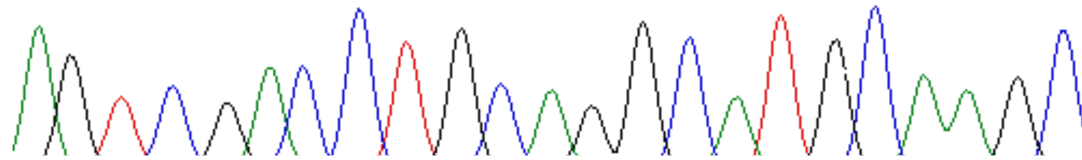


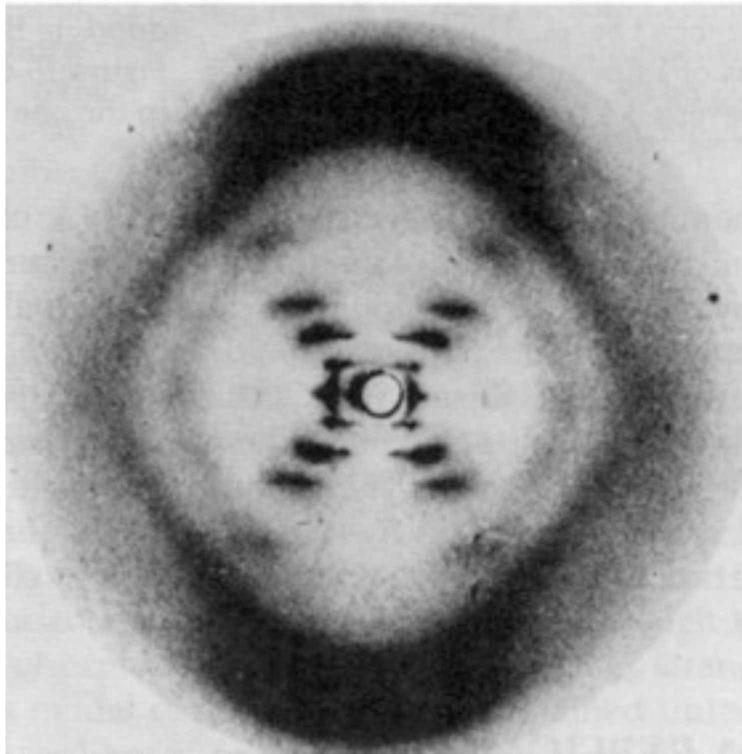
Genomics

Dr Mick Jones

MRC CSC Genomics Laboratory

Hammersmith Hospital Campus

Imperial College London



X-ray Diffraction pattern of DNA

Francis Crick

James Watson

Maurice Wilkins

Rosalind Franklin

April 25, 1953 NATURE

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

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

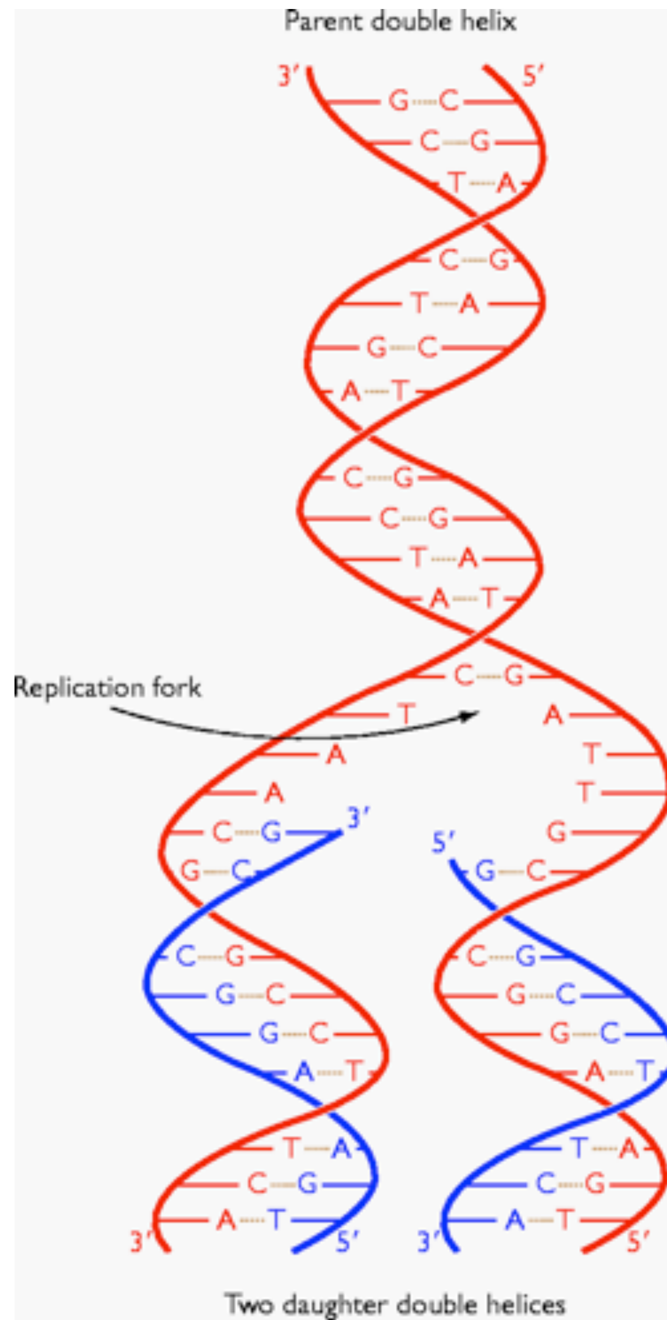
A Structure for Deoxyribose Nucleic Acid

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.

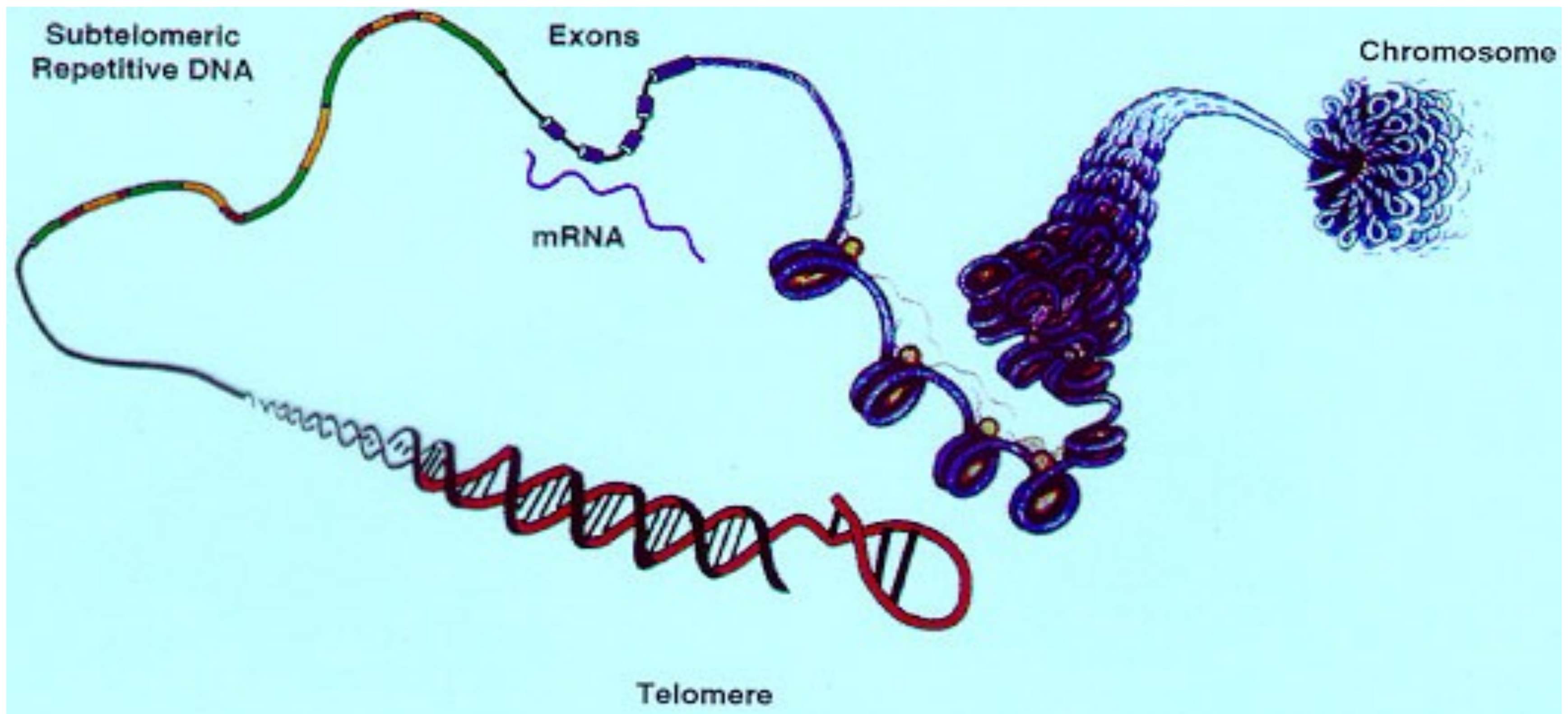
It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

J. D. WATSON
F. H. C. CRICK

Medical Research Council Unit for the Study of the Molecular Structure of Biological Systems,
Cavendish Laboratory, Cambridge.
April 2.


Parent double helix
3′
5′
Replication fork
3′
5′
3′
5′
3′
5′
Two daughter double helices

Human Genome Project was to
Sequence the 3 billion base pairs of human
DNA and identify the ~30,000 genes

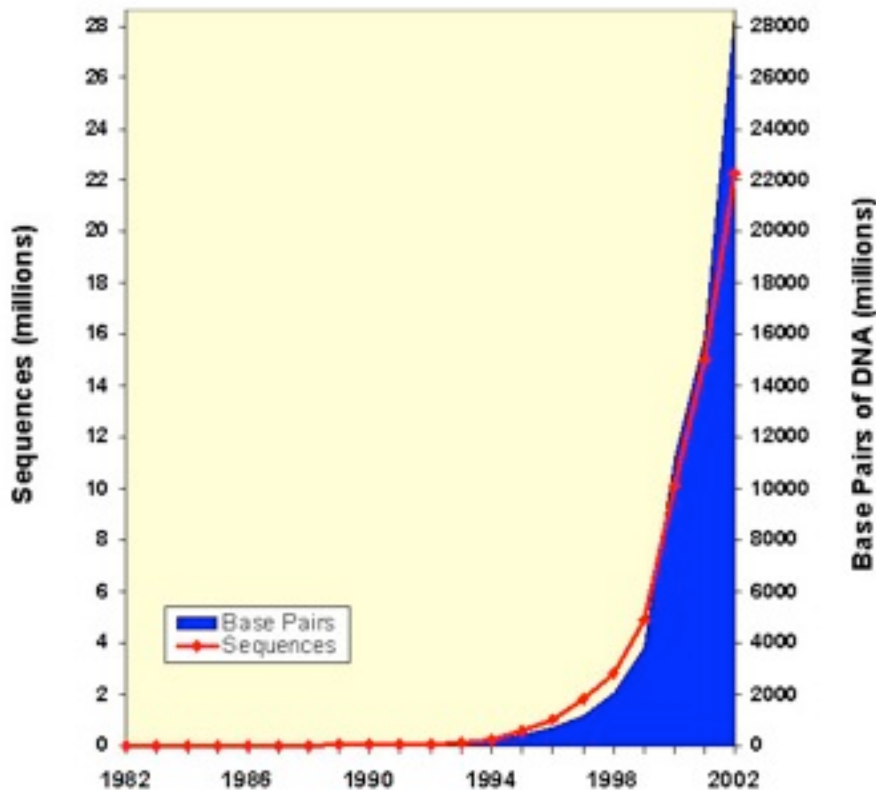


Genome Sizes

Human	3.0×10^9 base pairs
Mouse	3.0×10^9
Drosophila	1.1×10^8
Worm	1.0×10^8
Dictyostellium	3.4×10^7
Yeast	1.2×10^7
Bacteria	$1.0 - 5.0 \times 10^6$

Genome	Length of the longest contiguous sequence	Sequence Release Date	Contigs	Total length
Human chromosome 21q	**25,491,867**	**4/10/2000**	**5**	**33,827,477**
Human chromosome 22q	**23,051,000**	**12/2/1999**	**12**	**33,573,820**
Arabidopsis thaliana (Arabidopsis)-chromosome 2	**16,039,956**	**5/15/1999**	**2**	**19,647,091**
Caenorhabditis elegans - chromosome 5	**8,774,706**	**12/11/1998**	**27**	**20,818,150**
Escherichia coli	**4,639,221**	**9/5/1997**	**1**	**4,639,221**
Haemophilus influenzae Rd (strain kw20)	**1,830,138**	**7/28/1995**	**1**	**1,830,138**
***Saccharomyces cerevisiae* - chromosome 8**	**562,638**	**9/30/1994**	**1**	**562,638**
***E. coli* K-12 contig**	**338,534**	**8/22/1994**	**1**	**338,534**
***S. cerevisiae* chromosome 3**	**315,339**	**3/16/1992**	**1**	**315,339**
Human cytomegalovirus AD169	**229,354**	**12/6/1989**	**1**	**229,354**
Epstein-Barr Virus	**172,281**	**7/19/1984**	**1**	**172,281**
Bacteriophage Lambda	**48,502**	**12/25/1982**	**1**	**48,502**
Human Mitochondrion	**16,569**	**4/9/1981**	**1**	**16,569**
Bacteriophage phi X174	**5,375**	**2/24/1977**	**1**	**5,375**

Exponential Growth



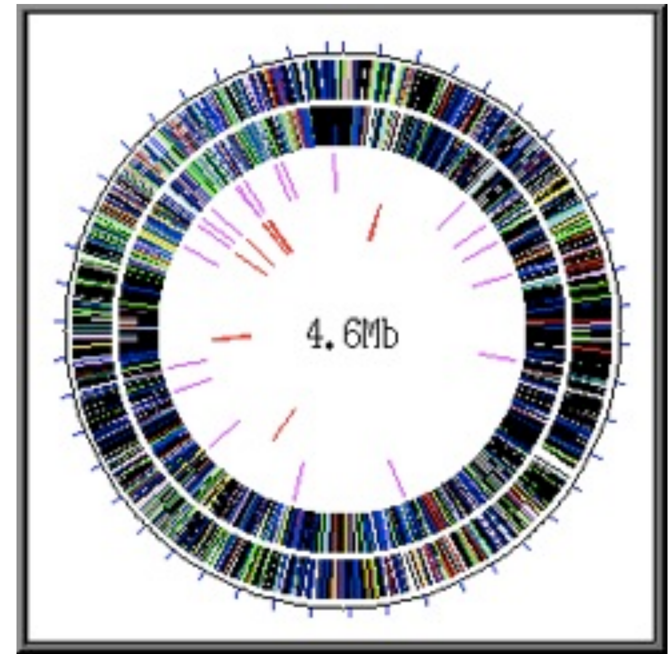
- GenBank release 149
  - February 2006
- 54.6 million entries
- 59.7 billion base pairs

Escherichia coli

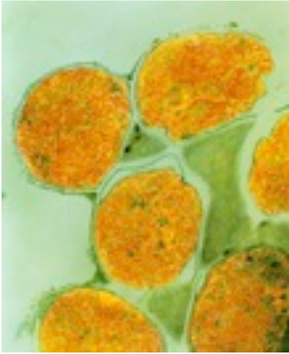
Escherichia coli K-12 genome consists of 4,639,221 base pairs
of 4,288 protein-coding genes annotated, 38% have no attributed function.

Taxonomy of *Escherichia coli K12-MG1655*

Kingdom:	Bacteria
Intermediate Rank 1:	Proteobacteria
Intermediate Rank 2:	gamma subdivision
Intermediate Rank 3:	Enterobacteriaceae
Intermediate Rank 5:	Escherichia coli
Genus:	Escherichia
Species:	coli
Strain:	K12-MG1655



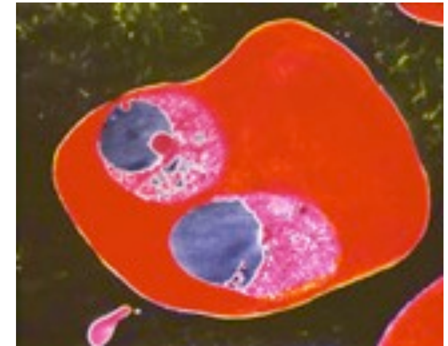
Mycobacterium leprae

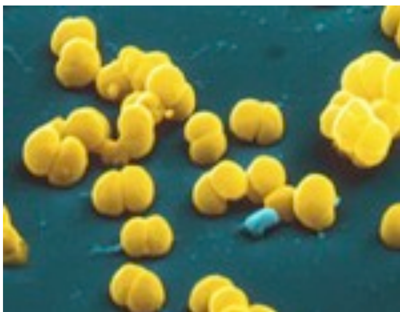


Examination of the genome sequence of the leprosy bacillus *Mycobacterium leprae* provides explanations for some of *M. leprae* 's most intriguing properties. The pathogen has the longest doubling time of all known bacteria and cannot be grown in culture, both probably a reflection of an extreme case of reductive evolution. Less than half of the genome contains functional genes, but there are many pseudogenes with functional counterparts in *Mycobacterium tuberculosis*.

Plasmodium falciparum

Malaria, the disease caused by the protozoan parasite *Plasmodium falciparum* and spread by mosquito vectors, affects around 400 million people, and kills over a million people each year. Efforts to eradicate malaria have been seriously hampered by the lack of an effective vaccine and the spread of resistance to prophylactic therapies.

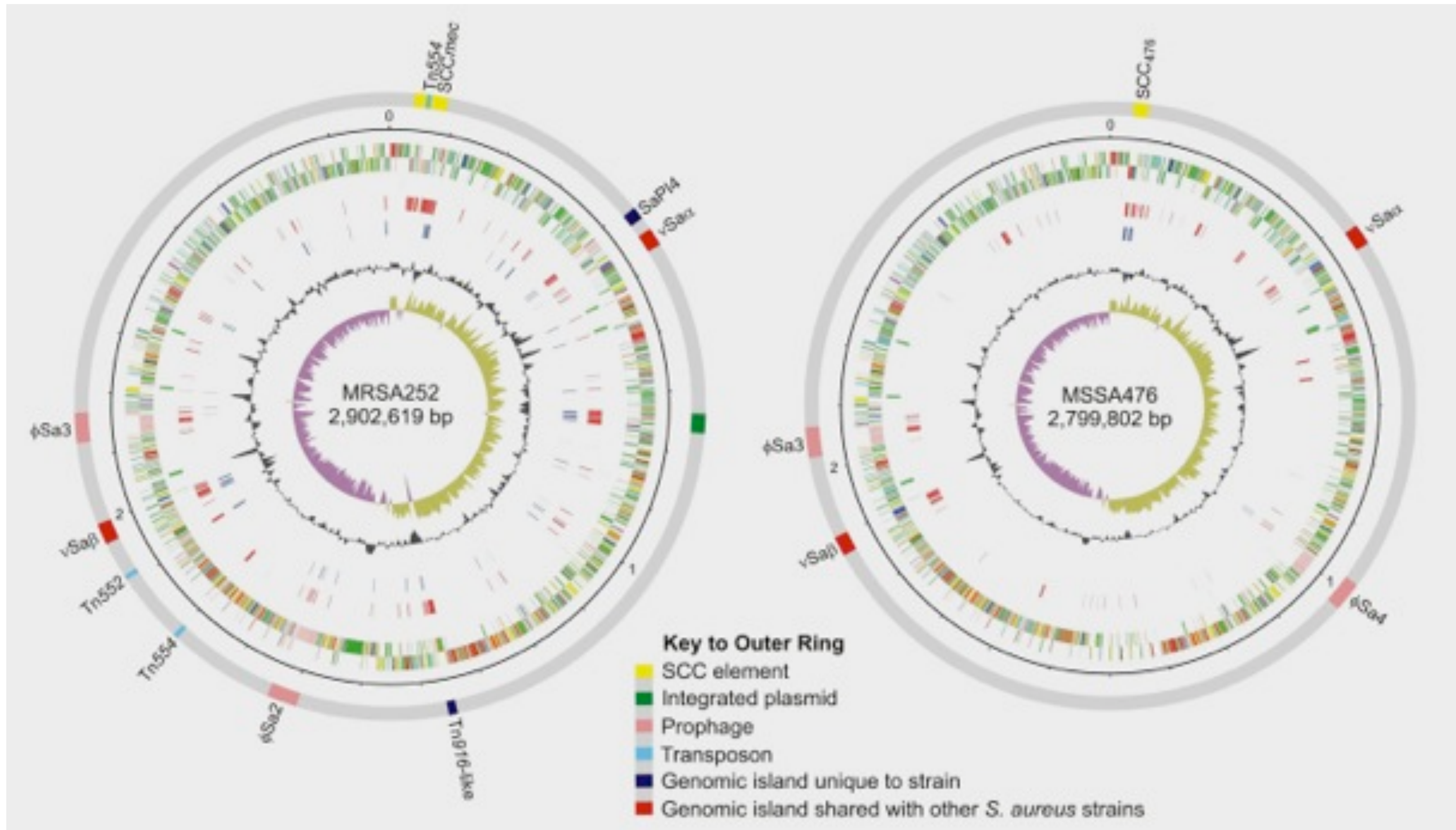




Neisseria meningitidis

infects half a million people each year, and is associated with major epidemics of meningitis in developing countries. The bacteria can change their surface coat and thereby evade detection by the body's natural defences.

Staphylococcus aureus



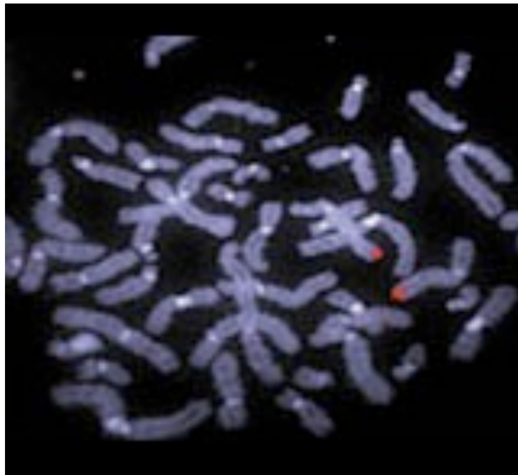
S. aureus is a Gram +ve pathogen that causes a wide range of diseases, and is becoming increasingly resistant to antibiotics. The two strains sequenced are a recent U.K. hospital-acquired methicillin-resistant S. aureus (MRSA) strain, representative of the epidemic strain EMRSA-16 (MRSA252), and a hyper-virulent community acquired methicillin-sensitive S. aureus (MSSA) strain (MSSA476).

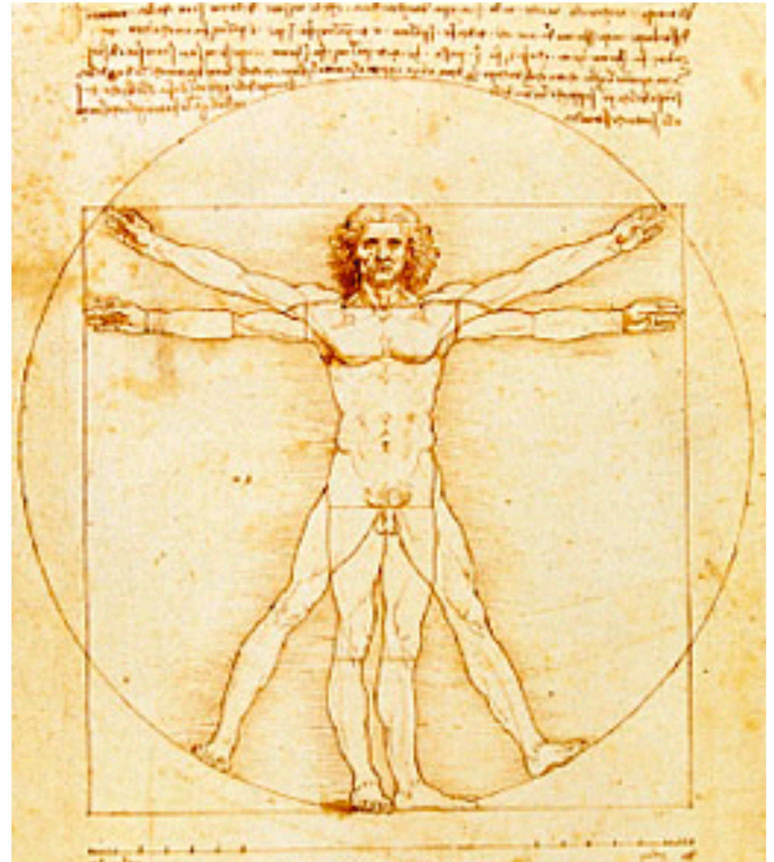
The Fruit Fly - *Drosophila melanogaster*

- The fruit fly is one of the most intensively studied organisms
- Serves as a model system for developmental and cellular processes common to higher eukaryotes, including humans.
- Nucleotide sequence of ~120-megabase euchromatin used a whole-genome shotgun sequencing strategy.
- Genome encodes ~13,600 genes, somewhat fewer than the smaller *Caenorhabditis elegans* genome, but with comparable functional diversity.

Goals of the Human Genome Project

Characterize all genes and enable studies of genetics, evolution and function.





Mouse Genome Project

Mus musculus

The mouse is one of the most widely used laboratory animals for studying mammalian biochemistry and developmental biology. Its popularity is largely due to an impressive range of transgenic and genetic techniques which allow researchers to manipulate, and even "knock-out", mouse gene expression. These techniques have been particularly useful in medical research.

Severo Ochoa

Arthur Kornberg

Francis Crick

James Watson

Maurice Wilkins

Gobind Khorana

Werner Arber

Danial Nathans

Hamilton Smith

Paul Berg

Wally Gilbert

Fred Sanger

Kary Mullis

J. Mol. Biol. (1971) **56**, 341-361

Studies on Polynucleotides

XCVI. Repair Replication of Short Synthetic DNA's as catalyzed by DNA Polymerases

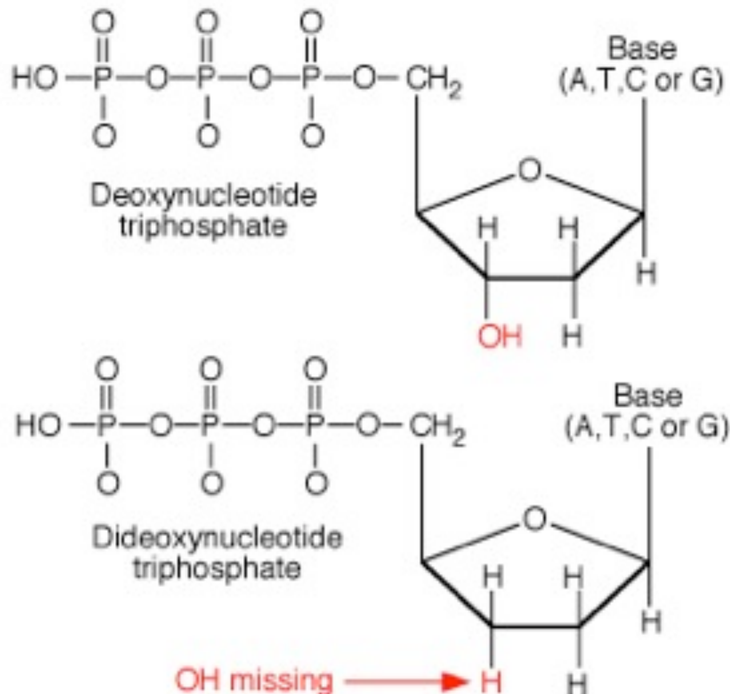
K. Kleppe, E. Ohtsuka, R. Kleppe, I. Molineux
and H.G. Khorana

Institute for Enzyme Research of the University of Wisconsin
Madison, Wisc. 53706, U.S.A.
(Received 20 July 1970)

The principles for extensive synthesis of the duplexed tRNA genes which emerge from the present work are the following. The DNA duplex would be denatured to form single strands. This denaturation step would be carried out in the presence of a sufficiently large excess of the two appropriate primers. Upon cooling, one would hope to obtain two structures, each containing the full length of the template strand appropriately complexed with the primer. DNA polymerase will be added to complete the process of repair replication. Two molecules of the original duplex should result. The whole cycle could be repeated, there being added every time a fresh dose of the enzyme. It is however, possible that upon cooling after denaturation of the DNA duplex, renaturation to form the original duplex would predominate over the template-primer complex formation. If this tendency could not be circumvented by adjusting the concentrations of the primers, clearly one would have to resort to the separation of the strands and then carry out repair replication. After every cycle of repair replication, the process of strand separation would have to be repeated. Experiments based on these lines of thought are in progress.

Chain Termination

Fred Sanger



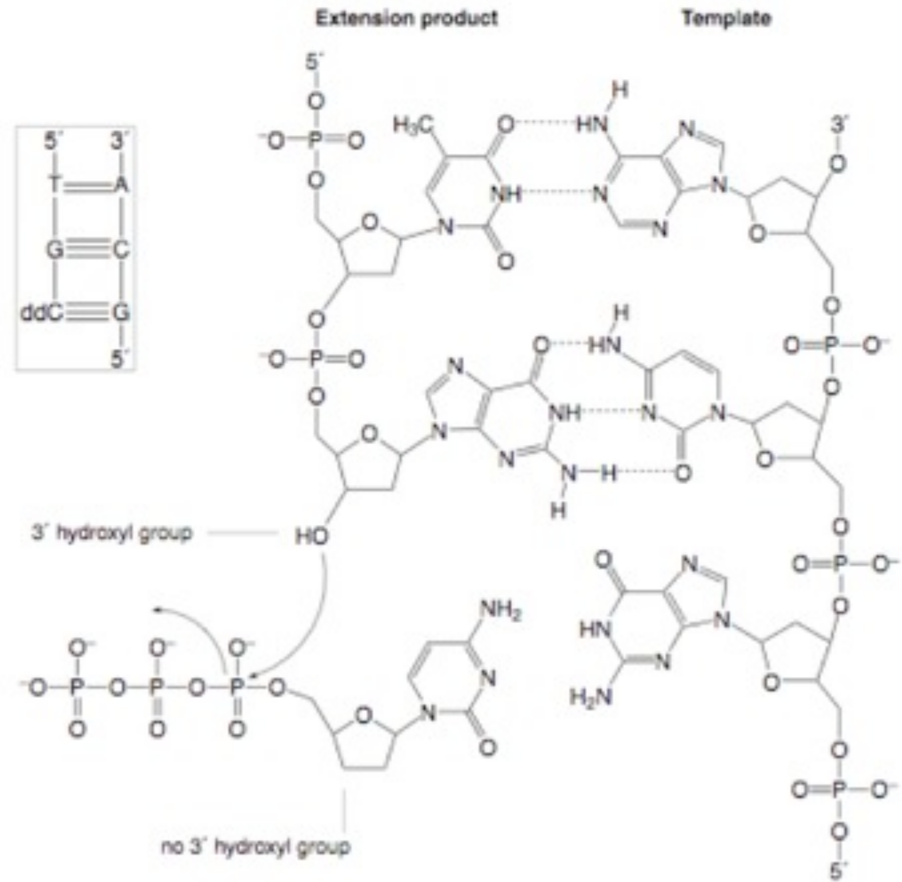


Figure 1-1 DNA strand synthesis by formation of phosphodiester bonds. The chain is terminated by the use of dideoxycytidine triphosphate (ddC) in place of deoxycytidine triphosphate (dCTP). The inset shows a schematic representation of the process.

DNA sequencing with chain-terminating inhibitors

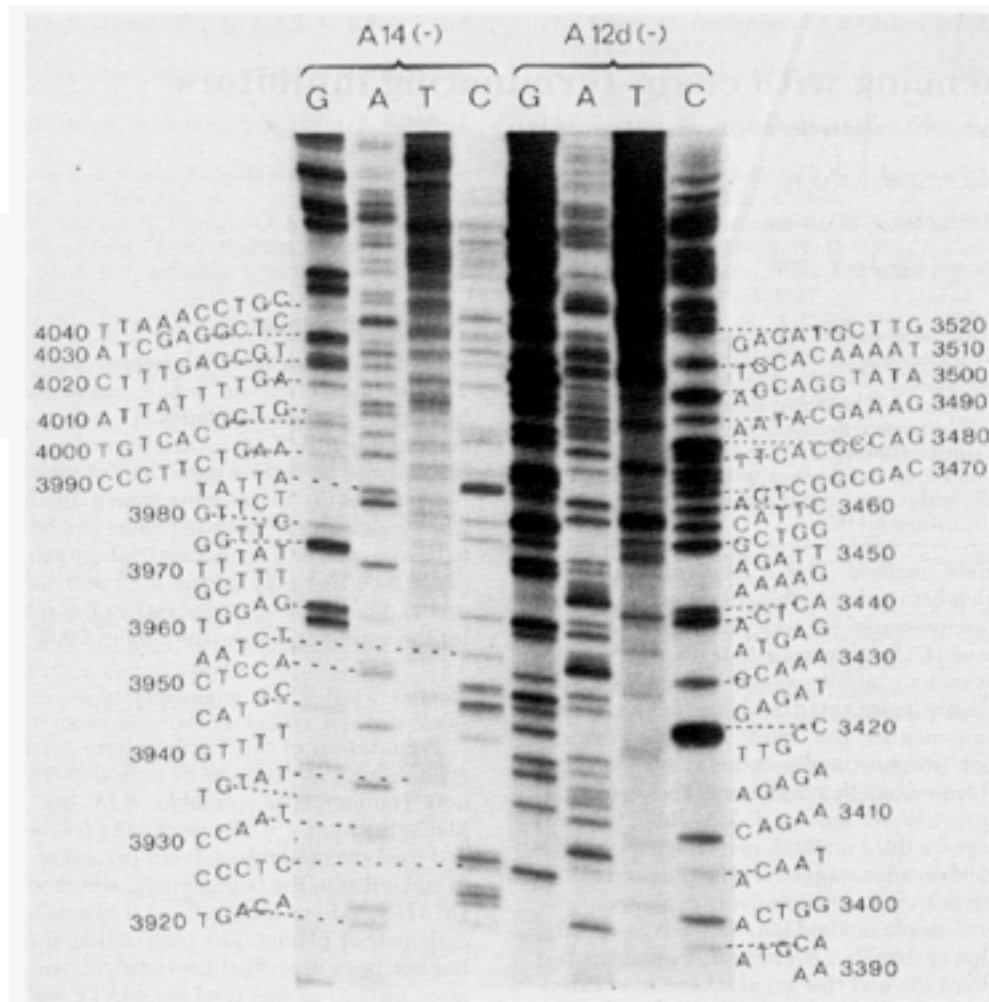
(DNA polymerase/nucleotide sequences/bacteriophage φX174)

F. SANGER, S. NICKLEN, AND A. R. COULSON

Medical Research Council Laboratory of Molecular Biology, Cambridge CB2 2QH, England

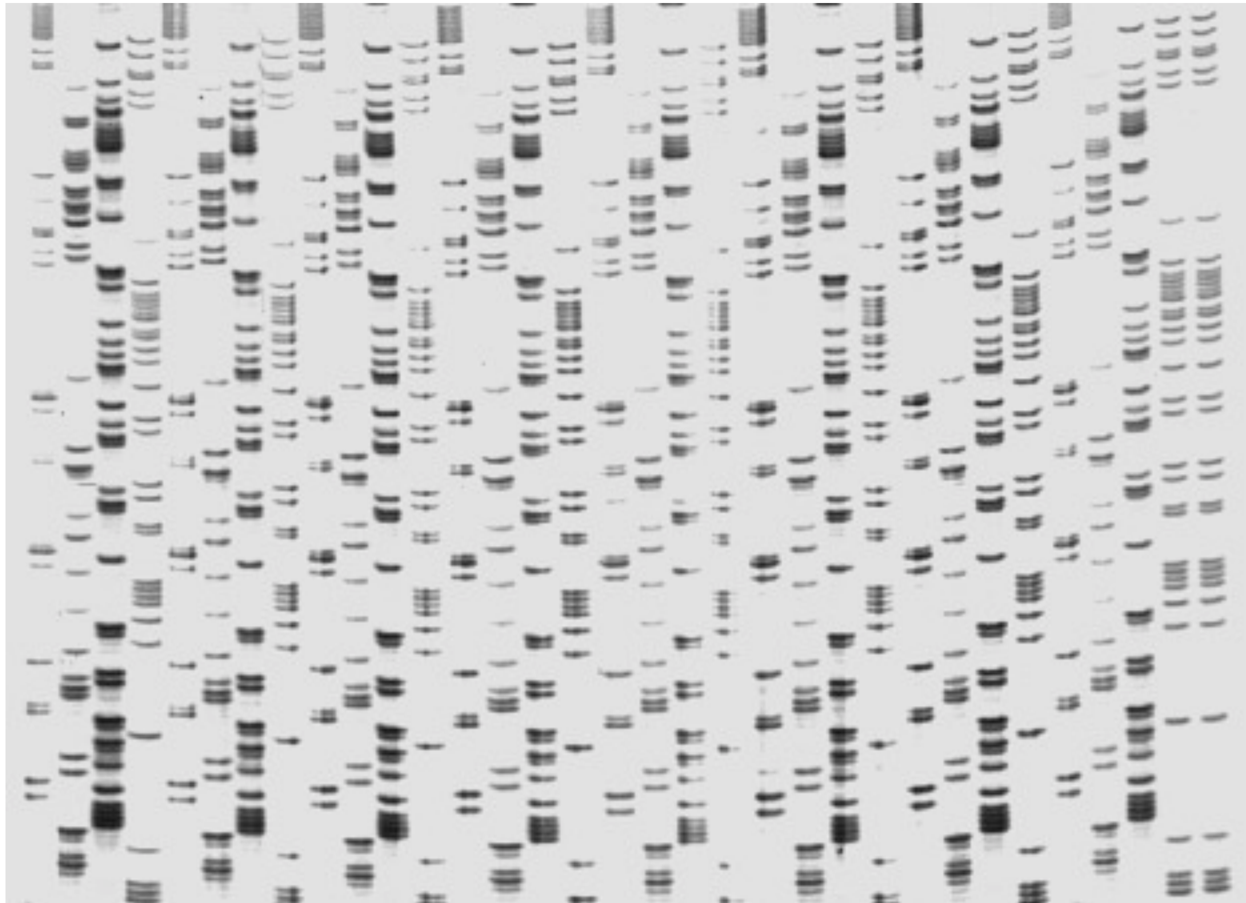
Contributed by F. Sanger, October 3, 1977

ddCTP was prepared from *N*-anisoyl-5′-*O*-monomethoxytrityldeoxycytidine (Collaborative Research Inc., Waltham, MA) by the above method but the final purification on DEAE-Sephadex was omitted because the yield was very low and the solution contained the required activity. The solution was used directly in the experiments described in this paper.



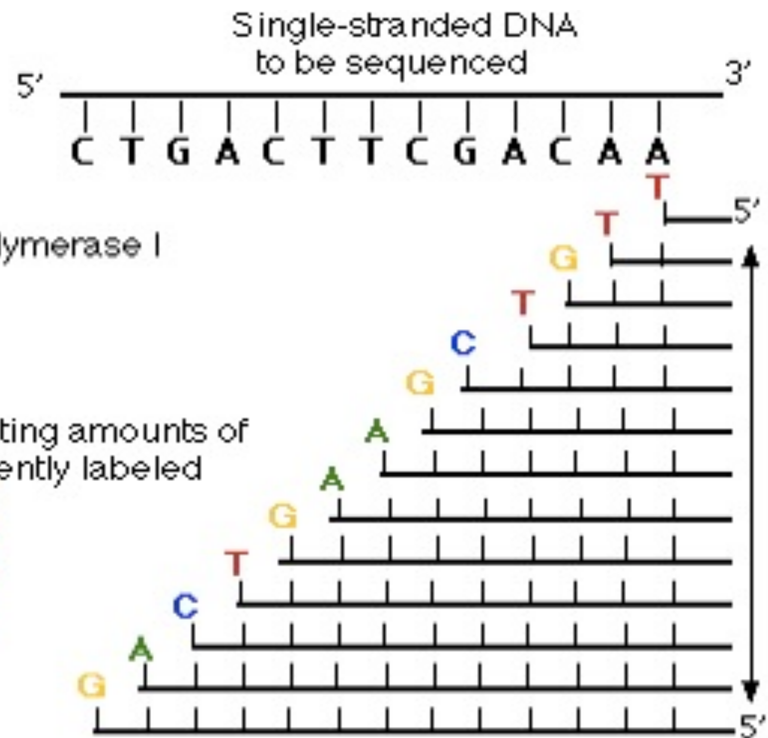
Proc. Natl. Acad. Sci. USA
Vol. 74, No. 12, pp. 5463–5467, December 1977
Biochemistry

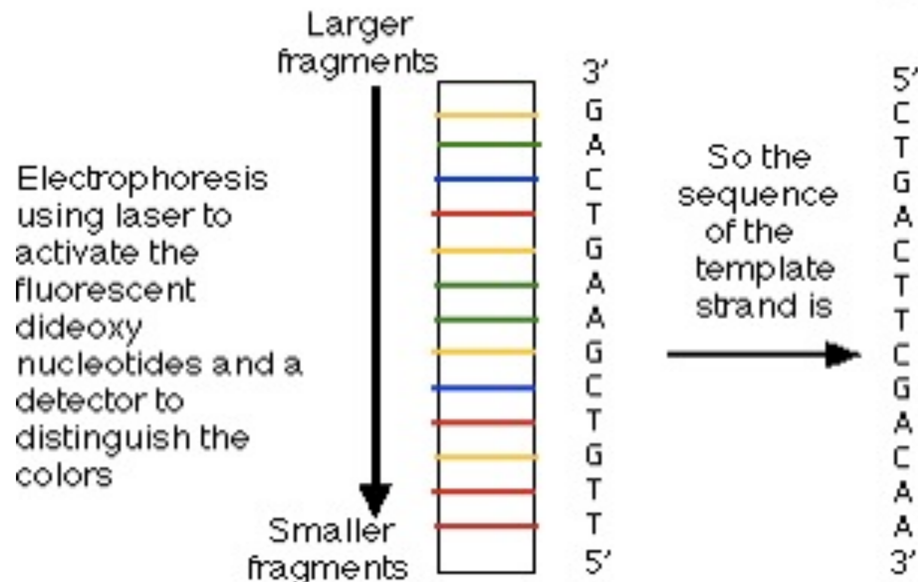
Radioactive Sequencing - 4 Lane Technology



DNA Sequencing Methodology

Sanger Sequencing or Dideoxy Chain Terminator Sequencing





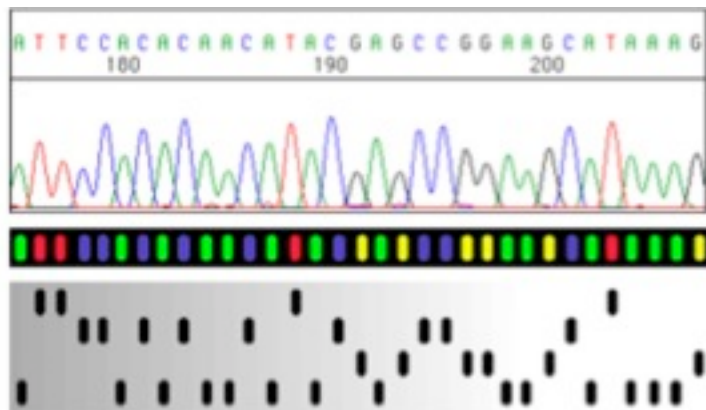
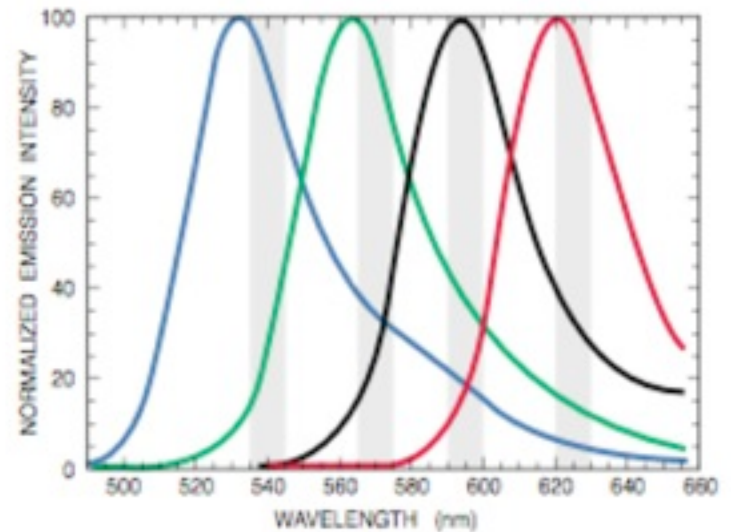
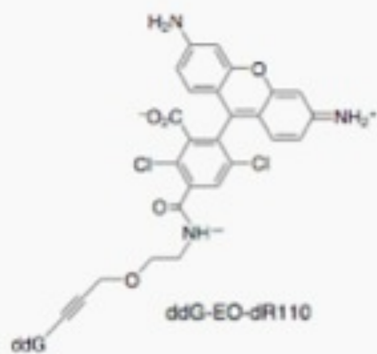
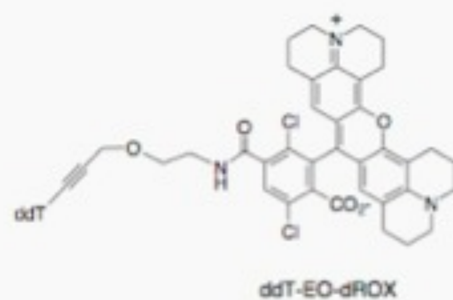
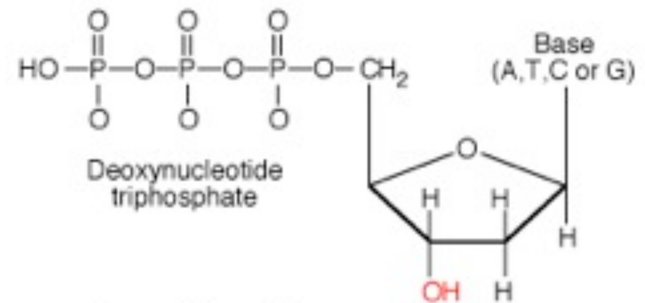


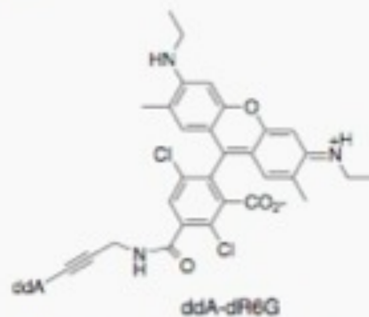
Figure 1-2 Four-color/one-lane fluorescent sequencing vs. one-color/four-lane method such as radioactive sequencing

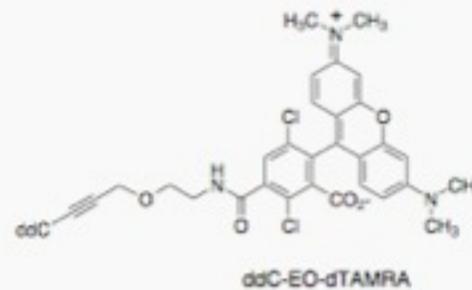












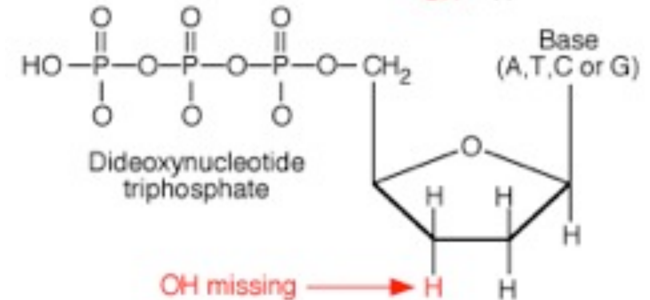


Figure 2-2 dRhodamine terminators

DNA Read Length Limitation

DNA Sequencing works because of denaturing gel matrix

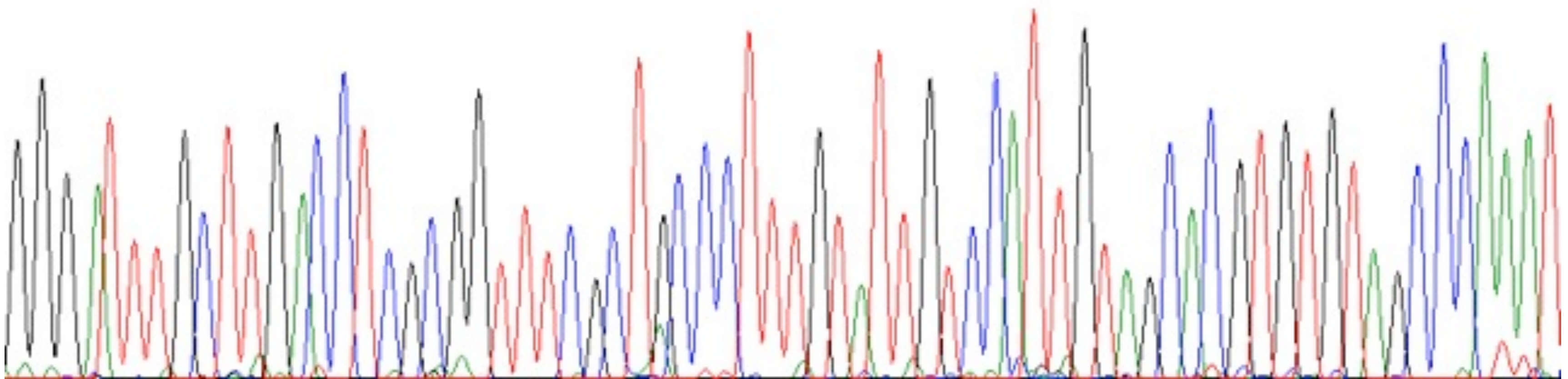
Radioactive method - 8 M Urea polyacrylamide gels

Fluorescent methods - capillary electrophoresis

Allows separation of DNA fragments differing by 1 base in size
From 1 to 1,000 bases

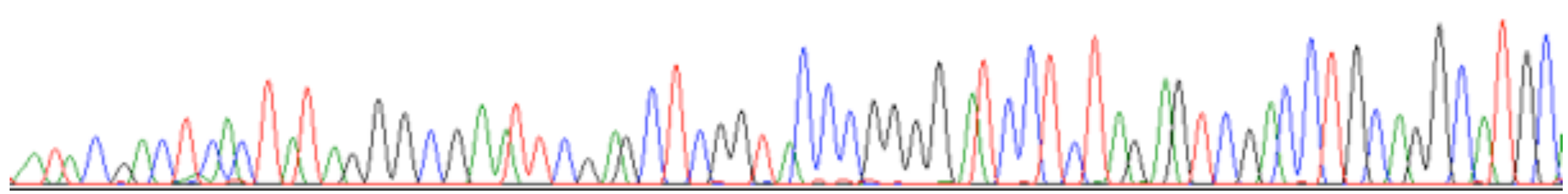
The larger the fragment, the less the separation.

DNA Sequence ‘Trace’ Chromatogram

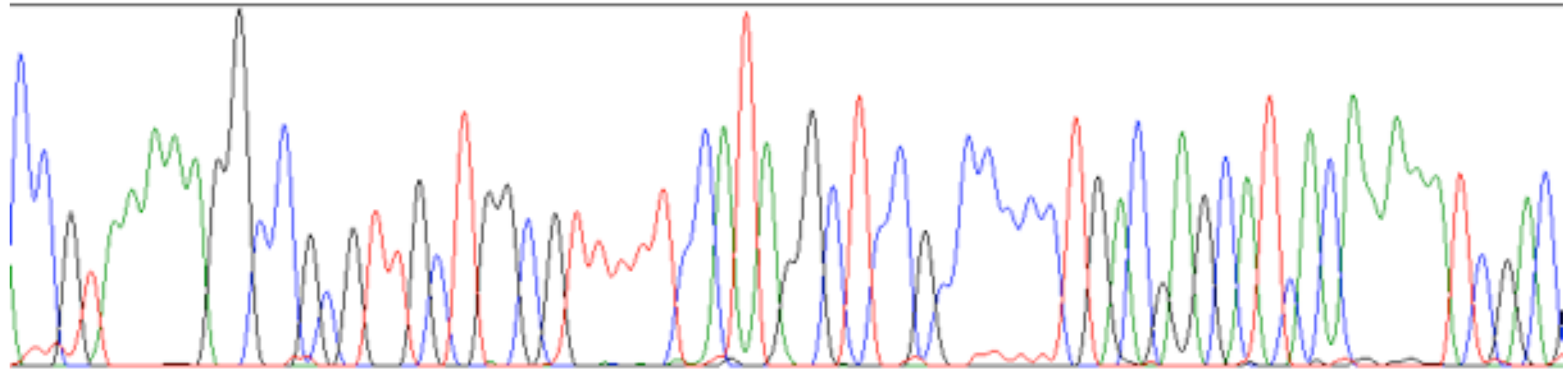


Smaller fragments, good base separation

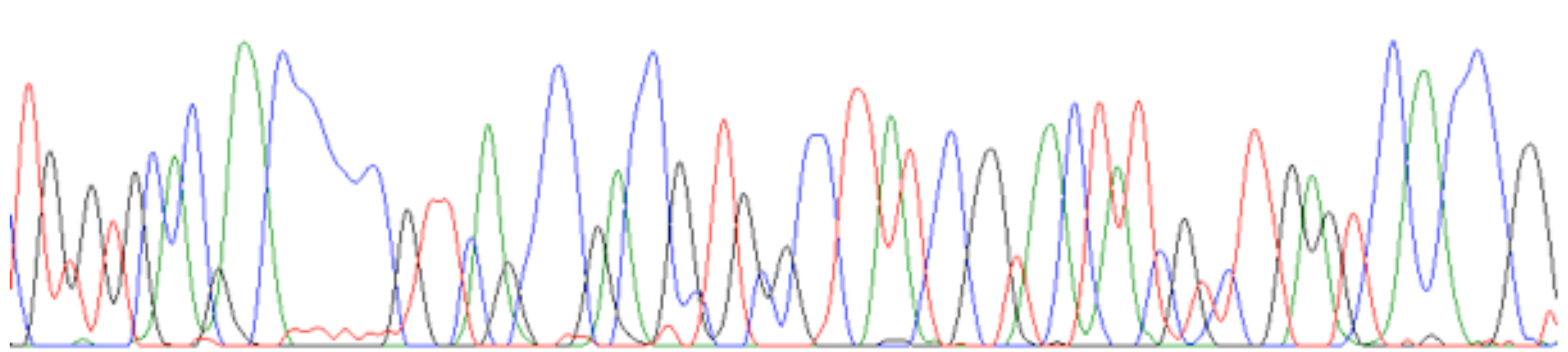
ATACGACTCACTATAGGGCGAATTCGAGCTCGGTACCCGGGGATCCTCTAGAGTCGACCTGCAGGCATGC
10 20 30 40 50 60 70

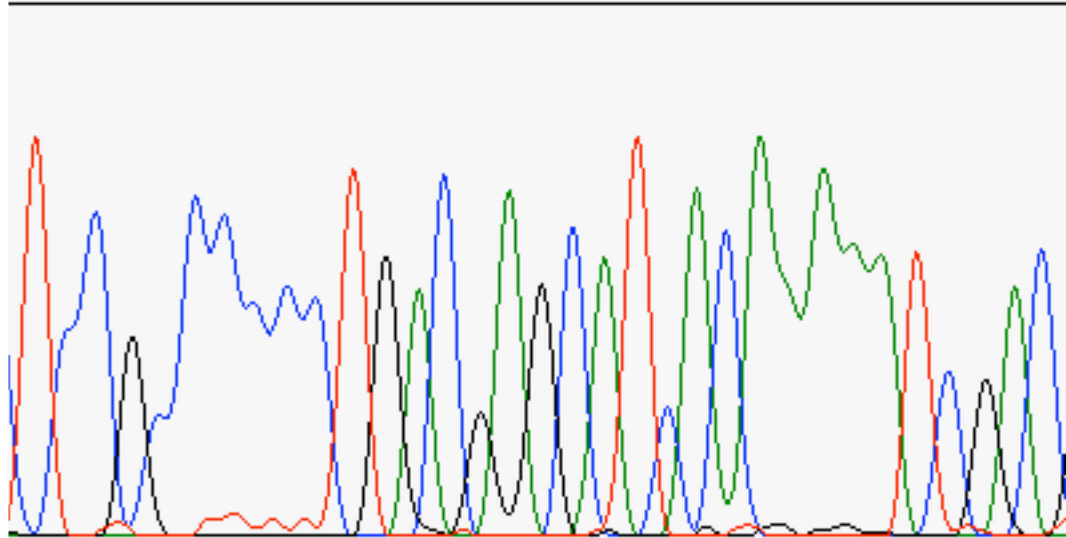


CCGTAAAAAGGCCGCGTTGCTGGCGTTTTTCCATAGGCTCCGCCCCCCTGACGAGCATCACAAAAATCGAC
500 510 520 530 540 550 560

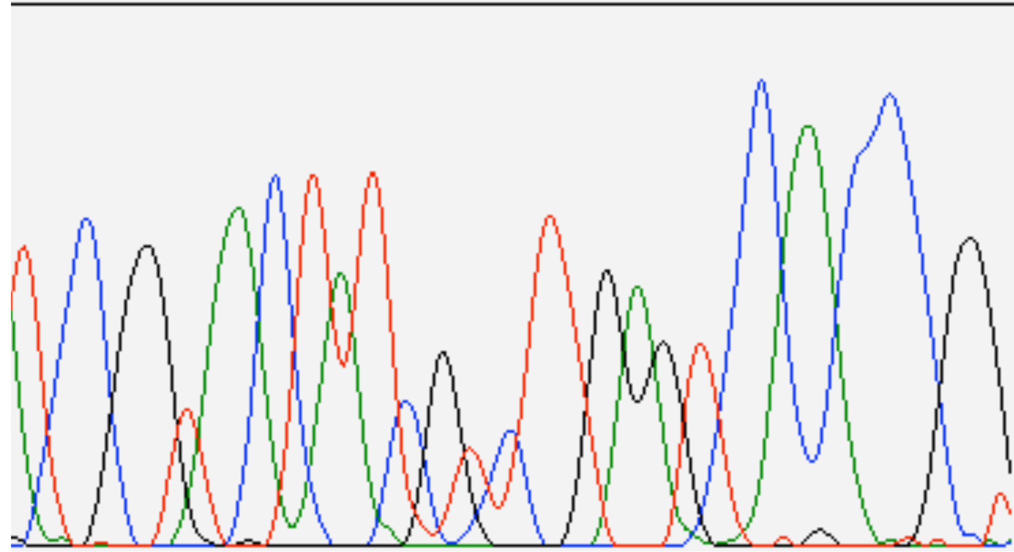


TGTGTGCACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATcCGGTAACTATCGTCTTGAGTCCAACCCGG
0 780 790 800 810 820 83 840





TCCGC CCCCCTG AC GAGCATCACAAAAATC GAC
540
550
560



TcCGGTAACTATCGT C TTGAGTCC AACCCGG
820
831
840

ABI PRISM® 3700*xl* DNA Analyzer

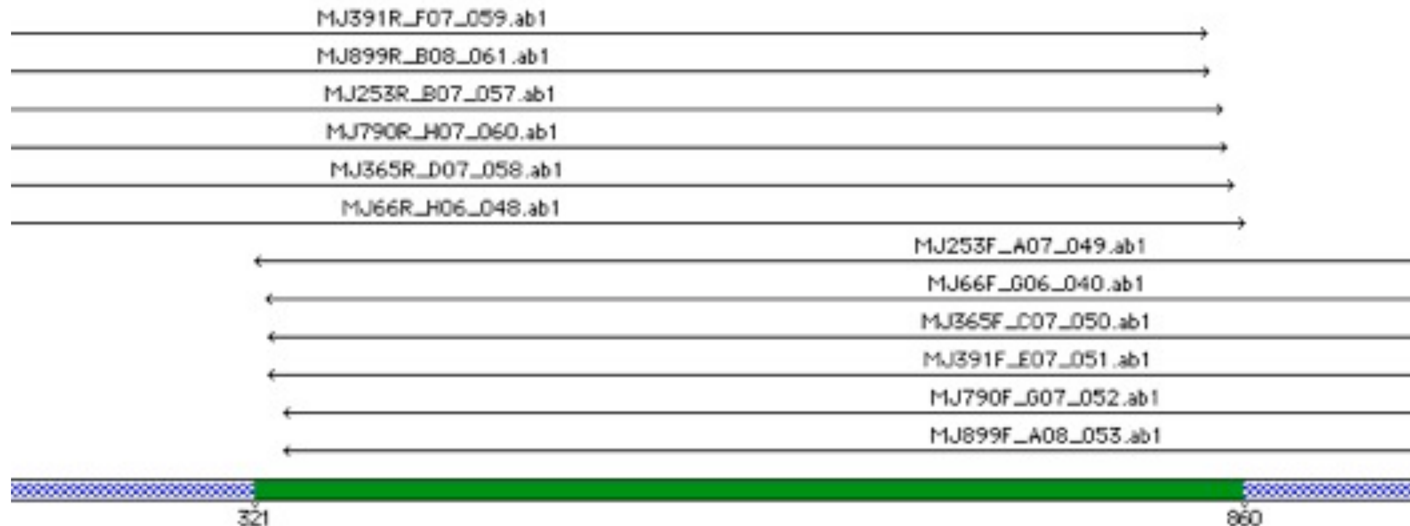
Bench top instrument

Analyse 96 samples in 1 hours
~800 bases/sample

Thus in 24 hours can generate
~1,000,000 bases of sequence

Cost: £3.60/sample

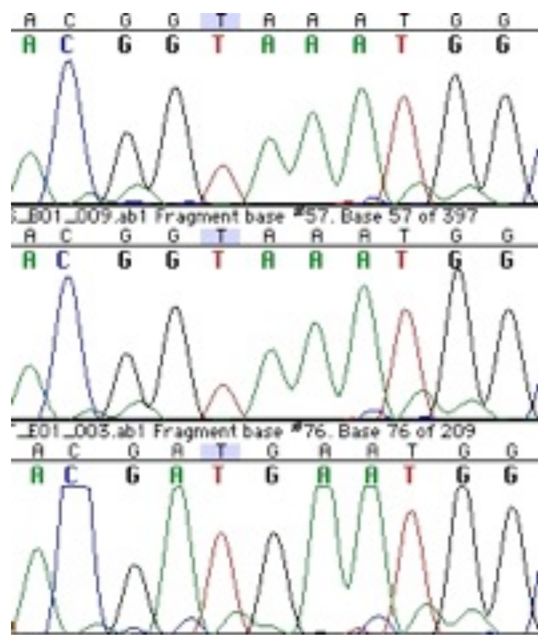
Sequence Alignment

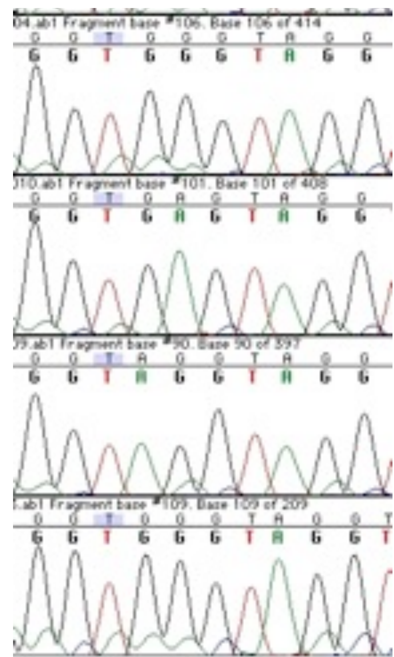


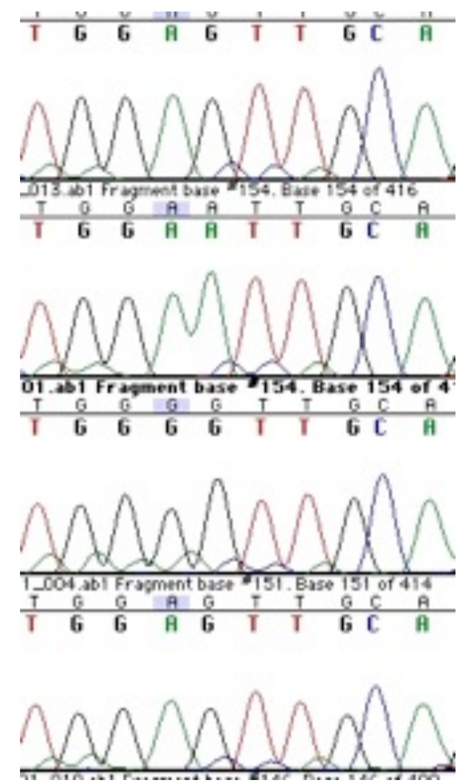

```
CCCCCTAACACTTAGCACTCATCGTTTACGGCGTGGACTACCAGGGTATNTAATCCTGTTTGATCCCCACNCTTTCNCACATCAGCGTCAGTTA
CCCCCTAACACTTAGCACTCATCGTTTACGGCGTGGACTACCAGGGTATCTAATCCTGTTTGATCCCCACGCTTTCGCACATCAGCGTCAGTTA
CCCCCTAACACTTAGCACTCATCGTTTACGGCGTGGACTACCAGGGTATCTAATCCTGTTTGATCCCCACGCTTTCGCACATCAGCGTCAGTTA
CCCCCTAACACTTAGCACTCATCGTTTACGGCGTGGACTACCAGGGTATCTAATCCTGTNTGATCCCCACGCTTTCGCACATCAGCGTCAGTTA
CCCCCTAACACTTAGCACTCATCGTTTACGGCGTGGACTACCAGGGTATCTAATCCTGTTTGATCCCCACGCTTTCGCACATCAGCGTCAGTTA
CCCCCTAACACTTAGCACTCATCGTTTACGGCGTGGACTACCAGGGTATNTAATCCTGTTTGATCCCCACGCTTTCGCACATCAGCGTCAGTTA
CCCCCTAACACTTAGCACTCATCGTTTACGGCGTGGACTACCAGGGTATCTAATCCTGTTTGATCCCCACGCTTTCGCACATCAGCGTCAGTTA
CCCCCTAACACTTAGCACTCATCGTTTACGGCGTGGACTACCAGGGTATCTAATCCTGTTTGATCCCCACGCTTTCGCACATCAGCGTCAGTTA
CCCCCTAACACTTAGCACTCATCGTTTACGGCGTGGACTACCAGGGTATCTAATCCTGTTTGATCCCCACGCTTTCGCACATCAGCGTCAGTTA
CCCCCTAACACTTAGCACTCATCGTTTACGGCGTGGACTACCAGGGTATCTAATCCTGTTTGATCCCCACGCTTTCGCACATCAGCGTCAGTTA
CCCCCTAACACTTAGCACTCATCGTTTACGGCGTGGACTACCAGGGTATCTAATCCTGTTTGATCCCCACGCTTTCGCACATCAGCGTCAGTTA
CCCCCTAACACTTAGCACTCATCGTTTACGGCGTGGACTACCAGGGTATCTAATCCTGTTTGATCCCCACGCTTTCGCACATCAGCGTCAGTTA

00       |510      |520      |530      |540      |550      |560      |570      |580      |590
CCCCCTAACACTTAGCACTCATCGTTTACGGCGTGGACTACCAGGGTATCTAATCCTGTTTGATCCCCACGCTTTCGCACATCAGCGTCAGTTA
..............................................................................................
                                                 +         +          +     +
```

```
CTGTAATGTGCTATGTACGGTAAATGGCTTTATGTACTATGTACTGTTAAAGATGGGTAGGTTTGTTGGTATCCTAGTGGGTGAGGGGTGGCCTTTGGAGTTGCAGTTGATGTGTGATAGTTGAGGGTTGATTGCCTGTACTTG
CTGTAATGTGCTATGTACGGTAAATGGCTTTATGTGCTATGTACTGTTAAGGGTGGGTAGGTTTGTTGGTATCCTAGTGGGTGAGGGGTGGCCTTTGGAGTTGCAGTTGATGTGTGATAGTTGAAGGTTGATTGCCTGTACTTG
CTGTAATGTGCTATGTACGGTAAATGGCTTTATGTACTATGTACTGTTAAGGGTGGGTAGGTTTGTTGGTATCCTAGTGGGTGAGGGGTGGCCTTTGGAGTTGCAGTTGATGTGTGATAGTTGAGGGTTGATTG:TTGTACTTG
CTGTAATGTGCTATGTACGGTAAATGGCTTTATGTACTATGTACTGTTAAGGGTGGGTAGGTTTGTTGGTATCCTAGTGGGTGAGGGGTGGCCTTTGGAGTTGCAGTTGATGTGTGATAGTTGAGGGTTGATTGCCTGTACTTG
CTGTAATGTGCTATGTACGGTAAATGGCTTTATGTGCTATGTACTGTTAAGGGTGGGTAGGTTTGTTGGTATCCTAATGGGTGAGGGGT:GACTTTGGAGTTGCAGTTGATGTGTGATAGTTGAGGGTTGATTGCCTGTACTTG
CTGTAATGTGCTATGTACGGTAAATGGCTTTATGTACTATGTGCTGTTAAGGATGGGTAGGTTTGTTGGTATCCTAGTGGGTGAGGGGTGGCCTTTGGAGTTGCAGTTGATGTGTGATAGTTGAGGGTTGATTGCCTGTACTTG
CTGTAATGTGCTATGTACGGTAAATGGCTTTATGTACTATGTACTGTTAAGGGTGGGTAGGTTTGTTGGTATCCTAGTGGGTGAGGGGTGGCCTTTGGAATTGCAGTTGATGTGTGATAGTTGAAGGTTGATTGCCTGTACTTG
CTGTAATGTGCTATGTACGGTAAATGGCTTTATGTGCTATGTACTGTTAAGGGTGGGTAGGTTTGTTGGTATCCTAGTGGGTGAGGGGTGGCCTTTGGGGTTGCAGTTGATGTGTGATAGTTGAGGGTTGATTGCCTGTACTTG
CTGTAATGTGCTATGTACGGTAAATGGCTTTATGTACTATGTACTGTTAAGGGTGGGTAGGTTTGTTGGTATCCTAGTGGGTGAGGGGTGGCCTTTGGAGTTGCAGTTGATGTGTGATAGTTGAAGGTTGATTGCCTGTACTTG
CTGTAATGTGCTATGTACGGTAAATGGCTTTATGTACTATGTACTGTTAAGGGTGAGTAGGTTTGTTGGTATTCTAGTGGGTGAGGGGTGGCCTTTGGAGTTGCAGTTGATGTGTGATAGTTGAAGGTTGATTGCCTGTACTTG
CTGTAATGTGCTATGTACGGTAAATGGCTTTATGTACTATGTACTGTTAAGGGTAGGTAGGTTTGTTGGTATCCTAGTGGGTGAGGGGTGG:CTTTGGAGTTGCAGTTGATGTGTGATAGTTGAAGGTTGATTGCCTGTACTTG
CTATAATGTGCTATGTACGATGAATGGCTTTATGTACTATGTACTGTTGAGGGTGGGTAGGTTTGTTGGTATCCTAGTGGGTGAGGGGTGG:CTTTGGAGTTGCAGTTGATGTGTGATAGTTGAAGGTTGATTG:CTGTACTTG
```







New DNA Sequencing Technologies

Current Sanger methods valuable for small scale projects

But

Expensive and time consuming for re-sequencing projects, i.e. sequencing another human genome

Sequencing human genome (3×10^9 bp) to 10 fold coverage required ~50,000,000 sequence reactions

One 3730*xl* DNA sequencer would take 25,000 days working 24 hours a day (*68.5 years*!)

New DNA Sequencing Technologies

New approaches to Sequencing large regions ~10^6 bp

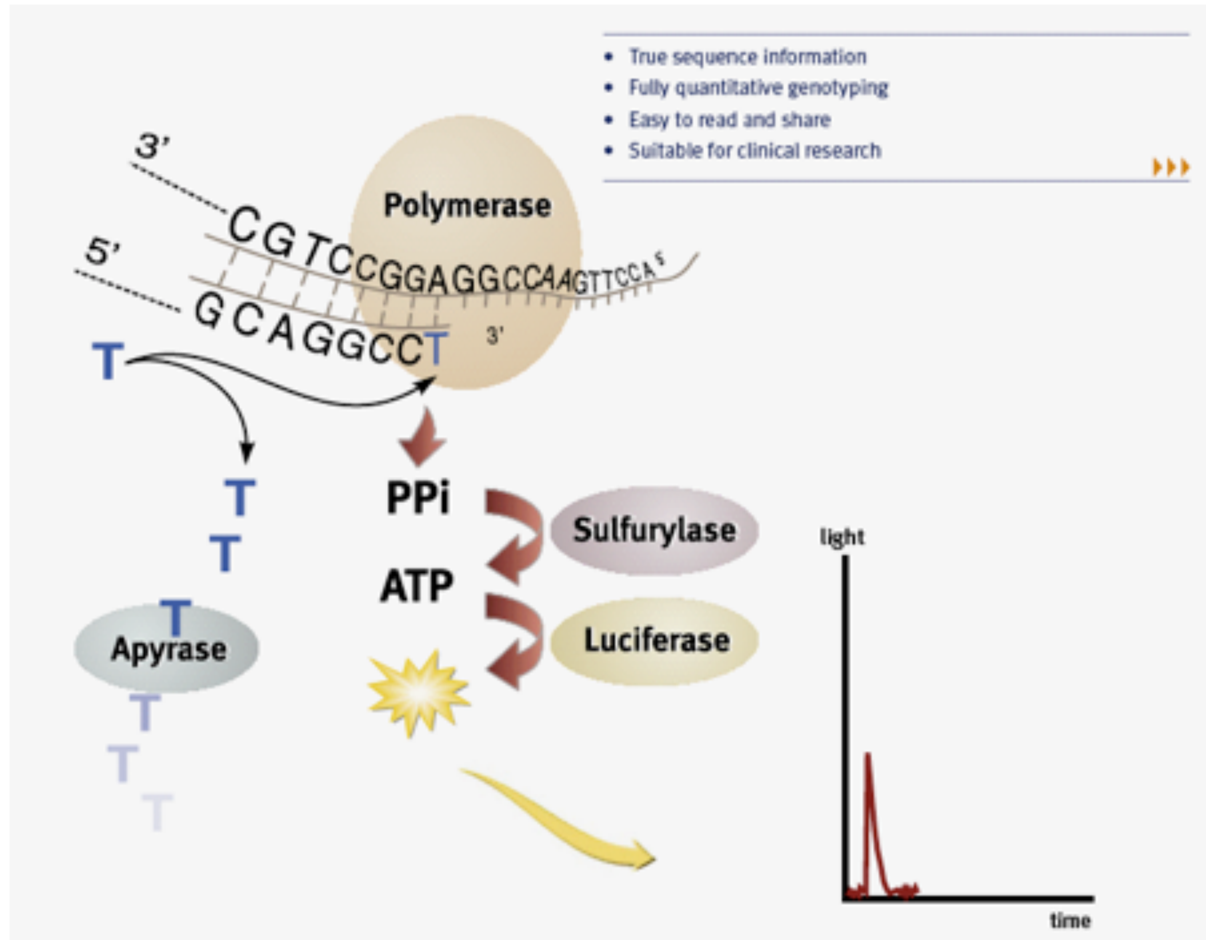
SBS - Sequence by Synthesis

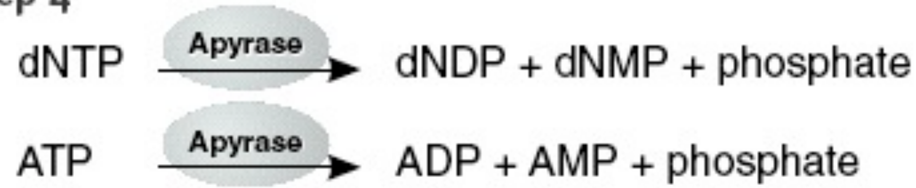
AIM: A Human Genome Sequence for $1,000

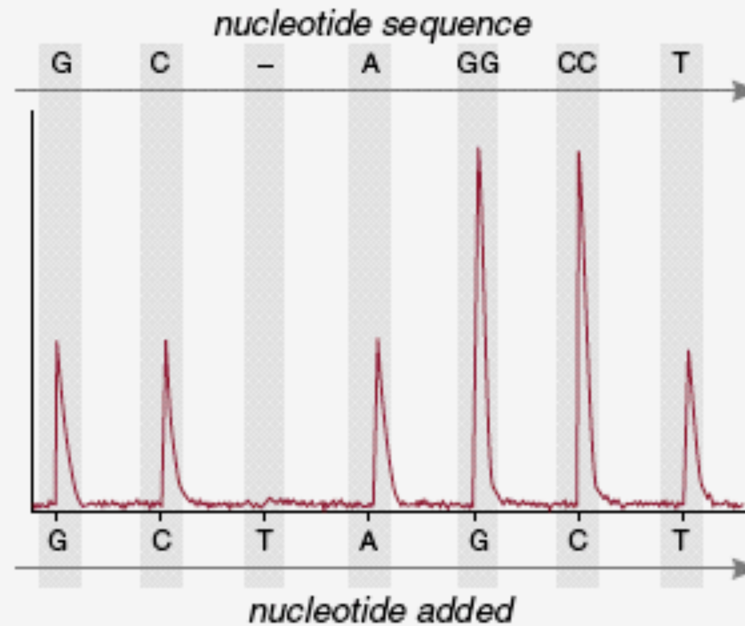
A Human Genome Sequence in One Day

SBS – Sequence by Synthesis

Pyrosequencing - Synthesis one base at a time, with real time detection.




Step 4
dNTP
Apyrase
dNDP + dNMP + phosphate
ATP
Apyrase
ADP + AMP + phosphate

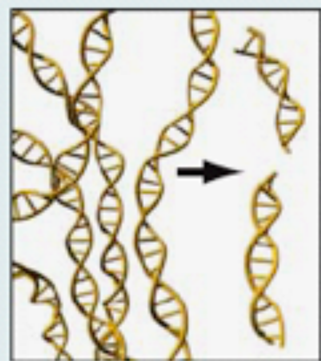

Step 5
nucleotide sequence
G
C
–
A
GG
CC
T
G
C
T
A
G
C
T
nucleotide added

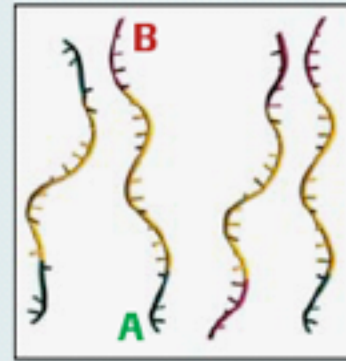
Read ~400 bases per sequence run

Pyrosequencing: As Easy as PCR, and As Reliable as Sanger

DNA sequence from the P3 region of the rnpB gene of *Streptococcus Pyogenes*

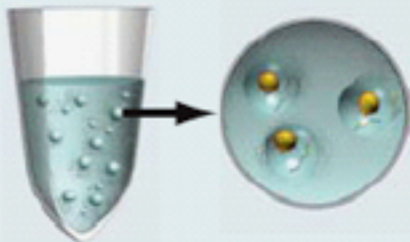
But this is smaller than Sanger Shotgun >700 bases of sequence



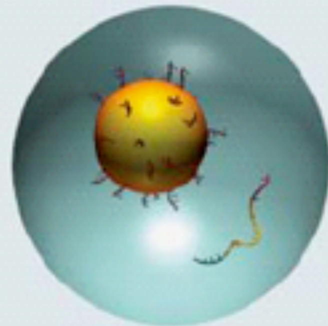


- Genome fragmented by nebulization
- No cloning; no colony picking
- sstDNA library created with adaptors
- A/B fragments selected using avidin-biotin purification

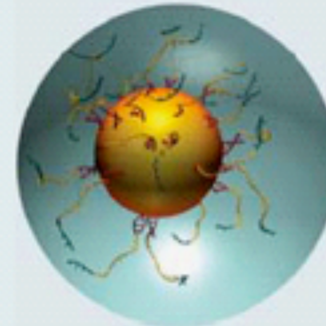
gDNA ⟶ **sstDNA library**



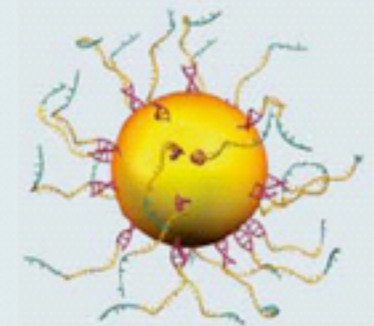
Anneal sstDNA to an excess of DNA Capture Beads



Emulsify beads and PCR reagents in water-in-oil microreactors



Clonal amplification occurs inside microreactors



Break microreactors, enrich for DNA-positive beads

sstDNA library ⟶ **Clonally-amplified sstDNA attached to bead**

Genome Sequencer FLX

Titanium Upgrade

- >1,000,000 reads/run
- >400 base read length/bead
- >400 million bases/run (10 hours)

The complete genome of an individual by massively parallel DNA sequencing

David A. Wheeler[1]*, Maithreyan Srinivasan[2]*, Michael Egholm[2]*, Yufeng Shen[1]*, Lei Chen[1], Amy McGuire[3], Wen He[2], Yi-Ju Chen[2], Vinod Makhijani[2], G. Thomas Roth[2], Xavier Gomes[2], Karrie Tartaro[2]†, Faheem Niazi[2], Cynthia L. Turcotte[2], Gerard P. Irzyk[2], James R. Lupski[4,5,6], Craig Chinault[4], Xing-zhi Song[1], Yue Liu[1], Ye Yuan[1], Lynne Nazareth[1], Xiang Qin[1], Donna M. Muzny[1], Marcel Margulies[2], George M. Weinstock[1,4], Richard A. Gibbs[1,4] & Jonathan M. Rothberg[2]†

Table 3 | SNPs matching HGMD mutations causing disease or other phenotypes

HGMD accession	Chromosome	Coordinate	HUGO symbol	Gene name	Cytogenetic	Phenotype	Zygosity
CM003589	1	97937679	DPYD	Dihydropyrimidine dehydrogenase	1q22	Dihydropyrimidine dehydrogenase deficiency	Heterozygous
CM950484	1	157441978	FY	Duffy blood-group antigen	1q	Duffy blood group antigen, absence	Homozygous*
CM942034	4	619702	PDE6B	Phosphodiesterase 6B, cGMP-specific, rod, beta	4p16.3	Retinitis pigmentosa 40	Heterozygous
CM021718	9	36208221	GNE	UDP-N-acetylglucosamine 2-epimerase	9p	Myopathy, distal, with rimmed vacuoles	Heterozygous
CM980633	10	50348375	ERCC6	Excision repair cross-complementing rodent repair deficiency, complementation group 6 protein (CSB)	10q	Cockayne syndrome	Homozygous†
CM050716	11	76531431	MYO7A	Myosin VIIA	11q13.5	Usher syndrome 1b	Homozygous†
CM950928	12	46812979	PFKM	Phosphofructokinase, muscle	12q13.3	Glycogen storage disease 7	Homozygous*
CM032029	14	20859880	RPGRIP1	Retinitis pigmentosa GTPase regulator interacting protein 1	14q11	Cone–rod dystrophy	Heterozygous
CM984025	19	18047618	IL12RB1	Interleukin-12 receptor, beta 1	19p13.1	Mycobacterial infection	Heterozygous
CM024138	19	41014441	NPHS1	Nephrosis-1, congenital, Finnish type	19q	Congenital nephrotic syndrome, Finnish type	Heterozygous
CM910052	22	49410905	ARSA	Arylsulphatase A	22q	Metachromatic leukodystrophy	Heterozygous

* Coverage at these SNP positions is less than 5. However, both produce benign phenotypes.
† Coverage at these SNP positions is greater than 5. Both would produce severe phenotypes if they were truly homozygous.

©2008 Nature Publishing Group

James Watson

Time: ~2 months

Coverage: ~7.4x

Sequence data: 106.5 million reads
~24.5 billion bases
~3.32 million SNPs
~260 runs on 454 instruments

Cost: ~$1 million

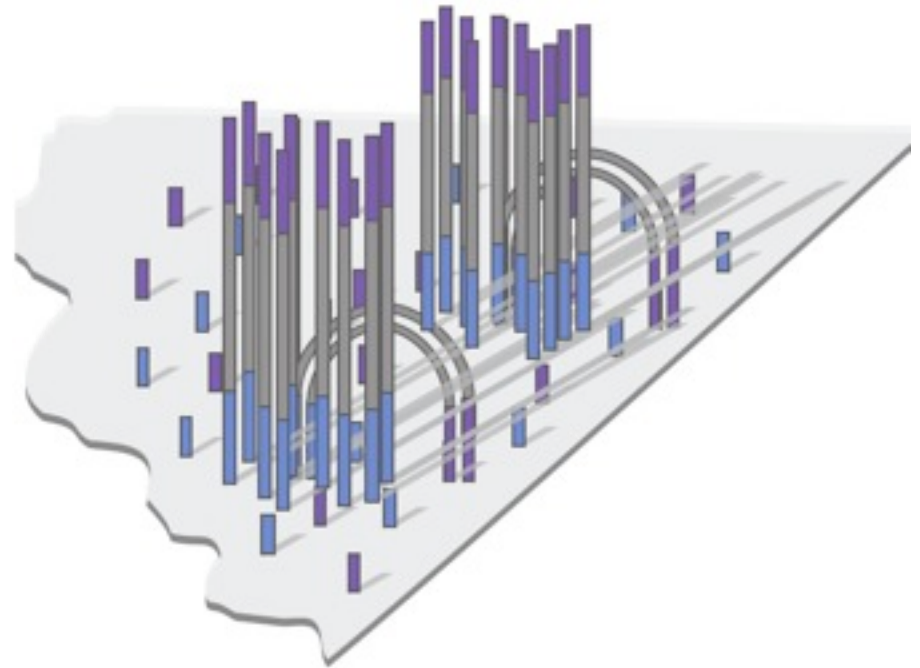
MRC Clinical Sciences Centre

Solexa Genome Analyzer II

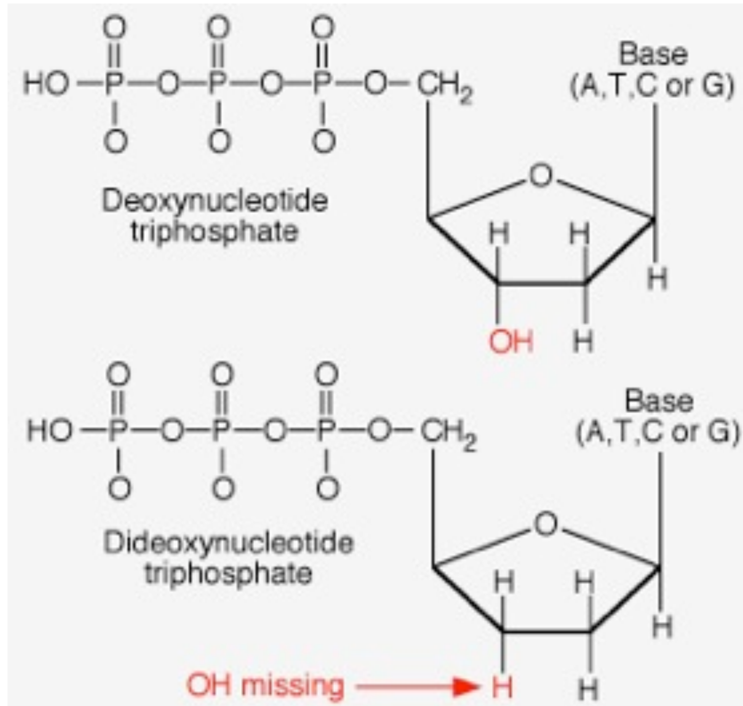
Solexa Genome Analyser II

Generate ssDNA fragments
~100 – 200 bp
Tagged with an 'A' and 'B' adapter

Amplified on Flow Cell by Bridge PCR to form clusters



Reversible Chain termination



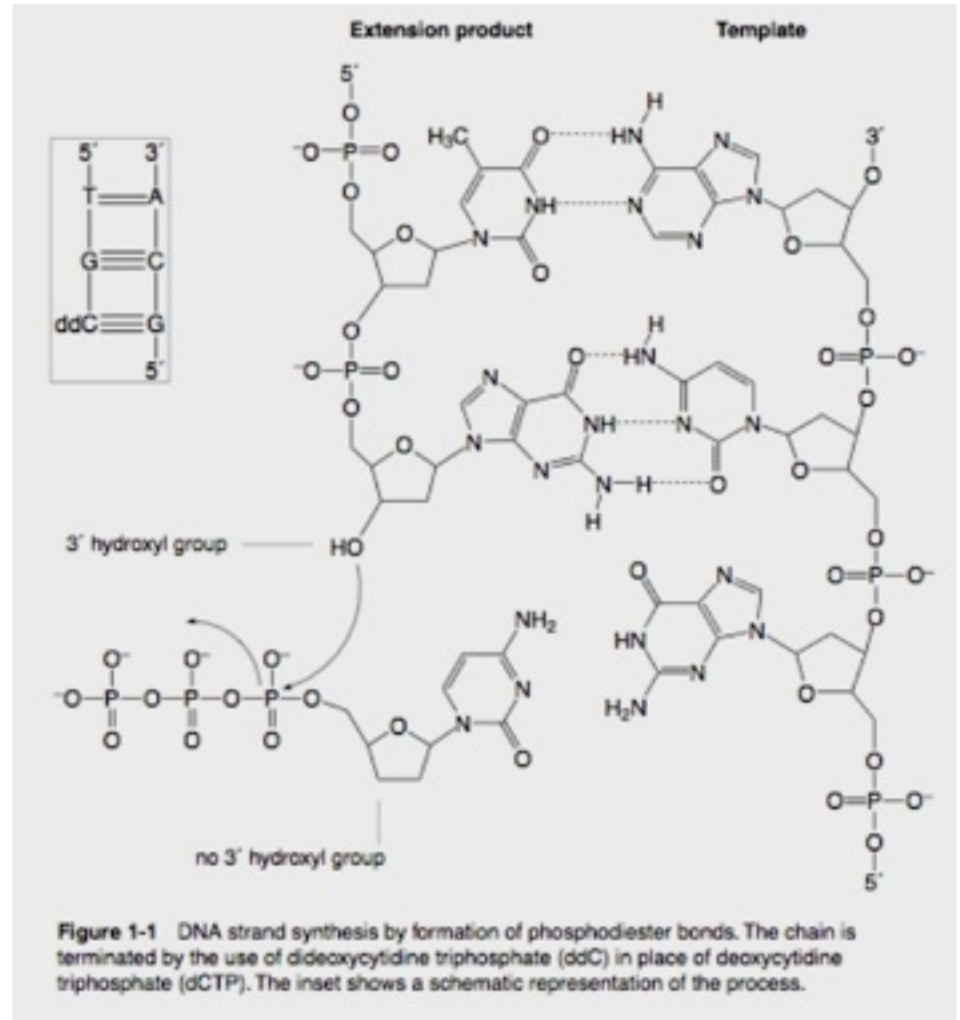
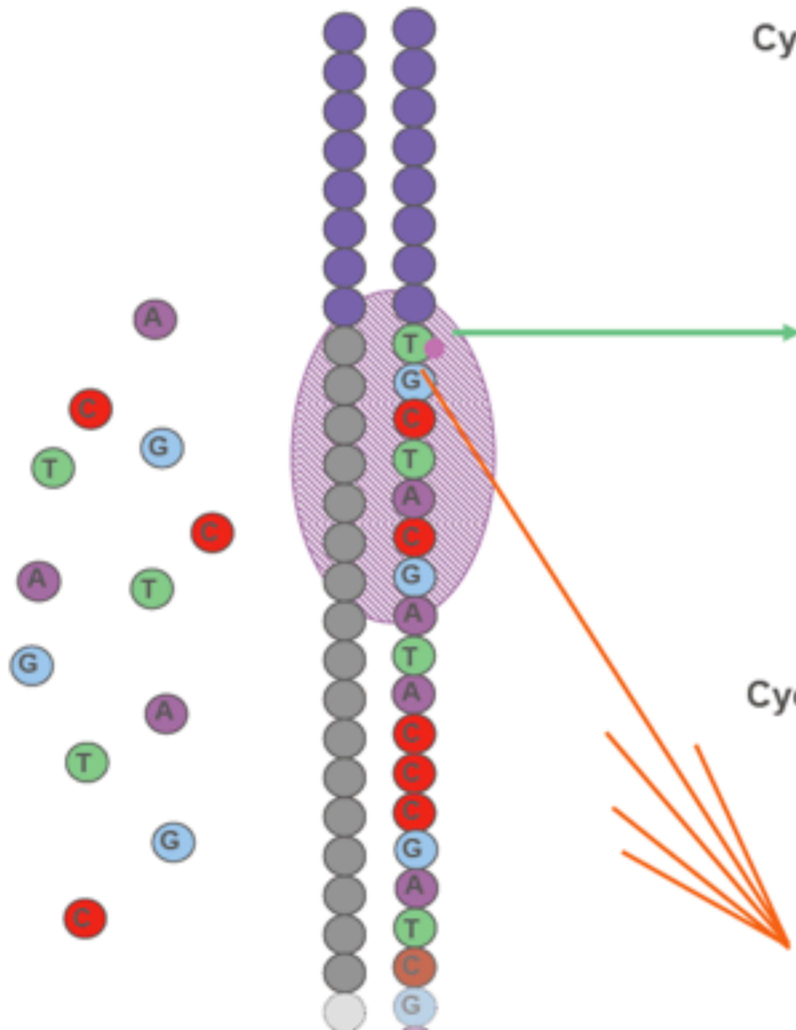


Figure 1-1 DNA strand synthesis by formation of phosphodiester bonds. The chain is terminated by the use of dideoxycytidine triphosphate (ddC) in place of deoxycytidine triphosphate (dCTP). The inset shows a schematic representation of the process.

Solexa Genome Analyser II



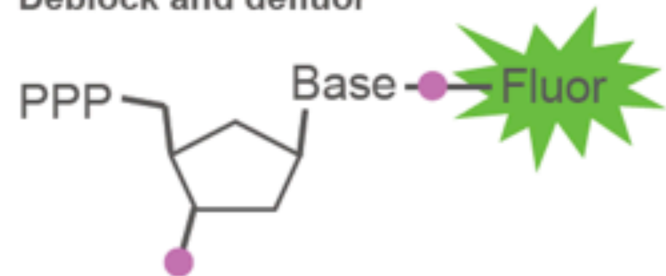
Cycle 1: Add sequencing reagents

First base incorporated

Remove unincorporated bases

Detect signal

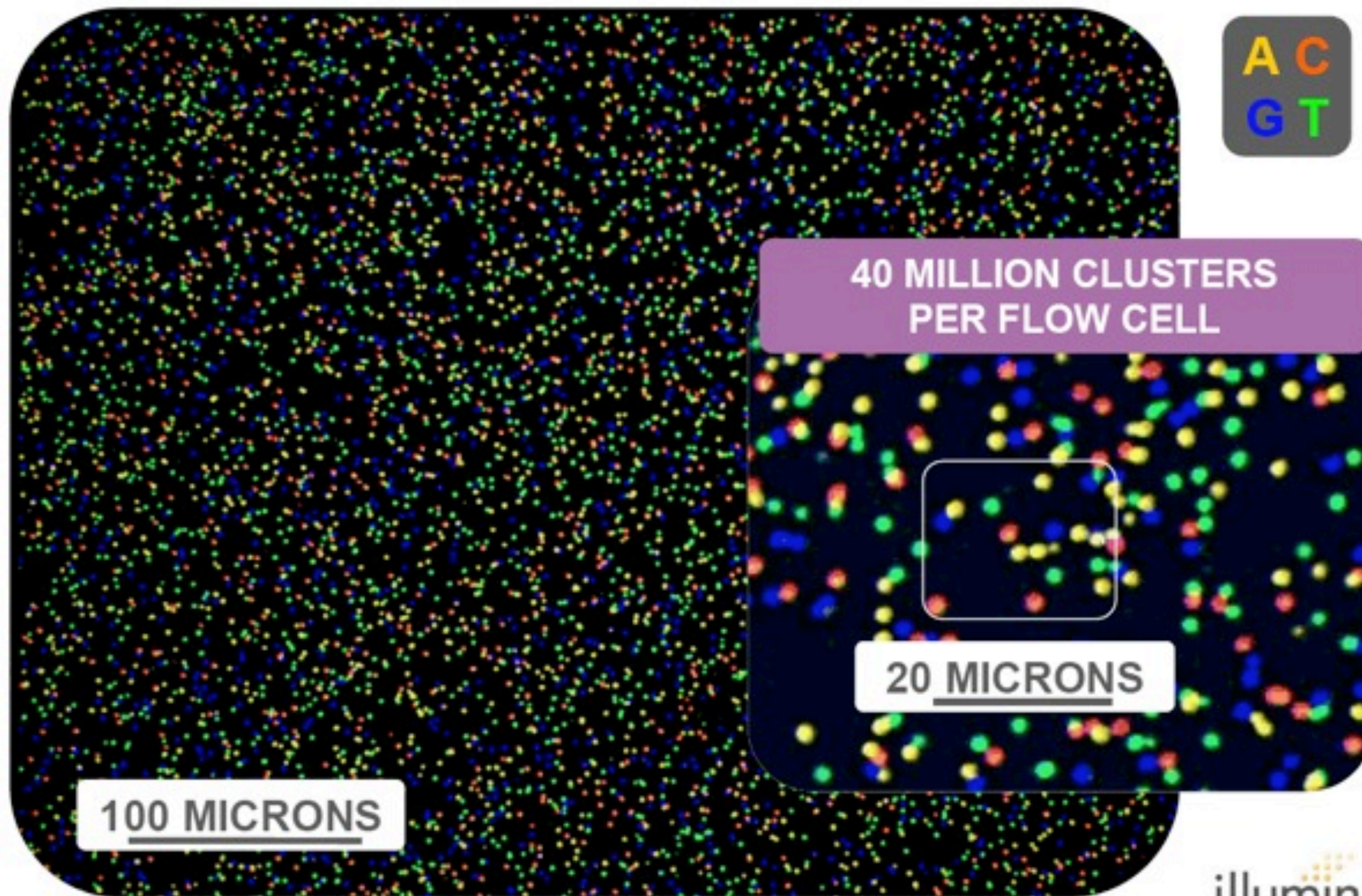
Deblock and defluor



Cycle 2-n: Add sequencing reagents and repeat

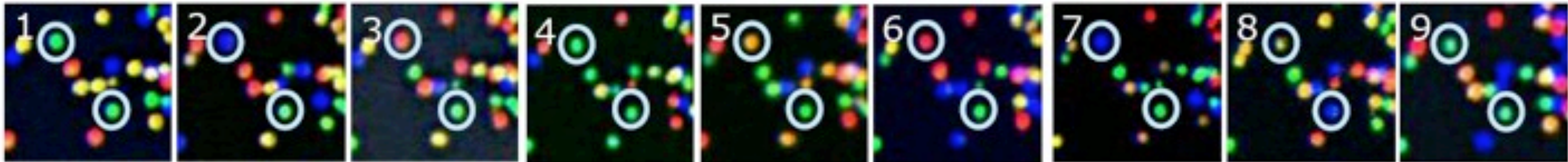
- All four labelled nucleotides in one reaction
- Base-by-base sequencing
- No problems with homopolymer repeats
- High accuracy

Solexa Genome Analyser II



Solexa Genome Analyser II

T G C T A C G A T ...



T T T T T T T G T ...

The New Technologies

Solexa HiSeq 2000

Read Length	*Run Time*	*Output*
2 x 50 bp	~ 5 days	~150 Gb
2 x 100 bp	~ 10 days	~300 Gb (~35 Gb/lane)

Reads: Up to 200 million clusters per lane

Tahiti and Fiji

Can sequence 8 complete human genomes in 2 weeks

MiSeq

2 x 150 base - 27 hours

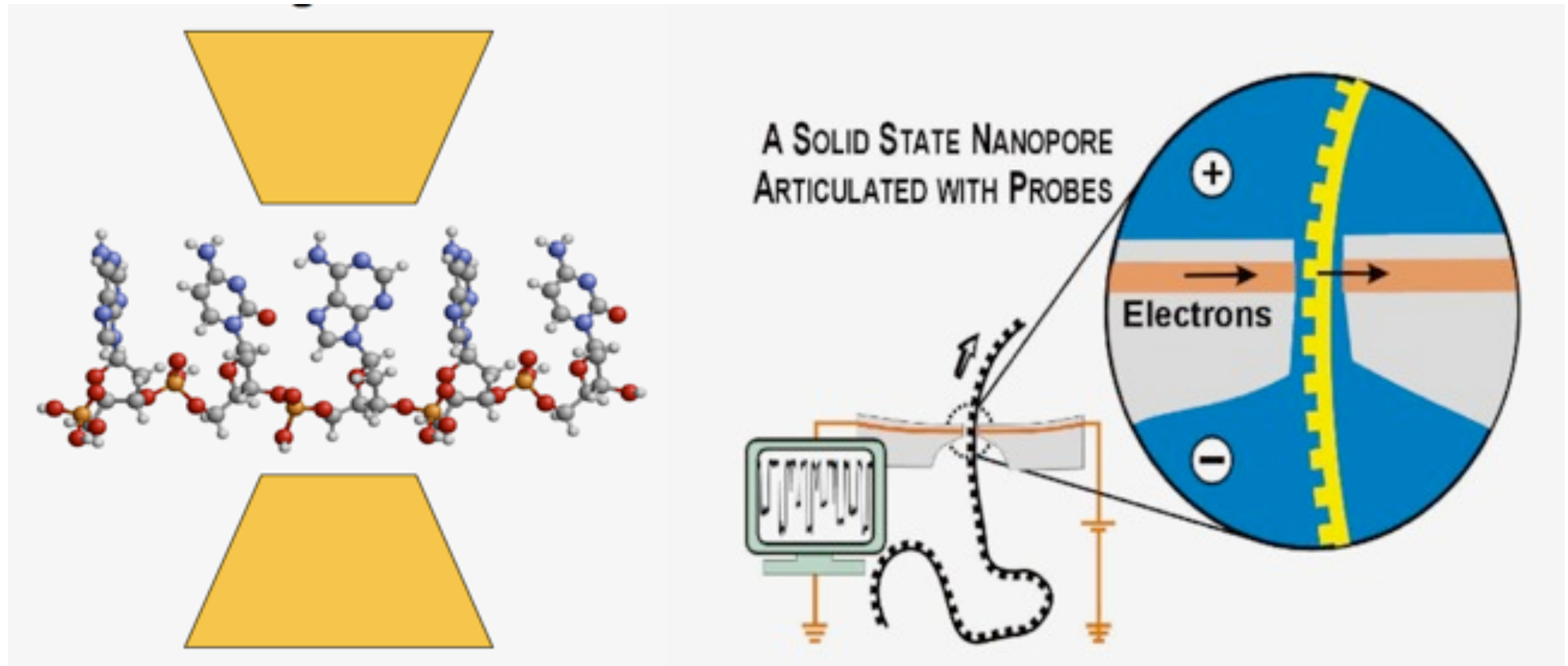
~1 gigabases

>3 million clusters

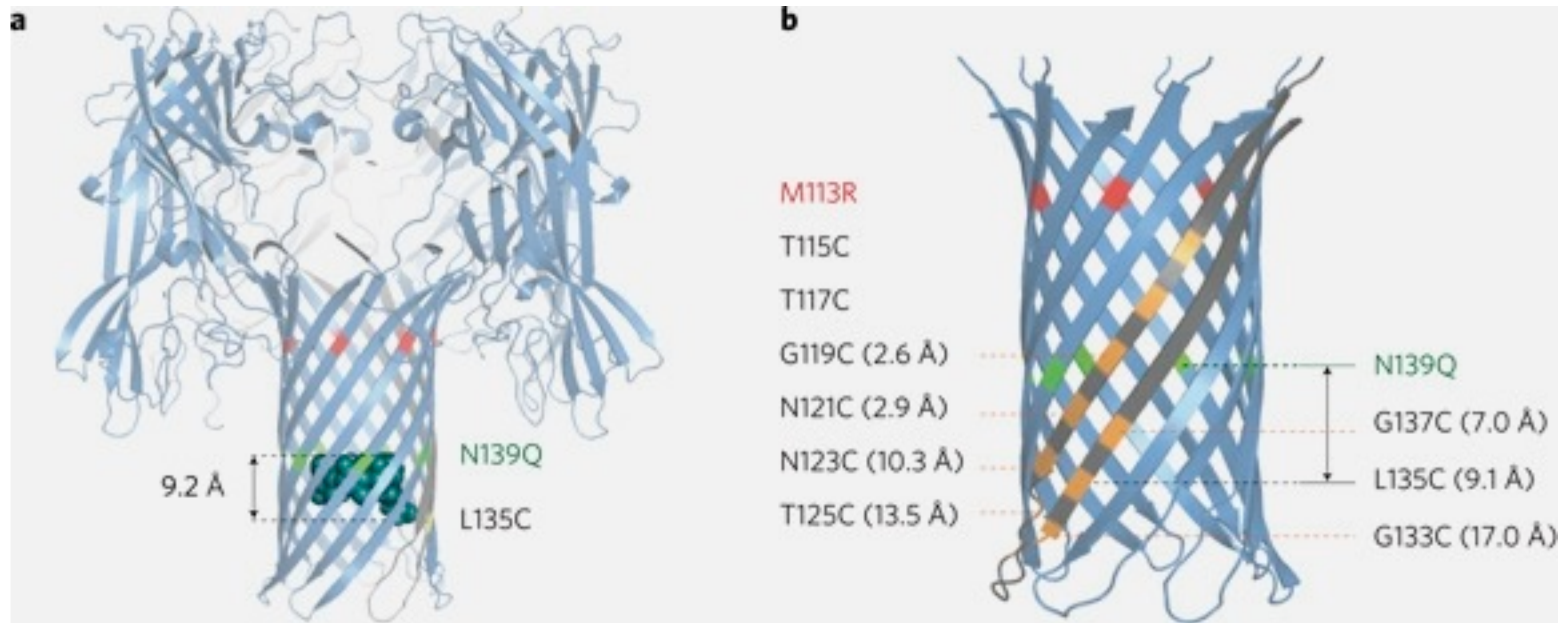
4 bacterial genomes to 50x coverage in 1 day

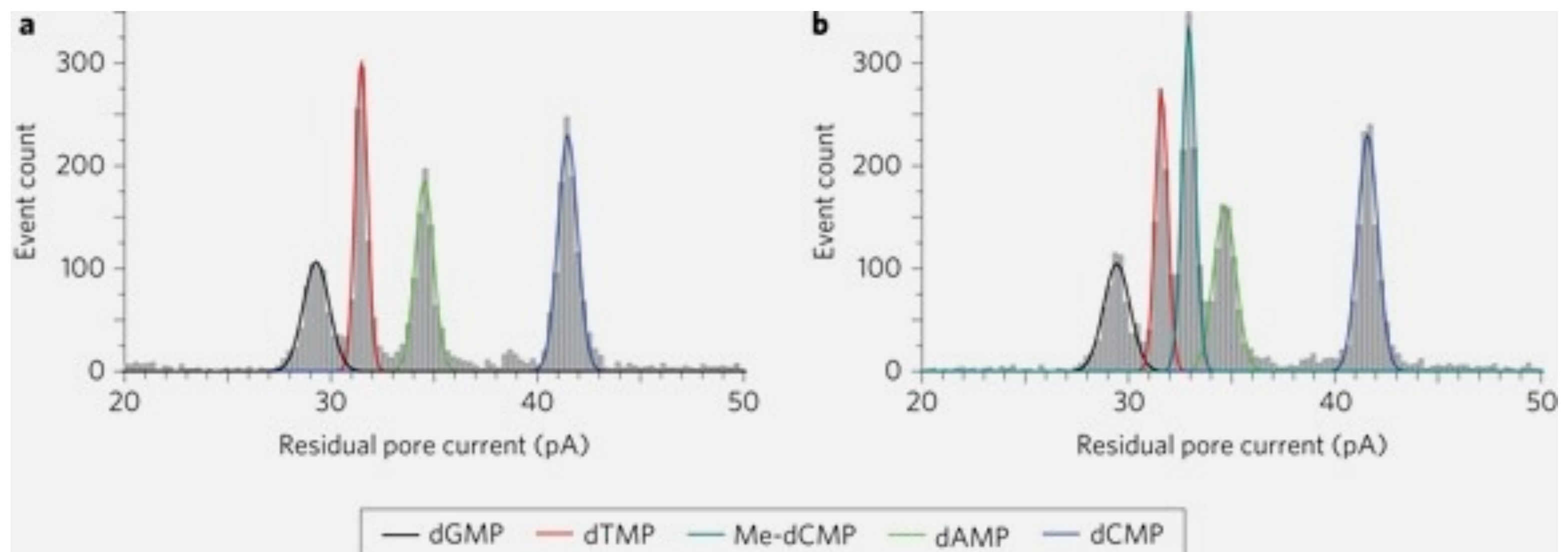
Single Molecule Nanopore Sequencing

Preliminary Experimental Stage - 5 to 10 years before instruments available
However, incredible potential - complete genome in 1 experiment!

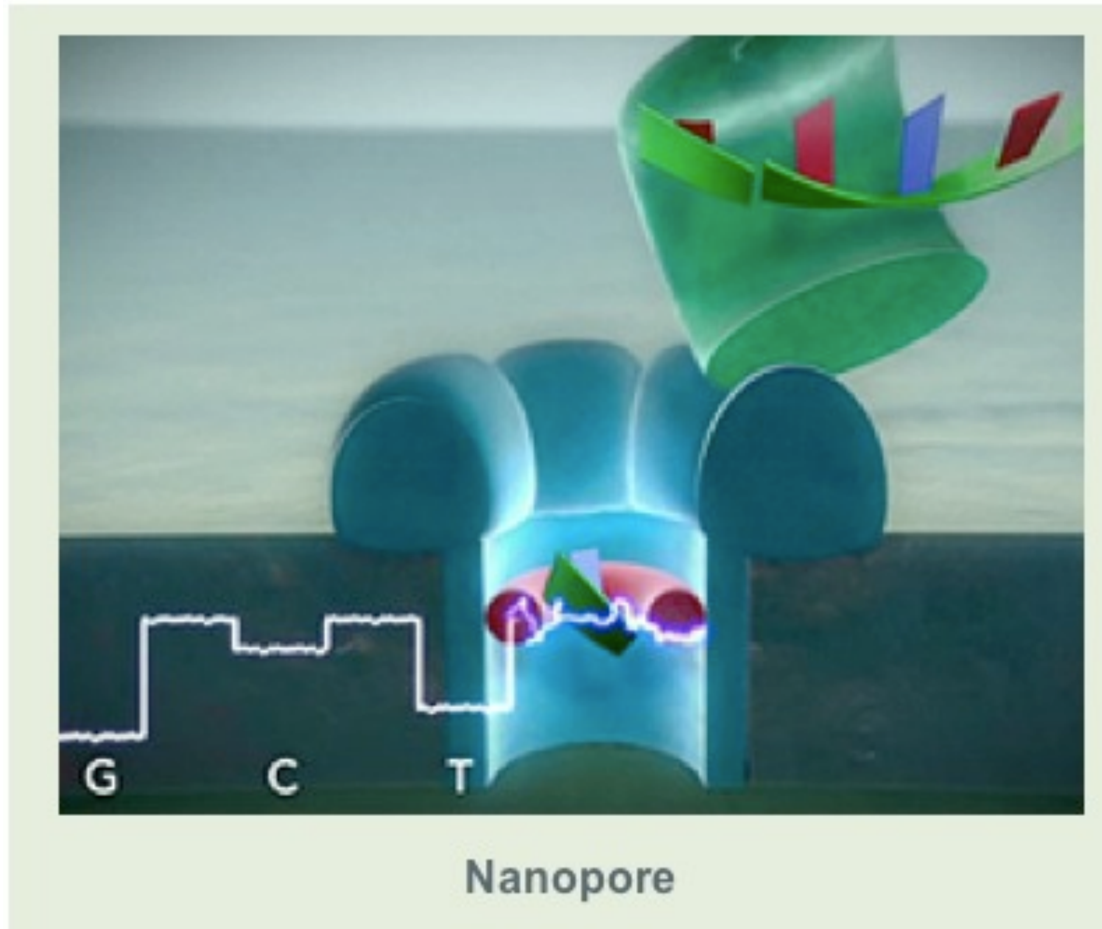


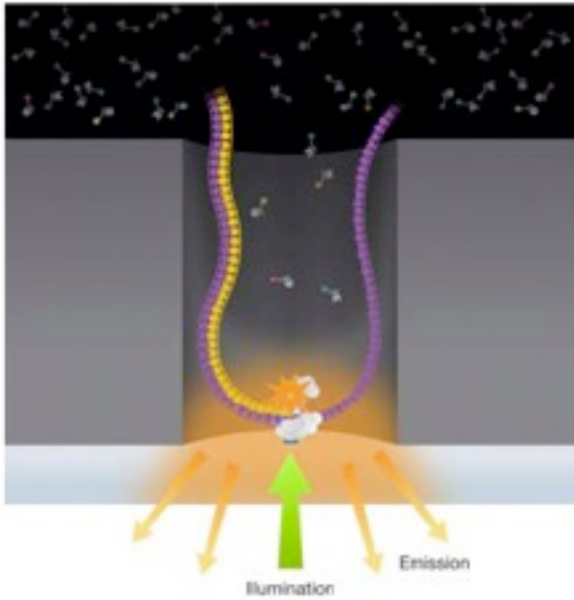
Oxford Nanopore Technologies Ltd



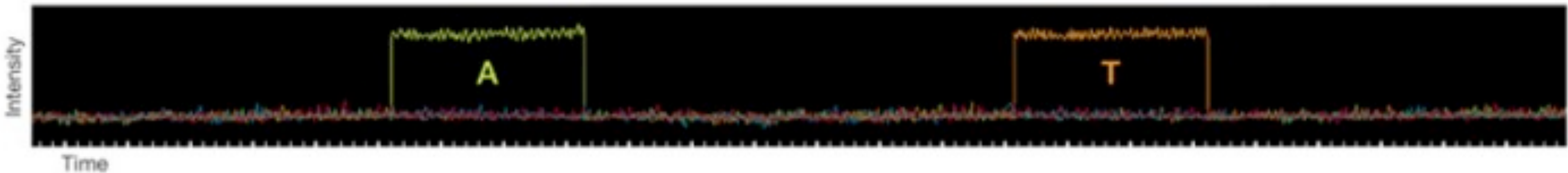


Oxford Nanopore Technologies Ltd

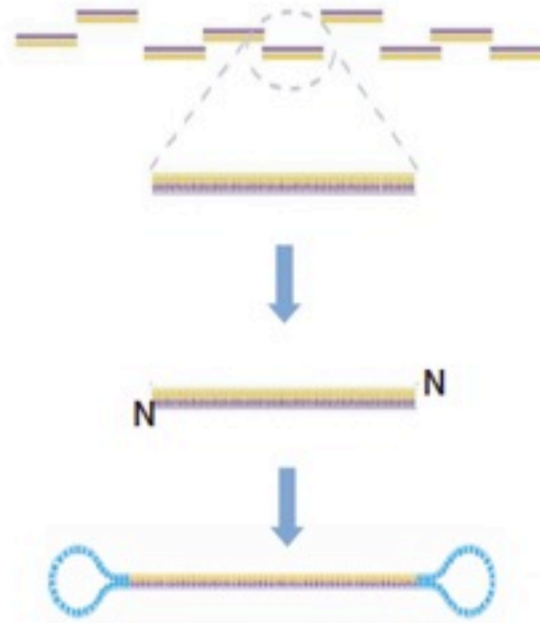


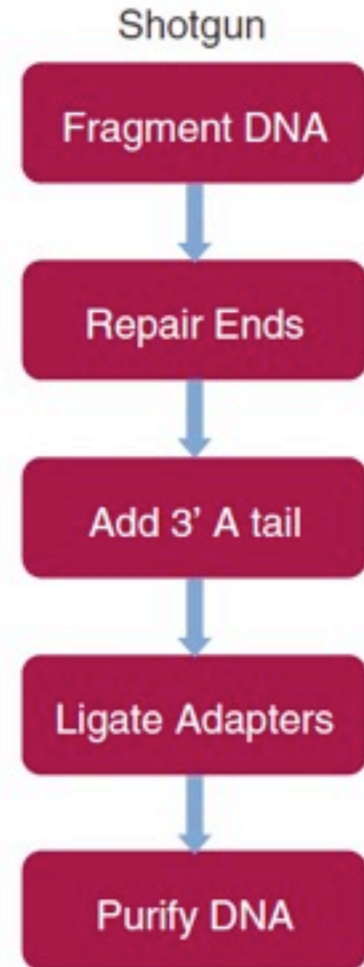


Zero-Mode Waveguides
~10 zeptolitres (10^{-21})

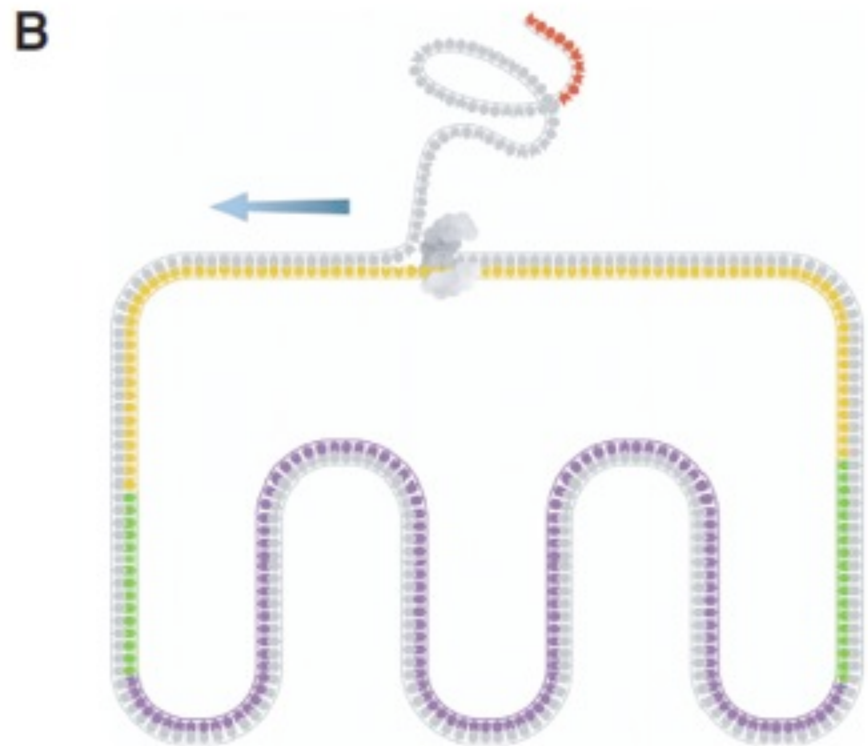


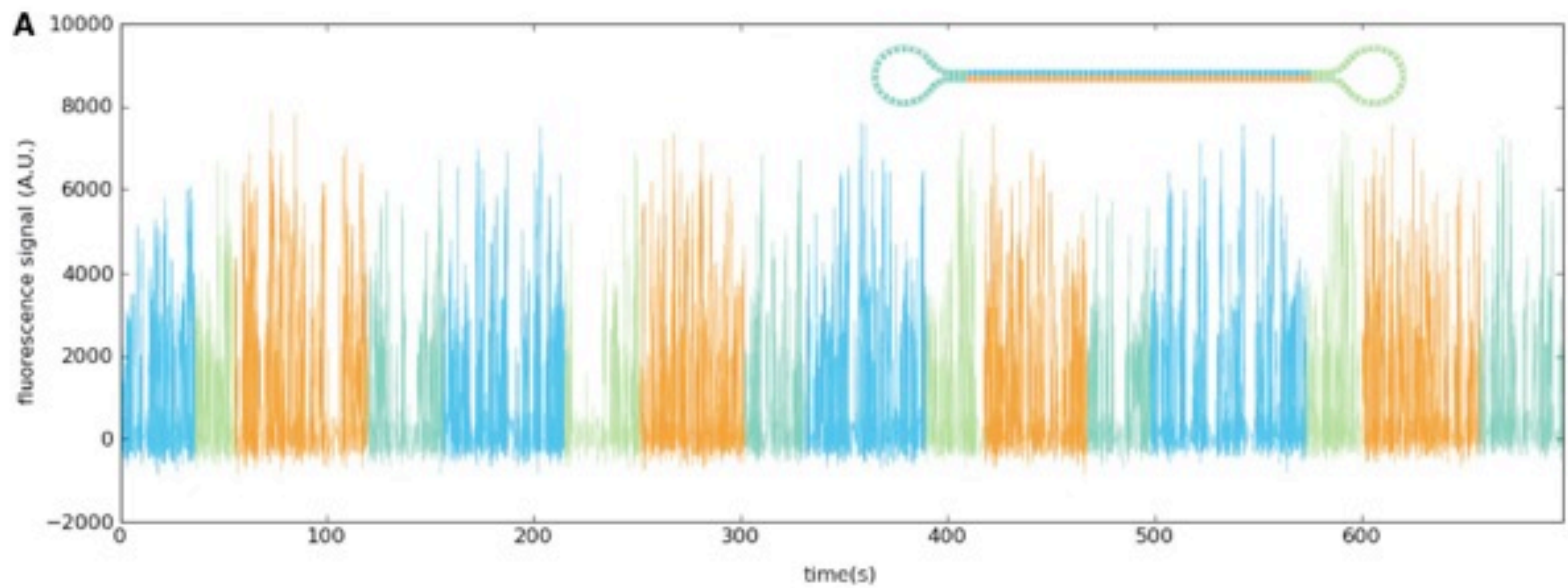
A

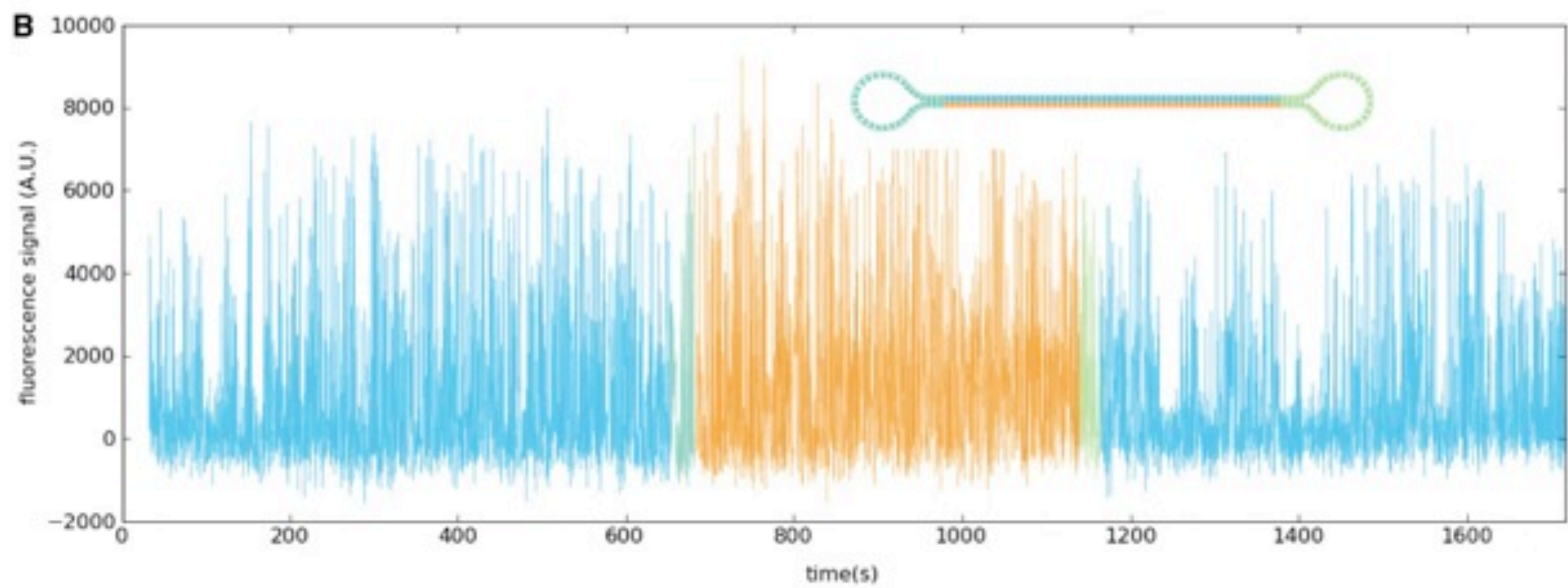


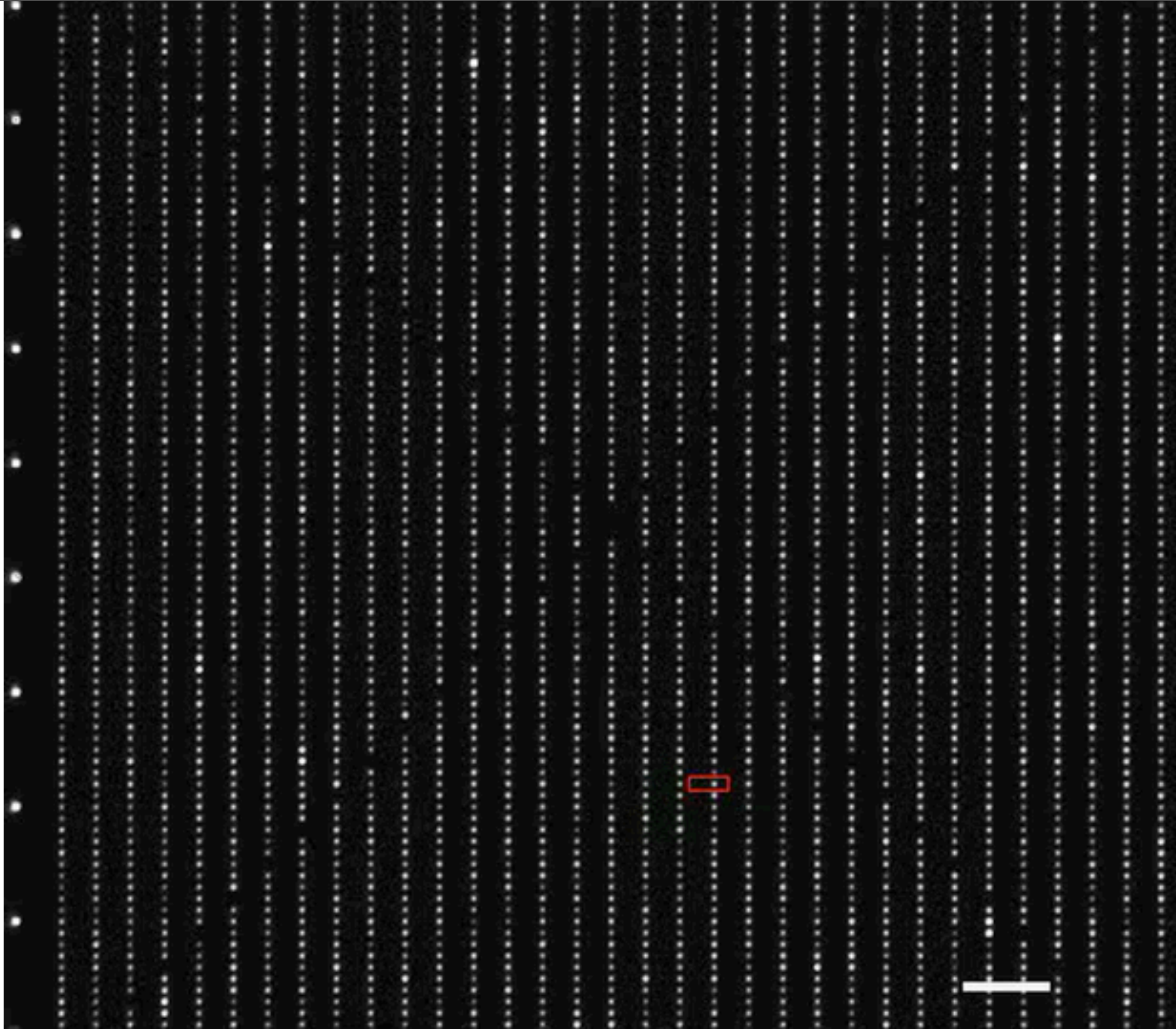


A


B


A
10000
8000
6000
4000
2000
0
−2000
fluorescence signal (A.U.)
0
100
200
300
400
500
600
time(s)


B
10000
8000
6000
4000
2000
0
−2000
fluorescence signal (A.U.)
0
200
400
600
800
1000
1200
1400
1600
time(s)



SMRT
Single Molecule Real Time

Prototype System:

80,000 ZMWs (Zero Mode Waveguides)
2 sets/SMRT Cell
Read length ~1,000 bases/ZMW
Speed ~2 bases/second

This yields: ~160 million bases/run in ~10 minutes

Version 2 System (2014):

1 million ZMWs/SMRT
Read length up to 3,000 bases/ZMW
Speed up to 50 bases/second

This yields: ~3 Gigabases in ~2 minutes

Length is irrelevant. Resolution depends upon the distance between each base, is the same at any point along a DNA chain.

Thus, could read a DNA molecule ~100,000 bases in size.

If had a chip with 1,000,000 pores, then can read ~100,000,000,000 bases (~30 fold coverage of the human genome).

Other Advantages:

1. No assembly issues - because of sequence read length

1. Most important - no cloning involved, so will get the regions not covered by Sanger Shotgun Method - possible methylated bases.

2. Potentially get complete chromosome sequences - No Gaps!

3. Sequence of both chromosomes - Mum & Dad

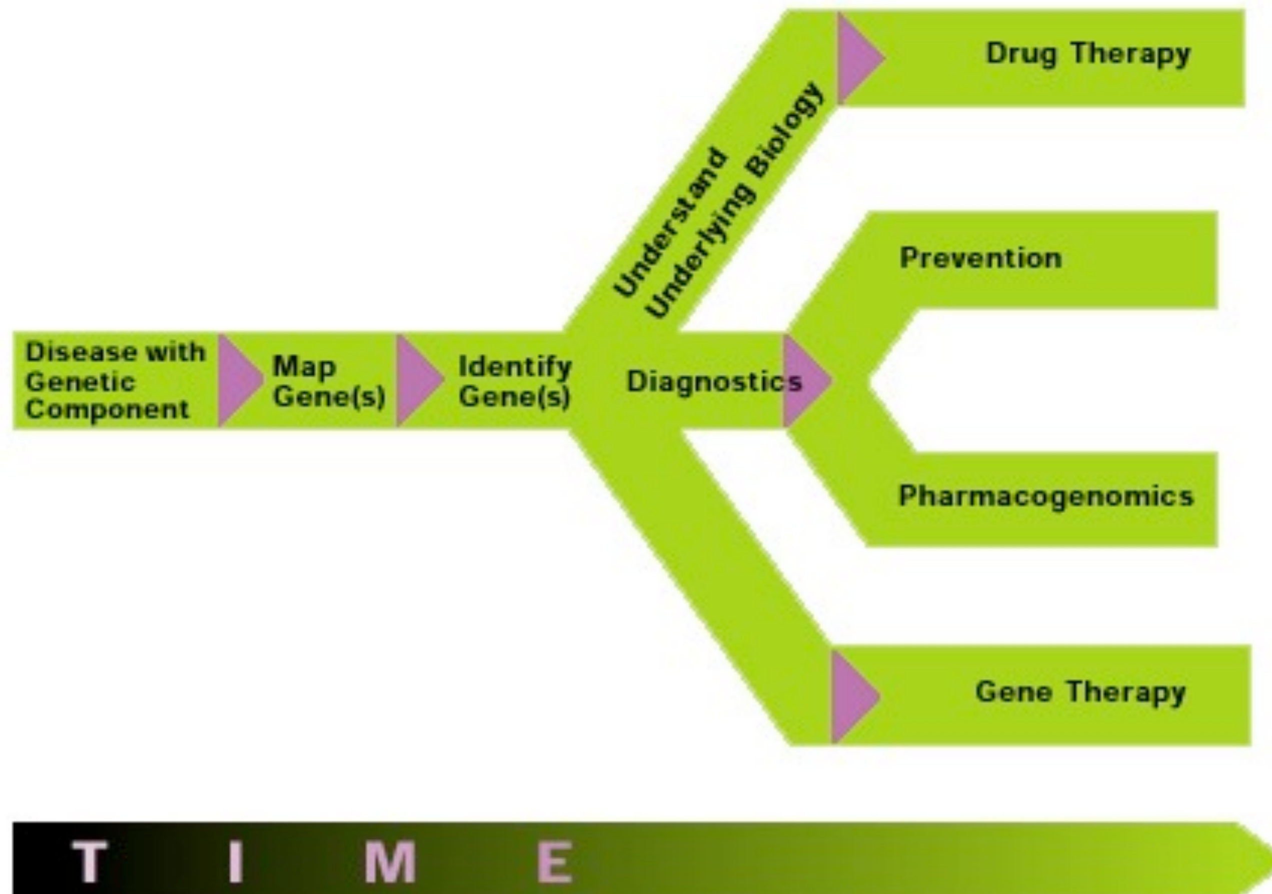
Timelines

Library Preparation:	Protocol dependent ~1 week
Roche – 454 Runs:	~24 hours (instrument time)
Solexa Runs:	~3 – 5 days (instrument time)
Data Analysis:	Eternity - *to infinity and beyond*

The Future

Pharmacogenomics Genetic or Genomic Medicine

Personalised medicines based on your genome



Pharmacogenomics

Genetic polymorphism of thiopurine methyltransferase and its clinical relevance for childhood acute lymphoblastic leukemia.

McLeod HL, Krynetski EY, Relling MV, Evans WE.

Thiopurine methyltransferase (TPMT) catalyses the S-methylation of thiopurines, including 6-mercaptopurine and 6-thioguanine

TPMT activity exhibits genetic polymorphism, with about 1/300 inheriting TPMT deficiency as an autosomal recessive trait

Standard doses of thiopurines, TPMT-deficient patients accumulate excessive thioguanine nucleotides in hematopoietic tissues, leading to severe hematological toxicity that can be fatal

However, TPMT-deficient patients can be successfully treated with a 10- to 15-fold lower dosage of these medications