ECS129
Information and Fluctuations of Information

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The Cell

1. **Quantum of life:**
   from 1 cell (bacteria), to $10^{13}$ in a human
   (trivia: there are approx. $10^{14}$ bacteria in our guts!
   - we generate approx. $10^{16}$ cells during our life time)

2. **Cells are “machines”:**
   They can produce chemical or mechanical work. They take energy from their environment.

3. **Cells self-replicate**

4. **Their blueprint is the DNA they contain**
All cells of an organism contain the same information...however, they may differ in aspect...and functions.
How to replicate a machine?
How to replicate a machine?

➢ list of parts and parts themselves
➢ a set of instructions on how to put parts together (design)
➢ an operator
➢ a manual on how to use the machine
The Cell

Blueprint: parts + design

Assembly

Operation "manual"

DNA, genes

Proteins, nanomachines

Processing: logic
Information and Fluctuations

Information support: DNA

Information fidelity: copying and proofreading

Fluctuations of information
Information: copying mechanism

(library.thinkquest.org)

(replicationdna.blogspot.com)
Information: Fidelity

Some facts about DNA replication:

- 6 billion nucleotides of the human genome are replicated in only a few hours
  \textit{Remark: DNA polymerase processes \textasciitilde 1000 nucleotides/s)}

- Spontaneous error rate < 1 mutation / genome /cell division

-- Where is this accuracy coming from?
  - Specificity
  - Proofreading
  - Post replication repair
Information: Fidelity

Determinants of DNA Replication Fidelity

Replication
Normal:
- Polymerase Selectivity
- Exonucleolytic Proofreading

Stalled Forks:
- Checkpoints
- Fork Regression
- Translesion DNA Synthesis
- Recombinational Repair

Pre-Replication
- Sanitizing dNTP Pools
- Base Excision Repair
- Nucleotide Excision Repair
- Interstrand Crosslink Repair
- Non-Homologous End Joining

Post-Replication
- DNA Mismatch Repair

(http://www.niehs.nih.gov/research/atniehs/labs/lmg/dnarf/)
Information: Fidelity

Base Substitution Error Rates

A⁺, B⁺, C⁺ Pols ← A⁻, B⁻, C⁻ Pols, RT⁻ → Y⁻ Pols
Replic. Complexes ← X⁻ Pols → Y⁻ Pols

10⁻⁸ 10⁻⁷ 10⁻⁶ 10⁻⁵ 10⁻⁴ 10⁻³ 10⁻² 10⁻¹ 1

A⁺, B⁺, C⁺ Pols

A⁻, B⁻, C⁻ Pols, RT⁻ ← X⁻ Pols → Y⁻ Pols

Single Base Deletion Error Rates

Kunkel T A J. Biol. Chem. 2004;279:16895-16898
Information: Fidelity

DNA Mismatch Repair in *E. coli*

Misincorporated Nucleotide

(mmr.med.ohio-state.edu)
Information: Fidelity

Damaged nucleotide

Uvr-A, Uvr-B, Uvr-C

DNA polymerase I
DNA ligase
Information and Fluctuations

Information support: DNA

Information fidelity: copying and proofreading

Fluctuations of information
Information and Noise

The Shannon-Weaver Mathematical Model, 1949

Concepts:
Entropy
Redundancy
Noise
Channel Capacity

Noise = unwanted signal
How do we measure longitude?

One approach is to look at the time difference between the current position and a Universal time (say at Greenwich).

Sailors would then carry a robust clock (chronometer) to identify Universal time:
- Cook (1772) carried one
- Darwin (1831) carried 22!
Unwanted noise

Computers also encounter noise!

The Ariane 5 tragedy: On June 1996, The first Ariane 5 was launched… And exploded after 40 seconds!

The failure of the Ariane 501 was caused by the complete loss of guidance and altitude information 37 seconds after start….due to a numerical error!
“Everything that living things do can be understood in terms of the jiggling and wiggling of atoms.”

Richard Feynman
Darwin’s view of mutation plays a central role in his theory of biological evolution:

- Mutation provides the variation (raw material) upon which natural selection acts.
- According to Darwin, the environment does not direct evolution, rather it passively selects among variants.
Evolution in the laboratory

In 1988, Lenski started a long term experiment: he prepared 12 identical flasks of Ecoli cultures on minimal medium, with glucose. Each day, an aliquote of each flask is used to inoculate a fresh medium.

The experiment has been running for more than 25 years, covering more than 50,000 generations.
Evolution in Lenski’s cultures

All 12 cultures lead to cells with larger volumes (better adapted to minimal medium)

Some bacteria in one of the 12 cultures started using citrate as a food source.
Luria and Delbruck experiments

The first step in the multiplication of a virus is its attachment to a host cell; more than one virus particle can simultaneously adsorb to a single cell.

** ADSORPTION **

Protective coat
Viral chromosome

Entrance of the viral chromosome into the host cell

** PENETRATION **

Lytic cycle (usually takes 15–60 min at 37 °C)

Release of new virus particles by lysis of the host cell wall

** LYSIS **

The viral chromosomes are surrounded by newly synthesized protective coats.

** SYNTHESIS OF EARLY PROTEINS **

Replication of viral DNA

** REPLICATION OF VIRAL DNA **

Multiplication of the viral chromosome

** ASSEMBLY **

SYNTHESIS OF LATE PROTEINS

(http://textbookofbacteriology.net/phage.html)
Luria and Delbruck experiments

After infection with a phage, a culture of E.Coli will clear up…to grow back again after a few hours: some resistant bacteria survived, leading to a new resistant colony.

How did these variants come to be? Two hypotheses:

-Hypothesis of acquired immunity
  The variants were exposed to the phage, but survived the attacks; their progeny maintained the immunity

-Hypothesis of mutation to immunity
  Immunity comes from mutations that occurred independently of the presence of the virus.
Hypothesis 1: Induced mutation

Resistant mutants *arise in response* to the bacteriophage. All progeny from the survivors are also resistant.

If correct, we expect:

- A large # of small cultures will have a nearly constant proportion of resistant cells.
- Mutant cells arise only after selection begins with the addition of phage, not before.
Hypothesis 2: Spontaneous mutation

Mutations *arise by chance* at a constant rate and at any point in time; the mutation is subsequently selected for.

**If correct, we expect:**

- The number of resistant cells will be determined by how early in a culture the mutation event occurred.
- A large # of small cultures will have the proportion of resistant cells fluctuate.
Luria and Delbruck experiments

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<td>variance/mean</td>
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The **mutation frequency** is the frequency or proportion at which a specific kind of mutation is found in a population of cells or individuals.

4 mutants out of 8 cells total

**mutation frequency** = \( \frac{4}{8} = \frac{1}{2} \)
The **mutation rate** is a measure of the basic tendency of a gene to mutate.  

1 in the total # of cell divisions (7 total)  

= $1/7$ (1 mutation per seven cell divisions)


Mutations of bacteria from virus sensitivity to virus resistance. Luria, S.E. & Delbrück, M. *Genetics* (1943), 28:491