BIOL8620 Eukaryotic Genetics

The Genetic Material: DNA Structure / Function

Chapters 1,

parts of chapters 2 & 11

Biol 8620 Fall '19: Course Overview

http://biotech.gsu.edu/home8620.html

Course:	BIOL8620 CRN80080
Location:	Class Room South 408
Time:	Tuesday & Thursday 12:45 pm - 2:30 pm
Credit Hours:	4 hrs

Lecturer:	Dr. Margo Brinton	Dr. John Houghton
Office:	623 Petit Science Center	520 Petit Science Center
Laboratory:	640 Petit Science Center	534 Petit Science Center
email:	*mbrinton@gsu.edu*	*jhoughton@gsu.edu*
Office hours:	Tues: 11:00am - 12:00pm	Tues: 3:00pm - 4:00pm

Drs. Brinton or Houghton will be happy to talk with you about any aspect of the class material or class assignments after class, during office hours, or by appointment..

Text: *Lewin's Genes XII: Jocelyn Krebs, Elliott Goldstein and Stephen Kilpatrick | Jones & Bartlett Publishers*

Vital Source: Lewin's Gene XII

Reading assignments in the text book are indicated in the lecture schedule. The background information for some of the lectures will either be in the form of web-links, handouts or assigned journal articles. Diagrams used in lectures that are not from the textbook will be posted on the web or in the form of a handout to be handed out in class or available as a download. Exams will be based primarily on lecture material. Reading assignments (text, papers and handouts) should be used to understand the lecture material and provide additional examples.

Grading Policy * : Grades will be divided amomg the various examinations in the following manner-

Exam I	100 pts
Exam II	100 pts
Exam III	100 pts
Critical thinking assignments (in class paper discussion & Gene Paper)	200 pts
In-Class Presentation	100 pts
Total	600 pts.

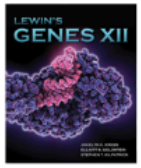
Grading Scale: 97-100= A+, 90-96= A, 88-89= A-, 86-87= B+, 80-85= B, 78-79= B-, 77-78= C+, 70-76= C, 68-69= C-, 60-67= D, less than 60= F

The exams (in-class) may contain a few short answer questions, but the majority will be essay questions. Each exam will cover only the material in those lectures given since the previous exam and so will not be comprehensive. However, conceptual foundations established in each of the lectures need to be well understood since they will provide the necessary foundation for understanding material in subsequent lectures. Students will be evaluated on their ability to successfully integrate material and concepts from different lectures when answering exam questions. Students are expected to write thoughtful, well-organized answers to the exam questions and can include labeled diagrams. Although the ability to integrate general concepts and critical details is most important, students are also expected to understand the relevant technical aspects of the course material.

Critical thinking assignments will be based on original research literature in the field of eukaryotic molecular genetics. The instructors will further explain each of these assignments in class. Students will be expected to participate in detailed in-class discussions of assigned research papers or complete a take home assignment. Because you will be graded on your participation in the scheduled in-class discussions, unexcused absences for these discussions will be graded as a zero. If previously arranged with the instructors or due to an emergency, one missed discussion can be made up by writing a summary of the literature article discussed in class.

Each student will also write a paper on an assigned human disease gene. Detailed instructions will be handed out when the genes are assigned. The writing assignments are NOT collaborative and should be done individually by each student without discussion with others. Any information obtained from published articles or websites and included by a student in a writing assignment must be paraphrased (put in your own words) and the source of the information appropriately referenced in the text as well as in a reference list at the end of the paper. Any sentences or phrases that are copied word for word from a published article are considered a direct quote and must be put in quotation marks.

Each student will be required to make one 20-minute in-class presentation on an original research paper using visual aids (typically PowerPoint slides). Students will first choose a topic within an area of eukaryotic molecular genetics from a list of topics provided by the instructors. Students will then choose a recent research paper (no more than 5 years old) that they wish to present on their assigned topic. At least two weeks prior to their presentation date, each student will give a hard copy of the paper or email a PDF file of the paper they have selected to the instructor indicated for that



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Spring '19

Biol 8620 home page (syllabus)

Syllabus (download pdf document)

Schedule

Lectures	Lectures cntd
Lecture 1	Lecture 13
Lecture 2	Lecture 14
Lecture 3	Lecture 15
Lecture 4	Paper Discussion II
Lecture 5	Presentations II
Lecture 6	Exam II
Lecture 7	Lecture 16
Lecture 8	Lecture 17
Paper Discussion I	Lecture 18
Presentations I	Lecture 19
Exam 1	Presentations III
Lecture 9	Lecture 20
Lecture 10	Paper Discussion
Lecture 11	III
Lecture 12	Exam III

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Schedule Fall 2019

#	Date	Lecture Description	Chapter(s)
1	27th August	**Organizational Meeting:** The Genetic Material DNA structure/function, what is a gene?	1.1 -1.7; 1.9 -1.10; 2.1 -2.6; 2. 8 - 2.11; **4**
2	29th. August	The Replicon and DNA Replication	**10**; 11:1 - 11.2, 11.9 -11.12;11.14 -11.15; 12.1-12.2; 12.11-12.12
3	3rd. September	Chromosomes, Nucleosomes & Chromatin	**8 & 10**
4	5th. September	Mutations & DNA Repair,	1.11- 1.15; 2.8; **14**
5	10th. September	Mitosis and Meiosis (Review) DNA Recombination	**Chapters 13, 14** and handouts
6	12th. September	Transposons and Retrotransposons	**15**
7	17th. September	Genome Content/Genome Sequences/Gene numbers, Clusters and Repeats Lecture 1Exam Question	**6 , 7 & 8**
8	19th. September	Human Gene Mapping; phenotype to genotype	Assigned articles & handouts
***	24th. September	**In class Paper Discussion I** Gene Paper Assignments	Assigned article
***	26th. September	**Student Presentations I**	
***	1st. October	**Exam I**	
9	3rd. October	Basal RNA Polymerase Initiation Complexes	18-1 -18.8; 19.15-19.17
10	8th. October	Transcription Regulatory Elements in Gene Promoters	26.7; 18.9-18.12
11	10th. October	Transcriptional Activation & Regulation	26.1 - 26.6
12	15th. October	Chromatin Structure II & Gene Regulation	26.9 - 26.13
***	**15th. October**	**Last day to withdraw and receive a " W"**	
13	17th. October	Other Gene Regulatory Mechanisms	Handouts
14	22nd October	Epigenetic Inheritance	**27** & 28
15	24th. October	Epigenetic Inheritance	Handouts
***	29th. October	**In class Paper Discussion II**	Assigned Articles
***	31st. October	**Student Presentations II**	

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***	31st. October	**Student Presentations II**	
	5th. November	**Exam II**	
16	7th. November	Nuclear Splicing **GENE PAPERS DUE**	19.1 - 19.11; 23.9;21.1 - 21.6; 21.9
17	12th. November	Post Transcriptional Regulatory Mechanisms	19.2 - 19.13; 21.10; 22.12 & Assigned Articles
18	14th. November	Regulatory RNA -siRNA, miRNA	30.3 - 30.4 & Assigned Articles
19	19th. November	Regulatory RNA-piwiRNA, lncRNA	29.3 & Assigned Article
***	21st. November	**Student Presentations III**	
***	**25th- 30th. Nov**	**Thanksgiving Break No Class**	
20	3rd. December	Gene Therapy	Assigned Articles & Handouts
***	5th. December	**In class Paper Discussion III**	Assigned Articles
***	11th. November	**Exam III**	

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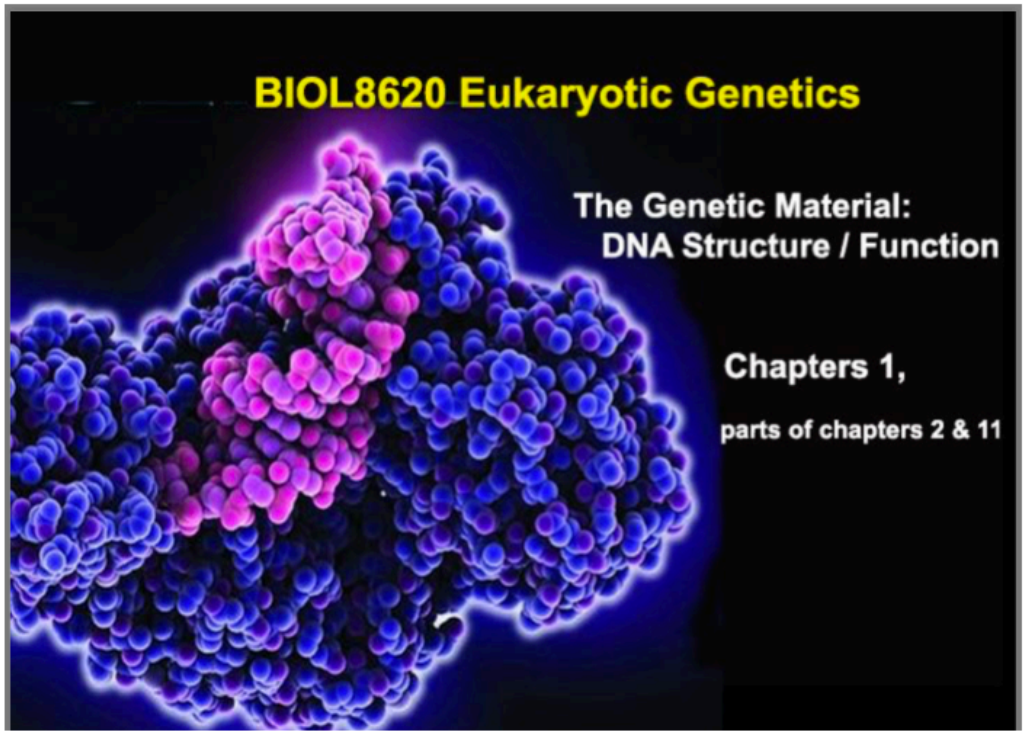
Lecture 1: The Genetic Material -from form to function

pdf download



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NATURE | NEWS

‘Three-parent baby’ claim raises hopes — and ethical concerns

Questions surround report of baby created using controversial mitochondrial-replacement technique.

Sara Reardon

28 September 2016 | Corrected: 29 September 2016

Courtesy of New Hope Fertility Center

Team leader John Zhang and the ‘three-parent’ baby have made headlines across the world.

Making better babies?

China’s embrace of embryo selection raises thorny questions

Fertility centres are making a massive push to increase preimplantation genetic diagnosis in a bid to eradicate certain diseases.

Recent | Read | Commented

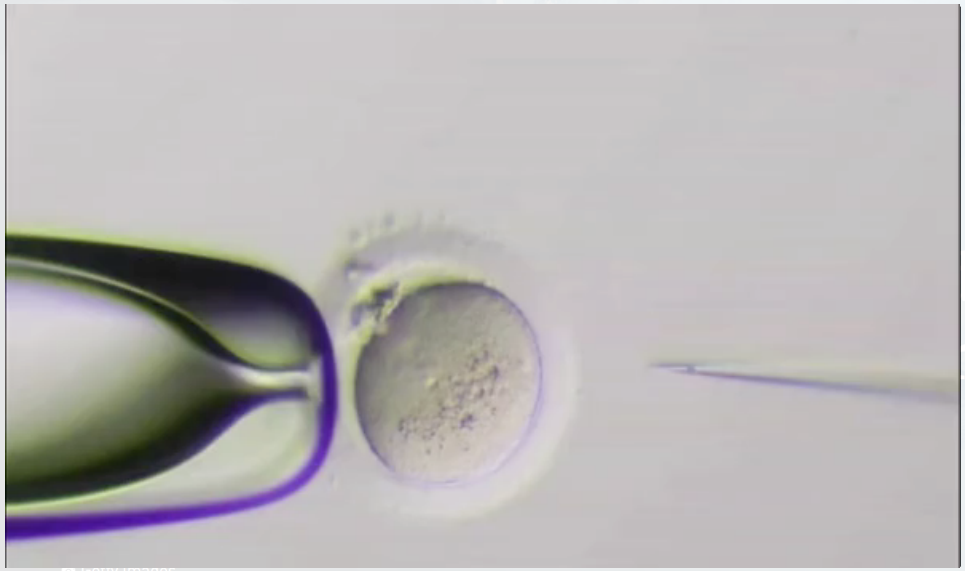
1. Mysteries of turbulence unravelled
   Nature | 21 August 2017
2. Martian weather kicks into high gear at night
   Nature | 21 August 2017
3. Theft of South African relics riles researchers
   Nature | 21 August 2017

Rewriting Life

First Human Embryos Edited in U.S.

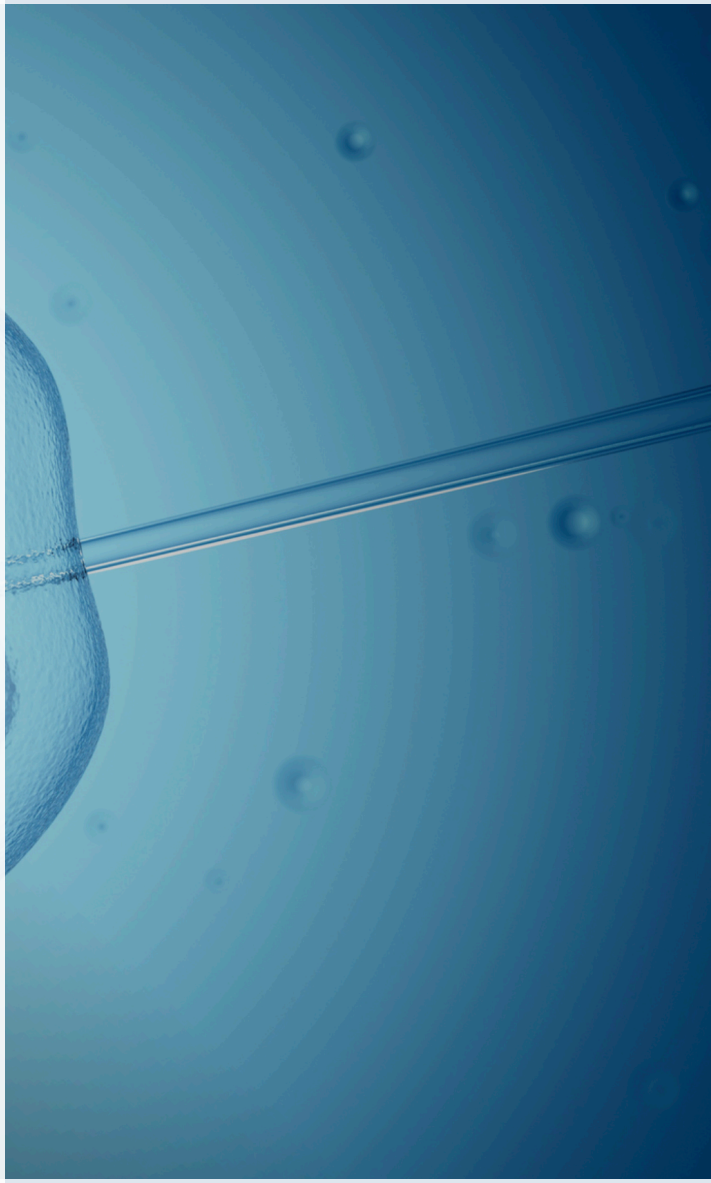
Researchers have demonstrated they can efficiently improve the DNA of human embryos.

by Steve Connor July 26, 2017



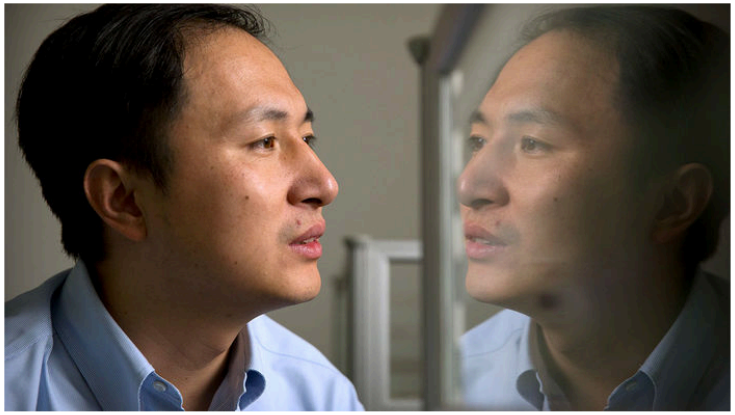
Getty Images

A video shows gene-editing chemicals being injected into a human egg at the moment of fertilization. Scientists used the technique to correct DNA errors present in the father's sperm.



The first known attempt at creating genetically modified human embryos in the United States has been carried out by a team of researchers in Portland, Oregon, *MIT Technology Review* has learned.

nature OUTLOOK
3 December 2015
Supplement to Nature
Publishing Group journals



He Jankui told The Associated Press that he carried out his experiment to protect the twin sisters from HIV infection later in life. MARK SCHIEFELBEIN/AP PHOTO

CRISPR bombshell: Chinese researcher claims to have created gene-edited twins

By Dennis Normile | Nov. 26, 2018 , 1:10 PM

HONG KONG, CHINA—On the eve of an international summit here on genome editing, a Chinese researcher has shocked many by claiming to have altered the genomes of twin baby girls born this month in a way that will pass the modification on to future generations. The alteration is intended to make the children's cells resistant to infection by HIV, says the scientist, He Jiankui of the Southern University of Science and Technology in Shenzhen, China.

The claim—yet to be reported in a scientific paper—initiated a firestorm of criticism today, with some scientists and bioethicists calling the work "premature," "ethically problematic," and even "monstrous." The Chinese Society for Cell Biology issued a statement calling the research "a serious violation of the Chinese government's laws and regulations and the consensus of the Chinese scientific community." And He's university **issued a statement** saying it has launched an investigation into the research, which it says may "seriously violate academic ethics and academic norms."

Other scientists, meanwhile, asked to see details of the experiment and its justification before passing judgment.

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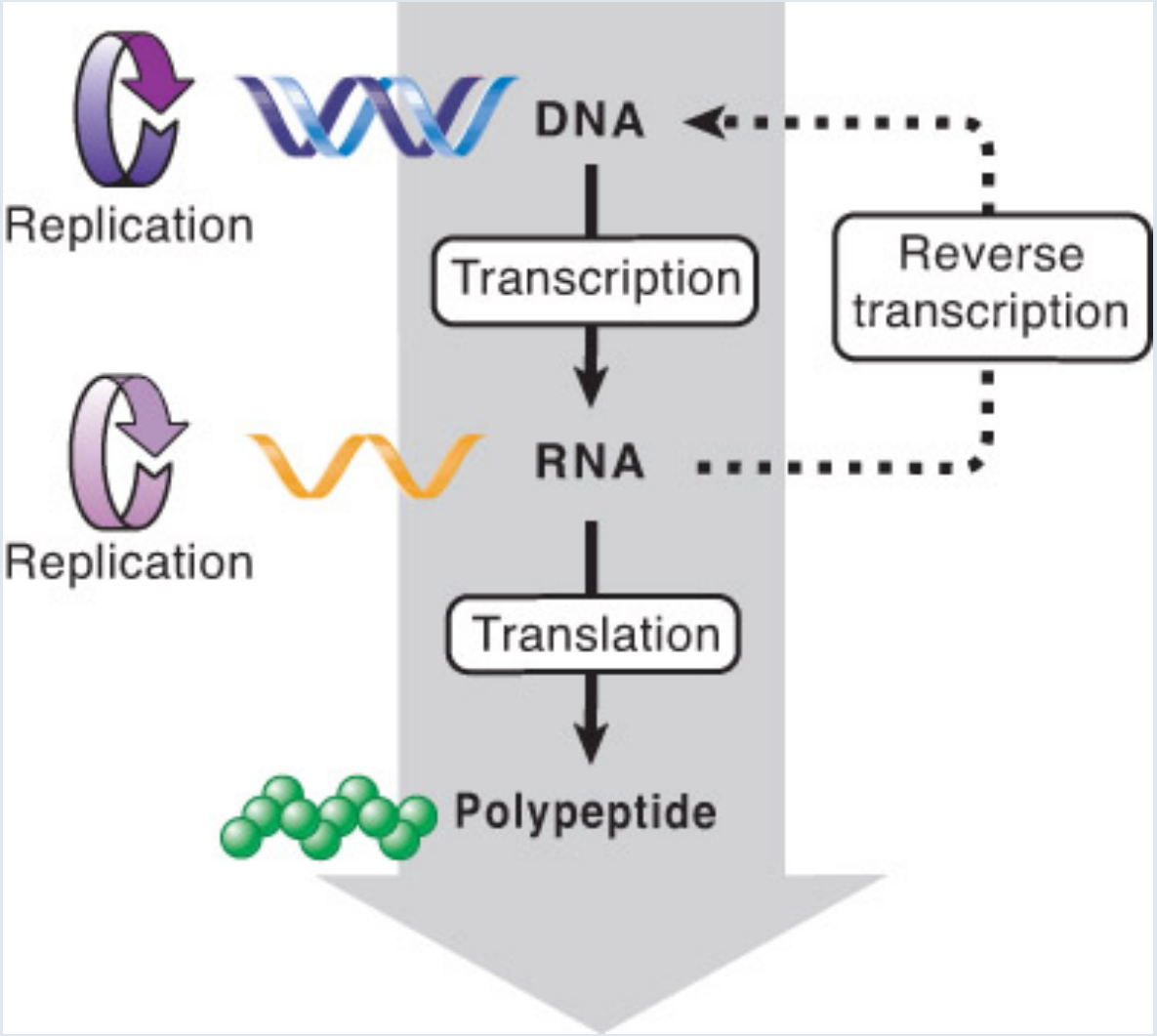
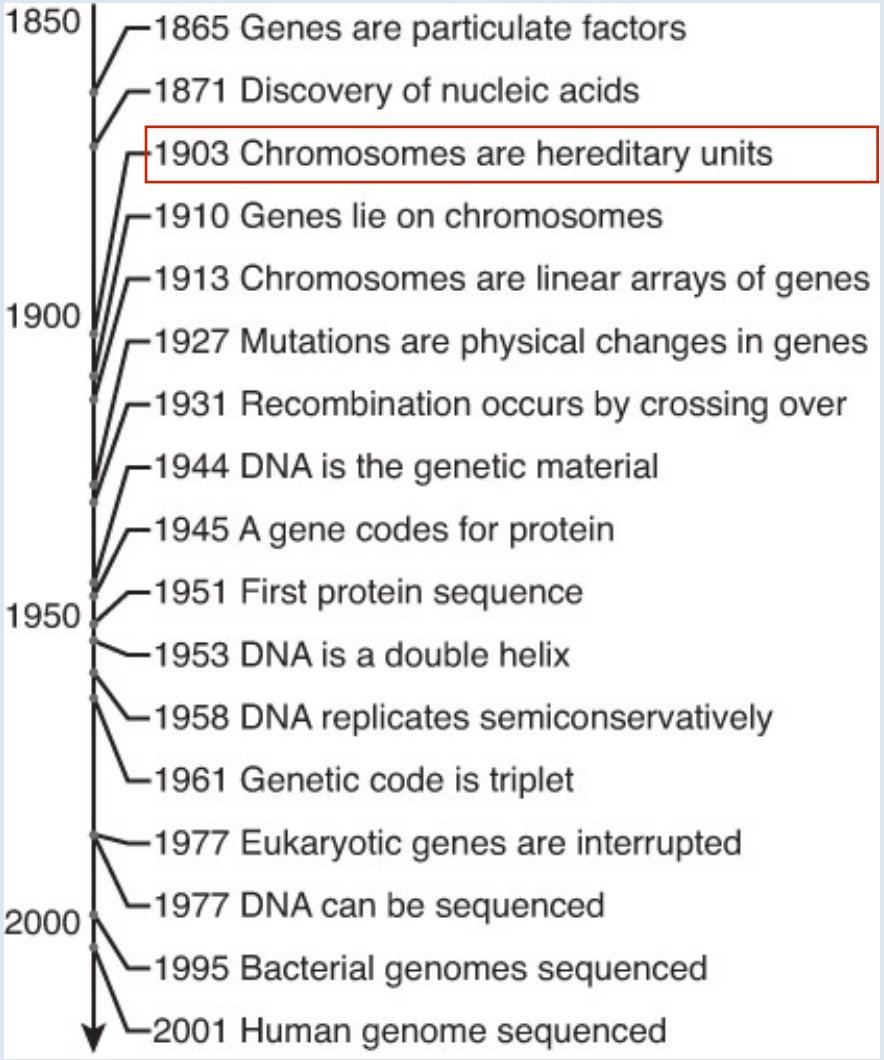
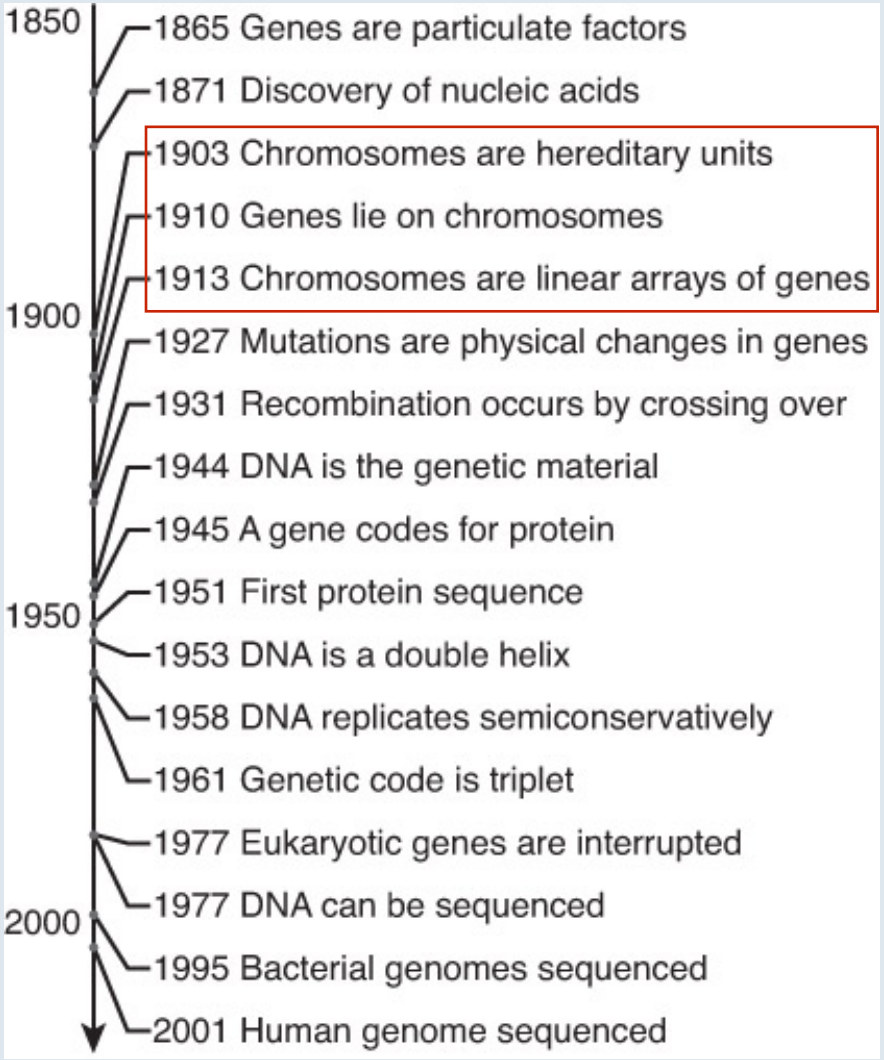


Information in nucleic acid can be perpetuated or transferred, but the transfer of information into a polypeptide is irreversible.



A brief history of genetics.



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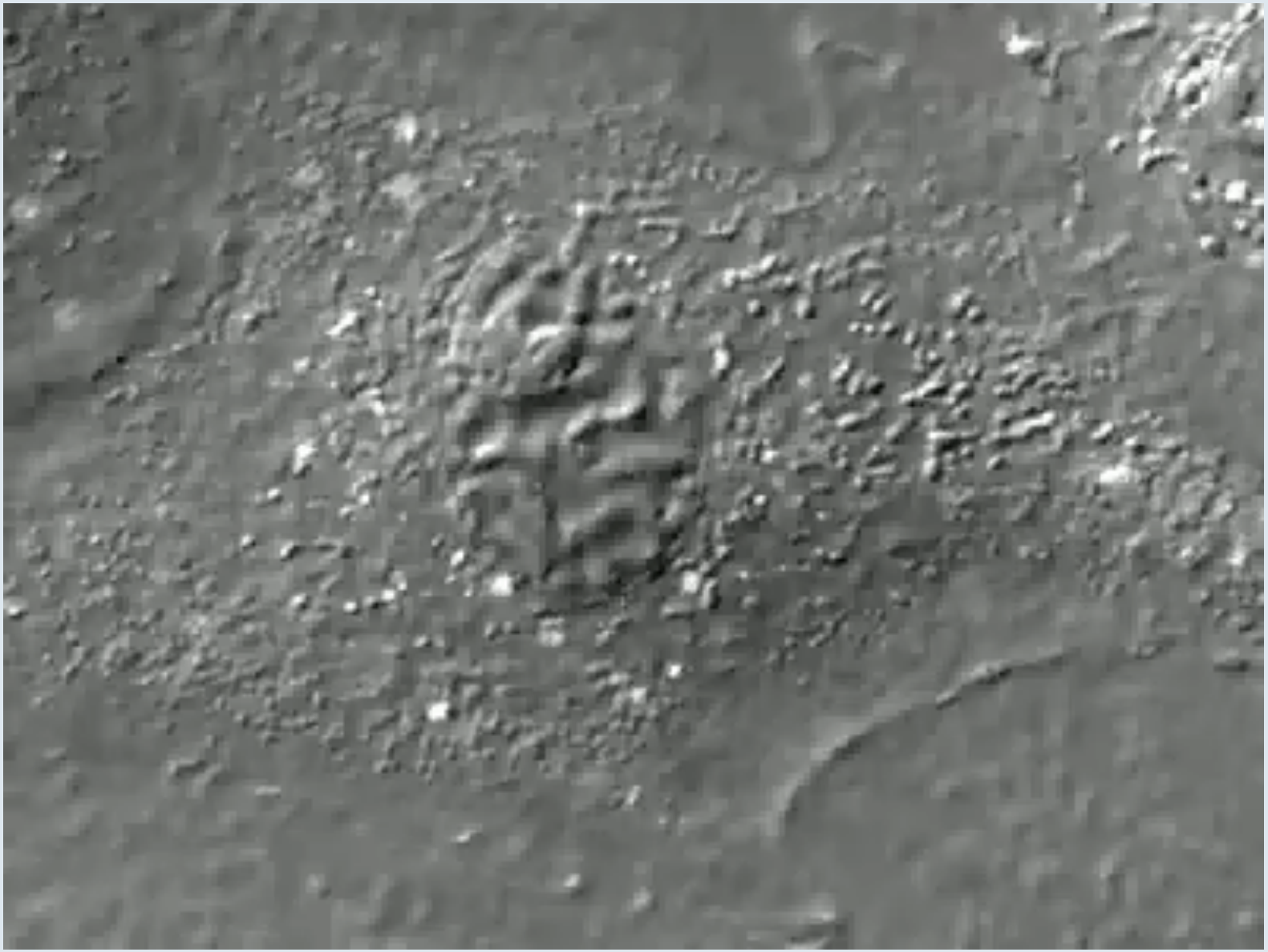

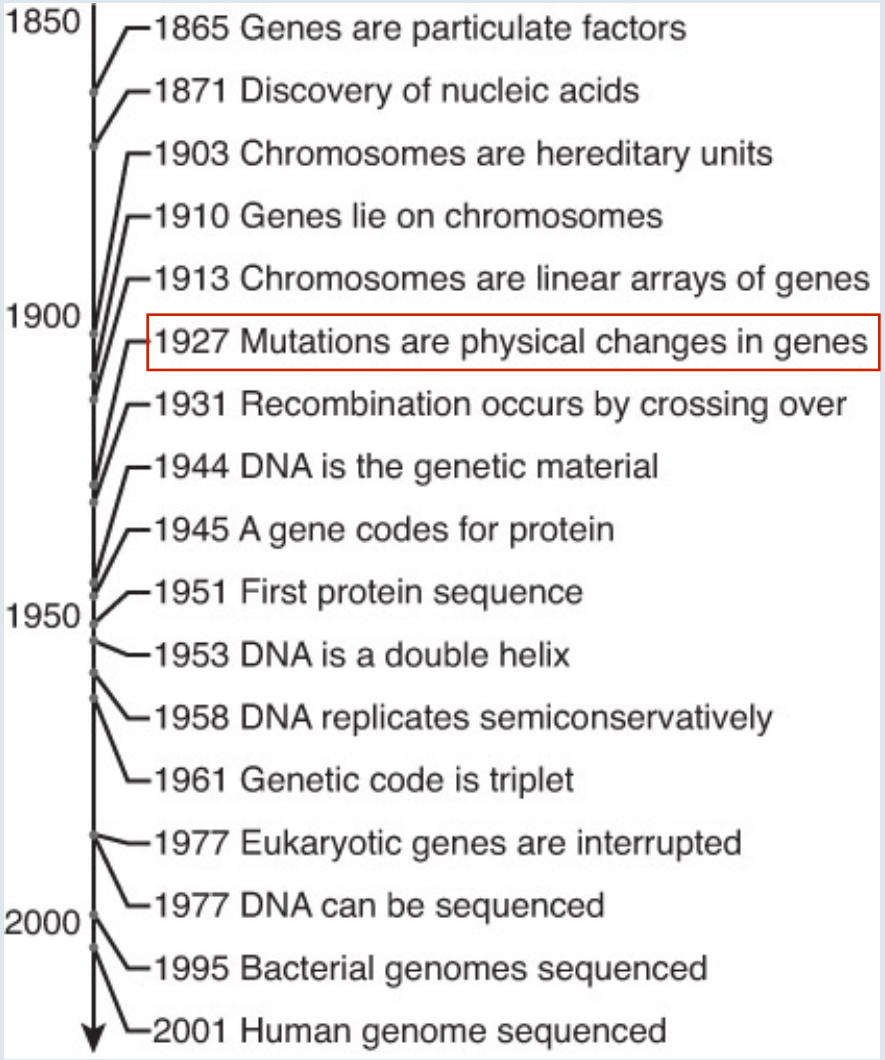

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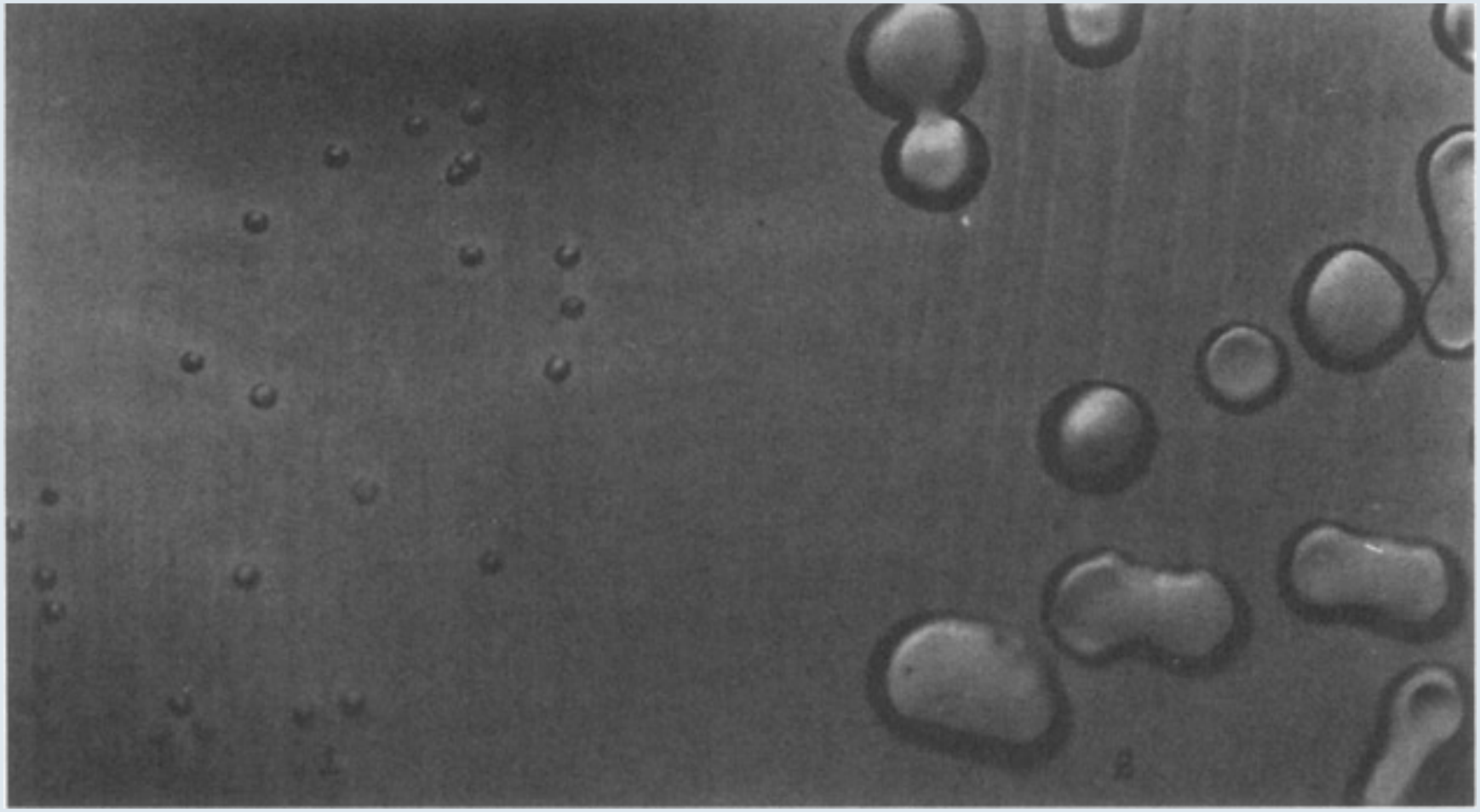
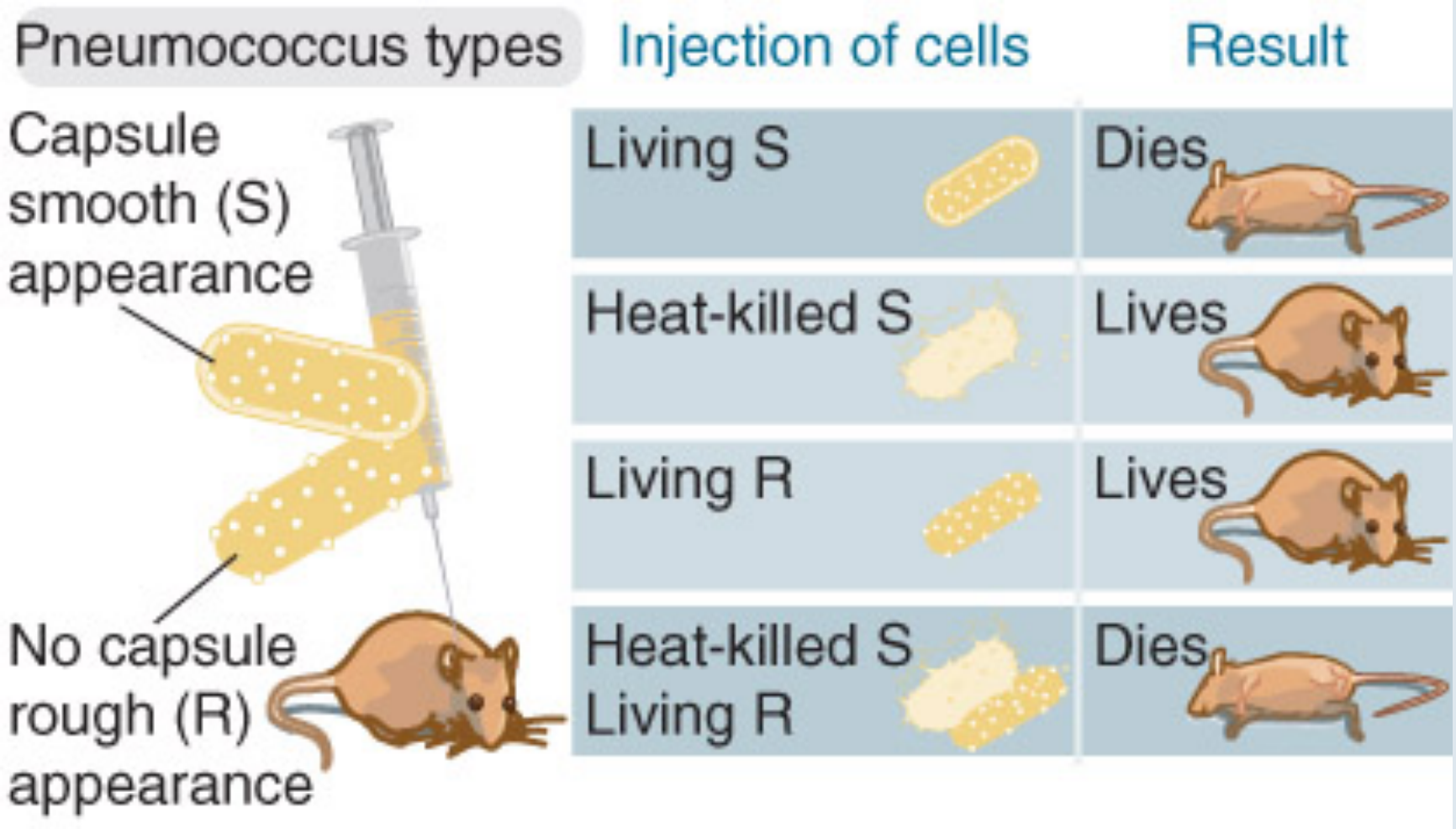
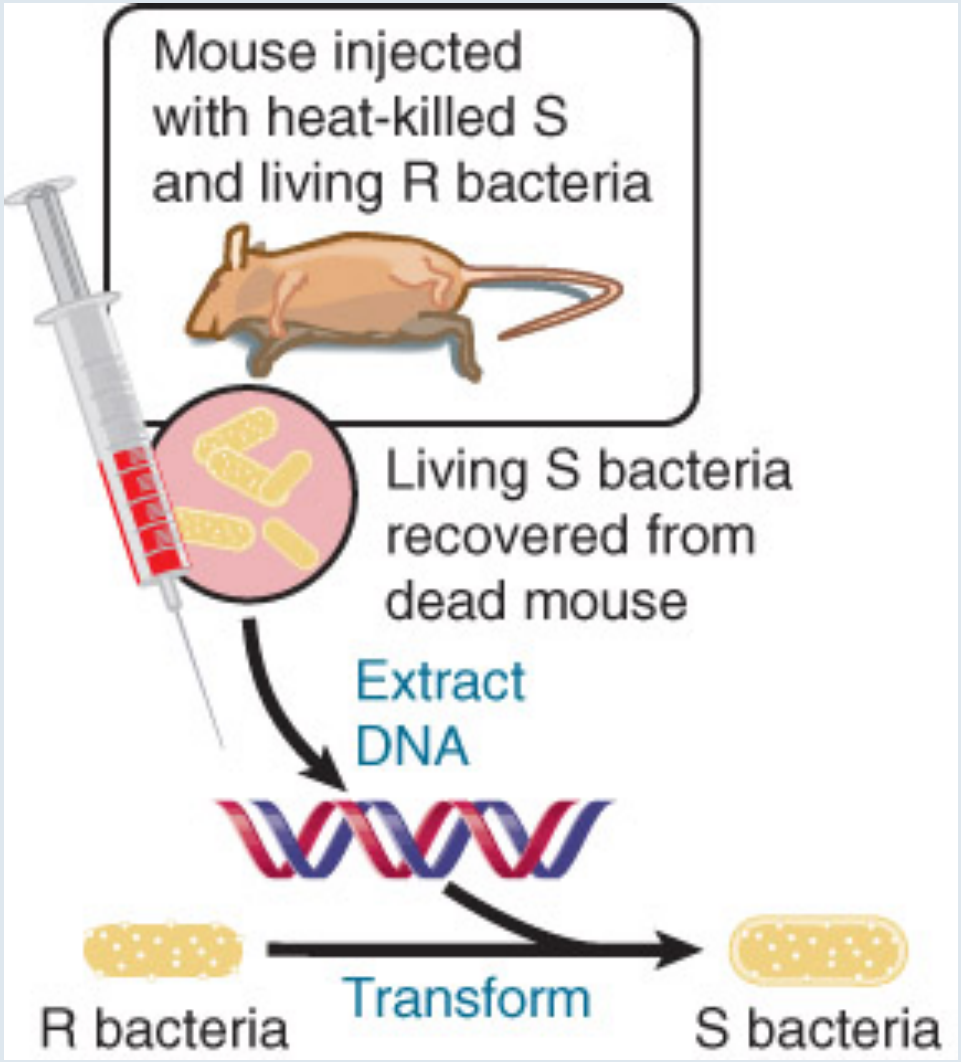


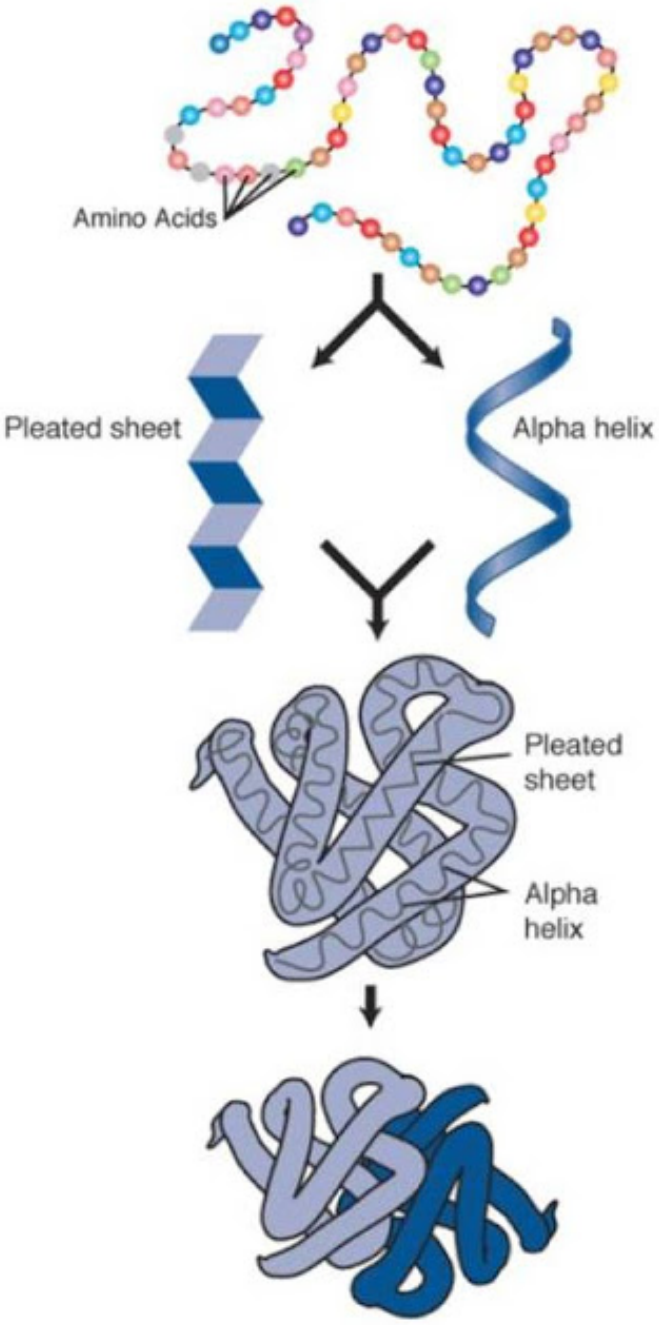
Rough (left) and Smooth (right) colonies of S. pneumoniae. (pneumococcus)



Simultaneous injection of both heat-killed S-type and live R-type bacteria can



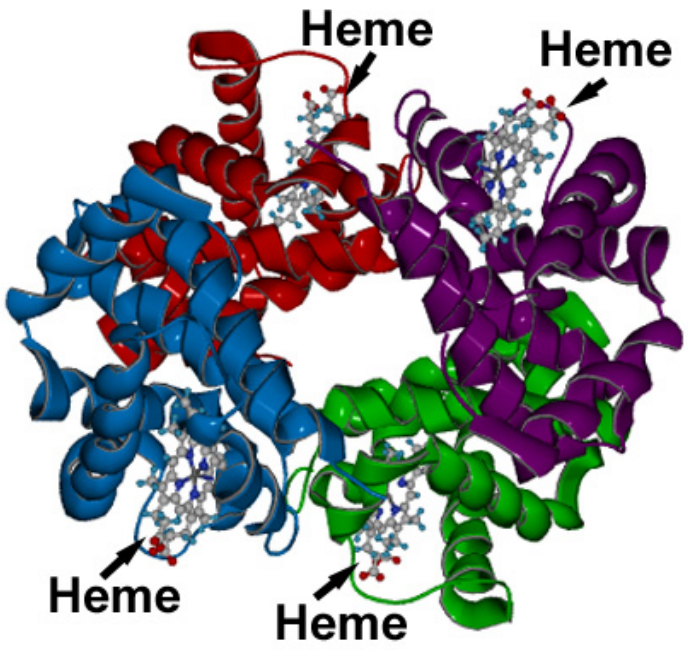
The DNA of S-type bacteria can transform R-type bacteria into the same S-type.

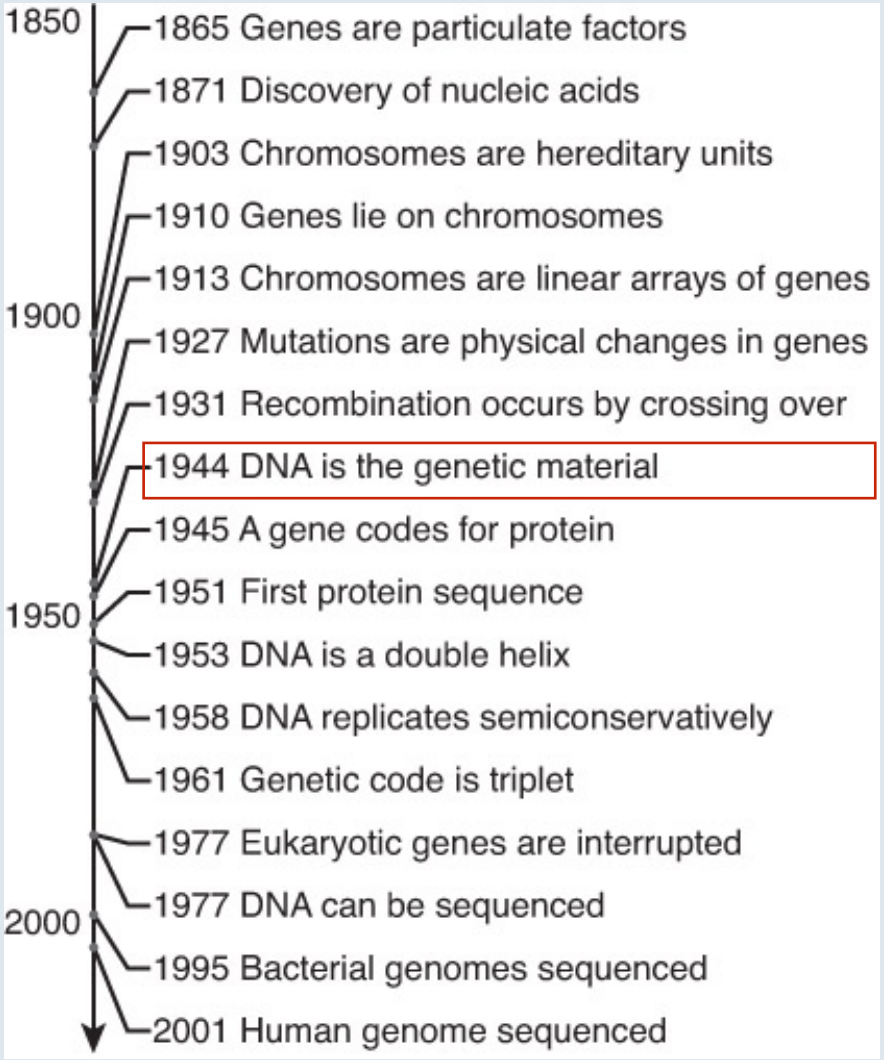


Levels of protein organization

Primary protein structure
is sequence of a chain of amino acids

Secondary protein structure
occurs when the sequence of amino acids are linked by hydrogen bonds





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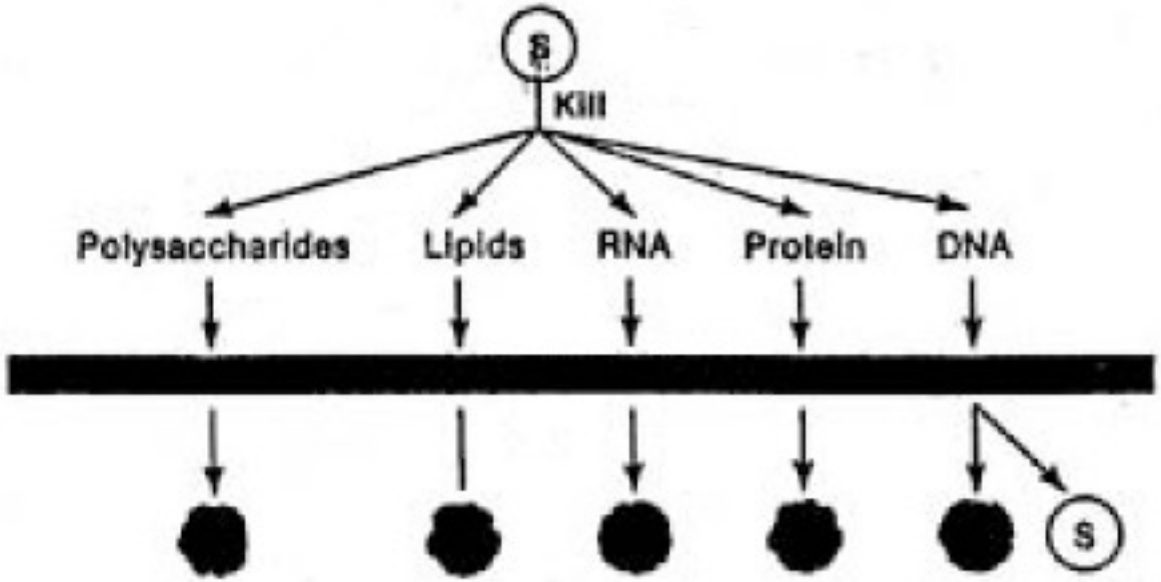
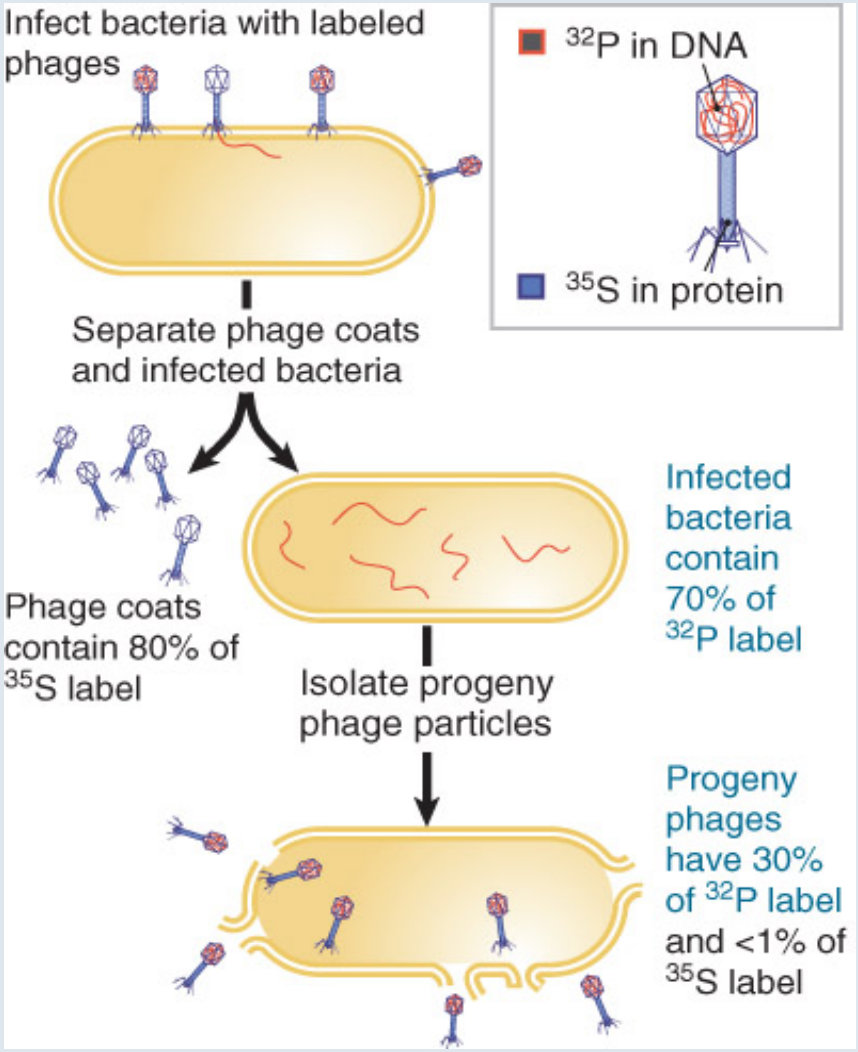
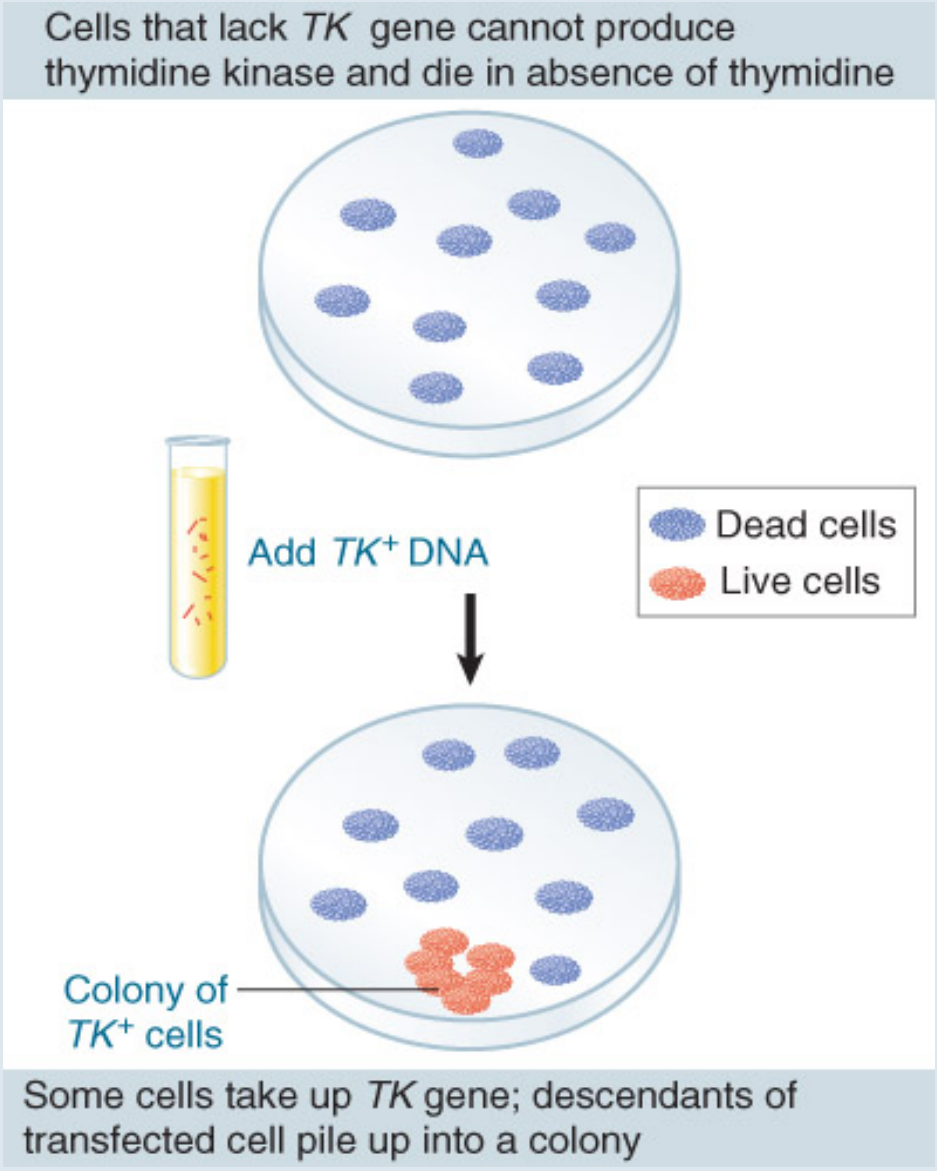


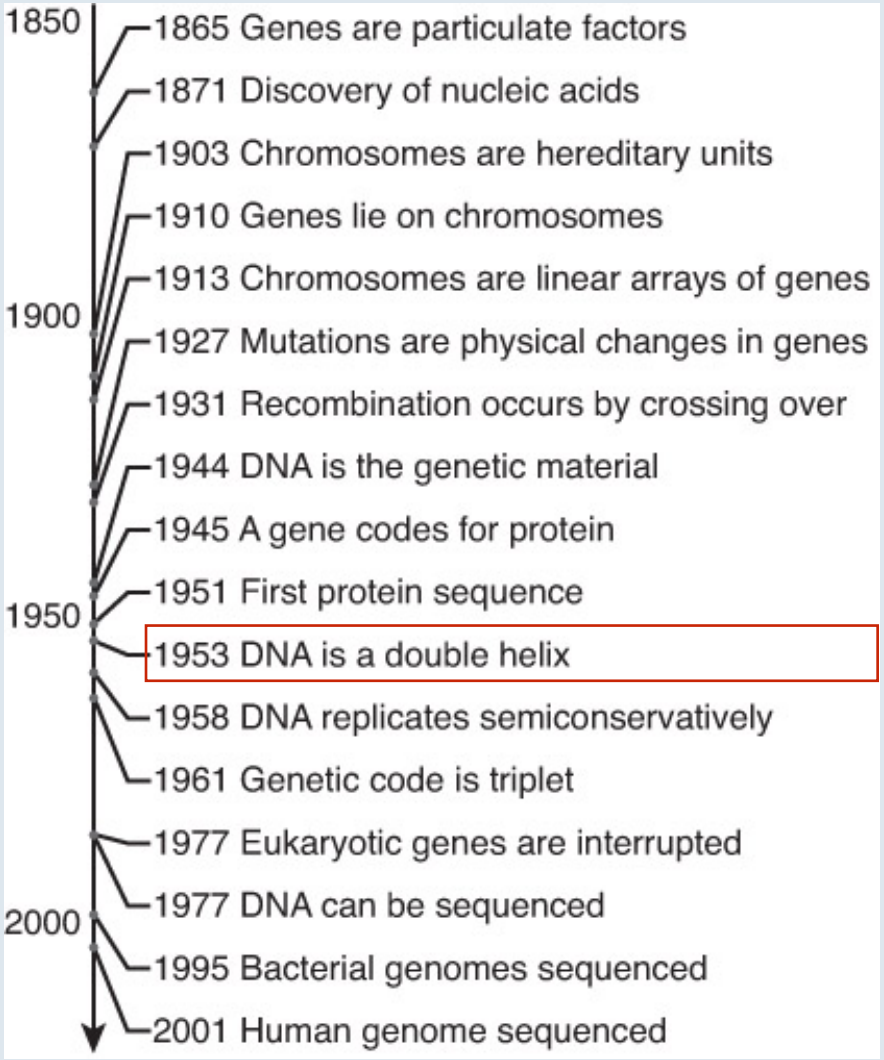
Figure 11-2. Demonstration that DNA is the transforming agent. DNA is the only agent that produces smooth (S) colonies when added to live rough (R) cells.



Hershey Chase experiment (1952)
The genetic material of phage T2 **is** DNA.



Eukaryotic cells can acquire a new phenotype as the result of transfection by added DNA.



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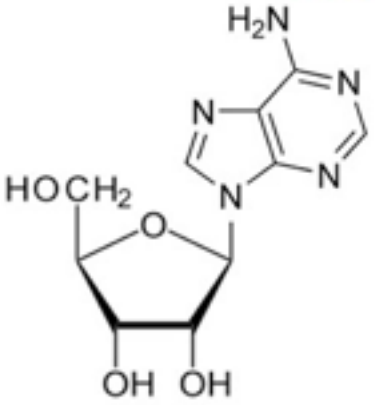
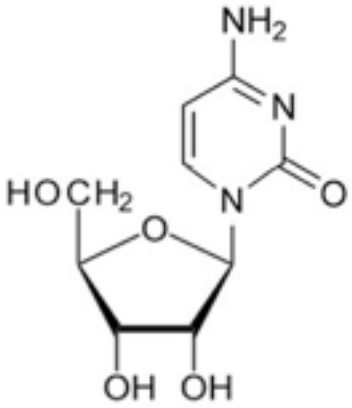
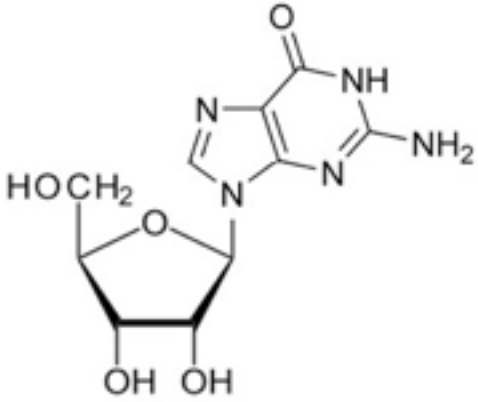
Adenosine



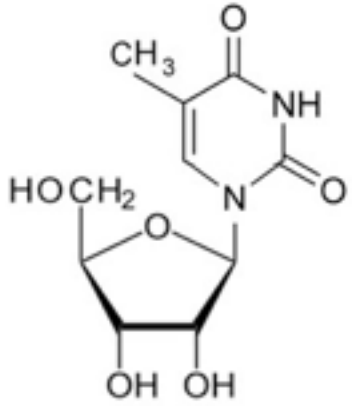
Cytidine

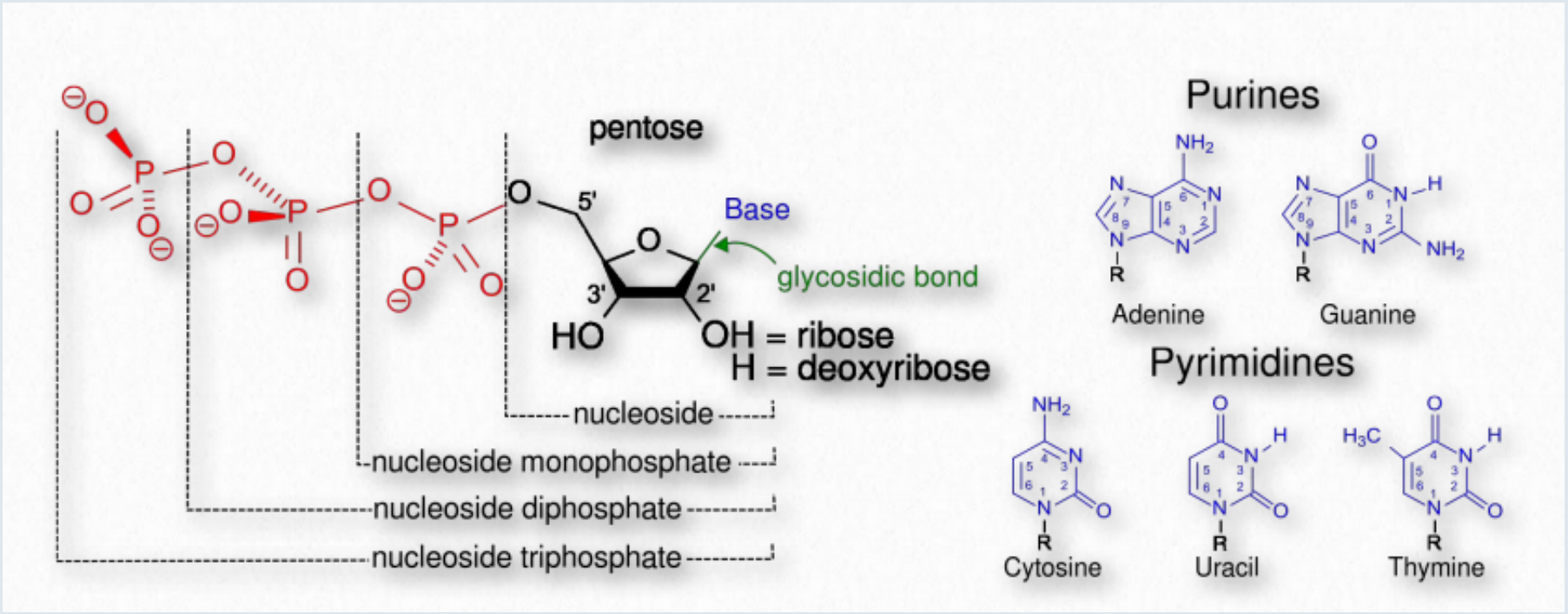


Guanosine



Thymidine




pentose
Base
glycosidic bond
5'
3'
2'
HO
OH = ribose
H = deoxyribose
nucleoside
nucleoside monophosphate
nucleoside diphosphate
nucleoside triphosphate
Purines
Adenine
Guanine
Pyrimidines
Cytosine
Uracil
Thymine

King's College

Rosalind Franklin Maurice Wilkins

Cambridge University

James Watson Francis Crick

equipment, and to Dr. G. E. R. Deacon and the captain and officers of R.R.S. *Discovery II* for their part in making the observations.

[1] Young, F. B., Gerrard, H., and Jevons, W., *Phil. Mag.*, **40**, 149 (1920).
[2] Longuet-Higgins, M. S., *Mon. Not. Roy. Astro. Soc., Geophys. Supp.*, **5**, 285 (1949).
[3] Von Arx, W. S., Woods Hole Papers in Phys. Oceanog. Meteor., **11** (3) (1950).
[4] Ekman, V. W., *Arkiv. Mat. Astron. Fysik. (Stockholm)*, **2** (11) (1905).

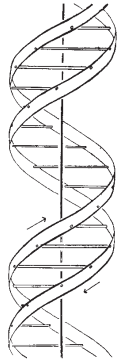
MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey[1]. They kindly made their manuscript available to us in advance of publication. Their model consists of three intertwined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.



This figure is purely diagrammatic. The two ribbons symbolize the two phosphate—sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups joining β-D-deoxyribofuranose residues with 3′,5′ linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furberg's[2] model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Furberg's 'standard configuration', the sugar being roughly perpendicular to the attached base. There is a residue on each chain every 3·4 A. in the *z*-direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 A. The distance of a phosphorus atom from the fibre axis is 10 A. As the phosphates are on the outside, cations have easy access to them.

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical *z*-co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol configurations) it is found that only specific pairs of bases can bond together. These pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

It has been found experimentally[3,4] that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

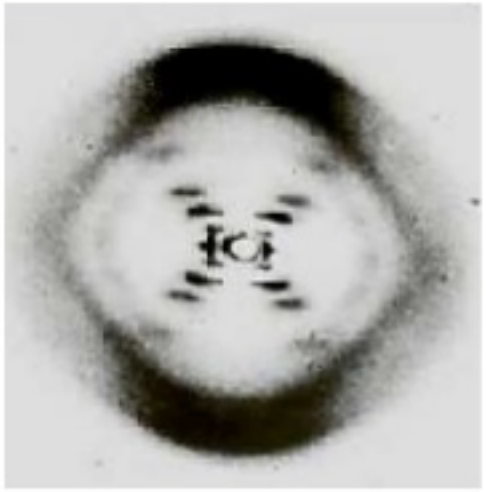
The previously published X-ray data[5,6] on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. Some of these are given in the following communications. We were not aware of the details of the results presented there when we devised our structure, which rests mainly though not entirely on published experimental data and stereochemical arguments.

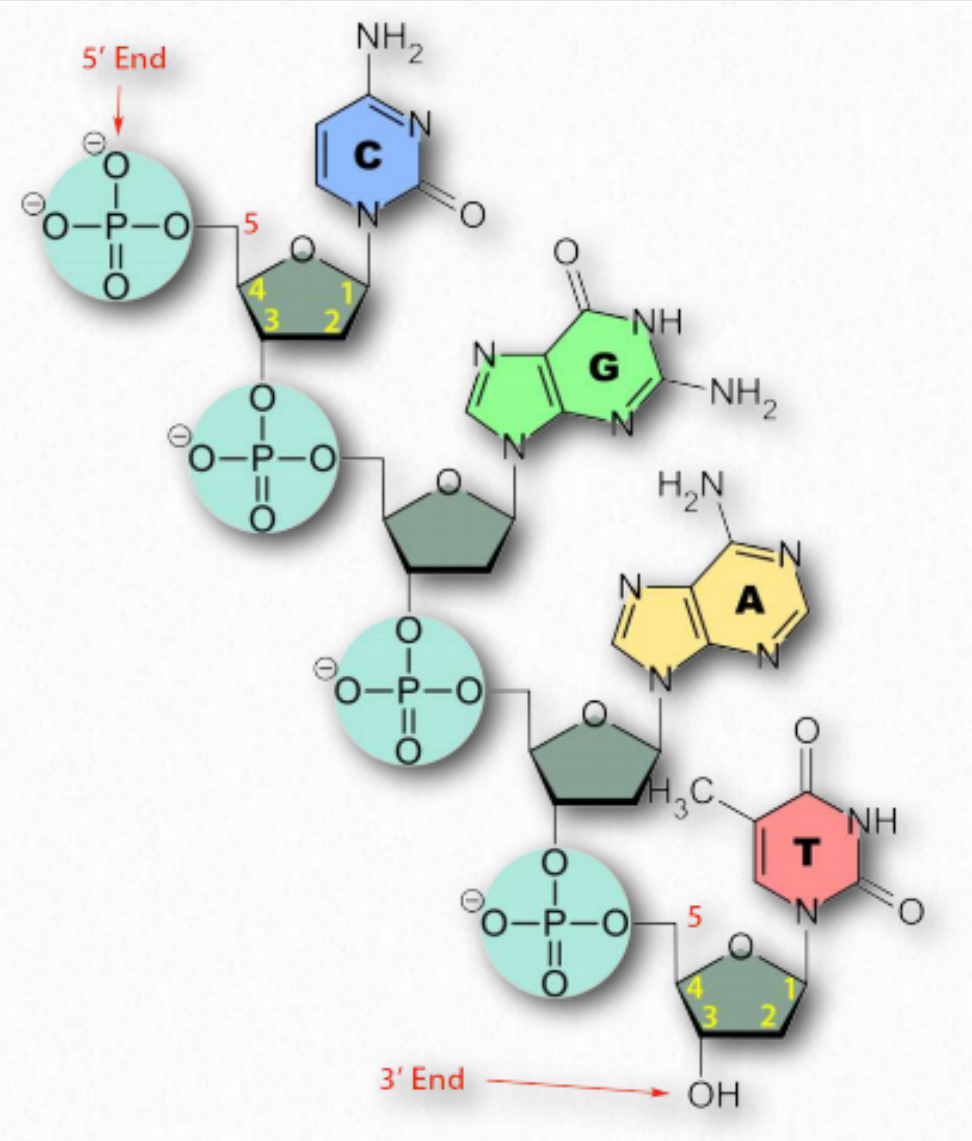
It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

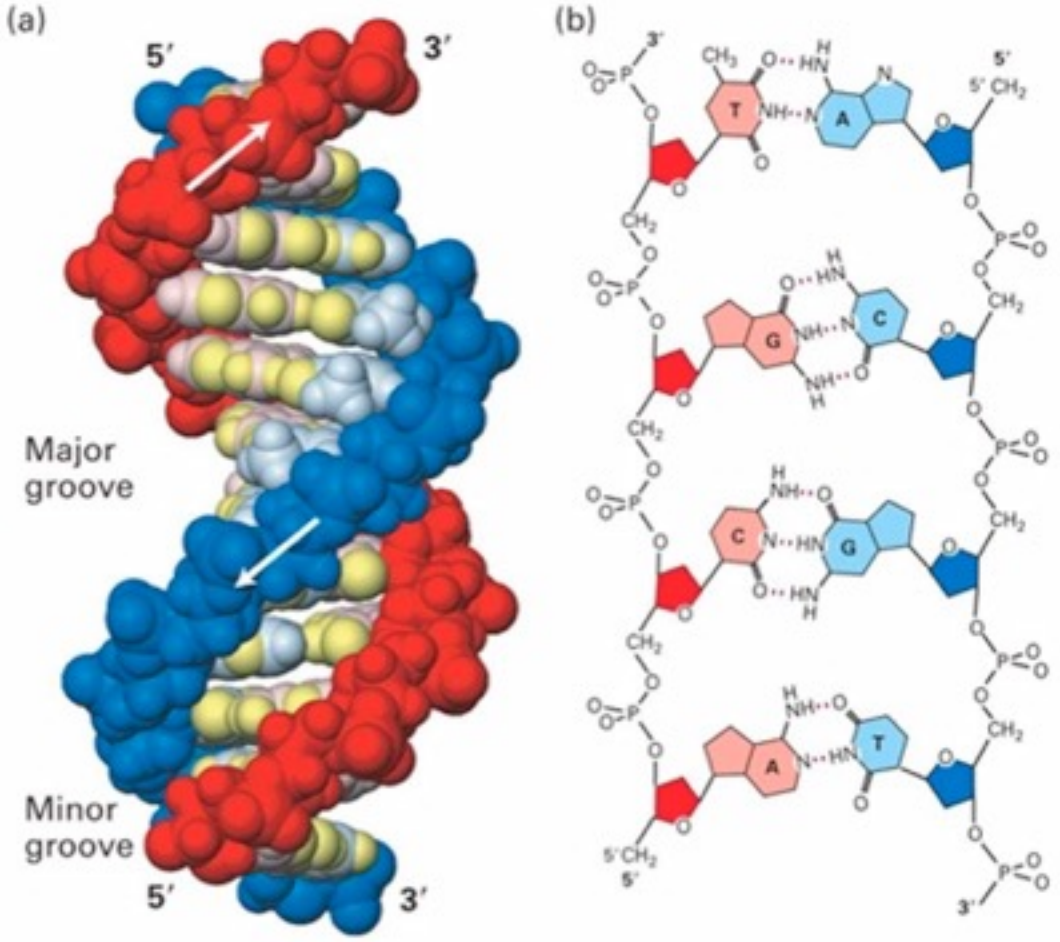
We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on interatomic distances. We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin and their co-workers at

- **Rosalind Franklin** worked at King's College in London as a technician doing X-ray crystallography.
- She improved the resolution of the cameras used in order to obtain the most detailed images yet of X-ray diffraction of DNA. These detailed images allowed her to make very exact measurements related to the structure of DNA.
- Her work was shared with James Watson *without her permission*.
- Watson and Crick used her measurements to show that the phosphate groups were on the outside of the DNA double helix, and that the nitrogenous bases were more hydrophobic and thus on the inside.
- Watson & Crick published the structure of DNA first, without crediting Franklin. They were awarded the Nobel prize. Franklin died of ovarian cancer she developed as a result of her work.



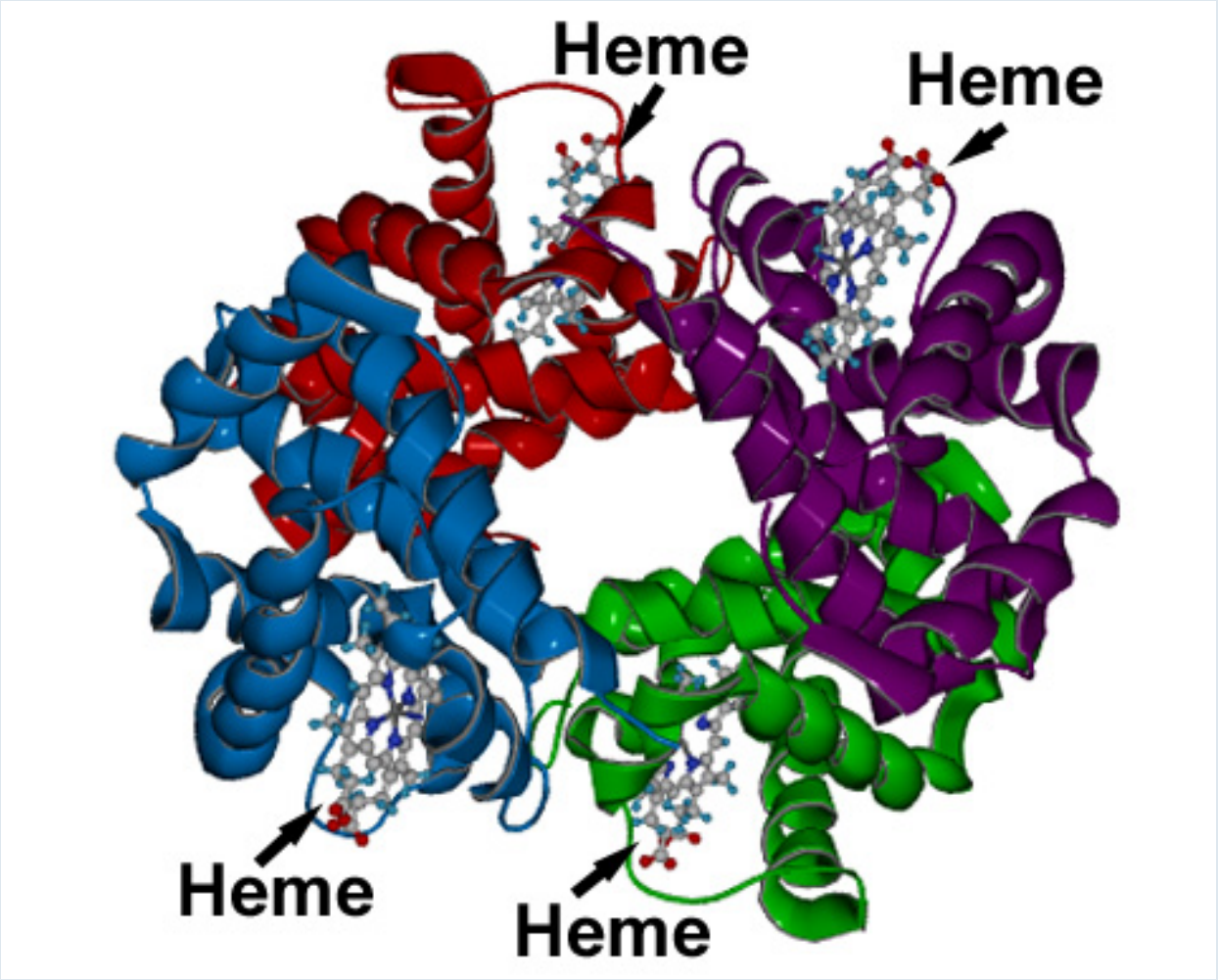


A polynucleotide chain consists of a series of 5’ –> 3' sugar-phosphate links that form an “external” backbone of the structure from which the bases protrude inward.

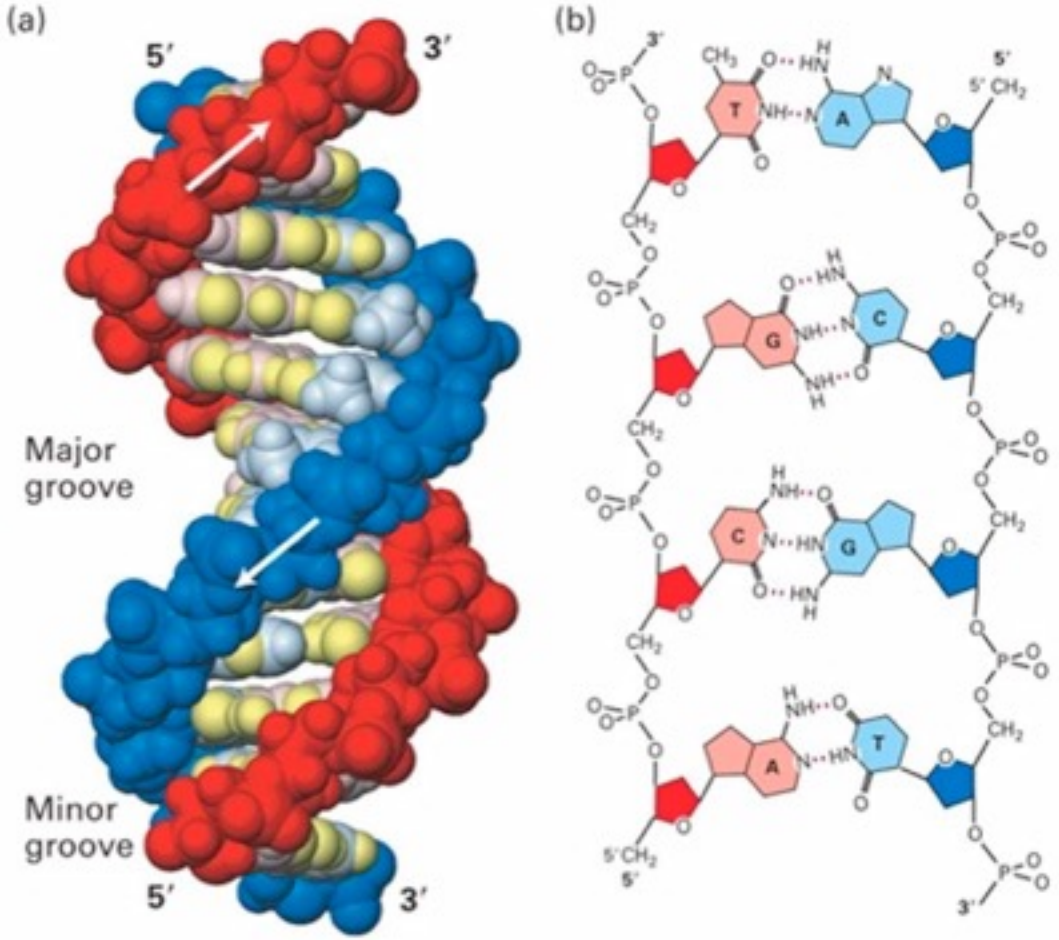


B form DNA

2.0 nM dia (20 Á)
0.36 nM (3.6 Á)
between bases
~10 bases per turn
antiparallel strands
bases perpendicular
to axis


Heme
Heme
Heme
Heme

Rubin’s Vase illusion



B form DNA

2.0 nM dia (20 Á)
0.36 nM (3.6 Á) between bases
~10 bases per turn
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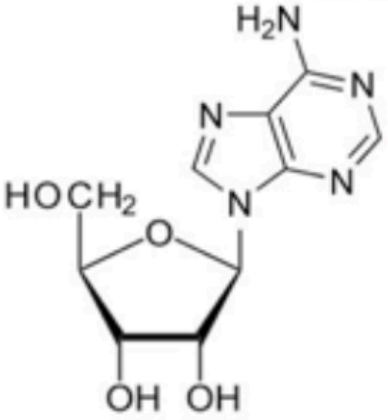
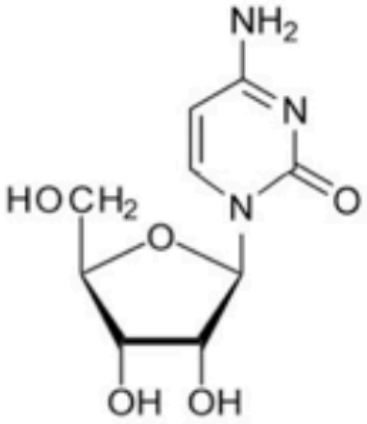
bases perpendicular to axis

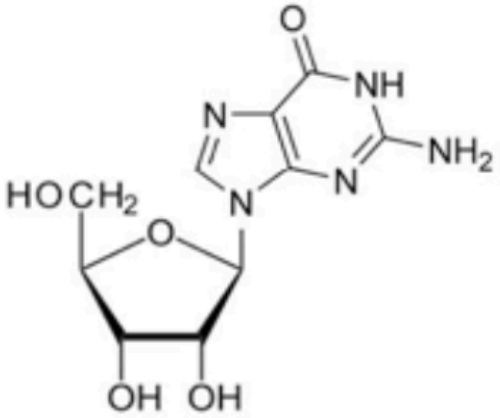
Adenosine



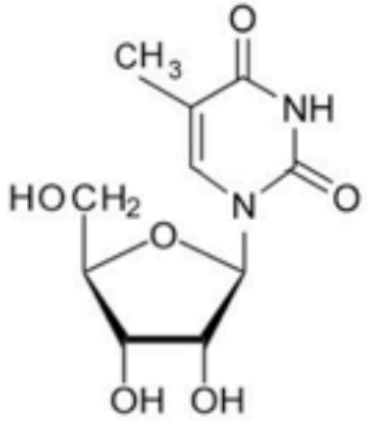
Cytidine

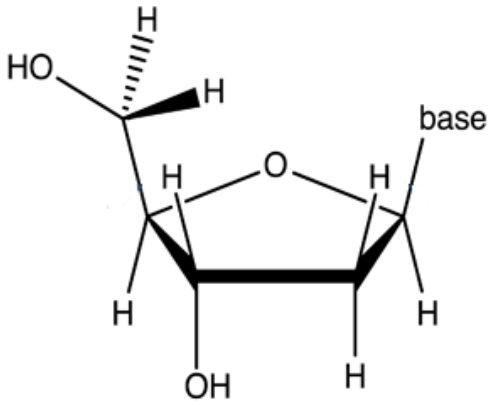


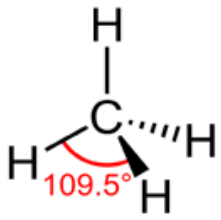
Guanosine

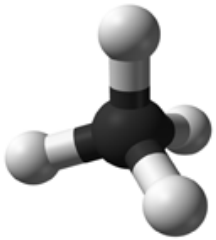


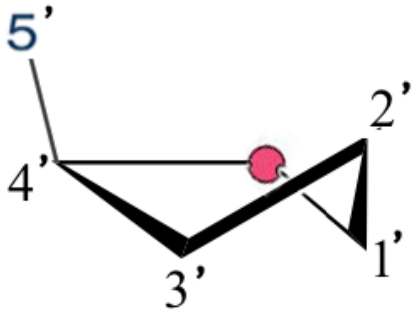
Thymidine

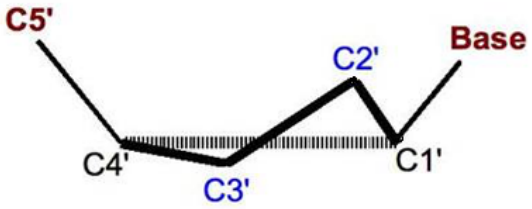




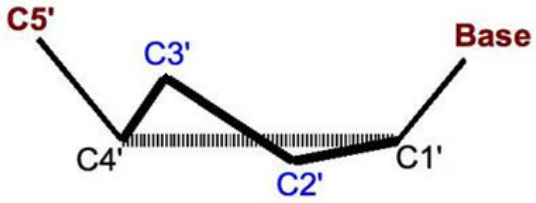




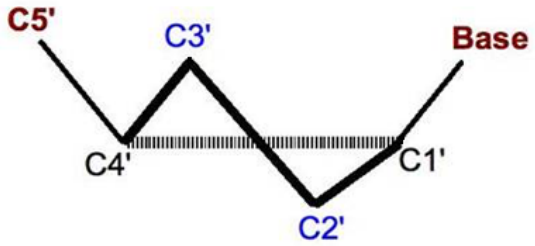




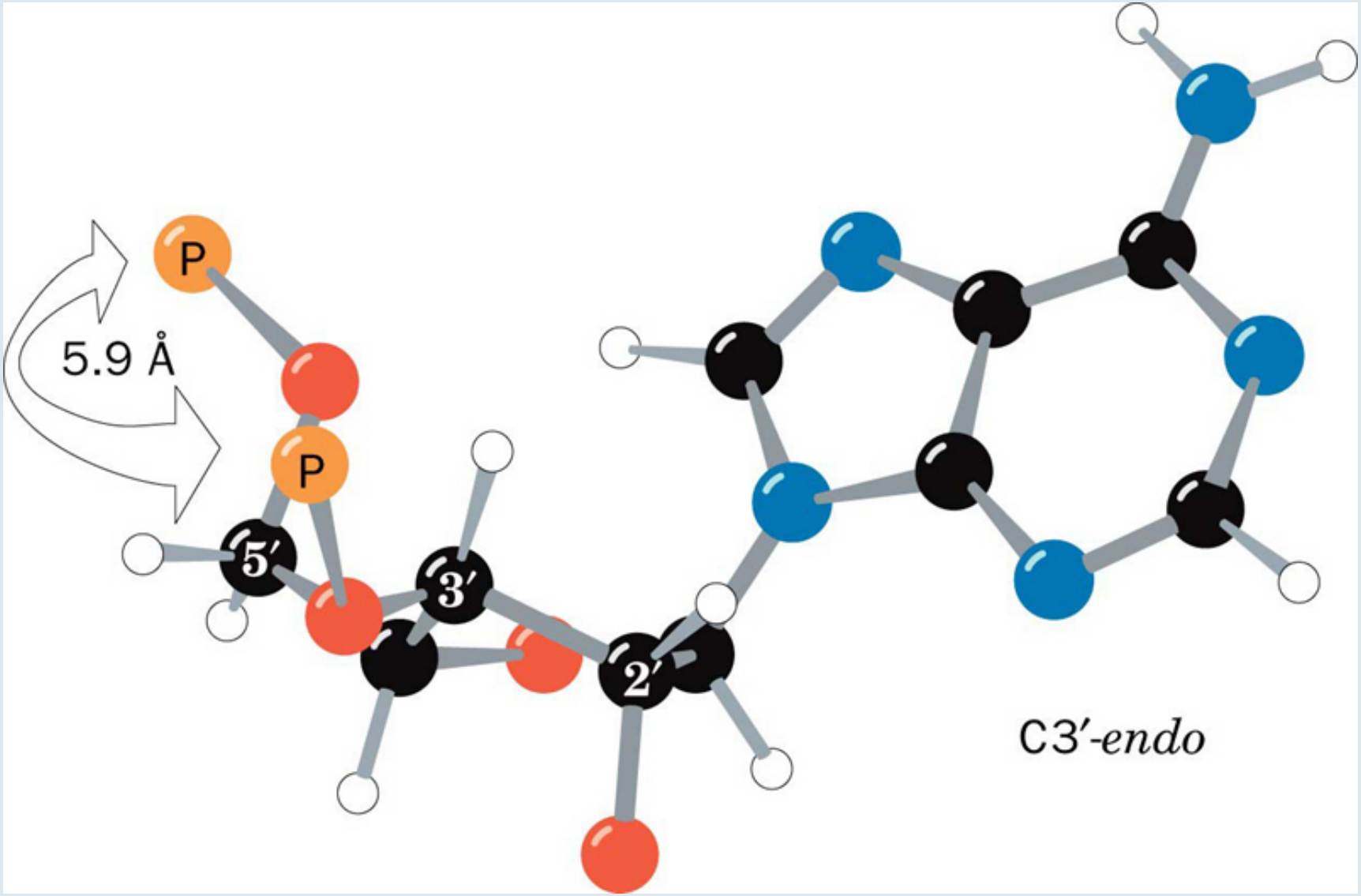
E C2'-endo

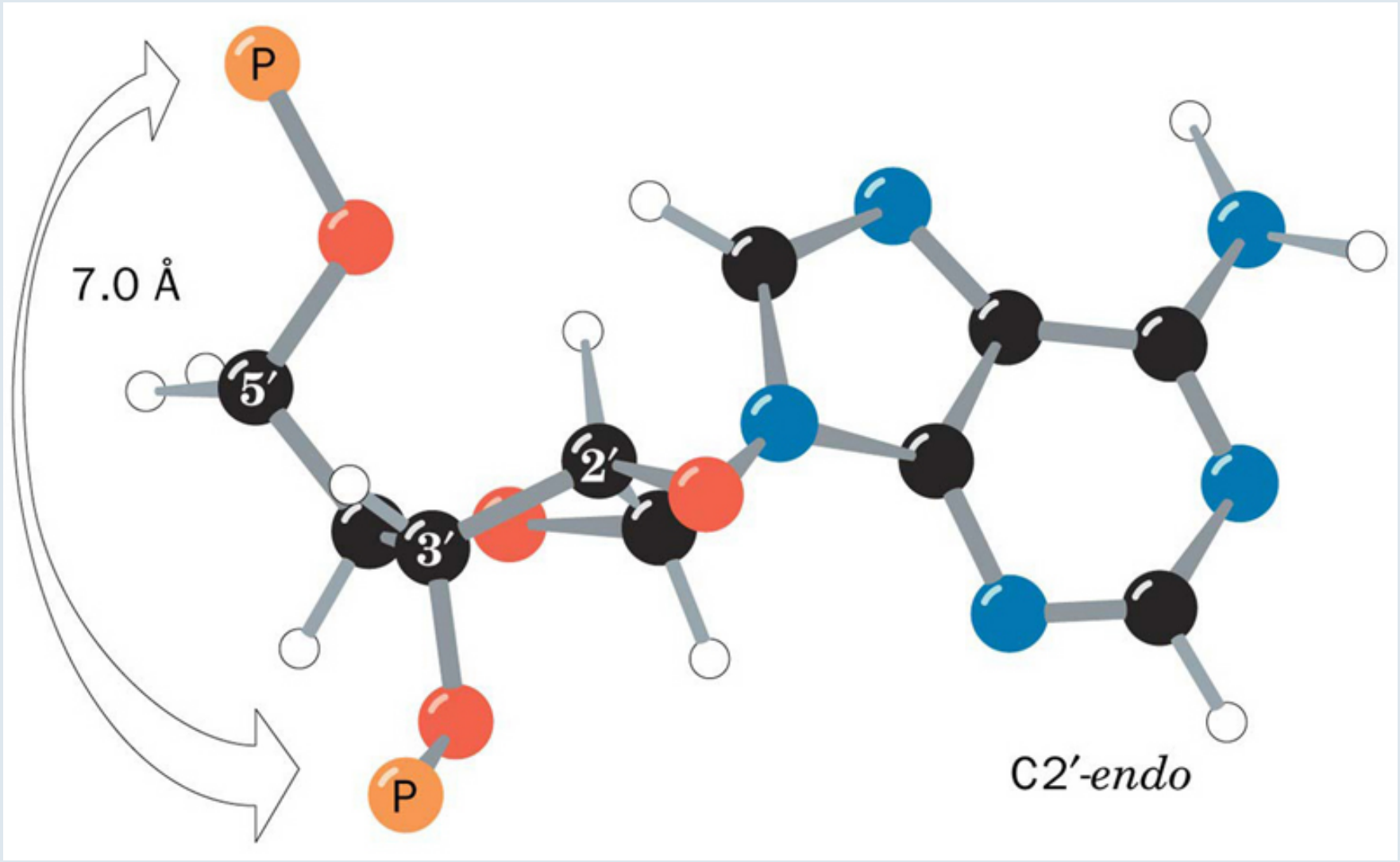


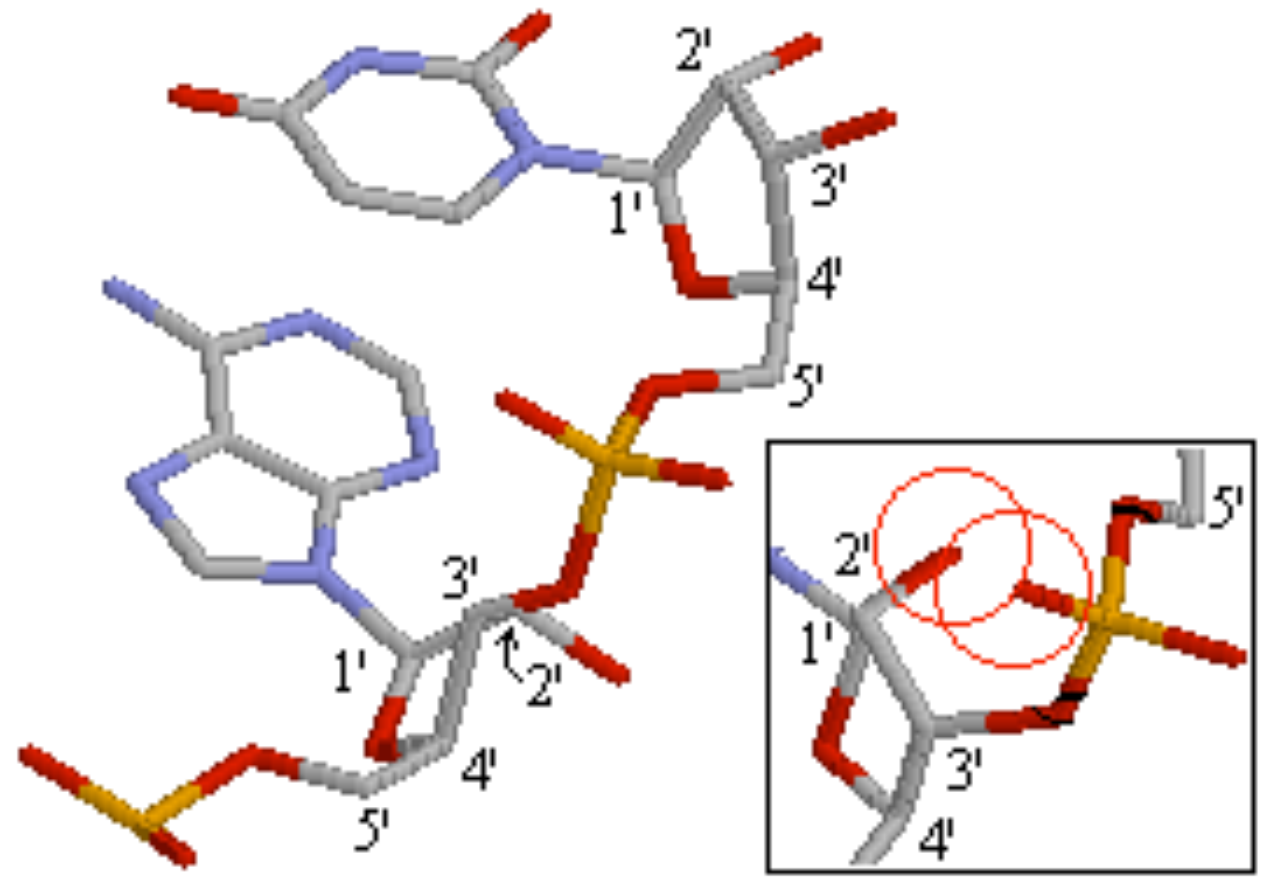
E C3'-endo



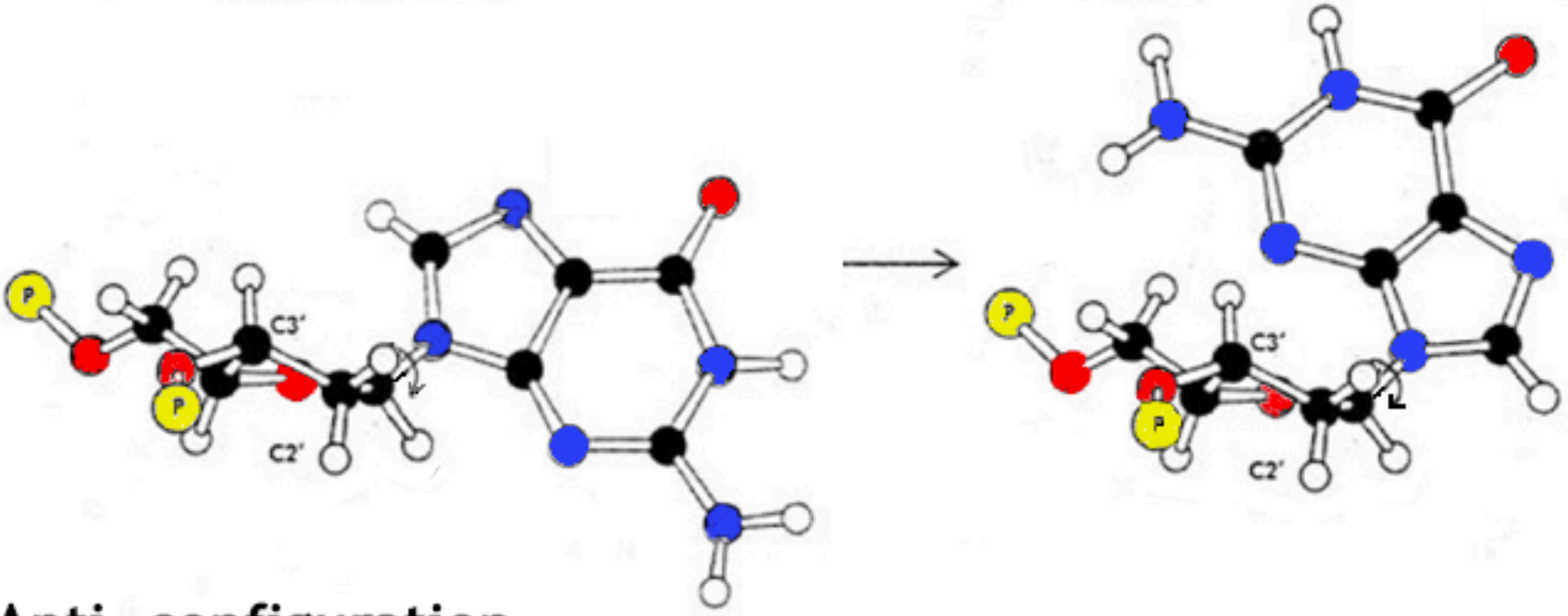
T C2'-exo-C3'-endo


P
5.9 Å
P
5′
3′
2′
C3′-endo


P
7.0 Å
5′
2′
3′
P
C2′-endo

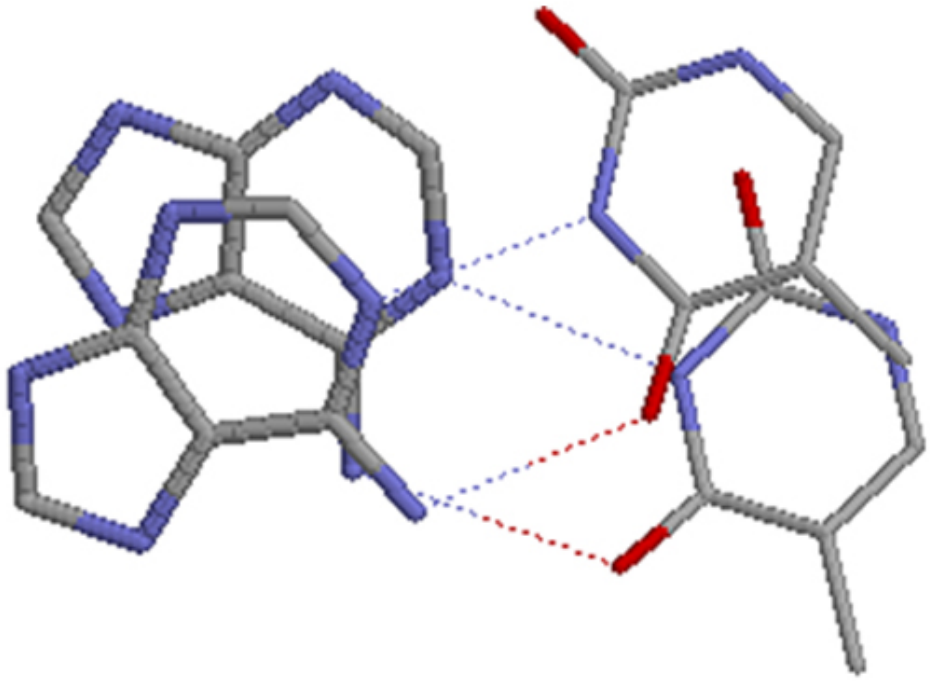

2'
3'
1'
4'
5'
3'
1'
2'
4'
5'
5'
2'
1'
3'
4'

Syn-configuration



Anti -configuration

C N O H P



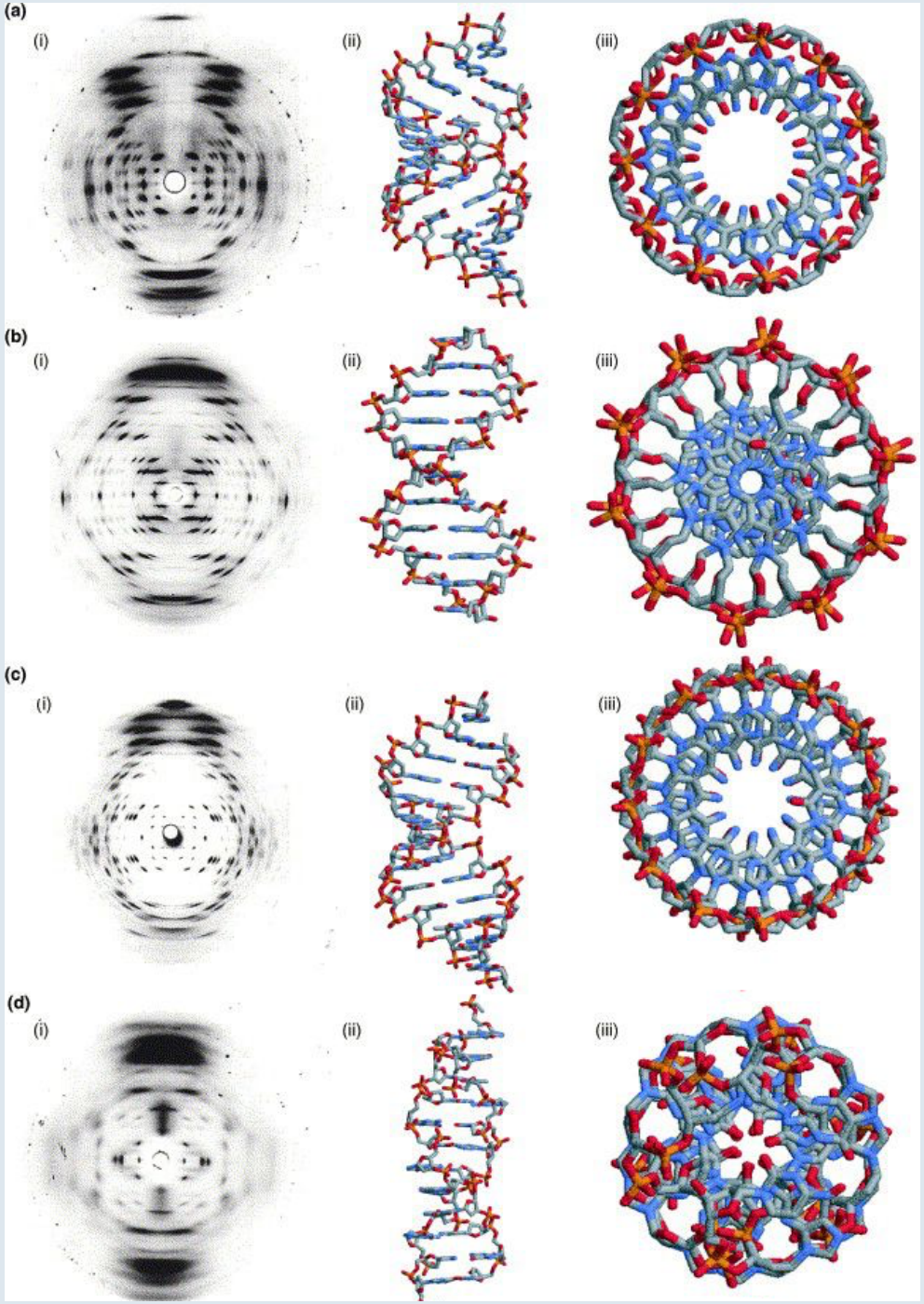
Step			Energy kJ/mol
C-G G-C			-61.6
C-G A-T	or	T-A G-C	-44.0
C-G T-A	or	A-T G-C	-41.1
G-C C-G			-40.6
G-C G-C	or	C-G C-G	-34.6
T-A A-T			-27.5
G-C T-A	or	A-T C-G	-27.5
G-C A-T	or	T-A C-G	-28.4
A-T A-T	or	T-A T-A	-22.5
A-T T-A			-16.0

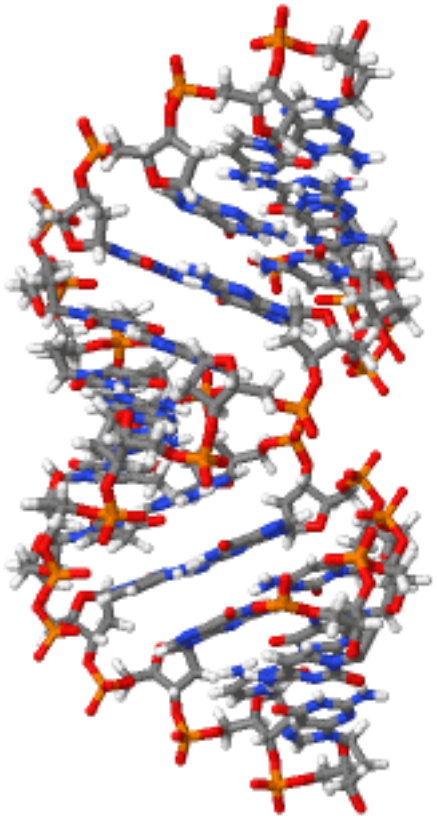
A-form double helix

B-form double helix

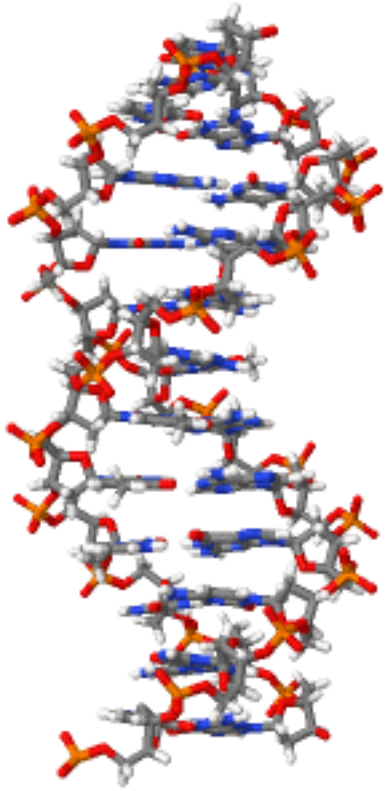
C-form double helix

Z-form double helix

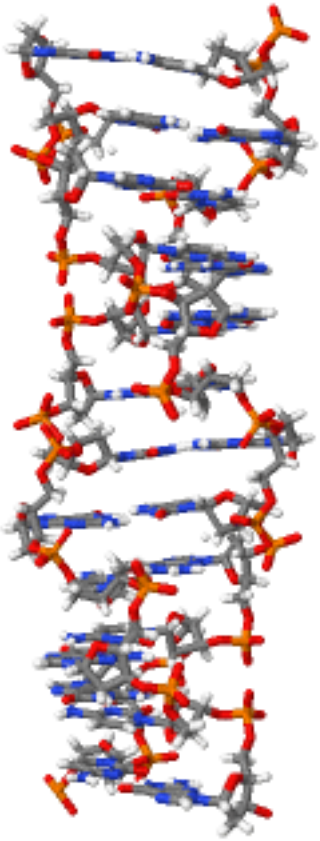




A DNA



B DNA



Z DNA

A DNA: **Right handed** double helix, **11 bases pairs** per turn, bases are tilted 20^{o}, no defined major or minor grooves, **2.9 Angstrom** rise per base, ***C3'-endo*** pucker preferred, bases adopt the ***anti*** **configuration**.

B DNA: **Right handed** double helix, **~10 base pairs** per turn, bases are perpendicular to helical axis**, 3.4 Angstrom** rise per base, clearly defined **major** and **minor** grooves, with the major grooves being **~22 Angstrom** across and the minor groove being only **12 Angstrom**, ***C2'-endo*** pucker preferred, and the bases adopt the ***anti-*** **configuration**.

Z-DNA: **Left handed** double helix, **12bp per turn**, irregular helix, bases irregularly tilted off the perpendicular axis, **~7.5 Angstrom** rise per dinucleotide repeat, some discernible irregularly defined grooves, bases alternate between both the ***C2'*** and *C3'-endo* pucker conformation, **as well as** the ***anti*** **and** ***syn*** **configuration**.

Geometry attribute	A-form	B-form	Z-form
Helix sense	right-handed	right-handed	left-handed
Repeating unit	1 bp	1 bp	2 bp
Rotation/bp	32.7°	35.9°	60°/2
bp/turn	11	10.5	12
Inclination of bp to axis	+19°	−1.2°	−9°
Rise/bp along axis	2.3 Å (0.23 nm)	3.32 Å (0.332 nm)	3.8 Å (0.38 nm)
Pitch/turn of helix	28.2 Å (2.82 nm)	33.2 Å (3.32 nm)	45.6 Å (4.56 nm)
Mean propeller twist	+18°	+16°	0°
Glycosyl angle	anti	anti	C: anti, G: syn
Sugar pucker	C3'-endo	C2'-endo	C: C2'-endo, G: C3'-endo
Diameter	23 Å (2.3 nm)	20 Å (2.0 nm)	18 Å (1.8 nm)

Mulholland *et al. Cell & Bioscience* 2012, **2**:3
http://www.cellandbioscience.com/content/2/1/3

Cell & Bioscience

RESEARCH Open Access

SWI/SNF-mediated chromatin remodeling induces Z-DNA formation on a nucleosome

Niveen Mulholland[1,3], Yan Xu[2], Hiroshi Sugiyama[2] and Keji Zhao[1*]

Abstract

Background: Z-DNA is a higher-energy, left-handed form of the double helix. A primary function of Z-DNA formation is to facilitate transcriptional initiation and activation. Sequences favoring Z-DNA formation are frequently located in promoter regions and Z-DNA is stabilized by torsional strain resulting from negative supercoiling, such as that generated by an actively transcribing polymerase or by a nucleosome remodeling event. We previously have shown that activation of the CSF1 gene by a chromatin remodeling event in the promoter results in Z-DNA formation at TG repeats within the promoter.

Results: We show that remodeling of a mononucleosome by the human SWI/SNF complex results in Z-DNA formation when the DNA within the mononucleosome contains Z-DNA favoring sequence. Nuclease accessibility patterns of nucleosome core particle consisting of Z-DNA are quite different from counterpart nucleosomes containing classic B-DNA. Z-nucleosomes represent a novel mononucleosome structure.

Conclusions: We present evidence that Z-DNA can form on nucleosomes though previous observations indicate the occlusion of nucleosome formation from Z-DNA.

https://cellandbioscience.biomedcentral.com/track/pdf/10.1186/2045-3701-2-3

Sci Rep. 2018; 8: 914. PMCID: PMC5772643

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Mitochondrial DNA damage and subsequent activation of Z-DNA binding protein 1 links oxidative stress to inflammation in epithelial cells

Bartosz Szczesny,[1] Michela Marcatti,[1] Akbar Ahmad,[1] Mauro Montalbano,[2] Attila Brunyánszki,[1] Sofia-Iris Bibli,[3] Andreas Papapetropoulos,[3,4] and Csaba Szabo[1]

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Abstract

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This report identifies mitochondrial DNA (mtDNA) as a target and active mediator that links low-level oxidative stress to inflammatory response in pulmonary epithelial cells. Extrusion of mtDNA into the bronchoalveolar lavage fluid occurs as an early event in mice subjected to cigarette smoke injury, concomitantly with the depletion of mtDNA in the lung tissue. In cultured lung epithelial cells, prolonged, low-level oxidative stress damages the mtDNA, without any detectable damage to the nuclear DNA. In turn, cellular depletion of the mtDNA occurs, together with a transient remodeling of cellular bioenergetics and morphology - all without any detectable impairment in overall cell viability. Damaged mtDNA first enters the cytoplasm, where it binds to Z-DNA binding protein 1 (ZBP1) and triggers inflammation via the TANK-binding kinase 1 /interferon regulatory factor 3 signaling pathway. Fragments of the mtDNA are subsequently released into the extracellular space via exosomes. MtDNA-containing exosomes are capable of inducing an inflammatory response in naïve (non-oxidatively stressed) epithelial cells. *In vivo*, administration of isolated mtDNA into the in lungs of naïve mice induces the production of pro-inflammatory mediators, without histopathologic evidence of tissue injury. We propose that mtDNA-specific damage, and subsequent activation of the ZBP1 pathway, is a mechanism that links prolonged, low-level oxidative stress to autocrine and paracrine inflammation during the early stages of inflammatory lung disease.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5772643/

COMMUNICATIONS BIOLOGY

Review Article | Open Access | Published: 07 January 2019

Z-DNA and Z-RNA in human disease

Alan Herbert

Communications Biology **2**, Article number: 7 (2019) | Download Citation

Abstract

Left-handed Z-DNA/Z-RNA is bound with high affinity by the Zα domain protein family that includes ADAR (a double-stranded RNA editing enzyme), ZBP1 and viral orthologs regulating innate immunity. Loss-of-function mutations in ADAR p150 allow persistent activation of the interferon system by Alu dsRNAs and are causal for Aicardi-Goutières Syndrome. Heterodimers of ADAR and DICER1 regulate the switch from RNA- to protein-centric immunity. Loss of DICER1 function produces age-related macular degeneration, a different type of Alu-mediated disease. The overlap of Z-forming sites with those for the signal recognition particle likely limits invasion of primate genomes by Alu retrotransposons.

Z-DNA is the left-handed conformer of double-stranded DNA that normally exists in the right-handed Watson-Crick B-form. The flip from the B-form to the Z-form occurs when processive enzymes such as polymerases and helicases generate underwound DNA in their wake. The existence of Z-DNA was unexpected and its discovery accidental, the structure trapped in the first synthetic DNA ever crystallized. Initially the biological importance of Z-DNA was overestimated, after which it has been underappreciated ("We tend to overestimate the effect of a technology in the short run and underestimate the effect in the long run" - Roy Anara). An important inflection point has been the identification of the Z-DNA binding domain named Zα[1,2] from the dsRNA editing protein ADAR[3,4]. This domain's specificity for the left-handed conformation of Z-DNA was shown in a series of high-resolution NMR and X-ray studies[5,6]. The interactions between Zα and Z-DNA are conformation-specific, with no base-specific contacts.

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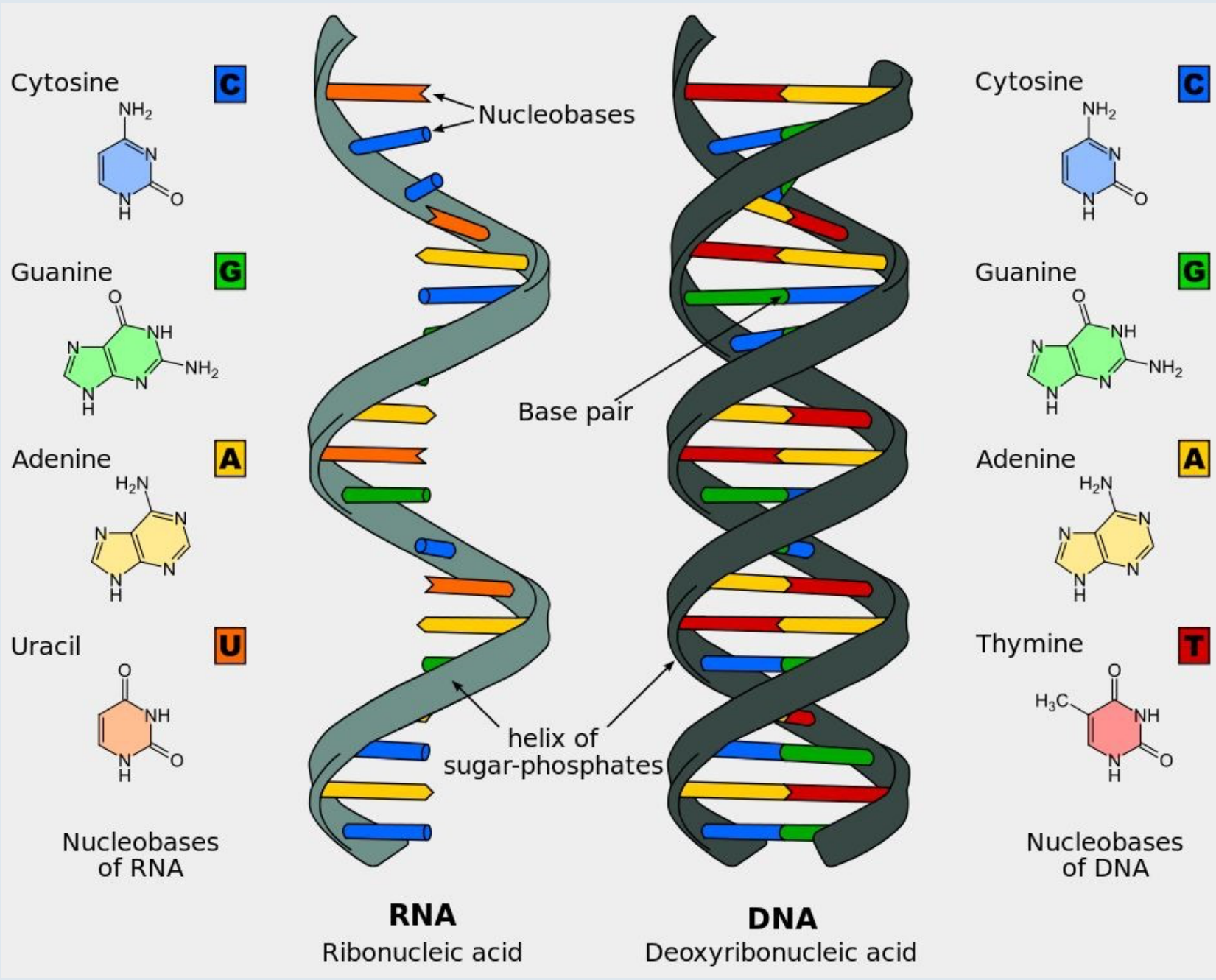
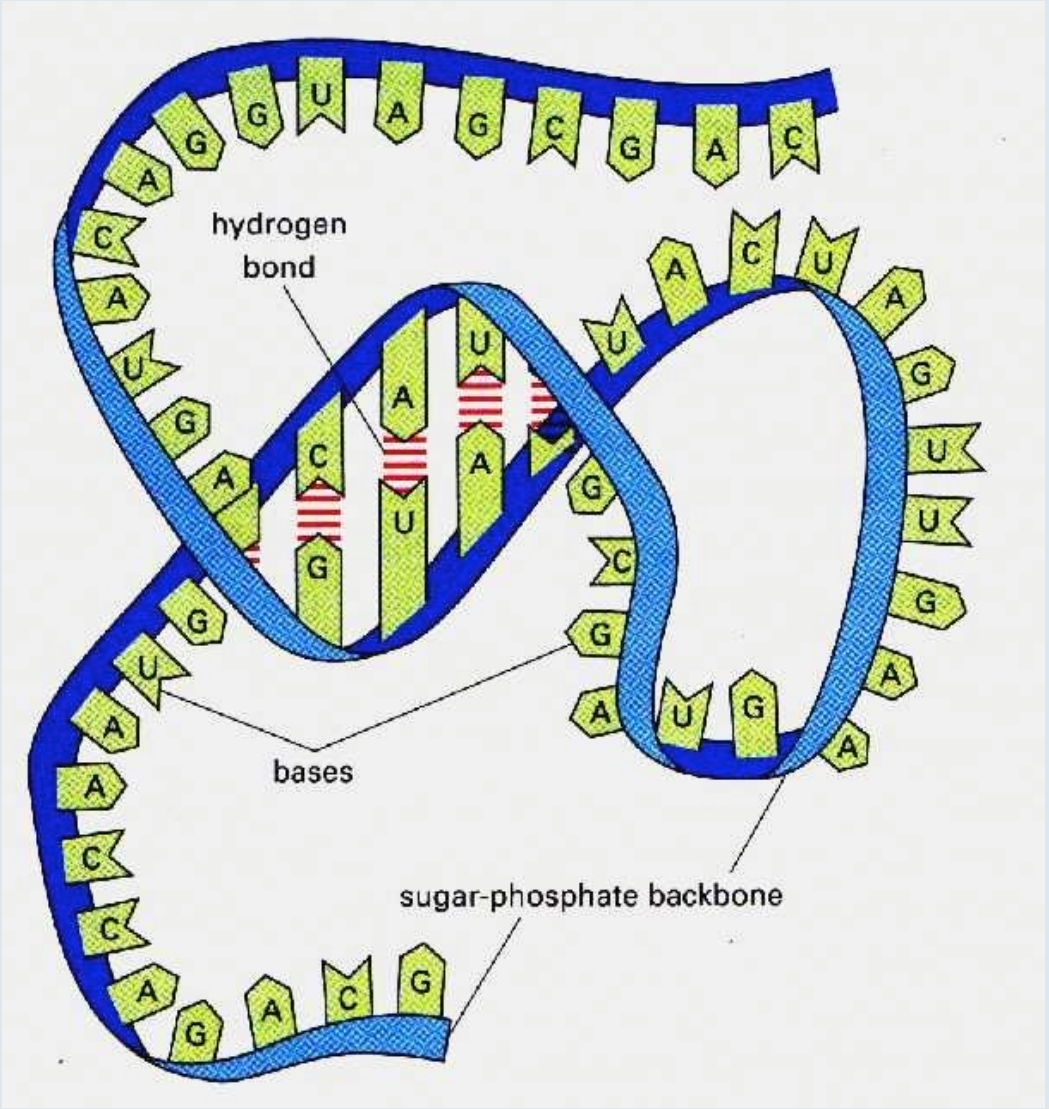
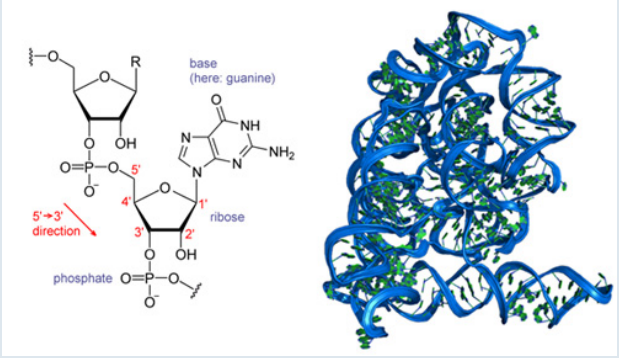
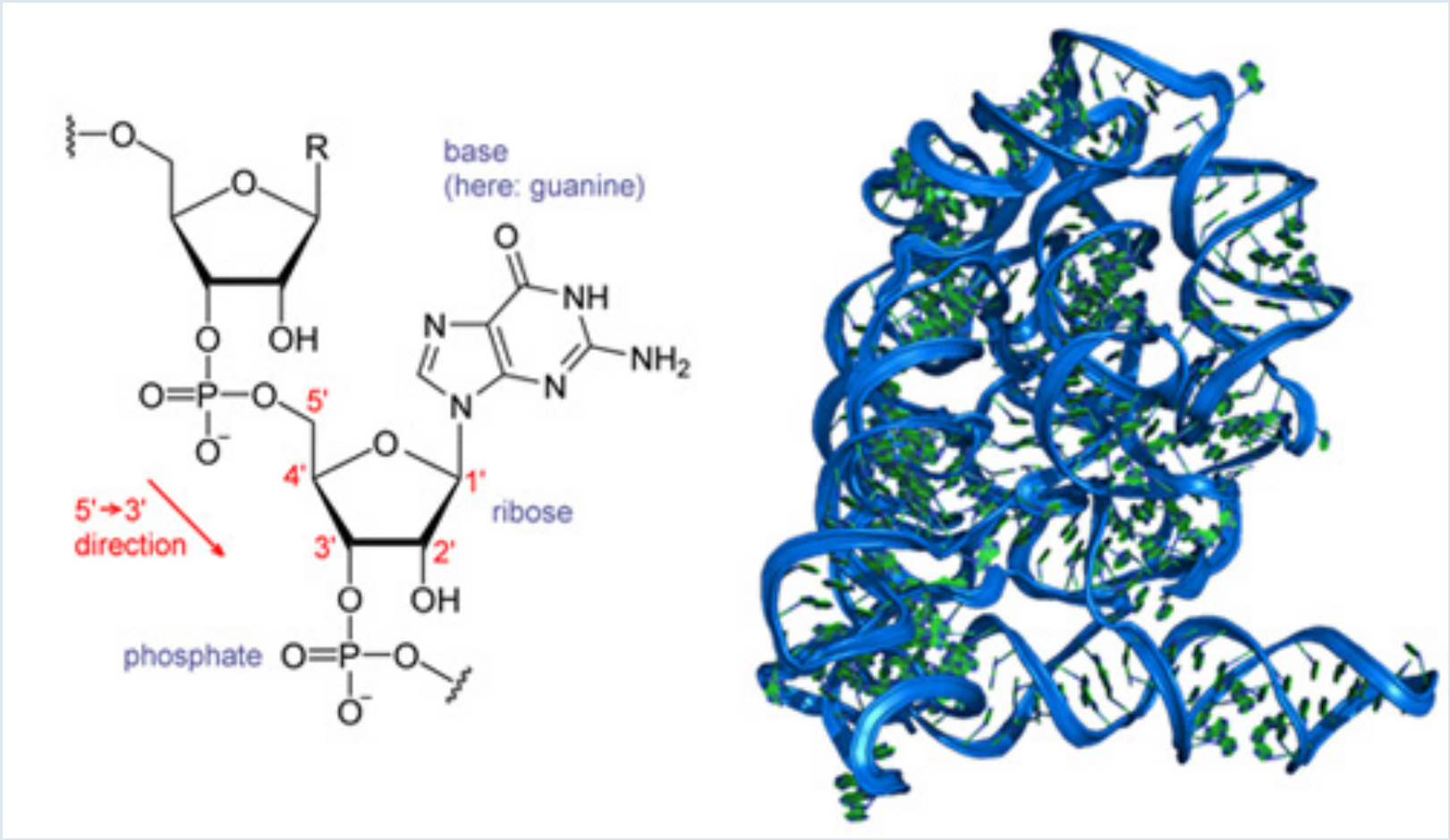
The Z-conformation, both as Z-DNA and Z-RNA, has likely played an essential role in limiting Alu retroelement invasion of primate genomes during evolution. Besides ADAR, key partners in this battle have been the signal recognition particle proteins SRP9 and SRP14 (on which Alu retrotransposition depends) and DICER1 (an endoribonuclease that heterodimerizes with ADAR and initiates RNA interference against single copy Alu transcripts, which are unlikely to form the long dsRNA required either for editing by ADAR or for the formation of Z-RNA). SRP9/14 dimers bind to Alu sequences capable of Z-formation, with stronger Z-formers found in those elements most successful at invading the genome. Indeed, loss of Z-forming potential is associated with loss of SRP9/14 binding and diminished Alu invasion. Recognition of Z-formation by the Zα domain targets Alu dsRNA for editing by ADAR, while recognition of Z-DNA by ADAR recruits DICER1 machinery to single copy genomic insertions, both enzymes serving to limit further retrotransposition. Loss of DICER1 function is associated with the accumulation of Alumers and inflammasome activation, leading to age-related macular degeneration (AMRD). The need to defend against retroelements provides a rationale for maintaining Z-forming segments in the genome. Other roles for the left-handed conformation in the readout of genomic information exist and these too show an association with disease. A genome-wide analysis reveals that both dsRNA editing and known disease genes are enriched for long Z-DNA forming segments.

In this review, I discuss the properties of Z-DNA and Z-RNA, and detail how the Zα domain of ADAR limits Alu retrotransposition and protects against human disease. I examine the impact of the Z-conformation on primate evolution, and outline key questions that remain in the field.


Cytosine
C
Guanine
G
Adenine
A
Uracil
U
Nucleobases of RNA
Nucleobases
Base pair
helix of sugar-phosphates
RNA
Ribonucleic acid
DNA
Deoxyribonucleic acid
Cytosine
C
Guanine
G
Adenine
A
Thymine
T
Nucleobases of DNA

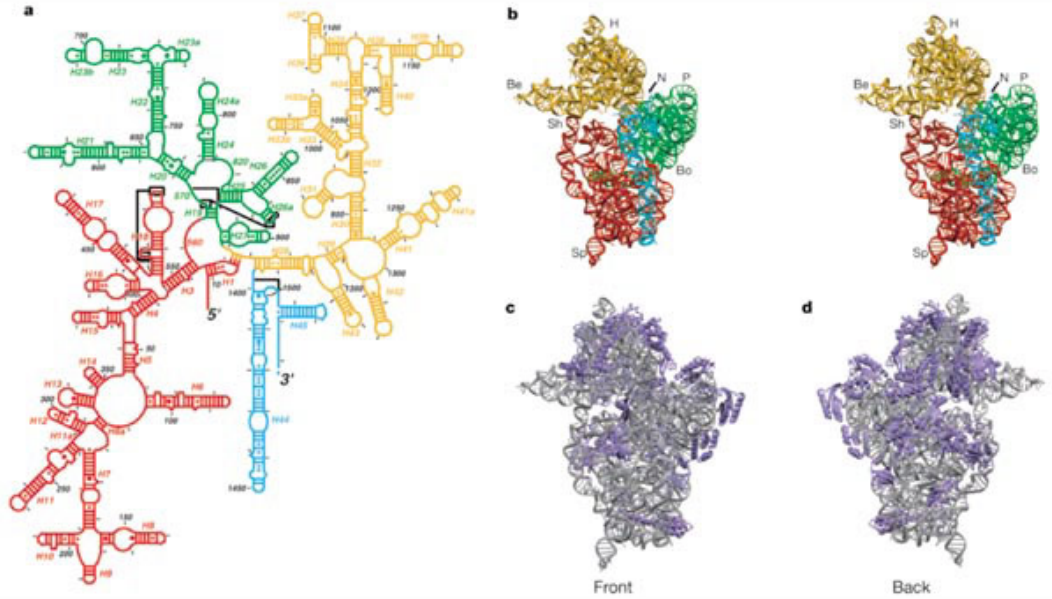

hydrogen
bond
bases
sugar-phosphate backbone


base
(here: guanine)
ribose
5'→3'
direction
phosphate


base
(here: guanine)
ribose
phosphate
5'→3'
direction

From the following article:
Structure of the 30S ribosomal subunit
Brian T. Wimberly, Ditlev E. Brodersen, William M. Clemons, Jr, Robert J. Morgan-Warren, Andrew P. Carter, Clemens Vonrhein, Thomas Hartsch and V. Ramakrishnan
Nature **407**, 327-339(21 September 2000)
doi:10.1038/35030006

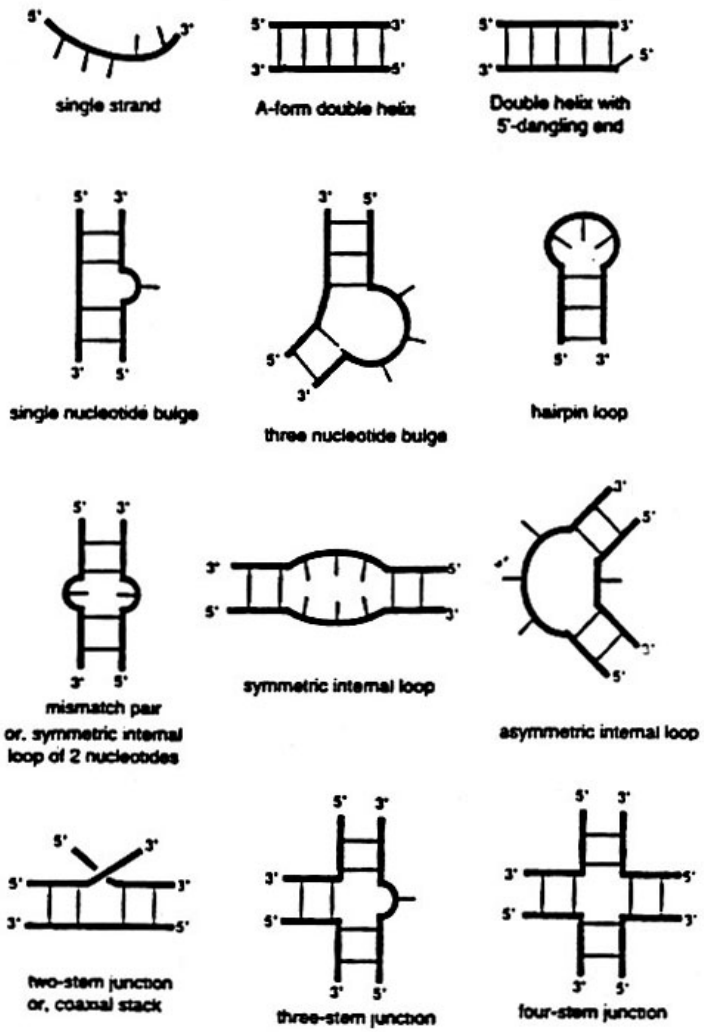
back to article



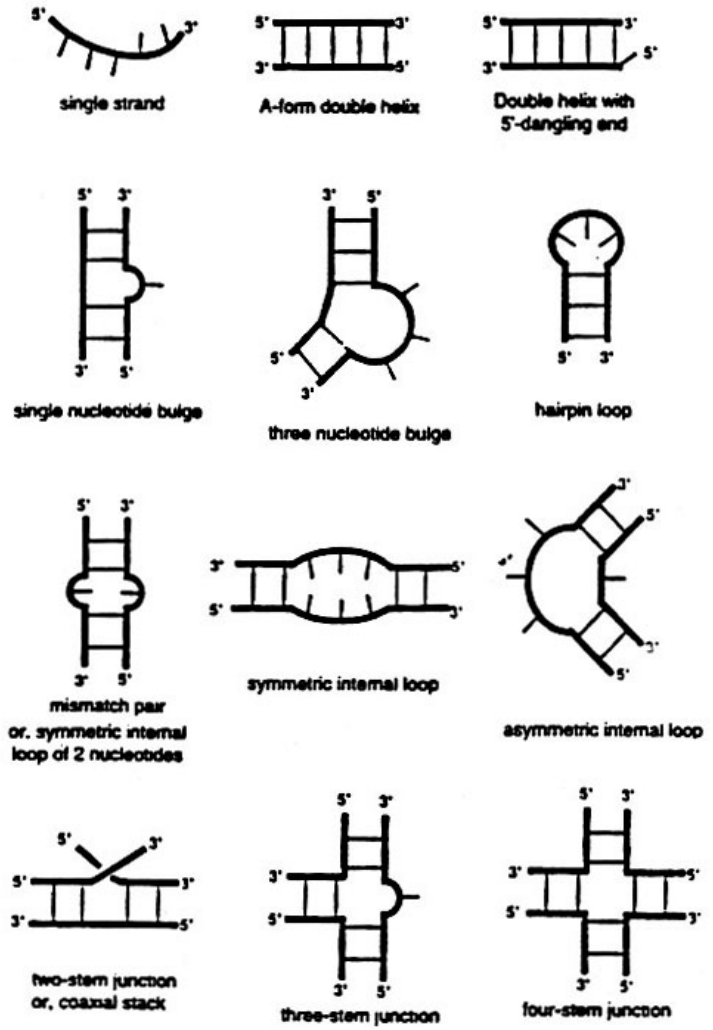
a, Secondary structure diagram of 16S RNA (modified with permission from http://www.rna.icmb.utexas.edu/CSI/2STR/Schematics/e.coli16s.27.5.5.schem.ps; see also ref. 21), showing the definition of the various helical elements used throughout the text. The numbering and diagram correspond to the *E. coli* sequence. Red, 5' domain; green, central domain; orange, 3' major domain; cyan, 3' minor domain. **b,** Stereo view of the tertiary structure of 16S RNA from our refined model, showing the 50S or 'front' view, with the same colouring for the domains. H, head; Be, beak; N, neck; P, platform; Sh, shoulder; Sp, spur; Bo, body. **c**, **d**, Front (50S) and back sides of the 30S. Grey, RNA; blue, proteins.

Previous figure | Figures & Tables index | Next figure

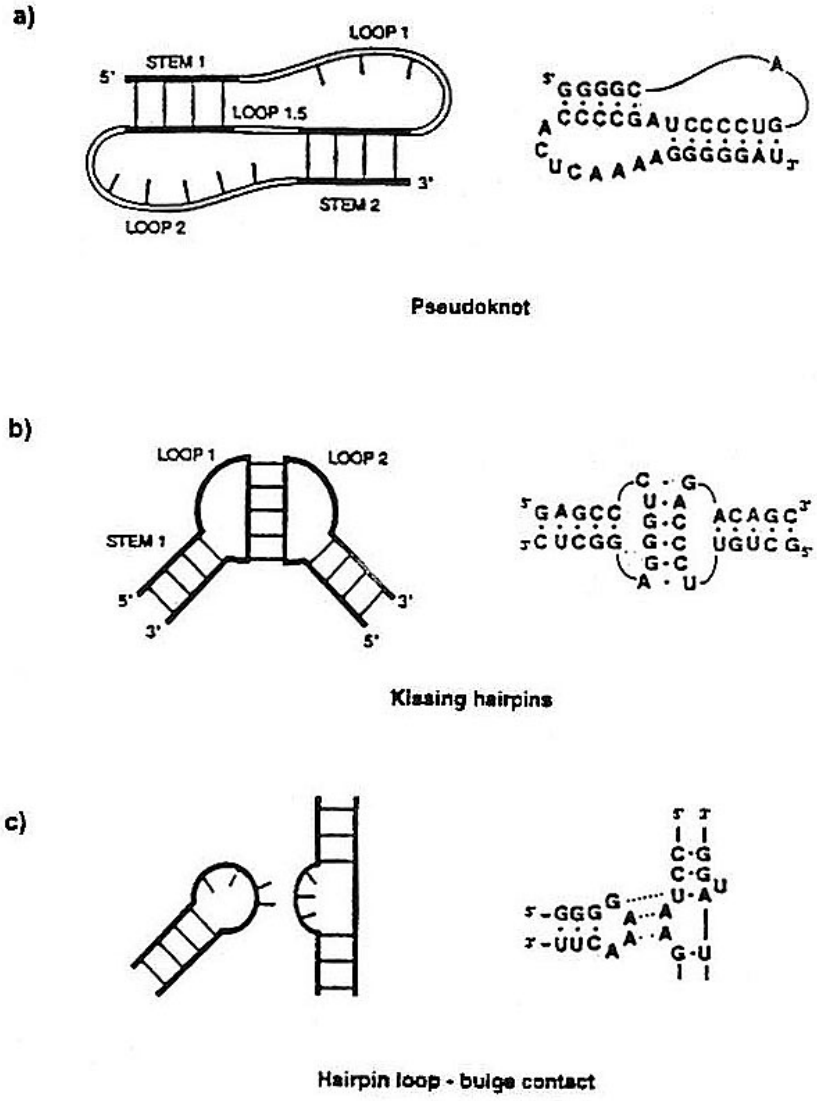
back to article



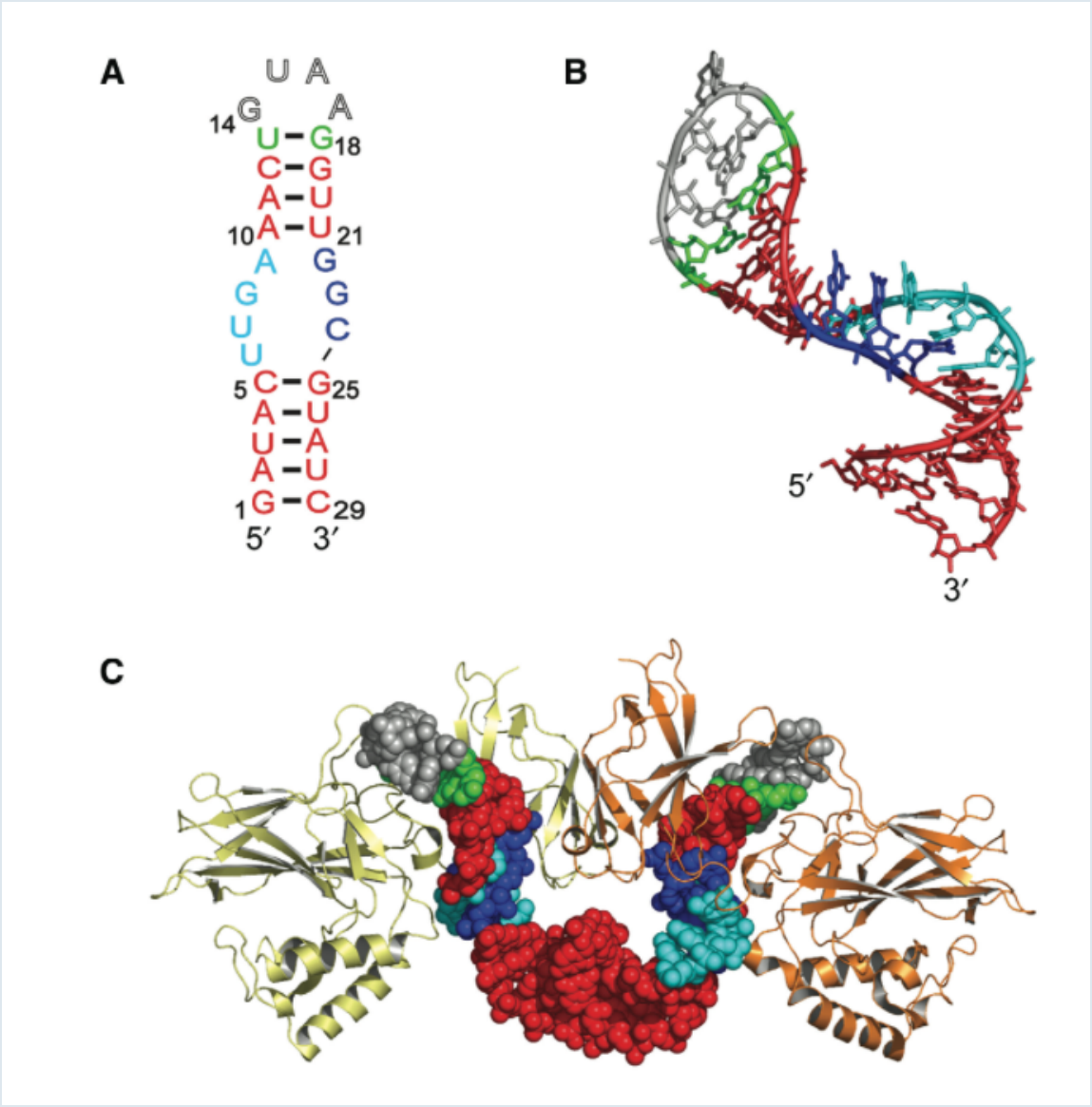
Secondary Structures



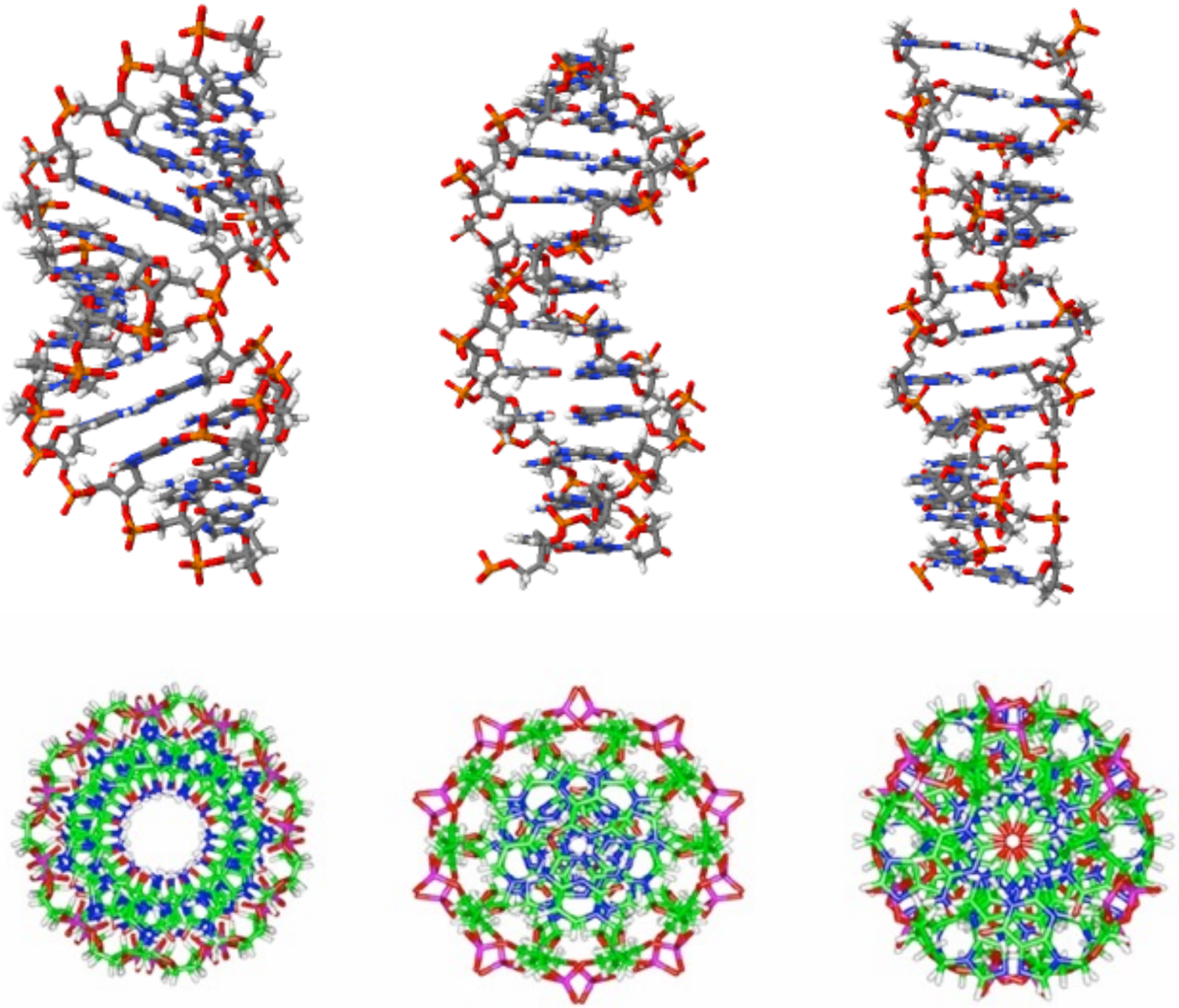
Secondary Structures

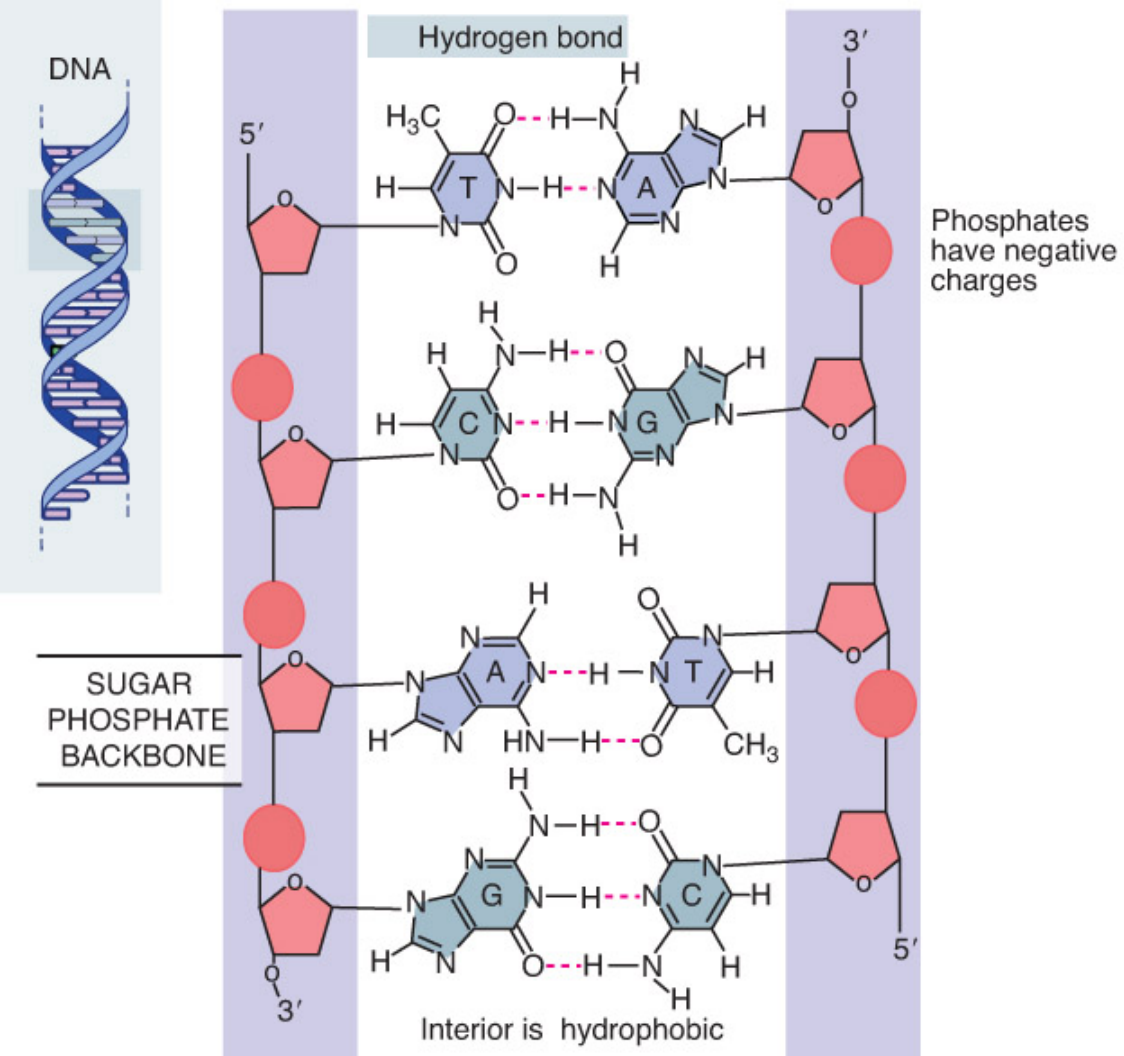


Tertiary Structures



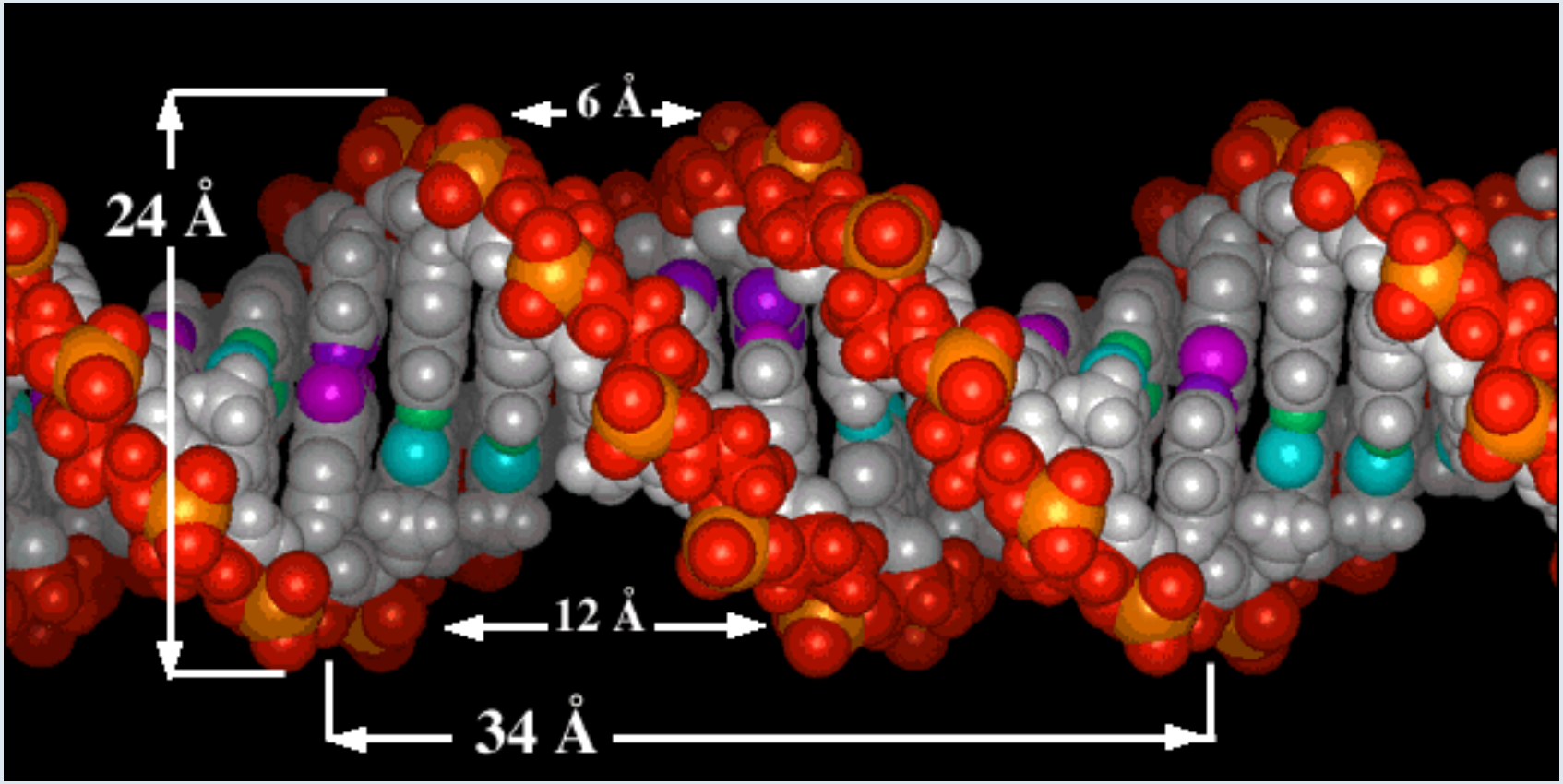
DNA mimicry by a high-affinity anti-NF-{kappa}B **RNA aptamer**
Nucleic Acids Research react-text: 55 36(4):1227-36 April 2008

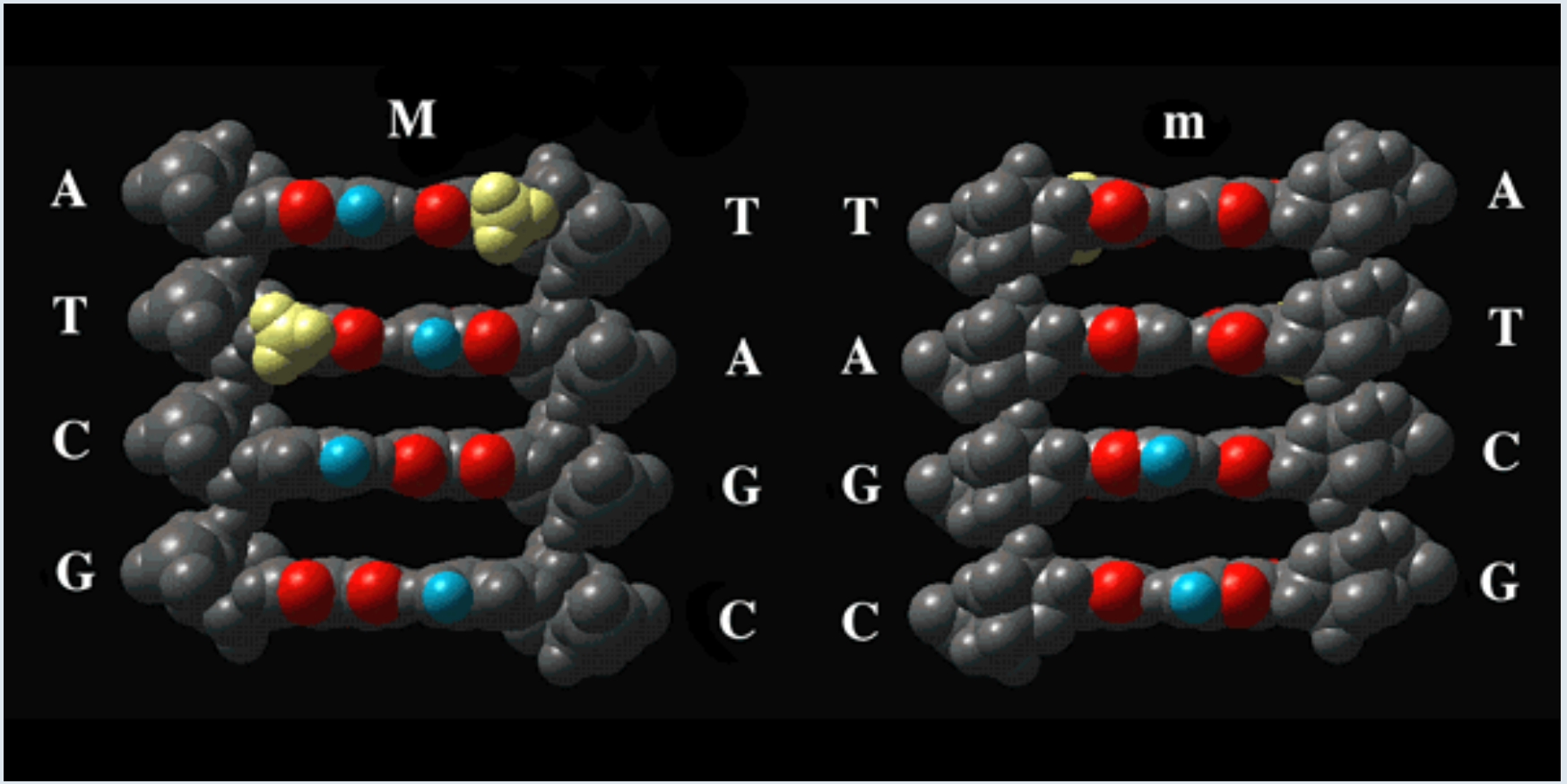


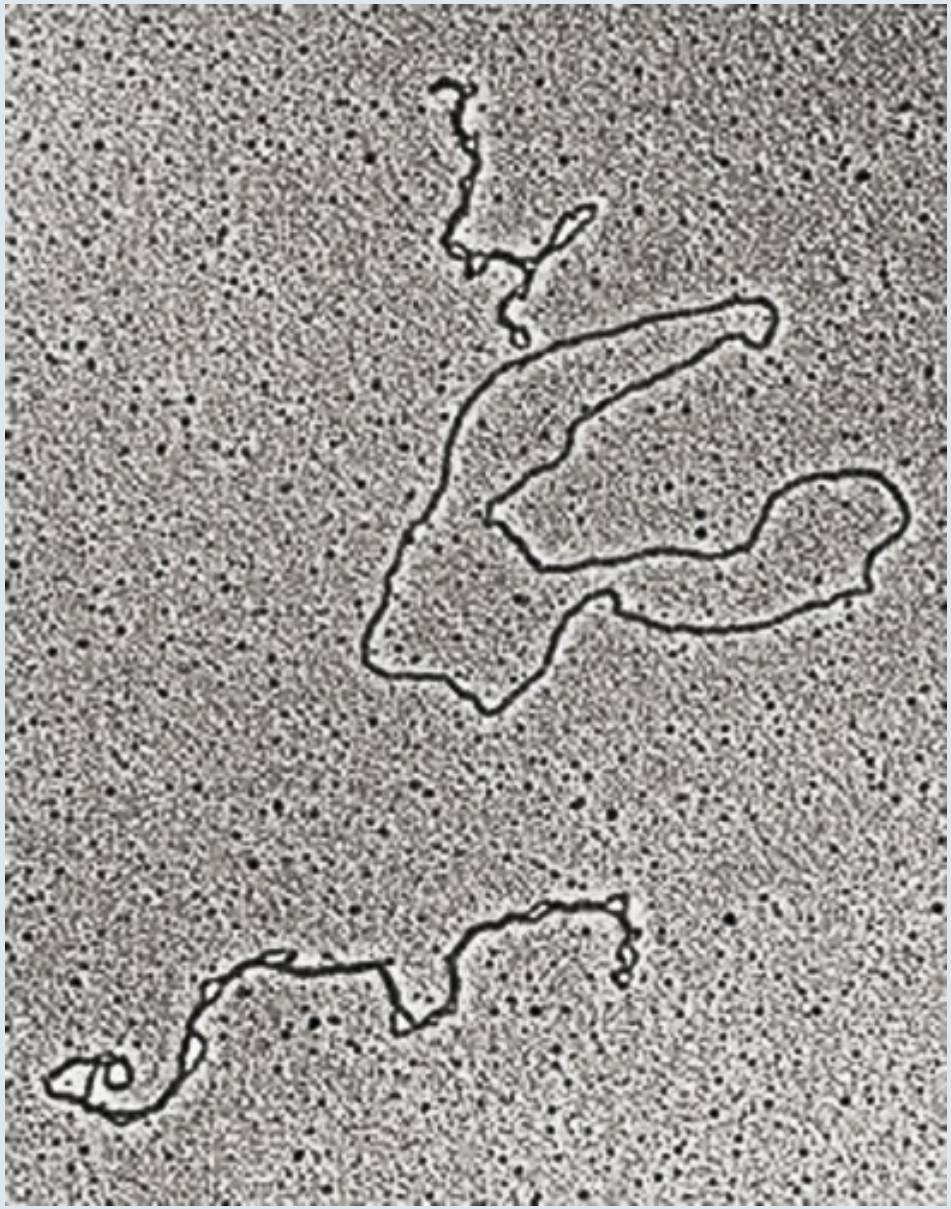


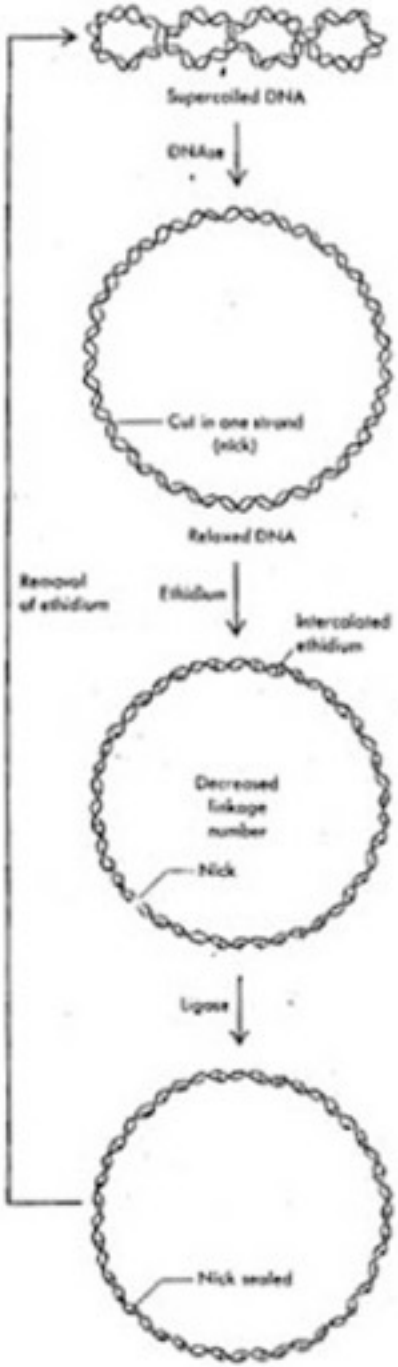
What difference does it make?

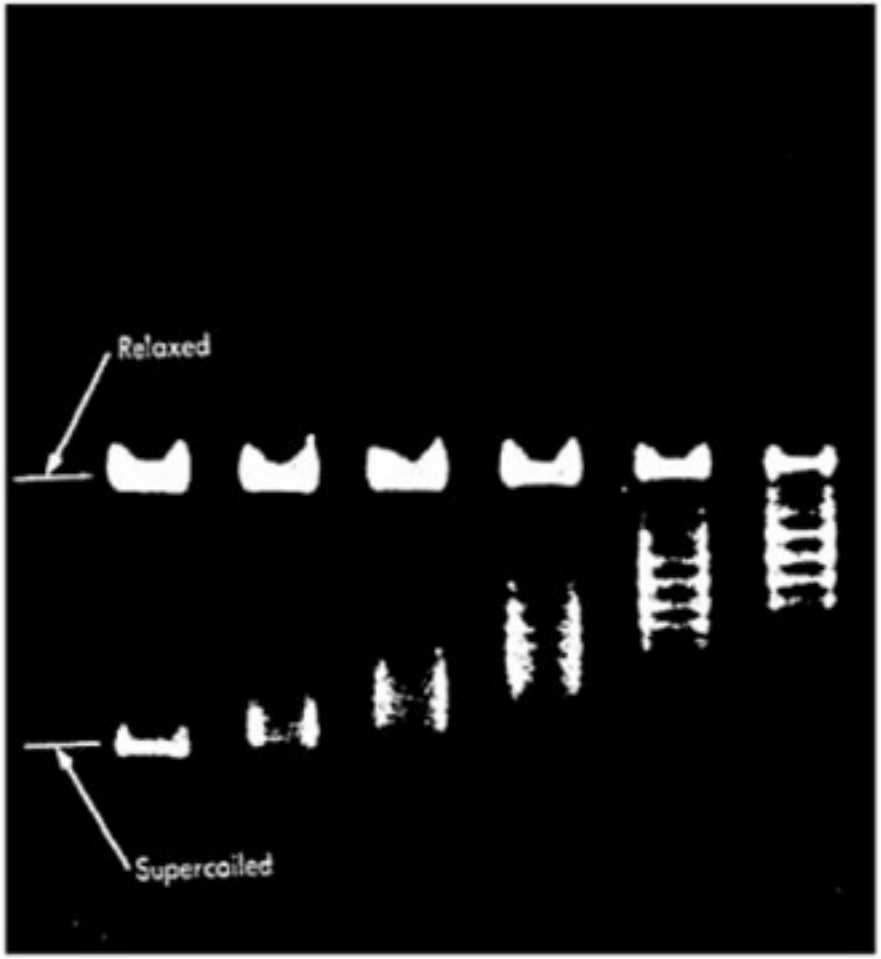
What benefits are potentially gained from having DNA being in one form or another??


6 Å
24 Å
12 Å
34 Å

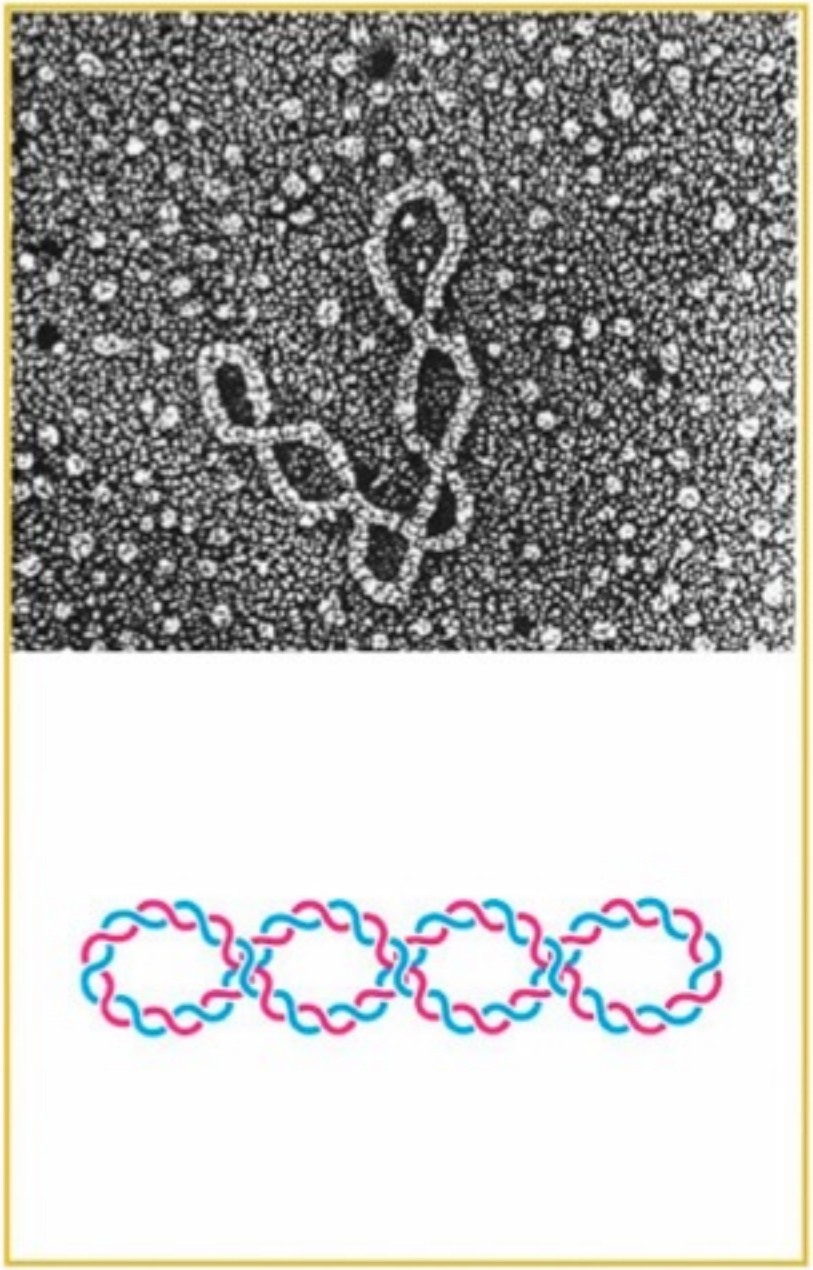

M
m
A
T
C
G
T
A
G
C
T
A
C
G
A
T
C
G



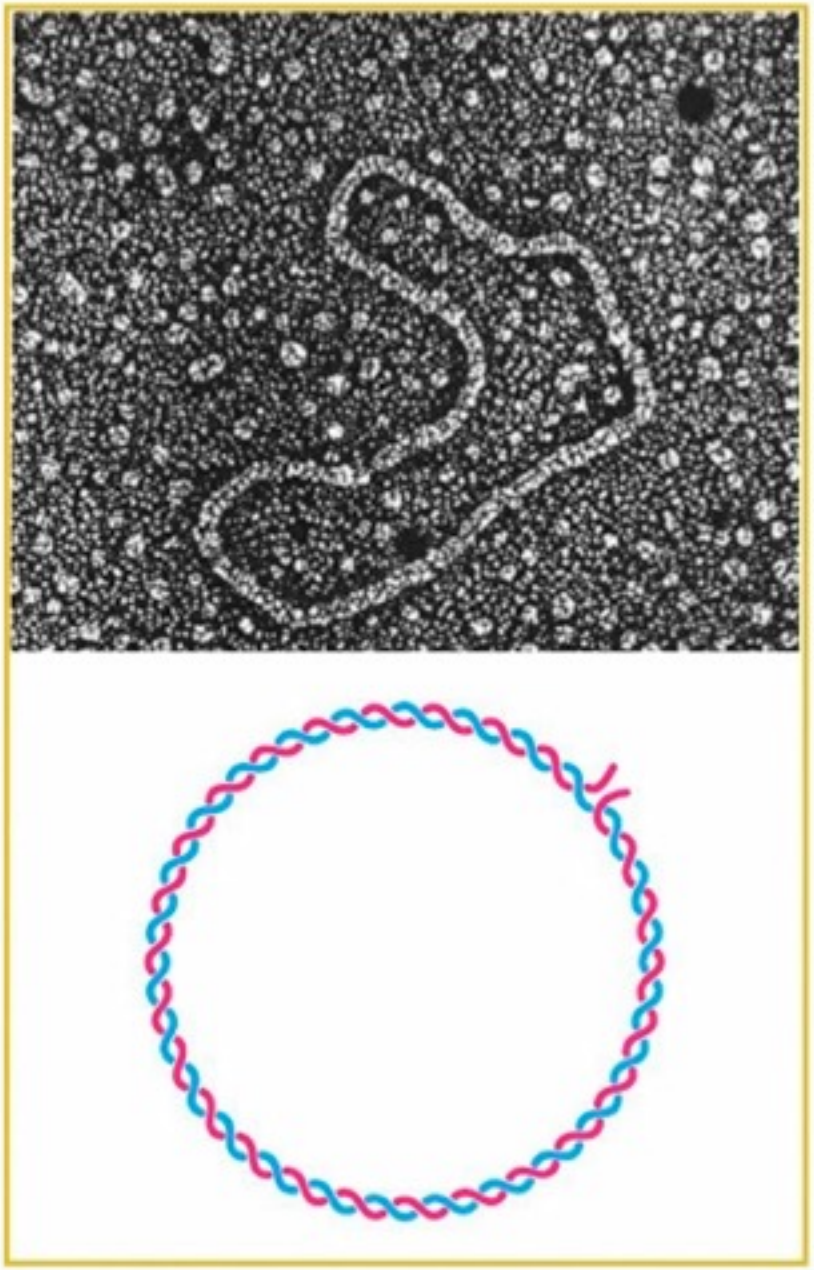

Supercoiled DNA
DNAse
Cut in one strand (nick)
Relaxed DNA
Removal of ethidium
Ethidium
Intercalated ethidium
Decreased linkage number
Nick
Ligase
Nick sealed

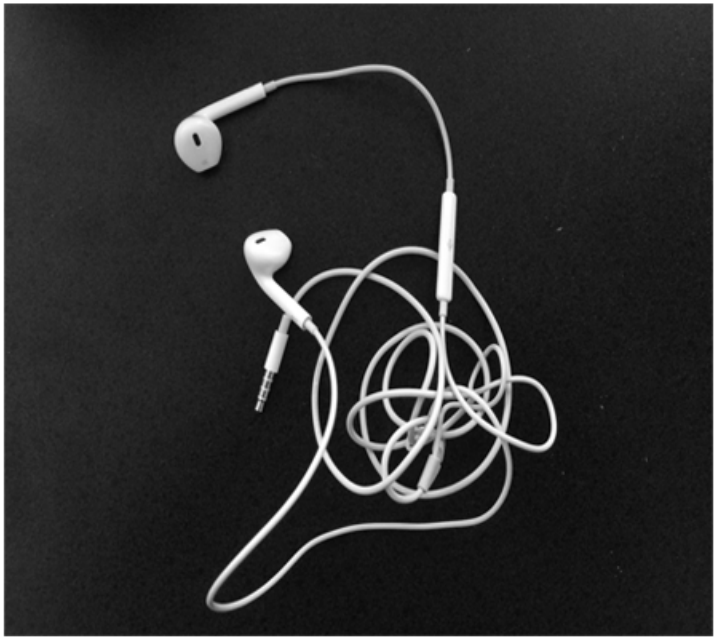

Relaxed
Supercoiled

(a) Supercoiled

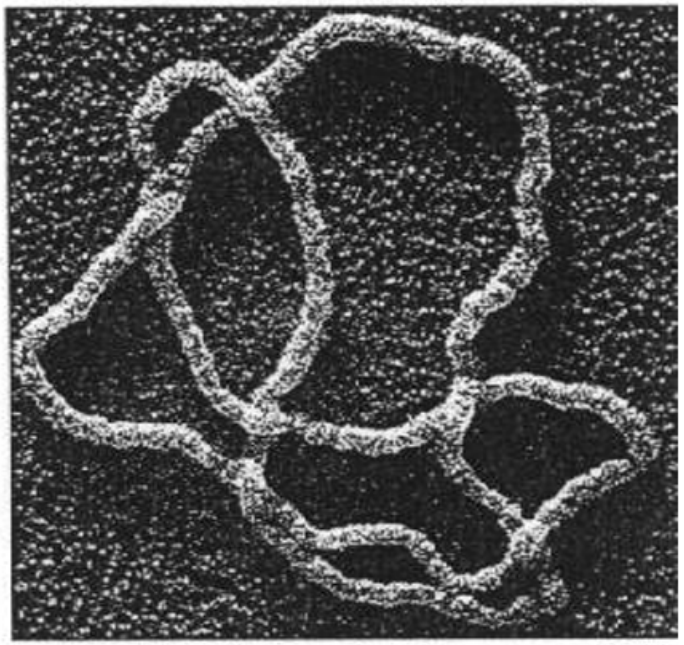


(b) Relaxed circle





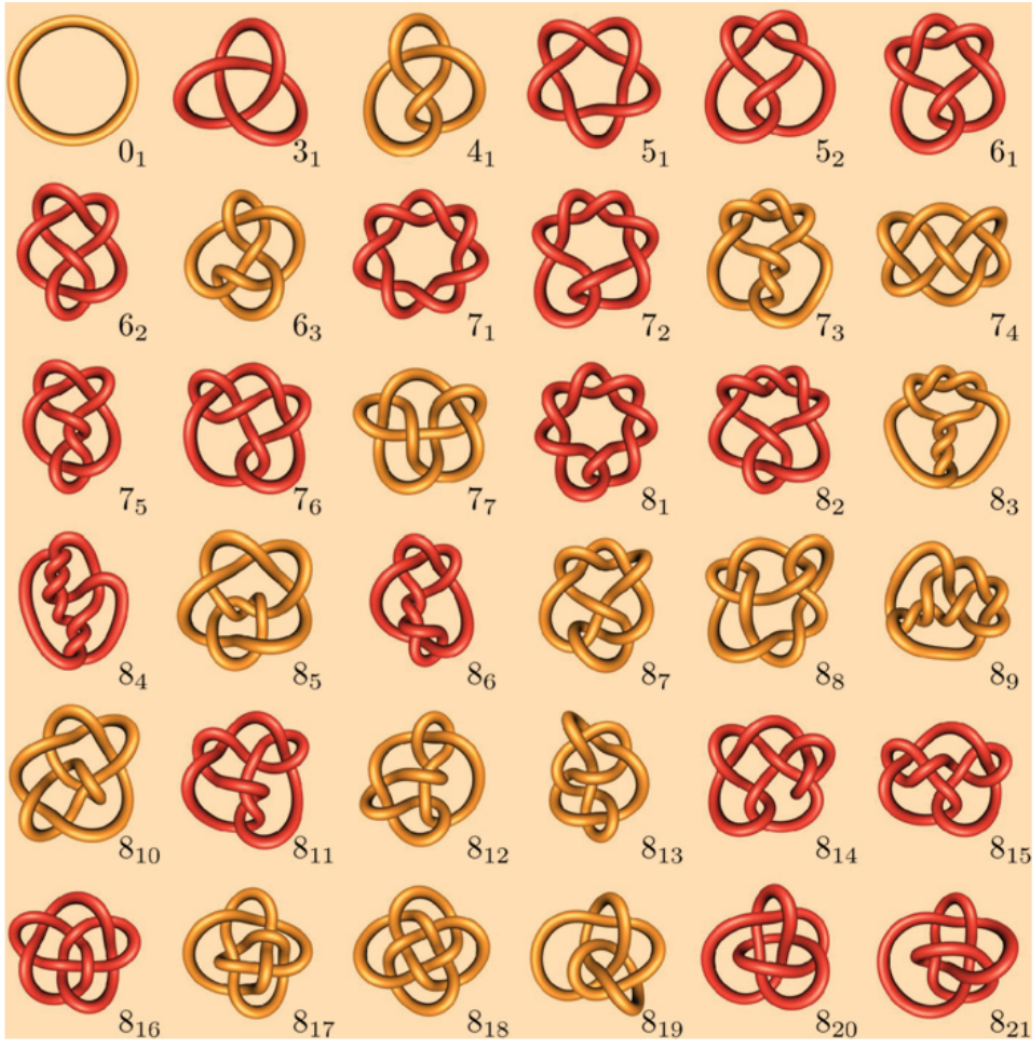
Houghton B. 2016 Typical state of iphone headphones



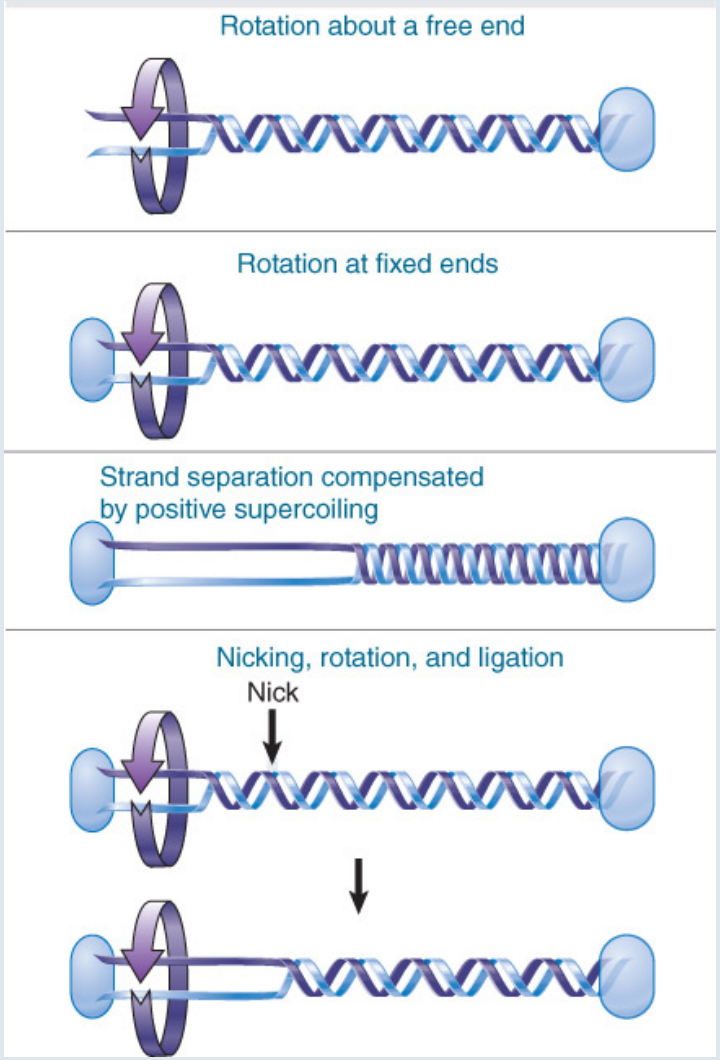
Sumners, D. 1995. Notices of the AMS 42:528-537.

Figure 1 | **The knot table of all of the knots with eight or fewer crossings with specification of the chirality, according to the writhe-guided naming convention [12]**

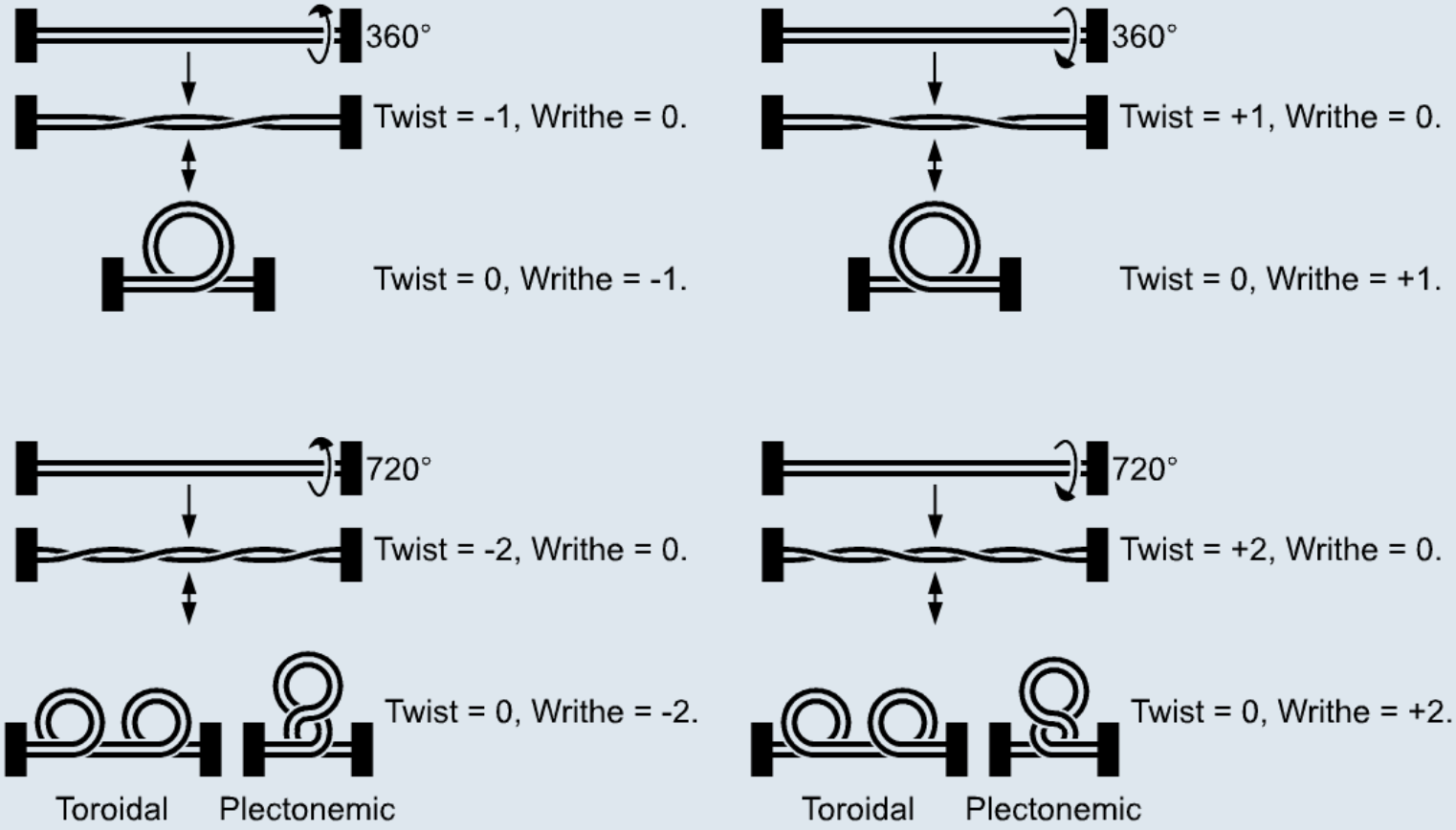
Knots in yellow have the same chirality as in Rolfsen's table [8], and those in red have chirality opposite to those of Rolfsen's.



New biologically motivated knot table
Reuben Brasher*, Rob G. Scharein † and Mariel Vazquez*1
Biochemical Society Transactions (2013) Volume 41, part 2



Separation of the strands of a DNA double helix could be achieved in several ways.

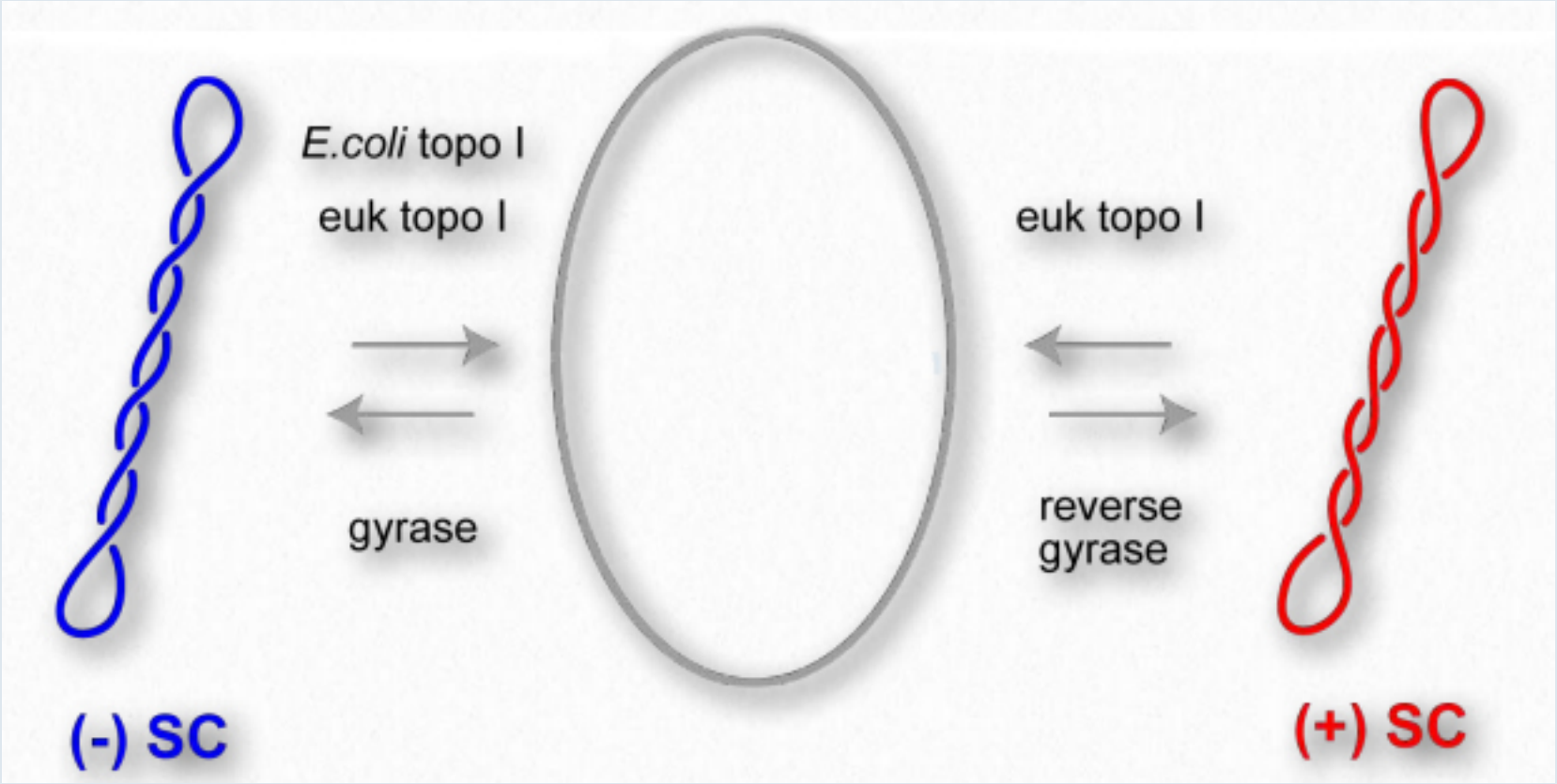


The difference in Gibbs free energy between the supercoiled circular DNA and uncoiled circular DNA with N > 2000 bp is approximated by:

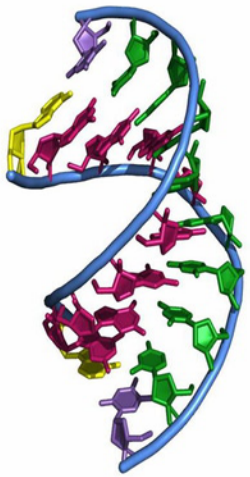
$$\Delta G/N = 700 Kcal/bp * (\Delta Lk/N)$$

or, 16 cal/bp.

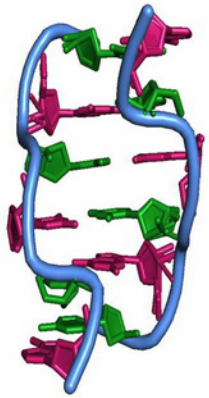
Negatively supercoiled DNA favors local unwinding of the DNA, effectively promoting processes such a transcription, replication and recombination


E.coli topo I
euk topo I
gyrase
euk topo I
reverse gyrase
(-) SC
(+) SC

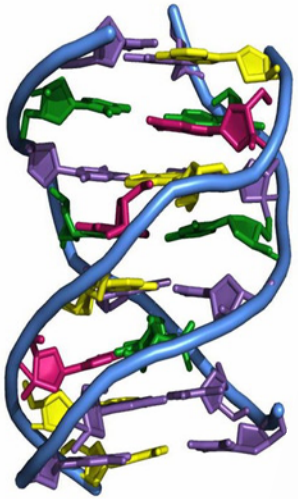
A-DNA

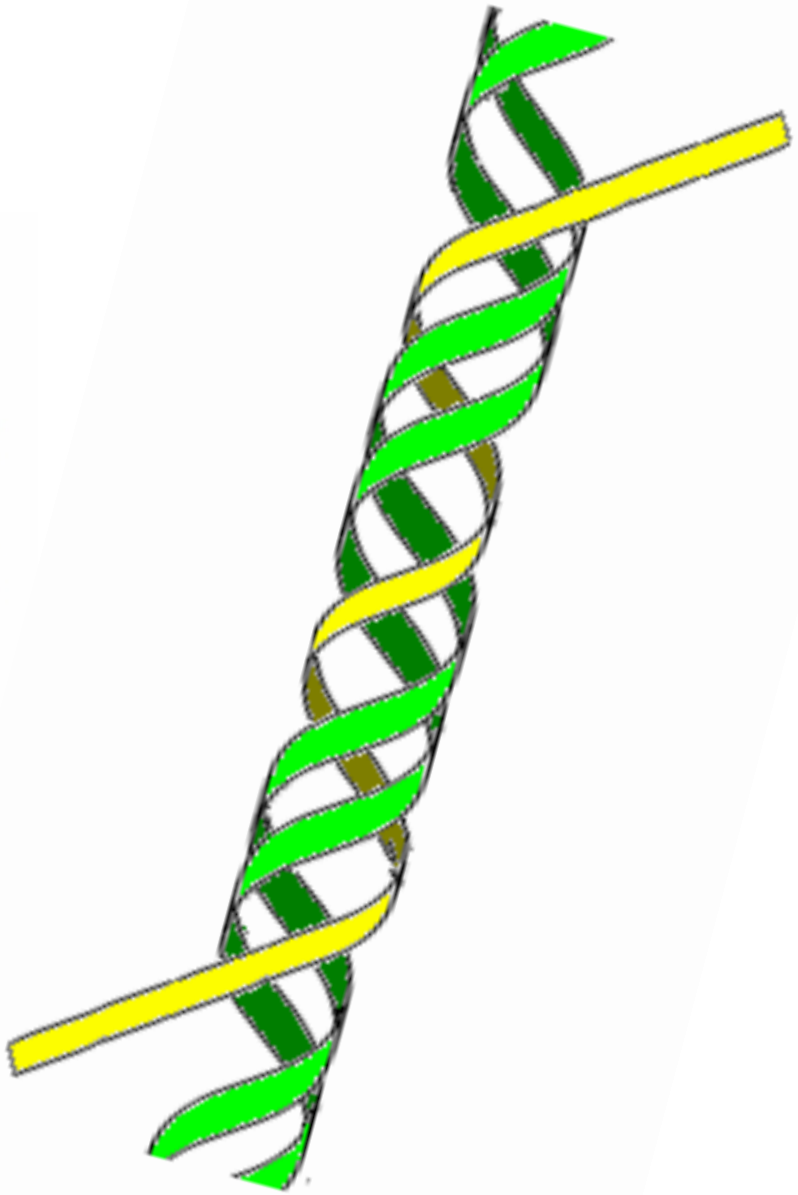


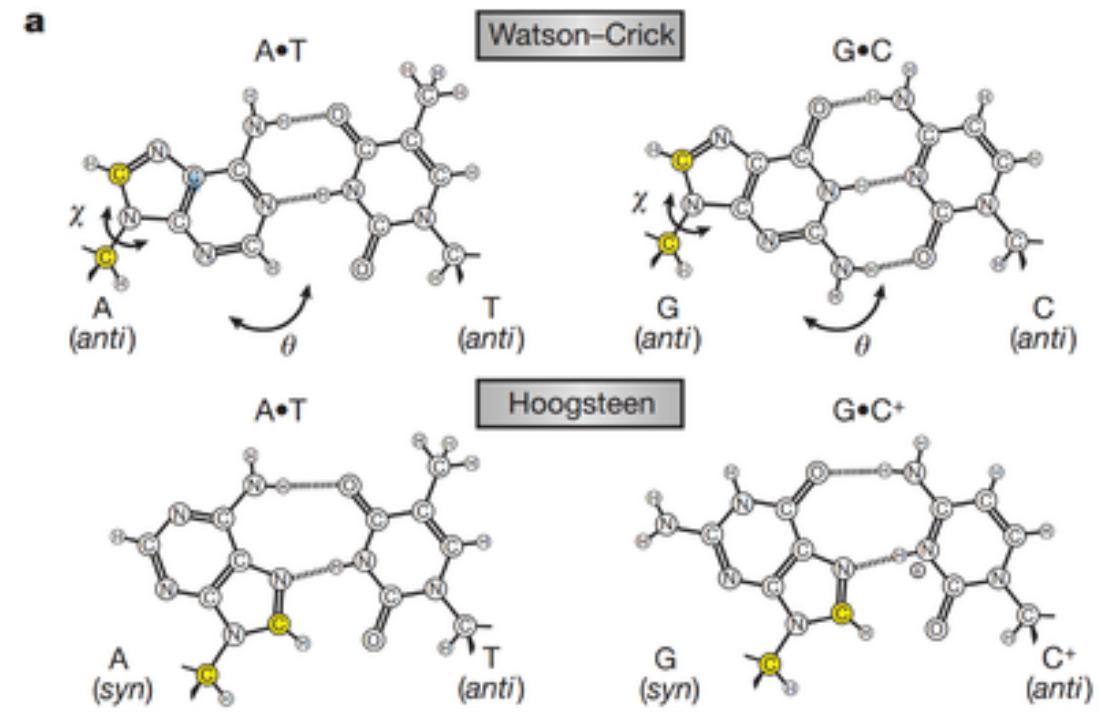
Z-DNA

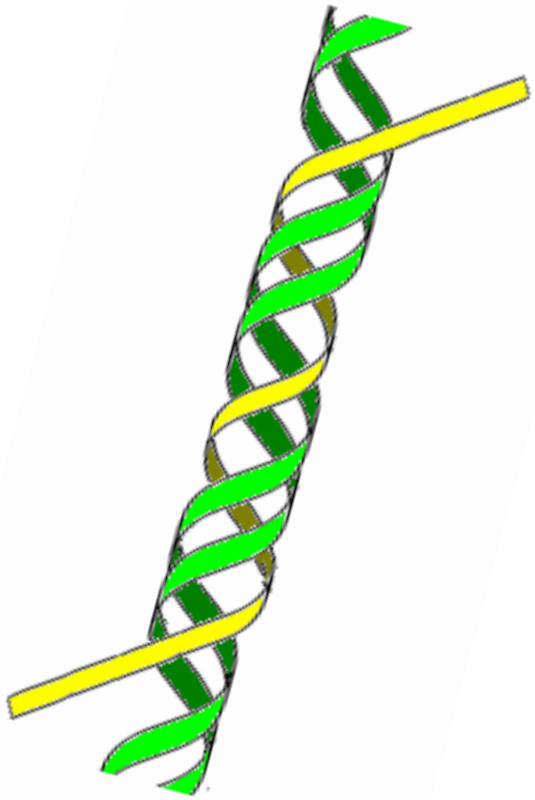


Triplex DNA

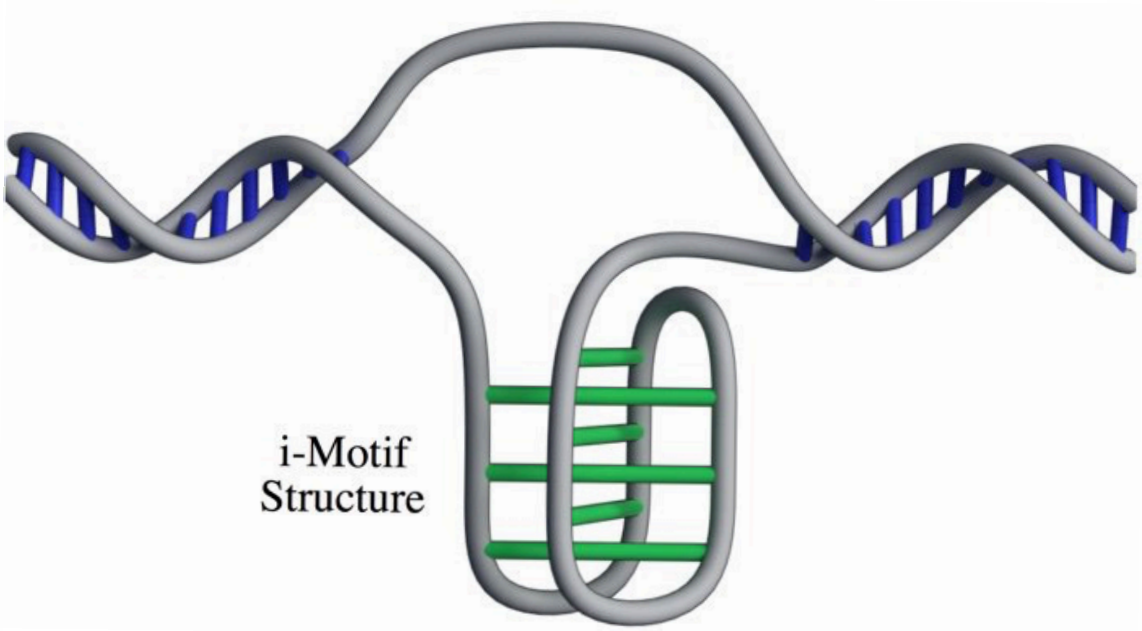


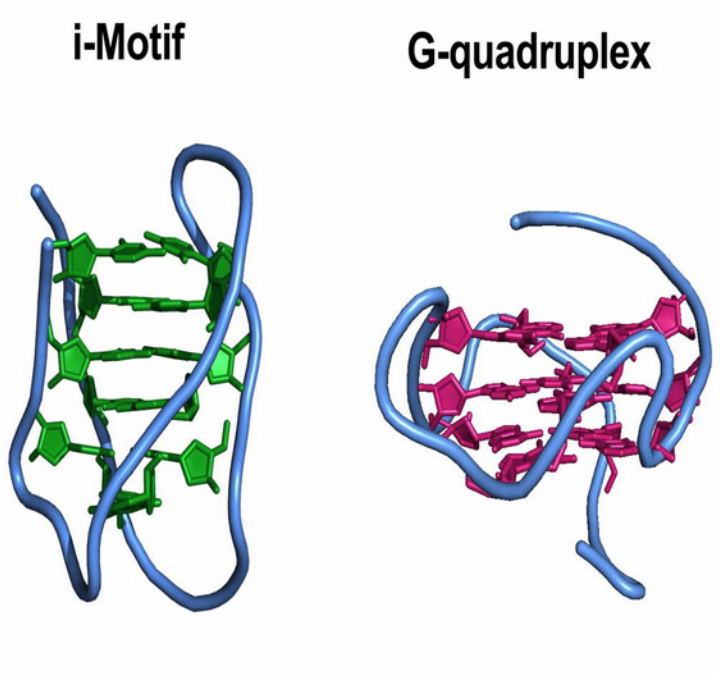






A Hoogsteen base pair is a variation of base-pairing in nucleic acids such as the A•T pair. In this manner, two nucleobases, one on each strand, can be held together by hydrogen bonds in the major groove. A Hoogsteen base pair applies the N7 position of the purine base (as a hydrogen bond acceptor) and C6 amino group (as a donor), which bind the Watson–Crick (N3–C4) face of the pyrimidine base.





i-Motifs are four-stranded DNA secondary structures which can form in sequences rich in cytosine. They are often stabilised by acidic conditions and are “dynamic structures” comprised of two parallel-stranded DNA duplexes held together in an antiparallel orientation by intercalated, **cytosine–cytosine+ base pairs**. Using antibodies, these structures have recently been shown to occur i*n vivo* and are often found upstream of gene sequences.....

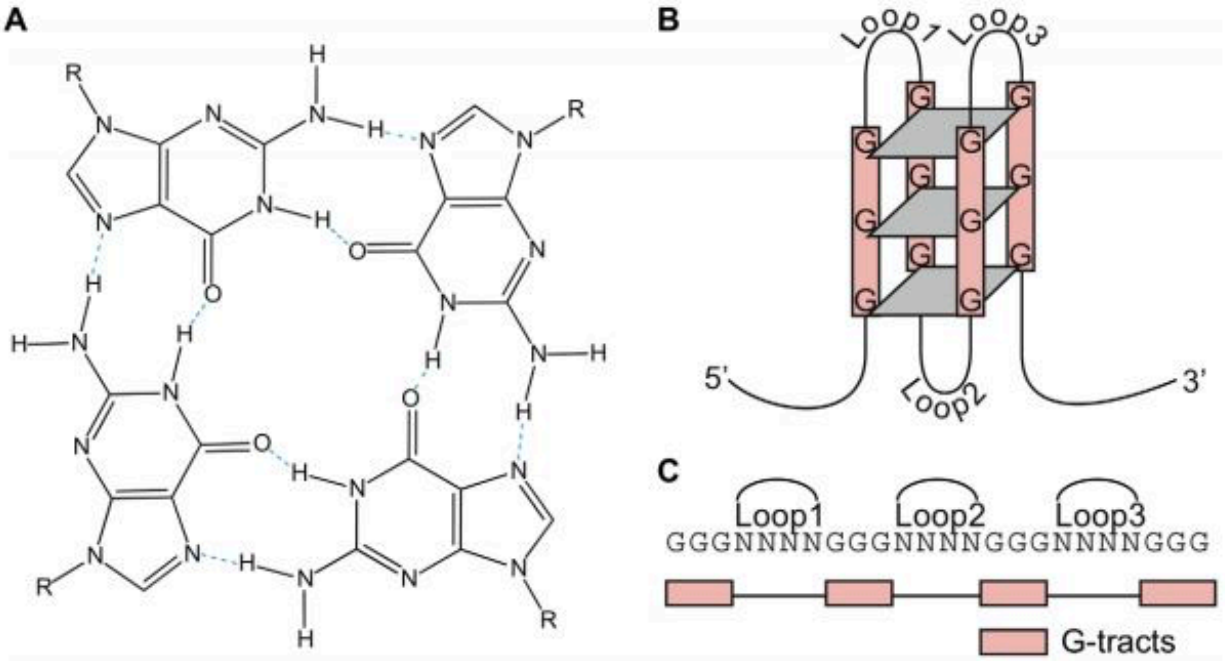
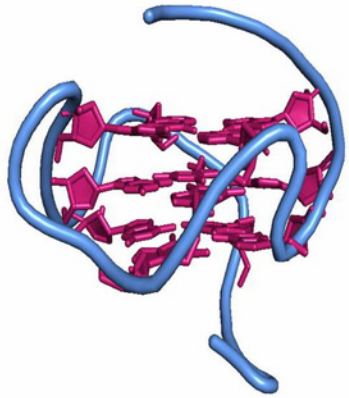
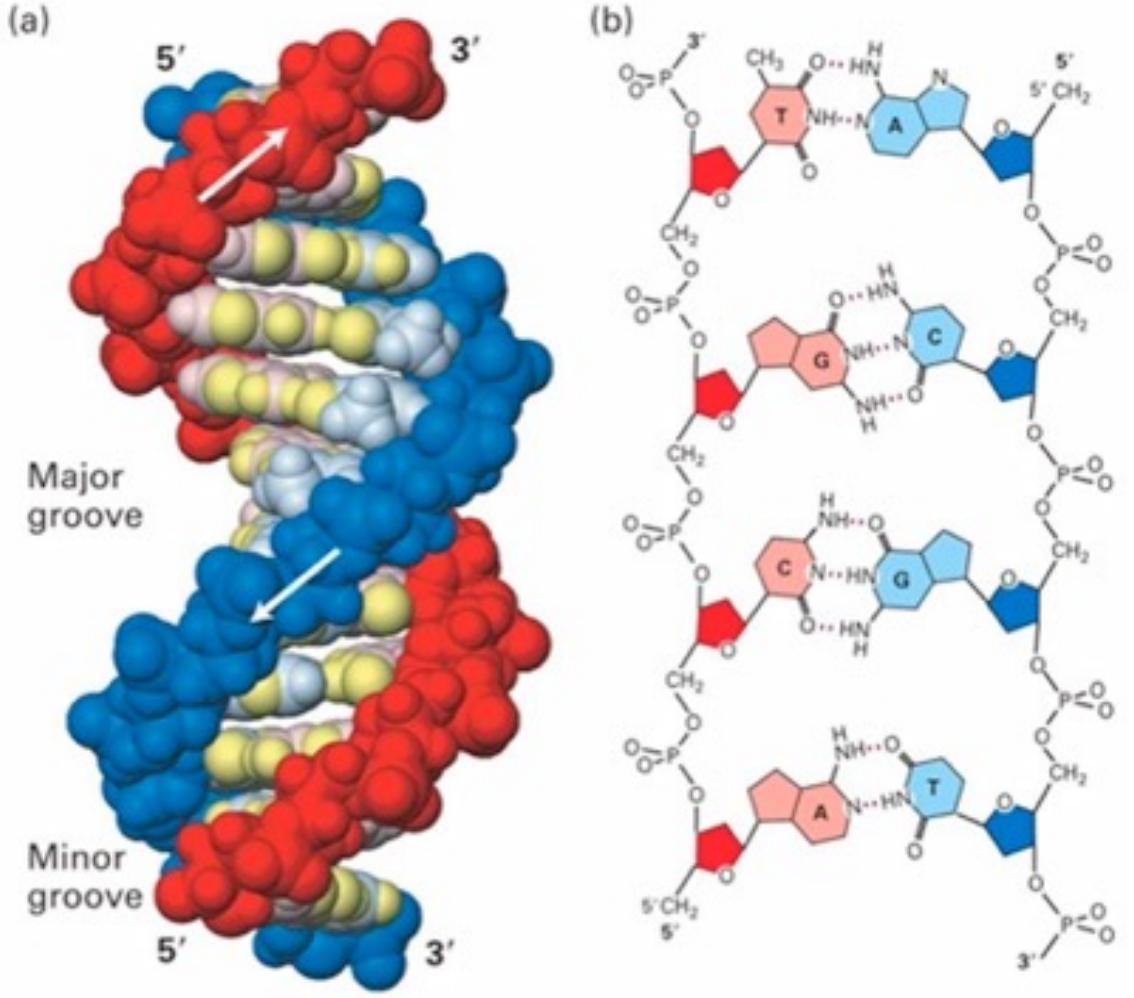


Figure 1. The G4 DNA structure and motif. (**A**) Structure of a G-quartet. The planar ring of four hydrogen-bonded guanines is formed by guanines from different G-tracts, which are separated by intervening loop regions in the intra-molecular G4 DNA structure. (**B**) Schematic of an intra-molecular G4 DNA structure consisting of three G-quartets. Inter-molecular G4 DNA structures can also form from two or four strands. (**C**) The G4 DNA motif sequence used in this study with four G-tracts of three guanines separated by loop regions.
doi:10.1371/journal.pcbi.1000861.g001

G-quadruplex

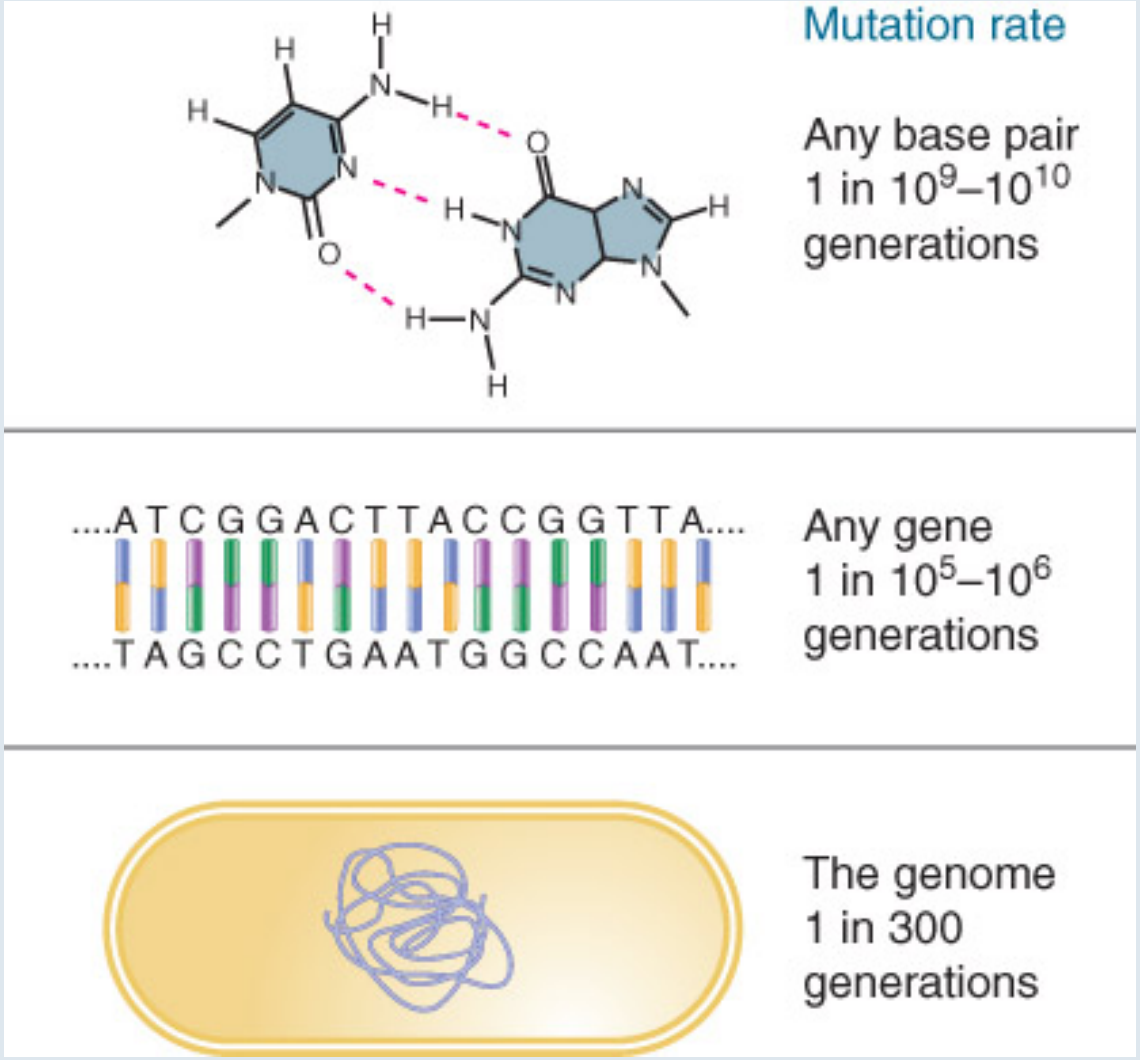




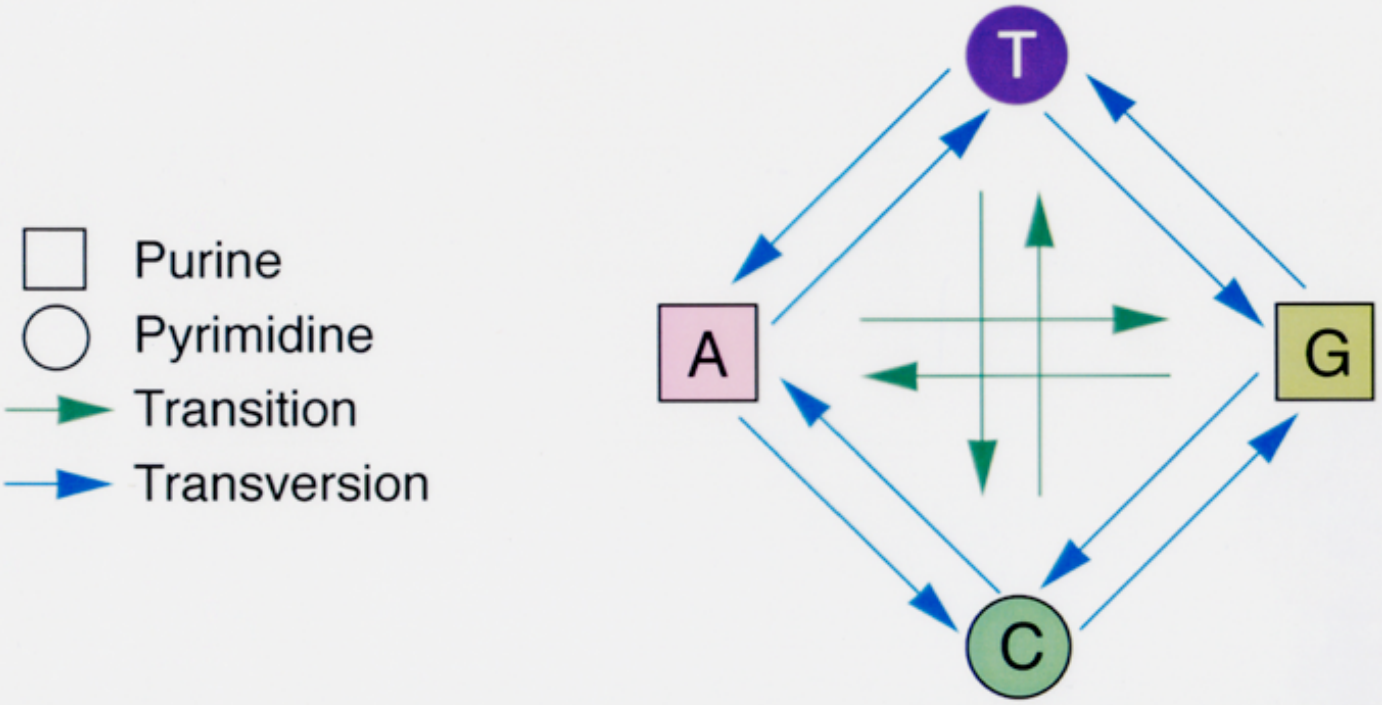
B form DNA

2.0 nM dia (20 Á)
0.36 nM (3.6 Á)
between bases
~10 bases per turn
antiparallel strands
bases perpendicular
to axis

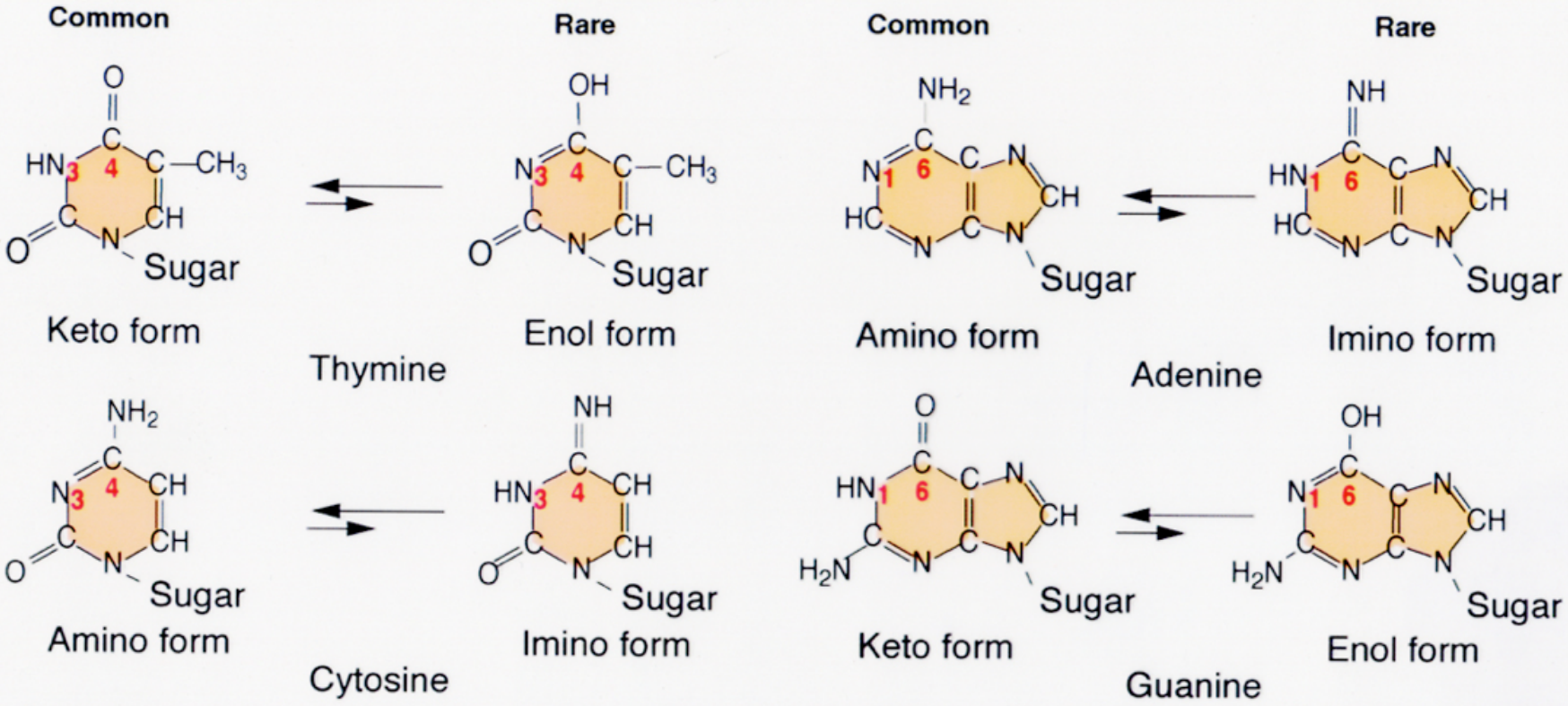
Figure 4-3

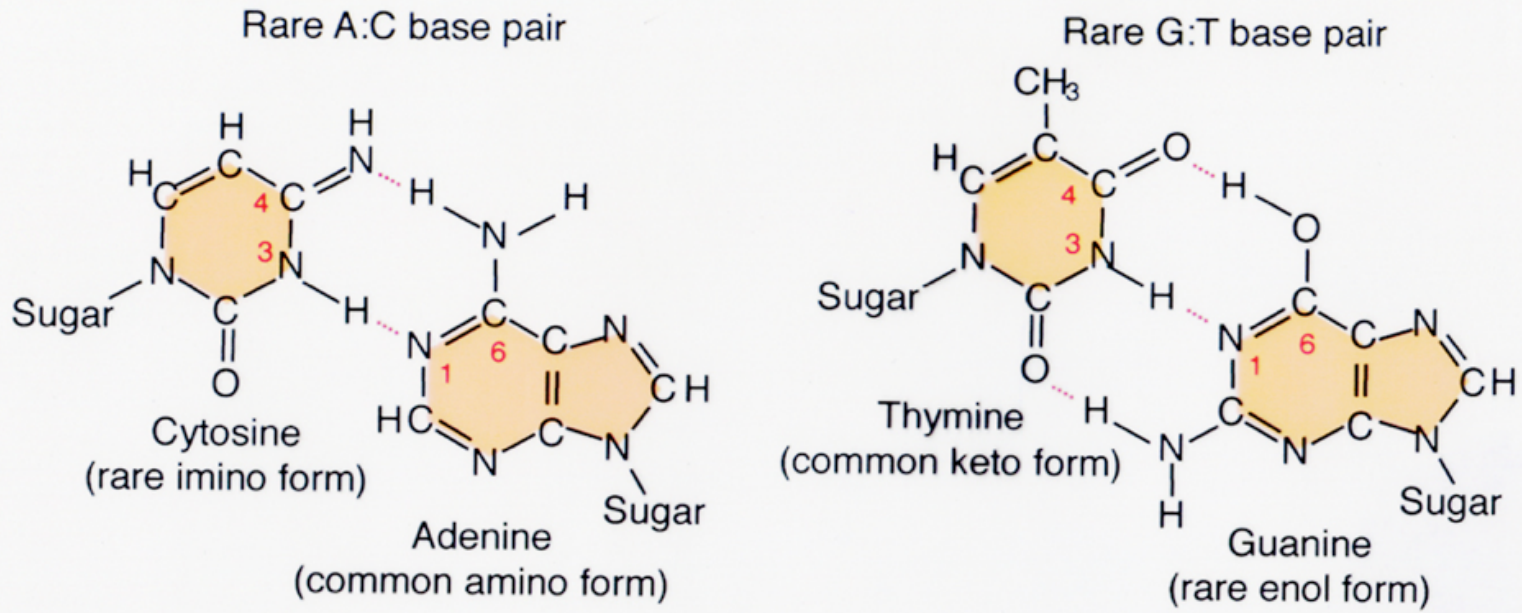


Base pair, gene, and bacterial genome mutation

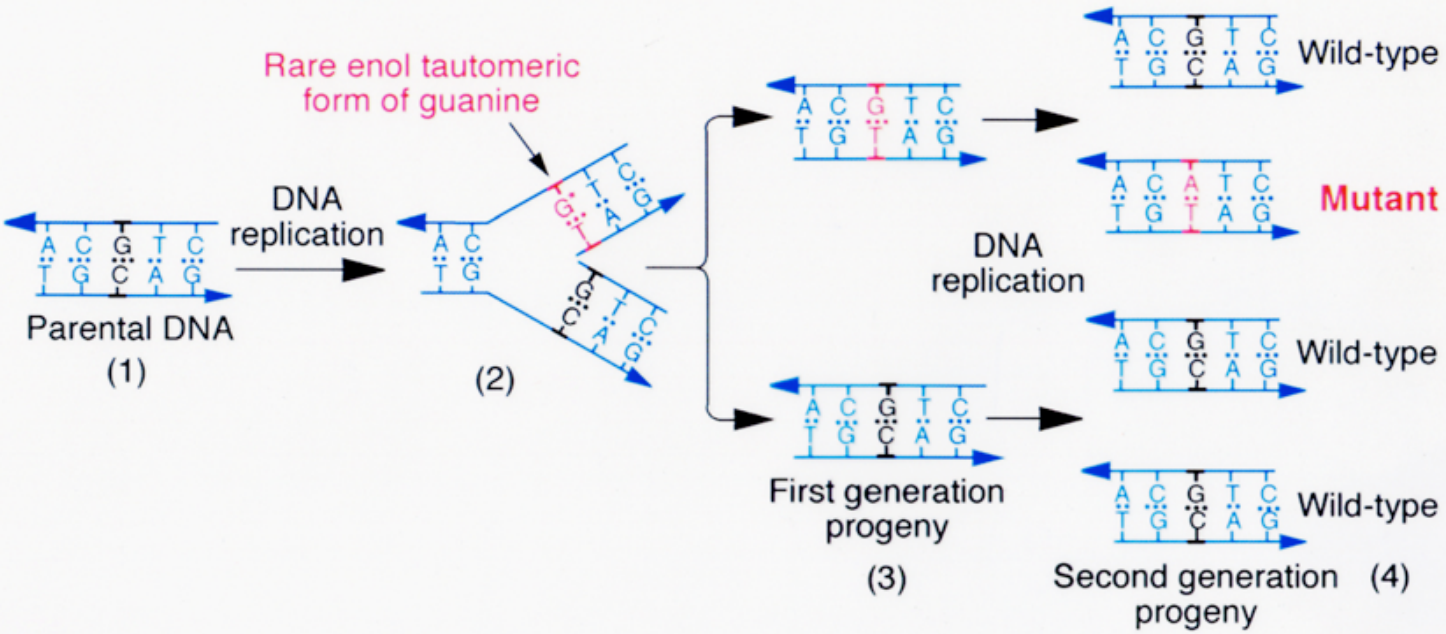


(a) Twelve different base substitutions can occur in DNA.



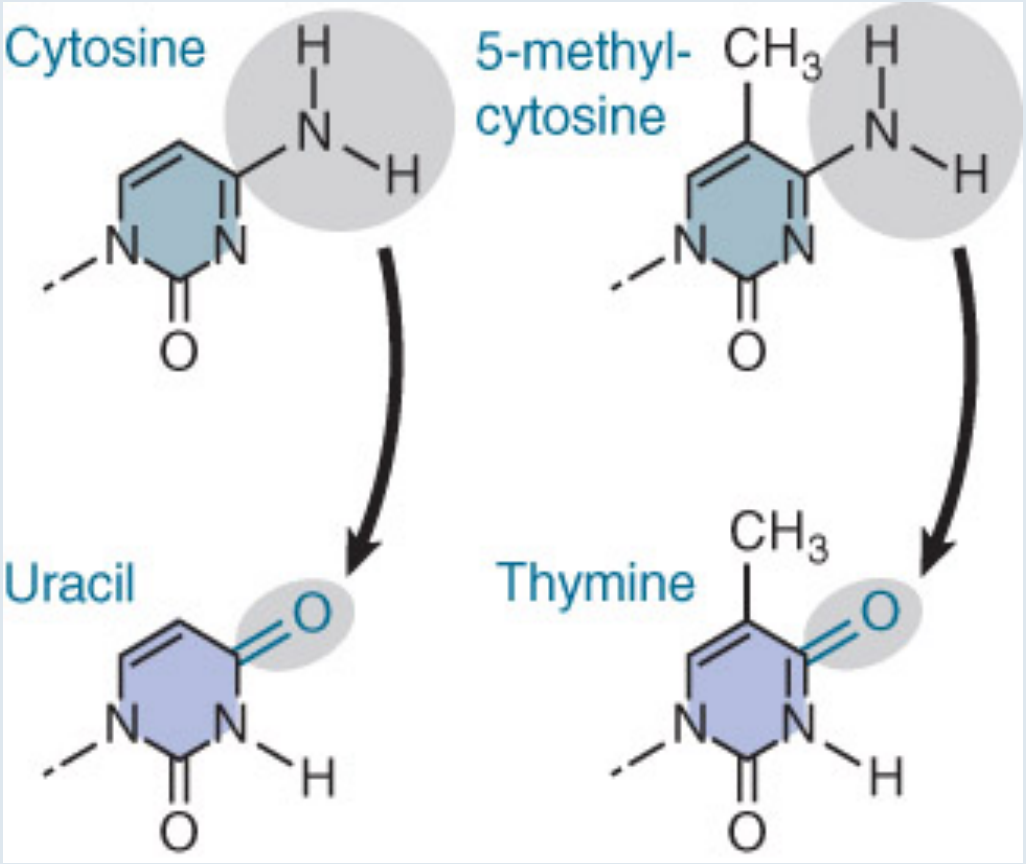


(a) Hydrogen-bonded A:C and G:T base pairs that form when cytosine and guanine are in their rare imino and enol tautomeric forms.

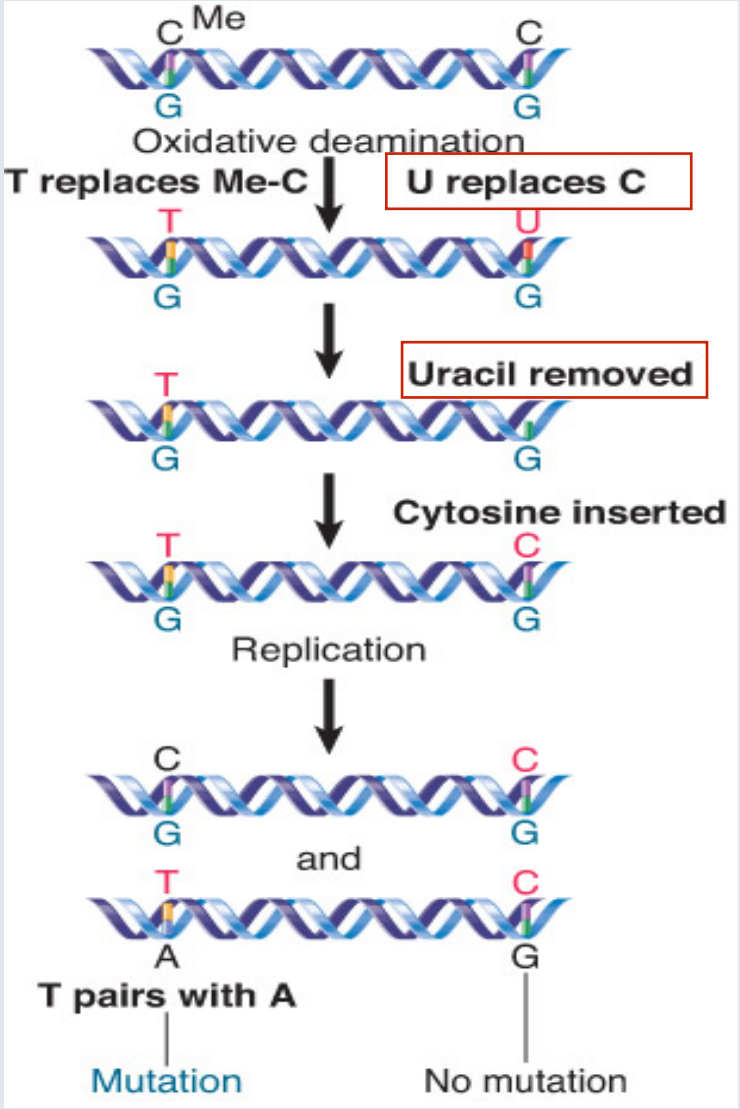


(b) Mechanism by which tautomeric shifts in the bases in DNA cause mutations.

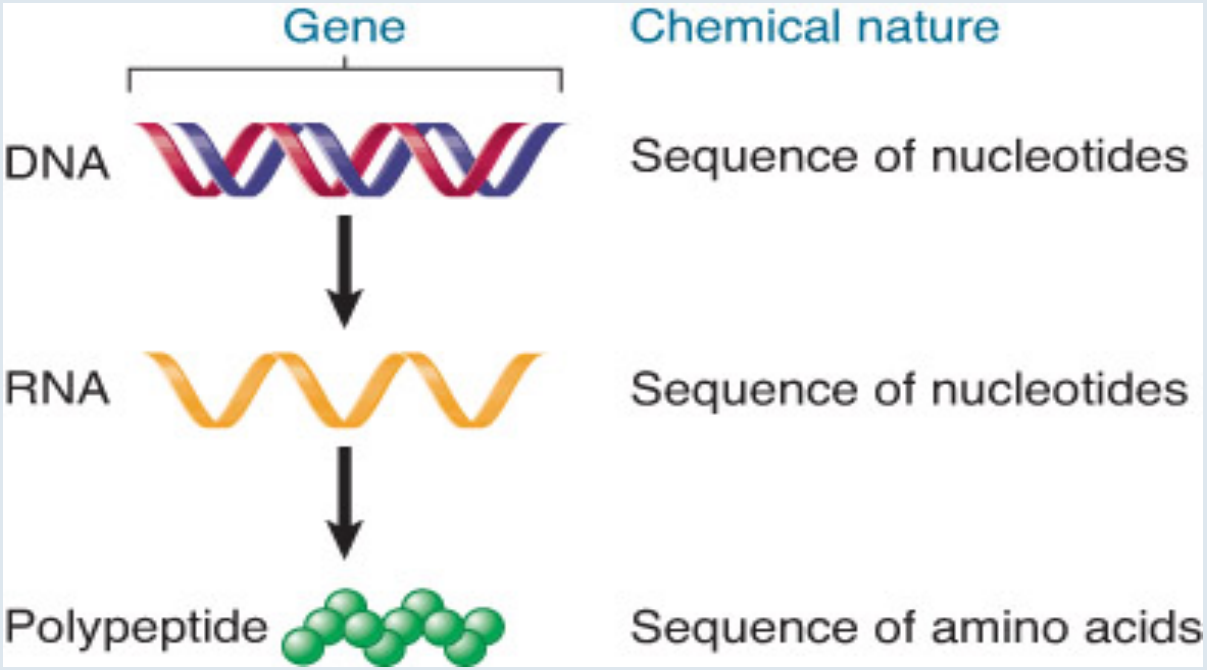
Since corrections of these changes can occur at either of these steps, the observed frequency of transitions is about 10^{-8} - 10^{-10} /base/replication cycle.



Deamination of cytosine produces Uracil, whereas deamination of 5-methylcytosine gives rise to Thymine.



The deamination of cytosine produces Uracil -eliciting a preferential replacement of this overtly “RNA” base.



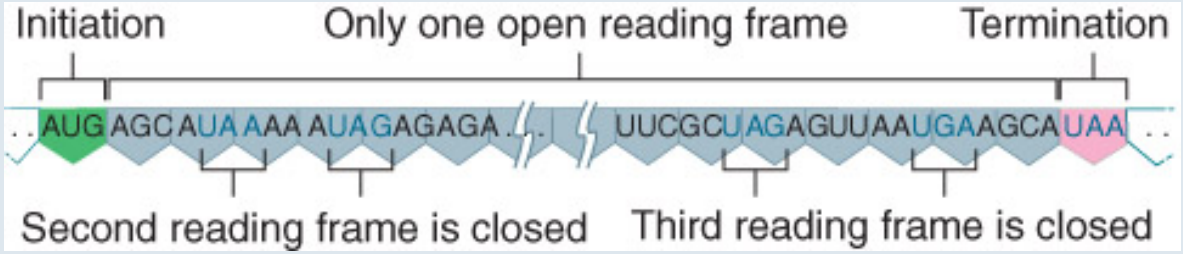
A “gene” is encoded within an RNA sequence, which <u>may</u> encode a polypeptide.

- The **genetic code** is read in triplet nucleotides called **codons**.

- The triplets are non -overlapping and are read from a fixed starting point.

Every Coding Sequence Has Three Possible Reading Frames

- Usually only one of the three possible **reading frames** is translated and the other two are closed by frequent termination signals.
- **open reading frame (ORF) –** A sequence of DNA consisting of triplets that can be translated into amino acids starting with an **initiation codon** and ending with a **termination codon**.



An open reading frame usually starts with “AUG” and continues in triplets to a termination codon.

- **Silent mutations** have no phenotypic effect, either because the base change does not change the sequence or amount of polypeptide, or because the change in polypeptide sequence has no effect.

- **Neutral mutations –** Substitutions in bases within the DNA sequence that causes changes in amino acids in the resulting protein -that do not affect activity.

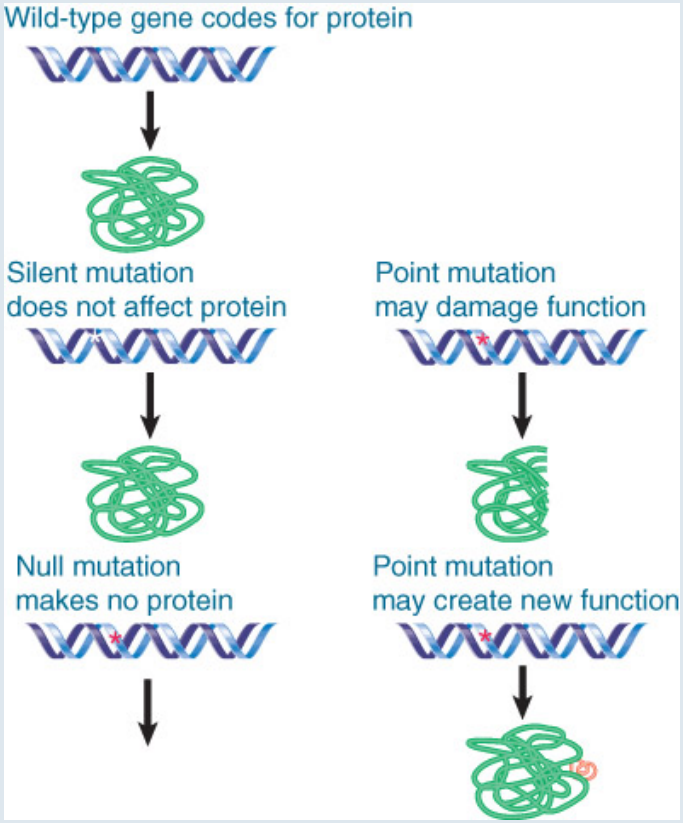
- Mutations that insert or delete individual bases cause a shift in the triplet sets after the site of mutation; these are **frameshift** mutations.

- Combinations of mutations that together insert or delete three bases (or multiples of three) insert or delete amino acids, but do not change the reading of the triplets beyond the last site of mutation.

As well as being functionally devastating at the level of expressed polypeptide sequence, Frameshift mutations also show that the genetic code is indeed read in triplets from a fixed starting point.

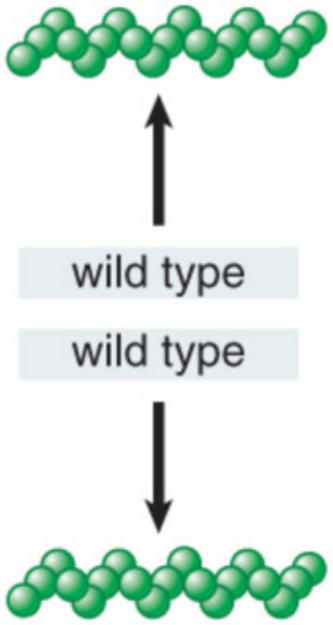
Mutations Within a "Coding Frame" May Cause **Loss of Function** or **Gain of Function**

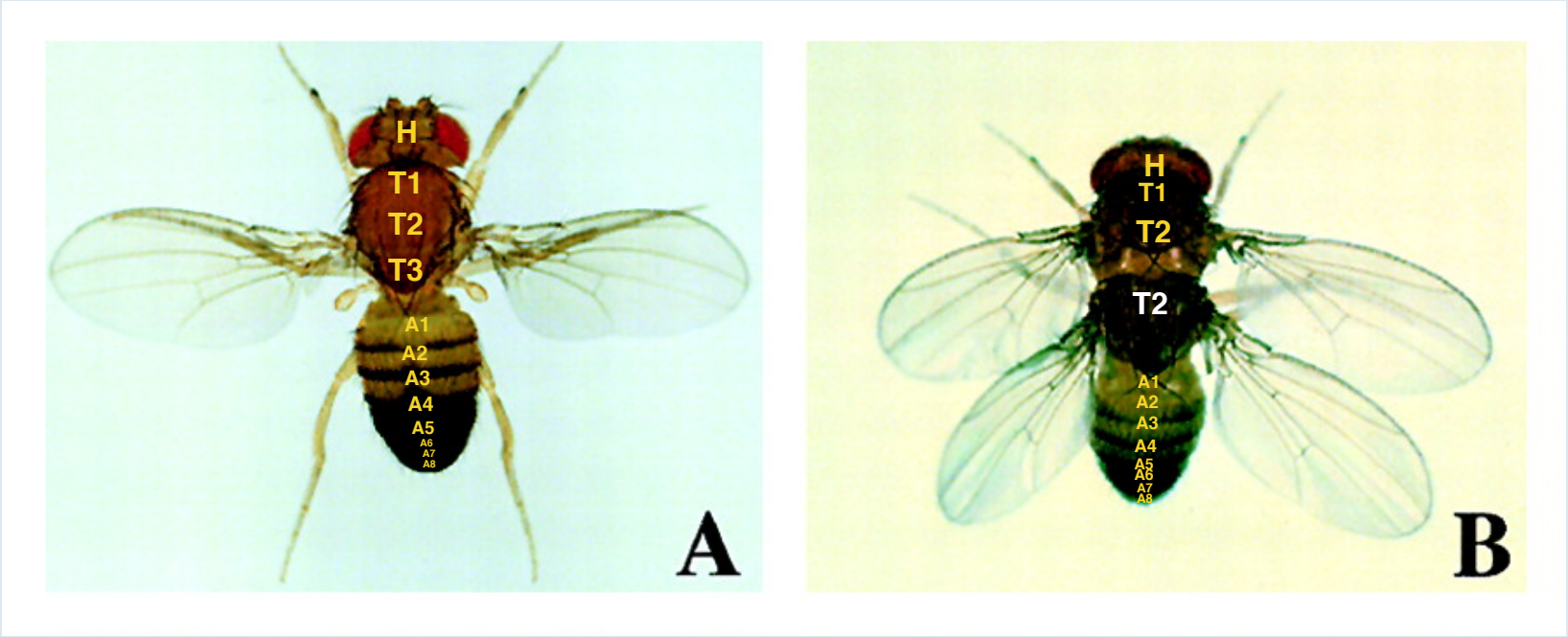
- Recessive mutations are due to **loss of function** by the polypeptide product.
- Dominant mutations result from a **gain of function**.
- Testing whether a gene is essential requires a **null mutation** (one that completely eliminates its function).



Mutations that do not affect protein sequence or function are silent.

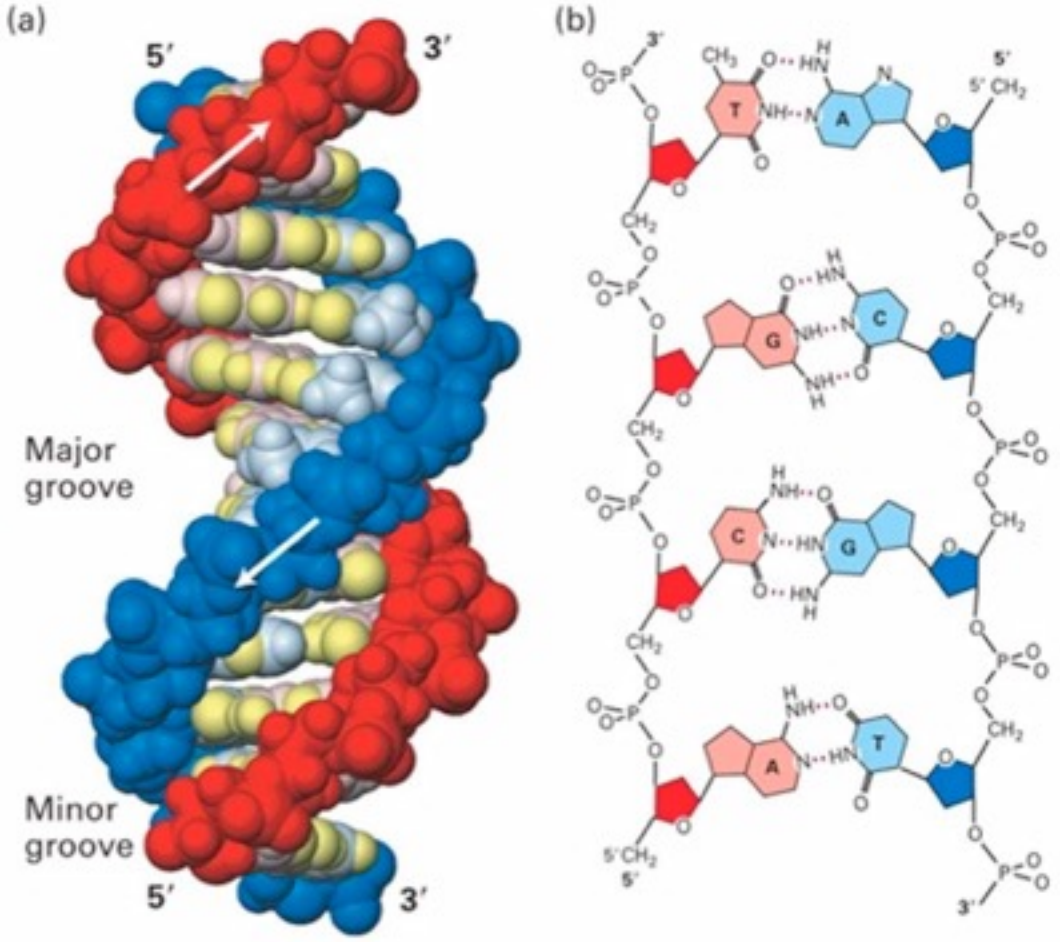
Wild-type homozygote	Wild-type/mutant heterozygote	Mutant homozygote
Both alleles produce active protein	One (dominant) allele produces active protein	Neither allele produces protein
wild type	wild type	mutant
wild type	mutant	mutant
Wild phenotype	Wild phenotype	Mutant phenotype





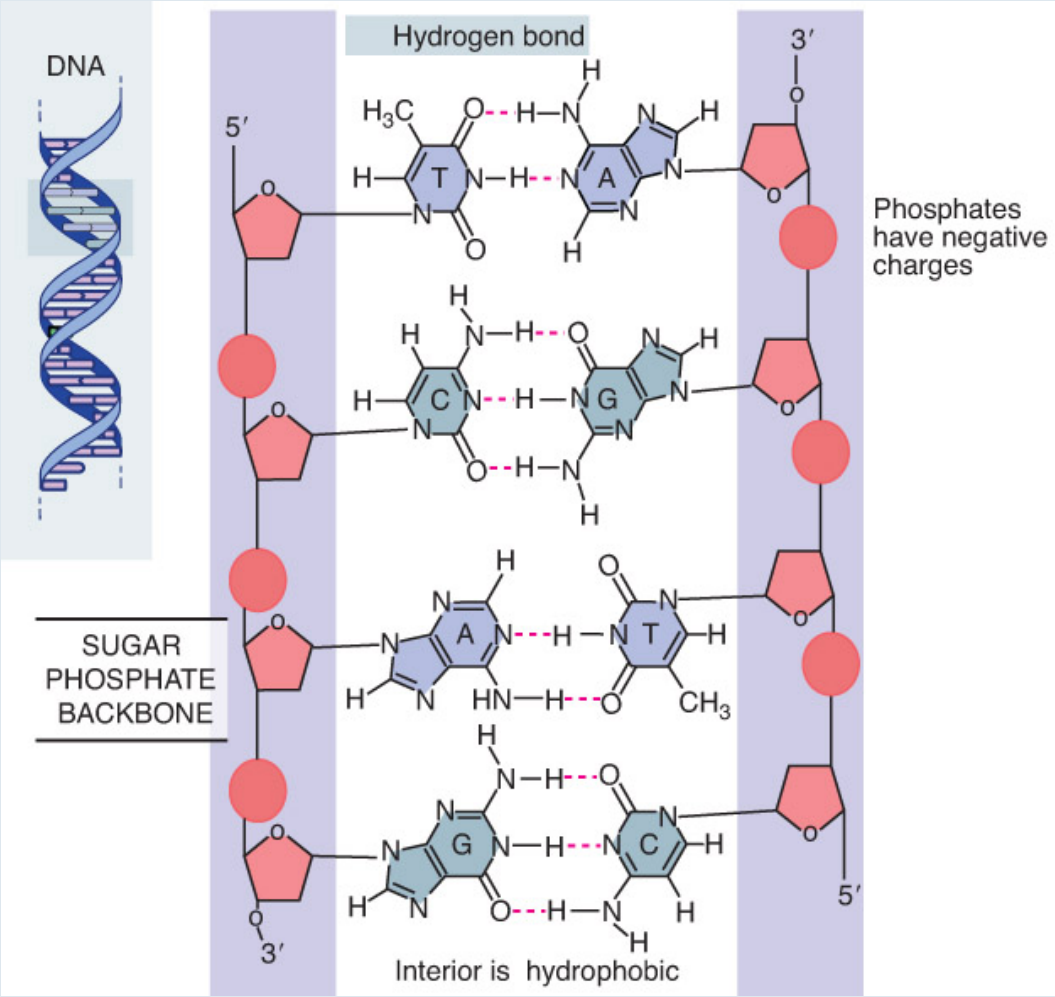
Lewis (1990's) proposed that, in general, dominant mutations in the BX-C changed segment identity to that of the next more posterior segment, while recessive mutations caused transformations in the opposite direction. For example, the recessive gene *bithoraxoid* (*bxd*) causes the first abdominal segment (A1) to take on the character of the third thoracic segment (T3). Since T3 normally carries a pair of legs as well as halteres (balancers), *bxd* mutants have four pair of legs instead of the normal three, as well as two pairs of halteres. Other recessive BX-C genes are *bithorax* (*bx*), mutations of which convert the anterior half of T3 to the anterior half of T2 (i.e. T3a -> T2a), *postbithorax* (*pbx*) which converts the posterior half of T3 to the posterior half of T2 (T3p ->T2p). Thus, the double recessive mutant (***bx, pbx***) carries two pairs of wings*.

Phenotypes of bithorax complex mutations.
(A) Dorsal view of a wild-type male. The **T2** segment produces the single pair of wings as well as almost all of the dorsal thorax. Dorsally, **T3** produces only the halteres, small club-shaped organs located posterior to the wings. (B) The famous four-winged fly, in which **T3** is transformed to **T2**. This male is **hemizygous** for the triple-mutant combination *abx* ***bx3*** ***pbx***. The *abx pseudoallele* has effects similar to ***bx*** mutations, but causes a stronger transformation of the very anterior portion of **T3**.

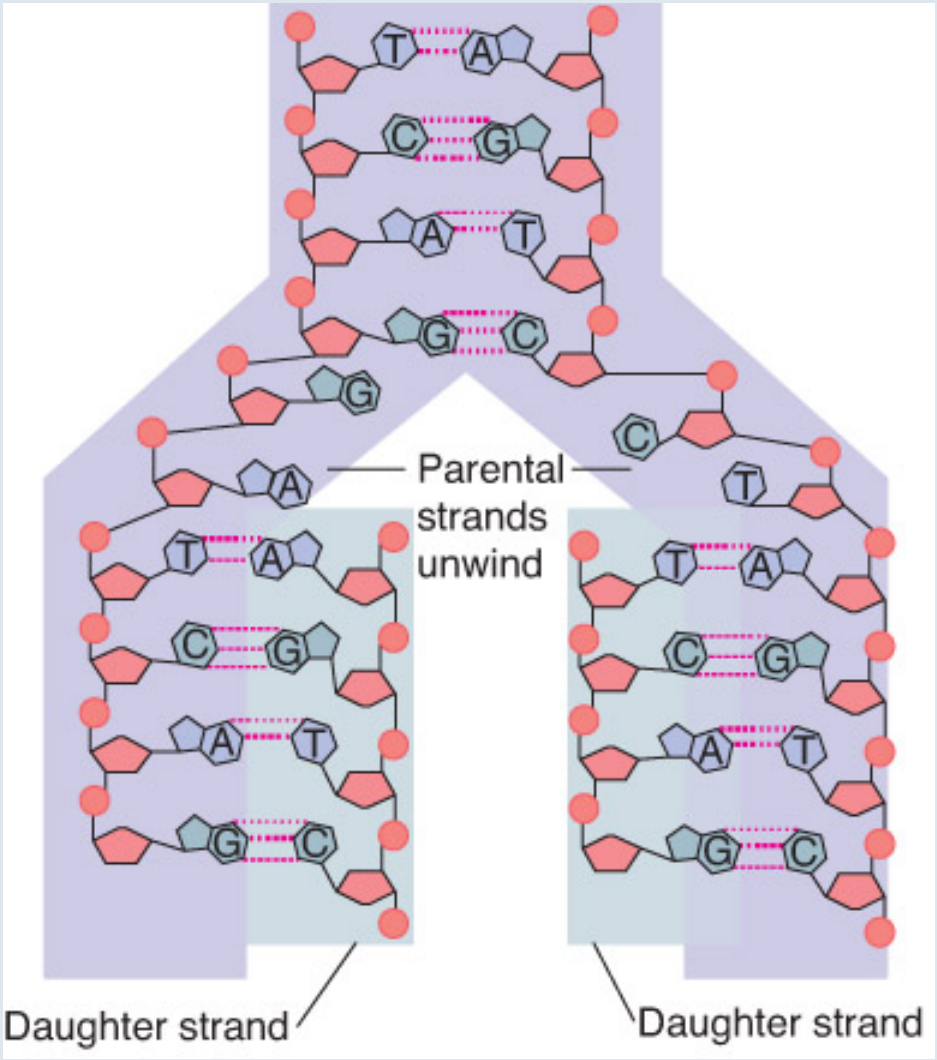


B form DNA

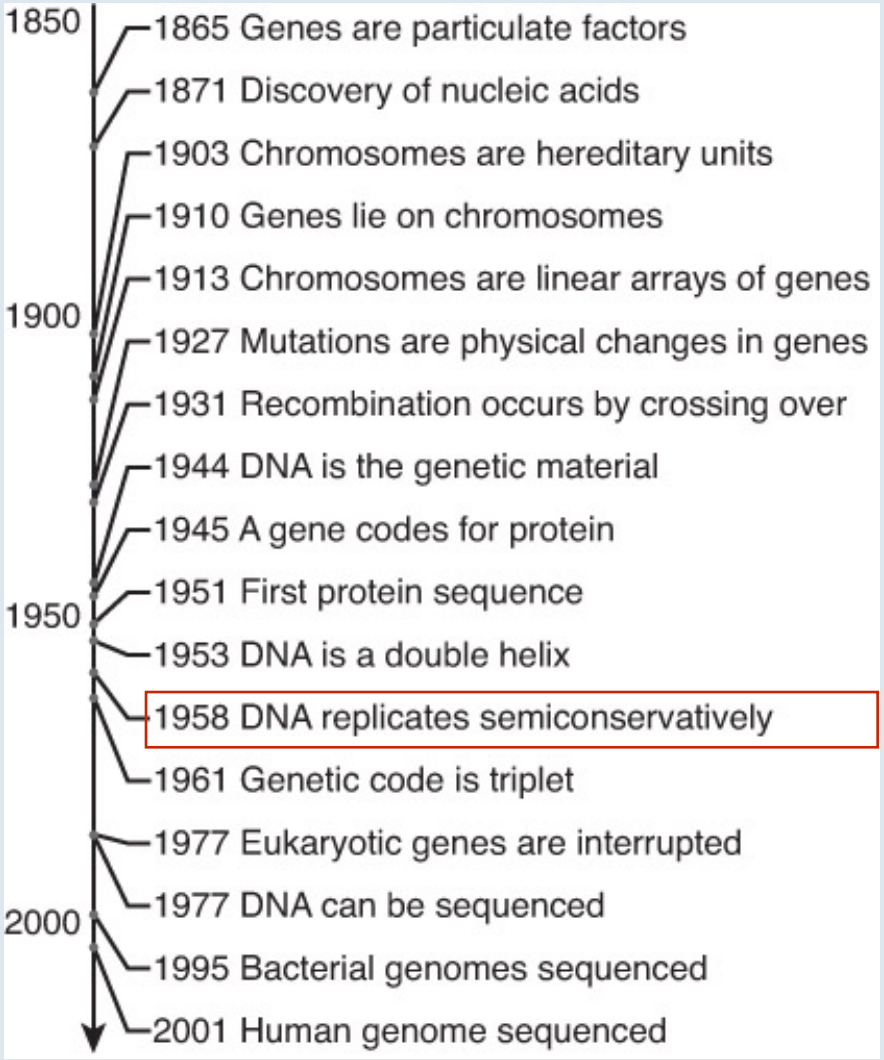
2.0 nM dia (20 Á)
0.36 nM (3.6 Á)
between bases
~10 bases per turn
antiparallel strands
bases perpendicular
to axis



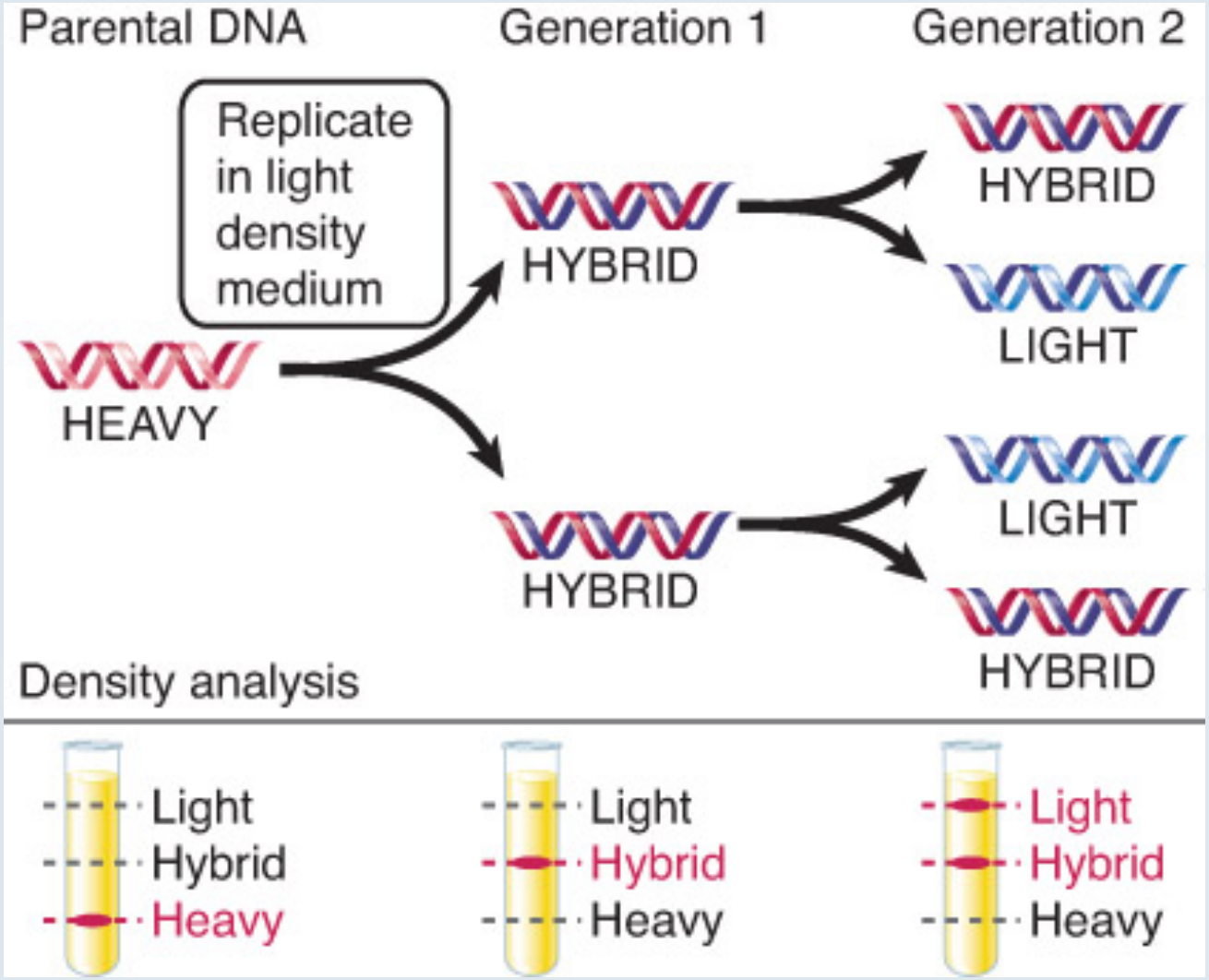
The double helical structure of DNA ultimately provides a mechanism in to how this structure can be be replicated… as purines always face pyrimidines in the complementary A-T and G-C base pairs.



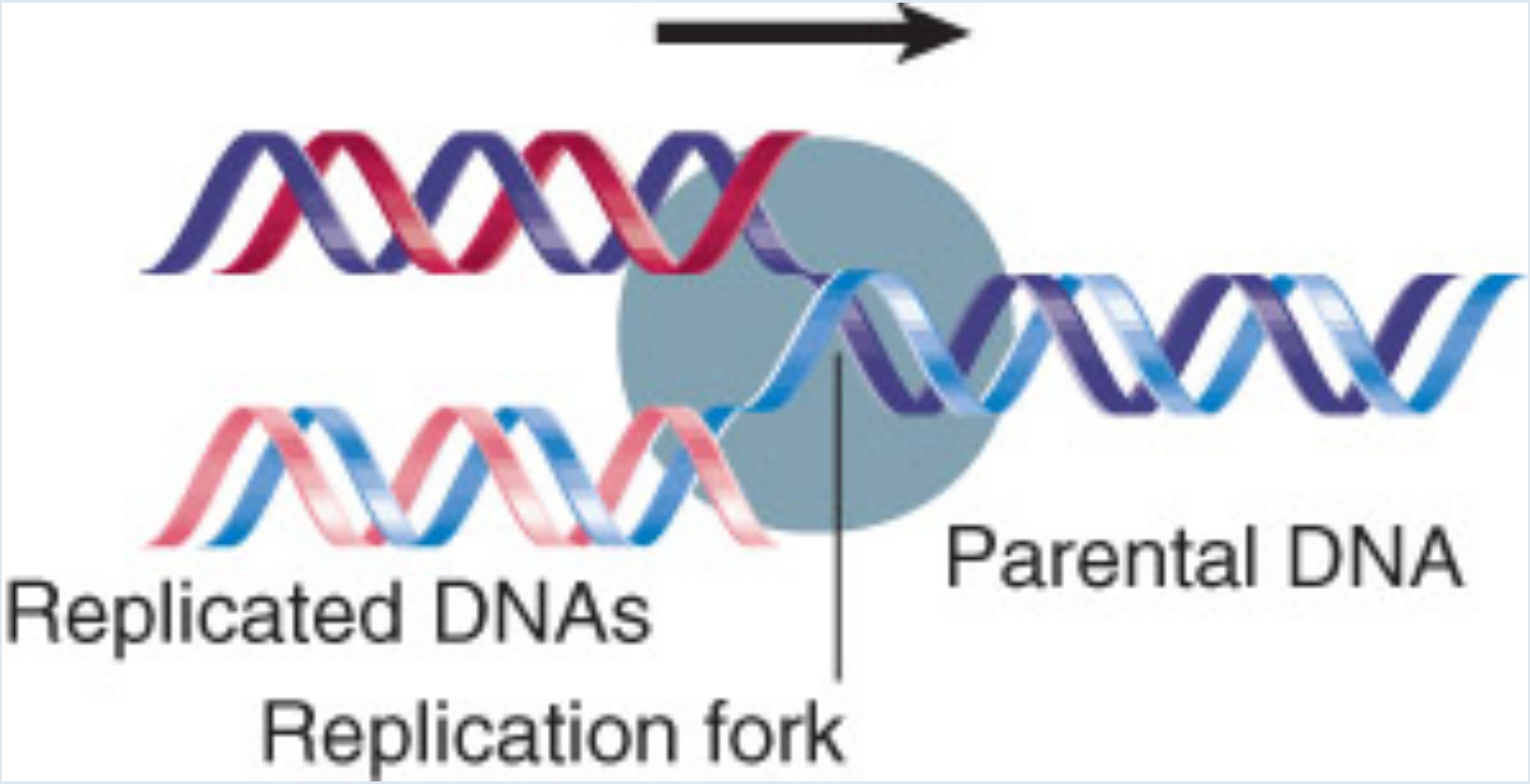
Base pairing provides the mechanism for replicating DNA.



A brief history of genetics.



F15: Replication of DNA is semiconservative.



The replication fork

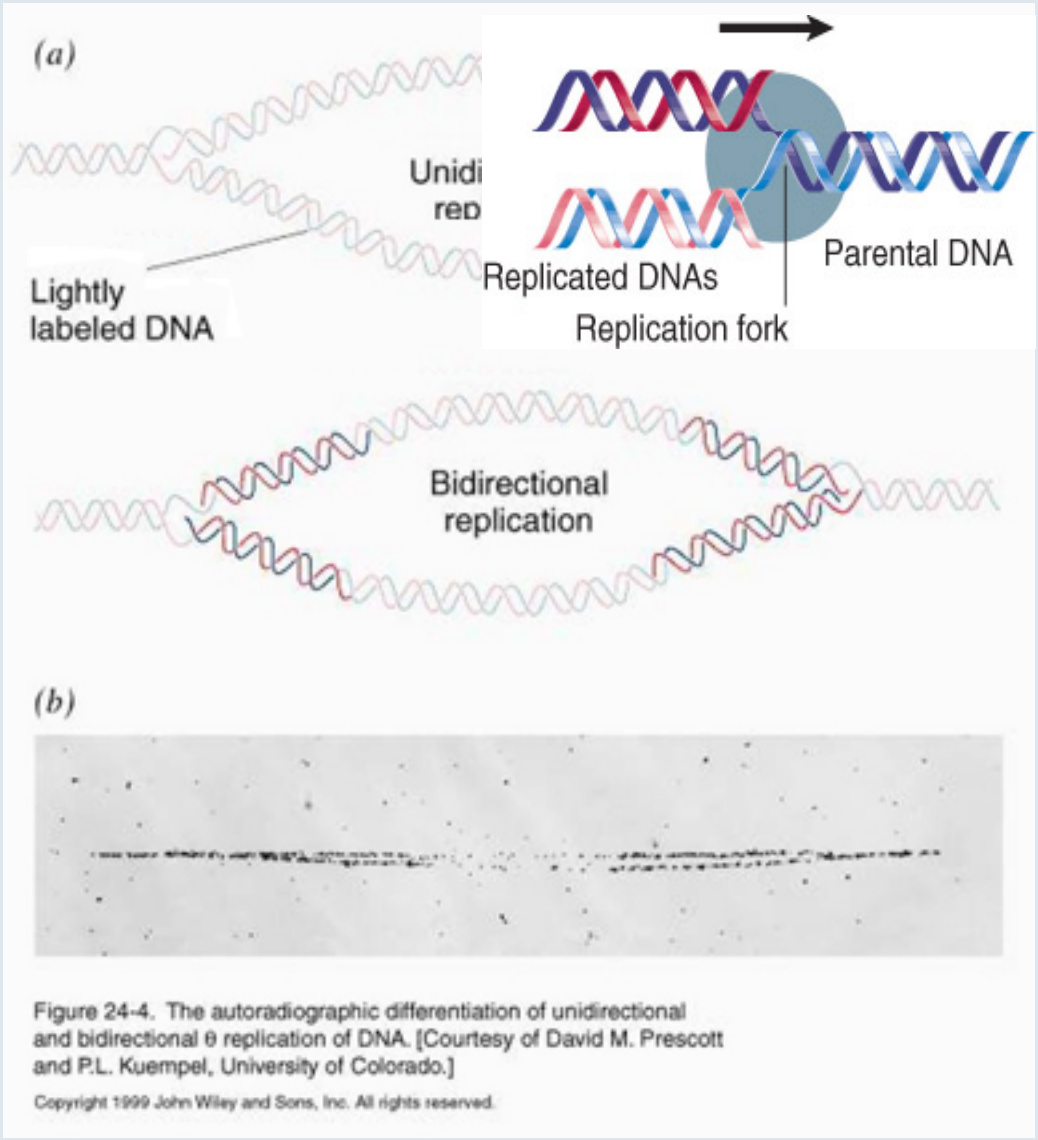


Figure 24-4. The autoradiographic differentiation of unidirectional and bidirectional θ replication of DNA. [Courtesy of David M. Prescott and P.L. Kuempel, University of Colorado.]