A Markov-chain model of chromosomal instability

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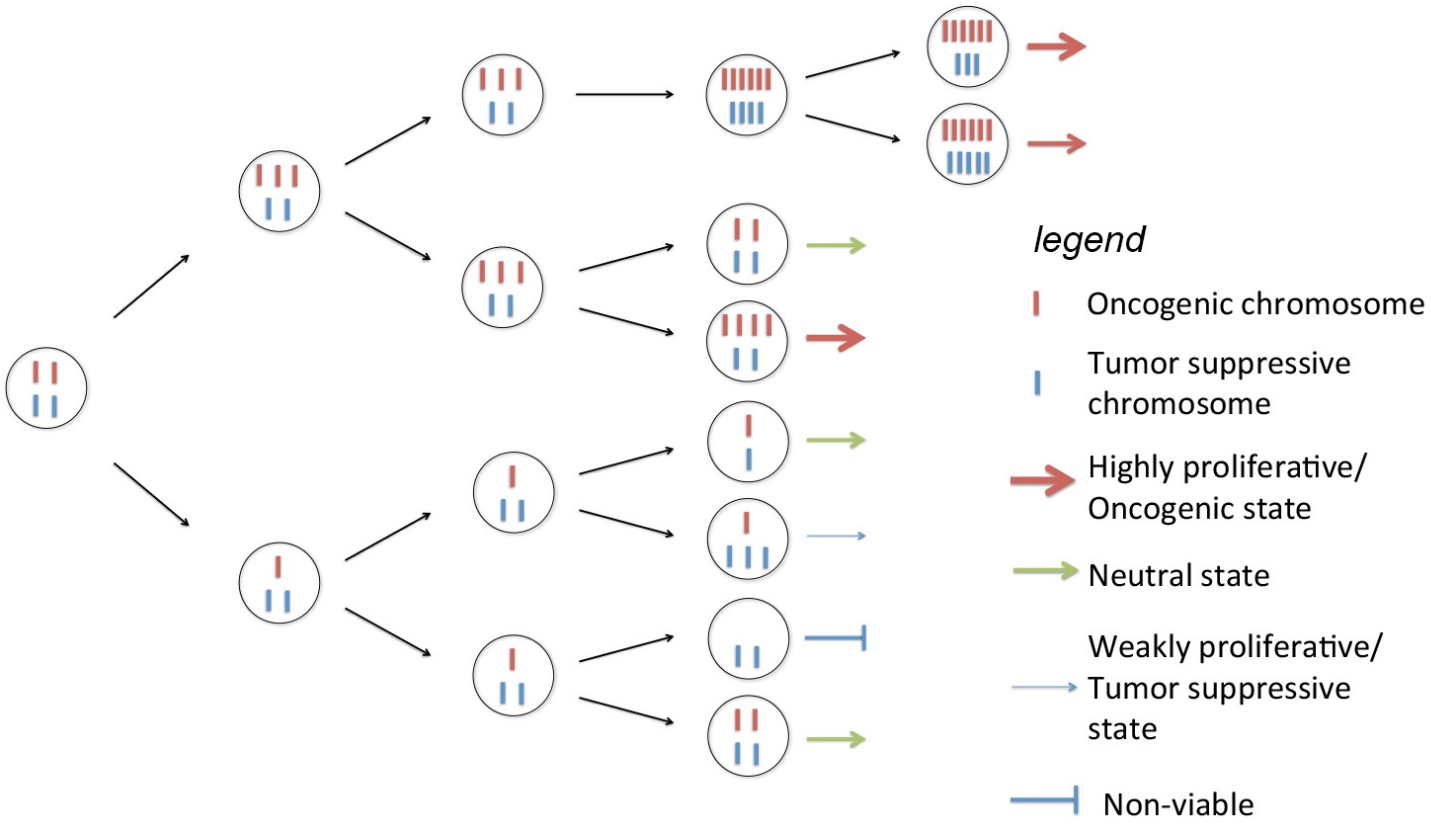
Missegregation

During mitosis, cancer cells undergo chromosome missegregation events, causing one of the two daughter cells to inherit more copies of a chromosome than the other.



Advantages of genomic instability

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A recent genomic analysis by Davoli et al. assigned scores to individual chromosomes based on the presence of such genes.

Since the karyotype of a cell affects its fitness level, genomic instability allows for Darwinian selection to occur.

History

The first stochastic model of missegregation was developed by Gusev, Kagansky and Dooley in 2000. It has a few disadvantages:

1. Simulations are very slow.
2. It can't be analyzed mathematically to find long-term behavior.
3. It doesn't account for chromosome scores, and consequently its predictions are unrealistic.

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To address 3, we will assign a survival probability to each cell based on the chromosome scores computed by Davoli et al.

Assumptions of our model

- Each chromosome copy has probability p (typically $p \approx 0.0025$) of missegregating at a given cell division, independent from other copies.

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- Starting from a single founder cell, all the cells in the colony divide simultaneously at each generation.

The karyotype of a cell is the vector $(i_1, i_2, \ldots, i_{23})$ where

$$i_k = \#\text{ copies of chromosome } k.$$

A live cell has $1 \leq i_k \leq N$ for all k.

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Instead, we will build a Markov chain that describes the distribution of karyotypes probabilistically. The advantages are:

- Computations are much faster, since they amount to taking powers of matrices.
- We can analyze the Markov chain mathematically to predict long-term behavior.

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Since missegregations of different chromosomes are independent, we focus on one type of chromosome at a time.

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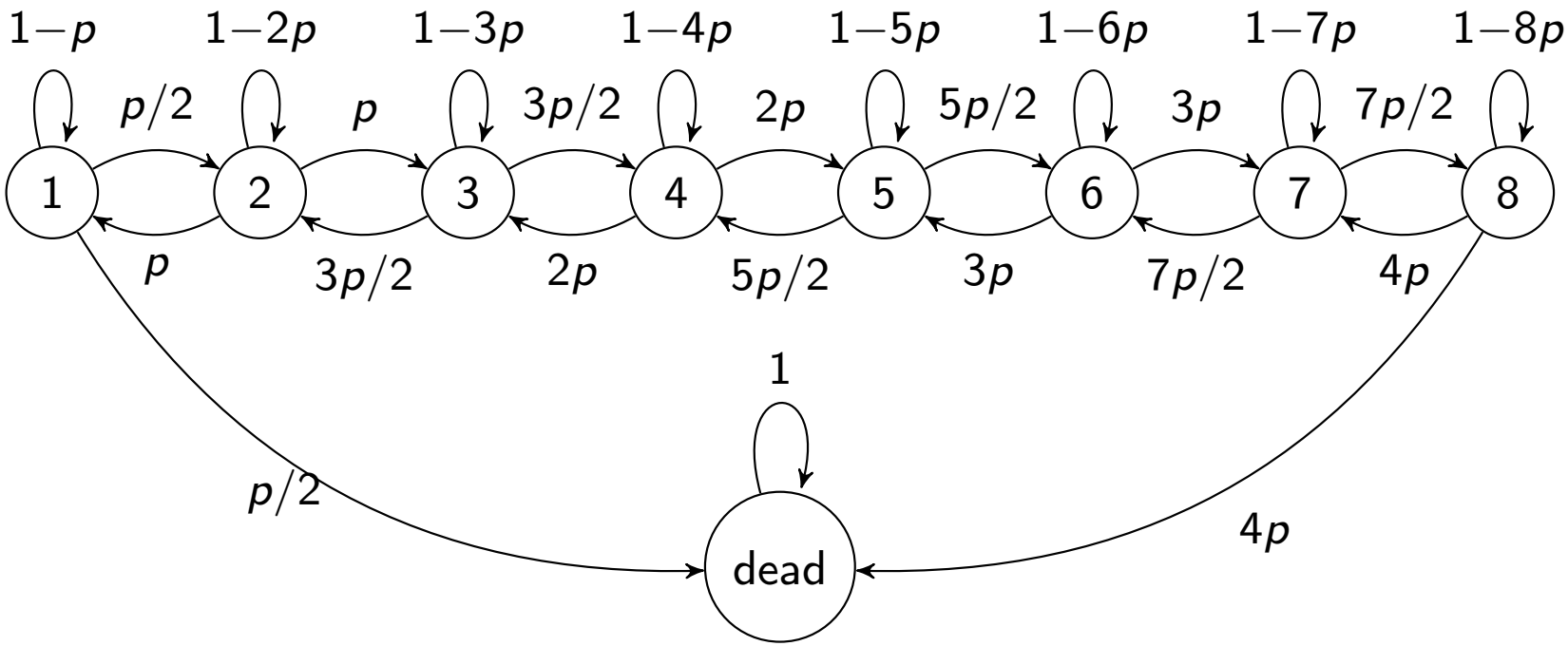
Each step is a cell division, and one of the 2 daughter cells is chosen with probability 1/2.

The Markov chain for the basic model without scores



(we ignore quadratic terms in p for simplicity)

The transition matrix

Ignoring quadratic terms in p, the transition matrix for the basic model (without chromosome scores) is

$$M_{ij} = \begin{cases} 1 - ip & \text{if } i = j, \\ ip/2 & \text{if } |i - j| = 1, \\ 0 & \text{if } |i - j| \geq 2, \end{cases}$$

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for $1 \leq i, j \leq N$.

Being more precise, M_{ij} is the coefficient of x^j in

$$\left(\frac{p}{2} + (1-p)x + \frac{p}{2}x^2\right)^i \approx \frac{ip}{2}x^{i-1} + (1-ip)x^i + \frac{ip}{2}x^{i+1} + [\text{terms involving } p^2].$$

The transition matrix

For example, for $N = 8$, we get

$$\left[\begin{array}{c|cccccccc} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \hline p/2 & 1-p & p/2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & p & 1-2p & p & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 3p/2 & 1-3p & 3p/2 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 2p & 1-4p & 2p & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 5p/2 & 1-5p & 5p/2 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 3p & 1-6p & 3p & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 7p/2 & 1-7p & 7p/2 \\ 4p & 0 & 0 & 0 & 0 & 0 & 0 & 4p & 1-8p \end{array}\right].$$

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Let $\mathbf{M}$ be the matrix obtained by removing the row and column corresponding to state 0.

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Properties of the transition matrix

- State 0 is an absorbing state, and so a high proportion of the 2^g potential cells after g generations are dead. Still, we are interested in the distribution of copy numbers among live cells.

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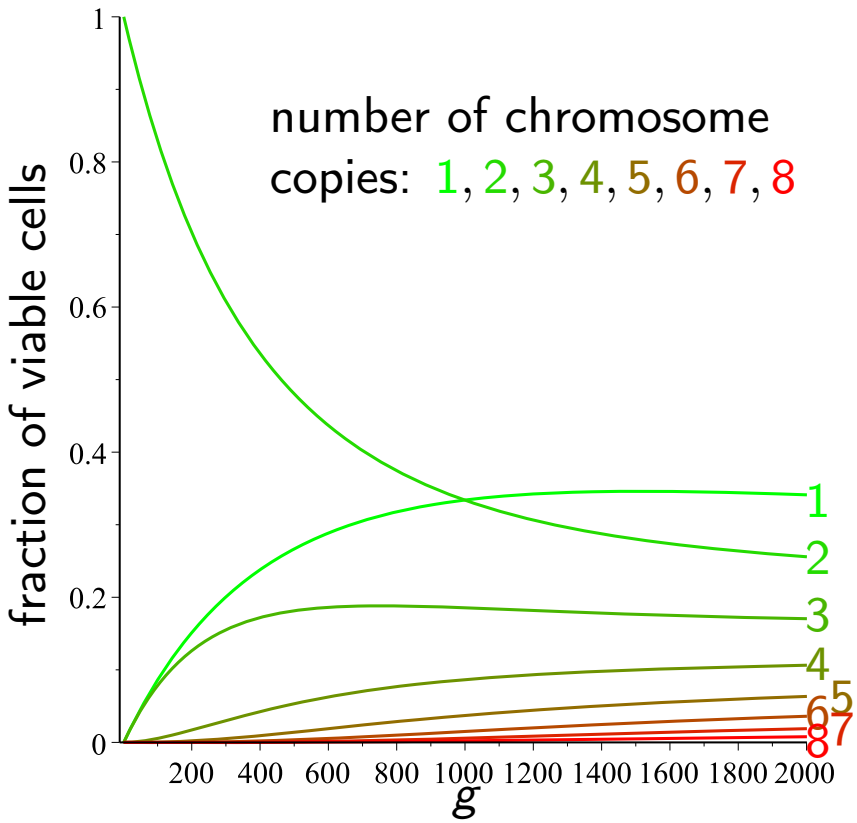
- Letting $s_g(i) =$ sum of the entries of the ith row of $\mathbf{M}^g$,

$$2^g \prod_{k=1}^{23} s_g(i_k)$$

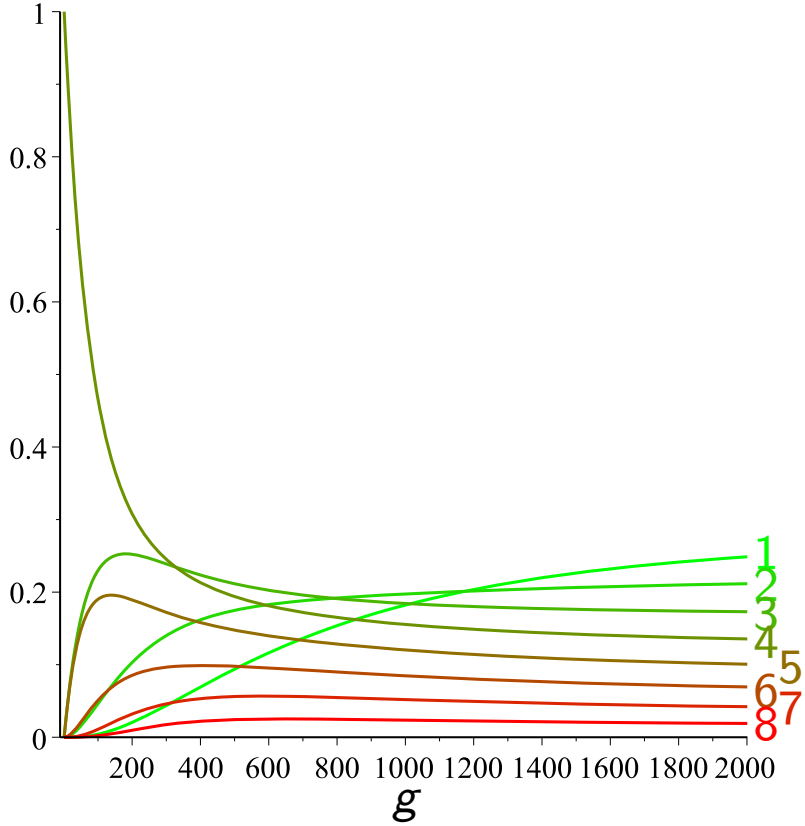
is the expected number of live cells after g generations when the founder cell has i_k copies of chromosome k for each k.

Evolution of the number of chromosome copies over time

Proportion of live cells having each number of copies, for the Markov chain model with $N = 8$ and a founder cell with f copies:



$p = 0.001,\ f = 2$



$p = 0.0025,\ f = 4$

The limiting behavior

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Since the Markov chain has an absorbing state, its stationary distribution is trivial and unhelpful.

However, we can use a result from probability theory to restrict to non-absorbing states (equivalently, live cells):

Theorem

Let ρ be the largest eigenvalue of $\mathbf{M}$. The limiting distribution conditional on the non-absorbing states is given by the vector $\mathbf{v}$ satisfying $\mathbf{vM} = \rho\mathbf{v}$ and $\sum_{i=1}^{N} v_i = 1$.

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In particular, this limiting distribution does not depend on the karyotype of the founder cell.

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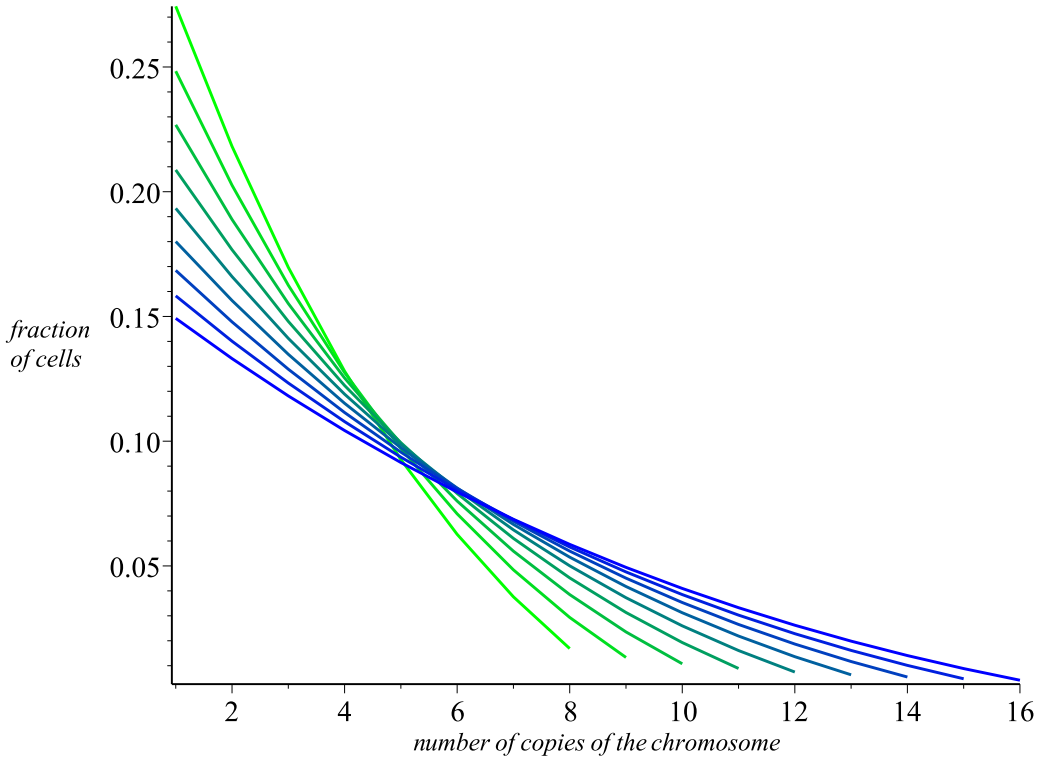
Surprisingly, it does not depend on the missegregation rate either:

Theorem

The limiting distribution of the above basic model conditional on the non-absorbing states is independent of p.

The limiting distribution

Limiting distributions for $N = 8, 9, 10, 11, 12, 13, 14, 15, 16$:



The most frequent copy number is always 1, which is not very realistic. This will change once we incorporate chromosome scores.

Chromosome scores and survival probability

Based on experiments by Davoli et al., we assign a score s_k to each chromosome k. The total score of a cell with karyotype $(i_1, \ldots, i_{23})$ is:

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Again, we can implement this algorithm and run lengthy simulations.

Instead, we'll incorporate the chromosome scores into the Markov chain, and use it to run fast computations and to determine limiting behavior.

Decomposing the survival probability

$$Q_{\text{surv}} = e^{c+dS} = e^{c+d\sum_k s_k i_k} = e^c \prod_{k=1}^{23} \underbrace{e^{ds_k i_k}}.$$

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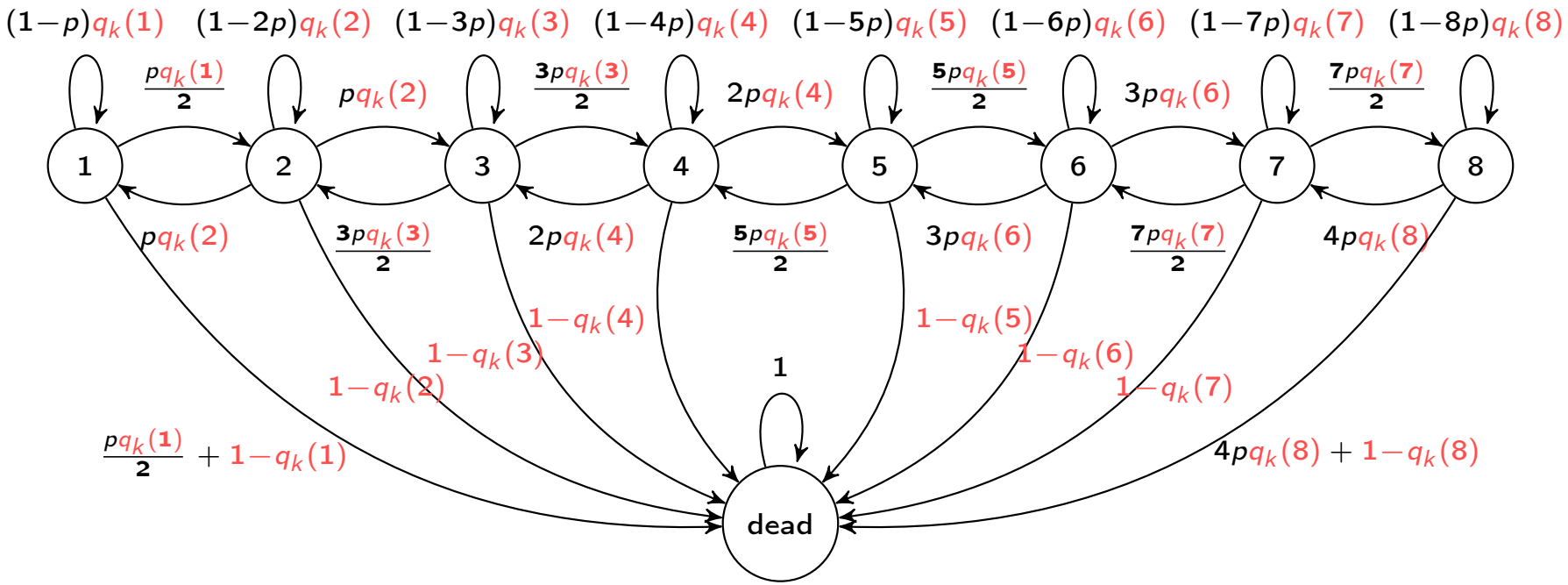
Oncogenic $\Leftrightarrow s_k > 0 \Leftrightarrow \mu > 1$.
Tumor-suppressive $\Leftrightarrow s_k < 0 \Leftrightarrow \mu < 1$.

This equation allows us to break up the model into 23 independent Markov chains, one for each type of chromosome.

The Markov chain for chromosome k



A cell with i copies of the chromosome has probability $1-q_k(i)$ of dying, and probability $q_k(i)$ of surviving and dividing as in the basic model.

The transition matrix

The transition matrix $\mathbf{A}^{(k)}$ restricted to live cells is:

$$A_{ij}^{(k)} = \begin{cases} (1-ip)\, q_k(i) & \text{if } i = j, \\ ip\, q_k(i)/2 & \text{if } |i-j| = 1, \\ 0 & \text{if } |i-j| \geq 2, \end{cases}$$

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Letting $s_g^{(k)}(i) =$ sum of the entries of the ith row of $(\mathbf{A}^{(k)})^g$,

$$2^g \prod_{k=1}^{23} s_g^{(k)}(i_k)$$

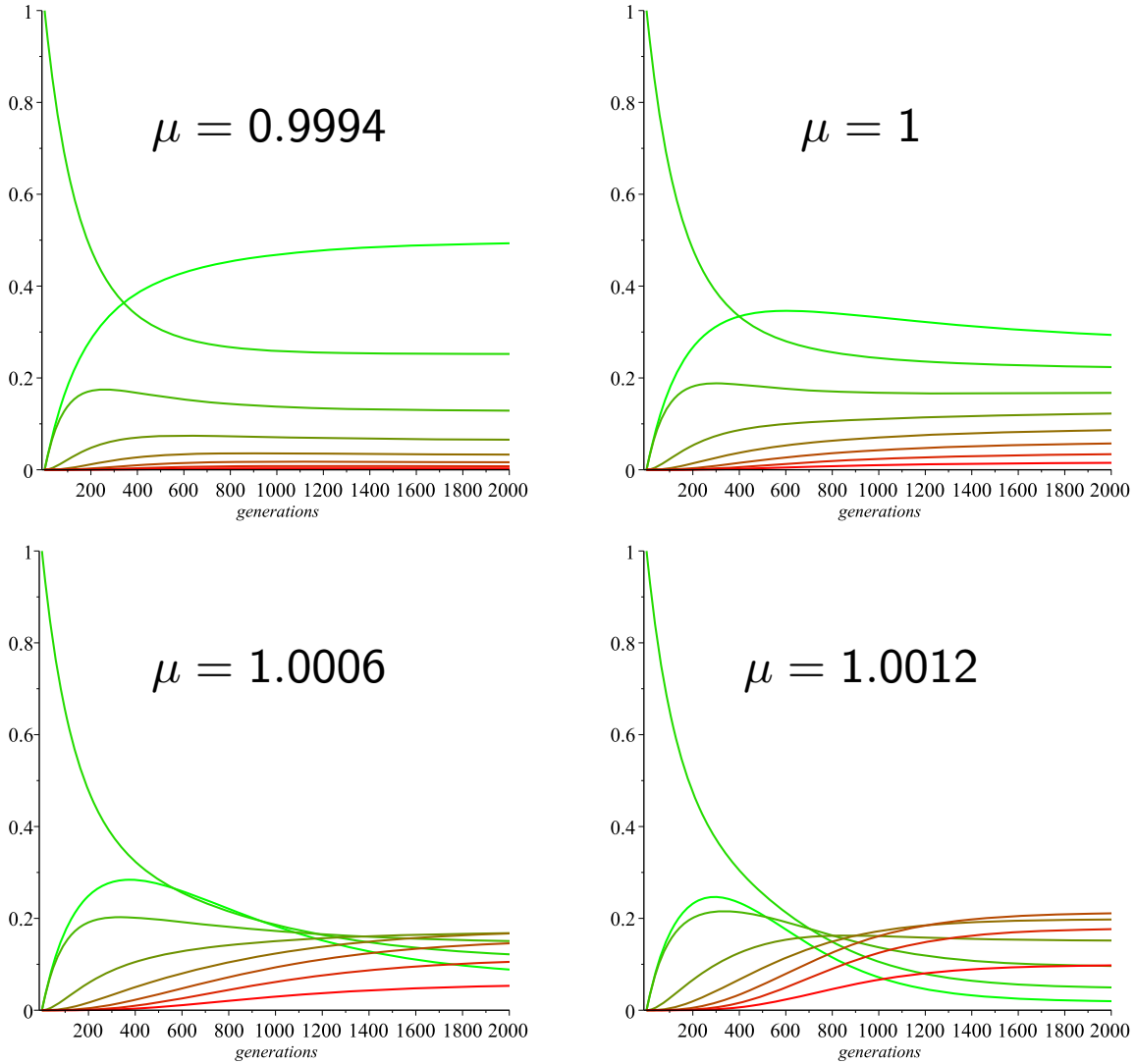
is the expected number of live cells after g generations when the founder cell has i_k copies of chromosome k for each k.

Distribution of the number of chromosome copies over time

In human chromosomes, $\mu \in [0.9994, 1.0012]$.

Fix $p = 0.0025$ and a founder cell with 2 copies.

Each curve represents a number of copies: 1, 2, 3, 4, 5, 6, 7, 8.



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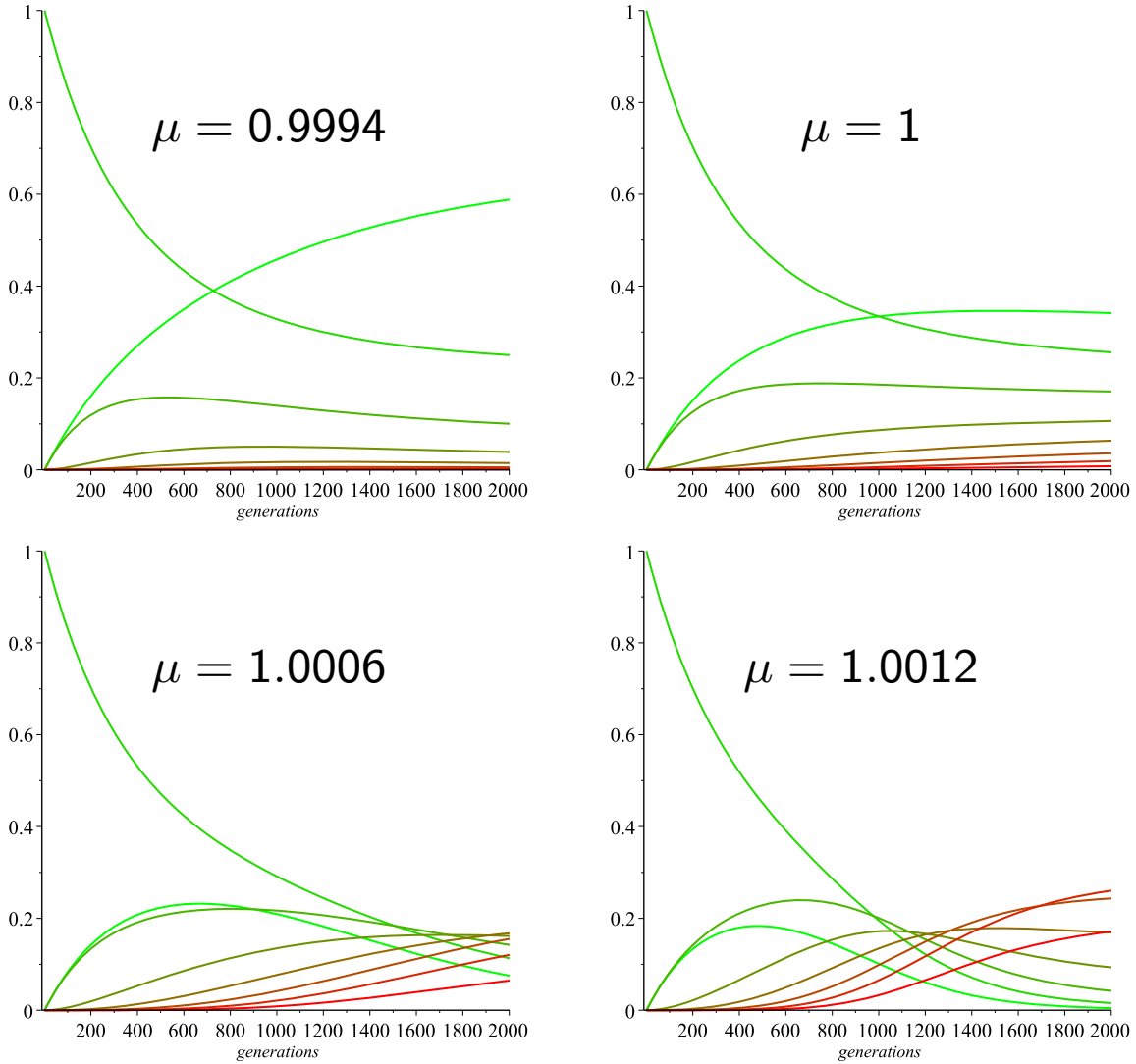

The limiting behavior

As before, if ρ is the largest eigenvalue of $\mathbf{A}^{(k)}$, the limiting distribution conditional on the non-absorbing states is given by the vector $\mathbf{v}$ satisfying $\mathbf{v}\mathbf{A}^{(k)} = \rho\mathbf{v}$ and $\sum_{i=1}^{N} v_i = 1$.

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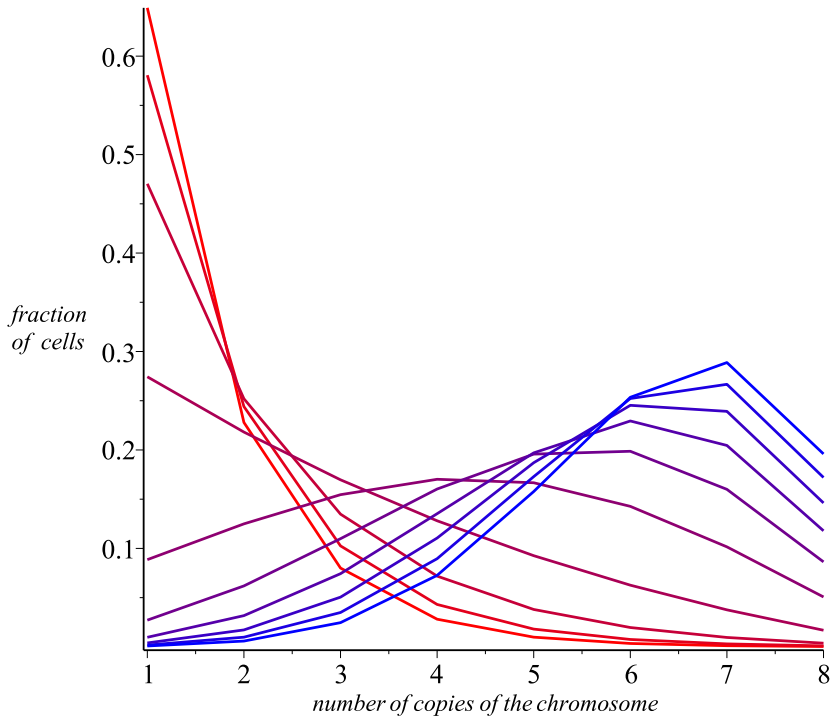
Again, this limiting distribution does not depend on the number of copies of the founder cell.

However, unlike for the model without scores, it now depends on p and on μ (i.e., on the chromosome score).

The limiting distribution

Liming distributions for $\mu = 0.9994$, 0.9996, 0.9998, 1.0000, 1.0002, 1.0004, 1.0006, 1.0008, 1.0010, 1.0012.



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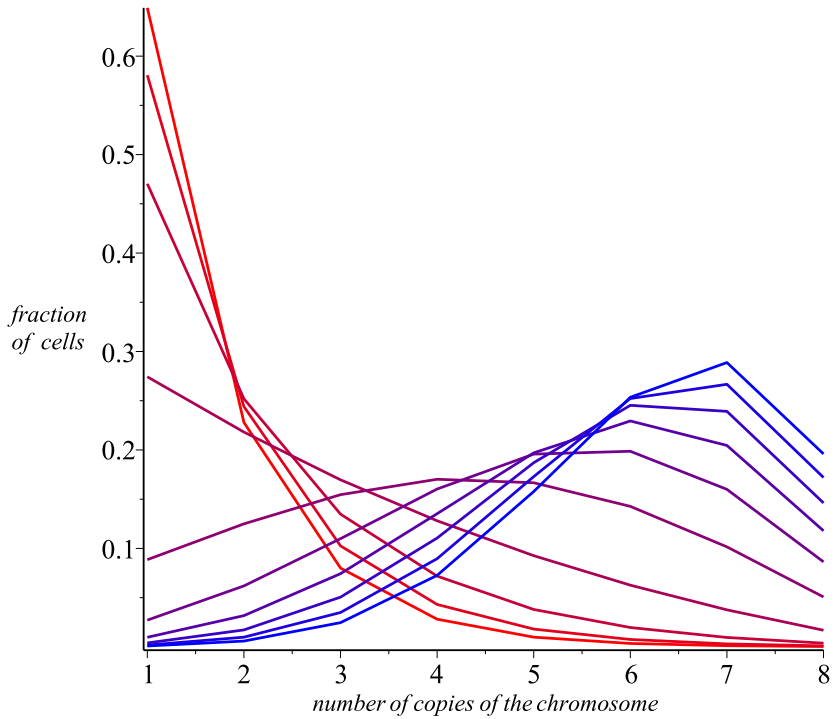

$p = 0.001$

For higher chromosome scores, the limiting distribution favors higher copy numbers.

For positive chromosome scores ($\mu > 1$), the most frequent copy number is no longer 1, making this model more realistic than the basic model without scores.

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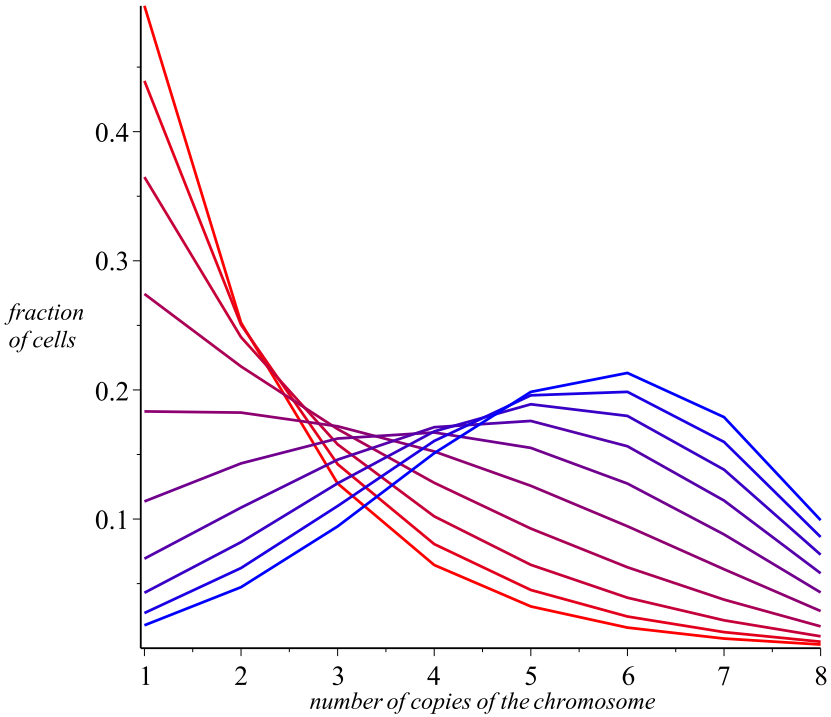
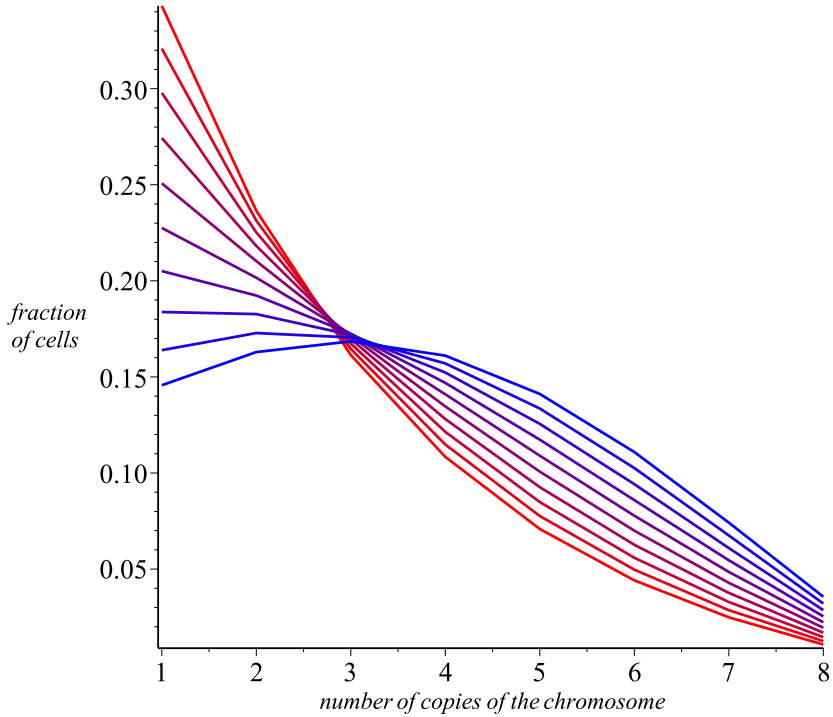


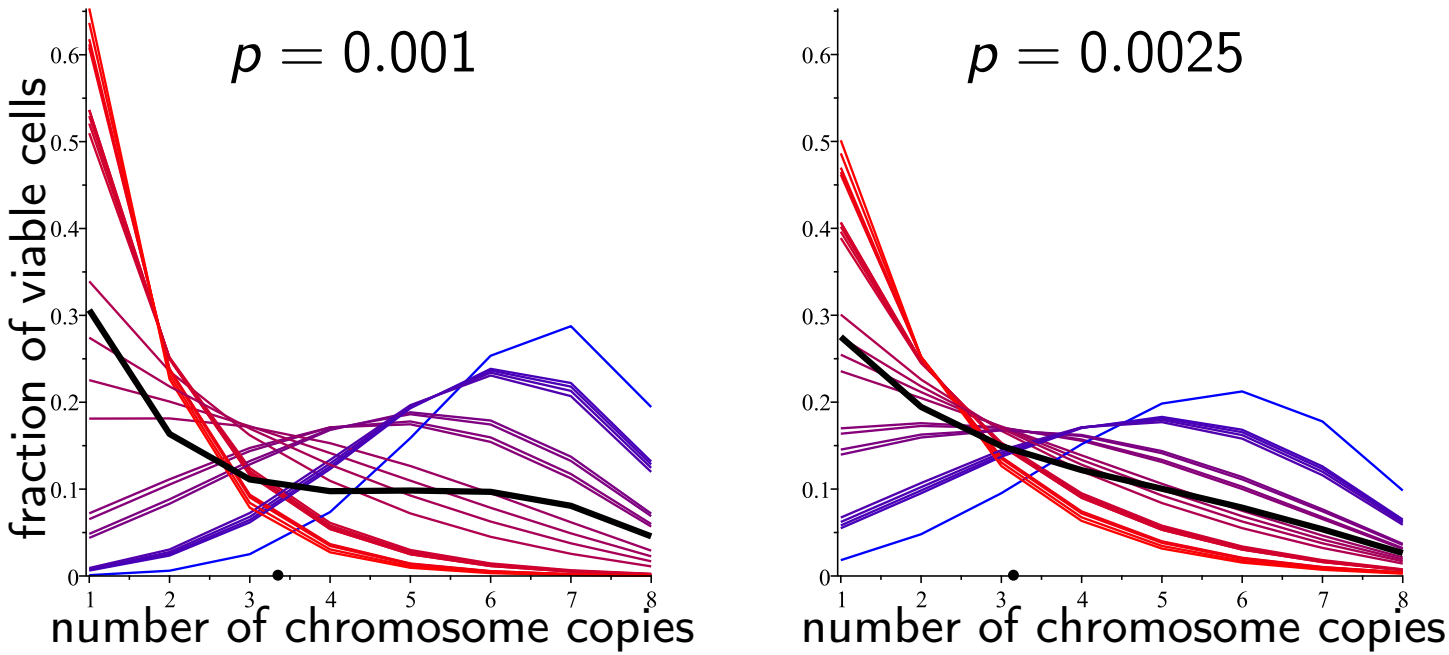
$p = 0.0025$



$p = 0.01$

The limiting distribution

Limiting distributions for the experimentally found values of μ corresponding to the 23 human chromosomes:



The black curve is the average of the 23 limiting distributions, and the black dot on the x-axis is the average number of chromosome copies.

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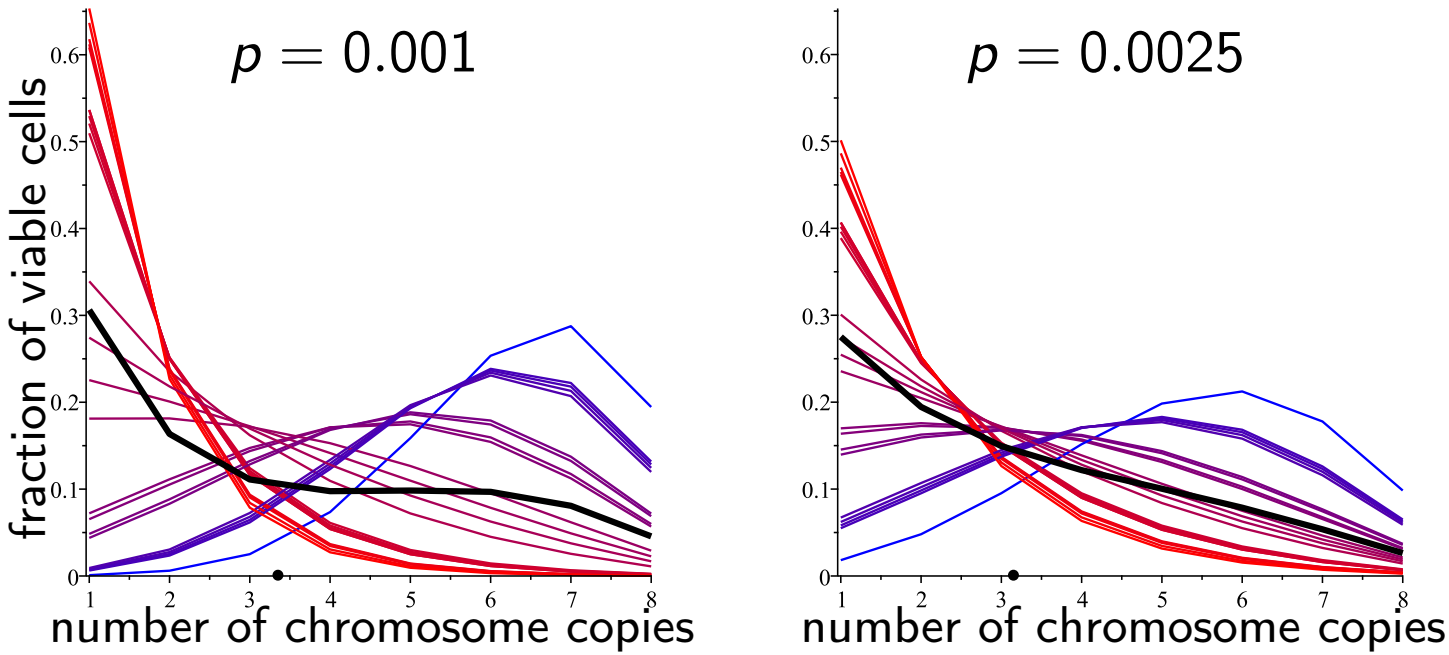
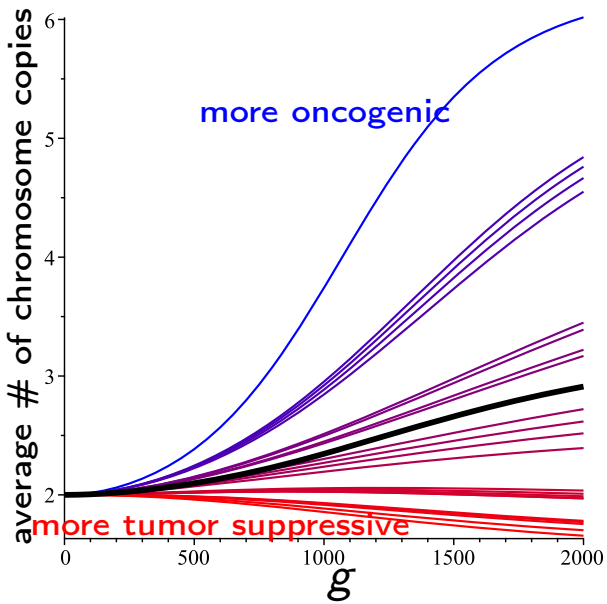


The black curve is the average of the 23 limiting distributions, and the black dot on the x-axis is the average number of chromosome copies. This average of about 3 copies agrees with observations.

The average number of copies over time

The evolution of the average number of copies of the 23 human chromosomes, starting with 2 copies of each.
The average of the 23 averages is shown in black.



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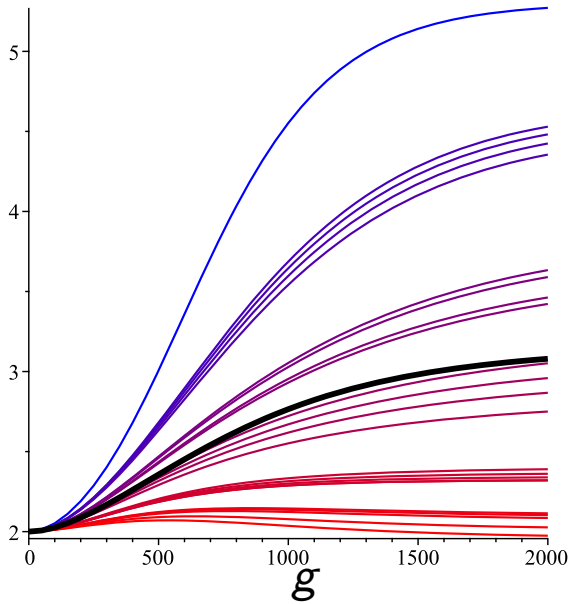
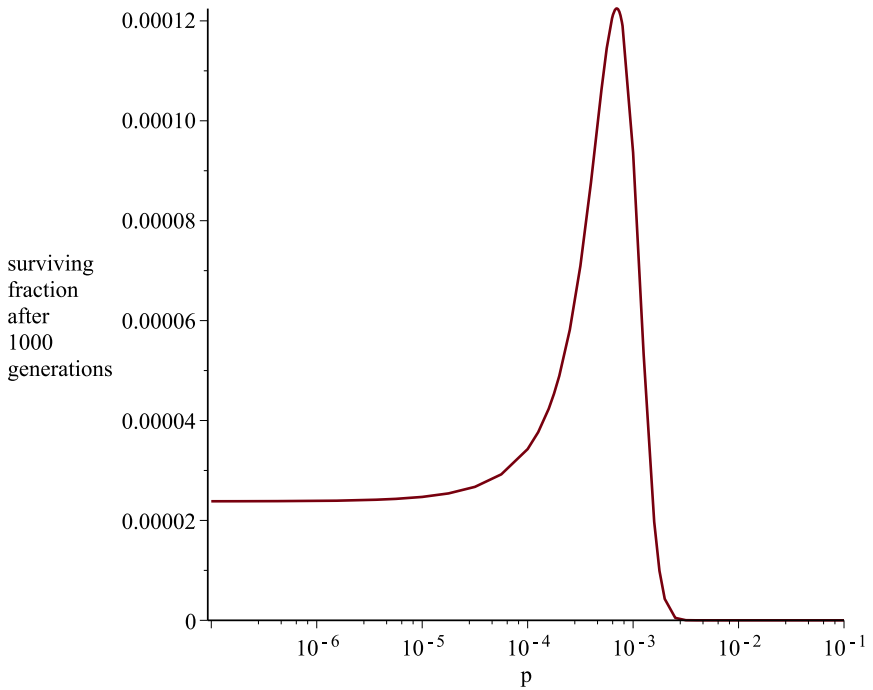


$p = 0.0025$

The convergence to ≈ 3 copies is observed in experiments.

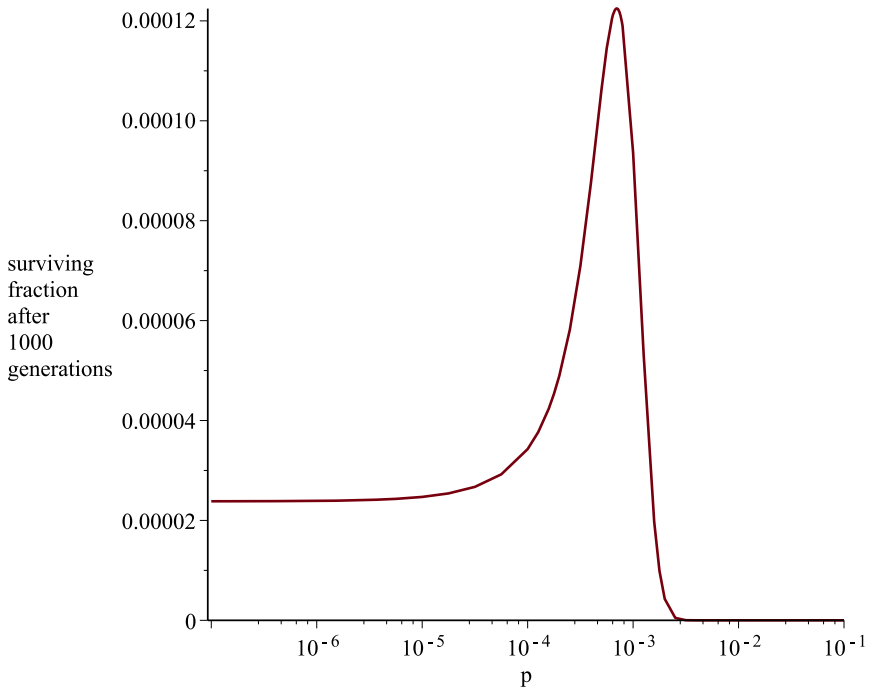
Fraction of live cells after 1000 generations

Using the experimentally found values for the chromosome scores.



Fraction of live cells after 1000 generations

Using the experimentally found values for the chromosome scores.



The number of live cells is maximized for missegregation rates around $p \approx 10^{-3}$. These are the rates observed in cancer!

Karyotypic diversity index

The *karyotype diversity index* measures the heterogeneity of the colony:

$$K = -\sum_{k=1}^{23}\sum_{i=1}^{N} a_{k,i} \ln a_{k,i},$$

where $a_{k,i}$ = fraction of live cells with i copies of chromosome k.

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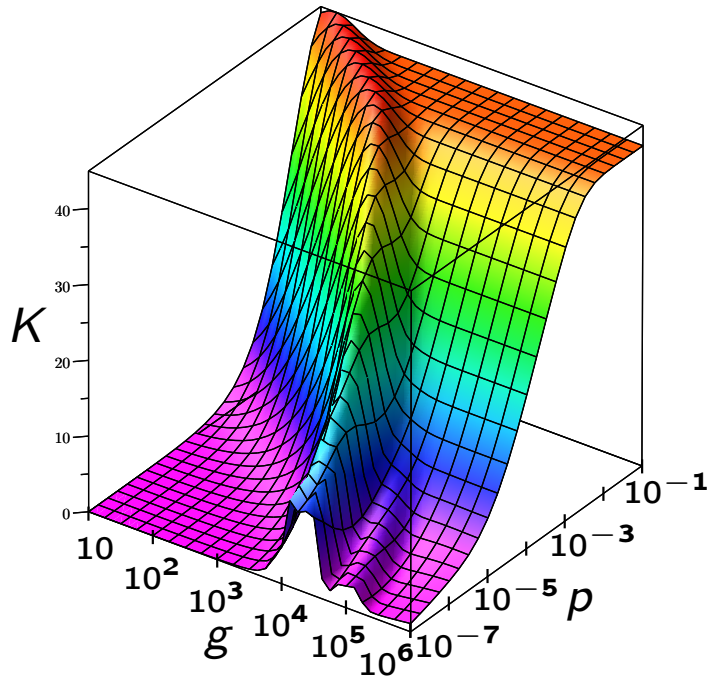
Plot of K as a function of g and p (both in a logarithmic scale):



Karyotypic diversity index

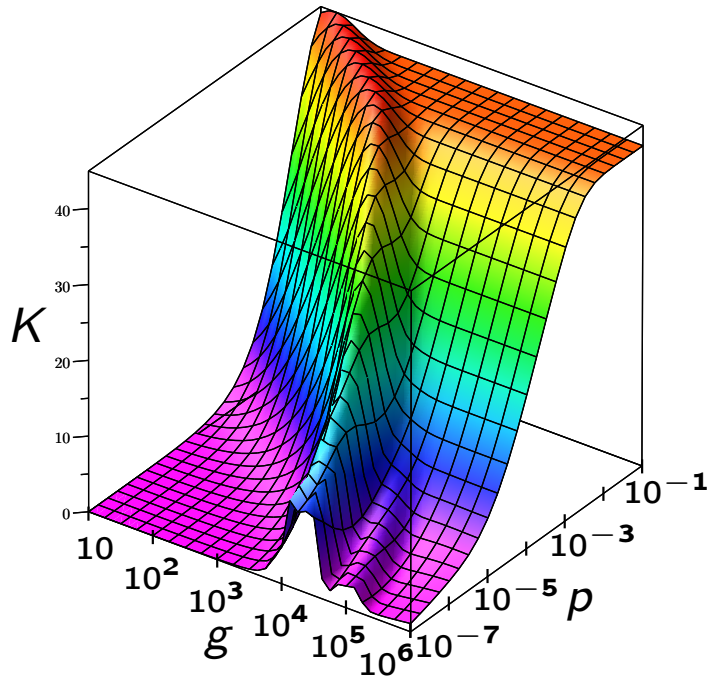
The *karyotype diversity index* measures the heterogeneity of the colony:

$$K = -\sum_{k=1}^{23}\sum_{i=1}^{N} a_{k,i} \ln a_{k,i},$$

where $a_{k,i}$ = fraction of live cells with i copies of chromosome k.

Plot of K as a function of g and p (both in a logarithmic scale):

After $g \approx 10^3$ generations, K is maximized when $p \approx 10^{-3}$ again.



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The survival probability of the cell depends on the number of mutated and normal copies of the treated chromosome.

Modeling mutations

We modify the Markov chain to incorporate mutations.

States are now indexed by pairs (i_1, i_2) with $1 \leq i_1 + i_2 \leq N$, representing cells having i_1 normal copies of the chromosome and i_2 mutated copies. For $N = 8$, there are 44 non-absorbing states.

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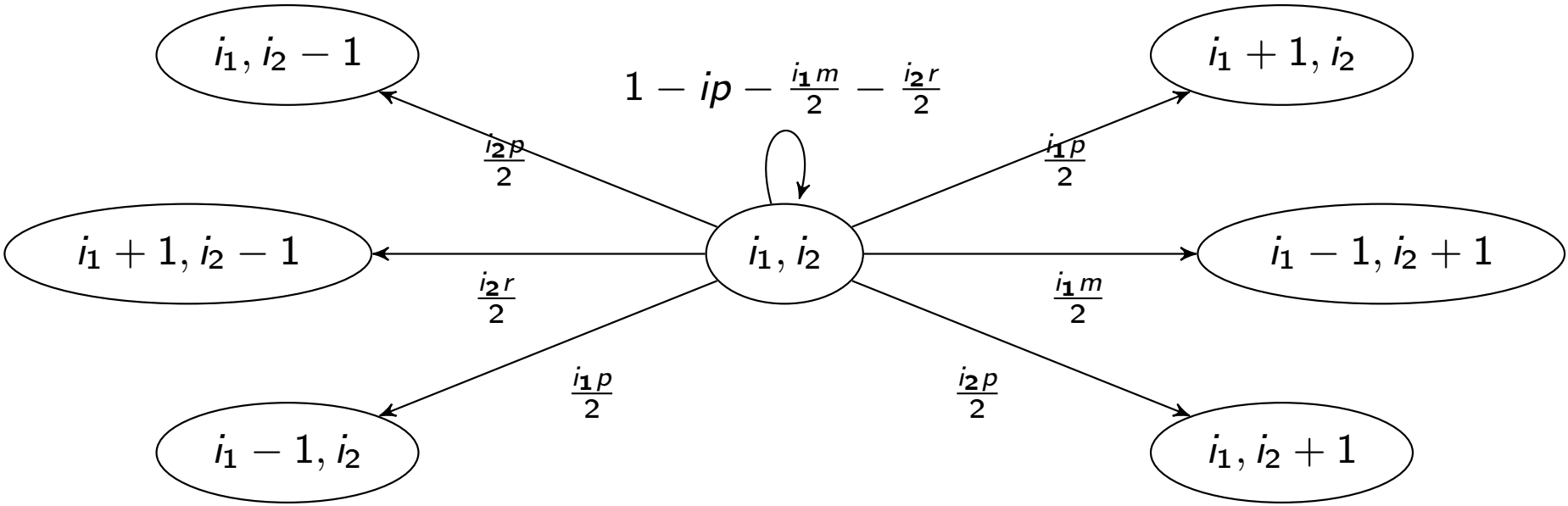
For simplicity, let's disregard highly unlikely events such as a mutation and a missegregation in the same cell division.

The modified Markov chain

Arrows leaving a typical node (i_1, i_2): (let $i = i_1 + i_2$)



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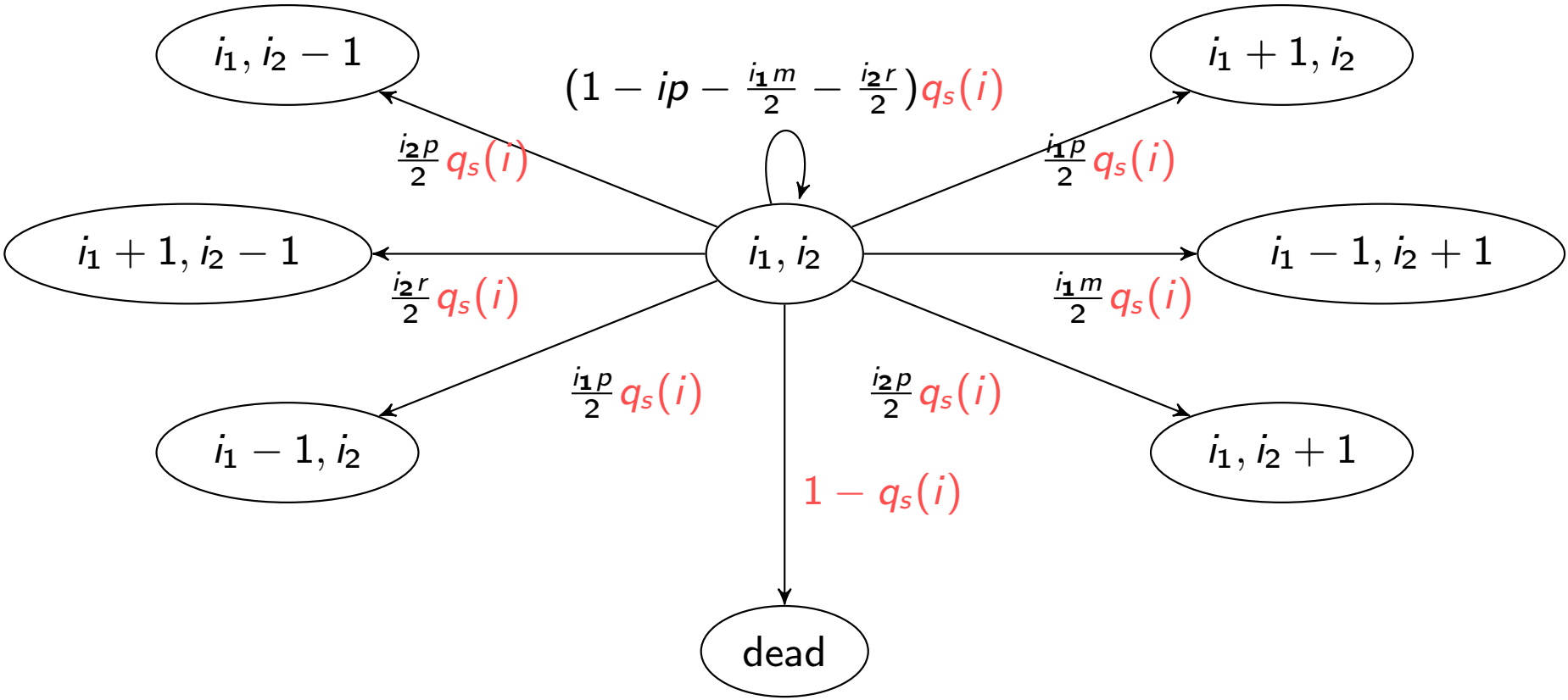

Missegregations and mutations, survival probability determined by scores

Modeling drug resistance

First, we let the tumor grow until it reaches about 10^9 cells and it becomes detectable with a CT scan.

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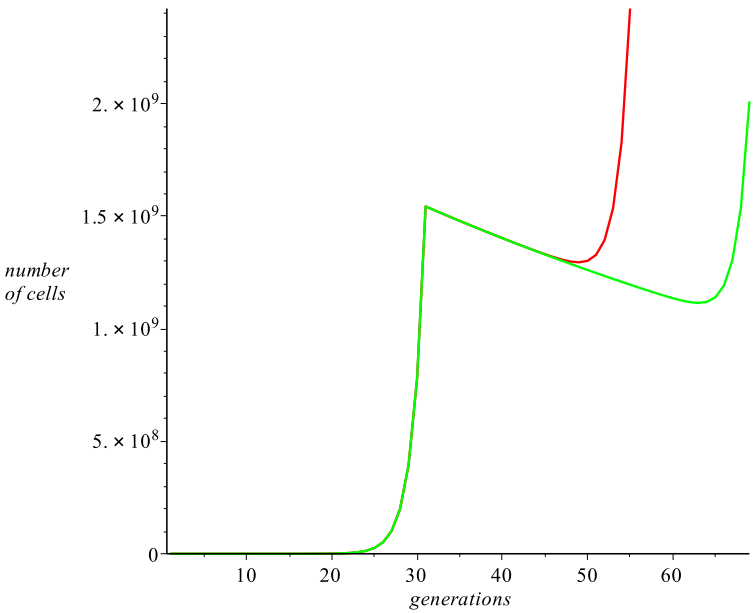
Then we apply a drug that targets a given gene, decreasing the survival probability of cells containing that gene.

Resistance to the drug can be modeled in several ways:

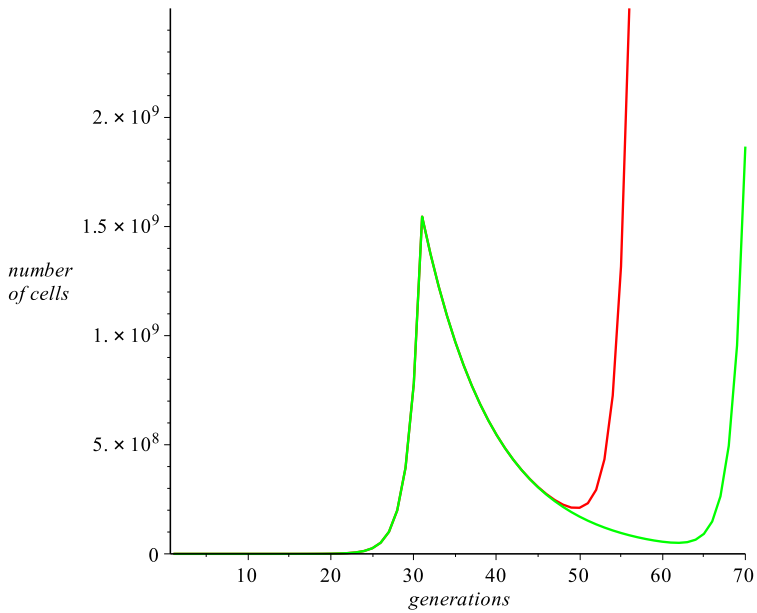
1. Binary resistance: cells with at least one mutated copy of the treated chromosome are resistant.
2. Graded resistance: the level of resistance depends on the ratio of copies of normal vs. mutated copies of the treated chromosome.

Modeling drug resistance

These plots show the evolution of the number of cells when applying targeted therapy to chromosome 1, comparing binary resistance and graded resistance.



weaker treatment



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- Study **time to resistance** for different parameters and validate with data obtained by applying different drugs on real patients.

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- Keep track of **maternal and paternal alleles**.

References

- A. Laughney, S.E., G. Genovese and S. Bakhoum, Dynamics of tumor heterogeneity derived from clonal karyotypic evolution, *Cell Rep.* 12 (2015), 809–820.
- S.E., A. Laughney and S. Bakhoum, A Markov chain for numerical chromosomal instability in clonally expanding populations, *PLoS Comput. Biol.* 2018; 14(9): e1006447.

Thank you!