Lecture 1

1. Cell cycle and function of the genome

- G1
- S (Synthesis of new DNA)
- G2
- M (Mitosis, i.e., cell division)
- New copies of sister chromatids
- Four copies of each chromosome
- Two homologous chromosomes

2. Genomes and genes

<table>
<thead>
<tr>
<th>Genome</th>
<th>Single-cell eukaryotes (e.g., yeast)</th>
<th>Higher eukaryotes (e.g., human)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td>5 x 10^6 bp</td>
<td>3.10^9 bp</td>
</tr>
<tr>
<td>S x 10^7 bp</td>
<td>x &quot;ploidy&quot;</td>
<td>x ploidy (i.e., 2 in 61, 4 in 62)</td>
</tr>
<tr>
<td>Number of genes</td>
<td>5000</td>
<td>25,000</td>
</tr>
<tr>
<td>Gene length</td>
<td>~ 500 bp</td>
<td>~ 10^3 bp</td>
</tr>
<tr>
<td></td>
<td></td>
<td>~ 10^3 - 10^5 bp (due to splicing)</td>
</tr>
</tbody>
</table>
**Bacteria**

- Gene

- Fraction of DNA genes

- Estimate by reversals

- $4 \times 10^6 / 5 \times 10^6$

- $\approx 80-50\%$

- $3 \times 10^6$

- $6 \times 10^5 / 5 \times 10^5$

- $\approx 10\%$

- Most of genomes are "non-coding" (i.e., not coding for proteins)

**Spherical eukaryote**

- or

- Few introns

- Higher Eukaryote

- Many long introns

- $2.5 \times 10^9 / 10^4$

- $2.5 \times 10^4 / 10^4$

- $3 \times 10^9$

- $5 \times 10^4 / 10^2$

- $\approx 1.5\%$

**Length scales**

- Cytoskeleton

- 2 microns

- 1-2 microns

- 0.5 microns

- Bacteria
Total length of DNA in each cell? [Estimate by themselves]

\[ 16 \text{bp} = 0.3 \text{nm} ; \quad \text{DNA} \phi = 2 \text{nm} \]

Bacteria

F4east

Human

\[ 1.5 \times 10^5 \text{nm} = 150 \mu \text{m} \]

\[ 1.5 \times 10^6 \text{nm} = 1.5 \text{mm} \]

\[ \sim 1 \text{m} (x \text{ploidy}) \]

\[ \sim 10^6 \mu \text{m} \]

[All much bigger than cell nucleus]

(4) Time scales

Bacteria

Yeast

Cell Division

\[ 20 \text{min} - 1 \text{h} \]

\[ \sim 50 \text{min} \]

Human and other higher eukaryotes

\[ \sim 24 \text{h} \]

but can be as fast as

\[ \sim 20 \text{min} \]

(e.g., early development)

(5) Gene expression aka "transcription"

DNA copying (synthesis; "replication"

new DNA

new DNA
Warm-up problem: How bacteria copy its DNA

DNA length: $5 \times 10^6$ bp

Speed of DNA polymerase: 500 bp/sec (200-1000 bp/sec)

- How long does it take to replicate the whole genome?

$5 \times 10^6 / 500 = 10^4$ sec $\approx 3$ hr

but the divide is 20 min!

$\Rightarrow$ need multiple origins of replication

$\Rightarrow$ nested replication

i.e. making DNA for your grandchildren

How big is a calf of DNA?
Intro to Polymer Physics

Polymers:

\[ \text{C monomers} \quad \xrightarrow{\text{E}} \quad \text{2 monomers} \]

Model: freely jointed chain

\[ R(N) = \text{Random Walk in 3D} \]

\[ \langle R^2(N) \rangle = a^2 \cdot N \]

end-to-end distance

How to measure flexibility of a real chain

\[ \langle \varepsilon(0) \varepsilon(5) \rangle \sim e^{-s/l_p} \]

where \( l_p \) is the persistence length

Can be shown that

\[ \langle R^2(L) \rangle = 2l_pL \]

\( l_p \) is the persistence length

if \( N = \frac{1}{2} l_p \) i.e. \( N \) segments of \( 2l_p \) each

then indeed

\[ \langle R^2 \rangle = 2l_pL = (2l_p)^2 \cdot N = a^2N \]

\[ a = 2l_p \]

Kuhn's length

Real chains can be represented as a set of \( 2l_p \) segments
Real continuous polymer can be represented as a series of segments where each segment = 2e_p

\[ a = 2e_p \quad \text{Khun's length} \]

lp for DNA = 50 nm = 150 bp
\[ (a = 3006 bp) \]

How large are coils of DNA in (10 minutes)?

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<tr>
<th>Bacteria</th>
<th>Yeast</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>All DNA: 5 \times 10^6 bp</td>
<td>12 \times 10^6 bp</td>
<td>3 \times 10^9 bp</td>
</tr>
<tr>
<td>( (5 \times 10^6 \div 3 \times 10^5)^2 )</td>
<td>15 \mu m</td>
<td>10^6 \mu m = 1 m</td>
</tr>
<tr>
<td>4 \times 10^4 bp</td>
<td>( \frac{15 \mu m}{6} = 2.5 \mu m \approx 10^6 \text{ bp} )</td>
<td>doesn't fit</td>
</tr>
</tbody>
</table>

One chromosome:
- Bacteria: 5 \times 10^6 bp
- Yeast: \( \sim 10^6 \) bp
- Human: \( \sim 10^8 \) bp

- Yeast: 3-4 \mu m
- Human: 10^5 \mu m

- Yeast: fits
- Human doesn't fit
3. How is it really packed?

Nucleosomes: (in euchromatin only)

- Protein core of a nucleosome
  - ~150 bp
  - 1.7 turns

- Higher i.e. provides
  - \( \approx \pi \times 1.7 = 5 \text{fold} \) linear compaction

- Nucleosome
  - Structure ~150 bp
  - Fiber structure ~10 nm

Size of coils

- Estimate: \( \frac{1}{1000} \) kb

R(L) chromosomes by this 10 nm chromatin fiber

- Estimate volume fraction of chromatin in the nucleus
2a) Estimate the number of nucleosomes in DNA.

Solution: assume 10μm fiber

\[ L = 10^8 \text{ bp} = \frac{10^8}{200} \text{ nucleosomes} \]

\[ l_p \approx 5 \text{ nucleosomes} \]

\[ R = \sqrt{2l_pL} = \sqrt{5 \cdot 10^8} = 200 \text{ nucleosomes in length} \]

\[ \text{Length of each nucleosome} = \frac{50 \text{ bp}}{15 \text{ nm}} \]

\[ L = 10 \text{ k} = \frac{10 \cdot 10^3}{200} \text{ nm} \approx 0.2 \text{ mm} \]

Short chromosome: \[ 2 \cdot 10^7 \text{ bp} \]

\[ R(L) \approx 1.2 \text{ μm} \leq \text{fits inside nucleus} \]

Human: \[ L = 10^8 \text{ bp} \]

\[ R = \sqrt{2L \cdot l_p} \approx \sqrt{\frac{10^8 \cdot 10}{200}} = \sqrt{5 \cdot 10^6} = 2 \times 10^3 \text{ nucleosomes} \]

Short chromosome: \[ L = 2 \cdot 10^7 \text{ bp} \]

\[ R \approx 20 - 40 \text{ μm} \leq \text{a bit bigger} \]

(or one "arm" of a chromosome) \[ R \approx 4 - 8 \text{ μm} \]

fits into large nucleus.
36. Volume fraction of DNA for bacteria
- Chromatin for eukaryotes

- DNA in bacteria
  \( L = 5 \times 10^6 \text{ bp} \)

  \[ \text{DNA 1 bp = 0.3 nm} \]
  \[ D = 2 \text{ nm}; \theta = 1 \text{ mm} \]

  \[ V_{\text{DNA}} = 1.6 \times 10^8 \text{ mm} \times 3 \text{ mm}^2 = 5 \times 10^6 \text{ mm}^3 \]

  \[ V_{\text{bacteria}} = 2.3 \times 10^6 \approx 10 \]

  \( \phi = 0.005 \)

  Small! plenty of room but DNA's big!

- Chromatin: assume 10 nm DNA fiber

  Yeast: \( L = \frac{12 \times 10^6}{200} = 6 \times 10^4 \text{ nucleosomes, each } \approx 4.125 \text{ nm} \)

  \( V_{\text{DNA}} = 3 \times 10^4 \text{ mm}^3 = 3 \times 10^7 \text{ mm}^3 \)

  \( V_{\text{nucleus}} (< 1 \mu m) = 4.10^3 \text{ nm}^3 \)

  \( \phi = 0.01 = 1 \% \)

  Still lots of space!

  Human: \( L = \frac{2.3 \times 10^9}{200} = 3.10^7 \text{ nucleosomes} \)

  \( V_{\text{DNA}} = 3 \times 10^9 \text{ mm}^3 \approx 1.5 \times 10^{10} \text{ mm}^3 \)

  \( V_{\text{nucleus}} = 500 \mu m^2 = 5 \times 10^9 \text{ mm}^3 \)

  \( \phi = 3 \times 10^{-2} = 3 \% \)