A Markov chain to probe chromosomal instability in tumor evolution and drug resistance

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Science In Progress

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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.
It has been observed that

- more copies of oncogenic chromosomes (with proliferative genes) increase the cell’s chances of surviving, while
- more copies of tumor suppressive chromosomes (with anti-proliferative genes) increase its chances of dying.
Advantages of genomic instability

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- more copies of tumor suppressive chromosomes (with anti-proliferative genes) increase its chances of dying.

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.
The first stochastic model of missegregation was developed by Gusev, Kagansky and Dooley in 2000.

Their model is quite straightforward but it has a few disadvantages:

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

We will build a Markov chain model that addresses these 3 issues.
Assumptions of our model

- Each copy of a chromosome has probability $p$ of missegregating at a given cell division, independent from other copies. Typically, $p \approx 0.0025$. 
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- If the number of copies of any chromosome reaches 0 or goes above $N$ (typically $N = 8$), the cell dies.

- 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 $(n_1, n_2, \ldots, n_{23})$ where $n_k$ is the number of copies of chromosome $k$. An alive cell has $1 \leq n_k \leq N$ for all $k$. 
Simulations vs. Markov chain

We can implement this model and run a forward simulation. However, simulations are slow because we keep track of the karyotypes of all the cells.

Instead, we will build a Markov chain that describes the average distribution of karyotypes. Main advantages:

- Computations are much faster, since they amount to taking powers of matrices.
- We can analyze the Markov chain mathematically to predict long-term behavior.
Since missegregations of different chromosomes are independent, we focus on one type of chromosome at a time.

Our Markov chain has states $0, 1, 2, \ldots, N$, where state $i$ corresponds to cells with $i$ copies of the chromosome, with an absorbing state $0$ corresponding to dead cells.

The probability of a given karyotype $(n_1, \ldots, n_{23})$ is obtained by multiplying the probability that the Markov chain corresponding to chromosome $k$ is in state $n_k$ for $1 \leq k \leq 23$. 
Additional simplifications

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The probability of a given karyotype $(n_1, \ldots, n_{23})$ is obtained by multiplying the probability that the Markov chain corresponding to chromosome $k$ is in state $n_k$ for $1 \leq k \leq 23$.

- We disregard the highly unlikely event that multiple copies of the same chromosome in a cell missegregate simultaneously.
The Markov chain for the basic model

1 \rightarrow 2 \rightarrow 3 \rightarrow 4 \rightarrow 5 \rightarrow 6 \rightarrow 7 \rightarrow 8 \rightarrow \text{dead}

Transition probabilities:
- From 1 to 2: \(1-p\), probability \(p/2\)
- From 2 to 3: \(1-2p\), probability \(p\)
- From 3 to 4: \(1-3p\), probability \(3p/2\)
- From 4 to 5: \(1-4p\), probability \(2p\)
- From 5 to 6: \(1-5p\), probability \(5p/2\)
- From 6 to 7: \(1-6p\), probability \(3p\)
- From 7 to 8: \(1-7p\), probability \(7p/2\)
- From 8 to dead: \(1-8p\), probability \(4p/2\)

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Markov chain for chromosomal instability in tumor evolution
The transition matrix

Each chromosome copy produces 0, 1 or 2 copies in a random daughter cell, with probability $p/2$, $1 - p$ and $p/2$, respectively.

For a cell with $i$ copies, the probability that a random daughter has $j$ copies is given by the coefficient of $x^j$ in

$$
\left( \frac{p}{2} + (1 - p)x + \frac{p}{2}x^2 \right)^i \approx \frac{ip}{2}x^{i-1} + (1 - ip)x^i + \frac{ip}{2}x^{i+1},
$$

ignoring quadratic terms in $p$. 
The transition matrix

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$$

ignoring quadratic terms in $p$.

This gives the transition matrix:

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

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

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

$$
\begin{pmatrix}
1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\frac{p}{2} & 1 - p & \frac{p}{2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & p & 1 - 2p & p & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 3p/2 & 1 - 3p & 3p/2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 2p & 1 - 4p & 2p & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 5p/2 & 1 - 5p & 5p/2 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 3p & 1 - 6p & 3p & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 7p/2 & 1 - 7p & 7p/2 & 0 & 0 & 0 \\
4p & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 4p & 1 - 8p & 0 & 0 \\
\end{pmatrix}
$$
The transition matrix

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

$$
\begin{bmatrix}
1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
p/2 & 1-p & p/2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
0 & 0 & 3p/2 & 1-3p & 3p/2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 2p & 1-4p & 2p & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 5p/2 & 1-5p & 5p/2 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 3p & 1-6p & 3p & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 7p/2 & 1-7p & 7p/2 & 0 & 0 & 0 \\
4p & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 4p & 1-8p & 0 \\
\end{bmatrix}
$$

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

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

$$M = \begin{bmatrix}
1 - p & p/2 & 0 & 0 & 0 & 0 & 0 & 0 \\
p & 1 - 2p & p & 0 & 0 & 0 & 0 & 0 \\
0 & 3p/2 & 1 - 3p & 3p/2 & 0 & 0 & 0 & 0 \\
0 & 0 & 2p & 1 - 4p & 2p & 0 & 0 & 0 \\
0 & 0 & 0 & 5p/2 & 1 - 5p & 5p/2 & 0 & 0 \\
0 & 0 & 0 & 0 & 3p & 1 - 6p & 3p & 0 \\
0 & 0 & 0 & 0 & 0 & 7p/2 & 1 - 7p & 7p/2 \\
0 & 0 & 0 & 0 & 0 & 0 & 4p & 1 - 8p
\end{bmatrix}.$$ 

Let $M$ be the matrix obtained by removing the row and column corresponding to the dead state.
Properties of the transition matrix

- $(M^g)_{i,j}$ is the proportion of cells that have $j$ copies after $g$ generations, starting with a founder cell with $i$ copies.
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- \((M^g)_{i,j}\) is the proportion of cells that have \(j\) copies after \(g\) generations, starting with a founder cell with \(i\) copies.

- Let \(s_g(i) = \text{sum of the entries of the } i\text{th row of } M^g\). Then
  \[
  2^g \prod_{k=1}^{23} s_g(n_k)
  \]
  is the expected number of alive cells after \(g\) generations when the founder cell has \(n_k\) copies of chromosome \(k\) for each \(k\).
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is the expected number of alive cells after \(g\) generations when the founder cell has \(n_k\) copies of chromosome \(k\) for each \(k\).

- For a vector \(v\) describing the initial distribution of the number of copies, the vector \(vM^g\), normalized so its entries sum to one, is the distribution among alive cells of the number of copies after \(g\) generations.
Deviance from modal chromosome copy number

Forward Matlab simulation:
(founder cell has $n_{chrom} = 4$ copies)
Deviance from modal chromosome copy number

Forward Matlab simulation:
(founder cell has $n_{chrom} = 4$ copies)

Markov chain model:
Average number of copies over time

Forward Matlab simulation:

\( p = 0.0025 \)
Average number of copies over time

Forward Matlab simulation:

\[ p = 0.0025 \]

We observe convergence to a near-triploid state.
The following figures are for the Markov chain model with $N = 8$ and a diploid founder cell. Each curve represents a number of copies: 1, 2, 3, 4, 5, 6, 7, 8.

$p = 0.001$

$p = 0.01$
Now take $p = 0.0025$ and run 2000 generations, with a tetraploid founder cell. Each curve represents a given number of copies: $1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16$. 

$N = 8$ 

$N = 16$
The limiting behavior

We are interested in the limiting distribution of the number of chromosome copies (among alive cells) when the number of generations $g$ tends to infinity.
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Since our Markov chain has an absorbing state, its stationary distribution only shows that $\frac{\#\text{alive cells}}{2^g} \to 0$ as $g \to \infty$. 
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Since our Markov chain has an absorbing state, its stationary distribution only shows that $\frac{\text{#alive cells}}{2^g} \to 0$ as $g \to \infty$.

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

**Theorem**

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

In particular, this limiting distribution does not depend on the number of copies of the founder cell.
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Surprisingly, we can prove that 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 modal chromosomal number is always 1, but this will change once we incorporate chromosome scores.
Following experiments by Davoli et al., we assign a score $s_k$ to each chromosome $k$. The total score of a cell with karyotype $(n_1, \ldots, n_{23})$ is:

$$S = \sum_{k=1}^{23} s_k n_k,$$
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and its survival probability at a given generation is

$$Q_{\text{surv}} = e^{c+dS}$$

for some parameters $c$ and $d > 0$. 
Chromosome scores and survival probability

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for some parameters $c$ and $d > 0$.

Again, we can implement this model and run simulations. Instead, we will incorporate the chromosome scores into the Markov chain, and use it to run fast computations and determine limiting behavior.
Decomposing the survival probability

\[ Q_{\text{surv}} = e^{c+dS} = e^{c+d} \sum_k s_k n_k = \prod_{k=1}^{23} e^{c/23+d s_k n_k} q_k(n_k). \]
Decomposing the survival probability

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Let

\[ q_k(i) = e^{c/23+d s_k i} = C \mu^i \]

denote the contribution to the survival probability from chromosome \( k \), where \( C = e^{c/23} \) and \( \mu = e^{d s_k} \).
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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.
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 $A^{(k)}$ restricted to alive cells is:

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

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

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

Letting $s^{(k)}_g(i) = \text{sum of the entries of the } i\text{th row of } (A^{(k)})^g$,

$$2^g \prod_{k=1}^{23} s^{(k)}_g(n_k)$$

is the expected number of alive cells after $g$ generations when the founder cell has $n_k$ copies of chromosome $k$ for each $k$. 

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Markov chain for chromosomal instability in tumor evolution
In human chromosomes, $\mu \in [0.9994, 1.0012]$.

Fix $p = 0.0025$ and a founder cell with 2 copies. Run for 2000 generations.

Each curve represents a number of copies: $1, 2, 3, 4, 5, 6, 7, 8$. 
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Fix $p = 0.001$ and a founder cell with 2 copies. Run for 2000 generations.

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

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

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 $\rho$ and on $\mu$ (equivalently, on the chromosome score).
The limiting distribution

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

\[
p = 0.001
\]
For higher chromosome scores, the limiting distribution favors higher copy numbers.

For positive chromosome scores ($\mu > 1$), the modal number of copies soon becomes higher than one, making this more realistic than the model without scores.

$p = 0.001$
The limiting distribution

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

$p = 0.0025$

$p = 0.01$
The limiting distribution

Liming distributions for $\mu$ in the refined range $1.0002, 1.00025, 1.0003, 1.00035, 1.0004, 1.00045, 1.005, 1.0055, 1.0006$.

\[ p = 0.0025 \]
The limiting distribution

Limiting distributions for the experimentally found values of $\mu$ corresponding to the 23 human chromosomes, and $p = 0.0025$:

![Graph showing fraction of cells vs. number of chromosome copies]
Limiting distributions for the experimentally found values of $\mu$ corresponding to the 23 human chromosomes, and $p = 0.0025$:

The average number of chromosomes per cell in the limit is 72.7, which is an average of 3.16 copies of each chromosome type.
Fraction of alive cells after 1000 generations

Using the experimentally found values for the chromosome scores and starting with a tetraploid founder cell.

Forward Matlab simulation:

![Graph showing fraction of surviving cells and Shannon diversity index as functions of missegregation rate.](image)
Fraction of alive cells after 1000 generations

Using the experimentally found values for the chromosome scores and starting with a tetraploid founder cell.

Forward Matlab simulation:

Markov chain model:

The number of alive cells is maximized for a narrow range of the missegregation rate, around $p \approx 10^{-3}$. 
Changing the survival probability

We can change the survival probability $Q_{\text{surv}}$ by multiplying it by a factor $F$. This is useful to model:

- when the tumor outgrows its blood supply;
- adding treatments to tumors (this makes the survival probability lower only for certain cells).
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- when the tumor outgrows its blood supply;
- adding treatments to tumors (this makes the survival probability lower only for certain cells).

If we multiply $Q_{\text{surv}}$ by $F$ for all cells in our current model with $p = 0.0025$, the size of the tumor increases if $F > 0.51$ and it decreases if $F < 0.50$. 
Targeted therapy and mutations

Targeted therapy targets genes located in a particular chromosome, decreasing the survival probability.
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However, at a given rate $m \approx 10^{-9}$ each target gene is mutated, becoming no longer responsive to treatment. Mutated genes are inherited.
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However, at a given rate \( m \approx 10^{-9} \) each target gene is mutated, becoming no longer responsive to treatment. Mutated genes are inherited.

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 as follows:

States are 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. E.g., for \(N = 8\), there are 44 non-absorbing states.
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In a cell division, each normal copy of the chromosome has probability \(m \approx 10^{-9}\) of mutating (and becoming resistant). Each mutated copy has probability \(r \approx 10^{-9}/4\) of reversing into a normal copy (amenable to treatment).
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In a cell division, each normal copy of the chromosome has probability \(m \approx 10^{-9}\) of mutating (and becoming resistant). Each mutated copy has probability \(r \approx 10^{-9}/4\) of reverting into a normal copy (amenable to treatment).

Again, we disregard highly unlikely events such as mutating and missegregating in the same cell division.
The modified Markov chain

Arrows leaving a typical node \((i_1, i_2)\): 

\[\frac{i_2 p}{2}, \ 1 - ip - \frac{i_1 m}{2} - \frac{i_2 m}{2}, \ \frac{i_1 p}{2}\] 

\((\text{let } i = i_1 + i_2)\)

Misseggregations and mutations
The modified Markov chain

Arrows leaving a typical node \((i_1, i_2)\):

\[
\begin{align*}
(i_1, i_2 - 1) & \quad \text{(let } i = i_1 + i_2) \\
(i_1 + 1, i_2 - 1) & \quad (1 - ip - \frac{i_1 m}{2} - \frac{i_2 m}{2})q_s(i) \\
i_1 - 1, i_2 & \quad \frac{i_2 p}{2}q_s(i) \\
i_1 - 1, i_2 + 1 & \quad \frac{i_1 p}{2}q_s(i) \\
i_1, i_2 + 1 & \quad \frac{i_2 p}{2}q_s(i) \\
i_1, i_2 & \quad \frac{i_1 m}{2}q_s(i) \\
i_1 + 1, i_2 & \quad \frac{i_2 p}{2}q_s(i) \\
dead & \quad 1 - q_s(i)
\end{align*}
\]

Misseggregations and mutations, survival probability
First, we let the tumor grow with the usual parameters $(p, Q_{\text{surv}}, m, r)$, until it reaches $10^9$ cells and it becomes detectable with a CT scan.

Then we apply a drug that targets a given chromosome.
Modeling drug resistance

First, we let the tumor grow with the usual parameters \((p, Q_{\text{surv}}, m, r)\), until it reaches \(10^9\) cells and it becomes detectable with a CT scan.

Then we apply a drug that targets a given chromosome.

This can be modeled in two ways:

1. **Binary resistance**: cells with at least one mutated copy of the treated chromosome are resistant.

2. **The level of resistance depends on the ratio of copies of normal vs. mutated target genes.**
Case 1: Binary resistance

For cells of type $(i_1, 0)$, multiply the survival probability by a factor $F$, which depends on the strength of the treatment.

Cells of type $(i_1, i_2)$ with $i_2 > 0$ behave like before.
Case 1: Binary resistance

For cells of type \((i_1, 0)\), multiply the survival probability by a factor \(F\), which depends on the strength of the treatment.

Cells of type \((i_1, i_2)\) with \(i_2 > 0\) behave like before.

Treatment applied to chromosome 1, tetraploid founder cell:

\[
F = 0.50
\]

\[
F = 0.45
\]
Case 2: Graded resistance

For cells of type \((i_1, i_2)\), multiply the survival probability by

\[
\frac{i_1F + i_2}{i_1 + i_2}.
\]

This factor is \(F\) for cells of type \((i_1, 0)\) and 1 for cells of type \((0, i_2)\).
Case 2: Graded resistance

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This factor is \(F\) for cells of type \((i_1, 0)\) and 1 for cells of type \((0, i_2)\).

Compare binary resistance and graded resistance:
Thank you