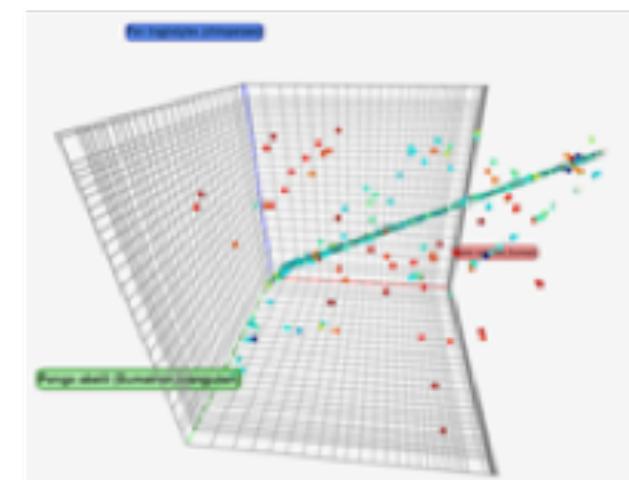
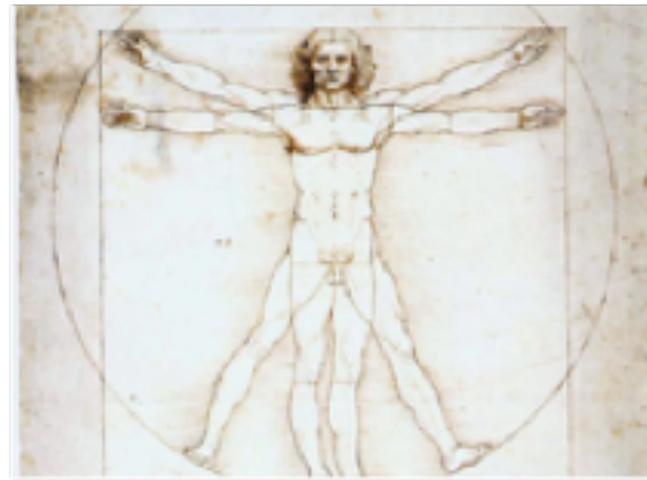
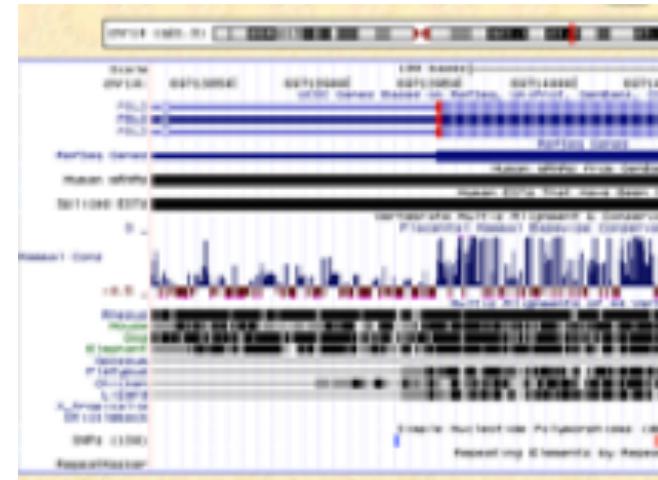


Computational Genomics

History of Genomics



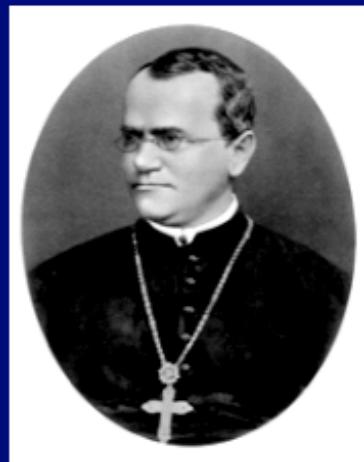


The Genomic Landscape: *circa 2010*

Eric Green, M.D., Ph.D.
Director, NHGRI

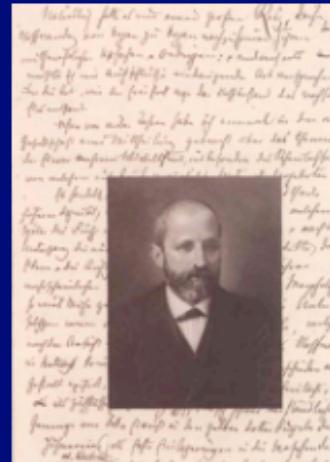


Foundational Milestones in Genetics & Genomics



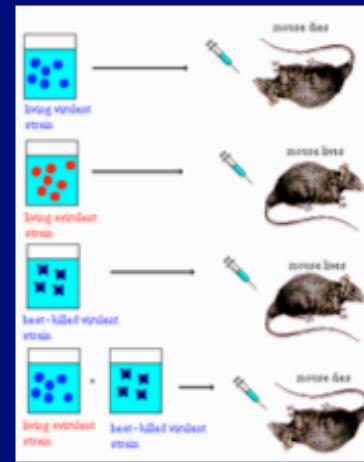
Mendel

1865



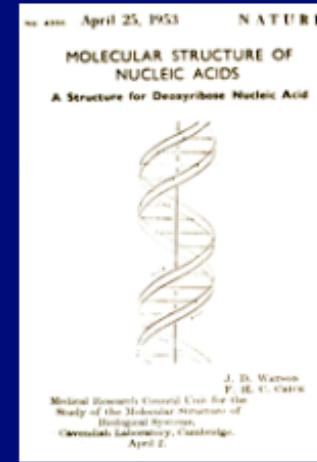
Miescher

1871



Avery

1944



**Watson
& Crick**

1953



Human Genome Project

1990

Human Genome Project (HGP) launched in the U.S.



Ethical, Legal, and Social Implications (ELSI) programs founded at NIH and DOE

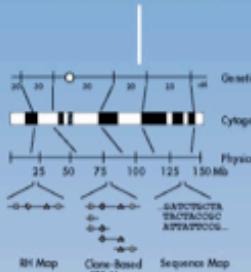


First gene for breast cancer (BRCA1) mapped



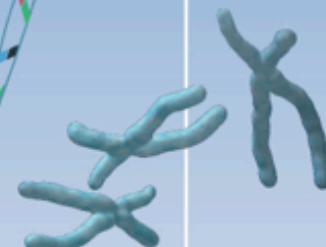
1991

First U.S. Genome Centers established



1992

Second-generation human genetic map developed



Rapid data release guidelines established by NIH and DOE

1993

New five-year plan for the HGP in the U.S. published



Sanger Centre founded (later renamed Wellcome Trust Sanger Institute)



The Wellcome Trust

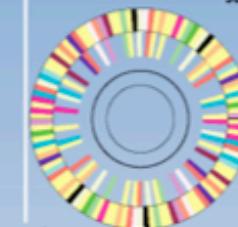
1994

HGP's human genetic mapping goal achieved



1995

HGP's human physical mapping goal achieved

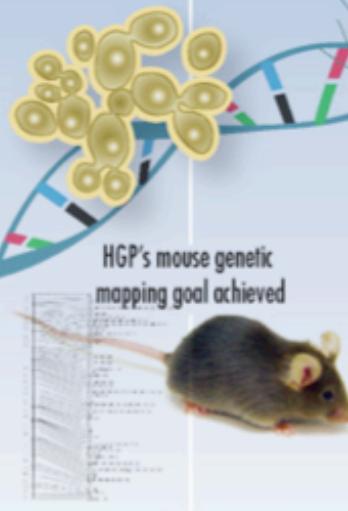


First human gene map established

Pilot projects for human genome sequencing begin in U.S.

First archaeal genome sequenced

Yeast (*S. cerevisiae*) genome sequenced



HGP's mouse genetic mapping goal achieved



Bermuda principles for rapid and open data release established

Human Genome Project

1997

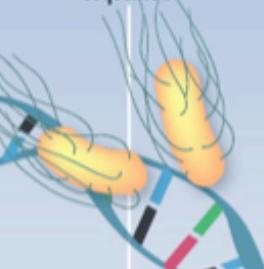
DOE forms Joint Genome Institute



NCHGR becomes NHGRI



E. coli genome sequenced



Genoscope (French National Genome Sequencing Center) founded

1998

Incorporation of 30,000 genes into human genome map

New five-year plan for the HGP in the U.S. published



1999

Full-scale human sequencing begins



RIKEN Genomic Sciences Center (Japan) established

Roundworm (*C. elegans*) genome sequenced



SNP initiative begins

GTGCT
GTCCT

Chinese National Human Genome Centers (in Beijing and Shanghai) established

2000

Draft version of human genome sequence completed

President Clinton and Prime Minister Blair support free access to genome information

Fruit fly (*D. melanogaster*) genome sequenced



Sequence of first human chromosome (chromosome 22) completed



Mustard cress (*A. thaliana*) genome sequenced



Executive order bans genetic discrimination in U.S. federal workplace

2001

Draft version of human genome sequence published



nature



2002

Draft version of mouse genome sequence completed and published



Draft version of rat genome sequence completed

10,000 full-length human cDNAs sequenced



Draft version of rice genome sequence completed and published

2003

Finished version of human genome sequence completed

HGP ends with all goals achieved

to be continued..

Outline

- I. Fundamentals of Genome Mapping & Sequencing**

- II. Mapping & Sequencing in the Human Genome Project**

- III. Comparative Sequencing**

- IV. New Frontiers in Genomics**

Genome Sizes

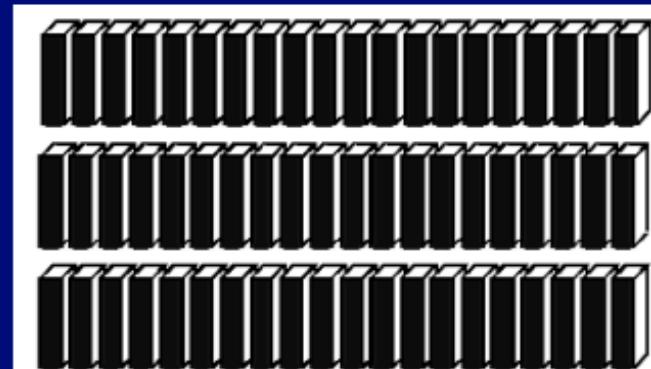
Human Genome
Mouse Genome

Fruit Fly Genome

Nematode Genome

Yeast Genome

***E. coli* Genome**



~3,000,000,000 bp



~160,000,000 bp



~100,000,000 bp

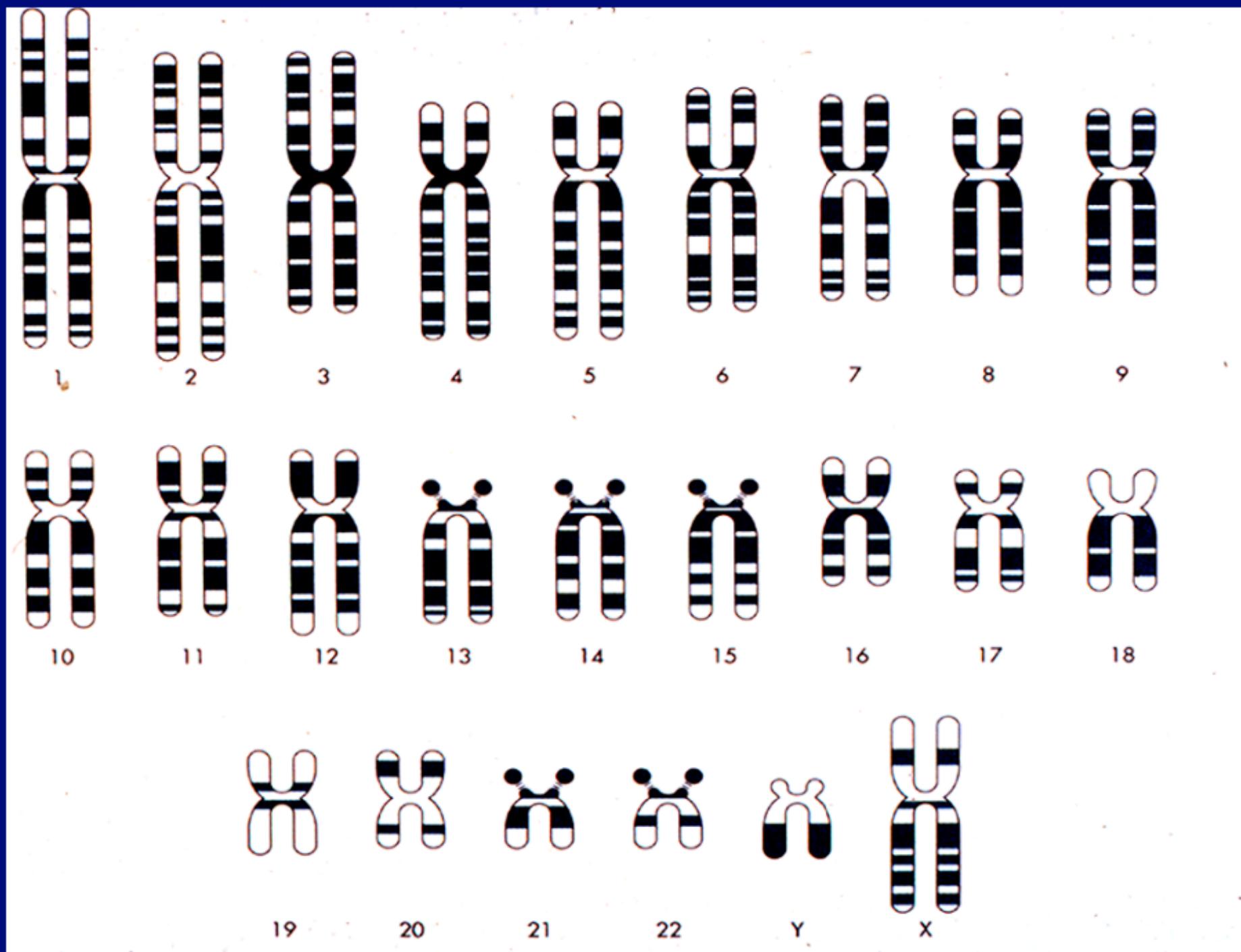


~15,000,000 bp

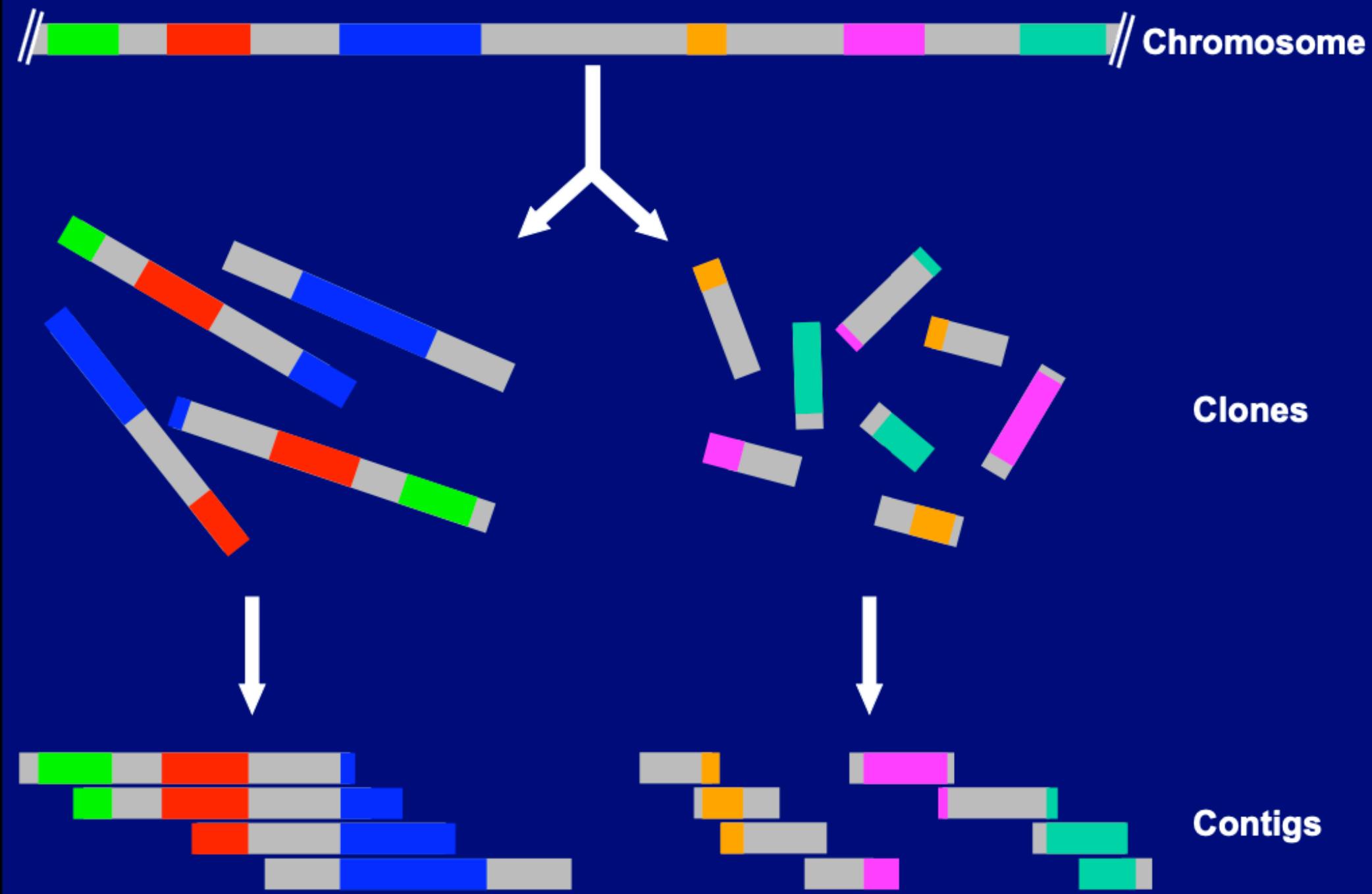


~5,000,000 bp

The Human Cytogenetic Map

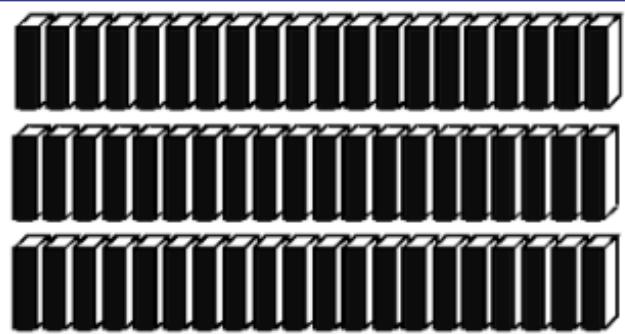


Clone-Based Physical Mapping



Genome Sizes

Human
Mouse



~3,000,000,000 bp

Fruit Fly



~160,000,000 bp



~100,000,000 bp



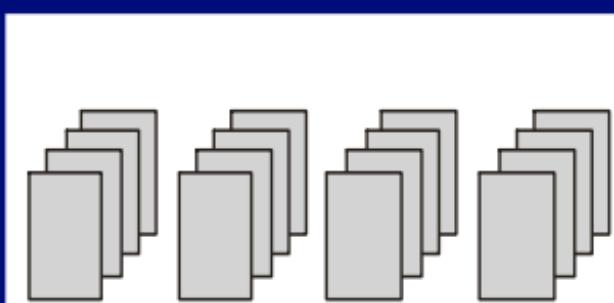
~15,000,000 bp



~5,000,000 bp

Cloning Capacity

YAC



~1,000,000 bp

BAC



~100,000 bp

Cosmid

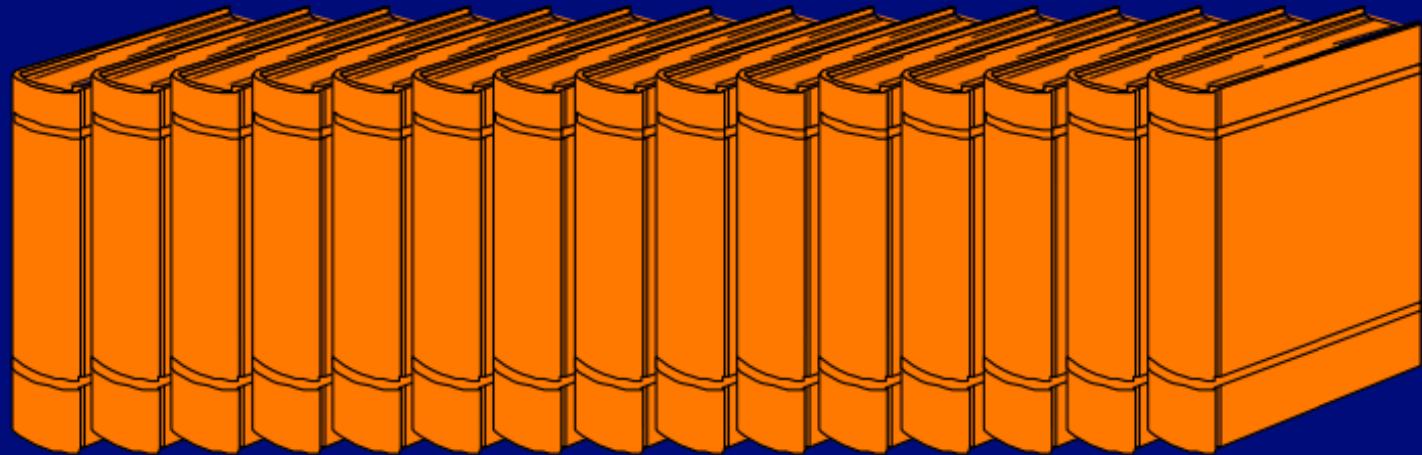


~45,000 bp

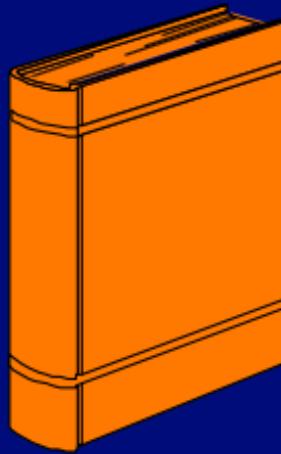
Bacteriophage



~25,000 bp



Genome
(~3000 Mb)



Chromosome
(~130 Mb)

G	G	G	G	G	G	GATCGTCTAGAATCTC
G	G	G	G	G	G	GAGATCTCTGAGAGTC
G	G	G	G	G	G	GTGGGAAACTGTGTGA
T	T	T	T	T	T	TGTGACTAGCCACAGT
T	T	T	T	T	T	TGTGACTAGCCACAGT
T	T	T	T	T	T	TACGTGTGAGAGATGT
A	A	A	A	A	A	ATGATGCACCTGACCC
G	G	G	G	G	G	GGGTTCACTCTCAAC
G	G	G	G	G	G	GACTCACTCCACCTCA
C	C	C	C	C	C	CCGGTTAGACATACAT
G	G	G	G	G	G	GAGGCCAACCGCCGCT
G	G	G	G	G	G	GTGACACGTCCACCAACC

YAC
(~0.5-1.0 Mb)

GATCGTCTAGAATCTC
GAGATCTCTGAGAGTC
GTGGGAAACTGTGTGA
TGTGACTAGCCACAGT
TAGGTATTGGGCATT
TACGTGTGAGAGATGT
ATGATGCACCTGACCC
GGGTTCACTCTCAAC
GACTCACTCCACCTCA
CCGGTTAGACATACAT
GAGGCCAACCGCCGCT
GTGACACGTCCACCAACC

BAC
(~0.1-0.2 Mb)

Sequence-Ready BAC Contig Map

N0315P01a	N0476P21a*	N0443J03a*	N0226B17a	N0389N18a*
252L07a	N0535K08a	N0483D22b*	N0329F08a*	N0440K08b*
214G08b	R022C01a	N0373K02a*	N0055I14a*	
79D08a*	N0134N03a*	G196A18*	R016J04c	089H22aw*
		N0481I07a*	N0263P13a*	N0482F14a*
N0077I08b*		N0263N12a*	N0544P11a	N0547A15b*
R067E13c*		N0563H17a*	1121E10a*	1008B19bw
N0373M05a*		N0456F21a*	N0407J08d	N0506N01b*
N0369G05a*		N0012D01a*	N0283N08a*	N0154E01a*
N0286H22a*			R481C05b	N0513F14a*
N0142N09b	N0187J16b*		G117E02*	N0385N12a*
R137C23a	N0285J24a		N0282J18b*	N0553F02a*
N0393C21a*	R043K06a		N0466P05a	RG021N08*
R022J17a*	N0497C08a*		R041D11a*	N0503N10b
N0200K11a	N0007H06a		N0451O05b	N0134N20a*
	N0380E08a			N0120J02a

Pairwise End Sequencing: A Unified Approach
to Genomic Mapping and Sequencing

JARED C. ROACH,^{*†} CECILIE BOYSEN,[†] KAI WANG,^{*} AND LEROY HOOD^{*}

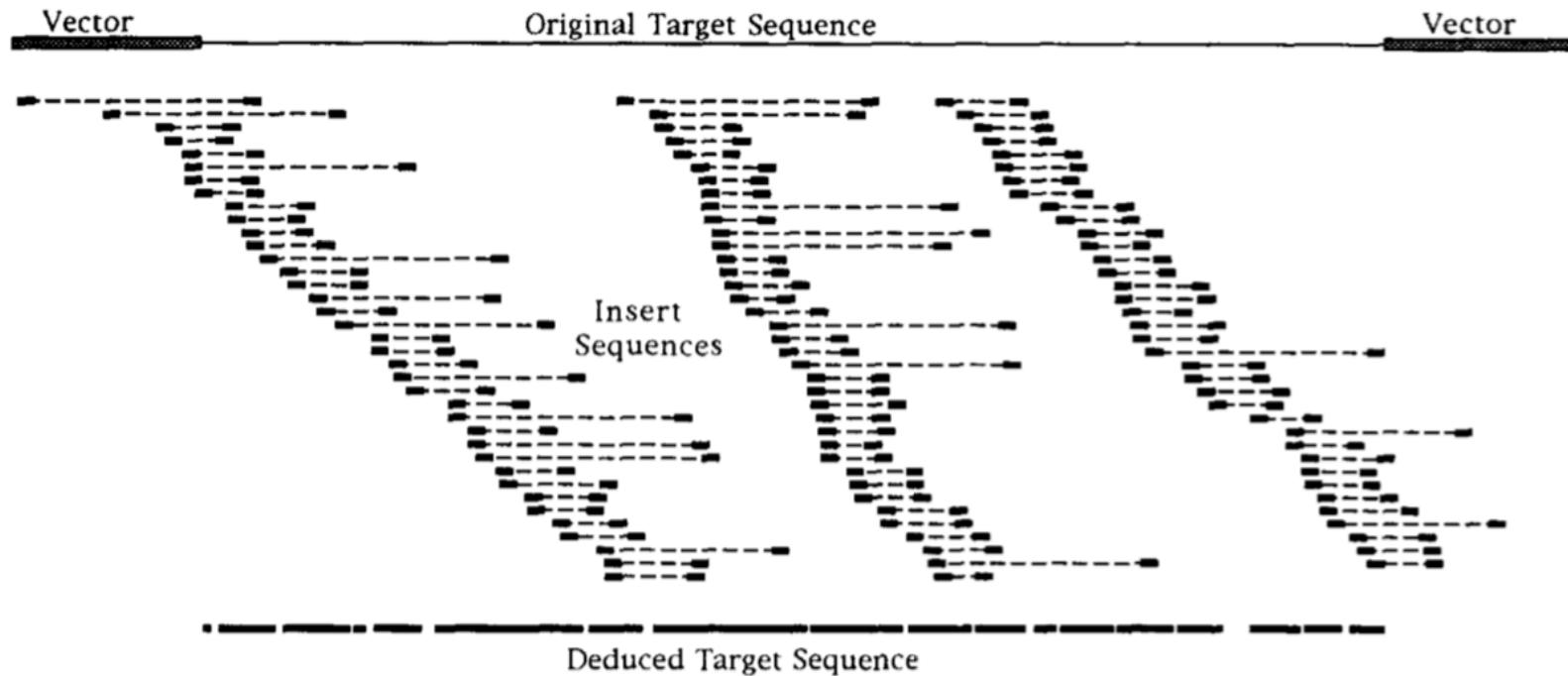
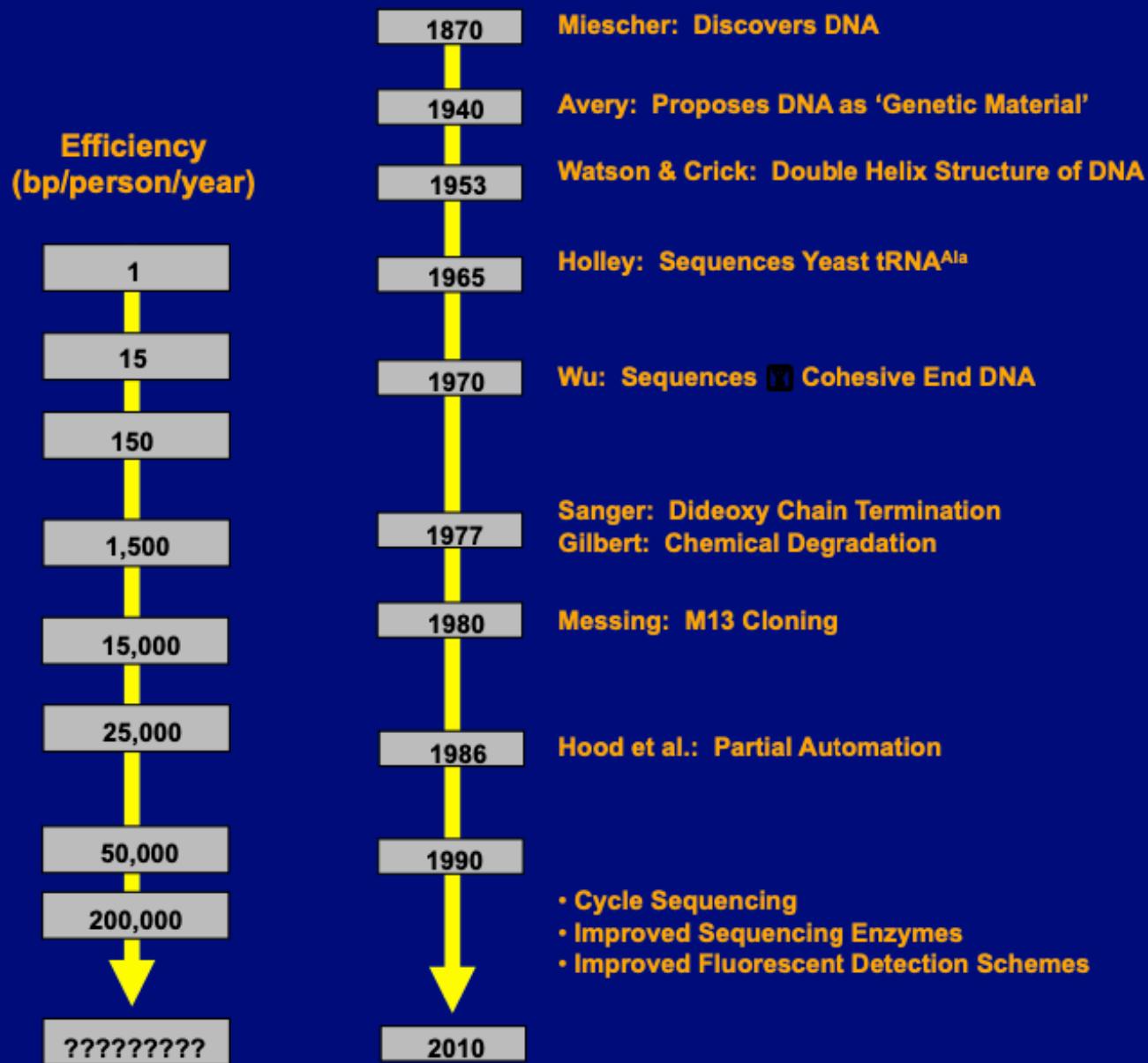


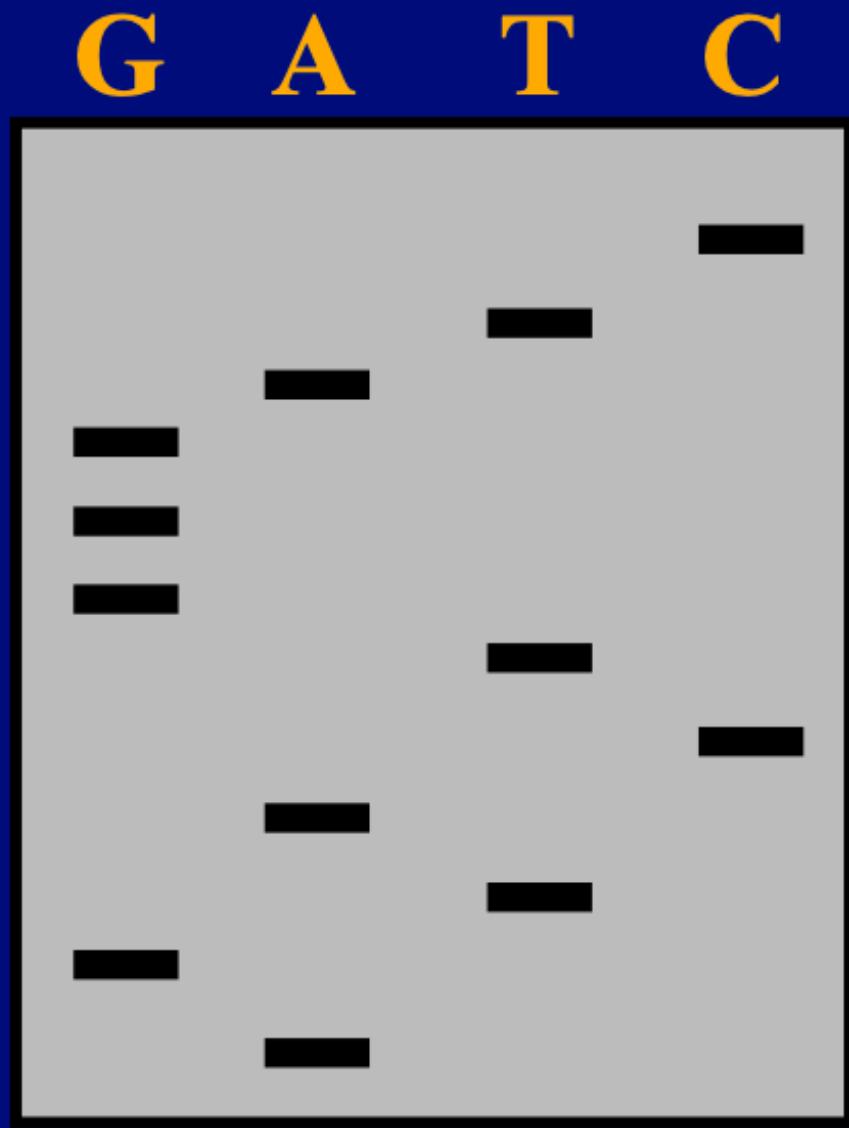
FIG. 1. A model “double-barrel shotgun” assembly. A 2.25 sequence redundancy produces 18 contigs that span 90% of an original target cosmid at 99.9% accuracy. Contig orientation and order are determined as shown. All but one gap are less than 400 bp; the remaining is 751 bp. More statistics are presented in Table 1.

DNA Sequencing

History of DNA Sequencing

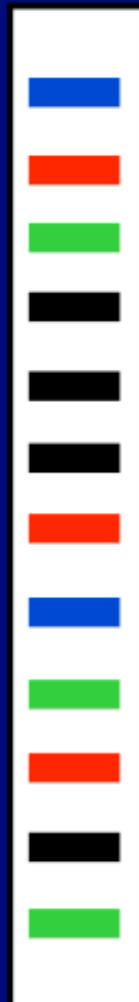


DNA Tagged with Radioactivity

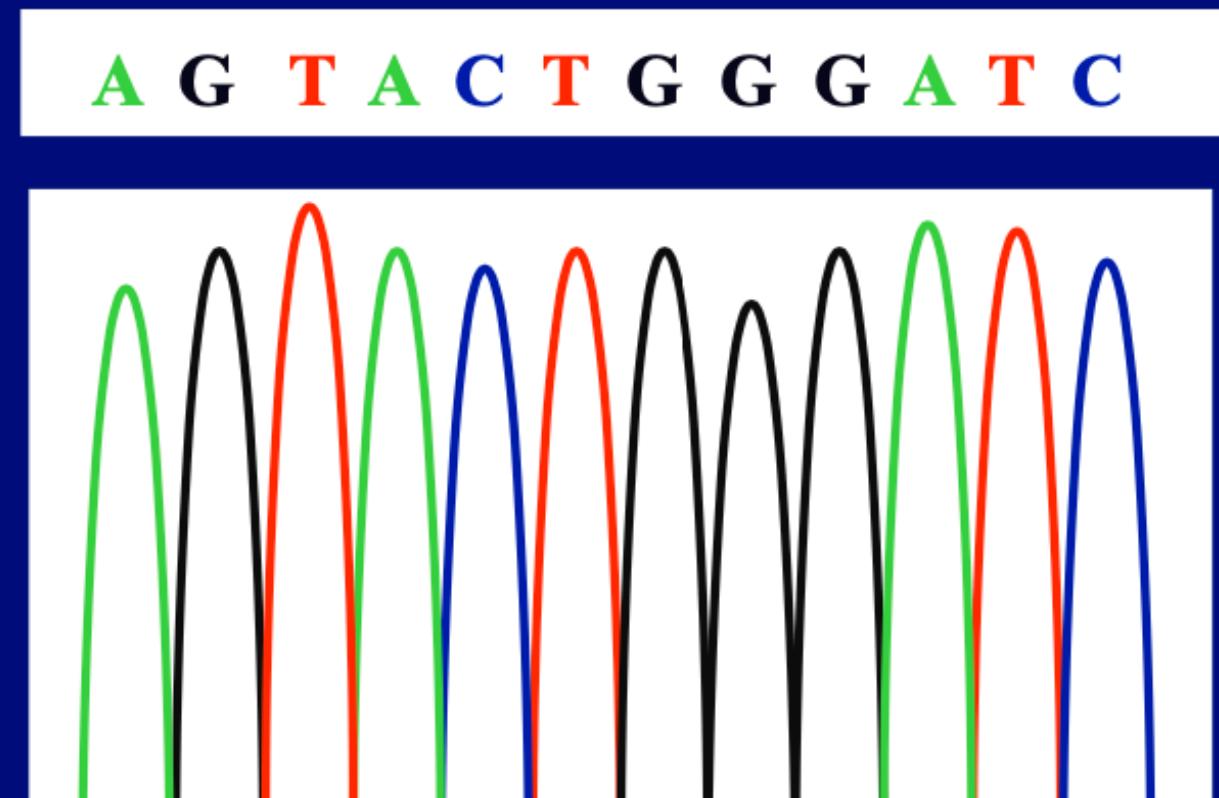


G: G Reaction
A: A Reaction
T: T Reaction
C: C Reaction

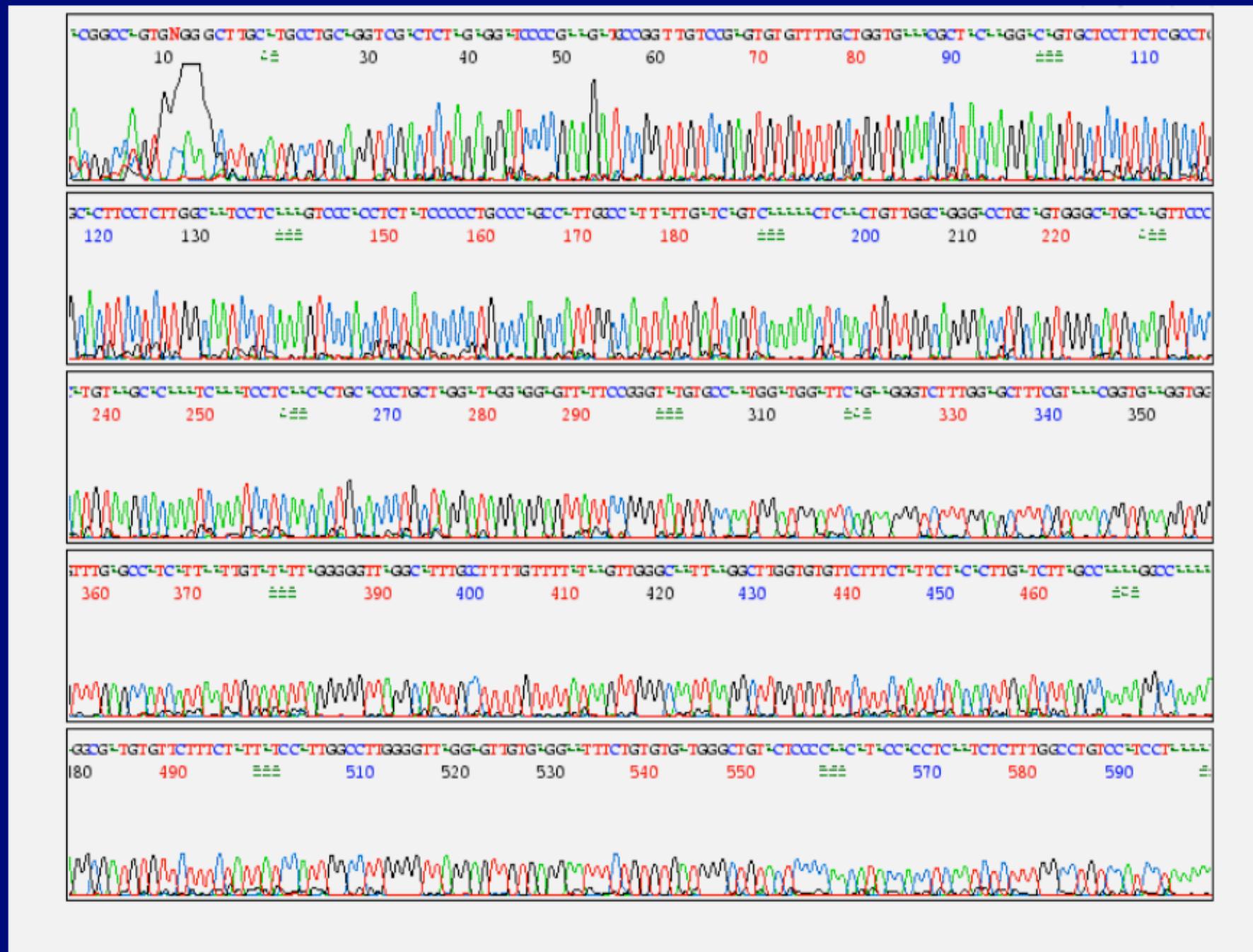
Analyzing Fluorescent DNA Sequencing Data



Computer
Analysis



Fluorescent DNA Sequencing Results



Analysis of Gene Expression

- ESTs: **Expressed-Sequence Tags**
- SAGE: **Serial Analysis of Gene Expression**
- Full-Insert (Full-Length) cDNA Sequencing



mgc.nci.nih.gov

Genome Sequencing



Shotgun Sequencing

Subclone Construction

```
GATCGTCTAGAAATCTC  
GAGATCTCTGAGAGTC  
GTGGGAAACTGTGTGA  
TGTGACTAGCCACAGT  
TACGTGTGAGAGATGT  
ATGATGCACCTGACCC  
GGTTTCACTCTAAC  
GACTCACTCACCTCA  
GAGGCCACCGCCGCT  
GTGCACGTCCCCACC  
GATTATTACCATTTA  
ATCCCTAGGATTGACA
```

BAC DNA



Prepare Multiple Copies

GA	GA	GA	GA	GATCGTCTAGAAATCTC
GM	GA	GA	GA	GAGATCTCTGAGAGTC
GT	GT	GT	GT	GTGGGAAACTGTGTGA
TG	TG	TG	TG	TGTGACTAGCCACAGT
TM	TM	TM	TM	TACGTGTGAGAGATGT
AT	AT	AT	AT	ATGATGCACCTGACCC
GG	GG	GG	GG	GGTTTCACTCTAAC
GM	GA	GA	GA	GACTCACTCACCTCA
GM	GA	GA	GA	GAGGCCACCGCCGCT
GT	GT	GT	GT	GTGCACGTCCCCACC
GA	GA	GA	GA	GATTATTACCATTTA
AT	AT	AT	AT	ATCCCTAGGATTGACA



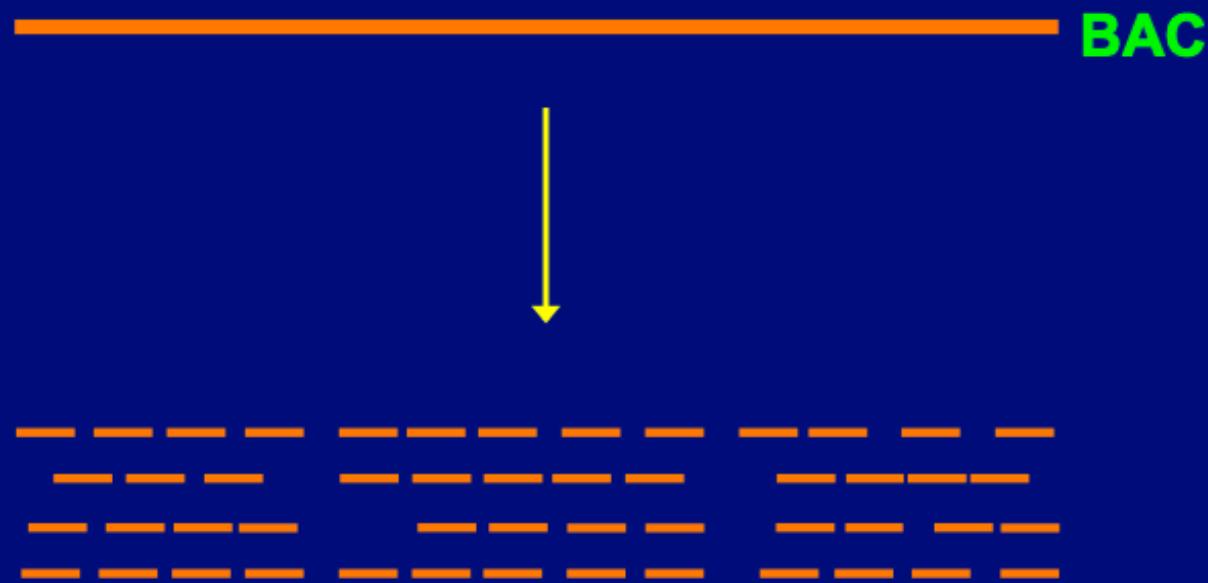
Randomly Fragment



Subclone Fragments



Shotgun Sequencing Strategy



Poisson Calculations

The sequencing strategy for the shotgun approach follows the Lander and Waterman application of the Poisson distribution

The probability a base is not sequenced is given by:

$$P_0 = e^{-c}$$

Where:

- c = fold sequence coverage ($c=LN/G$),
- LN = # bases sequenced, i.e. L = average sequencing read length and N = # reads
- G = target sequence length
- $e = 2.718$ ($e=2.718281828459$)

Fold Coverage	$P_0 = e^{-c}$	% not sequenced	% sequenced
1	0.37	37%	63%
2	0.135	13.5%	87.5%
3	0.05	5%	95%
4	0.018	1.8%	98.2%
5	0.0067	0.6%	99.4%
6	0.0025	0.25%	99.75%
7	0.0009	0.09%	99.91%
8	0.0003	0.03%	99.97
9	0.0001	0.01%	99.99%
10	0.000045	0.005%	99.995%

(a) Sequence reads

Read 1 CACATACACATGG

Read 2 TCAATGGGGCTAA

Read 3 AGCACGGACTTGTCACTACACATG

Read 4 ACACATGGAAATA

Read 5 GGGCTAATGATTGTCAC

Read 6 TGATTGTCACATA

Read 7 ATTCATGAAGCACGGA

Read 8 GTCACATACACATGATCAATGGGG

↓ Use computer to assemble sequence reads

(b)

7 ATTCATGAAGCACGGA

3 AGCACGGACTTGTCACTACACATG

8 GTCACATACACATGATCAATGGGG

2 TCAATGGGGCTAA

5 GGGCTAATGATTGTCAC

6 TGATTGTCACATA

1 CACATACACATGG

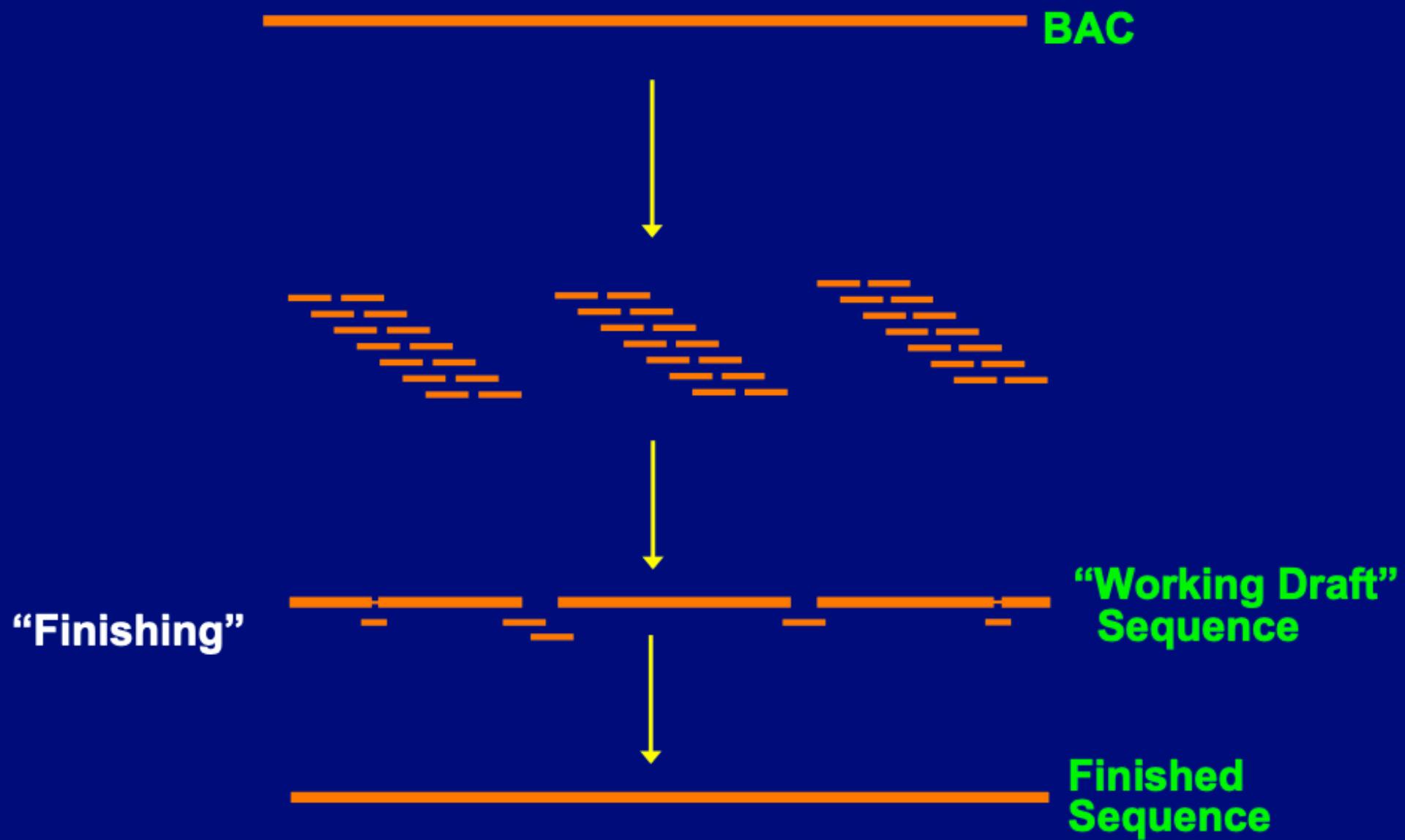
4 ACACATGGAAATA

↓ Assembled sequence

(c)

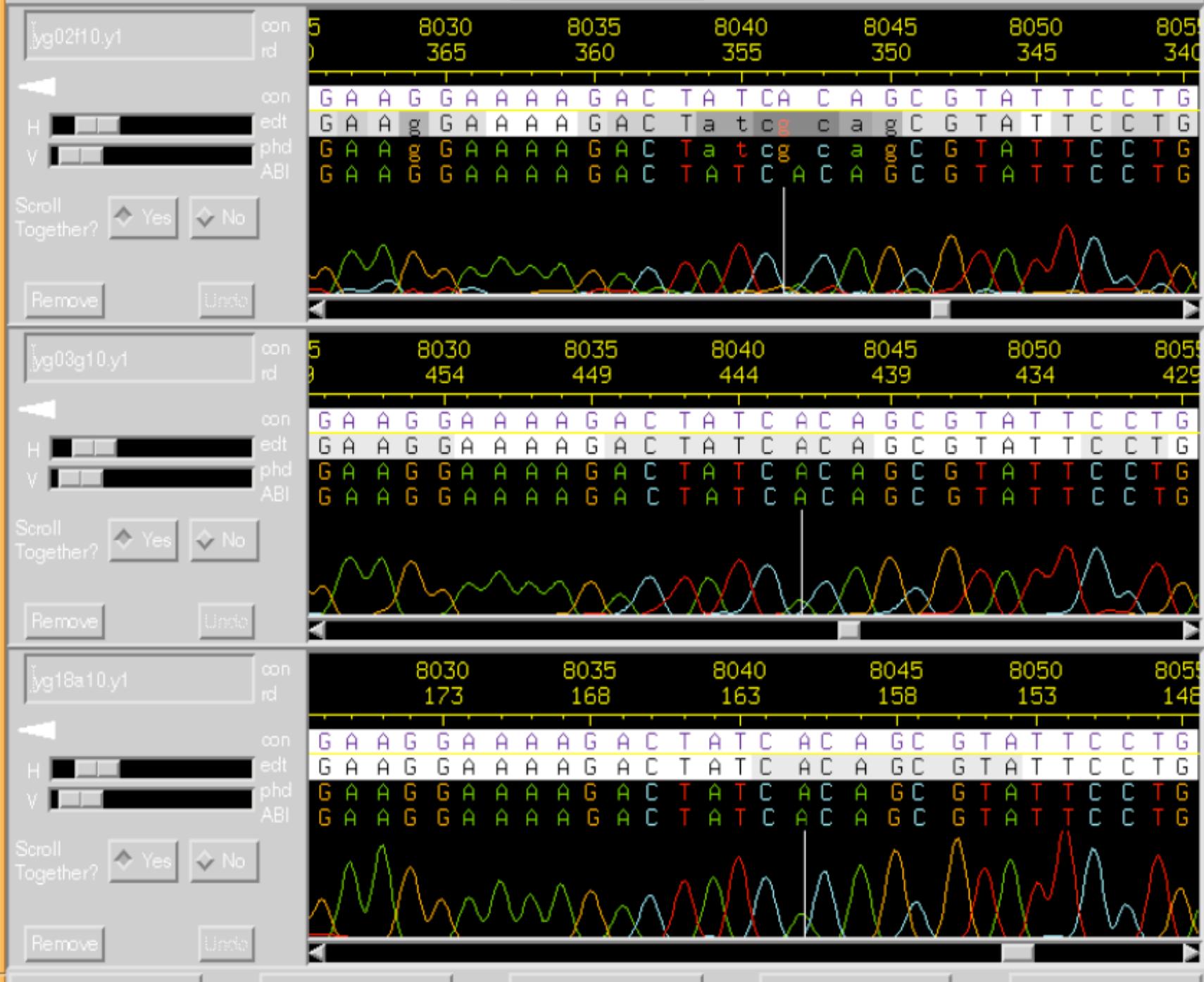
ATTCATGAAGCACGGACTTGTCACTACACATGATCAATGGGGCTAAATGATTGTCACATACACATGGAAATA

Shotgun Sequencing Strategy



Trace Window: Contig32

[Dismiss](#)



Sequence Finishing: Resolving Ambiguities



*** Sequence Finishing: Remains Relatively Expensive ***

Historically Significant Genome Sequencing Projects

First Eukaryotic Genome Sequence



Goffeau et al. (1997)

February, 2001 Draft Sequence

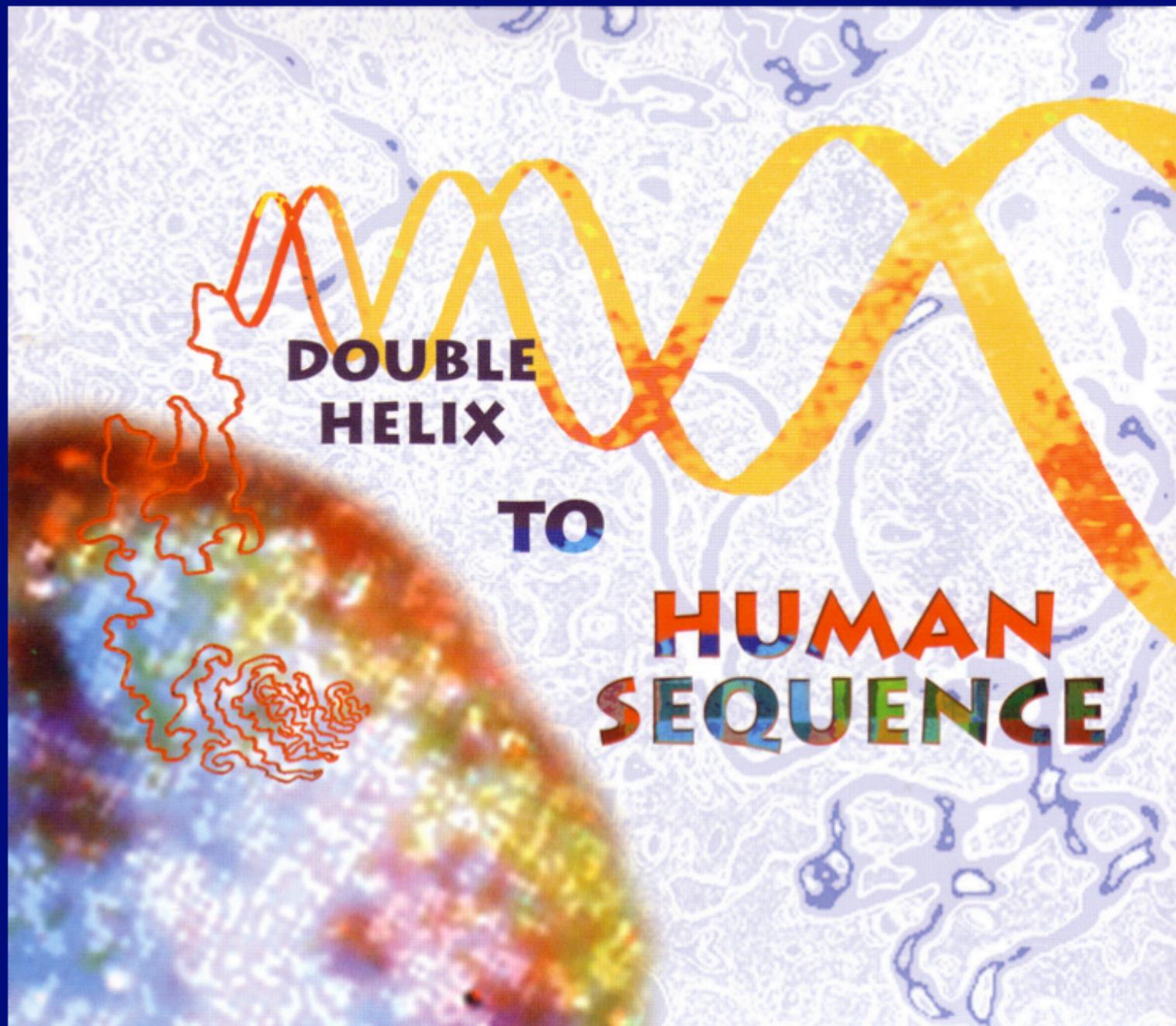


International Human Genome
Sequencing Consortium (2001)



Venter et al. (2001)

April, 2003 Completion



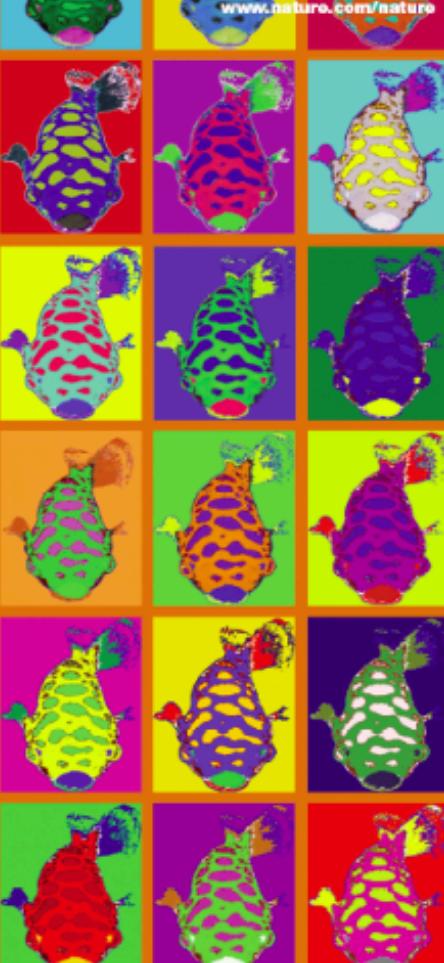
October, 2004 Publication

21 October 2004

International weekly journal of science

£18.00

nature



www.nature.com/nature

Tetraodon to human

Evolutionary history in genome sequences

General relativity

Did the orbit move for you?

The human genome

Going the last mile

Antibiotics crisis

Market forces fail to deliver

Medical ethics

Choosing deafness

naturejobs think Finland

articles

Finishing the euchromatic sequence of the human genome

International Human Genome Sequencing Consortium*

*A list of authors and their affiliations appears in the Supplementary Information

The sequence of the human genome encodes the genetic instructions for human physiology, as well as rich information about human evolution. In 2001, the International Human Genome Sequencing Consortium reported a draft sequence of the euchromatic portion of the human genome. Since then, the international collaboration has worked to convert this draft into a genome sequence with high accuracy and nearly complete coverage. Here, we report the result of this finishing process. The current genome sequence (Build 35) contains 2.85 billion nucleotides interrupted by only 341 gaps. It covers ~99% of the euchromatic genome and is accurate to an error rate of ~1 event per 100,000 bases. Many of the remaining euchromatic gaps are associated with segmental duplications and will require focused work with new methods. The near-complete sequence, the first for a vertebrate, greatly improves the precision of biological analyses of the human genome including studies of gene number, birth and death. Notably, the human genome seems to encode only 20,000–25,000 protein-coding genes. The genome sequence reported here should serve as a firm foundation for biomedical research in the decades ahead.

The Human Genome Project (HGP) was launched in 1990 with the goal of obtaining a highly accurate sequence of the vast majority of the euchromatic portion of the human genome. The initial work followed a two-pronged approach: (1) the mapping of the human and mouse genomes^{1–3} to allow the study of inherited disease and provide a crucial scaffold for genome assembly; and (2) the sequencing of organisms with smaller, simpler genomes^{4–6} to serve as a testbed for method development and assist in interpreting the human genome. With success along both paths, the sequencing of the human genome itself eventually became feasible. The International Human Genome Sequencing Consortium (IHGSC), an open collaboration involving twenty centres in six countries, was formed to carry out this component of the HGP.

In February 2001, the IHGSC⁷ and Celera Genomics⁸ each reported draft sequences providing a first overall view of the human genome. These sequences allowed systematic study of the human genome itself, including identification of genes, combinatorial architecture of proteins, regional differences in genome composition, distribution and history of transposable elements, distribution of polymorphism and relationship between genetic recombination and physical distance. Moreover, systematic knowledge of the human genome has enabled new tools and approaches that have markedly accelerated biomedical research.

Both draft sequences, however, had important shortcomings. The IHGSC sequence, for example, omitted ~10% of the euchromatic genome; it was interrupted by ~150,000 gaps; and the order and orientation of many segments within local regions had not been established. The IHGSC thus turned to the challenge of completing the sequence of the euchromatic genome. Operationally, a finished sequence was defined as having an error rate of, at most, one event per 10⁴ bases, and the goal for completion was coverage in finished sequence of at least 95% of the euchromatic genome, with the only gaps being those refractory to all available techniques⁹ (see <http://www.genome.gov/10000923>). The goal was challenging because the human genome is replete with such features as dispersed repeats and large segmental duplications, which greatly complicate the determination of genome structure and sequence. In fact, near-complete sequences have been obtained so far only for three multicellular organisms: the nematode¹⁰, mustard weed¹¹ and the fruitfly¹². These genomes are all roughly 30-fold smaller than the human genome and have much simpler structure.

We describe here the results of a multiyear effort by the IHGSC

towards the goal of a complete human sequence. The number of gaps has been reduced 400-fold to only 341, most of which are associated with segmental duplications and will require new methods for resolution. The assembled near-complete genome sequence has an error rate of only ~1 event per 100,000 bases; it contains 2.85 billion nucleotides and covers ~99% of the euchromatic genome. This paper describes the current genome sequence and the process used to produce it; examines the accuracy and completeness of the sequence; and illustrates biological analyses made possible by the sequence. We do not attempt here a comprehensive analysis of the contents of the human genome. An initial analysis was previously reported¹³ and a series of papers is being written describing the individual chromosomes^{14–16}, including annotation of genes and other features.

Current genome sequence

Finishing process

The process of converting the initial draft sequence into a near-complete sequence is referred to as 'finishing'. It is a complex iterative process that proceeds simultaneously at multiple scales, ranging from single nucleotides to the integrity of whole chromosomes. The fundamental challenge is that genomic regions that are not well represented or readily resolved through random shotgun sequencing tend to be highly enriched in problematic sequences. Resolving such regions required the development of special approaches, which evolved substantially over time and varied among centres.

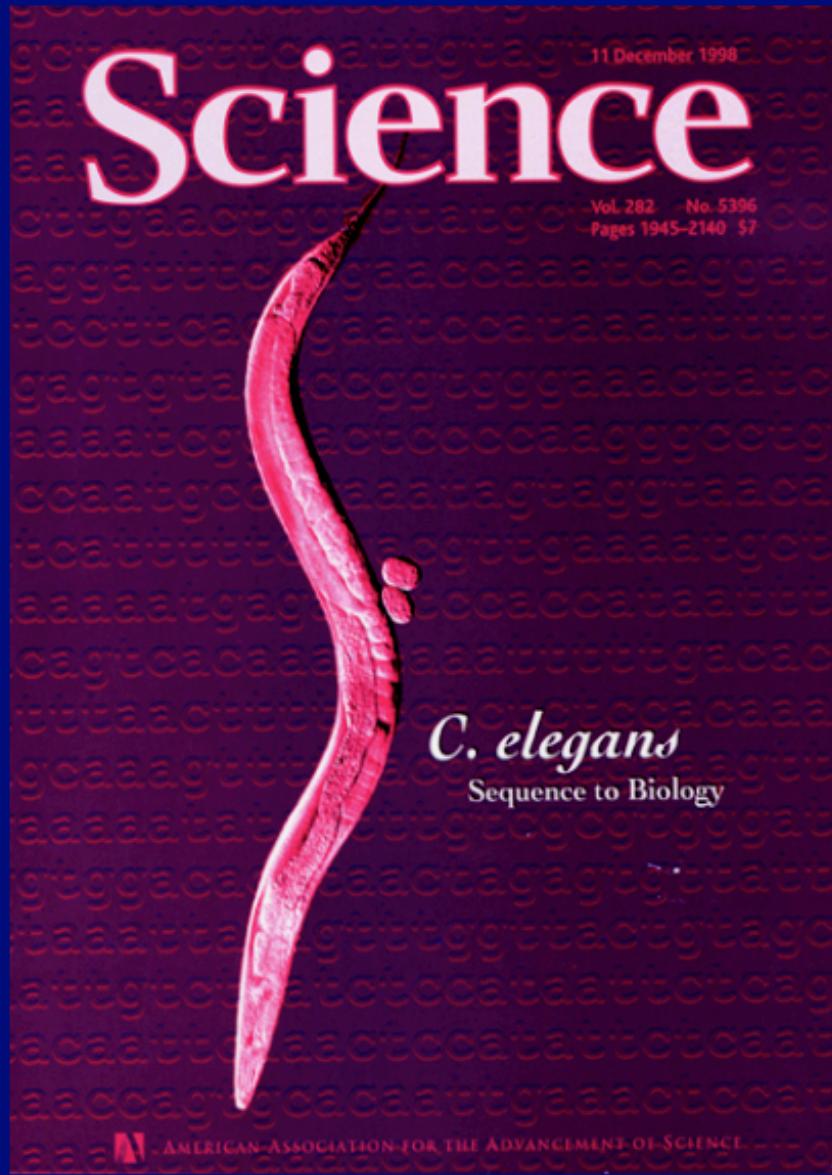
Broadly, the finishing process involved two distinct components: (1) producing finished maps, consisting of continuous and accurate paths of overlapping large-insert clones spanning the euchromatic region of each chromosome arm; and (2) producing finished clones, consisting of continuous and accurate nucleotide sequence across each large-insert clone. In practice, these two components were tightly intertwined in that progress in each often depended on results from the other. The components are described in Boxes 1 and 2. Further information about the finishing process and finishing standards can be found in the Supplementary Information (Note 1) and at <http://www.genome.gov/10000923>.

In total, we generated a shotgun sequence from 59,208 large-insert clones (total length ~5.84 gigabases (Gb)) and finished the sequence from 45,742 of these clones (total length ~3.67 Gb). The clones consisted primarily of bacterial artificial chromosomes

NATURE | VOL. 431 | 21 OCTOBER 2004 | www.nature.com/nature | ©2004 Nature Publishing Group 935

International Human Genome Sequencing Consortium (2004)

First Animal Genome Sequence

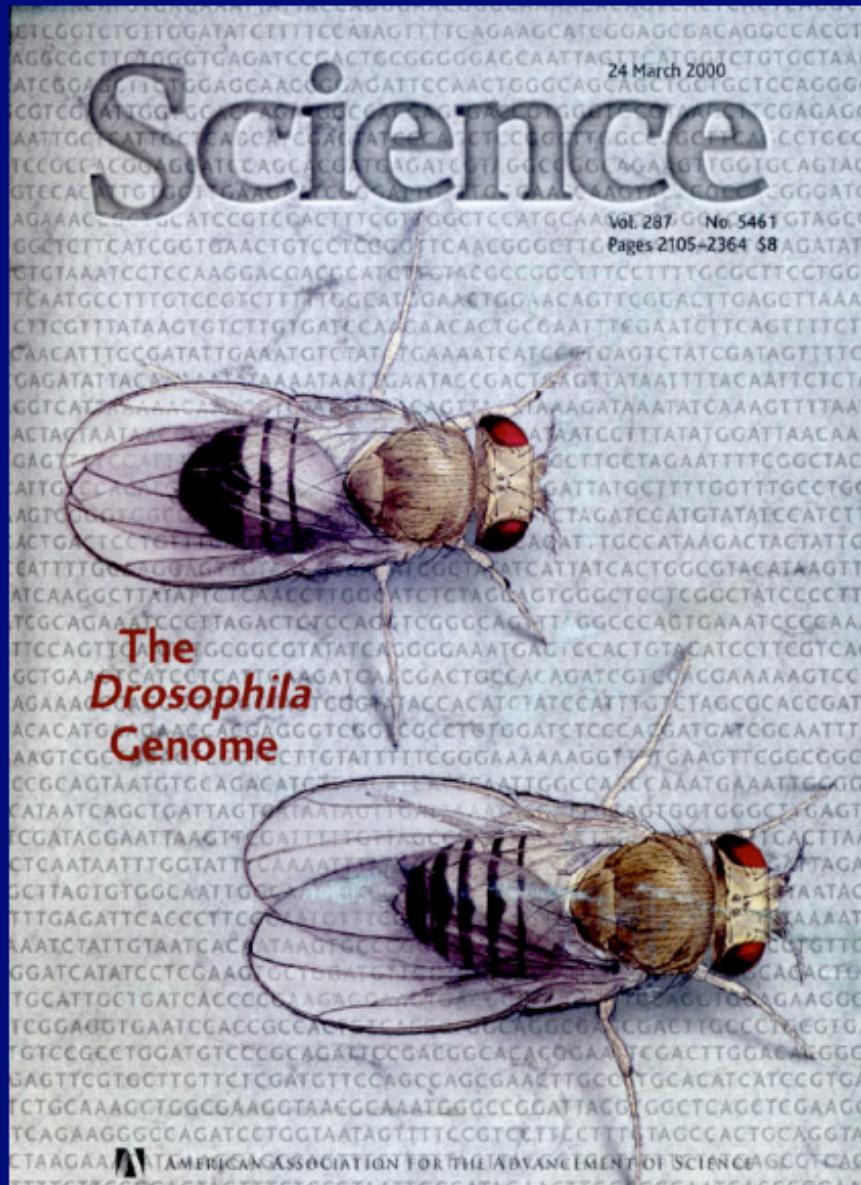


Genome Sequence of the Nematode *C. elegans*: A Platform for Investigating Biology

The *C. elegans* Sequencing Consortium*

***C. elegans* Sequencing Consortium (1998)**

Second Animal Genome Sequence



24 March 2000

Vol. 287 • No. 5467 • GTAGCC
Pages 2105–2364 \$8 AGATAT
GCTCTTACCGTCAACTGTCTGGCTTC
TCAACGGGTTGCAACAGTGGACTGAGCTAA
CTTCGTTATAAGTGTCTTGATECAACACTGG
CAACATTCCGATATTGAATGTCTATGAAAATC
GAGATTTACAAATAATGAAATACCGACTGAGT
GGTCAATTAATGAAATCTTCTGAGTAACTTCT
ACTAATAATGAAATCTTCTGAGTAACTTCT
GAGTAACTTCTGAGTAACTTCTGAGTAACTTCT
ATTGAGTAACTTCTGAGTAACTTCTGAGTAACTTCT
AGTGTAACTTCTGAGTAACTTCTGAGTAACTTCT
ACTGACTCTGAGTAACTTCTGAGTAACTTCT
CATTGAGTAACTTCTGAGTAACTTCTGAGTAACTTCT
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TCGCAGAATCCGTTAGACTCTTCAAGTGGGGCTCT
TTCAGTGGCTGGGGCTATATCAGGGAAATGAG
GCTGAACTCATCTCATTAAGATGCGACTGCC
AGAAAATCTGGGTTACACATCTATCCATTG
ACACATGCTAACCGAGGGTCGTCGGCTG
AAGTCGCTGGGGCTGGGGCTGGGGCTGGGG
CCGCACTAATGCAAGACATCT
CATAATCAGCTGATTAGTCTAAATG
TCGATAGGAATTAAAGTGGATTCTG
CTCAATAATTGGTATTCTG
GCTTAGTGTGGCAATTG
TTTGAGATTCACTTCTG
AAATCTATTGTAATCACTAAGTGGGG
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CTAACGAA

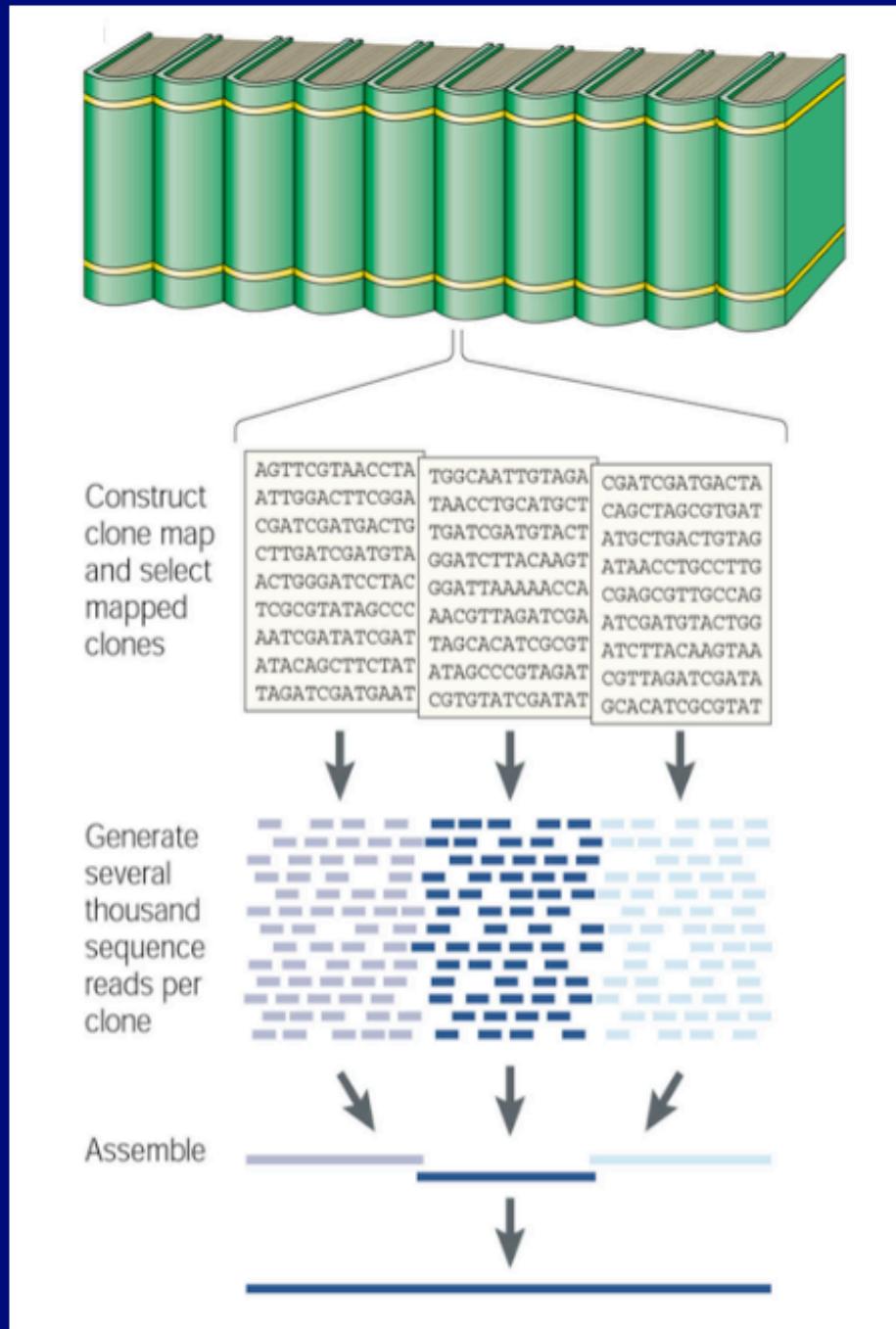
THE DROSOPHILA GENOME REVIEW

The Genome Sequence of *Drosophila melanogaster*

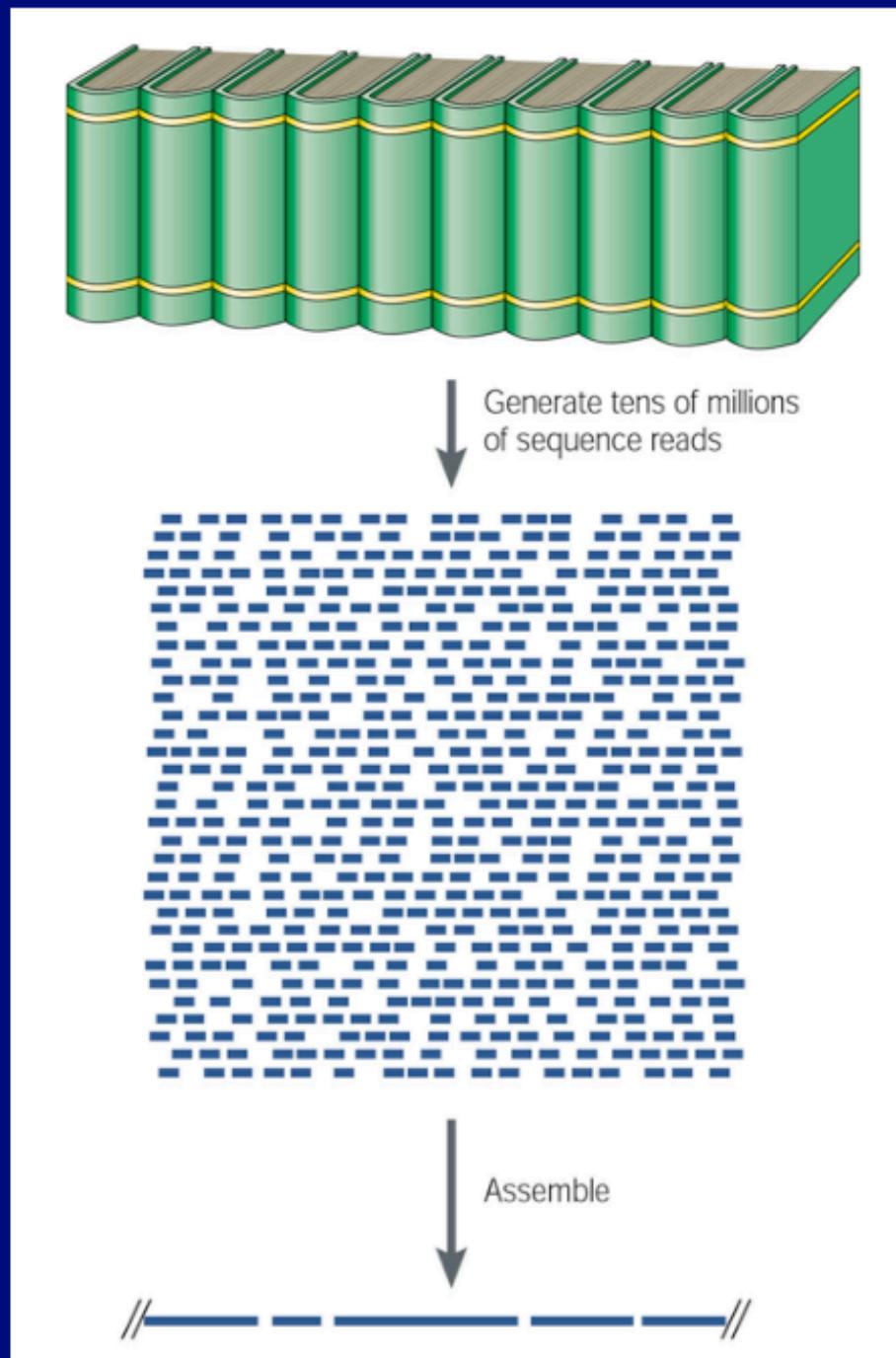
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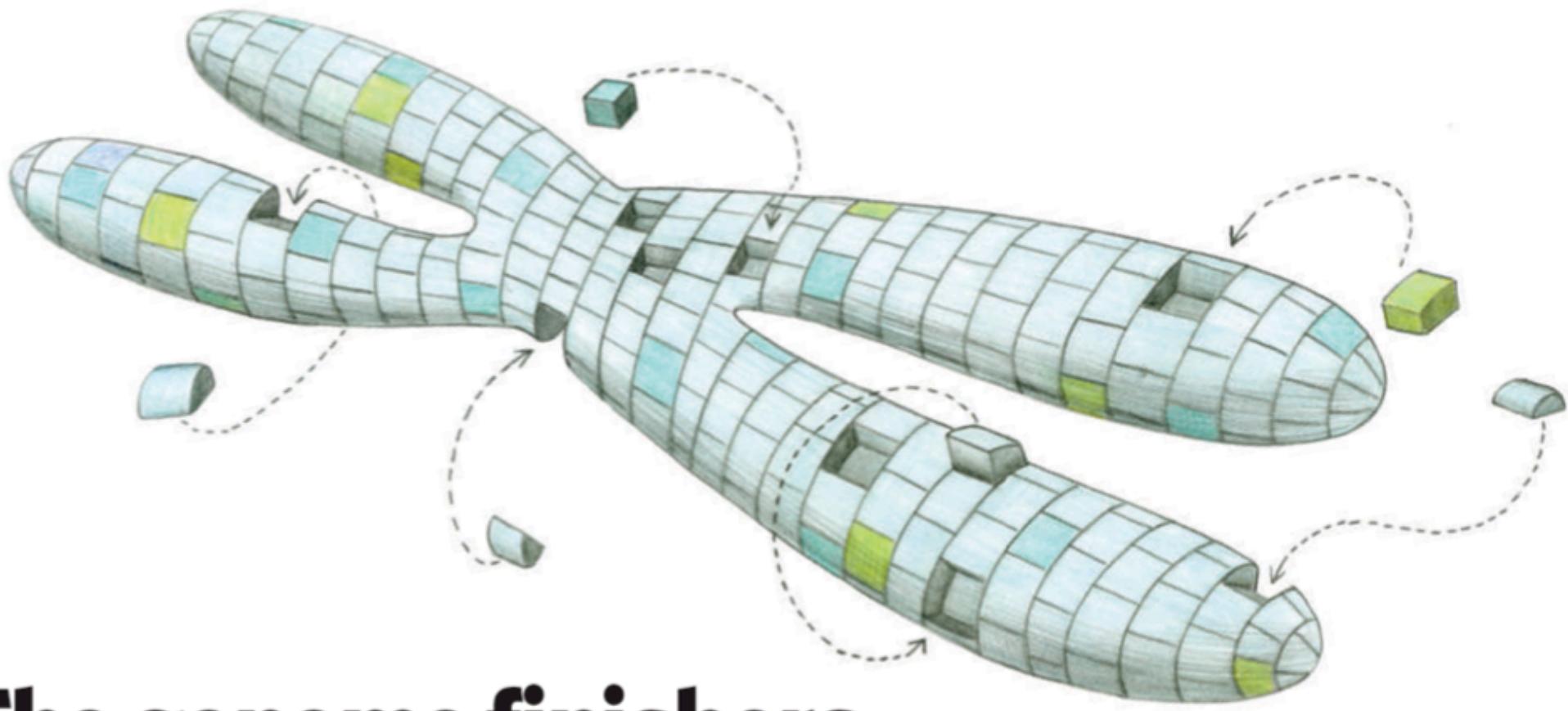
Adams et al. (2000)

Clone-Based Shotgun Sequencing



Whole-Genome Shotgun Sequencing





The genome finishers

Dedicated scientists are working hard to close the gaps, fix the errors and finally complete the human genome sequence. **Elie Dolgin** looks at how close they are.

Nature (2009)



Human Genome Project

D.T. Max: What Darwin Can Teach Us About Jane Austen; Alex Witchell: An Erma Bombeck for Military Wives

The New York Times Magazine

NOVEMBER 8, 2003 SECTION 6

What's Next
Dawn
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Genomic Medicine

The Dawn of Genomic Medicine

How a pediatrician working with the Amish is changing what it means to diagnose and treat disease.

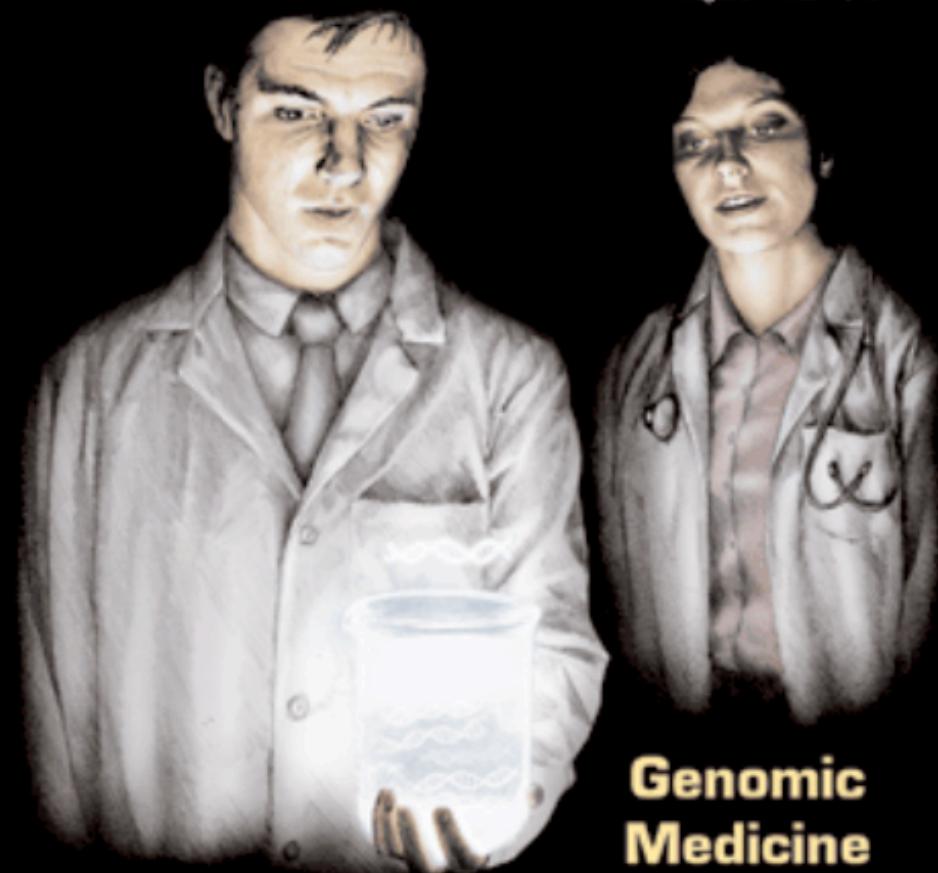
By Lisa Belkin

Why Waste Your Time Voting? (See *Freakonomics*, Page 30)

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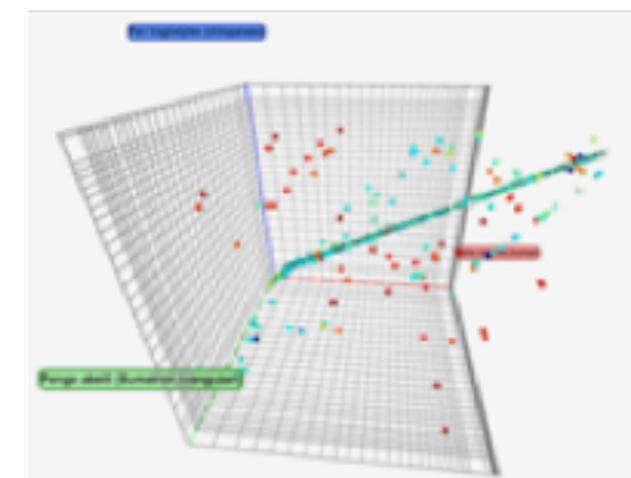
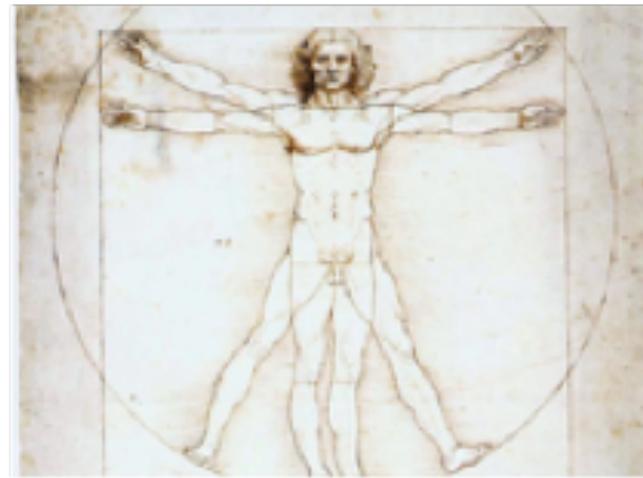
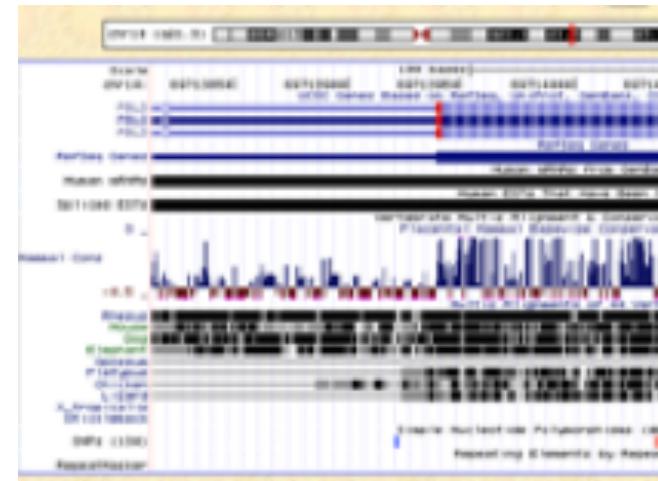
Genomic Medicine



AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

Computational Genomics

The Carbon and Clarke Formula



[27] Selection of Specific Clones from Colony Banks by Suppression or Complementation Tests

By LOUISE CLARKE and JOHN CARBON

METHODS IN ENZYMOLOGY, VOL. 68

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We have determined the transformant colony bank size needed to obtain a plasmid collection representing 90–99% of the *E. coli* or yeast genome as follows.² Given a preparation of cell DNA fragmented to a size such that each fragment represents a fraction (f) of the total genome, the probability (p) that a given unique DNA sequence is present in a collection of N transformant colonies is given by the expression

$$P = 1 - (1-f)^N$$

or

$$N = \ln(1-P)/\ln(1-f)$$

A sample calculation for *E. coli* (genome size, 2.7×10^9 daltons) for $P = 0.99$ is

$$N = \frac{\ln(1-0.99)}{\ln[1 - (8.5 \times 10^6 / 2.7 \times 10^9)]} = 1437$$

Thus, using a preparation of DNA randomly sheared to an average size of 8.5×10^6 daltons for the construction of annealed hybrid circular DNA, a colony bank of only about 1400 transformants for *E. coli* or 5400 transformants for yeast is adequate to give a probability of 99% that any *E. coli* or yeast gene will be on a hybrid plasmid in one of the clones.

$$N = \frac{\ln(1 - P)}{\ln(1 - f)}$$

where,

N is the necessary number of recombinants^[16]

P is the desired probability that any fragment in the genome will occur at least once in the library created

f is the fractional proportion of the genome in a single recombinant

f can be further shown to be:

$$f = \frac{i}{g}$$

where,

i is the insert size

g is the genome size

Thus, increasing the insert size (by choice of vector) would allow for fewer clones needed to represent a genome. The proportion of the insert size versus the genome size represents the proportion of the respective genome in a single clone.^[14] Here is the equation with all parts considered:

$$N = \frac{\ln(1 - P)}{\ln\left(1 - \frac{i}{g}\right)}$$

Vector selection example [edit]

The above formula can be used to determine the 99% confidence level that all sequences in a genome are represented by using a vector with an insert size of twenty thousand basepairs (such as the phage lambda vector). The genome size of the organism is three billion basepairs in this example.

$$N = \frac{\ln(1 - 0.99)}{\ln\left[1 - \frac{2.0 \times 10^4 \text{ basepairs}}{3.0 \times 10^9 \text{ basepairs}}\right]}$$

$$N = \frac{-4.61}{-6.7 \times 10^{-6}}$$

$$N = 688,060 \text{ clones}$$