

7 基因与基因组

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Outline

7.1 DNA 是遗传物质

7.2 DNA 复制

7.3 基因的概念与演变

7.4 基因组

7.5 非孟德尔式遗传

7.1 DNA 是遗传物质

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



R bacteria



S bacteria

Transform

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Figure 1. 转化因子是 DNA

T2 噬菌体感染实验

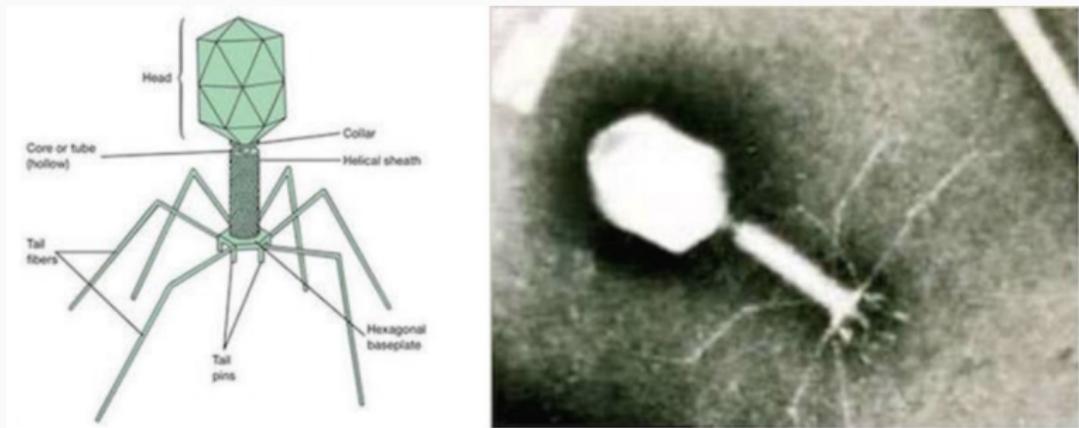


Figure 2. T2 噬菌体. 左: 结构示意图; 右: 透射电镜照片.

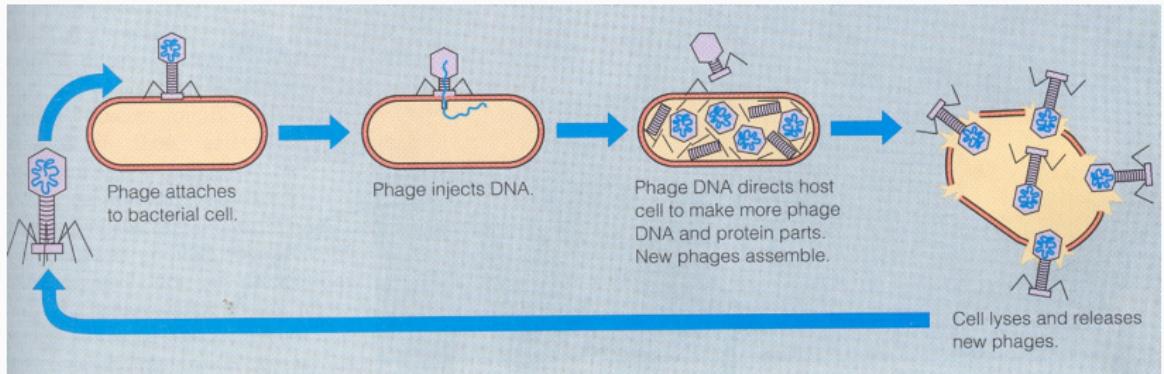


Figure 3. 噬菌体繁殖

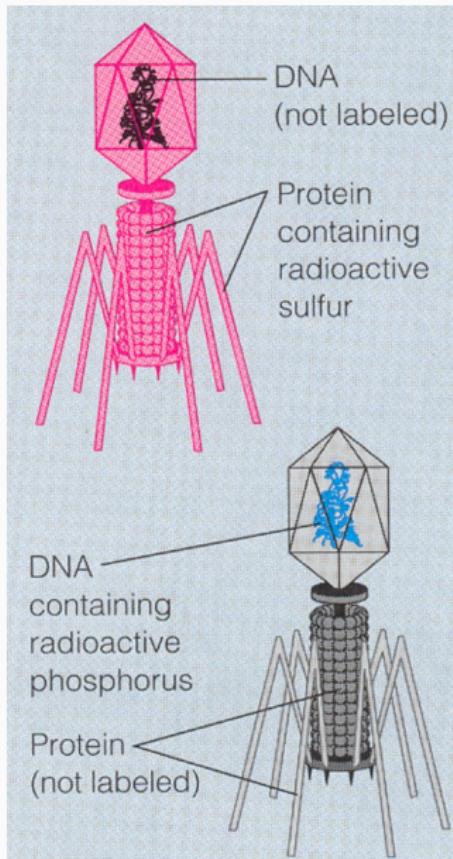
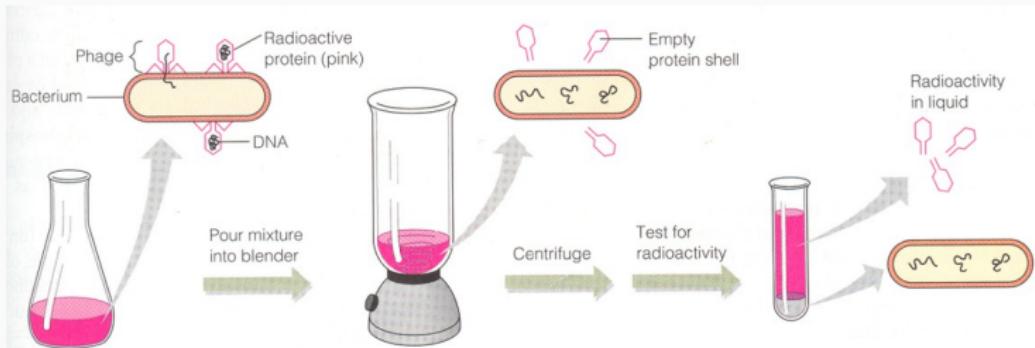


Figure 4. 放射性标记 T2 噬菌体



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.

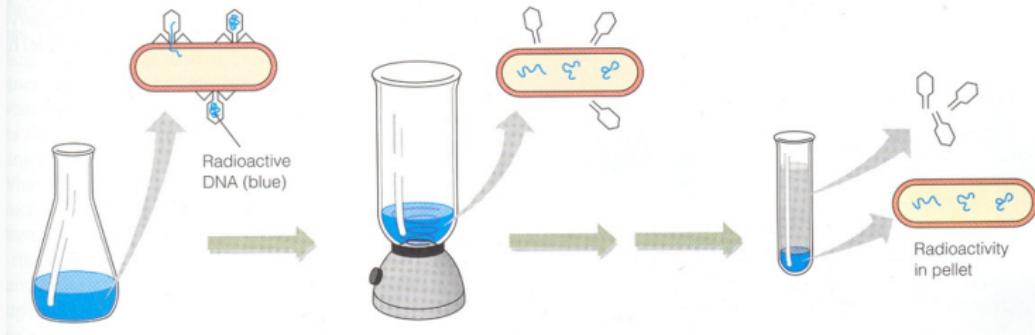


Figure 5. 赫尔希-蔡斯关于 T2 噬菌体的感染实验

部分病毒以 RNA 作为遗传物质

- 烟草花叶病毒
- SARS / SARS-CoV-2

7.2 DNA 复制

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

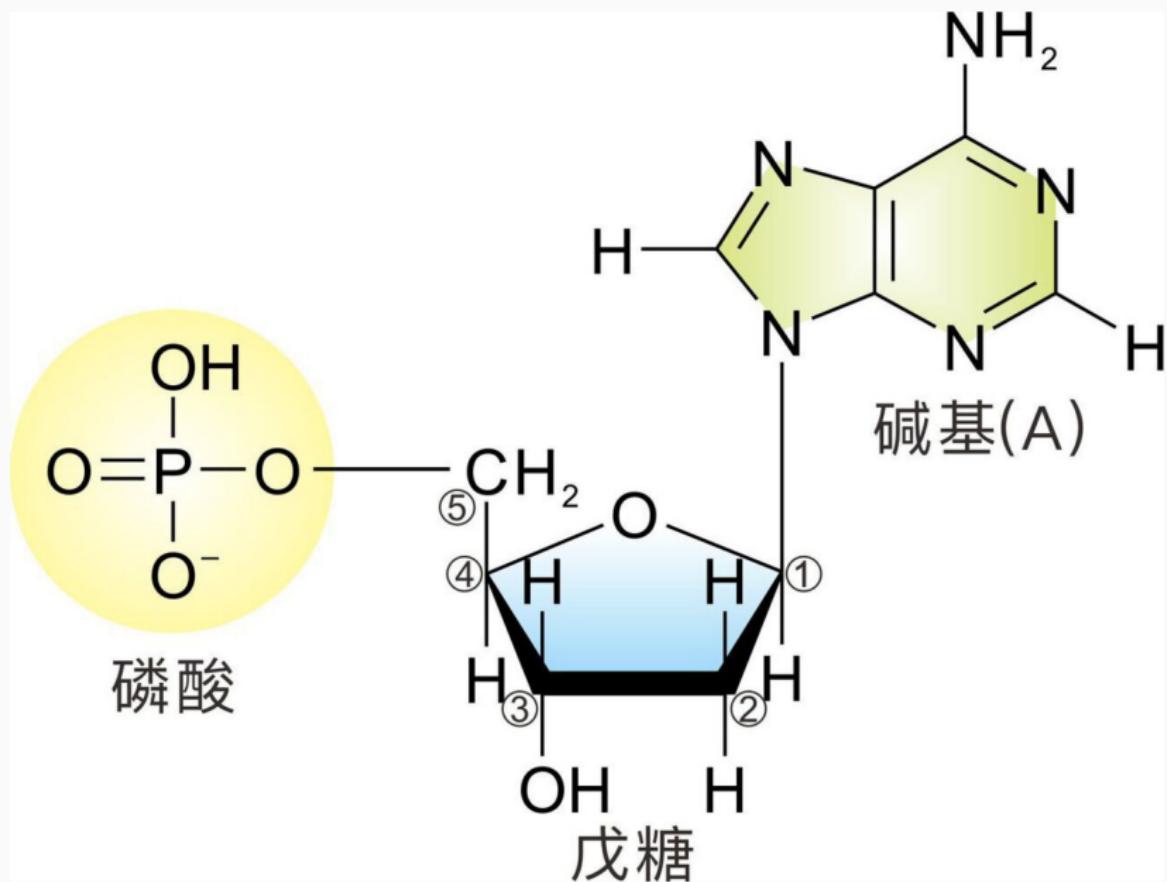


Figure 6. 核苷酸

A polynucleotide has a repeating structure

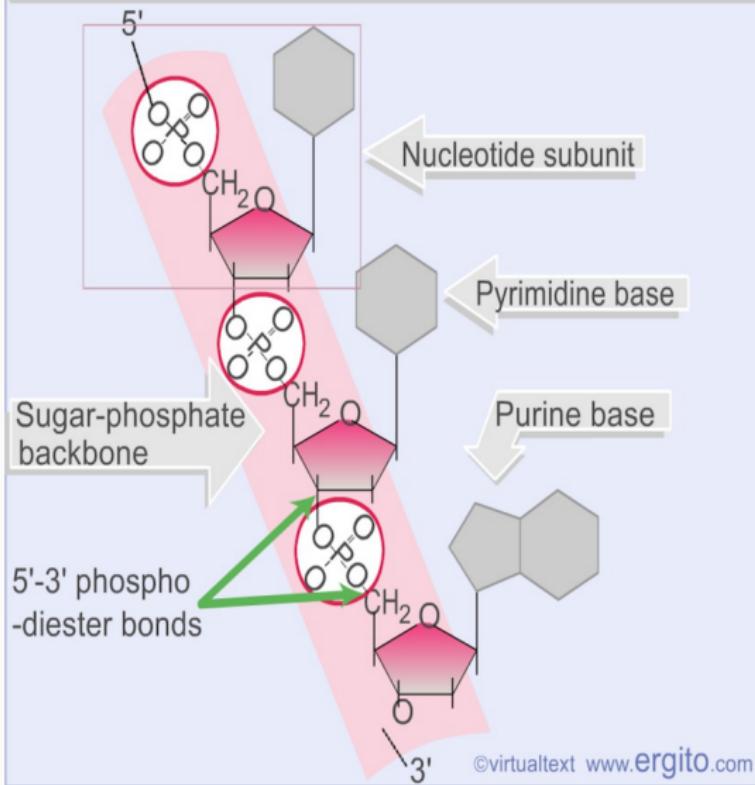


Figure 7. 多核苷酸中的重复结构

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.

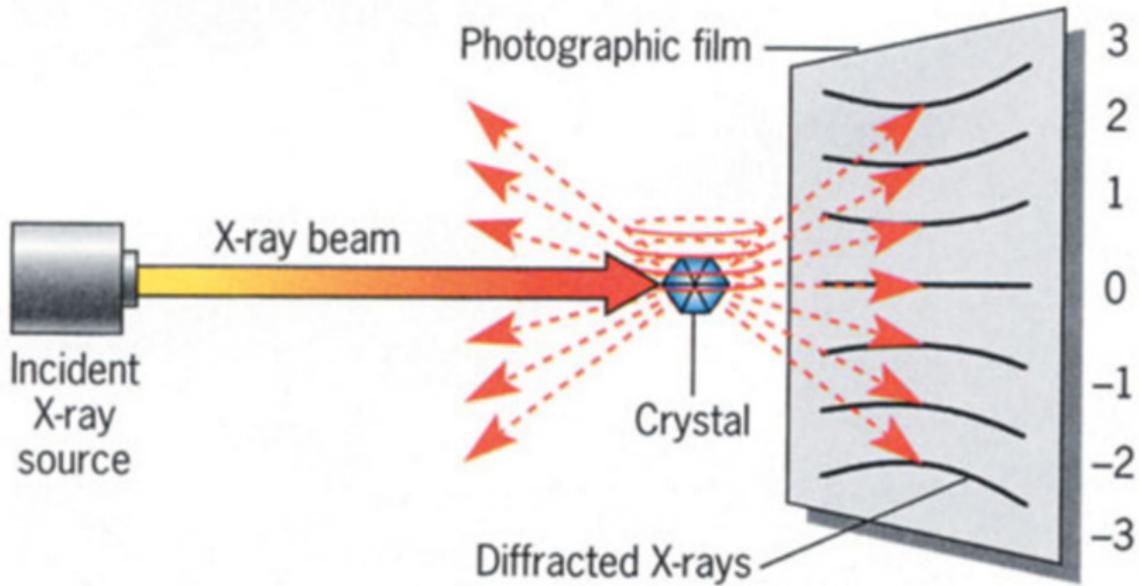


Figure 8. X-射线衍射实验

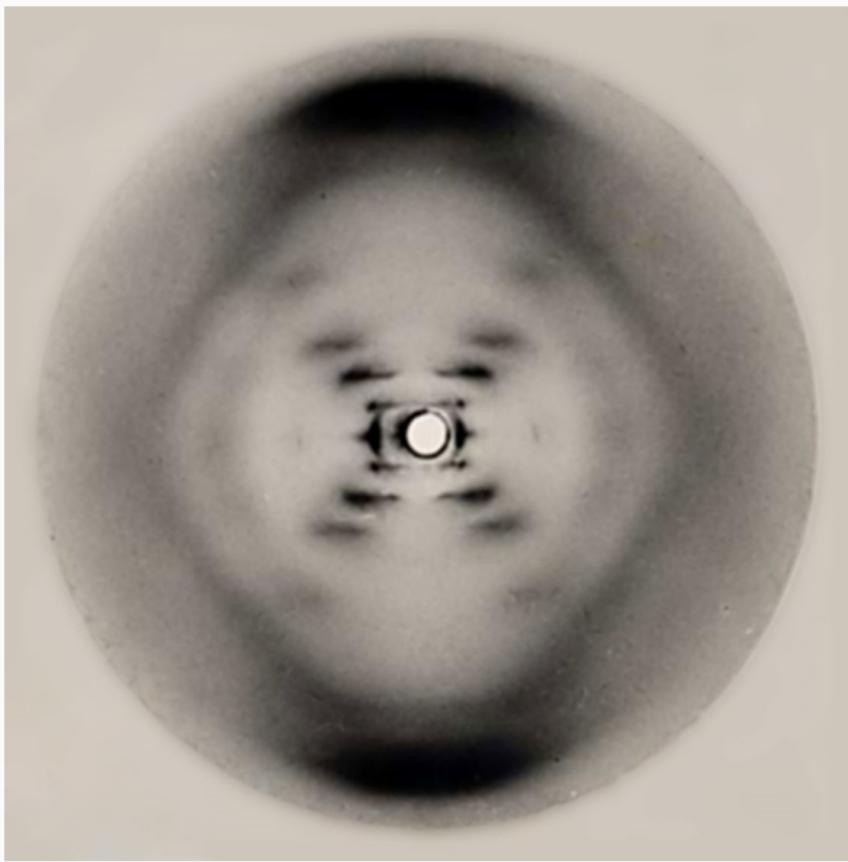


Figure 9. DNA 晶体的 X-射线衍射照片



(a) Rosalind Franklin



(b) Maurice Wilkins

Figure 10. 研究 DNA 晶体的科学家

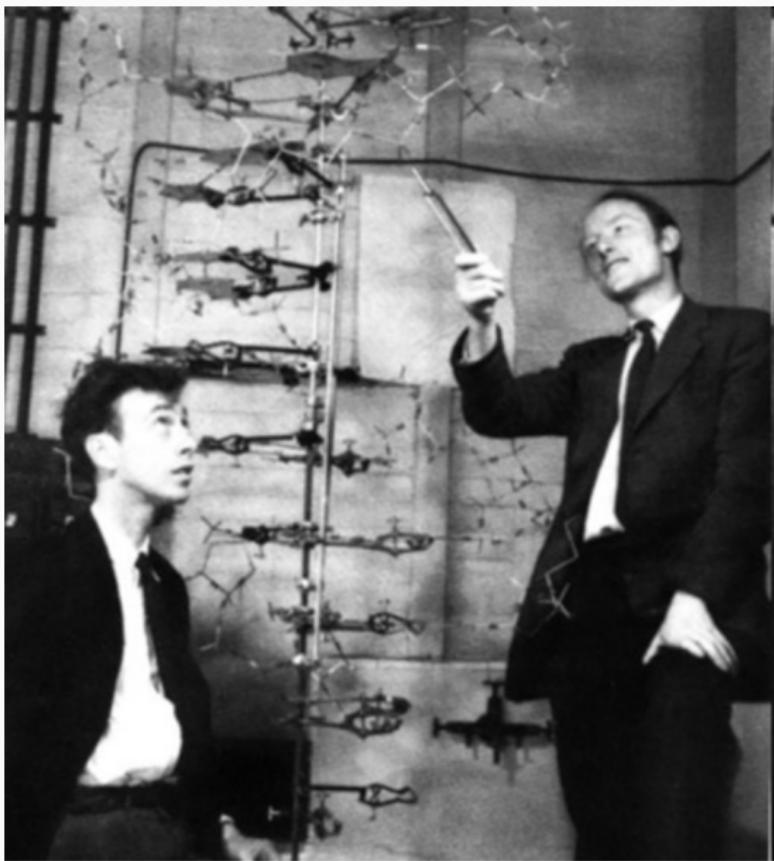


Figure 11. Watson 和 Crick

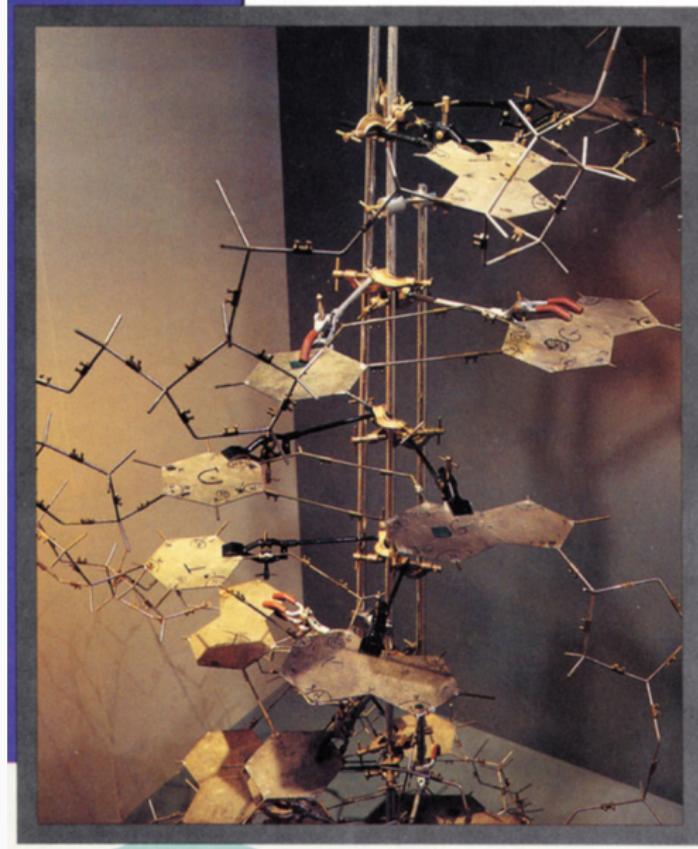


Figure 12. Model of DNA built by James Watson and Francis Crick at Cambridge University

› 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

NPG Subject areas

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- Evolution & Ecology
- Genetics
- 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)

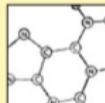


Figure 13. <http://www.nature.com/nature/dna50/archive.html>

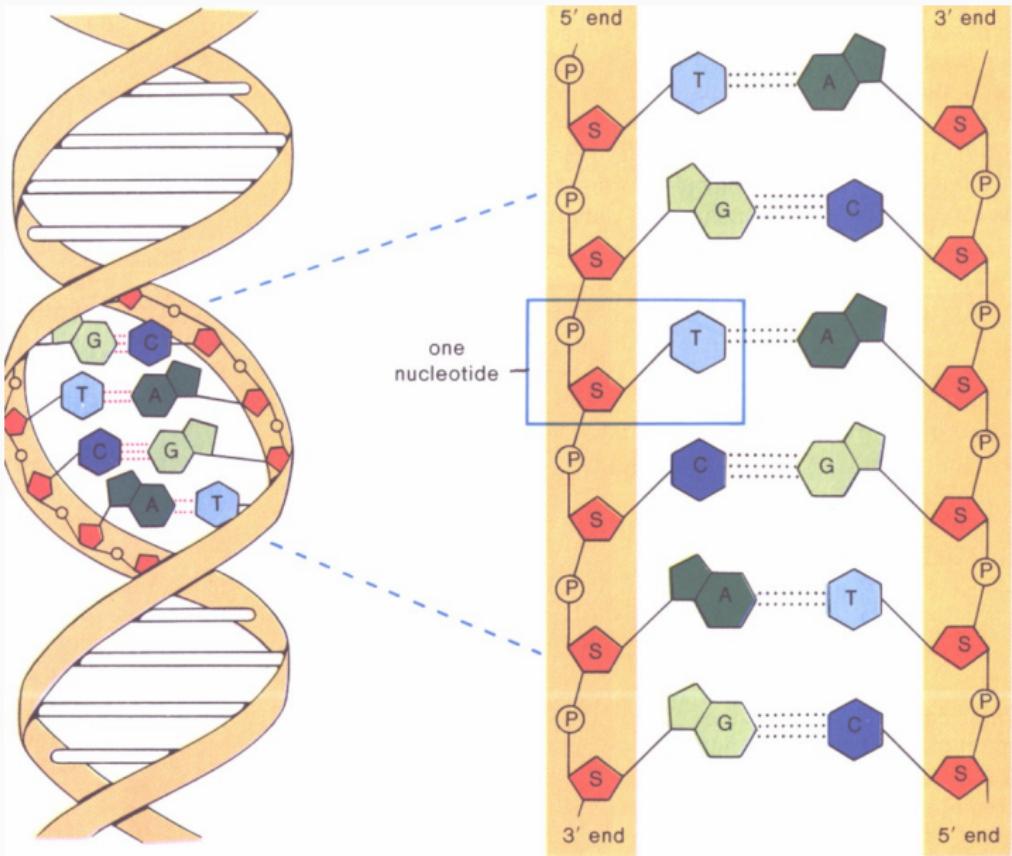


Figure 14. DNA 双螺旋结构

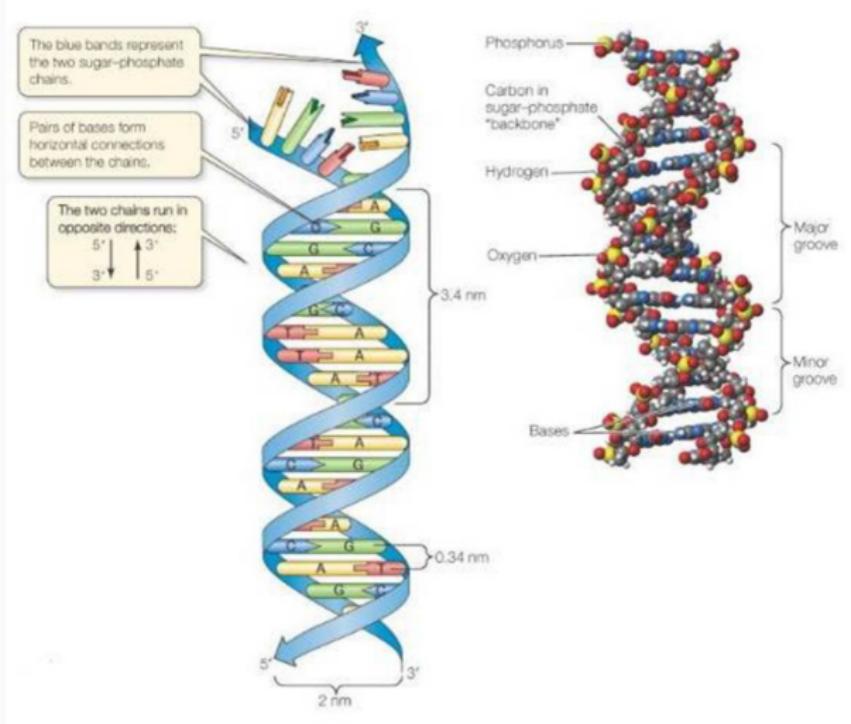


Figure 15. DNA 双螺旋结构

DNA 复制依赖于碱基配对

A 与 T, G 与 C 配对.

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.

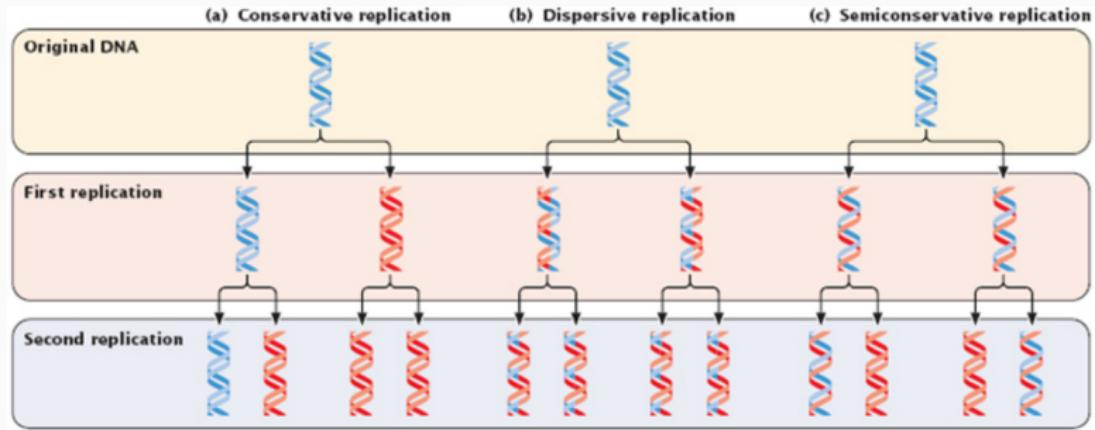


Figure 16. Three alternate schemes of replication

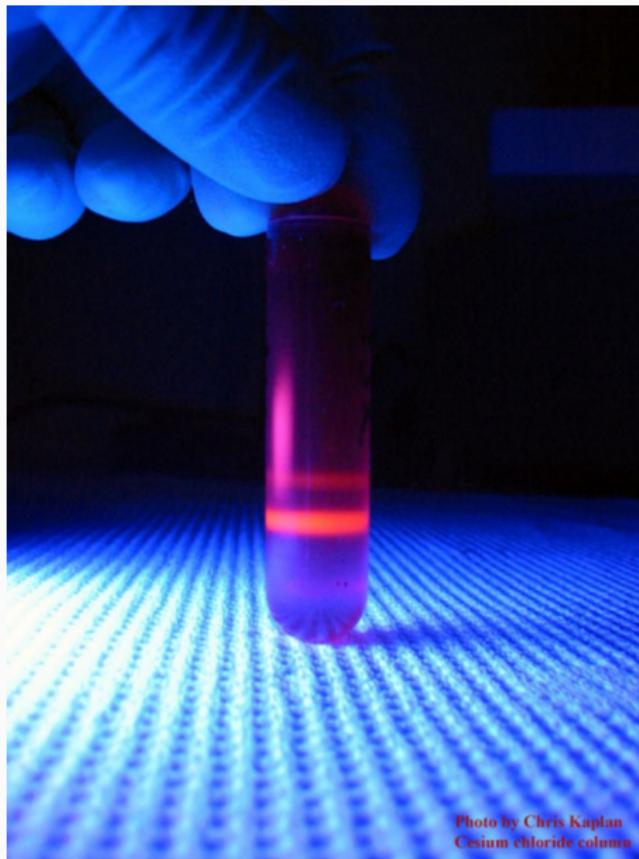


Photo by Chris Kaplan
Cesium chloride column

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*?

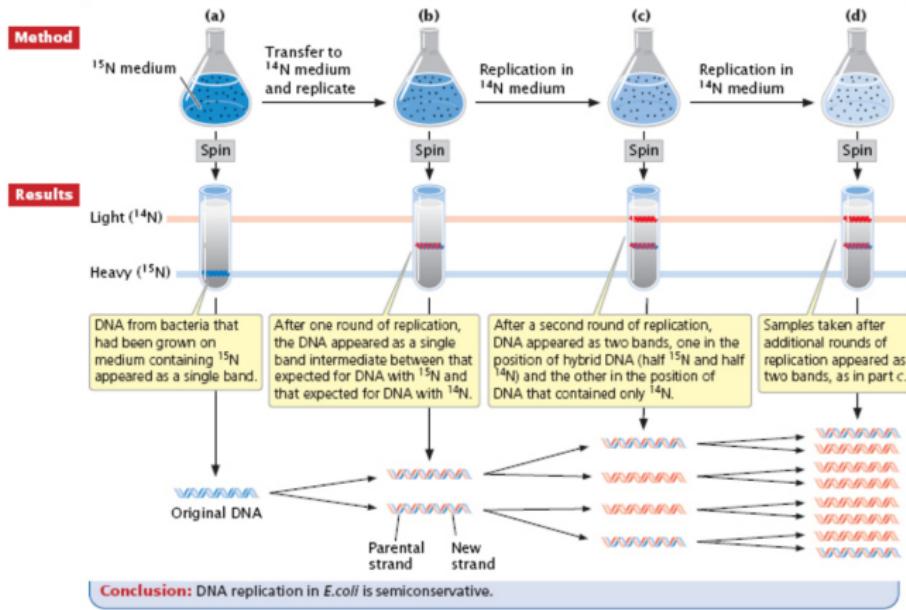


Figure 18. 大肠杆菌中的 DNA 复制¹

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

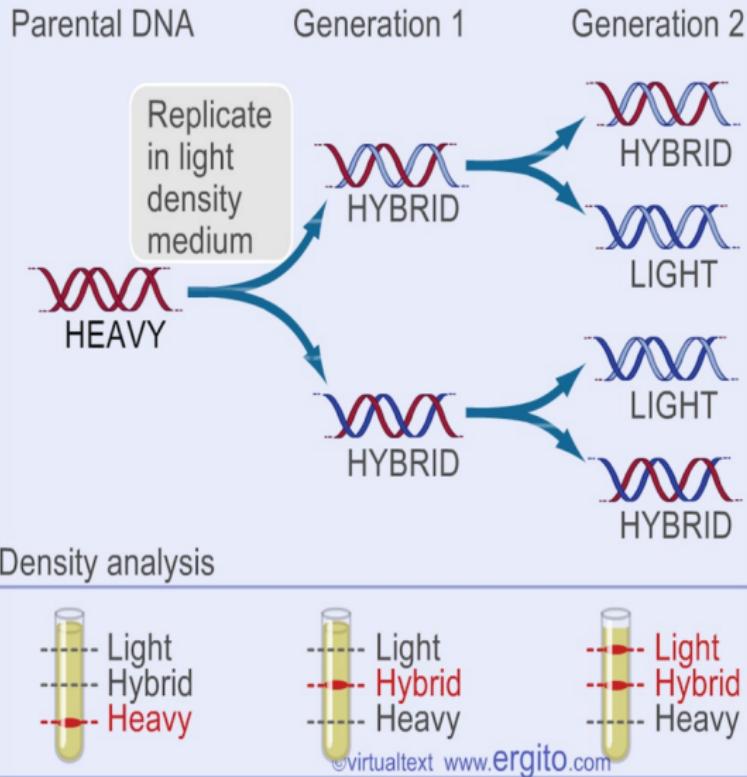


Figure 19. DNA 单链是保留的单元

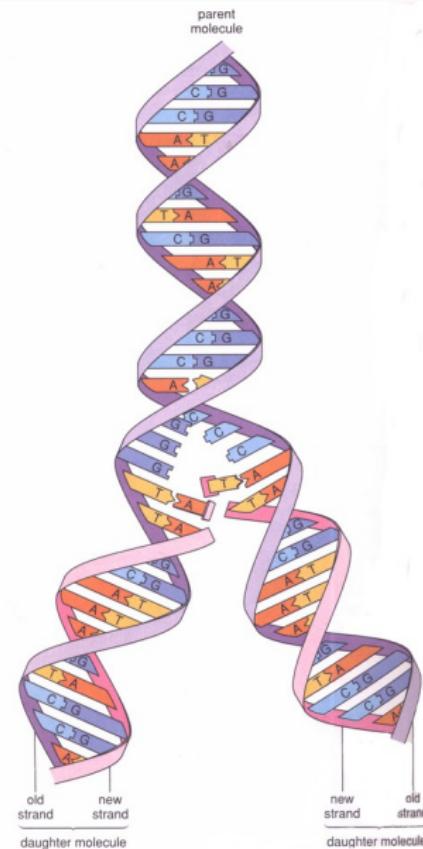


Figure 20. DNA 半保留复制

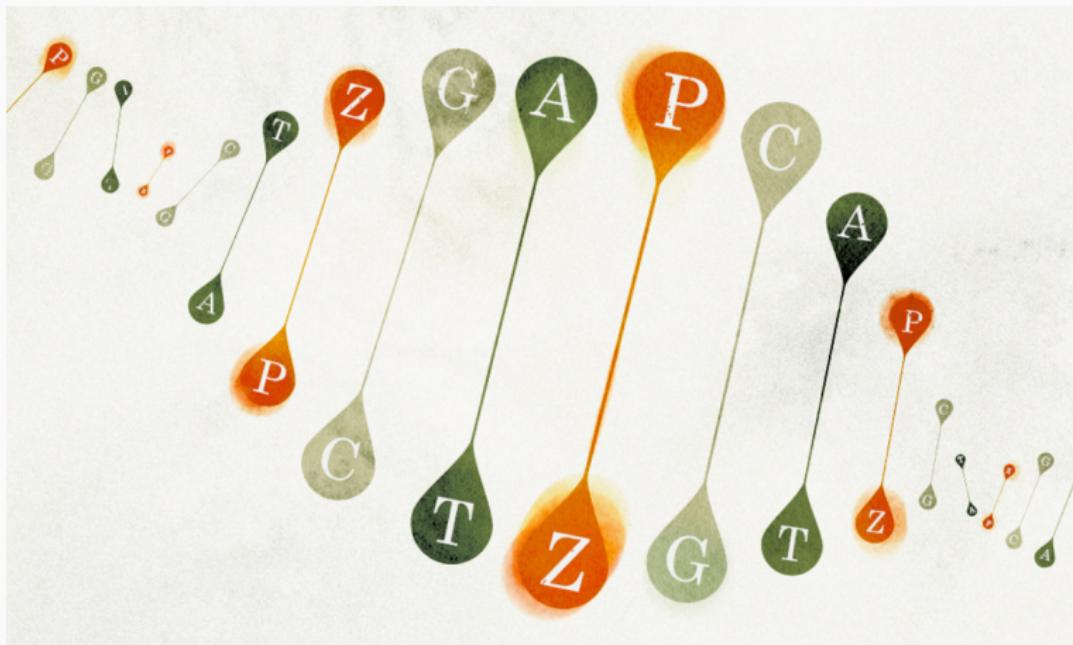


Figure 21. 合成的核苷酸 P 和 Z

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.

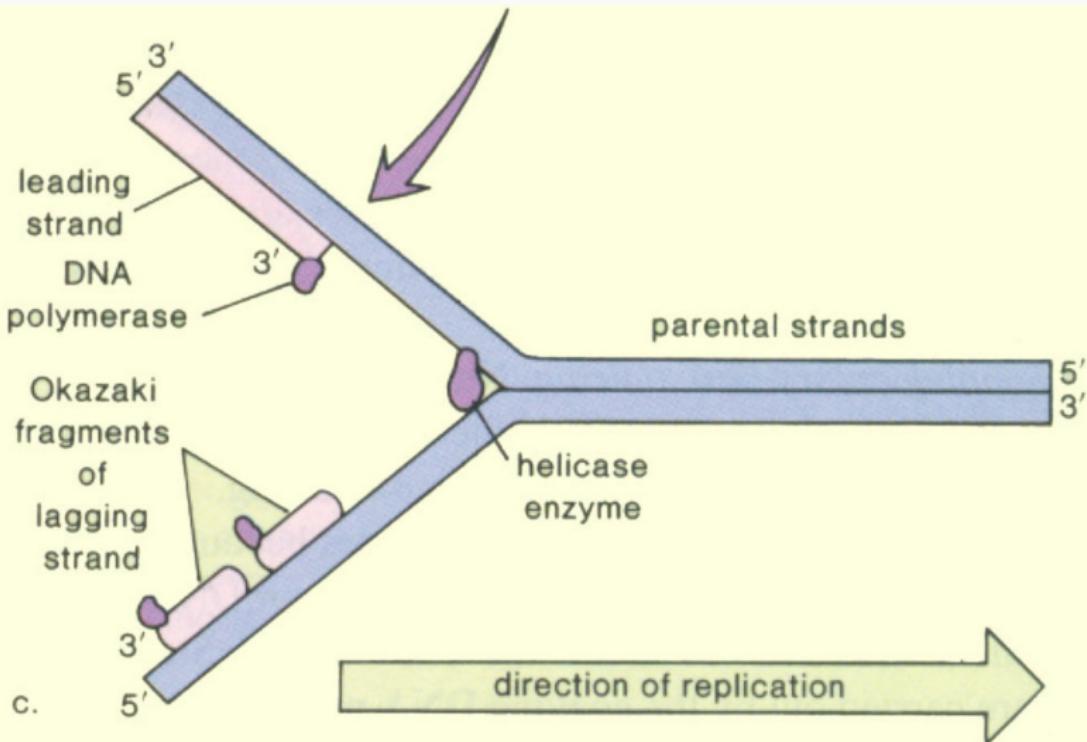


Figure 22. 复制叉

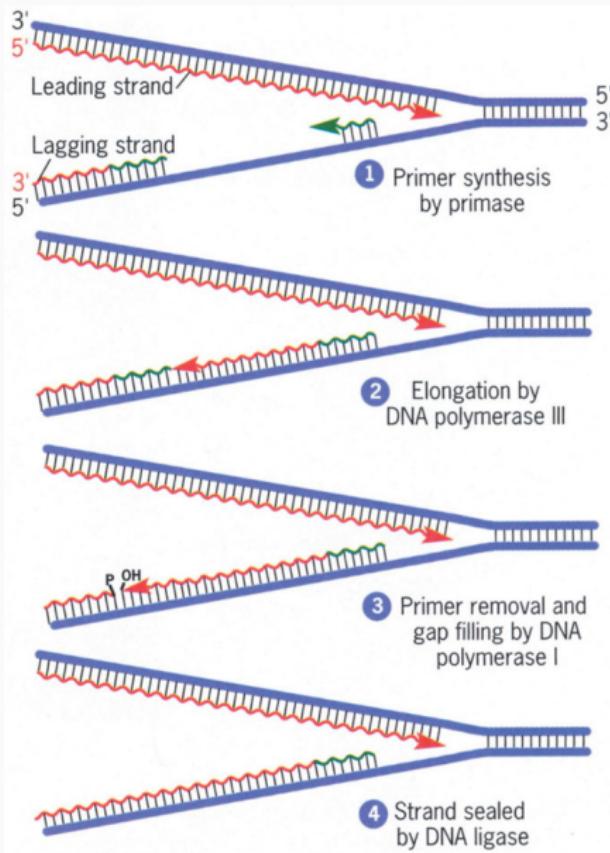


Figure 23. RNA 引物的去除

Replicon sizes can be measured by adjacent eyes

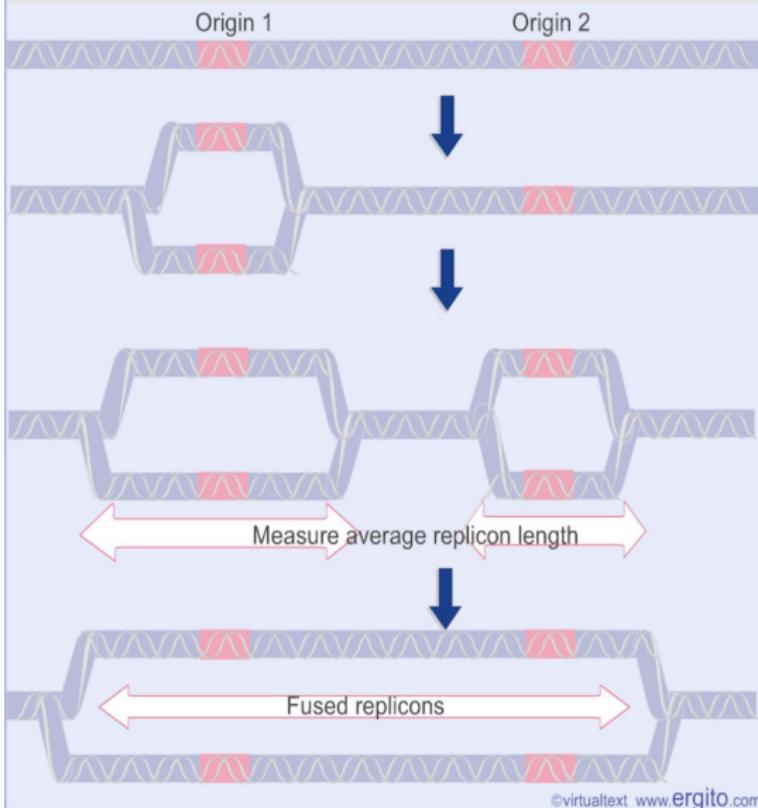


Figure 24. 真核生物的复制起始位点

7.3 基因的概念与演变

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

遗传学世纪的大事件 ii

- 1961 Genetic code is triplet
- 1977 Eukaryotic genes are interrupted
- 1977 DNA can be sequenced
- 1995 Bacterial genomes sequenced
- 2001 Human genome sequenced
- 蛋白质是表型特征的分子基础
- DNA 与蛋白质的合成
- 遗传信息在细胞质中被翻译
- 中心法则

7.4 基因组

基因组及基因组学

基因组 一个生物个体中, DNA 分子所携带的遗传信息总和.

- genome
- 核基因组
- 叶绿体基因组
- 线粒体基因组
- 病毒基因组
- 人的基因组 (22+X+Y)

基因组学 研究生物体的基因和基因组的结构, 组成和功能.

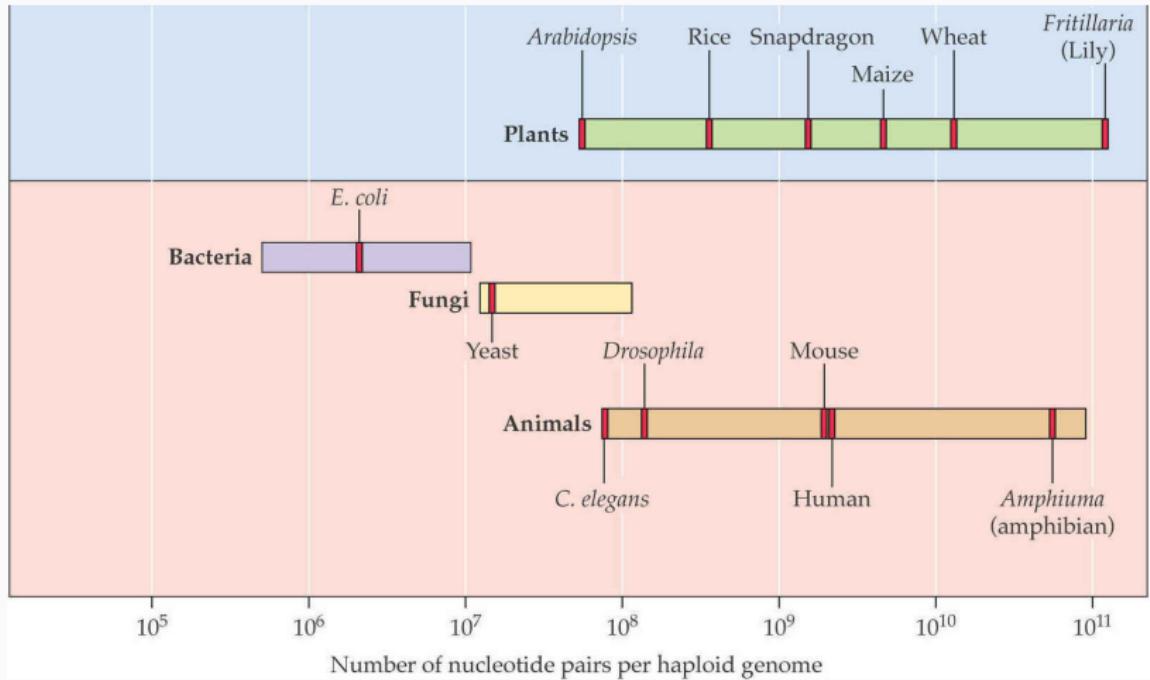


Figure 25. 不同生物基因组碱基对数目比较

人类基因组计划

- 1985 年, 美国能源部正式提出人类基因组测序.
 - 1990 年, 正式启动人类基因组测序.
-
1. 绘制人类基因组连锁图
 2. 绘制物理图
 3. 人类基因组测序
 4. 其他物种基因组分析



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Figure 26. “绘制”

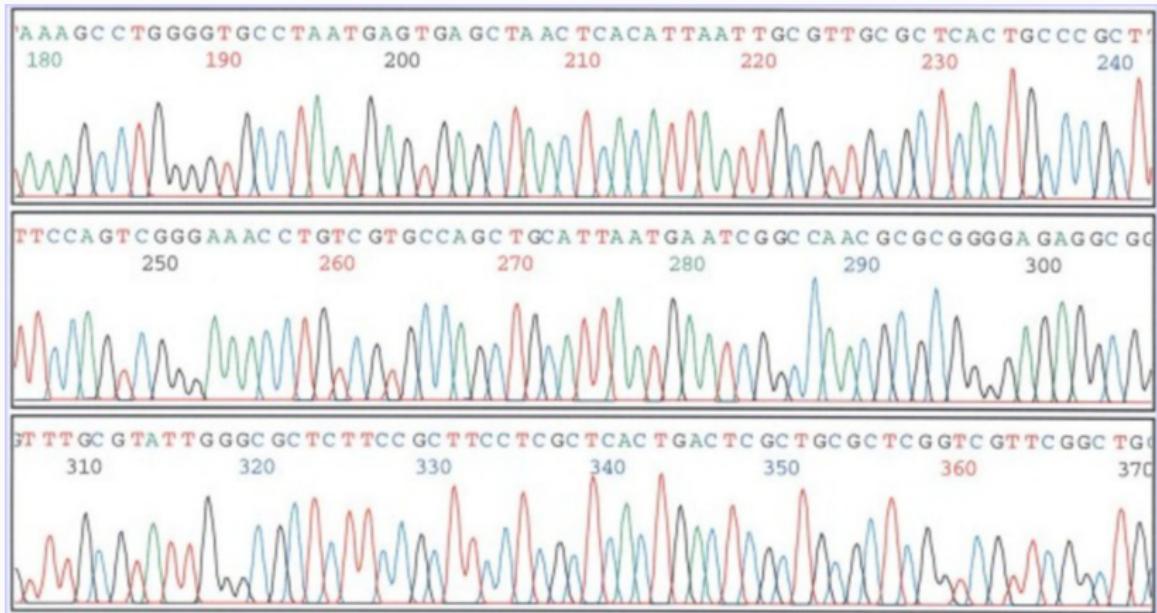


Figure 27. Electropherogram

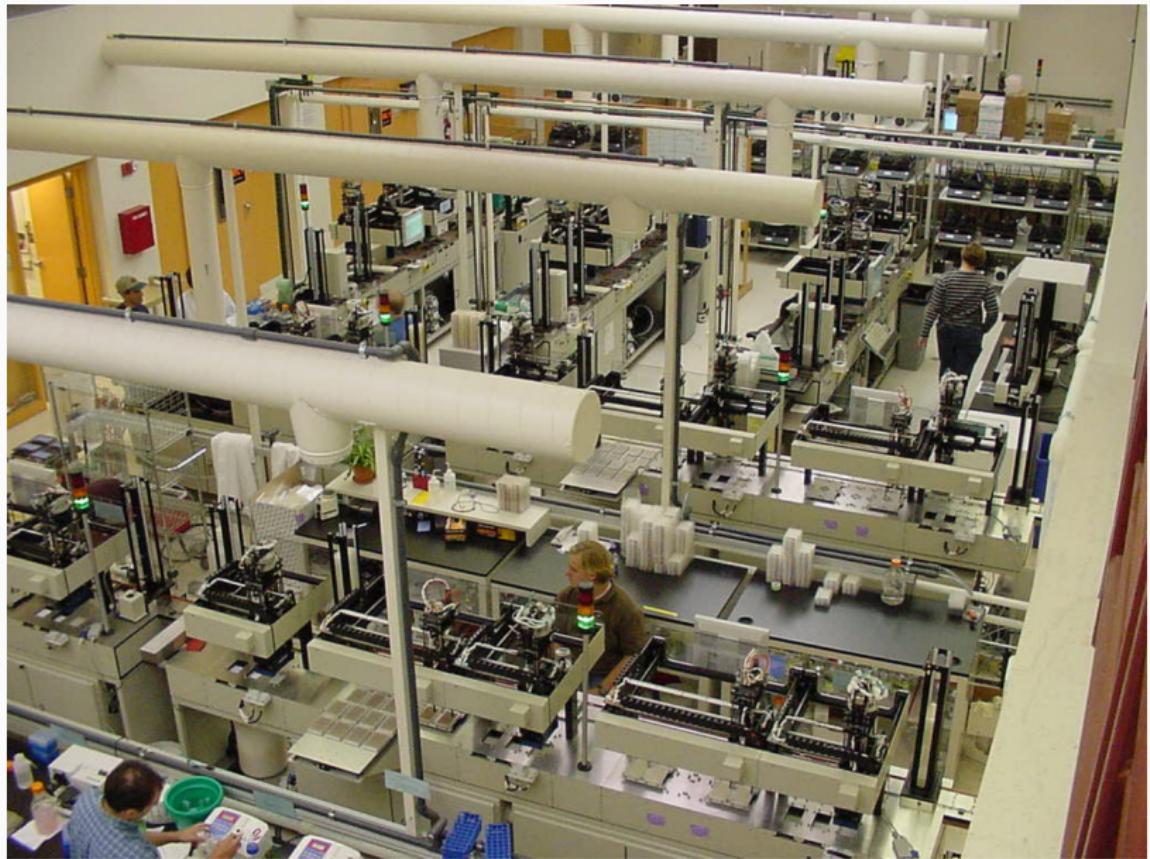


Figure 28. 模板与测序室

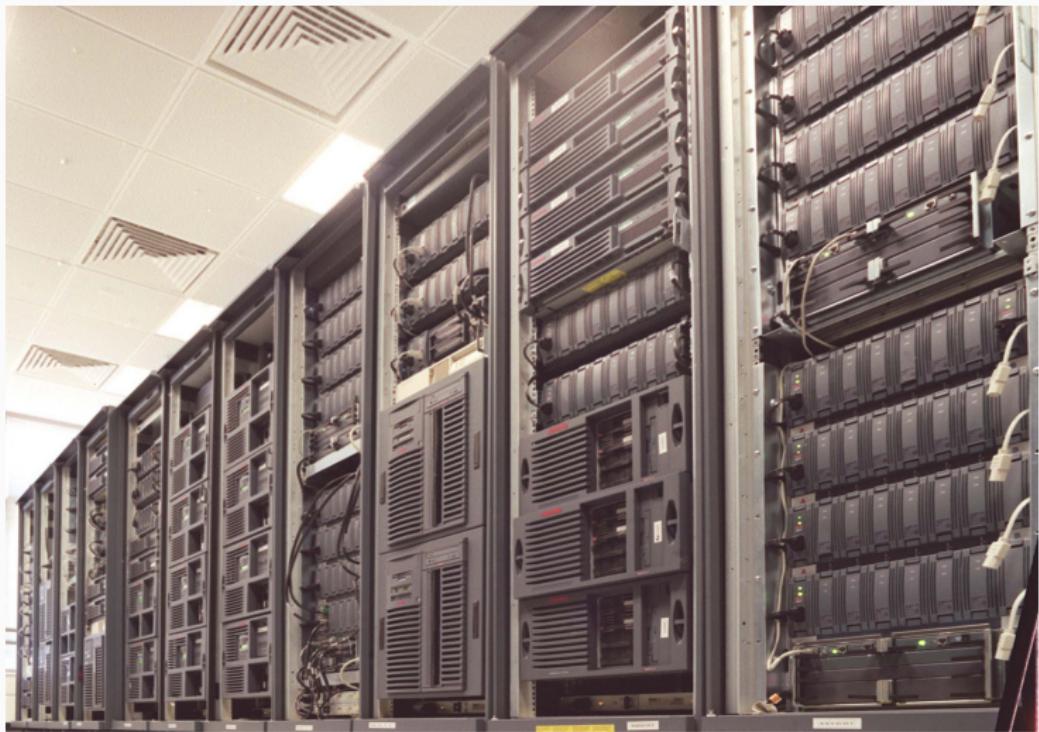


Figure 29. Clusters, Storages

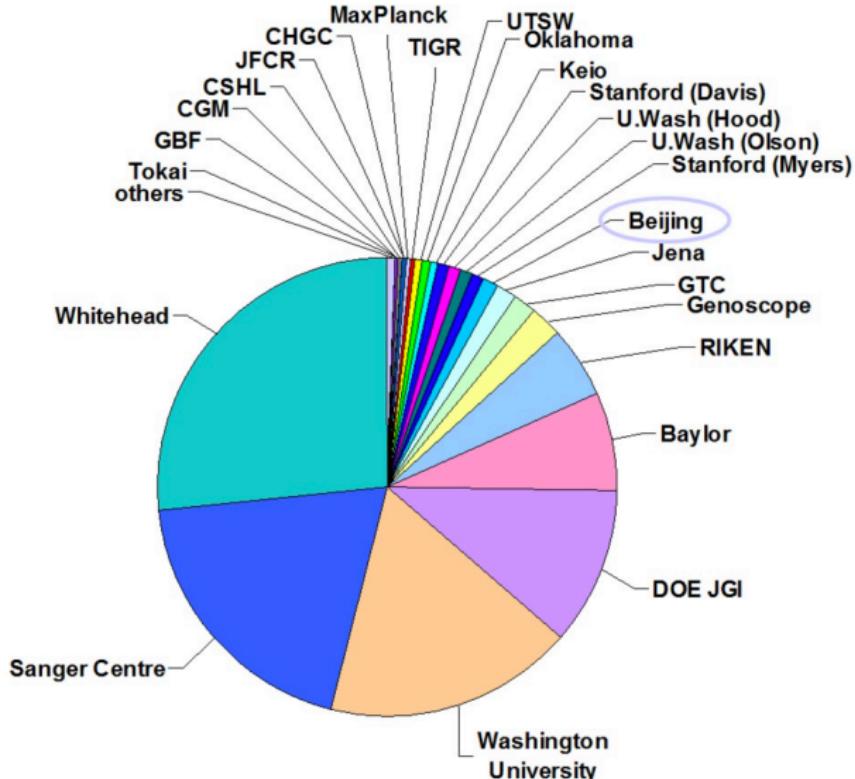


Figure 30. 贡献

基因专利

- Myriad genetics 公司拥有 *BRCA1* 和 *BRCA2* 基因的国际专利, 乳腺癌与卵巢癌的相关基因.
- Myriad 的测试费为 \$869.
- 现在有更便宜的方法, 只要 \$100, 但都侵犯了 Myriad 的专利.

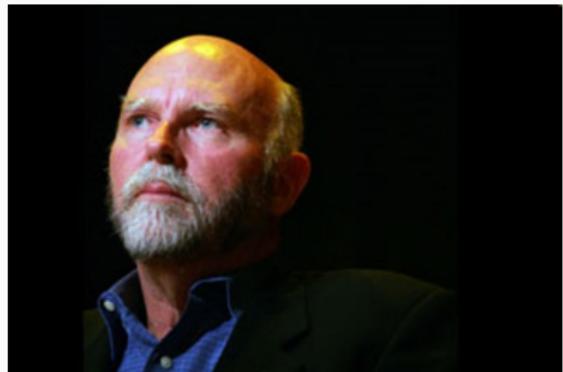


Figure 31. 文特尔, J. Craig Venter

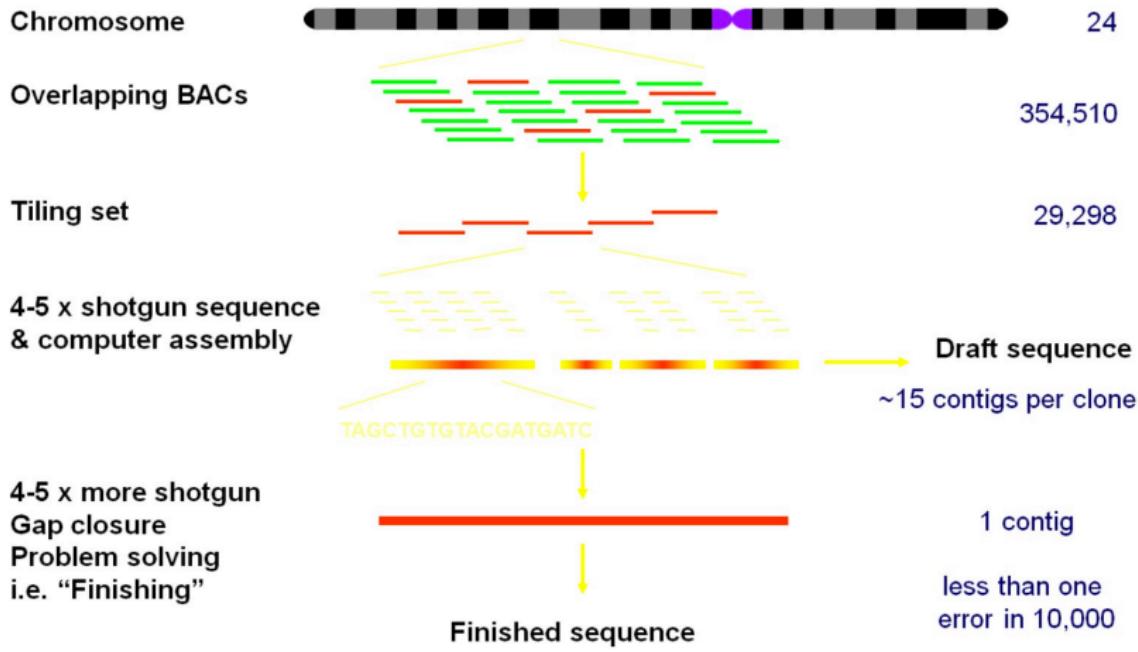
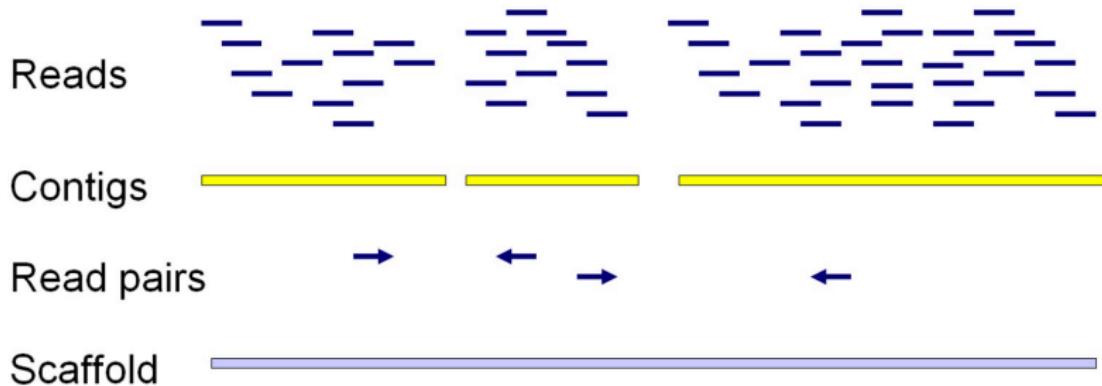


Figure 32. HGP sequencing strategy



Then order scaffolds on the chromosomes
using the HGP clone map and other
publicly available maps

Figure 33. Celera assembly strategy

Celera Corporation (CRA)

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2006

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2010

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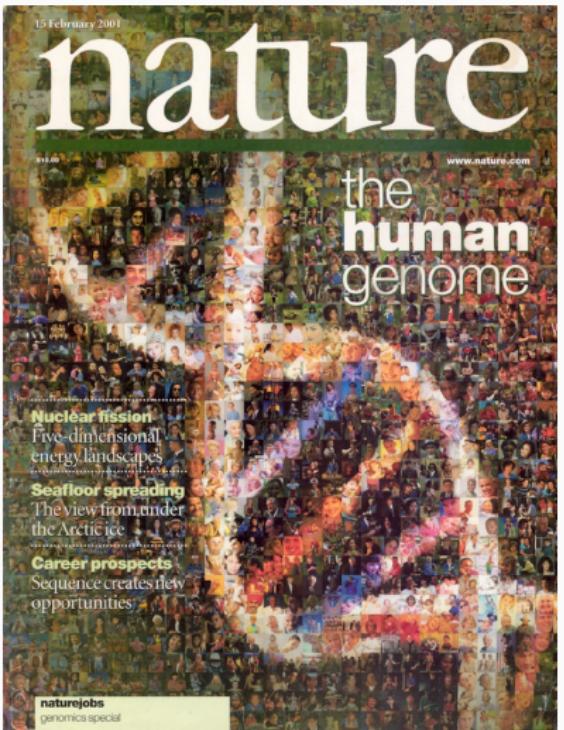
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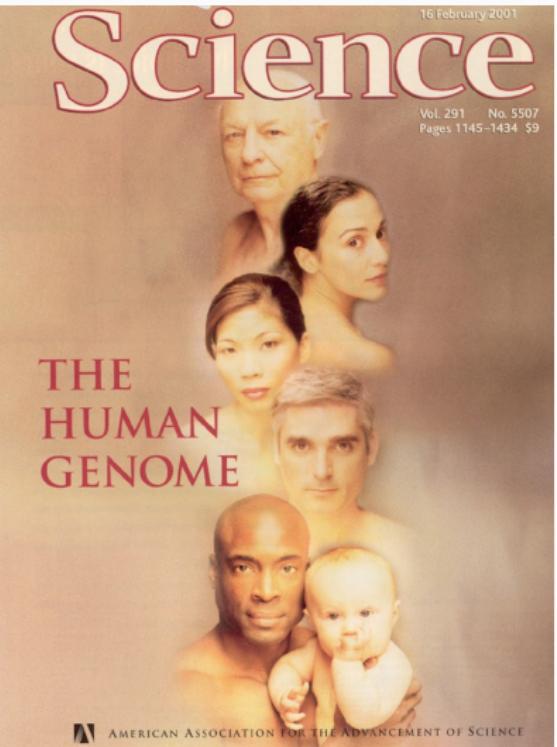
Figure 34. Celera stock

基因组草图, 2001

- International Human Genome Sequencing Consortium
 - ▶ 公共项目
 - ▶ Lander, E. S. et al. **Initial Sequencing and Analysis of the Human Genome.** *Nature* 409, 860–921 (2001)
- Celera Genomics, Venter JC et al.
 - ▶ 私有项目
 - ▶ Venter, J. C. et al. **The Sequence of the Human Genome.** *Science* 291, 1304–1351 (2001)



(a) Nature



(b) Science

Figure 35. 基因组草图, 2001

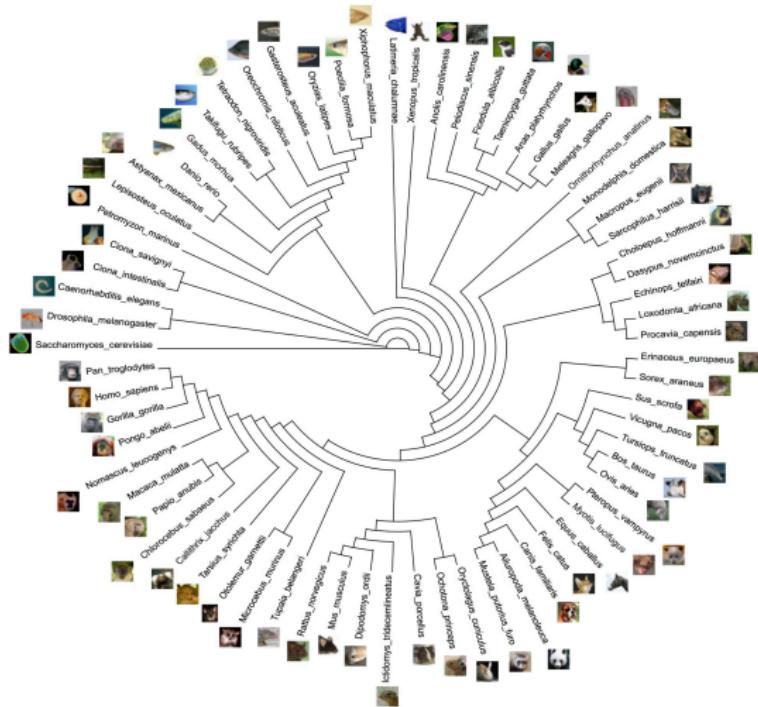
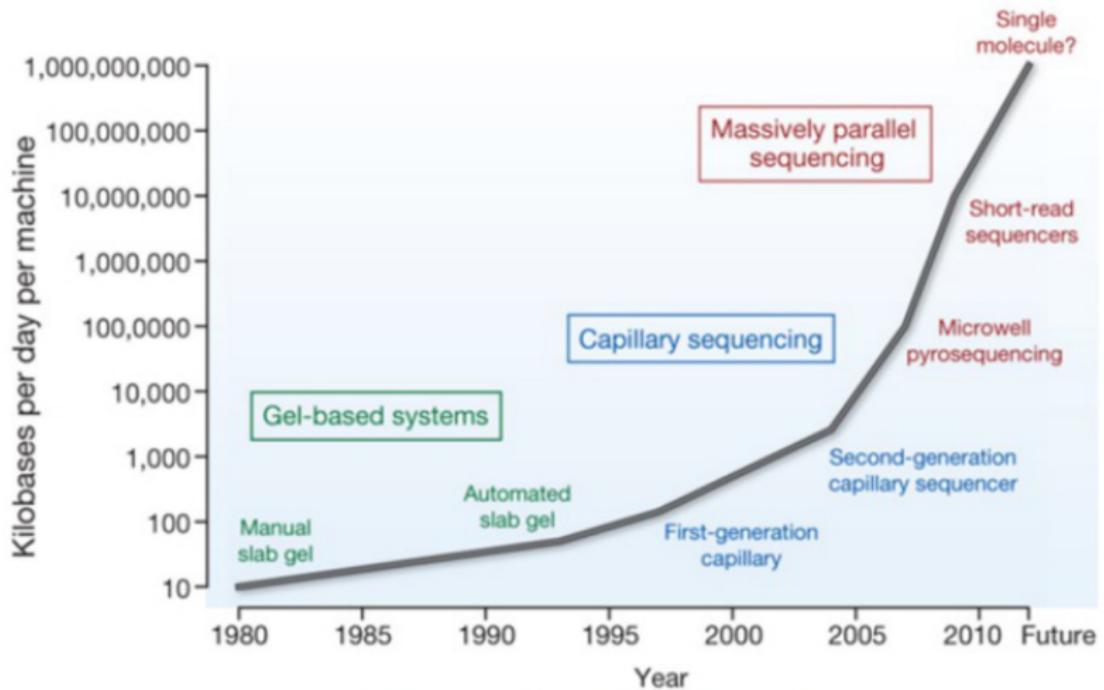


Figure 36. 全基因组测序的生物

基因组研究成果

- 3.2×10^9 bp
- 约 2 万个基因

测序已完成; 进一步的工作是确定各个基因的功能及他们之间的相互关系.



MR Stratton *et al.* *Nature* **458**, 719-724 (2009)

Figure 37. 测序能力的增长



NEW HiSeq 2500

Remarkable speed
and flexibility.

MiSeq

Simplicity, integration,
and ease-of-use.

Illumina announces
speed and
performance
enhancements.

Introducing the HiSeq 2500 and Triple the
Output on MiSeq.

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Figure 38. Illumina

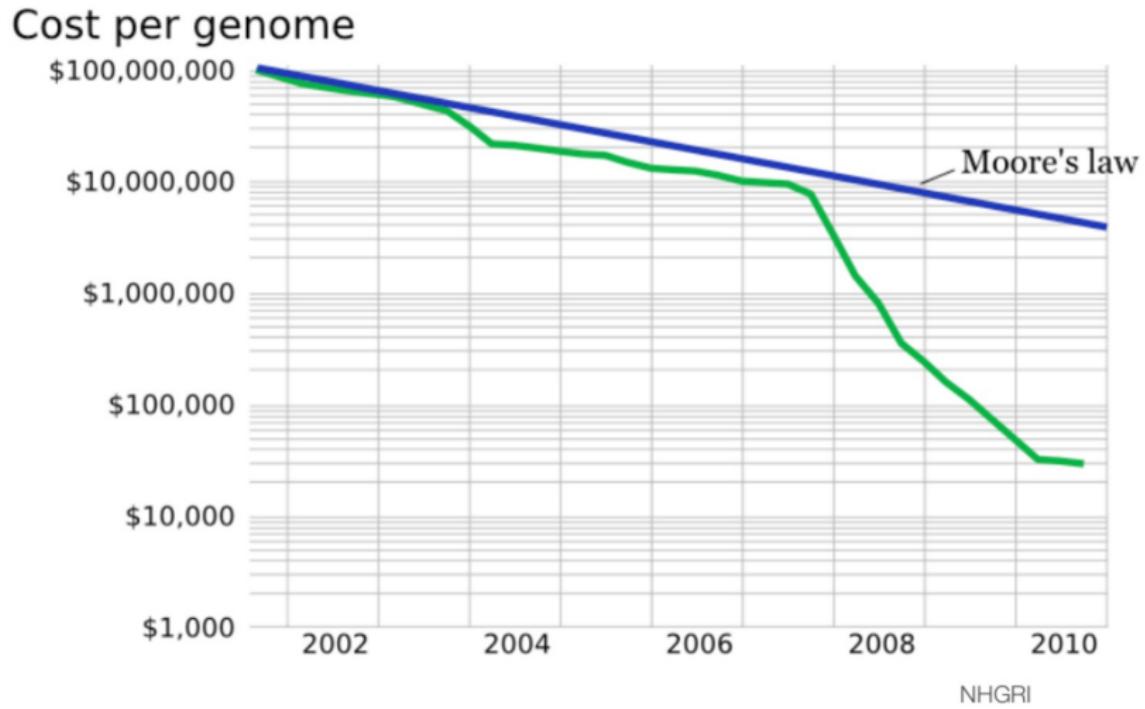
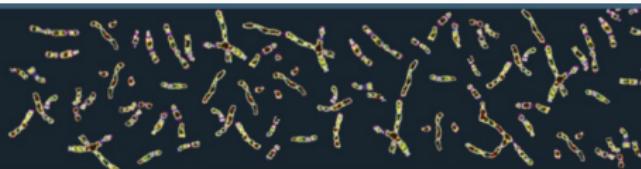


Figure 39. 比摩尔定律更快



1000 Genomes

A Deep Catalog of Human Genetic Variation

Home About Participants Data Contact Wiki

1000 GENOMES PROJECT DATA RELEASE

SNP data downloads and genome browser representing four high coverage individuals

The first set of SNP calls representing the preliminary analysis of four genome sequences are now available to download through the [EBI FTP site](#) and the [NCBI FTP site](#). The README file dealing with the FTP structure will help you find the data you are looking for.

The data can also be viewed directly through the 1000 Genomes browser at <http://browser.1000genomes.org>. Launch the browser and [view a sample region here](#).

More information about the data release can be found in the [data section](#) of this web site.

Download the 1000 Genomes Browser Quick Start Guide

[Quick start \(pdf\)](#)

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PRESS RELEASE

WEDNESDAY JUN. 11, 2008
Three Sequencing Companies Join 1000 Genomes Project

TUESDAY JAN. 22, 2008
International Consortium Announces the 1000 Genomes Project

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Figure 40. 千个基因组计划

Personal Genomes

- Craig Venter
- James Watson
- Stephen Quake
- George Church
- Marjolein Kriek
- Hermann Hauser
- Han Chinese
- Seong-Jin Kim
- Korean AK1
- Yoruban African
NA18507
- 14 others sequenced by Complete Genomics
- Unknown number sequenced by Knome
- 6 genomes sequenced at high depth by the 1000 Genomes Project
- 180 genomes sequenced at low coverage by the 1000 Genomes Project
- Two acute myeloid leukemia patients



(a) 脊椎动物



(b) 英国人健康计划

1001 Genomes
A Catalog of *Arabidopsis thaliana* Genetic Variation



(c) 拟南芥

Figure 41. 其它计划

What's in the NCBI FTP site?

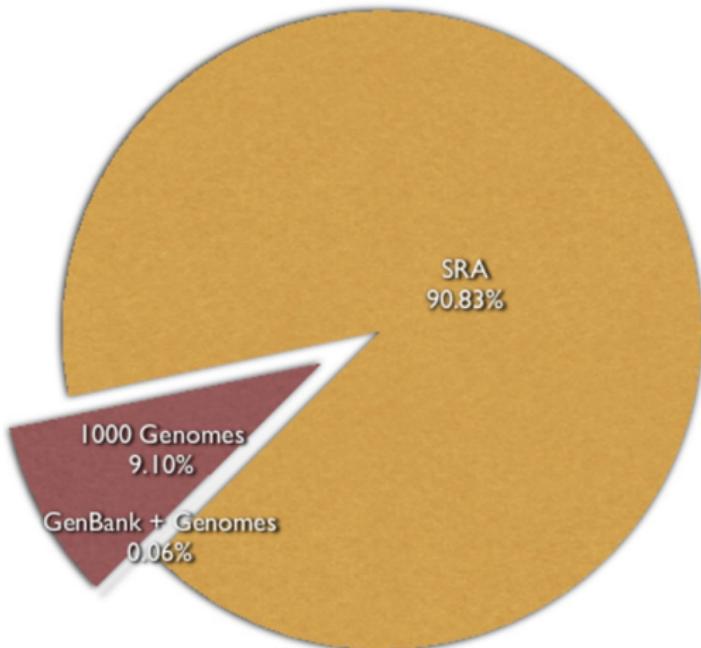


Figure 42. 爆发性增长的数据量

ORIGINAL ARTICLE

Whole-Genome Sequencing in a Patient with Charcot–Marie–Tooth Neuropathy

James R. Lupski, M.D., Ph.D., Jeffrey G. Reid, Ph.D., Claudia Gonzaga-Jauregui, B.S.,
David Rio Deiros, B.S., David C.Y. Chen, M.Sc., Lynne Nazareth, Ph.D.,
Matthew Bainbridge, M.Sc., Huyen Dinh, B.S., Chyn Jing, M.Sc.,
David A. Wheeler, Ph.D., Amy L. McGuire, J.D., Ph.D., Feng Zhang, Ph.D.,
Pawel Stankiewicz, M.D., Ph.D., John J. Halperin, M.D., Chengyong Yang, Ph.D.,
Curtis Gehman, Ph.D., Danwei Guo, M.Sc., Rola K. Irikat, B.S., Warren Tom, B.S.,
Nick J. Fantin, B.S., Donna M. Muzny, M.Sc., and Richard A. Gibbs, Ph.D.

Figure 43. 追踪罕见遗传疾病的致病基因²

² Lupski, J. R. et al. Whole-Genome Sequencing in a Patient with Charcot–Marie–Tooth Neuropathy. *N Engl J Med* 362, 1181–1191 (2010)

人类基因组各组成成分的基本特征

1. 基因
 - ▶ 断裂基因
2. 基因外 DNA
 - ▶ 单拷贝序列和低拷贝数序列占 70–80%
 - ▶ 中度和高度重复序列占 20–30%
3. 分散重复序列
4. 簇状重复序列

7.5 非孟德尔式遗传

高等植物的细胞质遗传

- 细胞质中的遗传物质控制的遗传, 质体和线粒体.
- 非孟德尔式.
- 母本贡献遗传物质, 而且是随机分配给子细胞.
- F1 通常只表现母本的性状, 后代一般不出现一定比例的分离.

Table 1. 紫茉莉绿白斑植株的细胞质遗传

母本枝条的类型	父本枝条的类型	子代的类型
白	白	白
绿	白	绿
绿白斑	白	绿, 白或绿白斑
白	绿	白
绿	绿	绿
绿白斑	绿	绿, 白或绿白斑
白	绿白斑	白
绿	绿白斑	绿
绿白斑	绿白斑	绿, 白或绿白斑