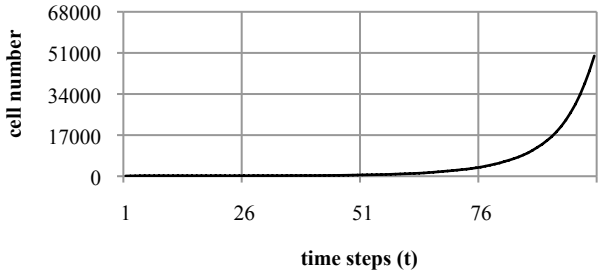

Figure 6- Total number of cells in a 100-time step simulation with Gene Configuration B.

representative simulation shown, ignoring the limits set by carrying capacity of the tissue, had a final number of 49,765 cells.

4.2.3 Analysis
An analysis of the emergent genotypes reveals that a newly evolved genotype takes over the population: Genotype state (1, 2, 2). From this novel genotype, two different kinds of genotypes are further evolved: an apoptosis-resistant genotype (0, 2, 2) and an over-proliferative genotype (1, 3, 3), which can be appreciated on Figure 9b.

The loss of function of the tumour suppressor-inspired *Apoptosis regulatory genes* through chromosome missegregation leads to the generation of a niche of these mutants. However, because of the low levels of chromosome missegregation, this population remains relatively homeostatic until the emergence of two cancer-like genotypes, as described by Table 3.

Genotype	t=0 (%)	t=25 (%)	t=50 (%)	t=75 (%)	t=100 (%)
(2, 2, 2)	**100**	**75.85**	9.74	0.72	0.14
(1, 2, 2)	0	19.81	**88.24**	**88.50**	**44.42**
(0, 2, 2)	0	0	0.41	4.50	**24.14**
(1, 3, 3)	0	0	0	4.90	**21.23**
(2, 3, 3)	0	2.42	1.42	0.72	0.15
(0, 3, 3)	0	0	0	0.17	9.04
(3, 2, 2)	0	0.97	0	0	0
(1, 1, 1)	0	0	0.20	0.49	0.36
(2, 1, 1)	0	0.97	0	0	0
(1, >3, >3)	0	0	0	0	0.36
(0, >3, >3)	0	0	0	0	0.14
(0, 1, 1)	0	0	0	0	0.02

Table 3- Genotype distribution (percentage) for a representative simulation of Gene Configuration B.

The evolution of the system with low levels of aneuploidy resulted in the generation of few very successful mutants that quickly dominated the entire population as seen in Table 3, suggesting a counterintuitive pathway for cancer-like behaviour with low aneuploidy. This kind of mutations are seen in leukemias, lymphomas and some mesenchymal tumours, where there are simple, disease-specific abnormalities (Johansson et al. 1996).

4.3 Gene Configuration C

4.3.1.Objective and Setup

To further study the role of the distribution of the genes in the chromosomes in a third configuration (Figure 7):

- Chromosome 1: *cell-division regulatory genes (D)*
- Chromosome 2: and *apoptosis regulatory genes (A) and chromosome segregation regulatory genes (S)*

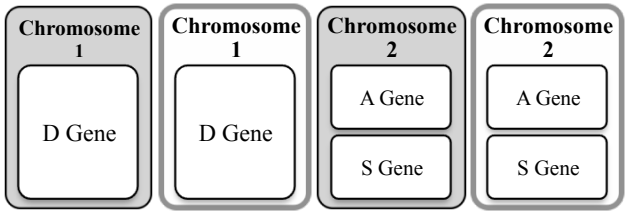

Figure 7- Distribution of Genes in Gene Configuration C

4.3.2.Results

Although this new genetic configuration yields a similar over-proliferative behaviour to that obtained through the simulations with Gene Configuration B, as seen in Figure 8, there are significant differences. The emergence of novel genotypes is less gradual, as can be appreciated in Figure 9c. In the representative simulation presented for this configuration, the total number of cells obtained at the last time step was 61,836 cells. The average final number of cells of the simulations carried out was 74,201, with a standard deviation of 114,736.

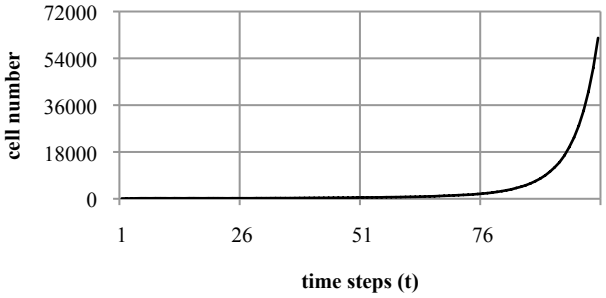

Figure 8- Total number of cells in a 100-time step Simulation with Gene Configuration C.

4.3.3 Analysis

An analysis of the genotype evolution sheds some light onto the emergence of the proliferative, cancer-like genotypes, as depicted in Figure 9c. Although the behaviour is similar to that of Gene configuration B, the evolution of a genotype that produces the cancer-like behaviour is significantly different. The analysis of the emergent genotypes reveals that the first mutation leads to an increase in the function of genes that model proto-oncogenes, increasing proliferation. However, contact inhibition induced cell death (the tumour suppressor genes) heavily restrict the mutant genotype from dominating the entire population. By acquiring mutations that reduce the contact inhibition forces, chromosomal instability is also induced. This instability leads to an explosion of genotypic diversity, as seen in Table 4, making it easier for cells to acquire mutations that lead to cancer-like behaviour.

This pathway may help shed some light on the reports of increasing levels of chromosome instability during premalignant neoplastic progression (Lai et al. 2007) and the development of tumours characterized by multiple and nonspecific aberrations, similar to most epithelial tumour types (Johansson et al. 1996)

Genotype	t=0 (%)	t=25 (%)	t=50 (%)	t=75 (%)	t=100 (%)
(2, 2, 2)	**100**	**92.38**	**40.88**	3.43	0.11
(2, 3, 2)	0	6.19	**40.25**	**31.17**	2.22
(1, 2, 1)	0	1.43	16.35	**31.93**	6.82
(2, >3, 2)	0	0	2.31	**17.71**	**24.70**
(1, 3, 1)	0	0	0.21	13.90	**21.71**
(1, >3, 1)	0	0	0	1.09	**24.80**
(0, 3, 0)	0	0	0	0.22	7.44
(0, >3, 0)	0	0	0	0	**11.22**
(0, 2, 0)	0	0	0	0.11	0.65
(1, 1, 1)	0	0	0	0.33	0.05
(3, >3, 3)	0	0	0	0	0.27
(3, 3, 3)	0	0	0	0.11	0.02
(0, 1, 0)	0	0	0	0	0.00

Table 4- Genotype distribution at different time intervals for Gene Configuration C.

5 Conclusions and Future Work

In this a work a computation model was created in order to investigate the role of chromosome missegregation in tumour evolution. By integrating the concept of chromosome missegregation in an otherwise homeostatic model, new genotypes were evolved. From the resulting novel genotypes, those that had acquired mutations that enabled them to express higher levels of cell division and lower levels of cell death quickly spread through the population. This gave rise to even more malignant genotypes exhibiting emergent cancer–like behaviour.

Although the model makes a number of assumptions including the assumption that the number of copies of a gene has a direct effect on the up or down regulation of that gene, the interactions and results can be interpreted in terms of actual biological behaviour (i.e, the up or down regulation of an oncogene or a tumour suppressor gene). The model suggests that through chromosome missegregation, the arrangement of genes on chromosomes has a profound effect on genetic diversity, giving rise to different kinds of cancer-like behaviours, which resemble key differences observed in real cancers (Cahill et al. 1999).

The role that *chromosome segregation regulatory genes* play in this model is largely determined by its position with respect to the other genes in the chromosomes. The model suggests that high levels of chromosome missegregation lead to a

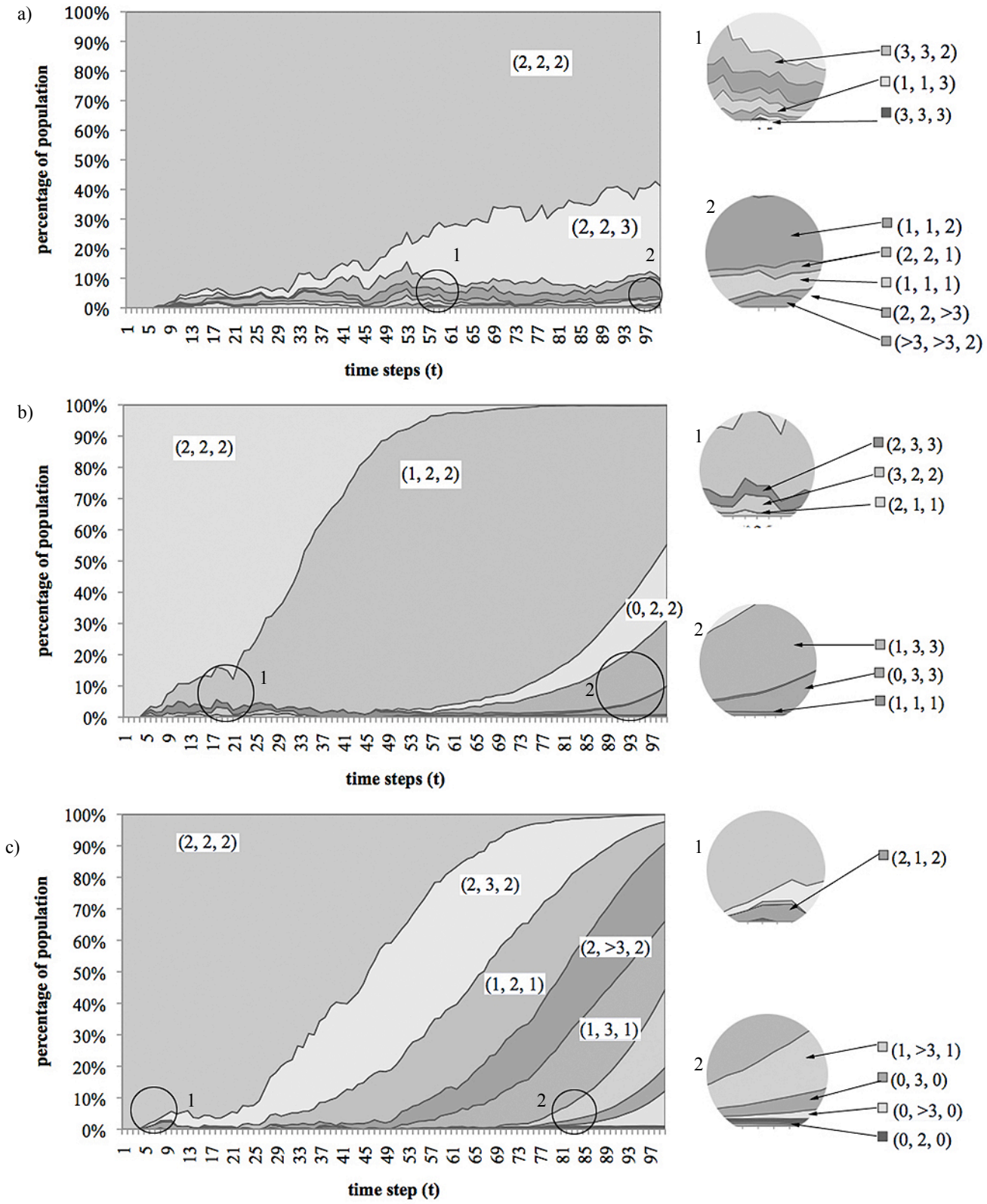

Figure 9. Genotype state population analysis for a) Gene Configuration A b) Gene Configuration B c) Gene Configuration C. The genotypes populations are stacked for each time step according to the percentage of the total population that they account for.

genetic diversity that help cells overcome the low probability of oncogenic mutations, as shown in the analysis of Gene Configuration C. Surprisingly, low levels of chromosome missegregation may also give rise to a different kind of cancer-like behaviour, as shown in the simulations of Gene Configurations B. By maintaining a relatively uniform population, specific mutations are conserved and spread throughout the population until a cancer-like genotype is reached. To determine the precise role of that *chromosome segregation regulatory genes* have in cancer systems, the development of appropriate tools for statistical analysis and further experiments are needed.

It is of interest to consider the real locations of known cancer genes to incorporate in an extension of the model. This could yield more realistic behaviour and may better inform theory and experiment. Mutations in oncogenes or tumour suppressor genes are not the only key players in real cancer systems though. Because microenvironment selection may also cooperate with aneuploidy to promote tumour progression (Anderson et al. 2006), it is also of interest to incorporate a more realistic version of the environment into the model.

Through computational models such as the one presented in this article, we anticipate that we may gain a deeper understanding of the effects of aneuploidy on cancer initiation. Identifying the key events in cancer progression may help us devise new cancer treatments that account aneuploidy and its dynamics.

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References

Abbott, R. G., S. Forrest, et al. (2006). "Simulating the hallmarks of cancer." Artif Life 12(4): 617-34.

Anderson, A., A. Weaver, et al. (2006). "Tumor morphology and phenotypic evolution driven by selective pressure from the microenvironment." Cell 127(5): 905-915.

Basanta, D. and A. Deutsch (2008). "A game theoretical perspective on the somatic evolution of cancer." Selected topics on cancer modelling: genesis, evolution, inmune competition, therapy. Birkhauser, Boston.

Cahill, D., K. Kinzler, et al. (1999). "Genetic instability and darwinian selection in tumours." Trends Biochem Sci 24(12): M57-M60.

Carmona-Fontaine, C., H. Matthews, et al. (2008). "Contact inhibition of locomotion in vivo controls neural crest directional migration." Nature. 456:957-961

Chin, K., S. DeVries, et al. (2006). "Genomic and transcriptional aberrations linked to breast cancer pathophysiologies." Cancer Cell 10(6): 529-541.

Dittrich, P., J. Ziegler, et al. (2001). "Artificial Chemistries—A Review." Artificial Life 7(3): 225-275.

Futreal, P., L. Coin, et al. (2004). "A census of human cancer genes." Nat Rev Cancer 4(3): 177-183.

Gatenby, R. A., K. Smallbone, et al. (2007). "Cellular adaptations to hypoxia and acidosis during somatic evolution of breast cancer." Br J Cancer 97(5): 646-53.

Gibbs, W. (2003). "Untangling the roots of cancer." Scientific American vol. 289 (1) pp. 56-65.

Gras, R., D. Devaurs, et al. (2009). "An Individual-Based Evolving Predator-Prey Ecosystem Simulation Using a Fuzzy Cognitive Map as the Behavior Model." Artif Life 15(4): 423-463.

Hanahan, D. and R. Weinberg (2000). "The hallmarks of cancer." Cell 100(1): 57-70.

Hanks, S., K. Coleman, et al. (2004). "Constitutional aneuploidy and cancer predisposition caused by biallelic mutations in BUB1B." Nature Genetics 36(11): 1159-1161.

Holland, A. J. and D. W. Cleveland (2009). "Boveri revisited: chromosomal instability, aneuploidy and tumorigenesis." Nature Rev Mol Cell Biol 10(7): 478-487.

Huettel, B., D. P. Kreil, et al. (2008). "Effects of aneuploidy on genome structure, expression, and interphase organization in Arabidopsis thaliana." PLoS Genetics 4(10): e1000226.

Johansson, B., F. Mertens, et al. (1996). "Primary vs, secondary neoplasia-associated chromosomal abnormalities - Balanced rearrangements vs, genomic imbalances?" Genes Chromosome & Cancer 16(3): 155-163.

Lai, L. A., T. G. Paulson, et al. (2007). "Increasing genomic instability during premalignant neoplastic progression revealed through high resolution array-CGH." Genes Chromosomes & Cancer 46(6): 532-542.

Nagl, S., M. Williams, et al. (2007). "Objective Bayesian nets for systems modelling and prognosis in breast cancer." Innovations in Bayesian networks: theory and applications. Springer.

Parkin, D. M., F. Bray, et al. (2005). "Global cancer statistics, 2002." CA: A Cancer Journal for Clinicians 55(2): 74-108.

Rajagopalan, H. and C. Lengauer (2004). "Aneuploidy and cancer." Nature 432(7015): 338-41.

Weaver, B. and D. Cleveland (2006). "Does aneuploidy cause cancer?" Current opinion in cell biology 18(6): 658-667.

Zeng, Q. and W. Hong (2008). "The emerging role of the hippo pathway in cell contact inhibition, organ size control, and cancer development in mammals." Cancer Cell 13(3): 188-92.