Randomness and information in biological data
BIO-369

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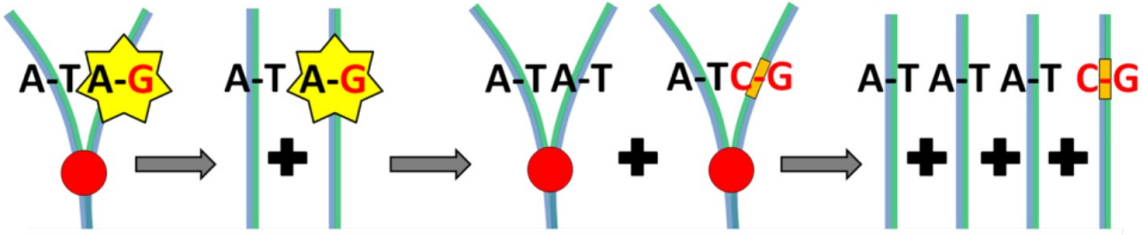
EPFL

Second lecture

Outline of the course

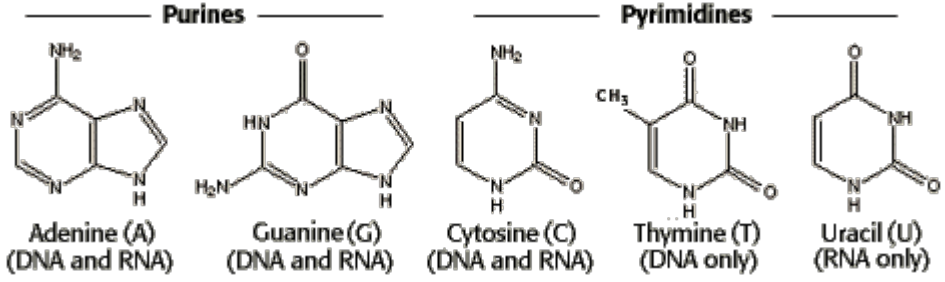
Motivation

- **Mutations are an important source of randomness in biology**
  - Replication errors (rare event)



L. Robert et al, Science 2018

  - Proofreading, mismatch repair system → even rarer
  - Human genome mutation rate ~1.1×10^{-8} per site per generation (from sequencing data)
  - Can be modeled with a fixed uniform rate per site (there are some subtleties, ex. transitions vs. transversions, with transitions changing a purine to an other purine, A ↔ G, or a pyrimidine to another pyrimidine, T ↔ C and transversions being other substitutions, we will neglect them here)
  - Also insertions, deletions – we will not consider them here
  - **Mutations are a major source of diversity and variation in evolution**

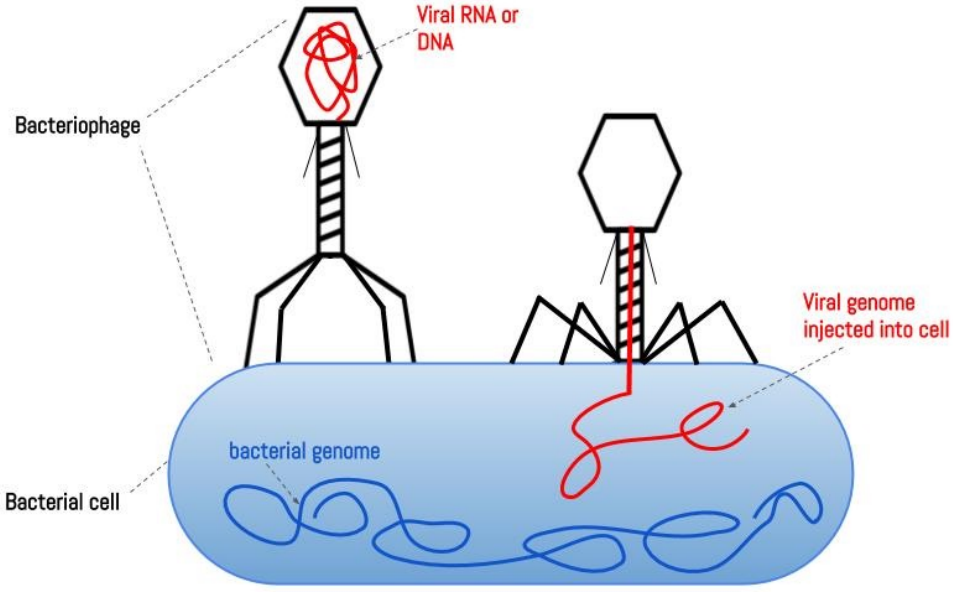


Motivation

- **Luria-Delbrück experiment: use of probabilities to test hypotheses about evolution**

Phage and bacteria (phage T1, obligately lytic virus of *E. coli*)

Bacteria can develop resistance to phage infection



- Is resistance to phage in bacteria a trait that:
  - appears randomly and is then selected upon exposure of bacteria to phage, or
  - appears upon exposure of bacteria to phage (in response to it)?

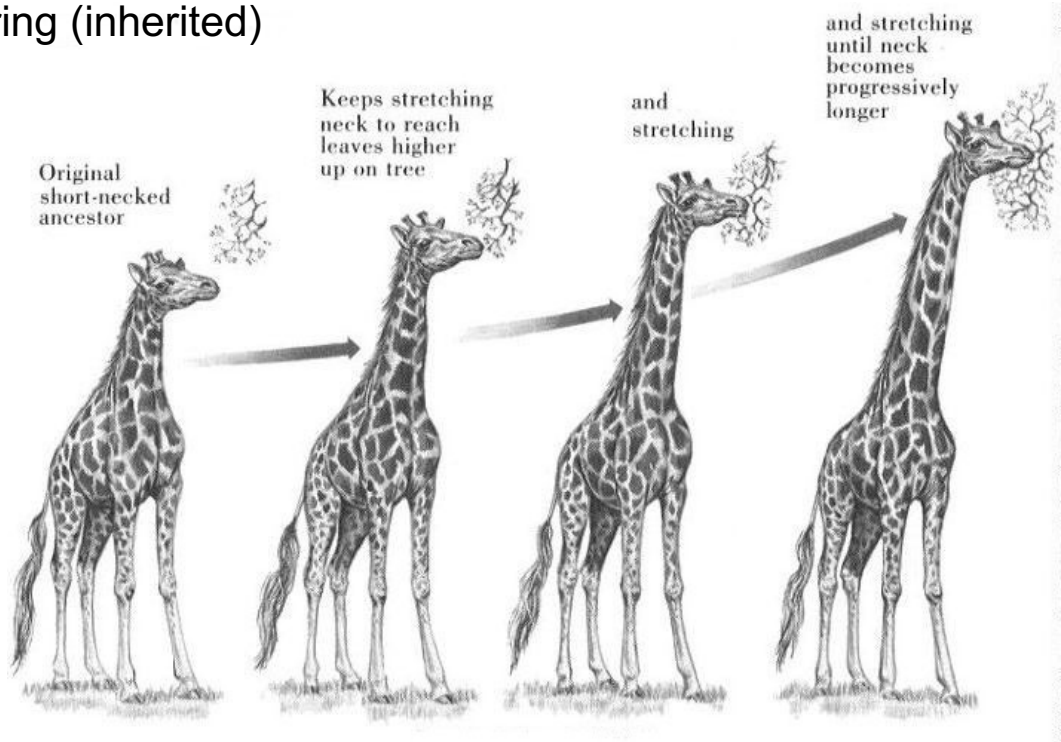
- Each hypothesis yields a different **probability distribution** for the number of phage-resistant bacteria

→ Quantitative test

Context

- **Darwinian evolution: mutations are random and then selection acts on them**
  - Mutations preexist selection (e.g. stress, here exposure to phage)

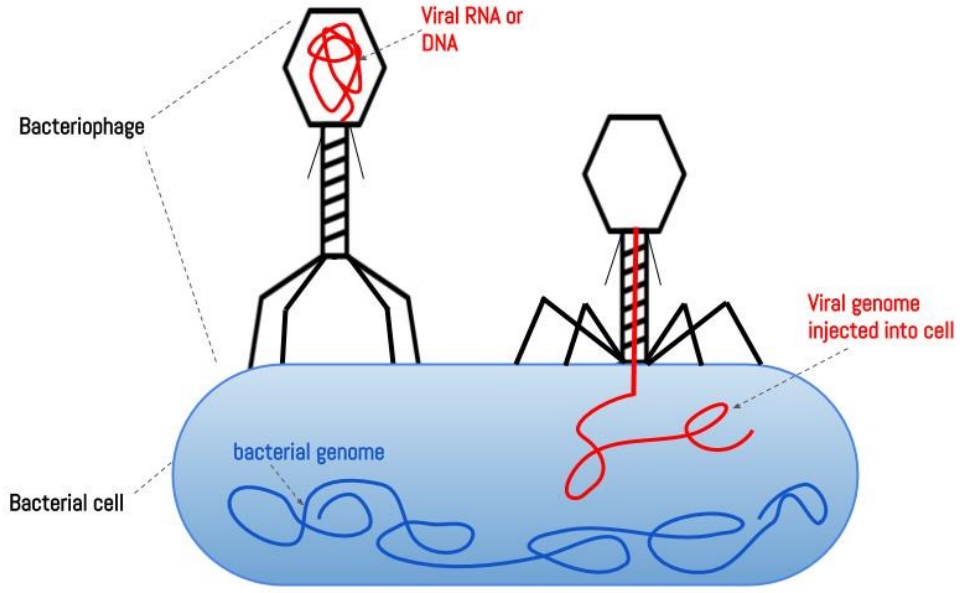
- **Other possibility that was considered historically: inheritance of acquired characteristics (known as Lamarckian evolution)**
  - Use or disuse of organs → adaptation (acquired characteristics)
  - Transmitted to offspring (inherited)



Context

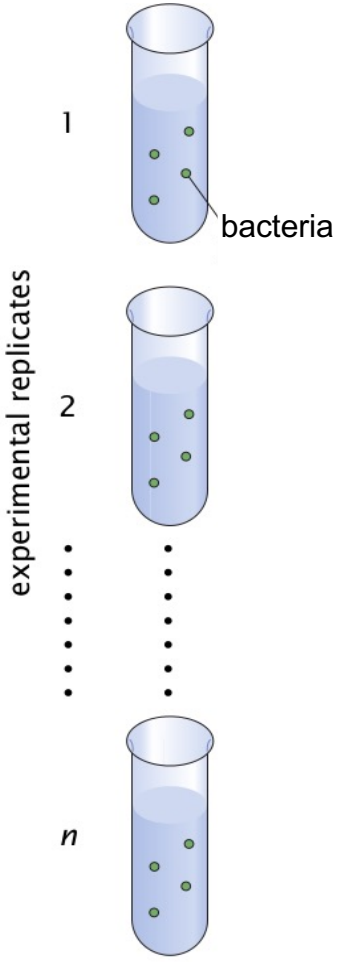
- **Lamarck vs. Darwin: 19th century**
  - Darwinian evolution + Mendelian inheritance → modern synthesis (early 20th century)
- **But it was not clear that these considerations also held for microorganisms / bacteria**

  → Luria-Delbrück experiment (1943): is resistance to phage in bacteria a trait that appears randomly and is selected, or a trait that appears upon exposure of bacteria to phage?



Luria-Delbrück experiment

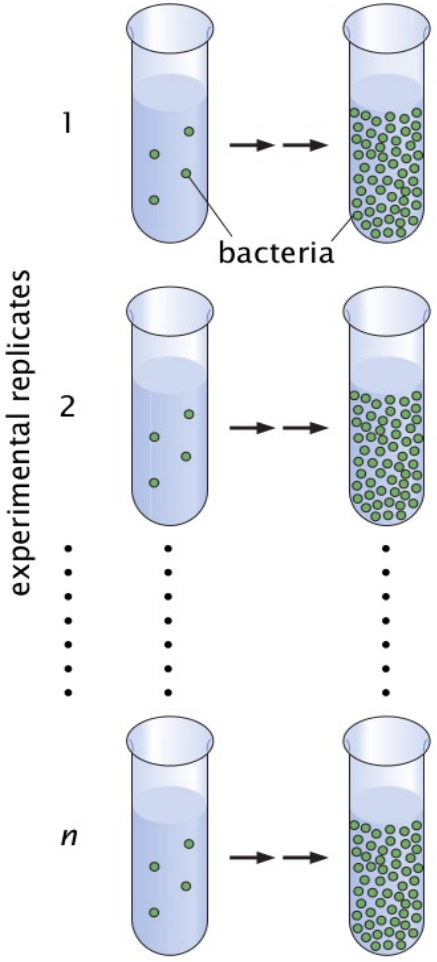
1. Prepare *n* separate identical cultures of the same bacteria



Luria-Delbrück experiment

1. Prepare *n* separate identical cultures of the same bacteria

2. Let them grow

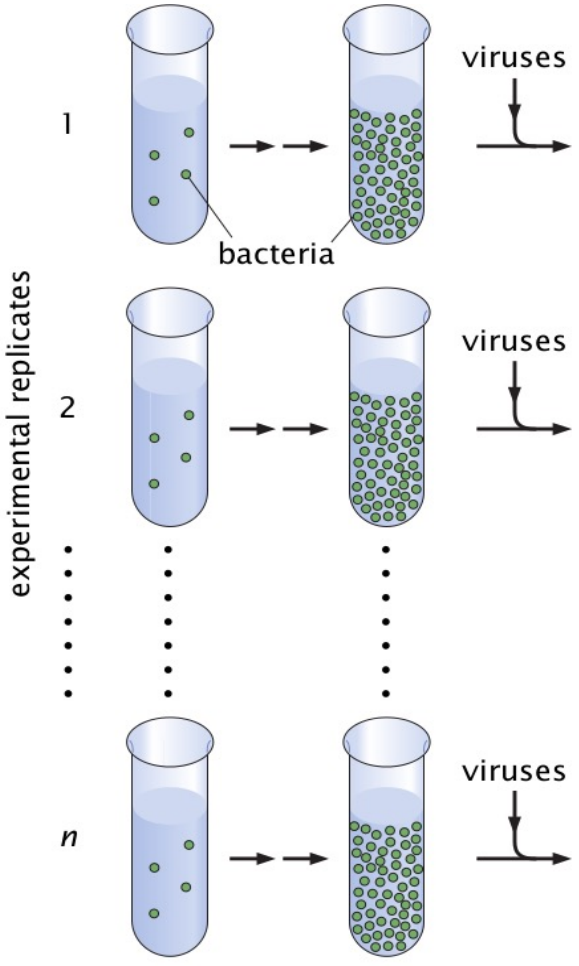


Luria-Delbrück experiment

1. Prepare *n* separate identical cultures of the same bacteria

2. Let them grow

3. Add an excess of bacteriophage viruses (phage T1)
→ most bacteria die; only phage-resistant ones survive



Luria-Delbrück experiment

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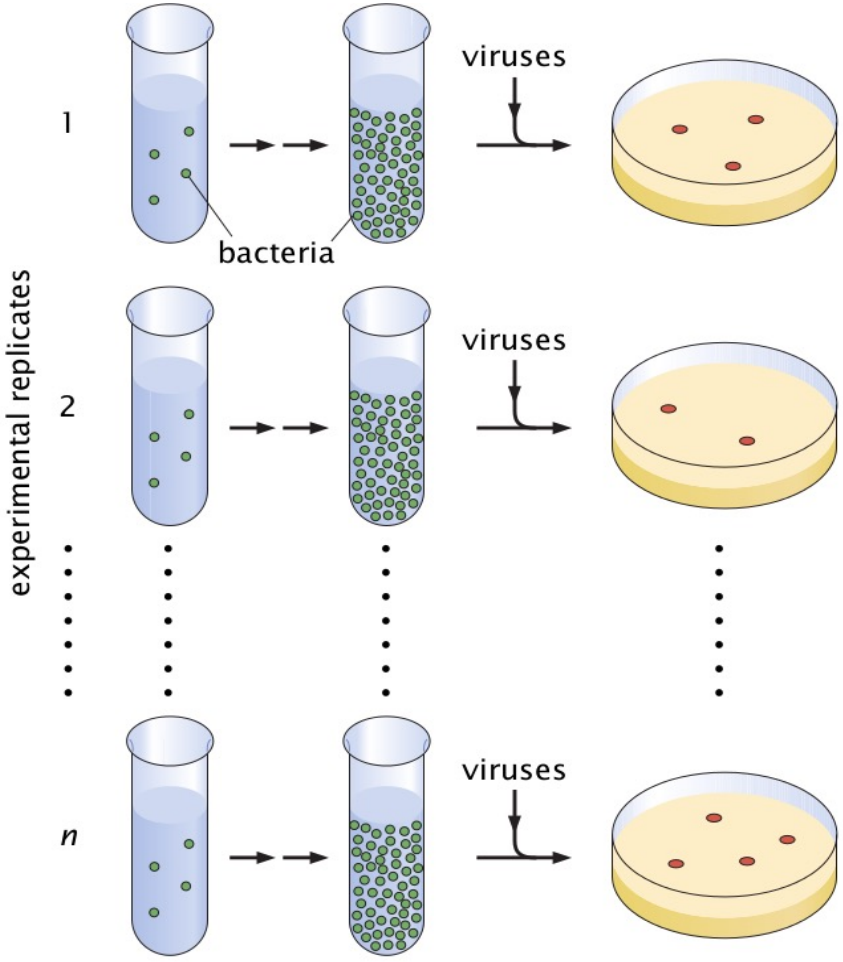
4. To count the survivors, plate each culture separately → each survivor forms a colony



Luria-Delbrück experiment

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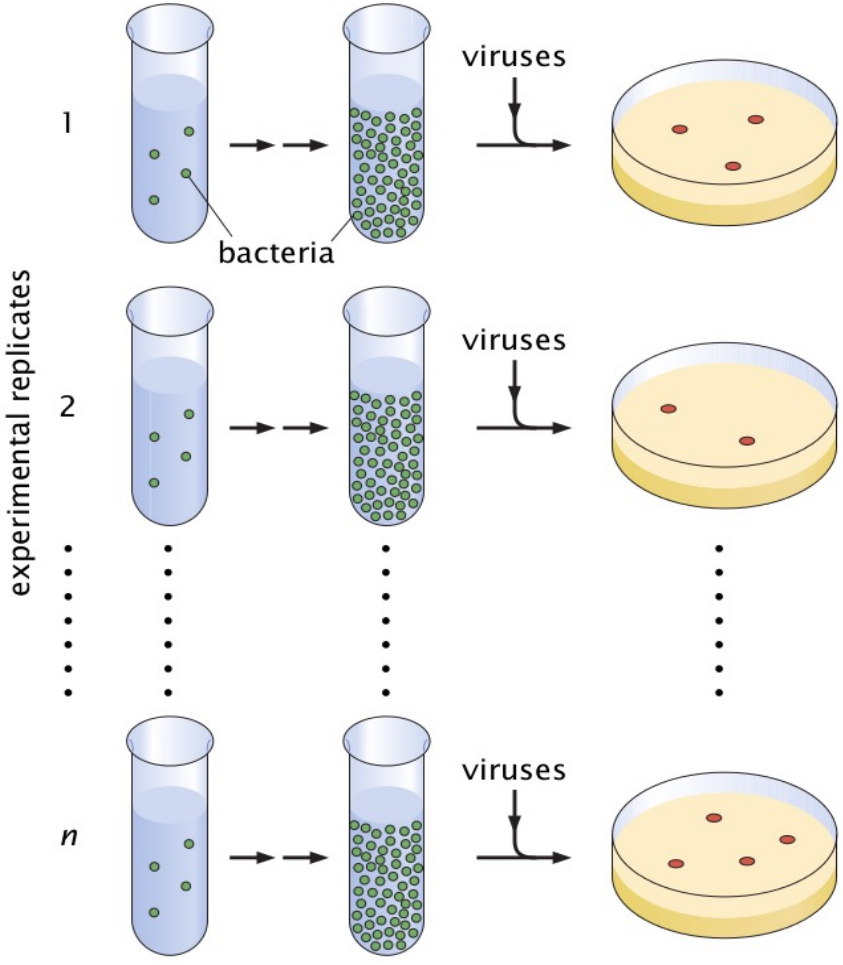
4. To count the survivors, plate each culture separately → each survivor forms a colony

5. Count the number *m* of colonies growing in each plate → get *n* values of *m*



Assume that each cell can mutate with probability μ (mu), and that mutations are independent. What distribution describes whether one cell mutates or not?

A. Bernoulli distribution
B. Binomial distribution
C. Poisson distribution
D. Uniform distribution

To answer, please:

- Connect to http://ttpoll.eu
- Enter the session ID **bio369**
- Select your answer

Assume that each cell can mutate with probability μ (mu), and that mutations are independent. What distribution describes the number m of mutants out of N cells?

A. Bernoulli distribution
B. Binomial distribution
C. Poisson distribution
D. Uniform distribution

To answer, please:

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Under the random mutation (Darwinian) hypothesis, do you expect the variance of the number of mutants to be:

0% A. The same as its mean – as in the Lamarckian case

0% B. Larger than its mean

0% C. Smaller than its mean

0% D. It depends

To answer, please:

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Assume that mutations occur upon division, and that one new mutation event yields one mutant daughter cell. If we start from one cell and there are two generations, what is the maximal number of mutant cells in the population?

A. 1
B. 2
C. 3
D. 4

To answer, please:

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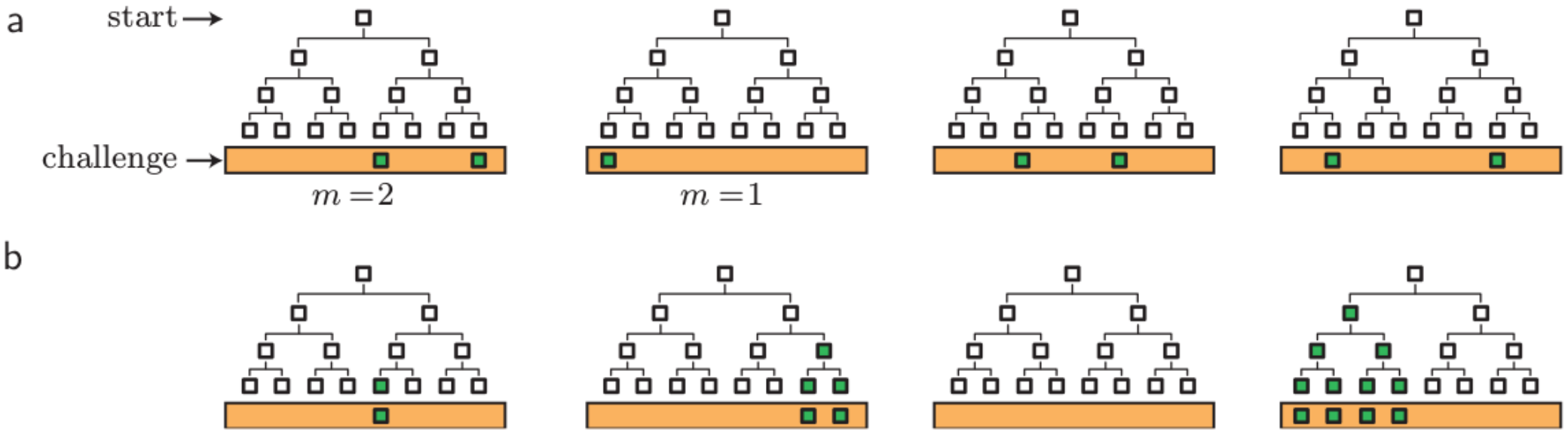
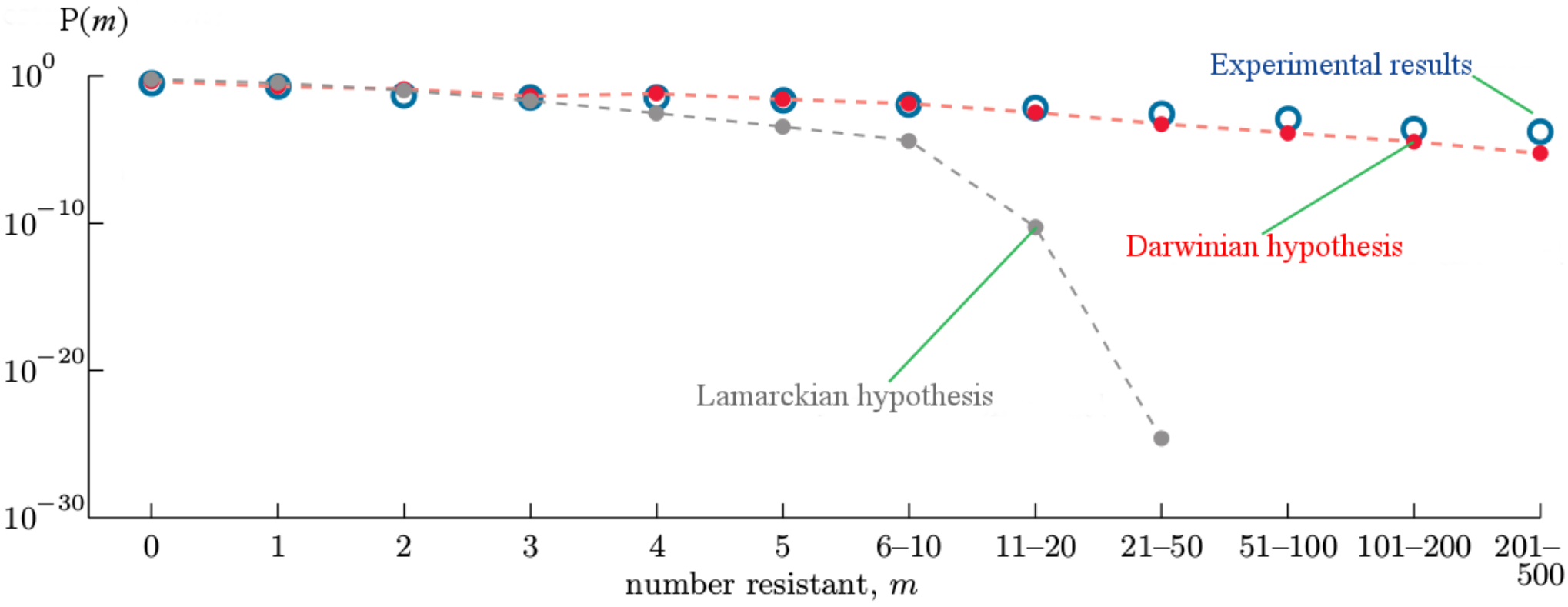
Luria-Delbrück experiment



a: Lamarckian hypothesis - resistance to phage in bacteria appears upon exposure of bacteria to phage

b: Darwinian hypothesis - resistance to phage in bacteria appears randomly and is selected upon exposure of bacteria to phage

Luria-Delbrück experiment



Conclusion

- The Luria-Delbrück experiment showed that mutations in bacteria occur spontaneously and randomly, not in response to a challenge (Nobel prize in Medicine 1969)

- **Importance of probabilities to formulate quantitative hypotheses about biological data**

- Impact: understanding mechanisms of resistance evolution

- The Luria-Delbrück experiment is at the base of standard methods used in labs to compute mutation rates (fluctuation test, ex. FALCOR software)

- Evolution is primarily Darwinian, with spontaneous mutations and selection, but:
  - CRISPR-Cas9 is an example of Lamarckian evolution
  - Horizontal gene transfer and stress-induced mutagenesis have some Lamarckian features
  - Epigenetics means that some acquired traits can be (at least temporarily) inherited

Koonin & Wolf, 2009

Outline of the course