

21 基因的分子生物学

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Outline

21.1 遗传物质是 DNA 的证明

21.2 DNA复制

21.3 遗传信息流是从DNA到RNA到蛋白质

21.4 基因突变

遗传学世纪的大事件 i

- 1865 Genes are particulate factors
- 1903 Chromosomes are hereditary units
- 1910 Genes lie on chromosomes
- 1913 Chromosomes are linear arrays of genes
- 1931 Recombination occurs by crossing over
- 1944 DNA is the genetic material
- 1945 A gene codes for protein
- 1951 First protein sequence
- 1953 DNA is a double helix
- 1958 DNA replicates semiconservatively
- 1961 Genetic code is triplet

遗传学世纪的大事件 ii

- 1977 Eukaryotic genes are interrupted
- 1977 DNA can be sequenced
- 1995 Bacterial genomes sequenced
- 2001 Human genome sequenced

21.1 遗传物质是 DNA 的证明

21.1.1 肺炎链球菌转化实验

Transformation of bacteria

Pneumococcus types	Injection of cells	Results
Capsule smooth (S) appearance	Living S	Dies
No capsule rough (R) appearance	Heat-killed S	Lives
	Living R	Lives
	Heat-killed S Living R	Dies

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The transforming principle is DNA

Mouse injected
with heat-killed S
and living R bacteria



Living S bacteria
recovered from
dead mouse

Extract
DNA



Transform



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Figure 1. 转化因子是 DNA

21.1.2 T2 噬菌体感染实验

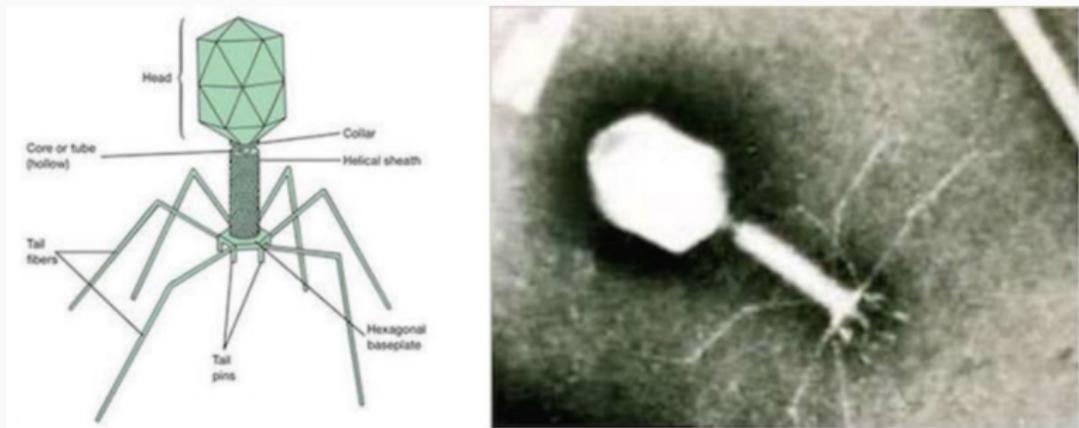


Figure 2. T2 噬菌体. 左: 结构示意图; 右: 透射电镜照片.

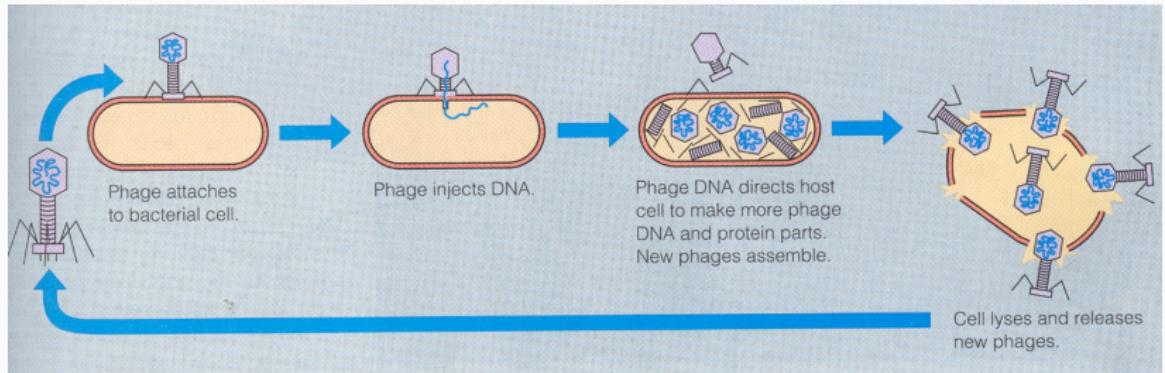


Figure 3. 噬菌体繁殖

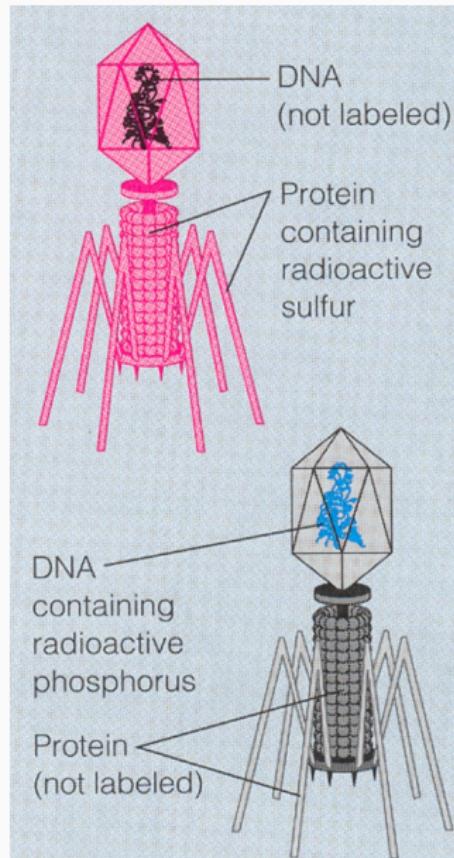
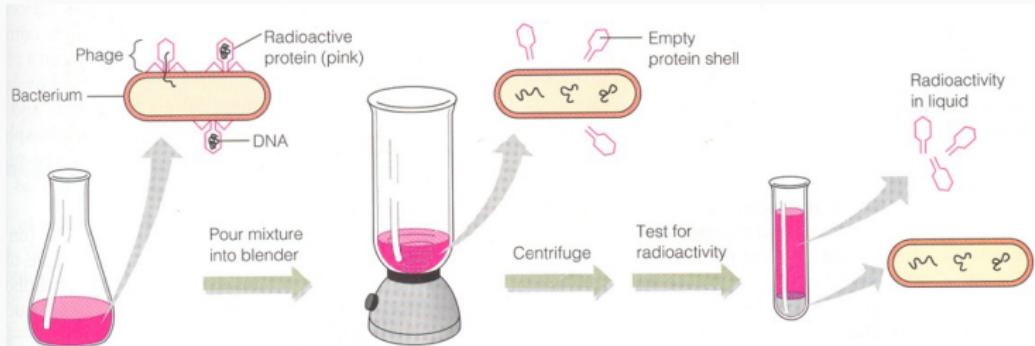


Figure 4. 放射性标记 T2 噬菌体



Mix radioactively labeled phages with bacteria. The phages infect the bacterial cells.

② Agitate in a blender to separate phages outside the bacteria from the bacterial cells and their contents.

③ Centrifuge the mixture.

④ Measure the radioactivity in the pellet and the liquid.

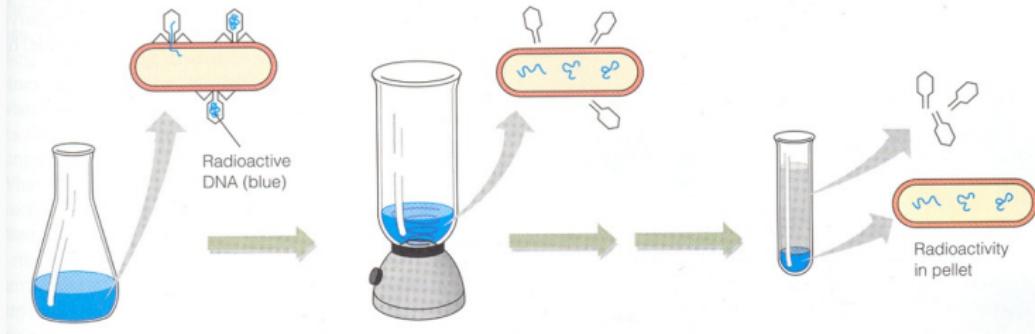


Figure 5. 赫尔希-蔡斯关于 T2 噬菌体的感染实验

21.1.3 DNA 与 RNA 是多核苷酸的聚合体

1. Chargaff 法则

- ▶ $[A]=[T]$ $[G]=[C]$

2. DNA 与 RNA 是多核苷酸的聚合体

- ▶ 核苷
- ▶ 核苷酸
- ▶ DNA 分子的**一级结构**

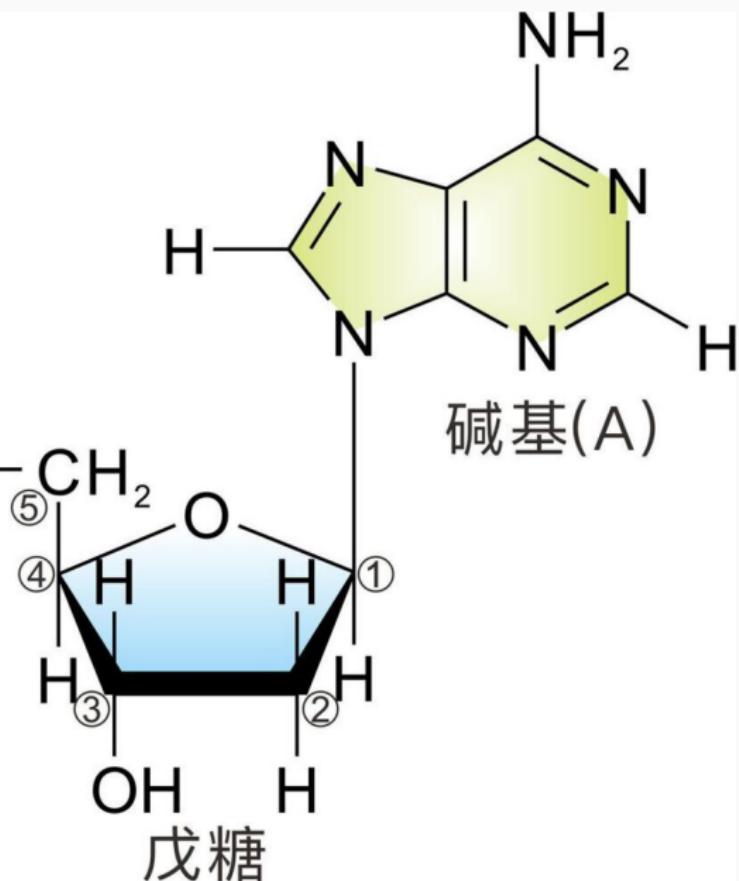
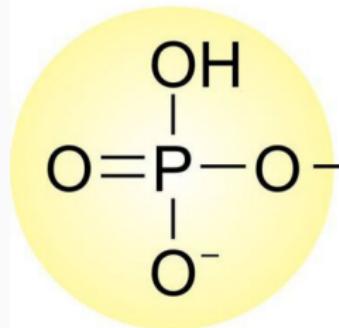
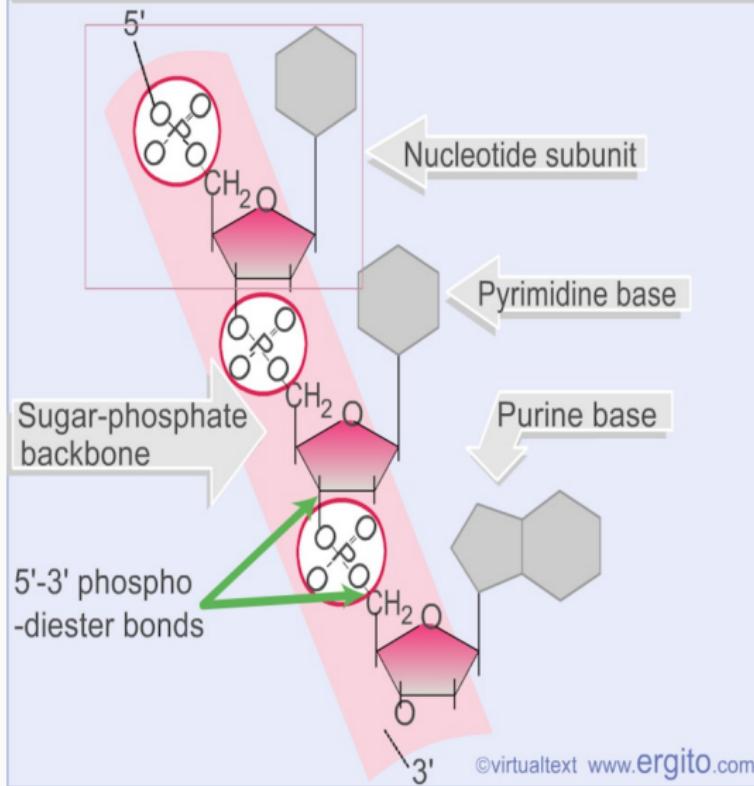


Figure 6. 核苷酸

A polynucleotide has a repeating structure



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Figure 7. 多核苷酸中的重复结构

21.1.4 DNA — 不朽的双螺旋

- Watson 和 Crick.
- DNA 分子由两条互补核苷酸单链组成; 两条核苷酸链总是按碱基 A 与 T, G 与 C 互补配对, 成反向平行, 通过氢键形成稳定的双螺旋结构.

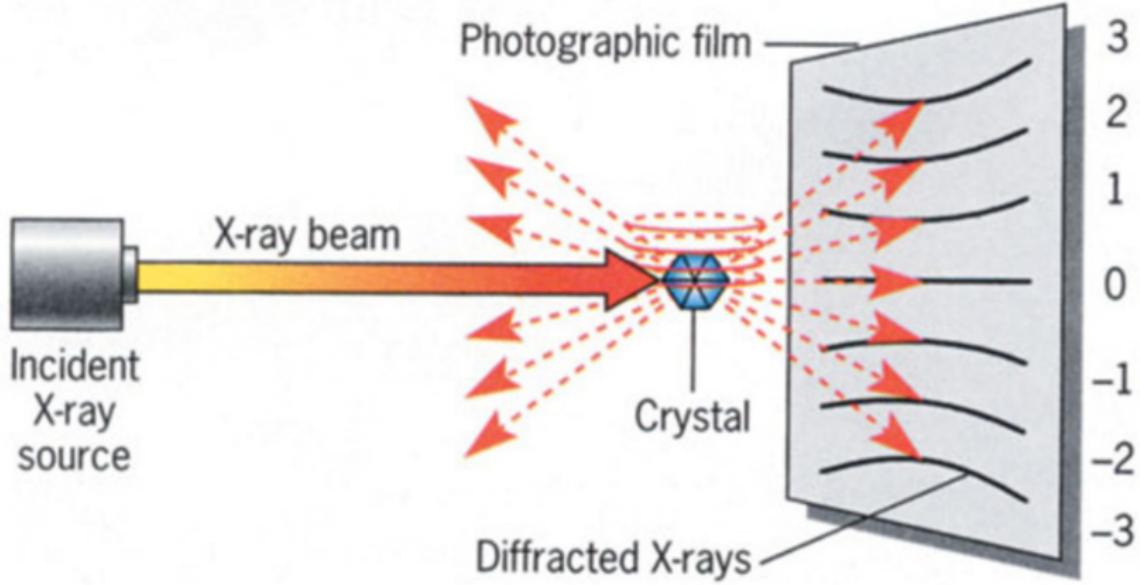


Figure 8. X-射线衍射实验

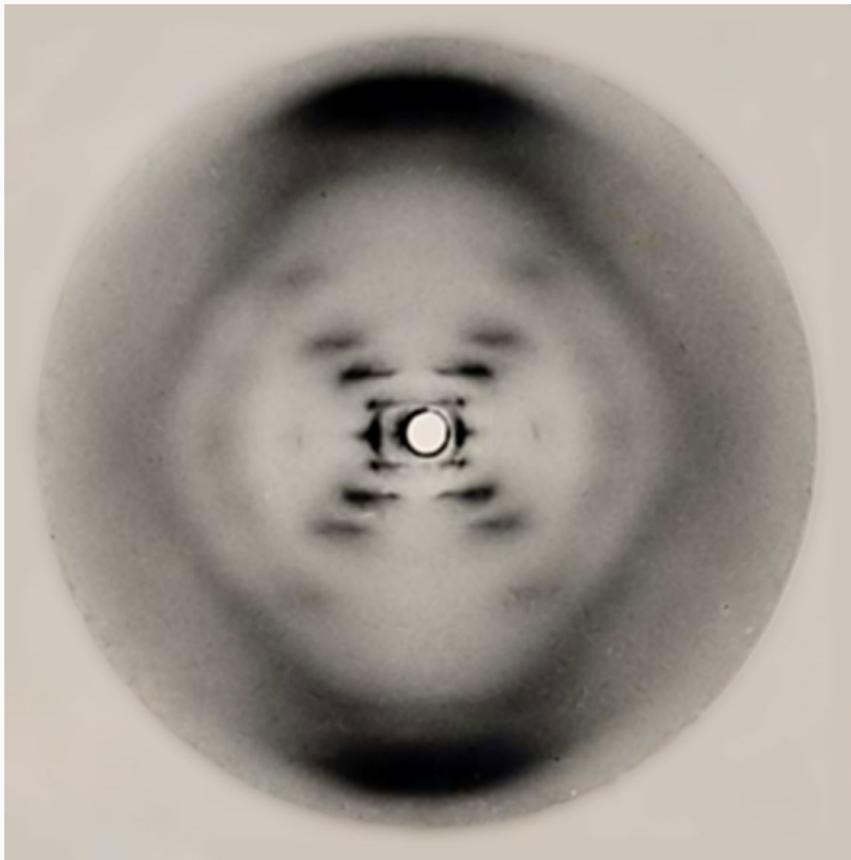


Figure 9. DNA 晶体的 X-射线衍射照片



(a) Rosalind Franklin



(b) Maurice Wilkins

Figure 10. 研究 DNA 晶体的科学家

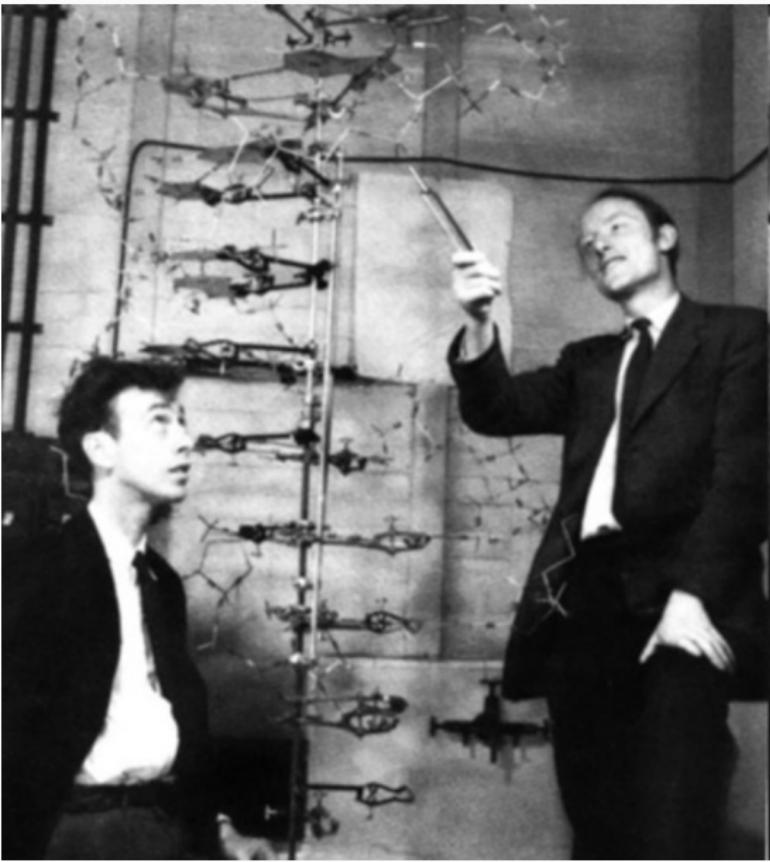


Figure 11. Watson 和 Crick

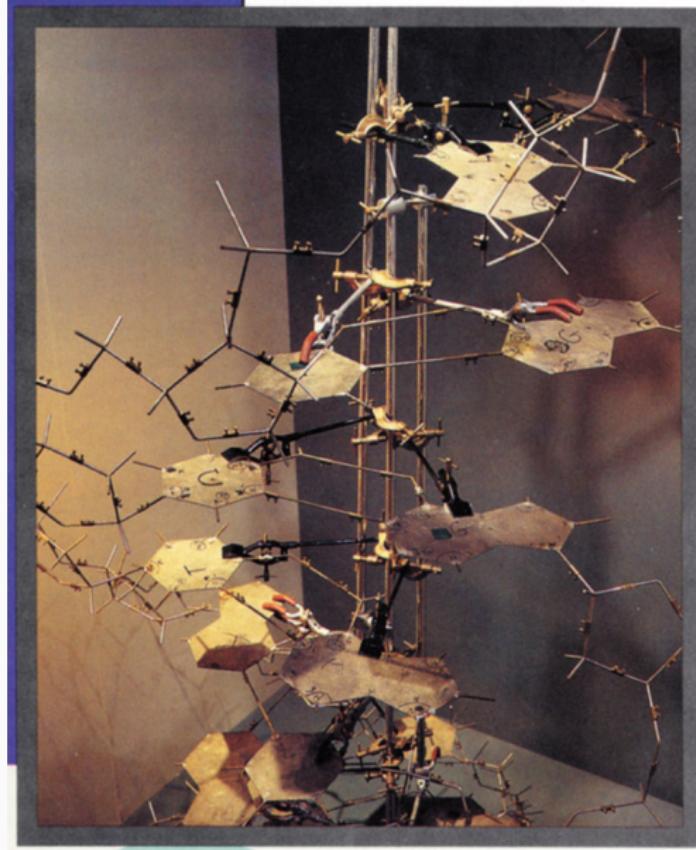


Figure 12. Model of DNA built by James Watson and Francis Crick at Cambridge University

› Nature Science Update

Genome Gateway

Nature Genetics

Nature Reviews Genetics

Encyclopedia of Life Sciences

Encyclopedia of the Human Genome

Cold Spring Harbor DNA50

BBC/Wellcome DNA photography competition

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- Immunology
- Materials Science
- Medical Research
- Microbiology

A Structure for Deoxyribose Nucleic Acid

Watson J.D. and Crick F.H.C.
Nature **171**, 737-738 (1953)



April 25, 1953: James Watson and Francis Crick's classic paper that first describes the double helical structure of DNA. With some understatement they note that the structure "suggests a possible copying mechanism for the genetic material".

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Molecular Structure of Deoxypentose Nucleic Acids

Wilkins M.H.F., A.R. Stokes A.R. & Wilson, H.R.
Nature **171**, 738-740 (1953)



April 25, 1953: From the same issue, Wilkins, Stokes and Wilson analyse the X-Ray crystallography evidence, and suggest evidence that the structure exists in biological systems.

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Molecular Configuration in Sodium Thymonucleate

Franklin R. and Gosling R.G.
Nature **171**, 740-741 (1953)



April 25, 1953: Rosalind Franklin and Ray Gosling provide further evidence of the helical nature of nucleic acids, and conclude that the phosphate backbone lies on the outside of the structure.

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Genetical Implications of the structure of Deoxyribonucleic Acid

Watson J.D. and Crick F.H.C.
Nature **171**, 964-967 (1953)

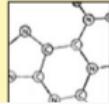


Figure 13. <http://www.nature.com/nature/dna50/archive.html>

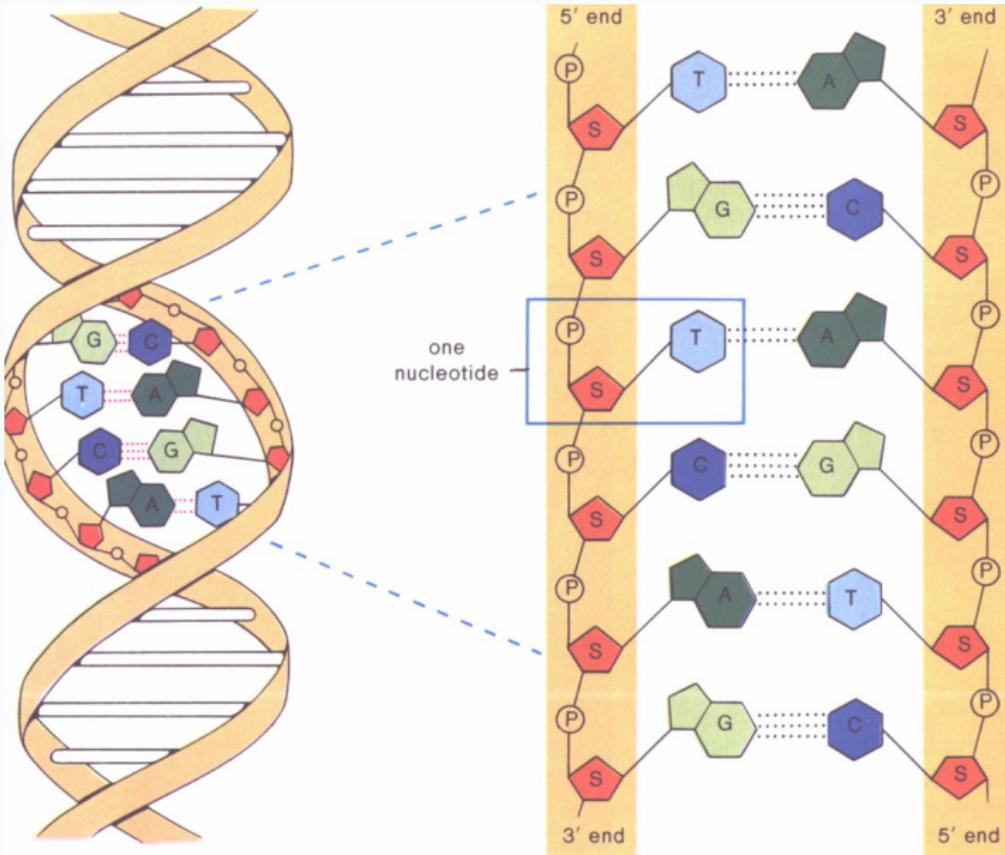


Figure 14. DNA 双螺旋结构

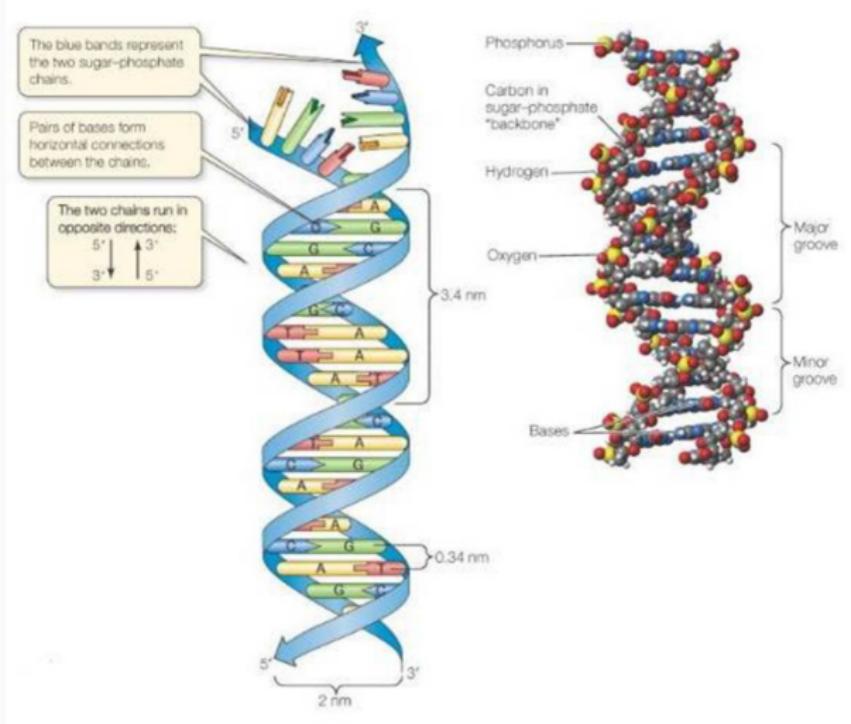


Figure 15. DNA 双螺旋结构

21.2 DNA复制

21.2.1 DNA复制依赖于碱基配对

A 与 T, G 与 C 配对.

21.2.2 DNA复制是半保留式的

DNA 复制形成的两个 DNA 分子, 每个都由一条新链和一条旧链组成.

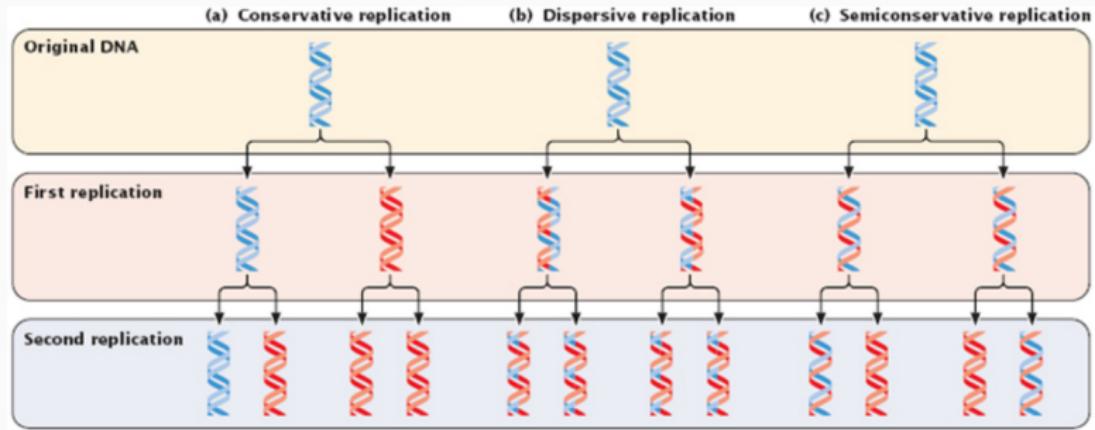


Figure 16. Three alternate schemes of replication

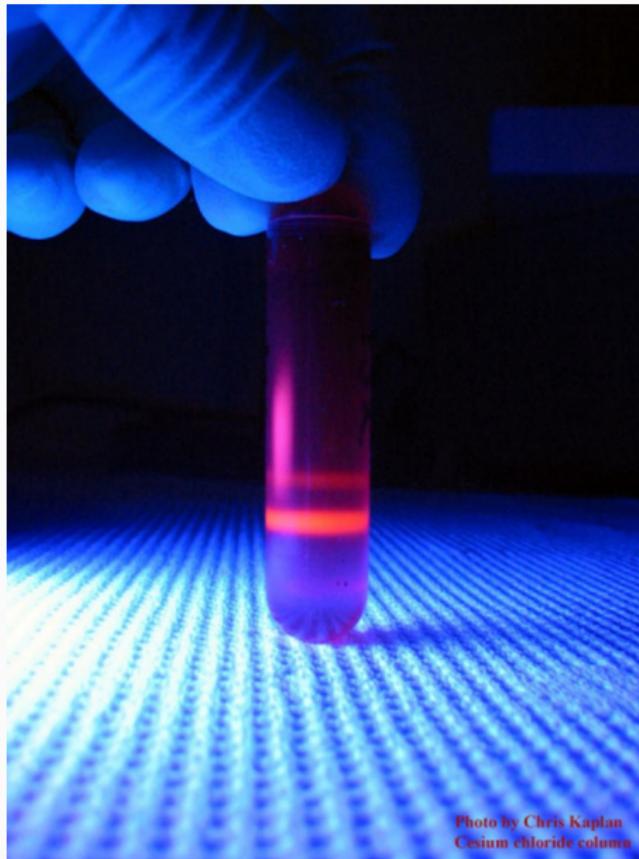


Photo by Chris Kaplan
Cesium chloride column

Figure 17. DNA 密度梯度离心 (CsCl, 氯化铯)

Experiment

Question: Which model of DNA replication—conservative, dispersive, or semiconservative—applies to *E. coli*?

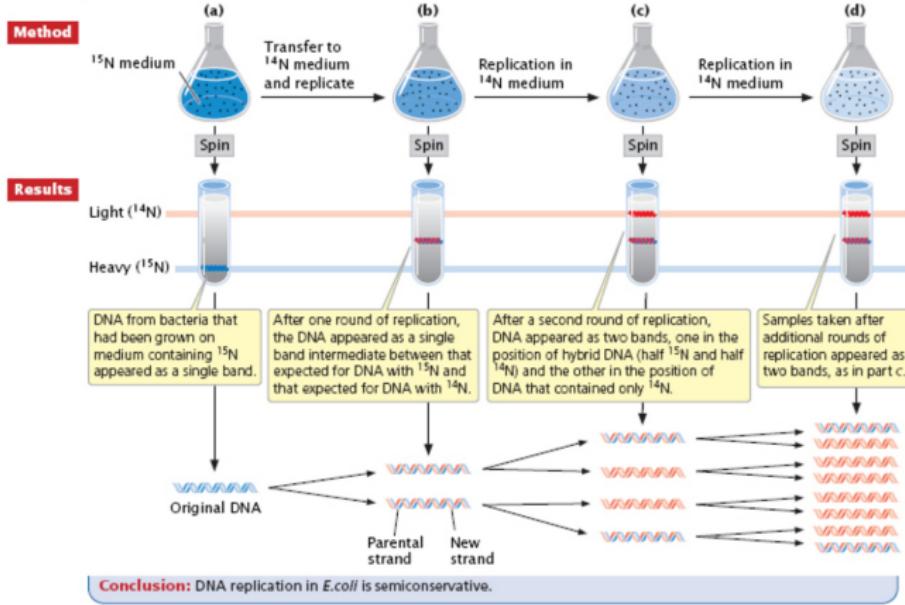


Figure 18. 大肠杆菌中的 DNA 复制¹

¹ Meselson, M. & Stahl, F. W. The Replication of DNA in *Escherichia Coli*. *Proceedings of the National Academy of Sciences* **44**, 671–682 (1958)

DNA single strands are the conserved units

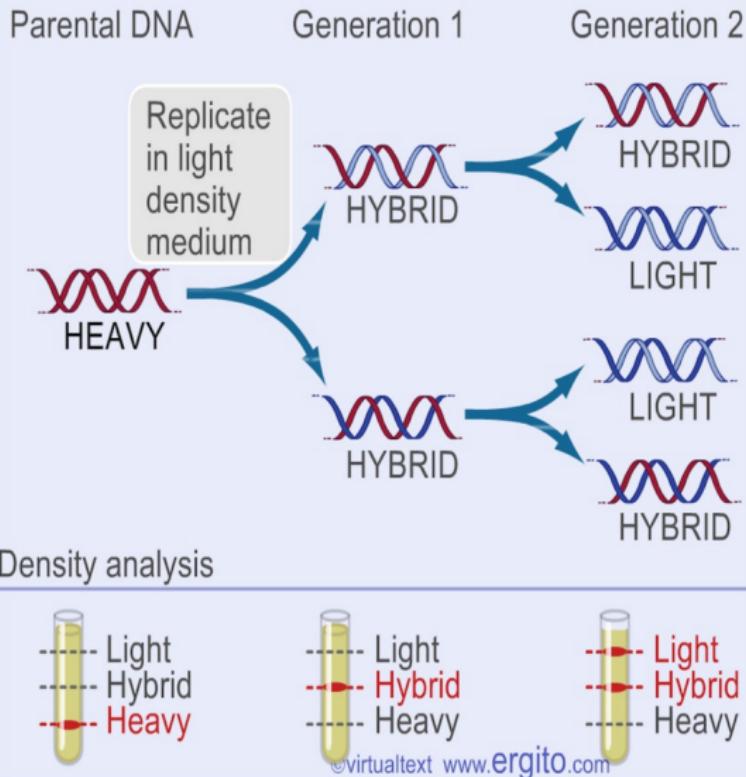


Figure 19. DNA 单链是保留的单元

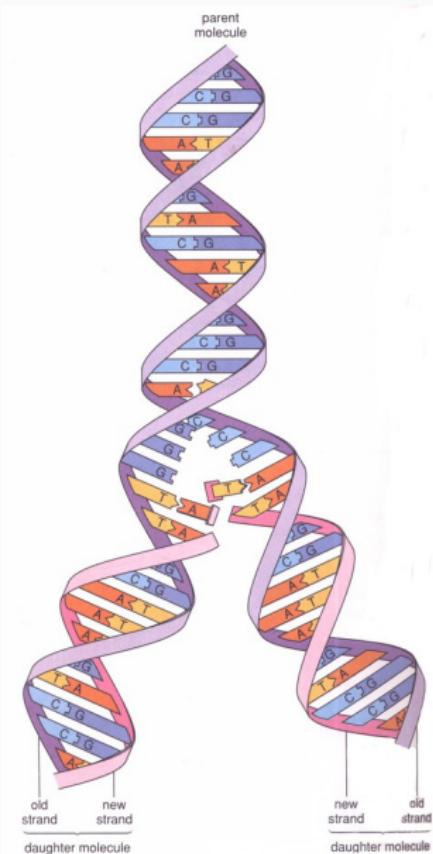


Figure 20. DNA 半保留复制

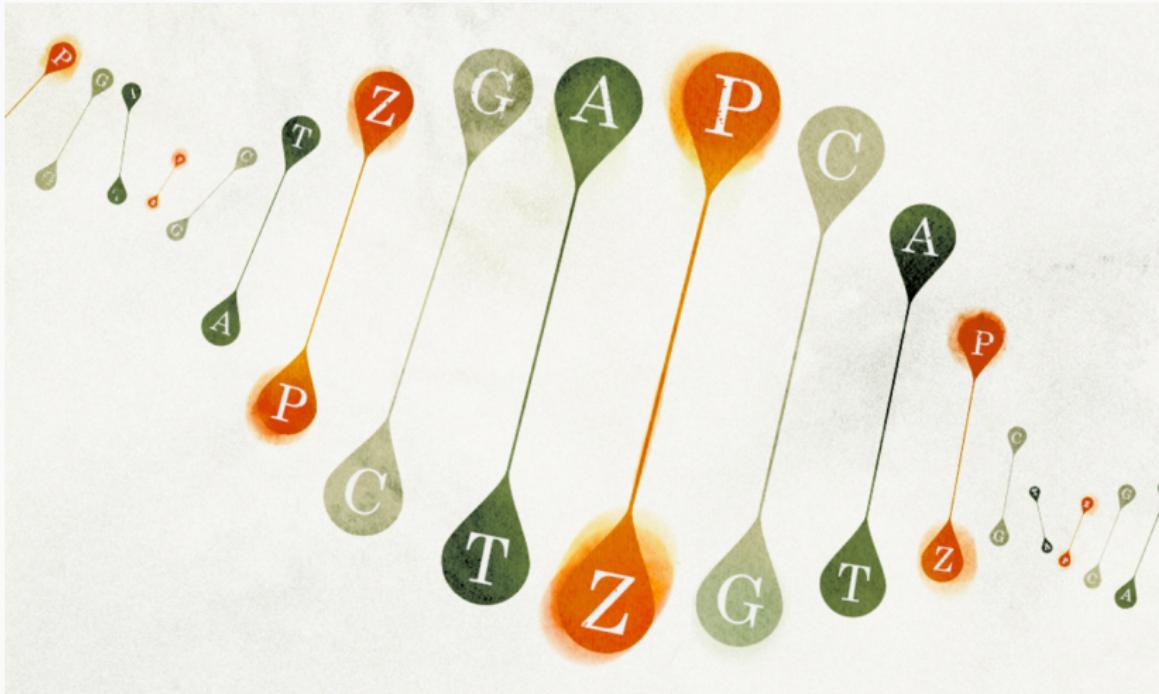


Figure 21. 合成的核苷酸 P 和 Z

21.2.3 复制的半不连续性

- DNA 聚合酶只能使核苷酸按 $5' \rightarrow 3'$ 方向连接成链
- 而 DNA 的两条链的方向相反, 这相反的一条链, DNA 聚合酶是通过冈崎片段来合成它的互补链的.

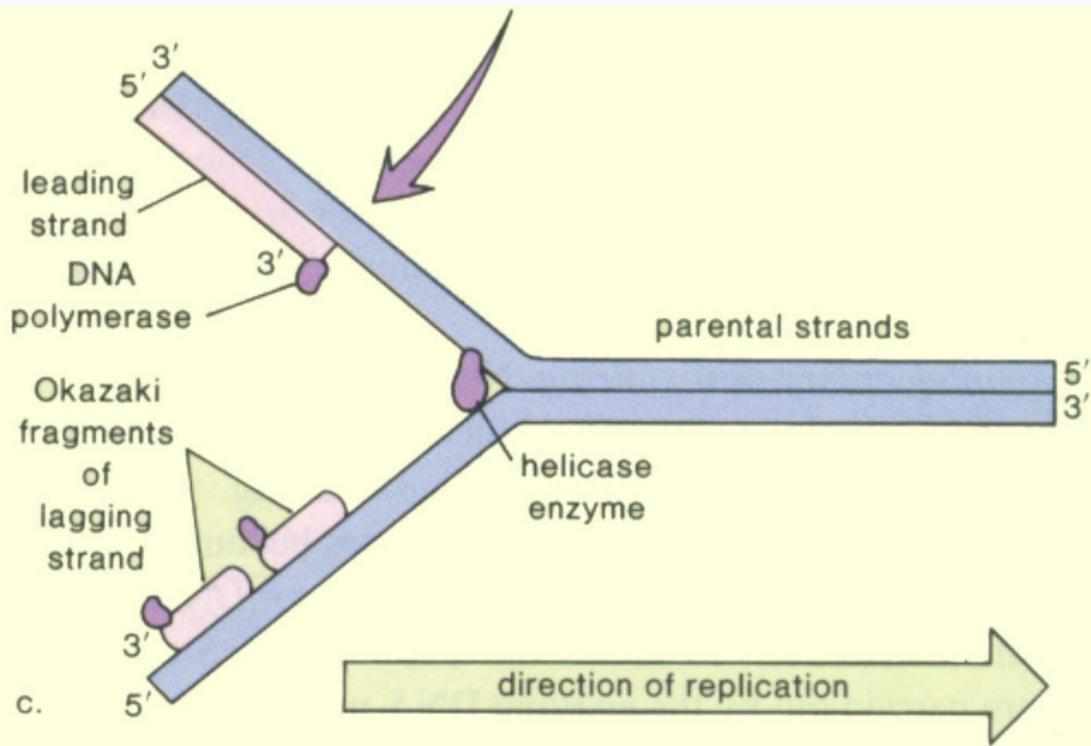


Figure 22. 复制叉

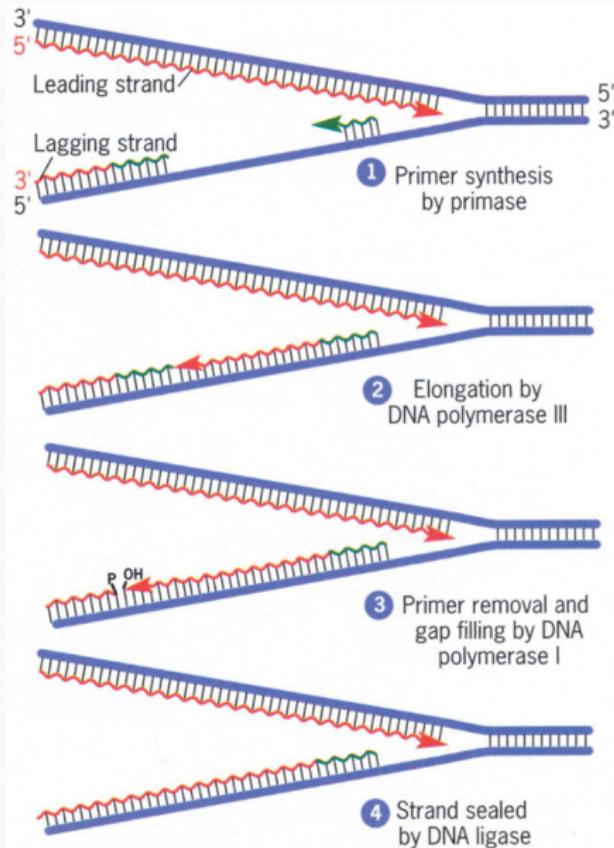


Figure 23. RNA 引物的去除

Replicon sizes can be measured by adjacent eyes

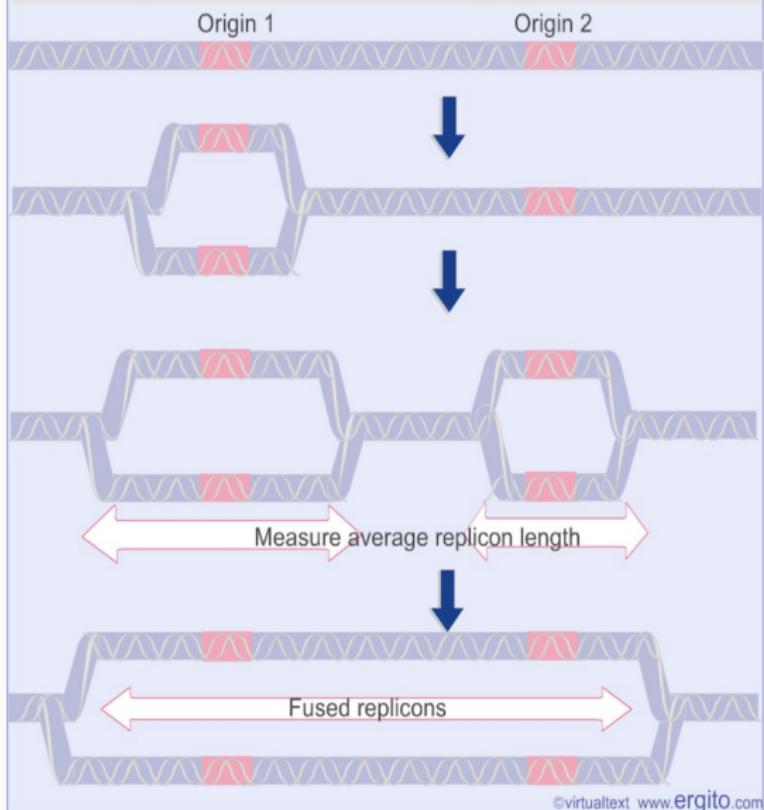


Figure 24. 真核生物的复制起始位点

21.3 遗传信息流是从DNA到RNA到 蛋白质

21.3.1 蛋白质是表型特征的分子基础

- 1909年, A. Garrod 尿黑酸症
 - ▶ 黑色尿(性状) – 酶 – 基因
- 1940年代, George Beadle 和 Edward Tatum
 - ▶ 一个基因一个酶
 - ▶ 一个基因一条多肽

Table 1. 粗糙脉孢菌 3 种精氨酸依赖型

突变型	生长所需氨基酸
1	精氨酸或瓜氨酸或鸟氨酸
2	精氨酸或瓜氨酸
3	精氨酸



21.3.2 DNA 与蛋白质的合成

1. RNA 的结构与功能

► 与 DNA 相比较, 其结构特点:

- 单链
- 戊糖是核糖
- 尿嘧啶代替胸腺嘧啶

► 功能

- 信使 RNA (mRNA)
- 核糖体 RNA (rRNA)
- 转运 RNA (tRNA)
- ...

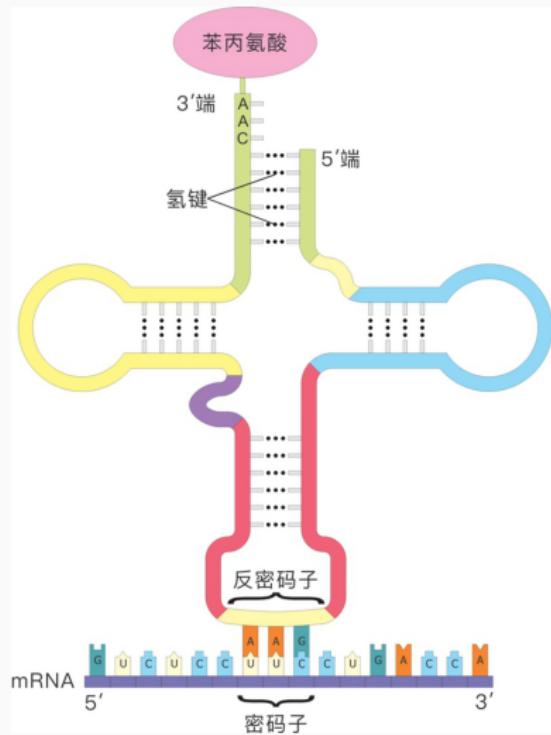


Figure 25. tRNA 结构

2. 转录 – 从 DNA 到 RNA

- ▶ 以 DNA 为模板, 通过 RNA 聚合酶使碱基互补配对合成 RNA 的过程.
- ▶ 过程: 转录启动, 延伸和终止.

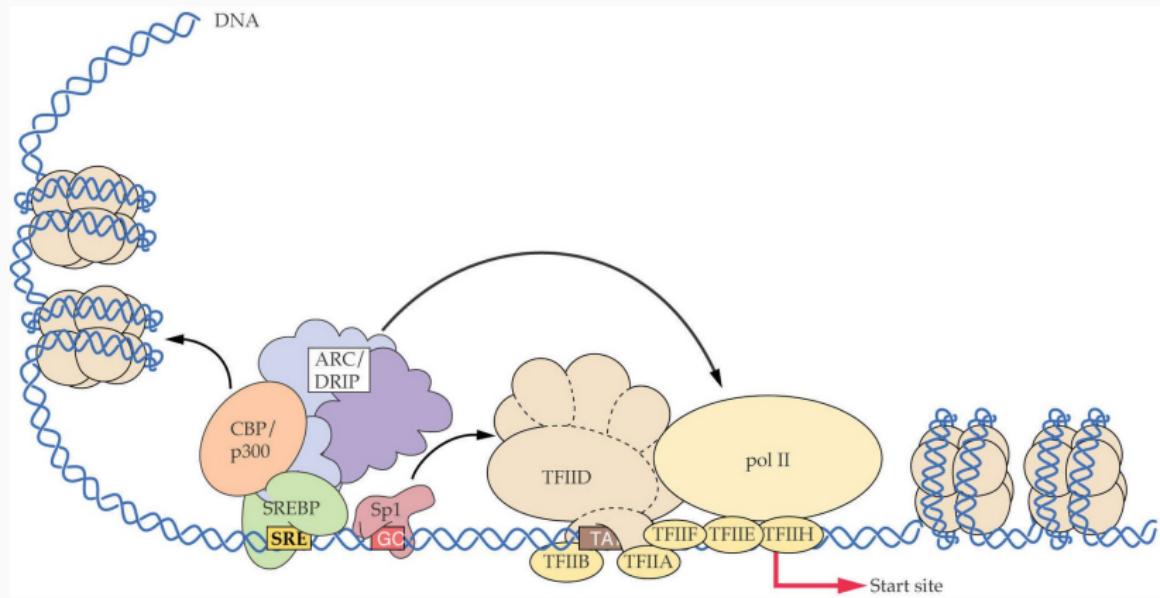


Figure 26. 基因转录起始

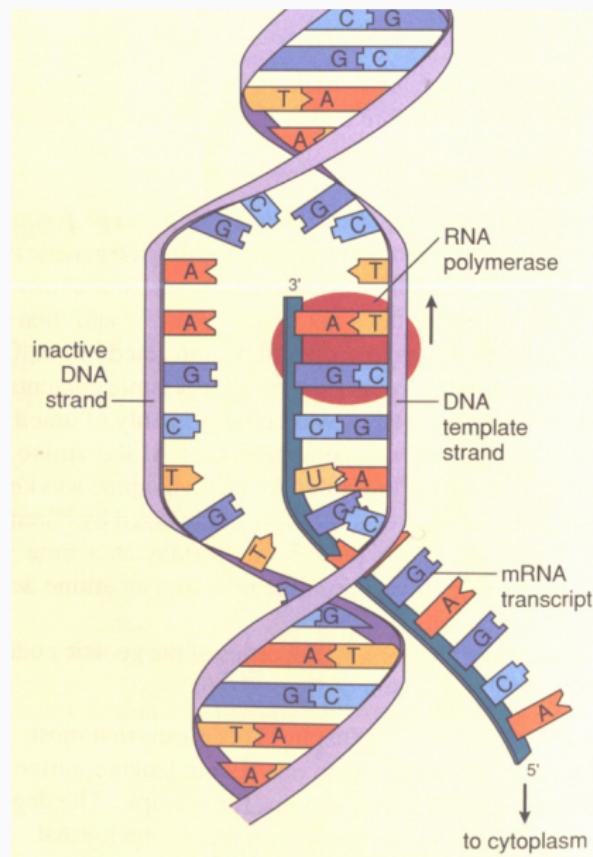


Figure 27. 转录

3. 遗传密码

- ▶ 三联体密码子
- ▶ 密码是连续的
- ▶ 密码的简并性

		SECOND BASE						
		U	C	A	G			
FIRST BASE	U	UUU UUC UUA UUG	UCU UCC UCA UCG	UAU UAC	Tyr	UGU UGC	Cys	
	C	CUU CUC CUA CUG	CCU CCC CCA CCG	CAU CAC CAA CAG	His	CGU CGC CGA CGG	Arg	
	A	AUU AUC AUA AUG	ACU ACC ACA ACG	AAU AAC AAA AAG	Asn	AGU AGC AGA AGG	Ser	
	G	GUU GUC GUA GUG	GCU GCC GCA GCG	GAU GAC GAA GAG	Asp	GGU GGC GGA GGG	Gly	
						THIRD BASE		
						U	C	A
						G	G	G
						U	C	A
						G	G	G

Figure 28. 遗传密码表

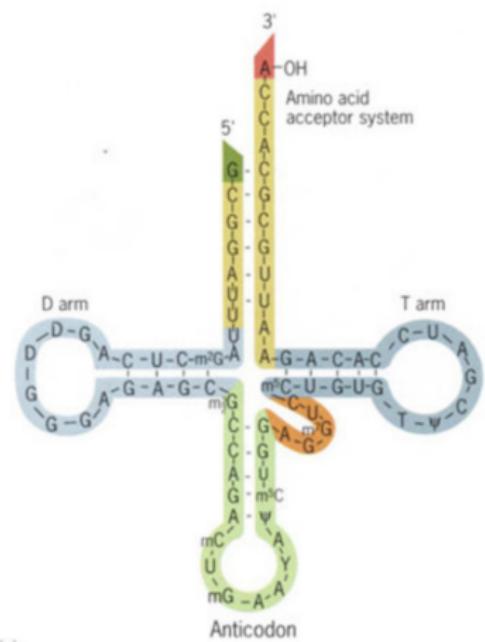
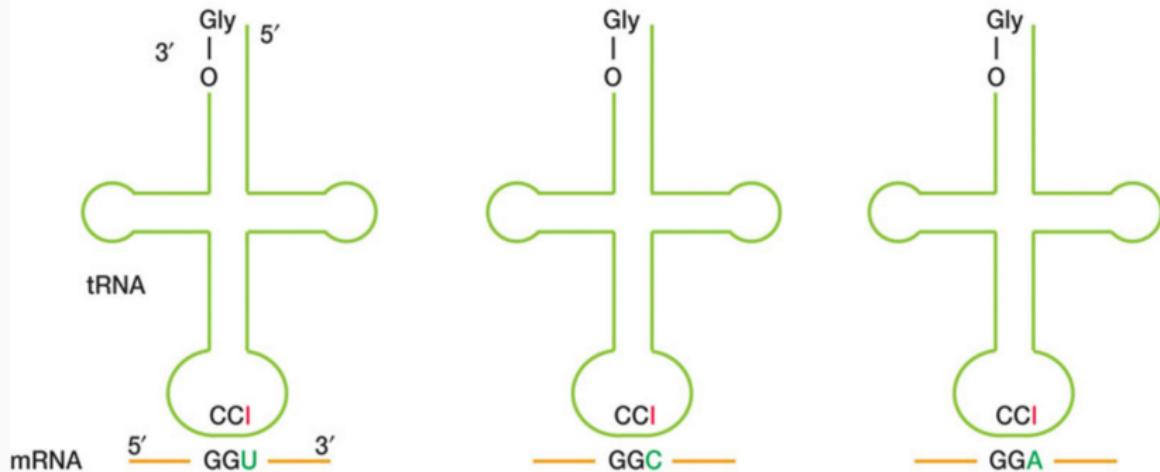


Figure 29. tRNA 三级结构

(a) Base pairing of one glycine tRNA with three codons due to wobble



(b) Glycine codons and anticodons (written in the 5' → 3' direction)

Glycine mRNA codons: GGU, GGC, GGA, GGG

Glycine tRNA anticodons: ICC, CCC

Figure 30. 摆动 (Wobble)

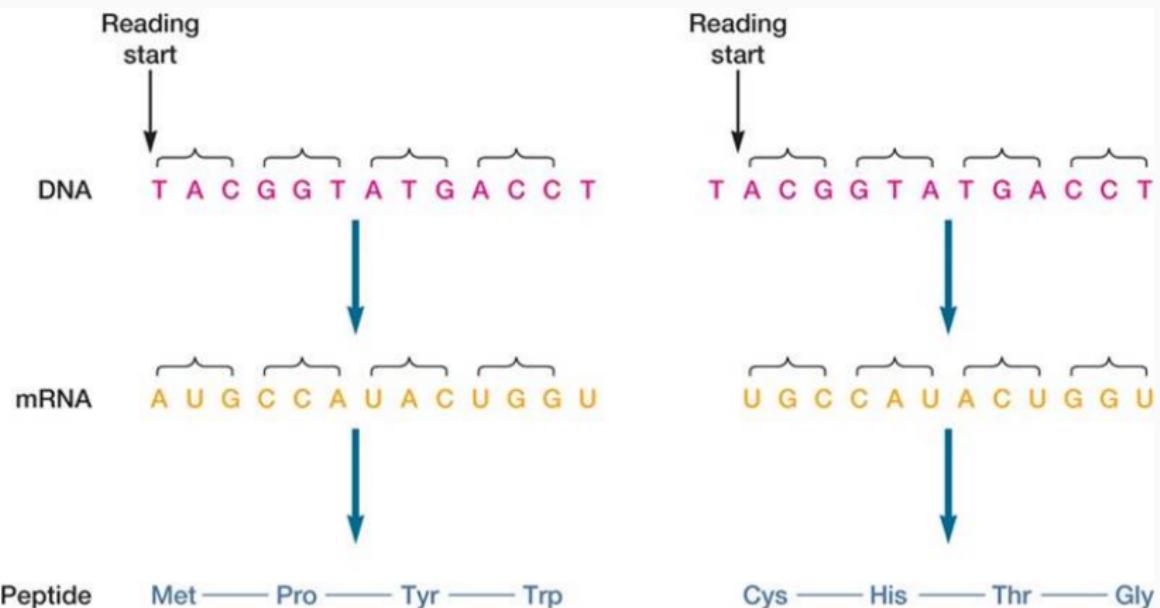
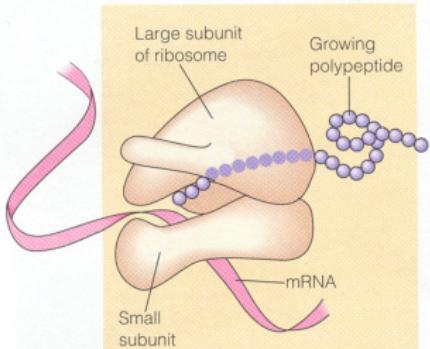


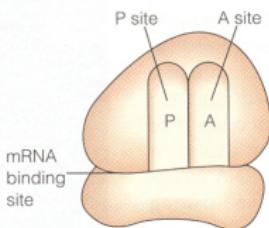
Figure 31. 阅读框及其重要性

21.3.3 遗传信息在细胞质中被翻译

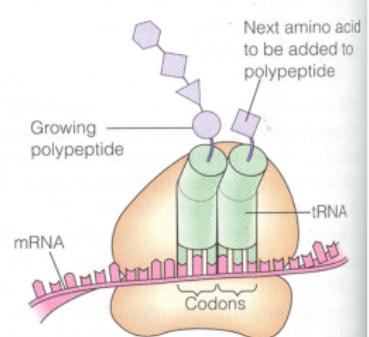
1. tRNA 携带氨基酸
2. 核糖体“阅读”密码子, 氨基酸连成多肽
 - ▶ 核糖体
 - ▶ 翻译的起始和连接
 - ▶ 翻译的终止



A. The true shape of a functioning ribosome



B. The binding sites of a ribosome

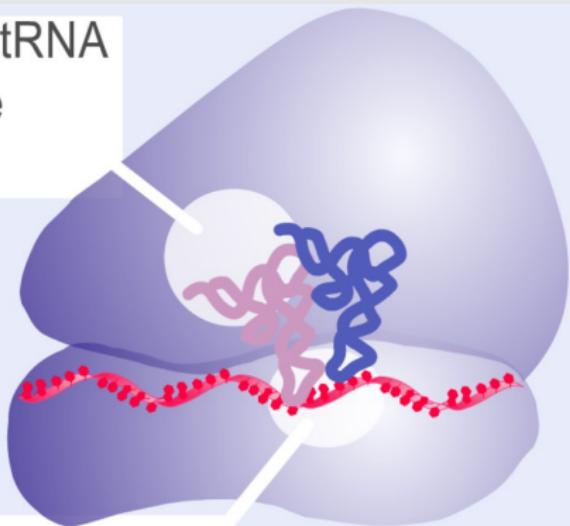


C. A ribosome with occupied binding sites

Figure 32. 核糖体

tRNA-binding sites extend across both subunits

Aminoacyl-ends of tRNA
interact within large
ribosome subunit



Anticodons are bound
to adjacent triplets on mRNA
in small ribosome subunit

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Figure 33. 核糖体中的 tRNA 结合位点

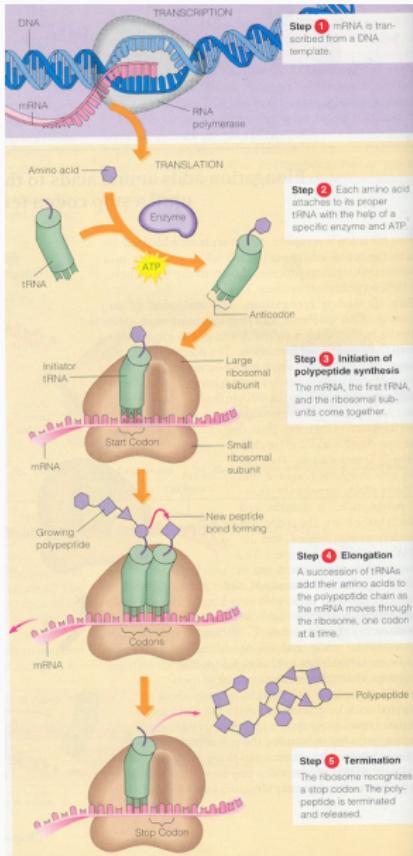


Figure 34. 转录和翻译

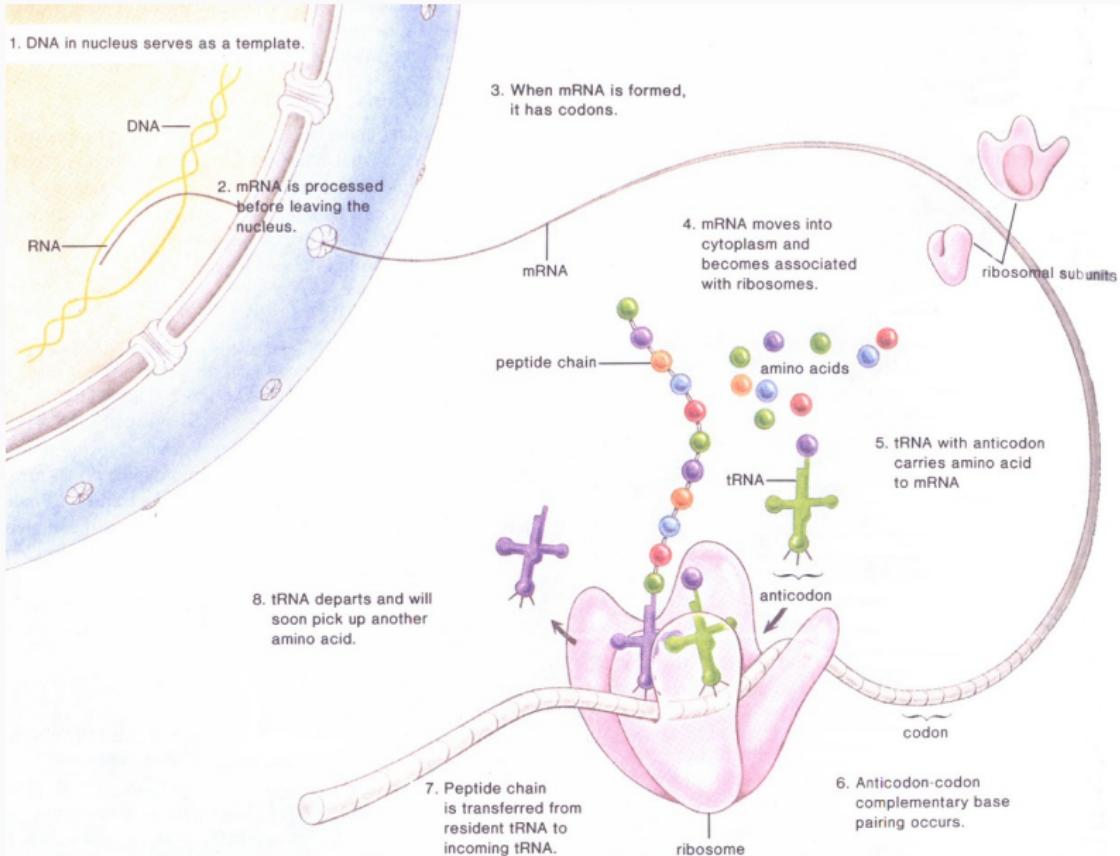
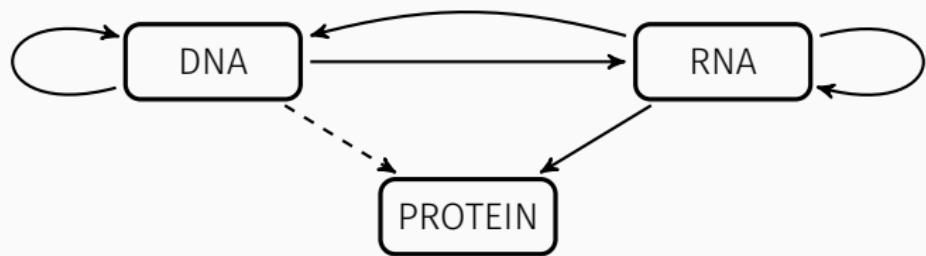


Figure 35. 转录和翻译

21.3.4 中心法则

■ 遗传信息从 DNA 到 RNA 到蛋白质





■ 脯粒与中心法则

- ▶ 新型克 - 雅氏病 (nv-CJD), 库鲁病 (Kuru), 牛海绵状脑病 (BSE), 羊摩擦症 (scrapie)
- ▶ 脯粒 (prion)
- ▶ *PrP*
- ▶ PrP^c , PrP^{sc}

21.4 基因突变

21.4.1 碱基置换

- 置换 (substitution)
 - ▶ 转换 (transition)
 - ▶ 颠换 (transversion)
- 镰刀形贫血症 ($\text{GAG} \rightarrow \text{GUG}$)

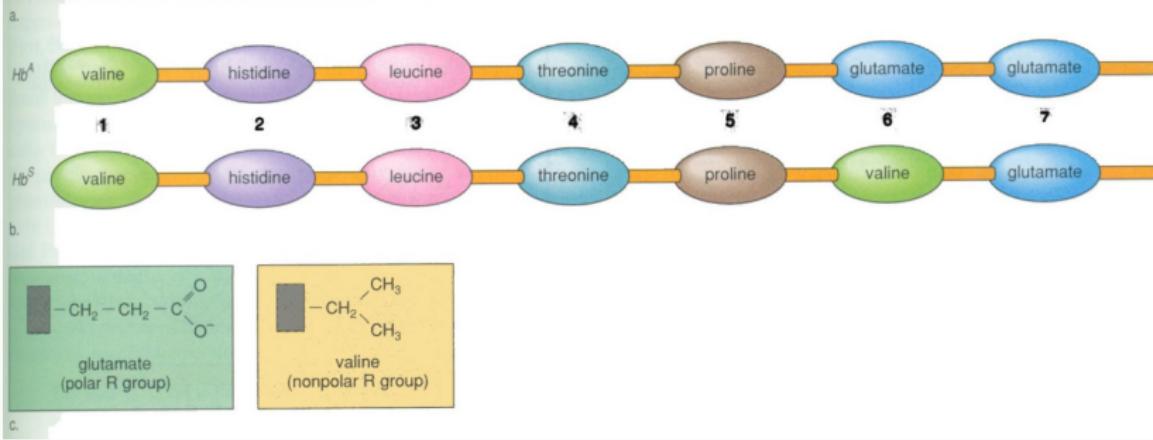
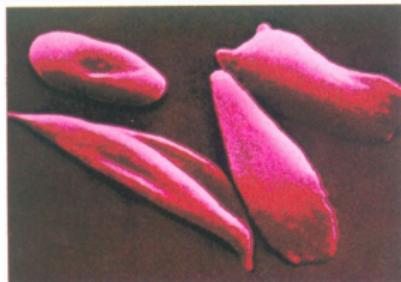
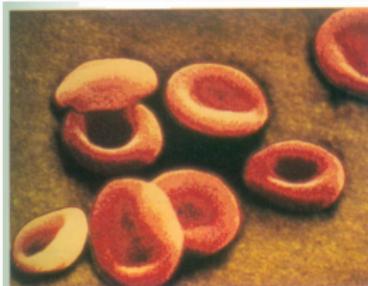


Figure 36. 镰刀形贫血症

21.4.2 移码突变

- 插入 (insertion)
- 缺失 (deletion)
- 基因的编码区非3的整倍数插入/缺失, 称为移码突变

21.4.3 DNA 损伤修复

■ 突变的诱发

- ▶ 辐射
- ▶ 化学诱变剂
- ▶ 其他诱变因素
 - 温度
 - DNA 修复系统发生错误

■ 损伤修复

- ▶ 切除修复
- ▶ 同源重组修复

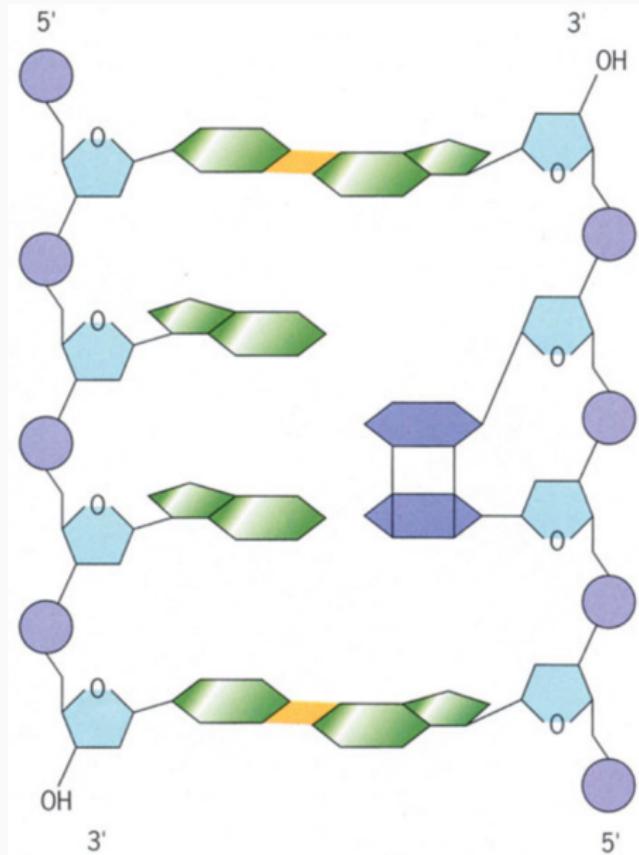


Figure 37. TT 二聚体