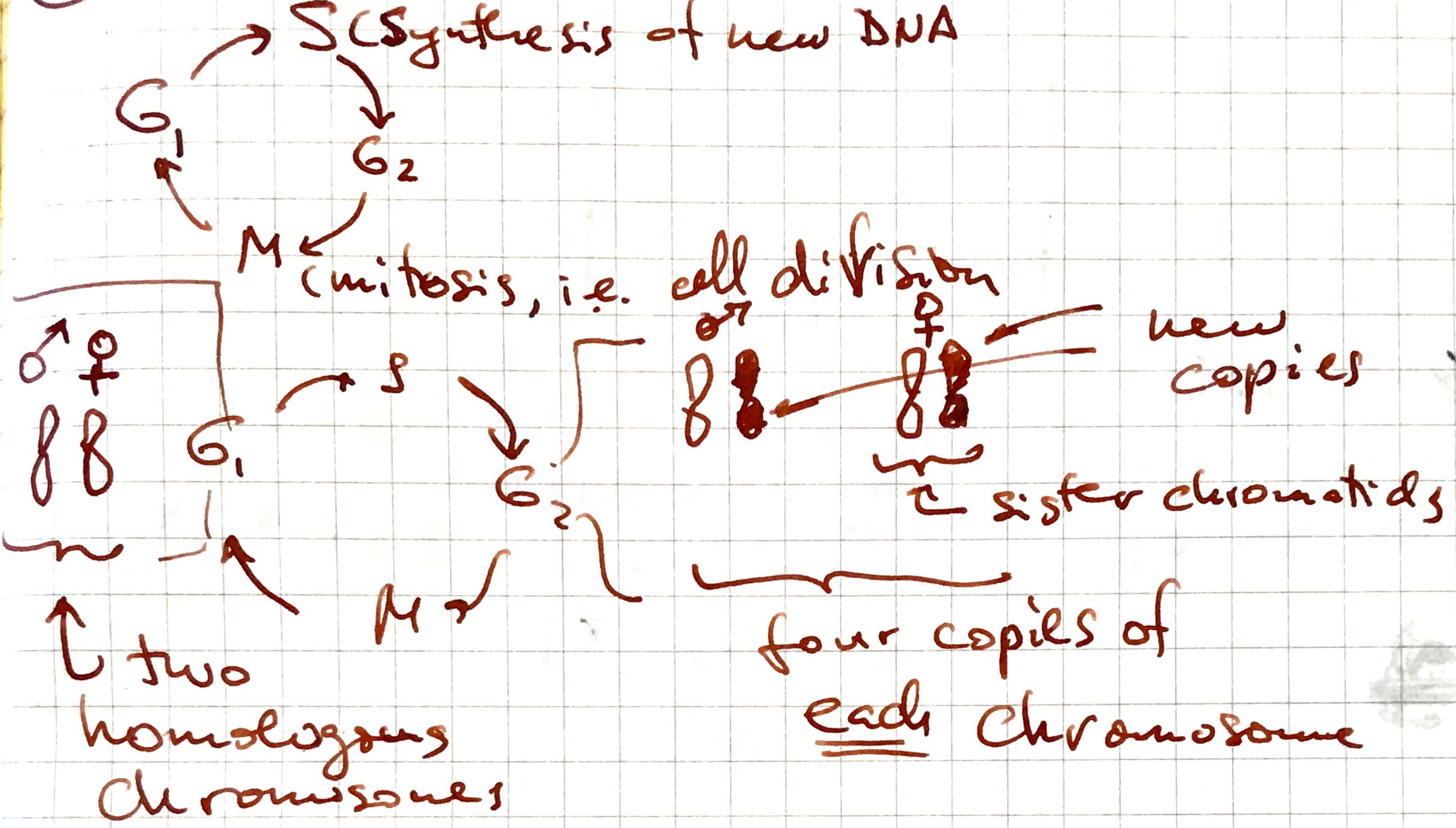
Datum / Date:

Lecture 1

(1.) Cell cycle and function of the genome

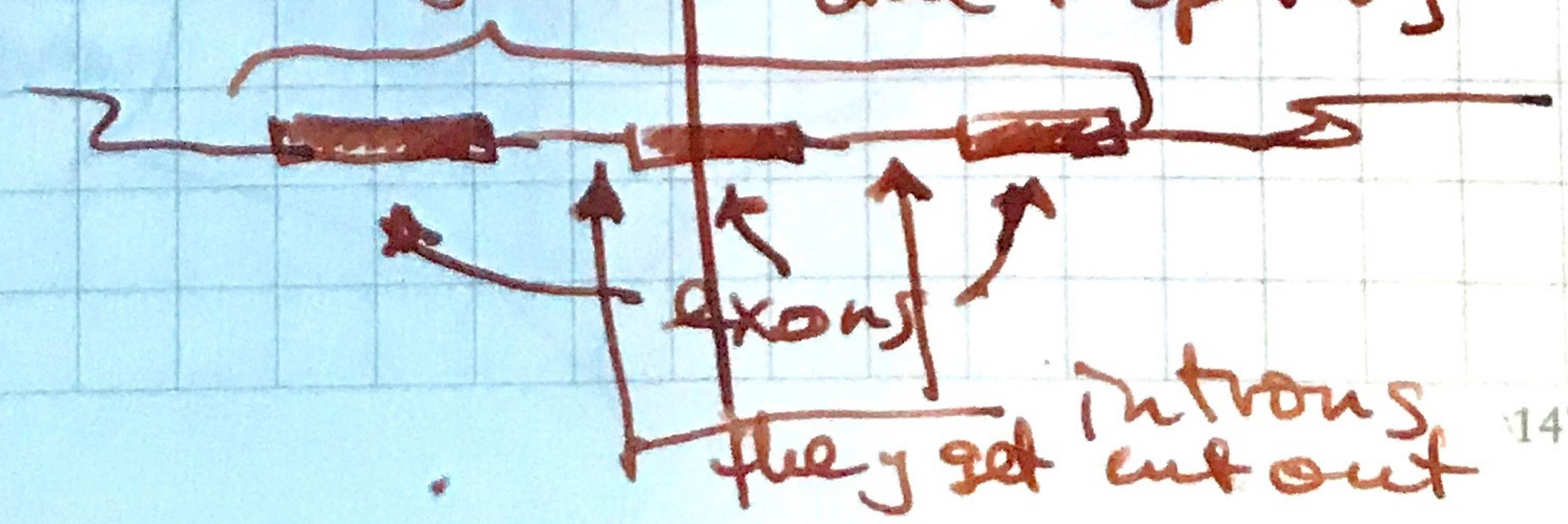


(2.) Genomes and genes

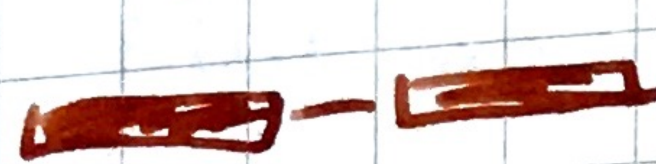
Bacteria	Single-cell eukaryotes (e.g. yeast)	Higher eukaryotes (e.g. human)
5×10^6 bp	5×10^7 bp × "ploidy" (i.e. 2-4)	$3 \cdot 10^9$ bp × ploidy (i.e. 2 in G1, 4 in G2)

Number of genes

Bacteria	Single-cell eukaryotes	Higher eukaryotes
4000	6000	25,000
Gene length ~ 500 bp	~ 10^3 bp	~ 10^3-10^5 bp due to splicing



Datum / Date:

Bacteria	Single-cell eukaryotes	Higher Eukaryotes
 gene	 or  few introns	 many long introns

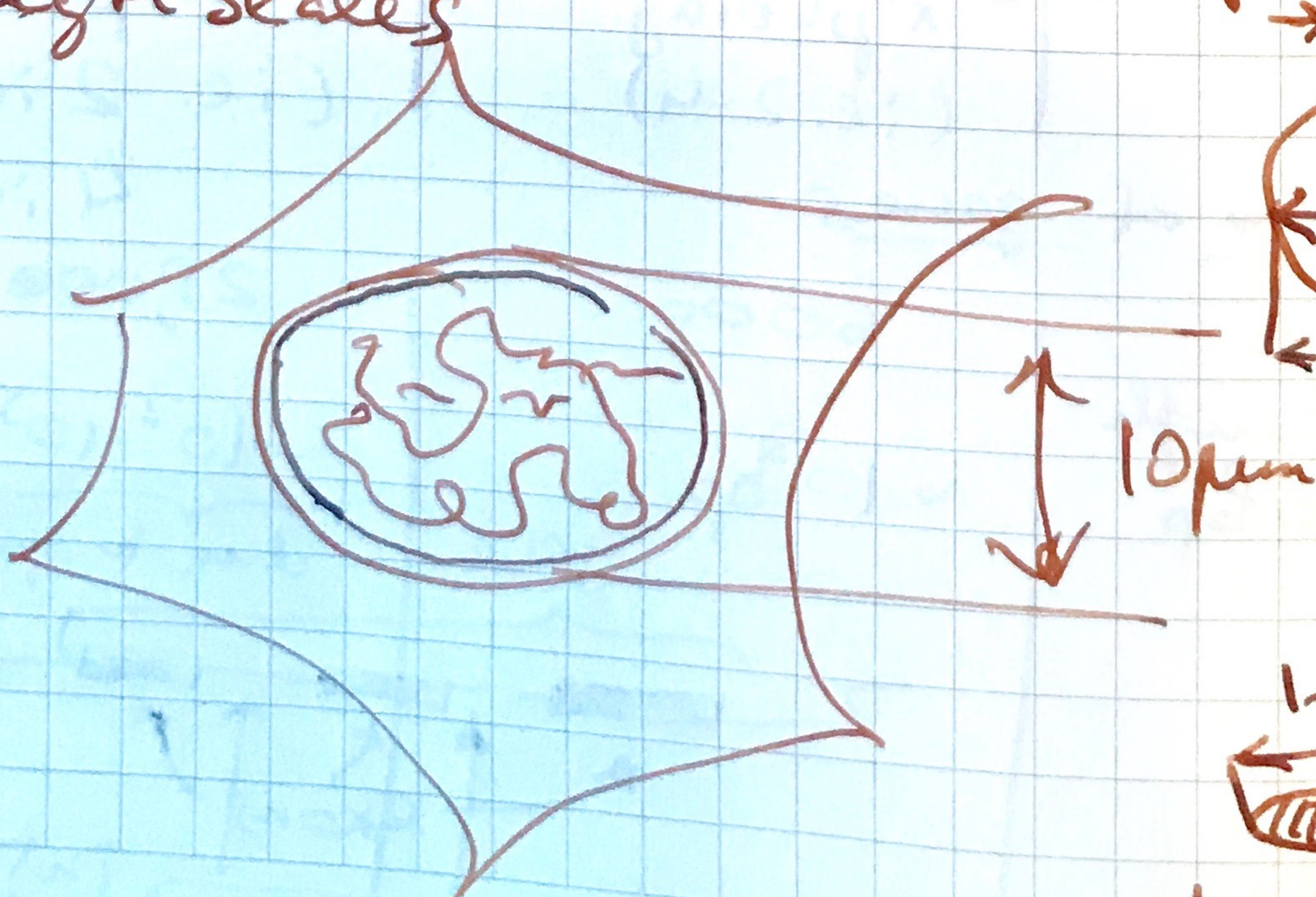
fraction of DNA in genes

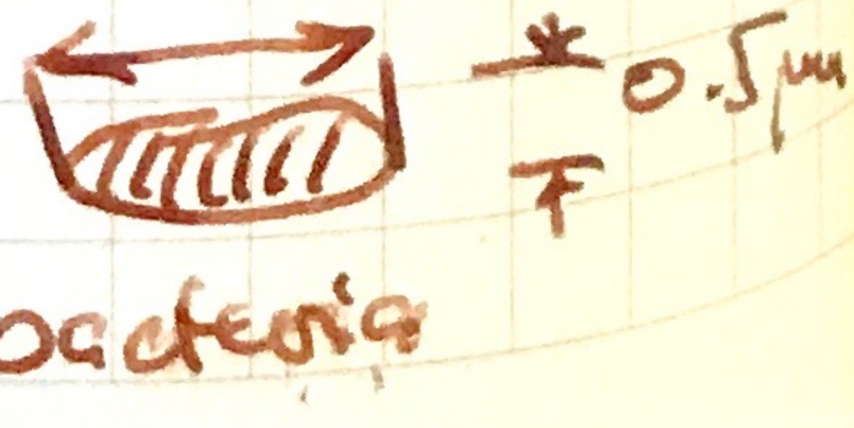
Bacteria	Single-cell eukaryotes (estimate by themselves)	Higher Eukaryotes
3000×500	$6000 \cdot 10^3$	↕ 5-10 min
$= 1.5 \cdot 10^6 / 5 \cdot 10^6$	$6 \cdot 10^6 / 5 \cdot 10^7$	$\frac{2.5 \cdot 10^4 \cdot 10^4 \cdot 2}{3 \cdot 10^9}$
$\simeq$ 30-50%	$\simeq 10\%$	$= \frac{5}{3} \cdot \frac{1}{10} \simeq 10\%$

but coding (i.e. exons) ~ 1.5%

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

③ Length scales





Total length of DNA in each cell?
[estimate by themselves] ↑ 10 min ↓

$1\,bp = 0.3\,nm$; DNA $\varnothing = 2\,nm$

Bacteria	Yeast	Human
$1.5 \cdot 10^5\,nm$ = $150\,\mu m$	$1.5 \cdot 10^6\,nm$ = $1.5\,mm$ ~ $10^3\,\mu m$	~ $1\,m$ (× ploidy) ~ $10^6\,\mu m$

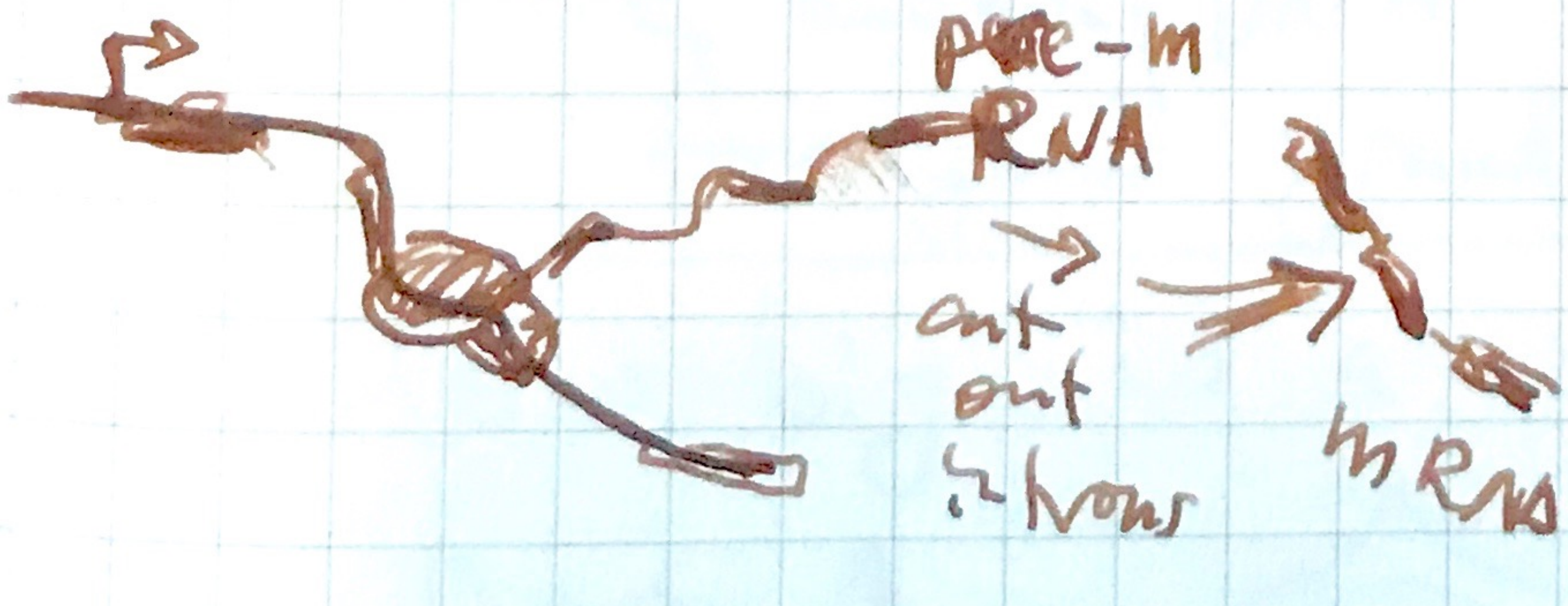
[all much bigger than cell nucleus]

④ Timescales

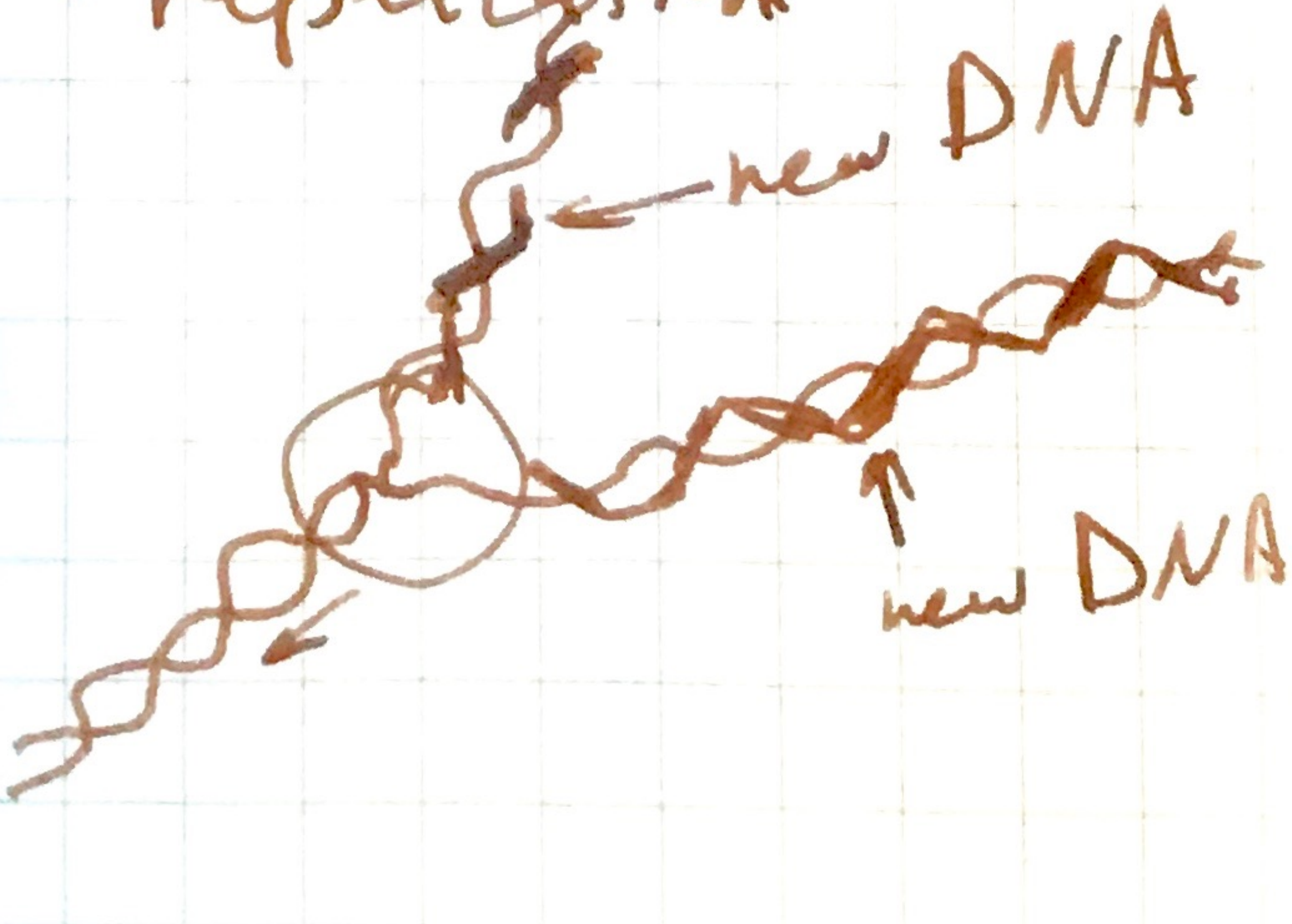
	Bacteria	Yeast	Human and other higher eukaryotes
Cell Division	20min – 1h	~ 90min	~ 24h but can be as fast as ~ 20min (e.g. in early development)

⑤ Gene expression

aka "transcription"



DNA copying (synthesis; "replication")



Lecture 2

Warm-up problem: How bacteria copies its DNA

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

10 min — Speed of DNA polymerase: 500 bp/sec
(200–1000 bp/sec)

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

$5 \cdot 10^6 / 500 = 10^4$ sec ~ 3h

but the divide in 20 min!

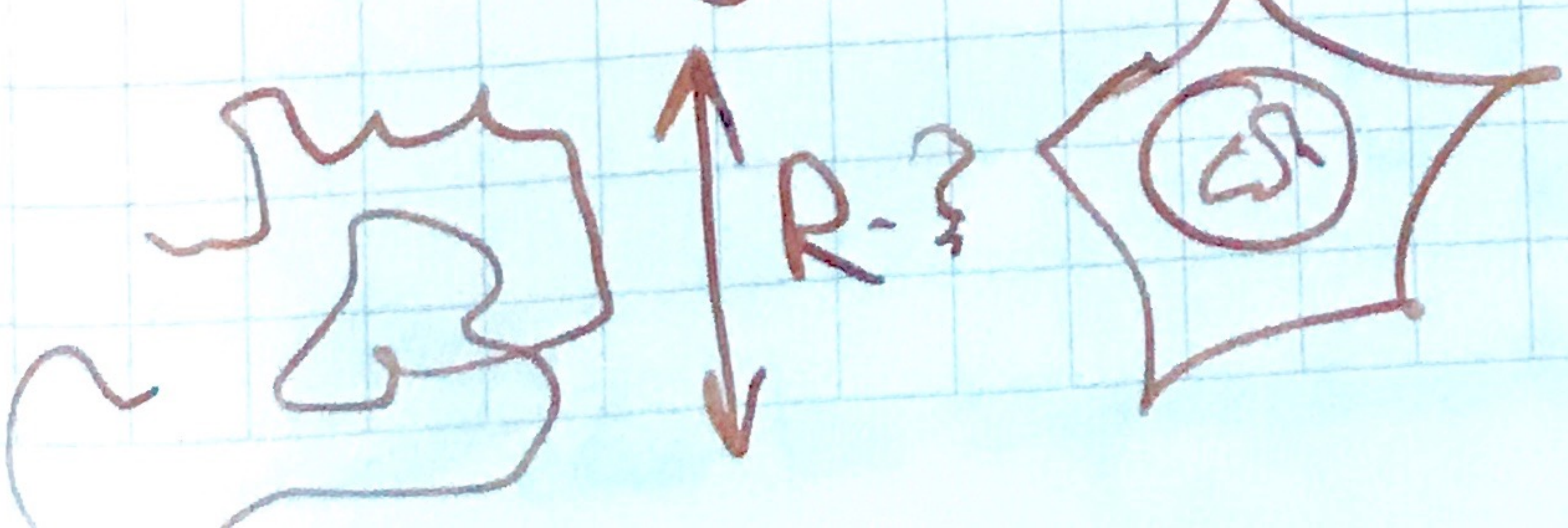
⇒ need multiple origins of replication

but there is only one origin ← how come?

⇒ nested replication

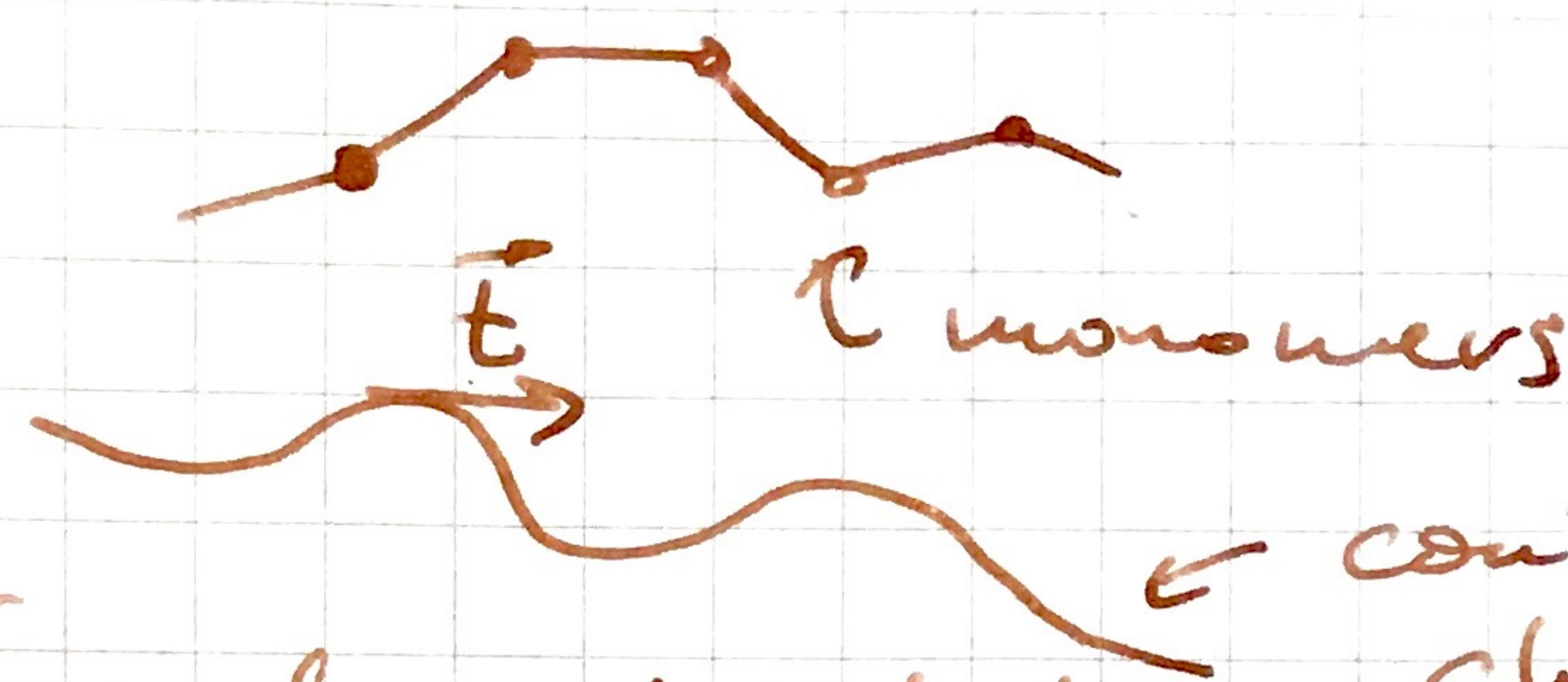
i.e. making DNA for your grandchildren

(1) How big is a coil of DNA?

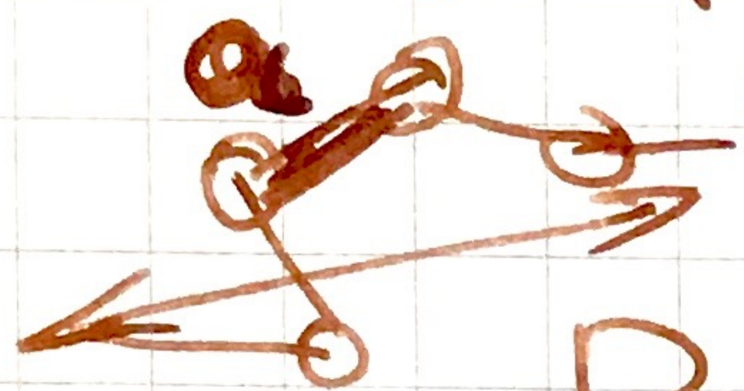


• Intro to Polymer Physics

Polymers :



model: freely-jointed ~~chain~~ chain

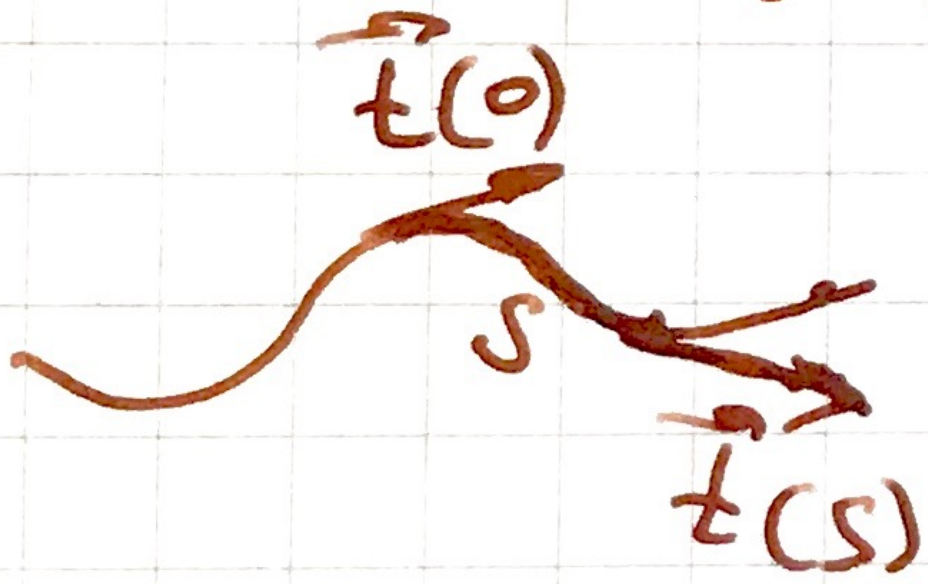


$R(N)$ = Random Walk in 3D (RW)

$\langle R^2(N) \rangle = a^2 \cdot N$
← size of monomer

end-to-end distance

• How to measure flexibility of a real chain



$\langle \vec{t}(0)\,\vec{t}(s) \rangle \sim e^{-s/l_p}$

where l_p is

measure of flexibility → the persistence length

Can be shown that $\langle R^2(L) \rangle = 2 l_p L$

if: $N = L/2 l_p$ i.e. N segments of $2l_p$ each

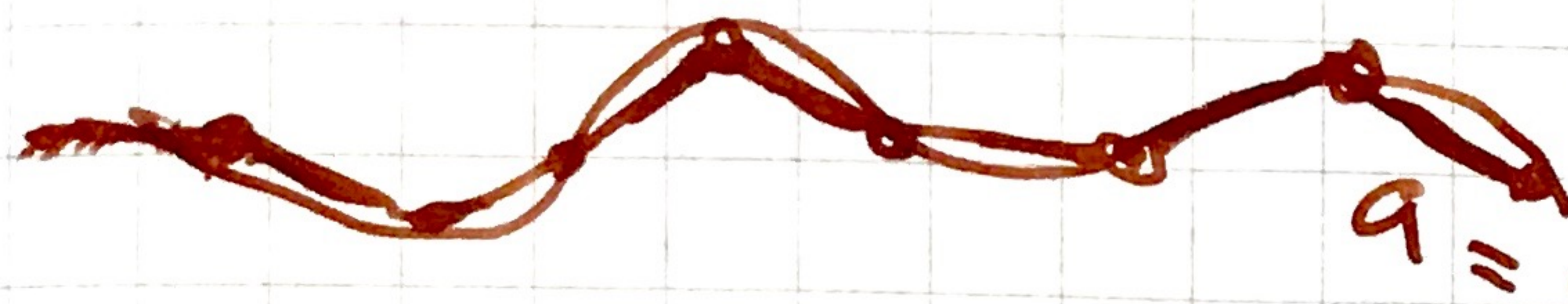
then indeed

$\langle R^2 \rangle = 2 l_p L = (2 l_p)^2 \cdot N = a^2 N$

→ $a = 2 l_p$
└ Khun's length

~~i.e. Real chain polymer can be represented as RW of $2l_p$ st~~

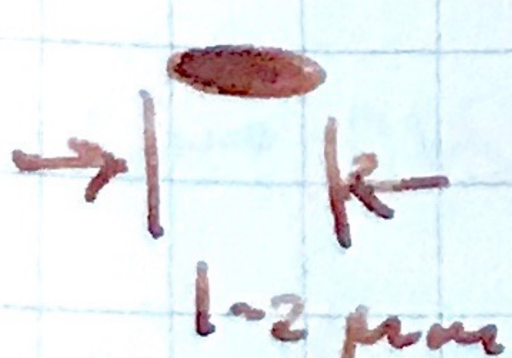
i.e. Real continious polymer can be represented as RW of segments where each segment $= 2 l_p$

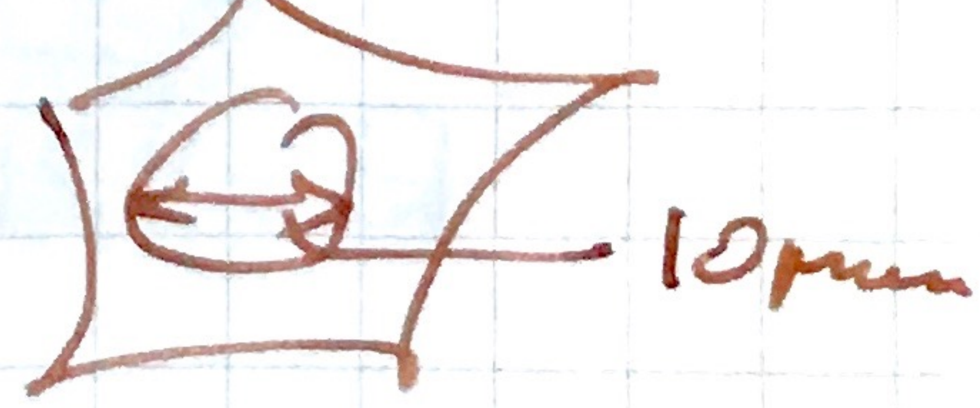


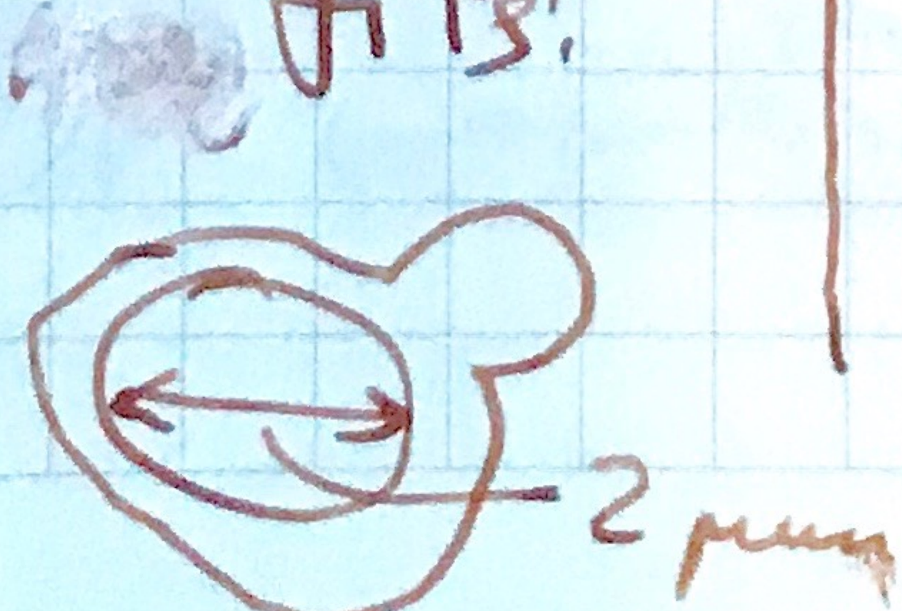
② l_p for DNA $= 50$ nm $= 150$ bp
($a = 300$ bp)

How large are coils of DNA
(10 minutes)

Bacteria	Yeast	Human
All DNA: $5 \cdot 10^6$ bp	$12 \cdot 10^6$ bp	$3 \cdot 10^9$ bp
$(5 \cdot 10^6 \cdot 3 \cdot 10^2)^{1/2}$	15 μm	10^6 μm = 1 m
$= 4 \cdot 10^4$ bp $= 10^4$ nm $= 10$ μm		doesn't fit!
One chromosome	(~10 chromosomes)	(~23 chromosomes)
$5 \cdot 10^6$ bp	$\sim 10^6$ bp	$\sim 10^8$ bp
10 μm	3-4 μm	$2 \cdot 10^5$ μm
Doesn't fit!	Short chromosome	doesn't fit
	$2 \cdot 10^5$ bp	
	~ 1.5-2 μm	
	fits!	

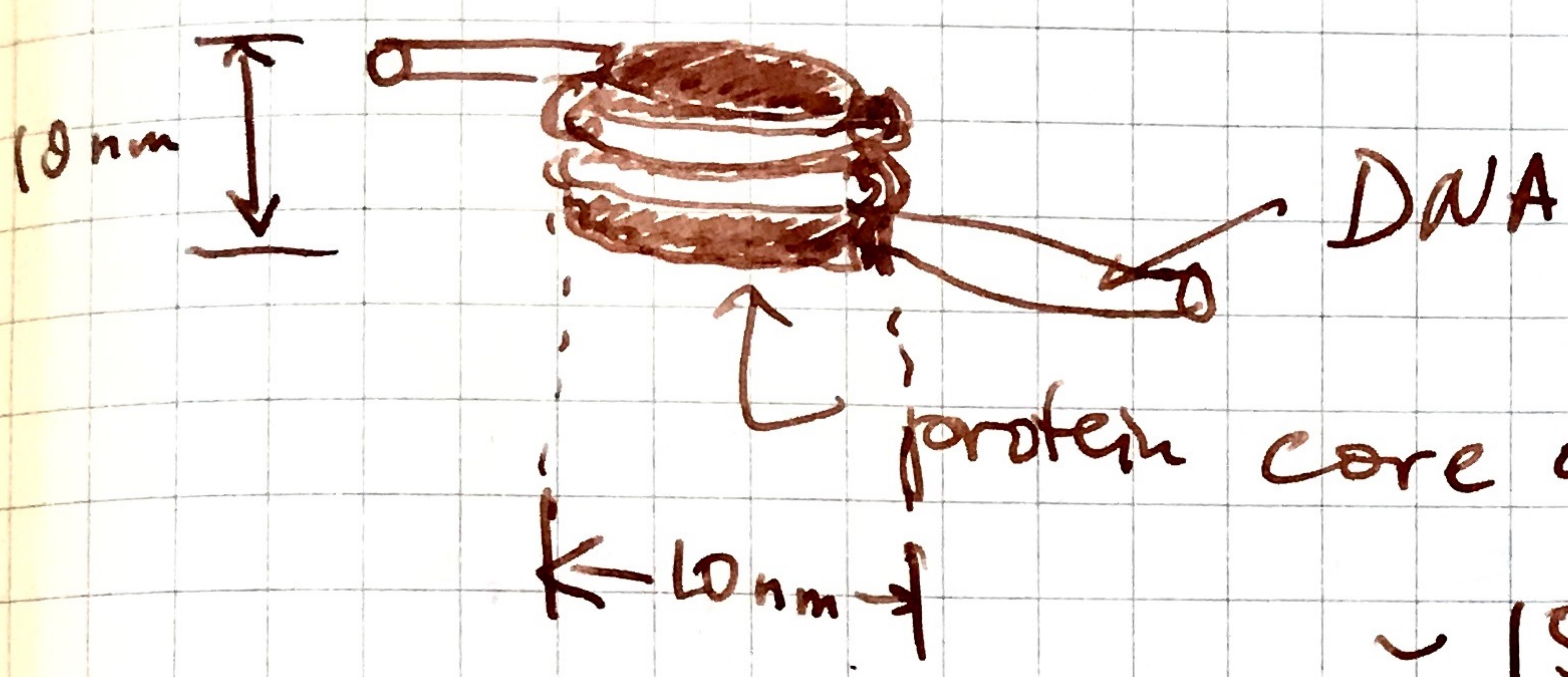






③ How is it really packed?

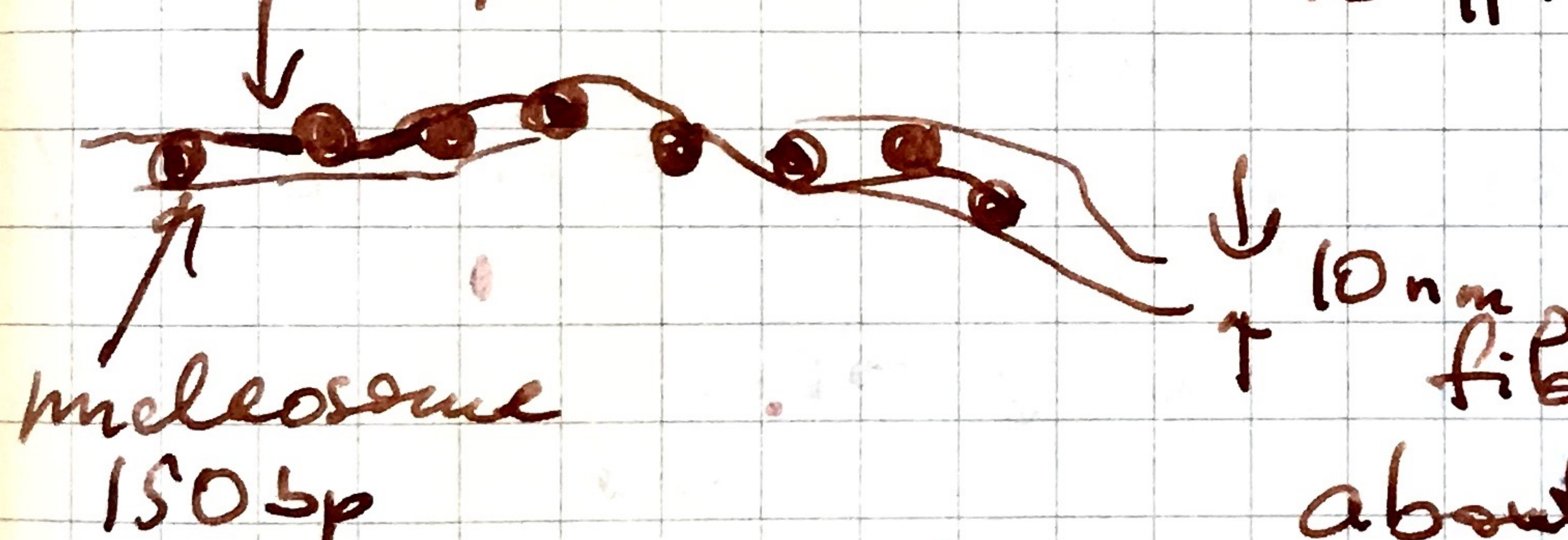
Nucleosomes: (in eukaryotes only!) (maybe archea)



~150 bp

1.7 turns

i.e. provides $\approx \pi \cdot 1.7 = 5$ fold linear compaction



about 5 times shorter

$l_p \Leftarrow$ unknown $\approx$ 3-6 nucleosomes i.e. (3-6) × 300 bp $\approx$ **1kB**

• Estimate ~~length of coil~~ size of coils R(L) chromosomes ~~...~~ by this 10nm chromatin fiber

• Estimate volume fraction of chromatin in the nucleus

Datum / Date:

(3a) Estimate ~~volume fraction~~ coil of chromatinized ~~of~~ DNA

Solution: assume 10 nm fiber

Yeast chromosome: $L = 10^6$ bp $= \frac{10^6}{200}$ nucleosomes

$l_p \approx 5$ nucleosomes.

$R = \sqrt{2 l_p L} = \sqrt{5 \cdot 10^4} = 200$ nucleosomes in length

1 nucleosome

$\approx$ 

50bp = 15 nm

block $\approx$ 10-20 nm $\approx$ 2-4 μm may fit!

Short chromosomes $2 \cdot 10^5$ bp

$R(L) \approx 1$-2 μm ⇐ fits inside nucleus!

Human: $L = 10^8$ bp (one long chromosome)

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

$\approx$ 20-40 μm ← a bit Bigger.

Short chromosome: $L = 2 \cdot 10^7$ (or one "arm" of a chromosome)

$R \approx 4$-8 μm fits into large nucleus!

(3b) Volume fraction of ϕ

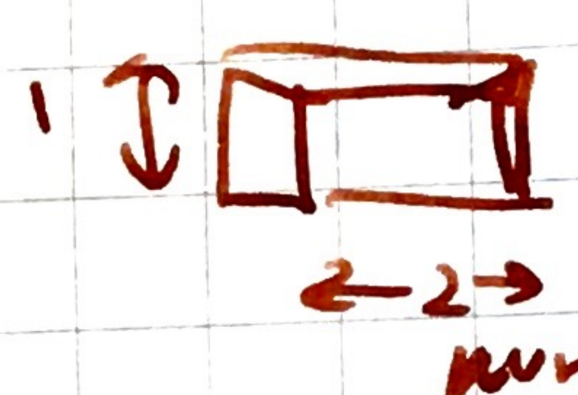
- DNA for bacteria
- Chromatin for eukaryotes

• DNA in bacteria $L = 5\cdot10^6$ bp

DNA 1bp = 0.3 nm
D = 2 nm ; R = 1 nm (Diameter)

$V_{DNA} = 1.6\cdot10^8\,nm \times 3\,nm^2$
$= 5\cdot10^8\,nm^3$

$V_{bacteria} \simeq 2\cdot10^3\cdot10^6 \simeq 10^9$



$\phi \simeq 0.005$
small! plenty of room but DNA is long!

• Chromatin : assume 10 nm ϕ fiber

Yeast: $L = \frac{12\cdot10^6}{200} = 6\cdot10^4$ nucleosomes, each $\simeq 4\cdot125\,nm$ $\simeq 500\,nm^3$

(linker is negligible: $15\,nm \times 3\,nm^2 \simeq 50\,nm^3$)

$V_{DNA} = 3000\cdot10^4\,nm^3 = 3\cdot10^7\,nm^3$

$V_{nucleus}\,(r = 1\,\mu m) = 4\cdot10^9\,nm^3$

$\phi \simeq 0.01 = 1\%$

still lots of space!

Human: $L = \frac{2\cdot3\cdot10^9}{200} = 3\cdot10^7$ nucleosomes (2 = ploidy)

$V_{DNA} =$ ~~[illegible]~~ $= 1.5\cdot10^{10}\,nm^3$

$V_{nucleus} \simeq 500\,\mu m^3 = 5\cdot10^{11}\,nm^3$

$\phi \simeq 3\cdot10^{-2} = 3\%$

$\simeq$ ~~[illegible]~~