Simulating Chromosome Segregation

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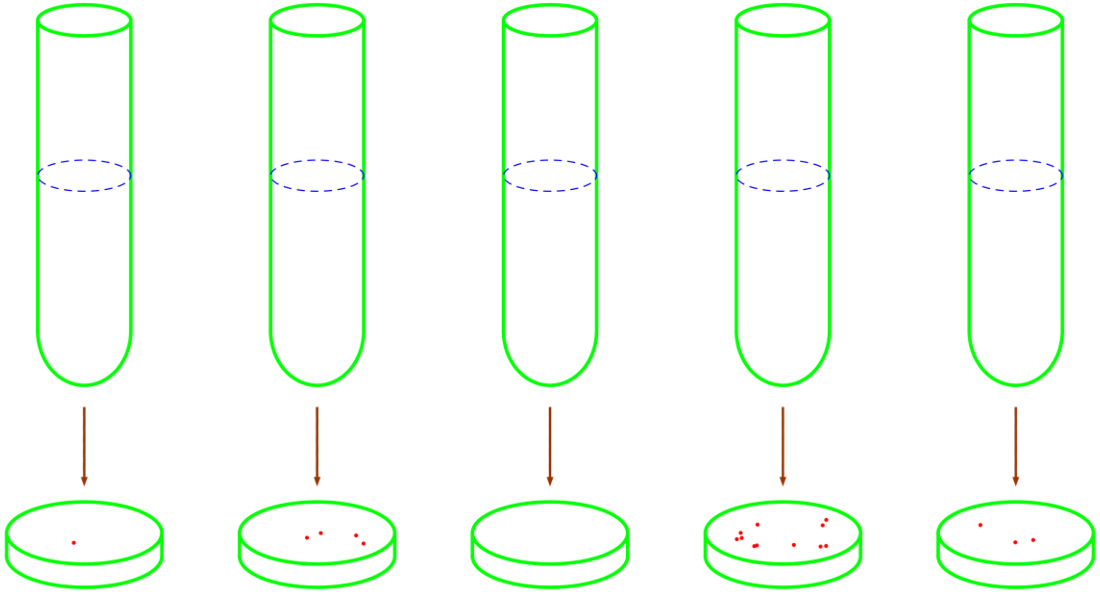
What motivated this study?

- The fluctuation experiment of Luria and Delbrück
- Growing wild type cells in tubes and let mutation occur
- Selecting mutants (e.g., drug resistant mutants) on plates
- Computing a mutation rate from the number of mutants



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Why care about polyploidy?

- A cell may have more than one chromosome
- A cell has a ploidy value of *k* if it has *k* chromosomes
- The classic Luria-Delbrück protocol assumes *k*=1
- Polyploidy complicates the estimation of mutation rates
- So we need to take into account the ploidy value when calculating mutation rates
- The following cells have a ploidy value of 1, 2, 3, 5 and 8

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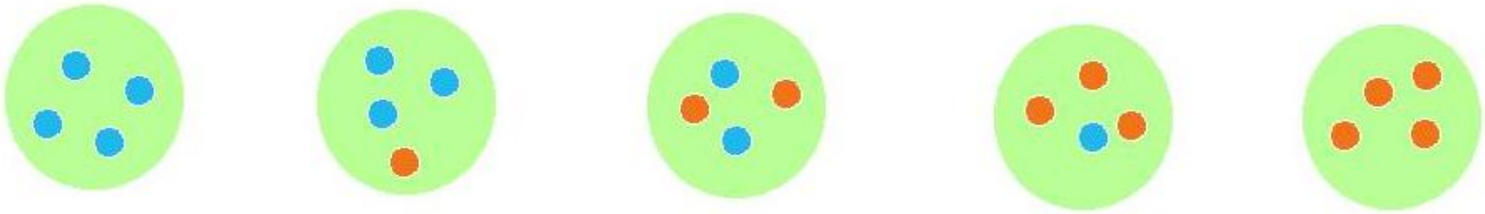
What is the key issue?

- A cell having *k* mutated chromosomes is called a type *k* cell
- With ploidy value = 4, there are 5 types of cells: type 0, type 1, ..., type 4.



- If a cell population starts with a type 1 cell, it may eventually have all possible types of cells
- With a small probability μ, a wild type chromosome may generate a mutated daughter chromosome
- How does a cell population evolve starting with a type 1 cell?

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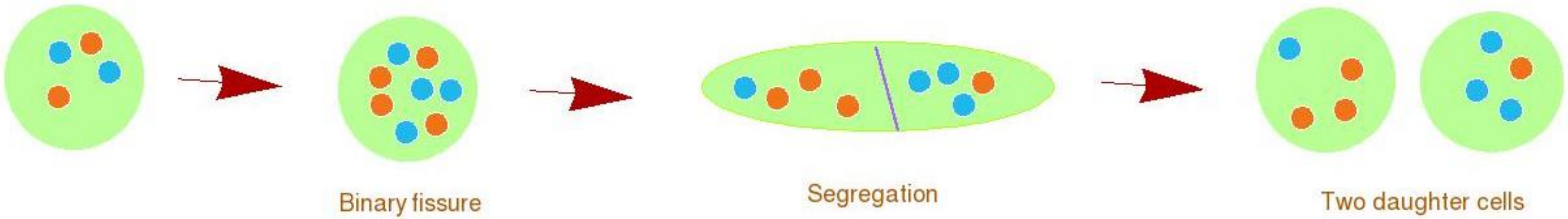
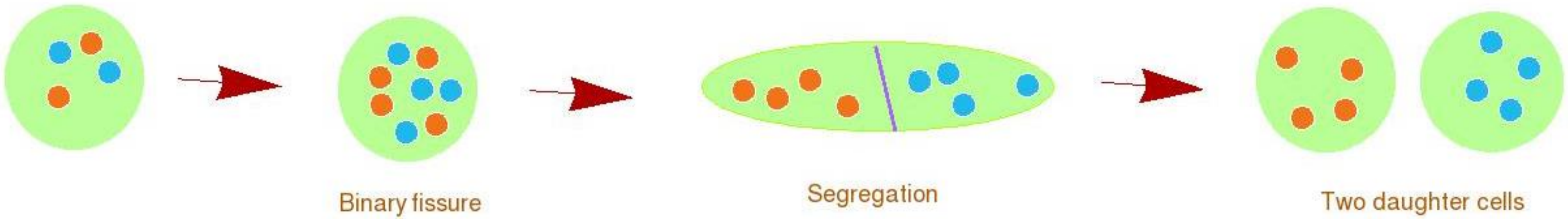
What is random chromosome segregation?



- In this example cells have a ploidy value of 4
- 8 daughter chromosomes are randomly assigned to 2 daughter cells
- A type 2 cell may lead to a type 3 cell and a type 1 cell
- But there are other possibilities, e.g.:



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The fraction of homozygous cells

- If a cell contains only mutated chromosomes, call it a homozygous cell for convenience
- The fraction of homozygous cells is a function of g, the elapsed number of cell generations, and the mutation probability μ
- Current belief: this fraction approaches 1.0 as g increases, at least for cases where the ploidy value is a power of 2
- This claim was derived intuitively
- This claim has not yet been subjected to theoretical verification or rigorous simulation testing

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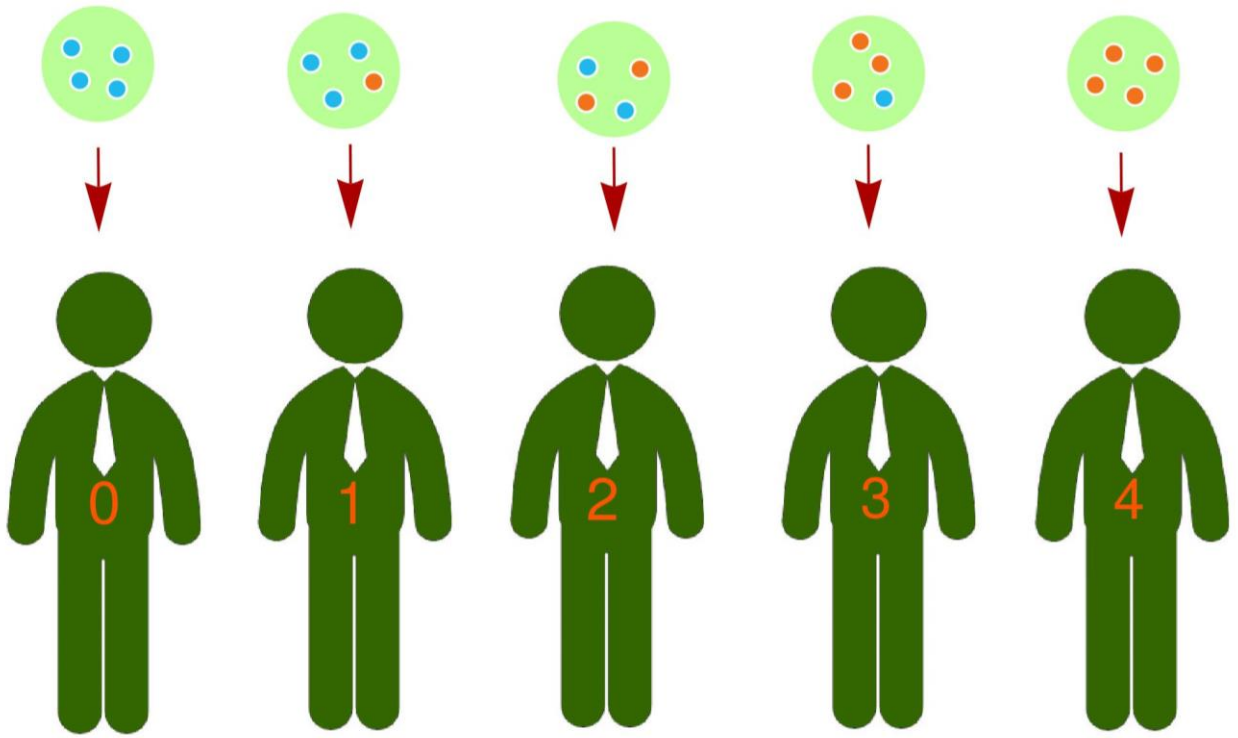
Tackling the key issue by simulation

- Agent based simulation: let each cell be an agent having the number of mutated chromosomes as its attribute
- The model was encoded with NetLogo



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What resources were needed?

- For *g*=25 generations, more than 33 million agents will be generated for each cycle
- With so many agents, running the simulation requires a node having 1 TB of random memory
- For reliable results, at least 500 cycles are needed
- For *g*=27, it requires a node having 2 TB of memory
- It then generates 134 million agents
- One cycle of simulation consumes about 1 hour of CPU time

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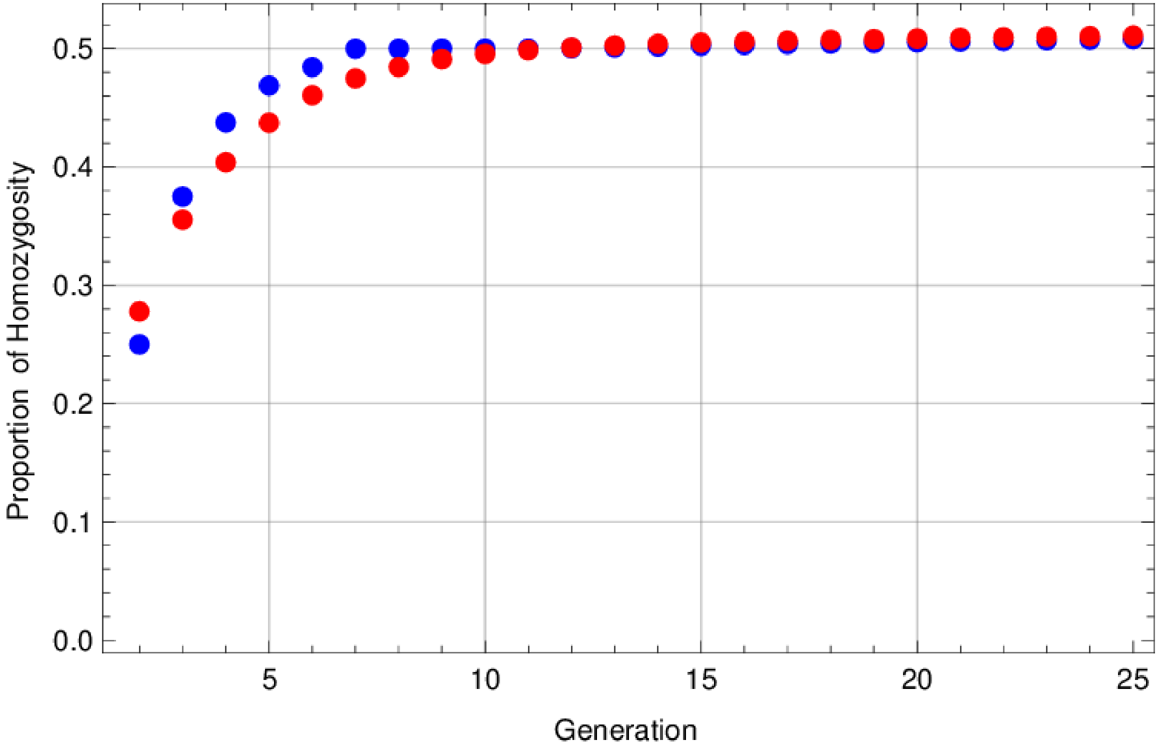
What were discovered?

- It challenges current belief: the proportion of homozygous cells does not approach 1.0
- When ploidy value = 2, μ=0.001, the asymptotic proportion is about 0.5
- Blue = median proportion, red = mean proportion



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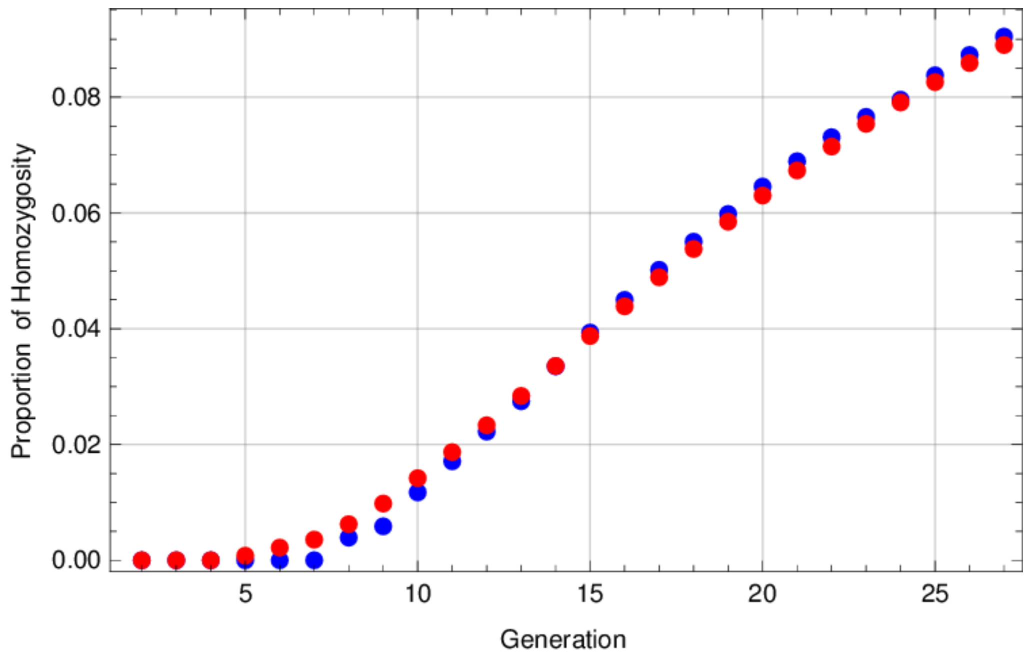
Conjectures and challenges

- Simulations have generated interesting conjectures, e.g.:
- There may be unknown simple relations between the ploidy value and the fraction of homozygous cells
- Challenges: with ploidy value = 8, g=27 may not be sufficient



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