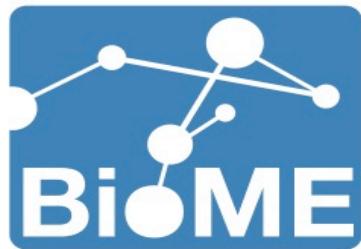


Next Generation Sequencing Technologies

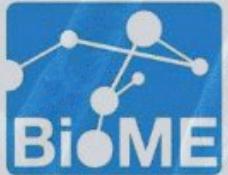
Sandro J. de Souza



Bioinformatics
Multidisciplinary
Environment

Centro
Multiusuário
de Bioinformática





Bioinformatics
Multidisciplinary
Environment



Centro
Multiusuário
de Bioinformática





- Established in 2011.
 - Technical courses.
 - IT undergrad. (BTI).
 - Ms and Ph.D programs
 - INOVA: business incubator
-
- Bioinformatics Emphasis @ BTI
(recruitment of new PIs)



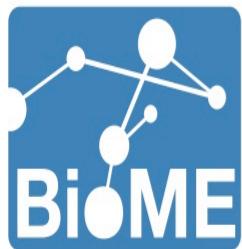
Ms and Ph.D Programs

- Started on 01/2016.
- 24 PIs (19 from UFRN and 5 from other universities).
- 37 students (19 Ms and 18 Ph.D).



Ms and Ph.D Programs

- ✓ Genômica
- ✓ Biologia de Sistemas
- ✓ Desenvolvimento de produtos e processos



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de Bioinformática



GRADUATE PROGRAM ▾

RESEARCH ▾

CORE FACILITY ▾

CORPORATE

ABOUT US ▾



<http://bioinfo.imd.ufrn.br>

João Paulo Matos
Genomics and structural
bioinformatics)



Rodrigo Dalmolin
(Systems Biology)



Jorge E. de Souza
(Genomics)



César Renno-Costa
(Comp. neuroscience)



Marcus Nunes
(Biostatistics)



Samuel X. de Souza
(High Perf. Computing)



Gustavo A. de Souza
(Proteomics)



Beatriz Stransky
(Modelling of
biological systems)



Euzébio Barbosa
(Drug design)



Umberto Fulco
(Comput. biophysics)



Daniel Lanza
(Biotechnology)



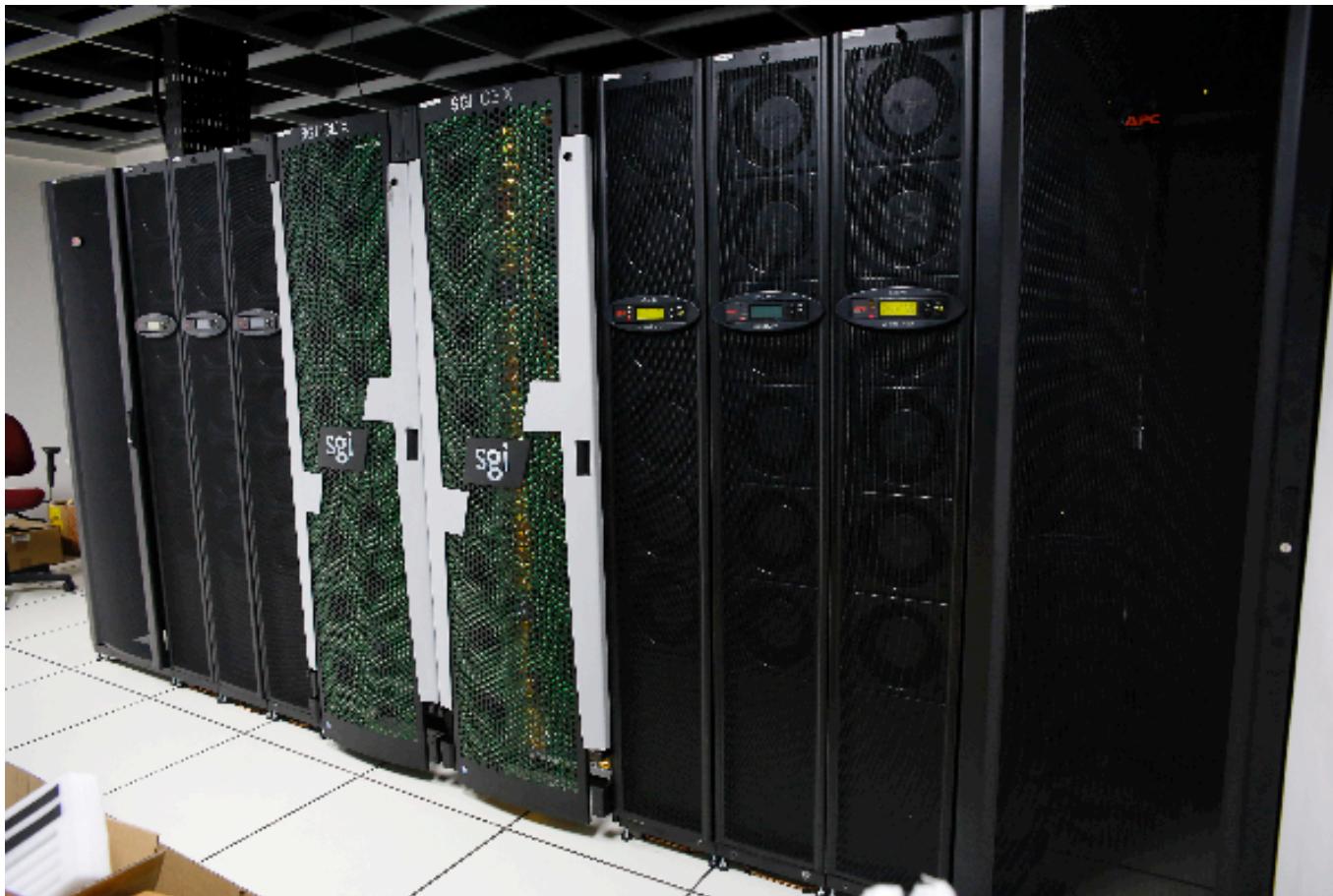
Daniel Sabino
(Machine Learning)

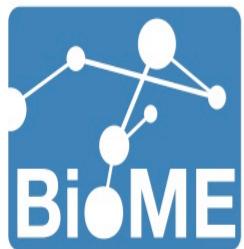
Sandro J. de Souza
(Genomics and systems
biology)



CENTRO MULTIUUSUARIO
BIOINFORMÁTICA
BIOINFORMÁTICA
MULTIDISCIPLINAR







Bioinformatics
Multidisciplinary
Environment

Centro
Multiusuário
de Bioinformática



- ✓ **Research: ~ 40 papers since 2016
(Nat. Comm., Nat. Meth.)**
- ✓ **Education: Undergrad + Ms + PhD**
- ✓ **Strong entrepreneurial mentality
(core facility + events)**

Novo Marco Legal de C&T&I

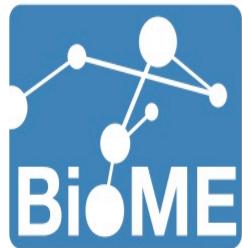


Presidência da República
Casa Civil
Subchefia para Assuntos Jurídicos

[LEI Nº 13.243, DE 11 DE JANEIRO DE 2016.](#)

Dispõe sobre estímulos ao desenvolvimento científico, à pesquisa, à capacitação científica e tecnológica e à inovação e altera a Lei nº 10.973, de 2 de dezembro de 2004, a Lei nº 6.815, de 19 de agosto de 1980, a Lei nº 8.666, de 21 de junho de 1993, a Lei nº 12.462, de 4 de agosto de 2011, a Lei nº 8.745, de 9 de dezembro de 1993, a Lei nº 8.958, de 20 de dezembro de 1994, a Lei nº 8.010, de 29 de março de 1990, a Lei nº 8.032, de 12 de abril de 1990, e a Lei nº 12.772, de 28 de dezembro de 2012, nos termos da Emenda Constitucional nº 85, de 26 de fevereiro de 2015.

Parceria entre universidade e ONG



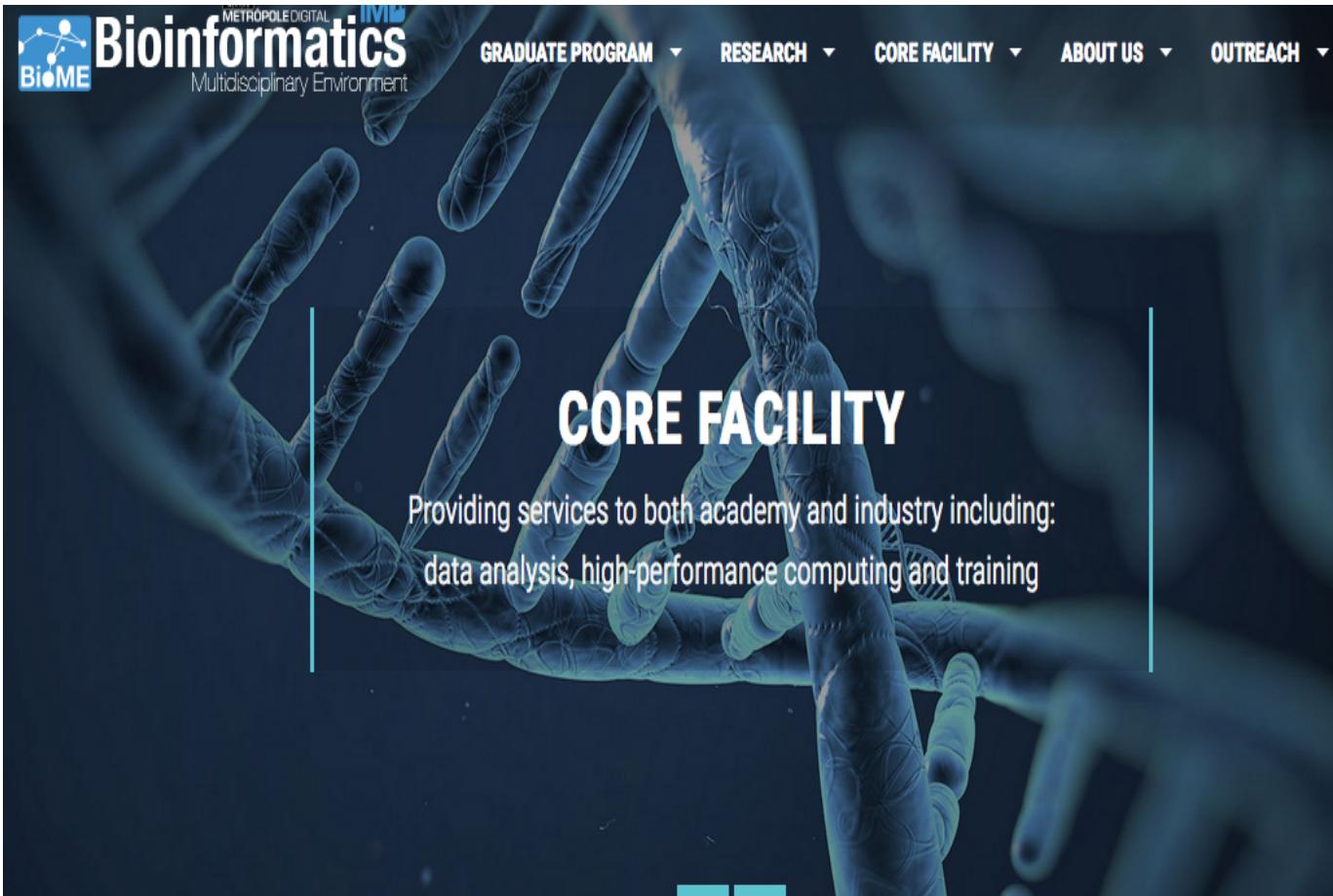
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2Bio

Instituto de
Bioinformática e
Biotecnologia



Bioinformatics
Multidisciplinary Environment

GRADUATE PROGRAM ▾ RESEARCH ▾ CORE FACILITY ▾ ABOUT US ▾ OUTREACH ▾

CORE FACILITY

Providing services to both academy and industry including:
data analysis, high-performance computing and training

BioME's Core Facility

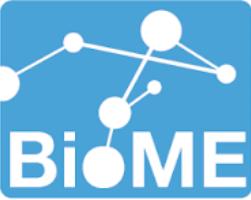
Products

- ✓ Advising in several areas of Bioinformatics
- ✓ Genome assembly
- ✓ RNA-Seq Analysis
- ✓ Variant calling
- ✓ Mass-spectrometry-based Bioinformatics
- ✓ Rational drug design
- ✓ Protein modelling
- ✓ Systems Biology
- ✓ Computational neuroscience
- ✓ Modelling of biological systems
- ✓ Customized pipelines and protocols

Market

- ✓ Academy
- ✓ Industry
- ✓ National level
- ✓ International level

biome@imd.ufrn.br



Viewer of Variants

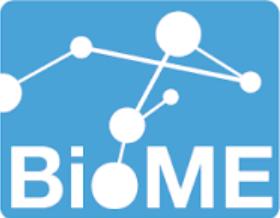


✓ Management

✓ Processing

✓ Visualization

José Eduardo Kroll
Priscilla M. do Nascimento
Jorge E.S. de Souza
Sandro J. de Souza



Viewer of Variants

BiOME Main Explorer Viewer Users Issues Tracker

ViNa sandro ▾

Views

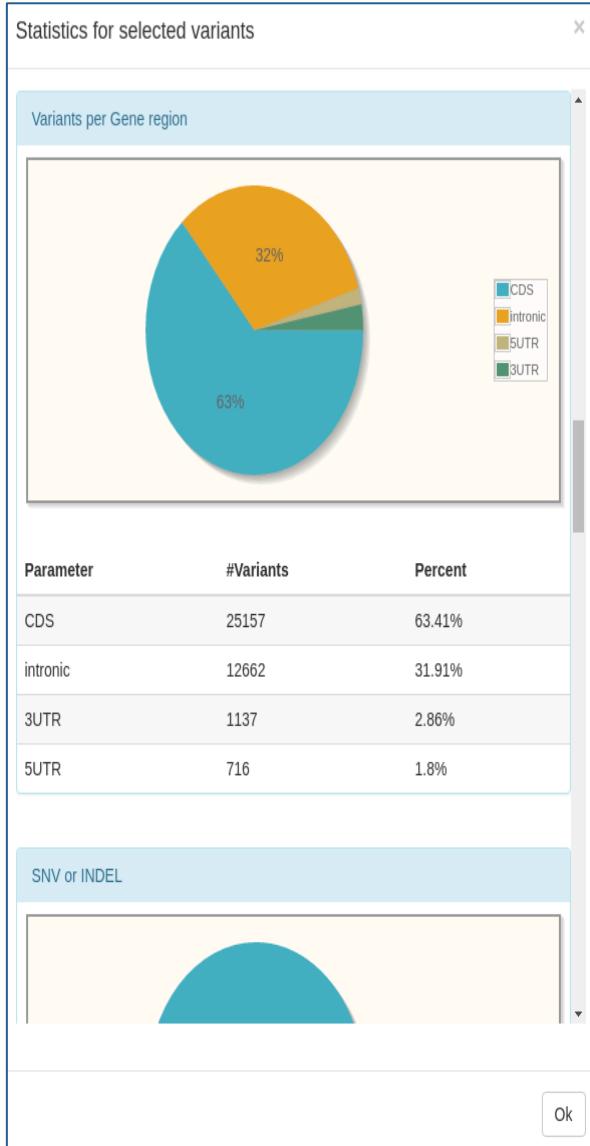
Create	Name	Desc
<input type="button" value="Search"/>	<input type="text" value="Search"/>	<input type="button" value="Search"/>

Mutations

Chrom	Position	Essential Info					Sample Coverage	Gene	Refseq	Region
		Reference	Variant	Quality	Filter	Coverage				
chr1	9782556	C	T	154868.44	D21-AG-PAINEL	3254 3300		PIK3CD	NM_005026.3	intronic
chr1	11181327	C	T	135999.42	D21-AG-PAINEL	4520		MTOR	NM_004958.3	CDS
chr1	11184593	A	G	70476.19	D21-AG-PAINEL	2651 2549		MTOR	NM_004958.3	CDS
chr1	11187893	T	C	279628.2	D21-AG-PAINEL	4172		MTOR	NM_004958.3	intronic
chr1	11190646	G	A	93117.19	D21-AG-PAINEL	2843		MTOR	NM_004958.3	CDS
chr1	17380497	G	T	112234.2	D21-AG-PAINEL	2578		SDHB	NM_003000.2	CDS
chr1	36937059	A	G	211943.19	D21-AG-PAINEL	2687 2148		CSF3R	NM_156039.3	CDS
chr1	43812075	G	A	207190.19	D21-AG-PAINEL	6025		MPL	NM_005373.2	intronic
chr1	45796269	G	C	417705.2	D21-AG-PAINEL	6166		MUTYH	NM_001128425.1	intronic
chr1	45798555	T	C	545507.2	D21-AG-PAINEL	7898		MUTYH	NM_001128425.1	intronic
chr1	65303659	C	T	42143.19	D21-AG-PAINEL	2109 1921		JAK1	NM_002227.2	CDS
chr1	65310489	T	C	193075.19	D21-AG-PAINEL	4293		JAK1	NM_002227.2	CDS
chr1	65321388	G	A	127902.19	D21-AG-PAINEL	3061		JAK1	NM_002227.2	OTHER

Export to VCF ?

Description Columns Filter Compare



Description Columns Filter Select genes Compare

Comparation type:
'de novo' or 'New'

Samples (hold shift to select more than one):
MAE
PAI

Clear Filter

Minimum coverage filter

Sample:	Total (#reads)	Var (#reads)	Var (%)
FILHA_A:	100	Var	100
FILHA_B:	100	Var	100

Description Columns Filter Select genes Compare

Filter by Coverage

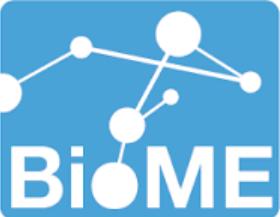
Quality	Greater or Equal	100	45013
Impact	Equal	high	457
Pass or Equal	0.01	0.01	180

Description Columns Filter Select genes Compare

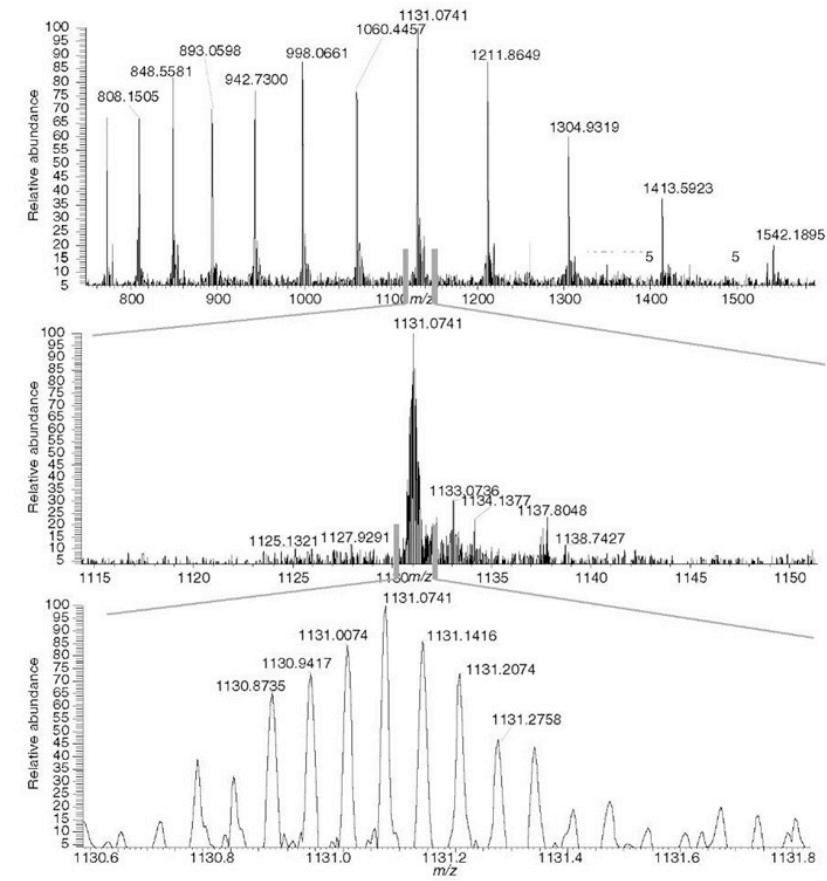
Genes to filter:

- MST1L
- CDCP2
- L1TD1
- NBF8

Chrom	Position	Reference	Variant	Quality	Sample Coverage
chr1	17086439	C	T	462.98	FILHA_A --> ref:253 var:42 14.237288135593221% FILHA_B --> ref:2
chr1	117142868	C	T	1661.94	FILHA_A --> ref:104 var:14 11.864406779661017% FILHA_B --> ref:2
chr1	117156585	G	A	1122.94	FILHA_A --> ref:111 var:21 15.909090909090908% FILHA_B --> ref:2
chr1	144619346	G	A	6232.94	FILHA_A --> ref:84 var:57 40.42553191489361% FILHA_B --> ref:2
chr1	144619346	G	A	6232.94	FILHA_A --> ref:84 var:57 40.42553191489361% FILHA_B --> ref:2
chr1	144852390	C	T	14461.94	FILHA_A --> ref:138 var:111 44.5783125301205% FILHA_B --> ref:2
chr1	144873962	CT	C	10947.9	FILHA_A --> ref:131 var:59 31.05263157894737% FILHA_B --> ref:2
chr1	145103947	T	C	5432.94	FILHA_A --> ref:82 var:62 43.05555555555556% FILHA_B --> ref:2
chr1	145112420	C	T	4344.94	FILHA_A --> ref:260 var:39 13.043478260869565% FILHA_B --> ref:2
chr1	204159611	CT	C	9299.86	FILHA_A --> ref:89 var:73 45.06172839506173% FILHA_B --> ref:2



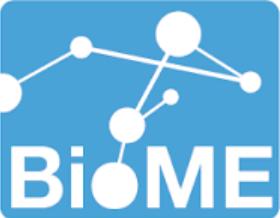
Mass-Spec based Proteomics



Prof. Gustavo A. de Souza

How to better visualize the data

- ✓ Peptide – genome alignment
- ✓ Spectra quality assignment for novel sequences
- ✓ “Novel” peptide uniqueness in the database



Proteogenomics Browser

Integrando dados de proteoma e transcriptoma

A screenshot of the Proteogenomics Browser interface displayed on a tablet. The browser window is titled "Viewer: Q59" and shows a "Gene Information" panel. On the left, there is a sidebar with "Control Functions" including "Open gene:" (set to Q59), "Find sequence:", "Gene View:" (selected), "Peptides on focus:" (listing peptides like FEEDKQSTK, GPKNGCQDPDQAEVYPOR, GPKNGCQDPDQAEVYPORPEK, and RQALQVSR), and "Total of 3 peptides". Below this are sections for "Peptide Spectrum" and "Peptide Expression", with filters for "Filter PEP:" (set to 1) and "Filter by Sample:" (set to "ALL SAMPLES #0"). On the right, the main panel displays a genomic track for gene Q59. The track includes multiple horizontal lines representing different genomic features, with a red vertical line indicating the focus. A legend at the bottom defines four colors: red for "Selected MS/MS Peptide", yellow for "Focused MS/MS Peptides", green for "MS/MS Supported", and brown for "No MS/MS support". The bottom of the browser window shows the text "View 1: 8 of 8" and a zoom control. The tablet is resting on a white stand, and the word "chrome" is visible at the bottom of the tablet's bezel.

Controle

Control Functions

Open gene:
OS9
OS9 successfully loaded

Find sequence:

Gene View:
Peptides on focus:
FIEELKGGTK
GKPNIGQEQPVDDAAEVPOR
GKPNIGQEQPVDDAAEVPORKEK
KGLTAAKG
SPADLIR

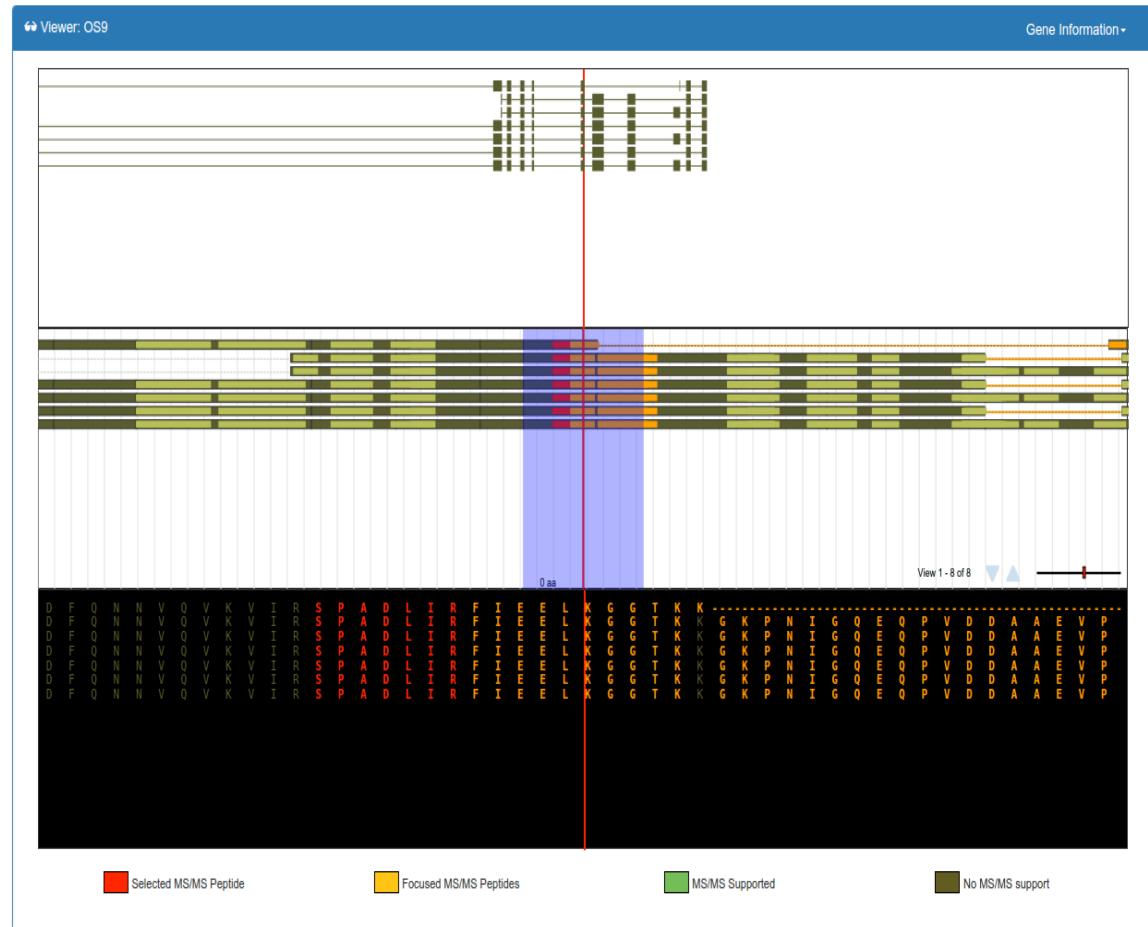
Total of 5 peptides

Peptide Spectrum
Peptide Expression

Filter PEP:
1

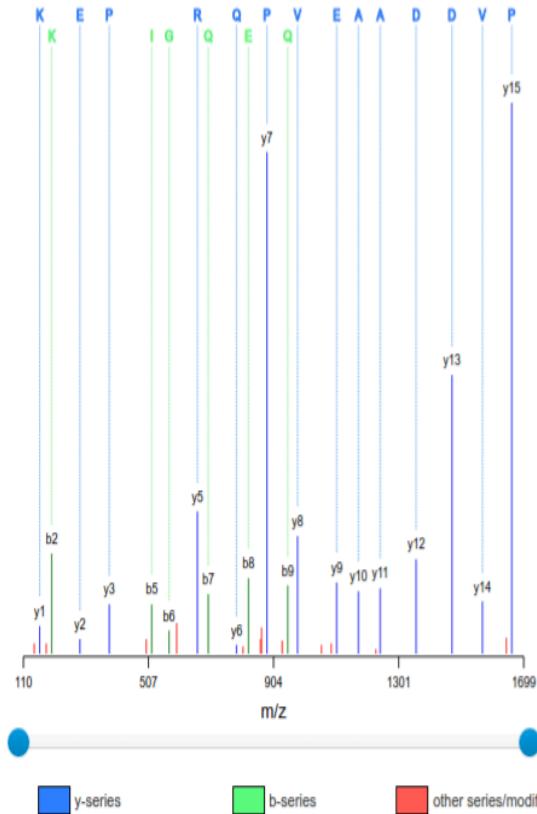
Filter by Sample:
ALL SAMPLES ##
A549
Adult_Colon_(Kim)
Adult_Liver_(Kim)
Adult_Pancreas_(Kim)
Adult_Prostate_(Kim)

Total of 0 samples



Visualizador

Peptide Spectrum: GKPNIQEQQPVDDAAEVPQREPEK
(Score: 82.475, PEP: 3.057E-08)



Peptide Expression: GSPESRLSFQHDPETSVLVLRK

Samples where peptide was detected

Sample Name	Expression
Prostate-LysC_(Wilhelm)	0.215
Testis-LysC_(Wilhelm)	0.699
Liver-LysC_(Wilhelm)	0.744
Ovary-LysC_(Wilhelm)	0.813
Spleen-LysC_(Wilhelm)	0.998

Genes where peptide was observed

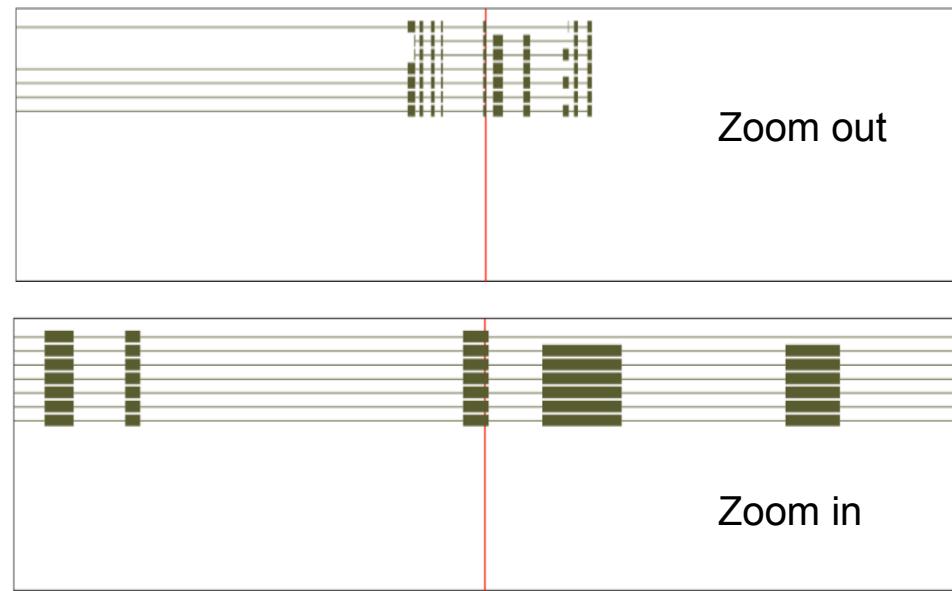
GANAB 105

Close

Close

Gene	#Isoforms	#Peptides
TPM4	7	386
XRCC5	7	507
PFKL	7	309
ZNF638	7	490
CSN1S1	7	120
UQCRC2	7	166
PCM1	7	598
RANBP2	7	1437
OS9	7	215
PUM1	7	241
TKT	7	307
PSMD11	7	283
UQCRC1	7	191
MYO1B	7	587
HUWE1	7	1414
DBN1	7	311
PPFIBP1	7	564
ANK3	7	636
ATP5A1	7	451
HSP90AA1	7	524
POSTN	7	435
TTC37	7	524
...	7	616

Page 1 of 31 View 1 - 500 of 15,060



Close

Protein
Expression

Source: Uniprot
Name: sp|Q13438|OS9_HUMAN

pos: 361

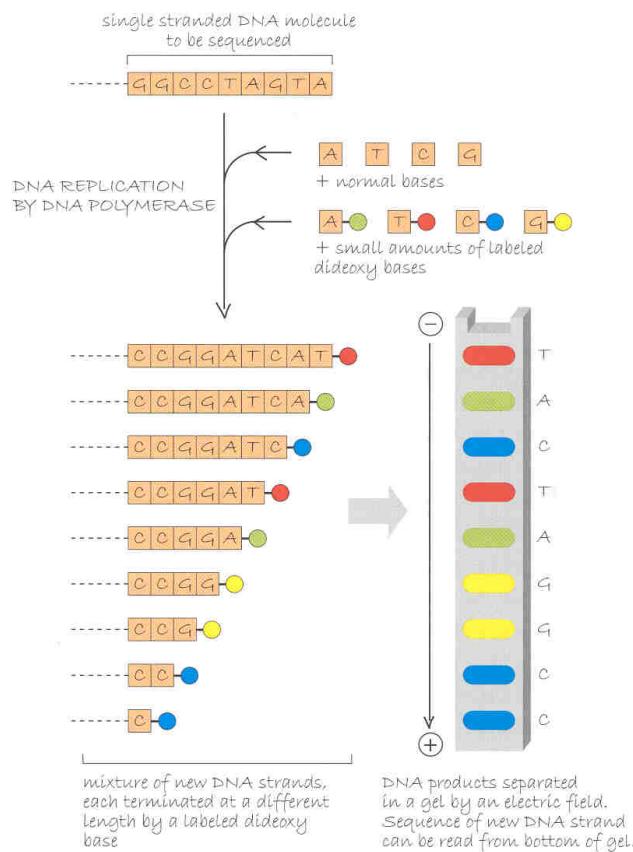
PFAM Domain Analysis
UNIPROT Blast
InterPro Analysis

A revolução da Genômica e da Bioinformática?

- 1910's :** Mendel e as leis da hereditariedade.
- 1944:** DNA como elemento carreador da informação genética (Avery)
- 1953:** Watson/Crick e a estrutura do DNA
- 70's e 80's:** Biologia Molecular/Biotecnologia
- 90's e séc. 21:** Genômica/Bioinformática

DNA Sequencing

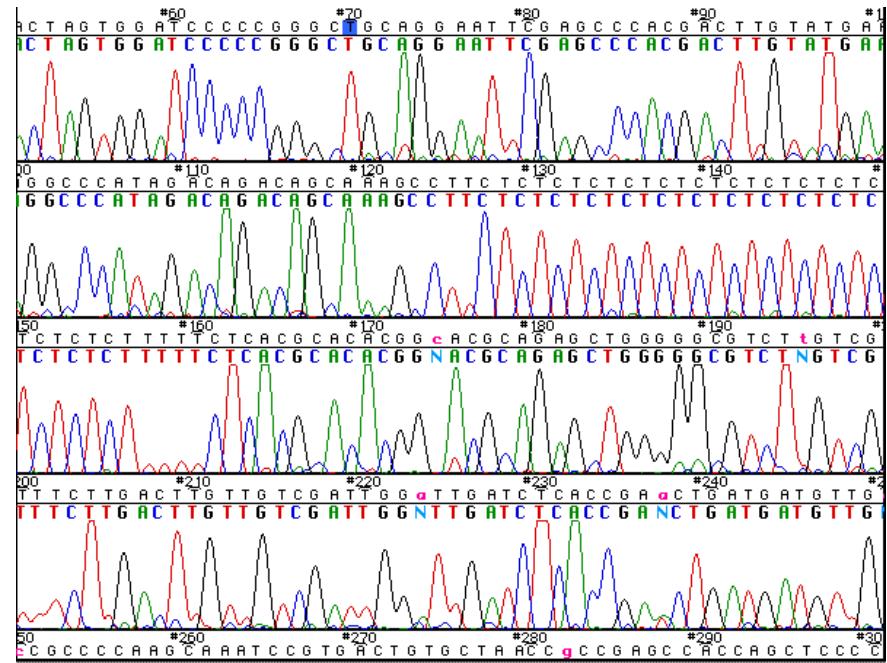
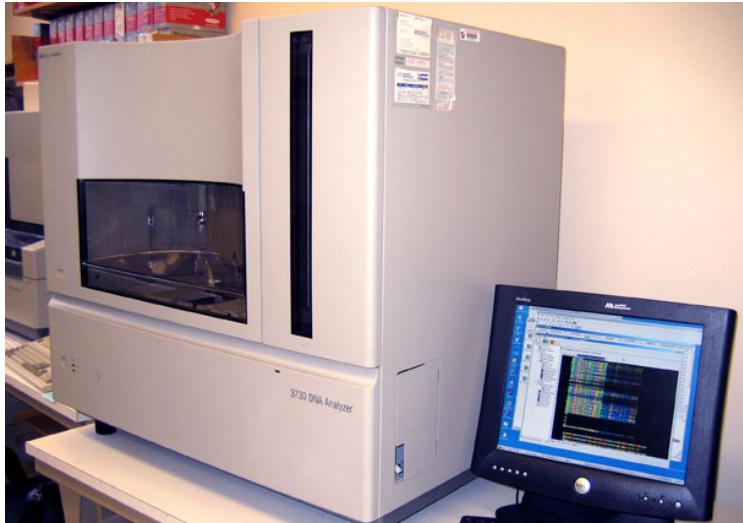
Sanger, Gilbert (Nobel 1980)



Automatic Sequencing

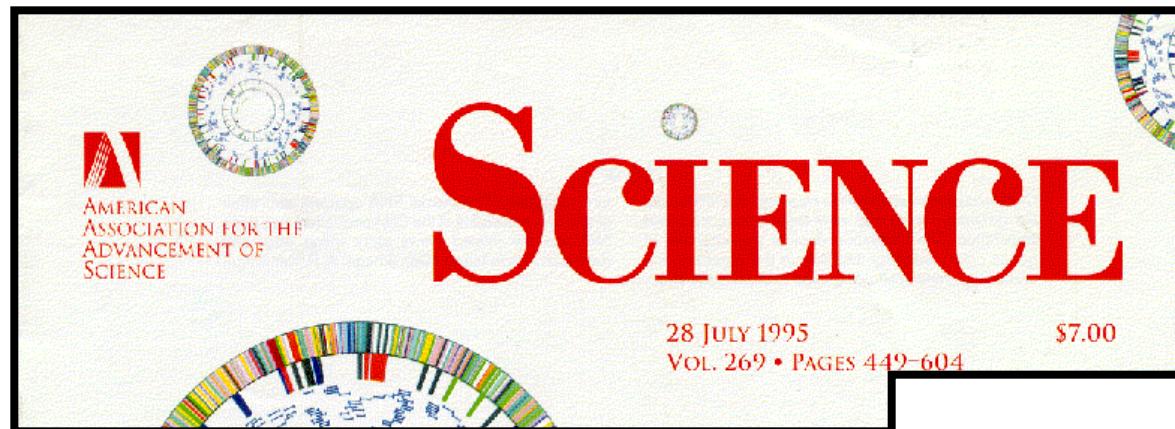


Leroy Hood



40kb per run

Genomics Era



28 de Julho, 1995

Primeiro organismo vivo a ter o seu
genoma completamente conhecido.

Whole-Genome Random Sequencing and Assembly of *Haemophilus influenzae* Rd

Robert D. Fleischmann, Mark D. Adams, Owen White, Rebecca A. Clayton, Ewen F. Kirkness, Anthony R. Kerlavage, Carol J. Bult, Jean-Francois Tomb, Brian A. Dougherty, Joseph M. Merrick, Keith McKenney, Granger Sutton, Will FitzHugh, Chris Fields,* Jeannine D. Godayne, John Scott, Robert Shirley, Li-Ing Liu, Anna Glodek, Jenny M. Kelley, Janice F. Weidman, Cheryl A. Phillips, Tracy Spriggs, Eva Hedblom, Matthew D. Cotton, Teresa R. Utterback, Michael C. Hanna, David T. Nguyen, Deborah M. Saudek, Rhonda C. Brandon, Leah D. Fine, Janice L. Fritchman, Joyce L. Fuhrmann, N. S. M. Geoghegan, Cheryl L. Gnehm, Lisa A. McDonald, Keith V. Small, Claire M. Fraser, Hamilton O. Smith, J. Craig Venter†

An approach for genome analysis based on sequencing and assembly of unselected pieces of DNA from the whole chromosome has been applied to obtain the complete nucleotide sequence (1,830,137 base pairs) of the genome from the bacterium *Haemophilus influenzae* Rd. This approach eliminates the need for initial mapping efforts and is therefore applicable to the vast array of microbial species for which genome maps are unavailable. The *H. influenzae* Rd genome sequence (Genome Sequence DataBase accession number L42023) represents the only complete genome sequence from a free-living organism.

Human Genome

2001

- International Initiative
- Celera Genomics, Inc



Bioinformatics

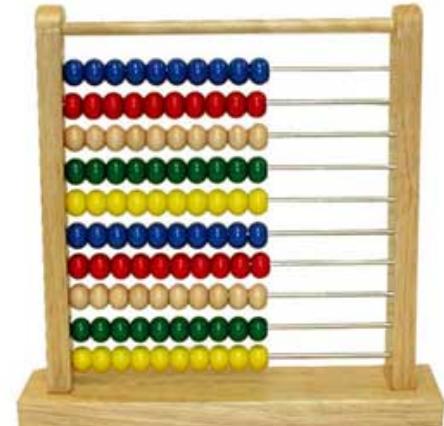
Biology



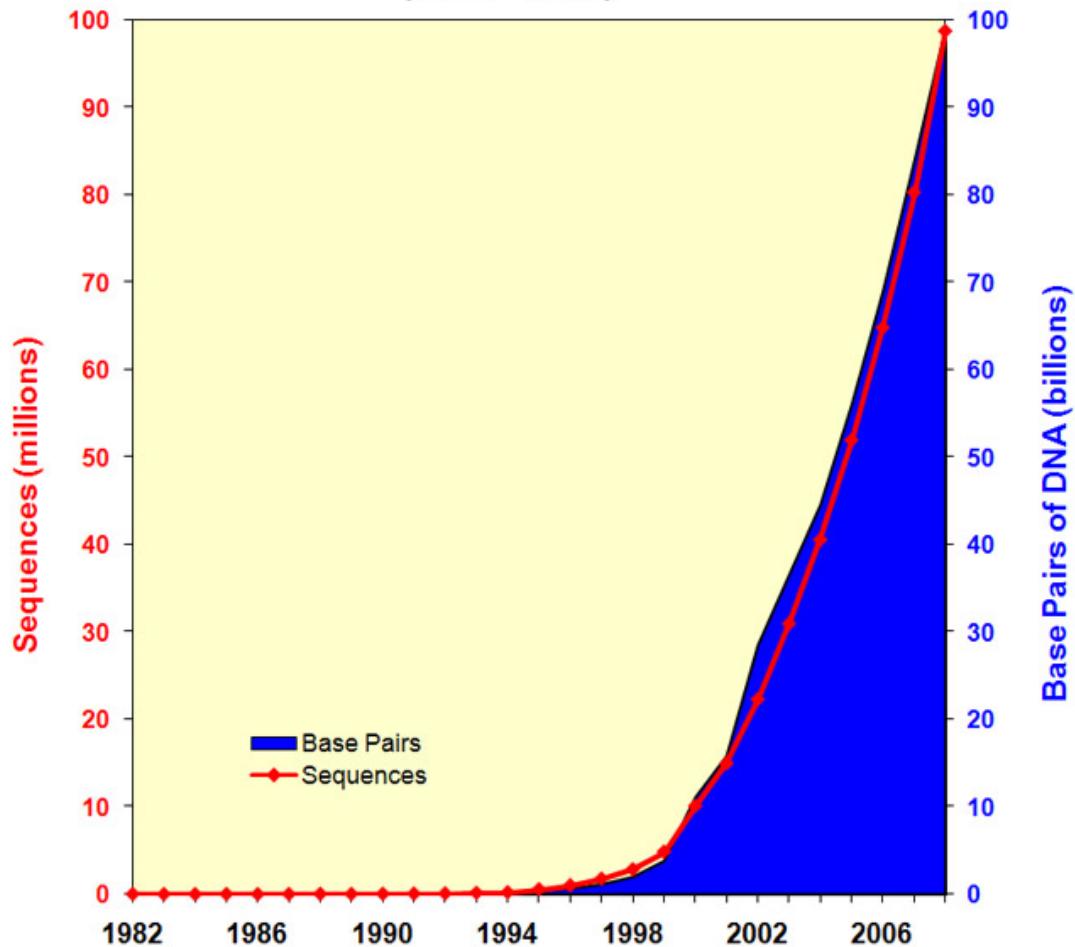
Computer Sci.



Math

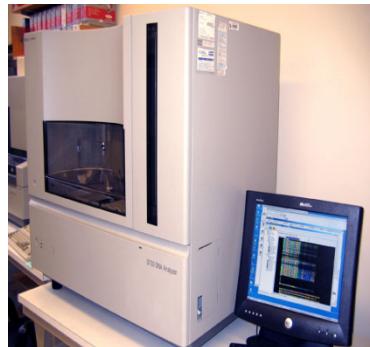


Growth of GenBank (1982 - 2008)





Next Generation DNA Sequencing



ABI

~40 KB DNA
por corrida

0.5KB/US\$



FIGURE 1

454 - Roche

0,5 GB de DNA
por corrida

50KB/US\$



Solexa - Illumina

~90 GB de DNA
por corrida

9MB/US\$



SOLiD - ABI

~100 GB de DNA
por corrida

10MB/US\$

NGS

Sequenciadores de Segunda Geração



HiSeq X Five*



HiSeq X Ten*

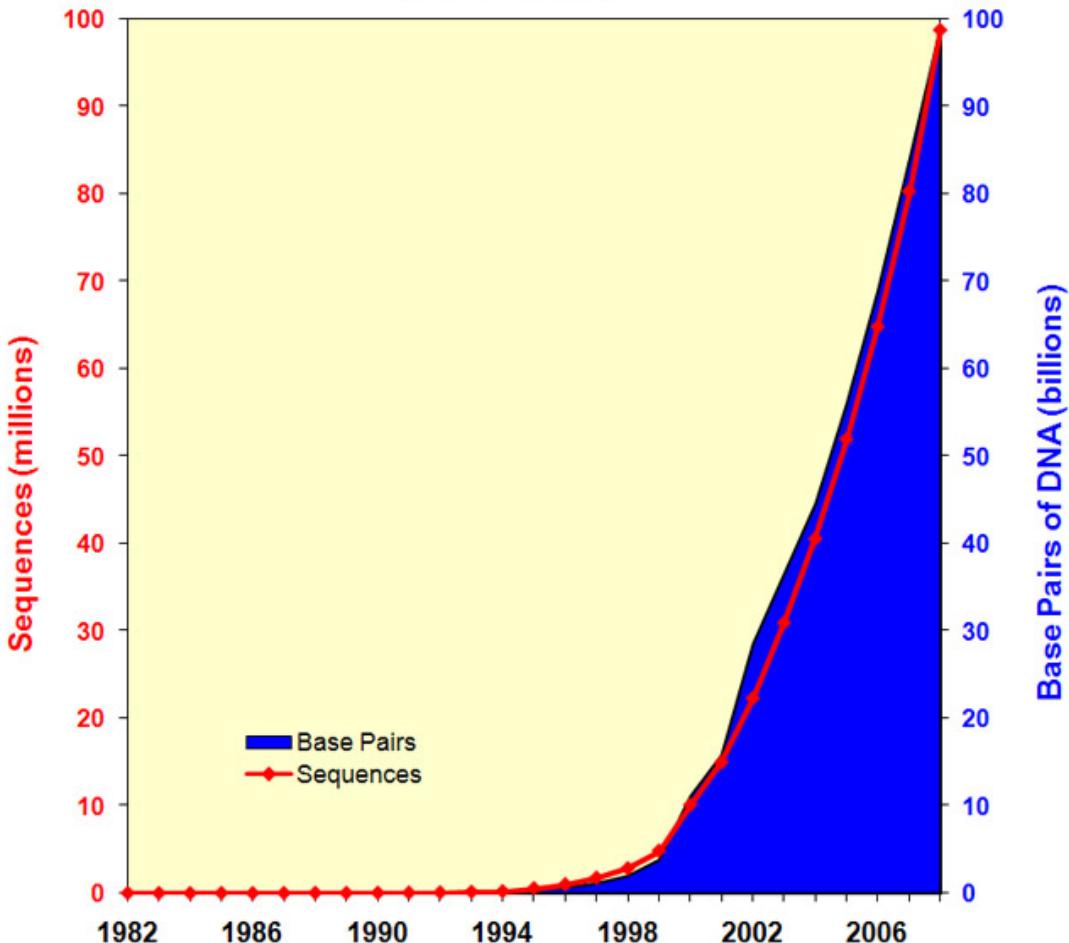
Run Mode	N/A	N/A
Flow Cells per Run	1 or 2	1 or 2
Output Range	900-1800 Gb	900-1800 Gb
Run Time	<3 days	<3 days
Reads per Flow Cell†	3 billion	3 billion
Maximum Read Length	2 x 150 bp	2 x 150 bp

© 2014 Illumina, Inc. All rights reserved.

Benchtop NGS



Growth of GenBank (1982 - 2008)



**26 anos para gerar
 10^{11} bp.**

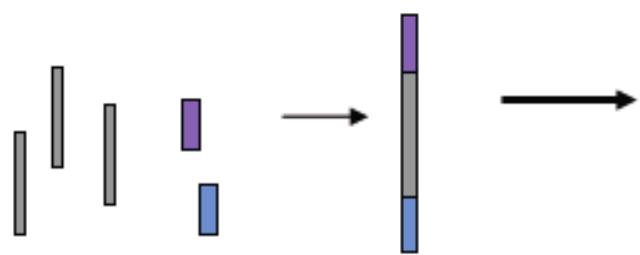
**Quanto tempo hoje
para gerar a mesma
quantidade de
dados?**

Third Generation of DNA Sequencers



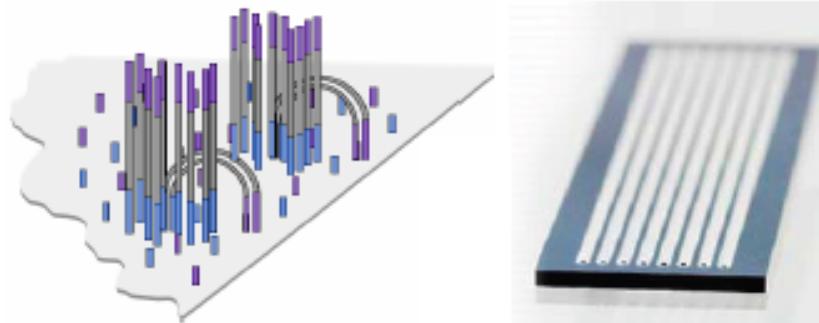
Illumina Sequencing pipeline

1. Sample Prep (1-5 days)



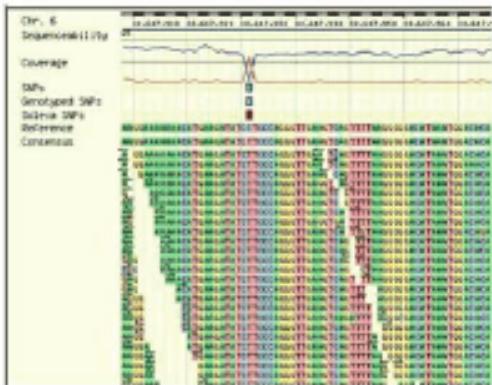
Ligate adapters

2. Cluster generation on flow cell (1.5 day)

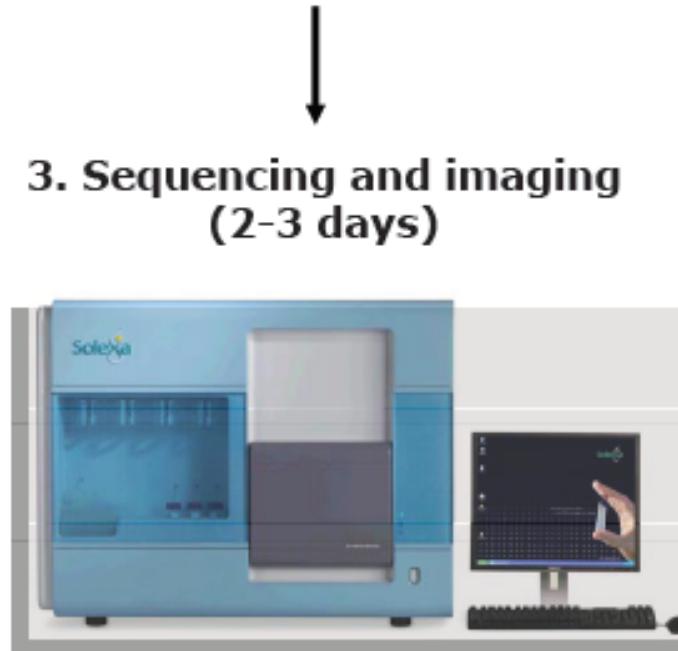


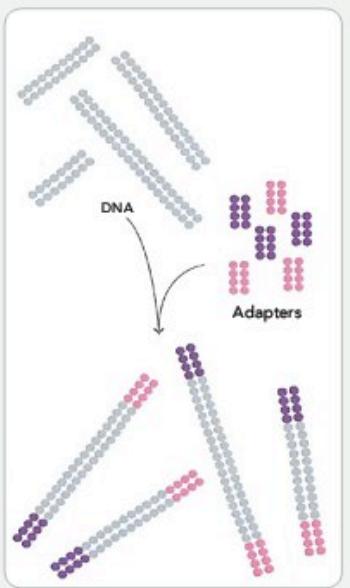
Clonal Single molecular Array

4. Data Analysis (days-months)

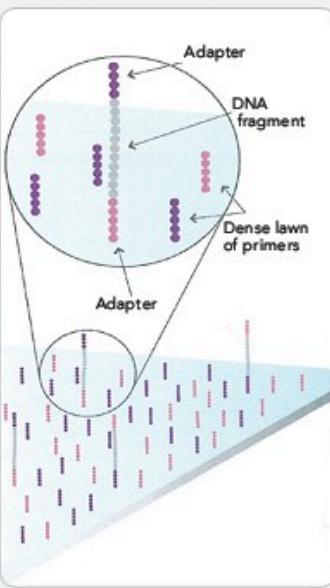


3. Sequencing and imaging (2-3 days)

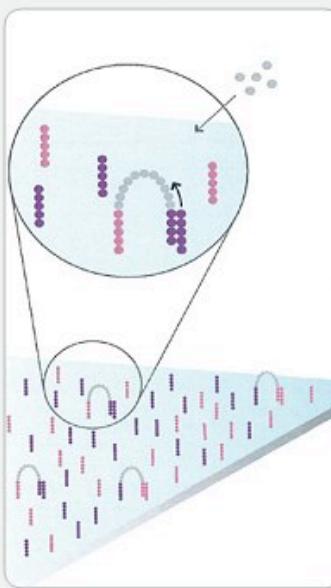


1. PREPARE GENOMIC DNA SAMPLE

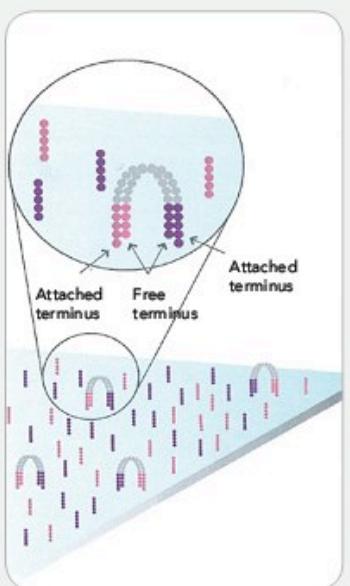
Randomly fragment genomic DNA and ligate adapters to both ends of the fragments.

2. ATTACH DNA TO SURFACE

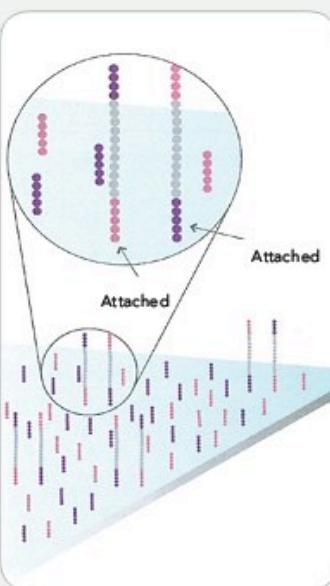
Bind single-stranded fragments randomly to the inside surface of the flow cell channels.

3. BRIDGE AMPLIFICATION

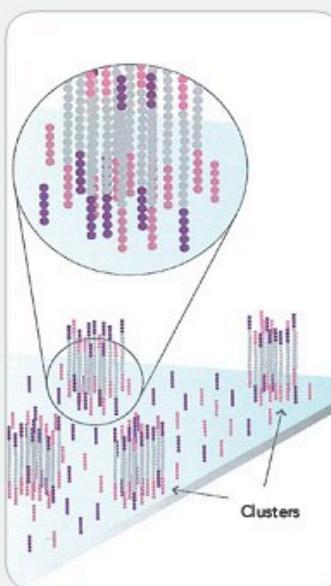
Add unlabeled nucleotides and enzyme to initiate solid-phase bridge amplification.

4. FRAGMENTS BECOME DOUBLE STRANDED

The enzyme incorporates nucleotides to build double-stranded bridges on the solid-phase substrate.

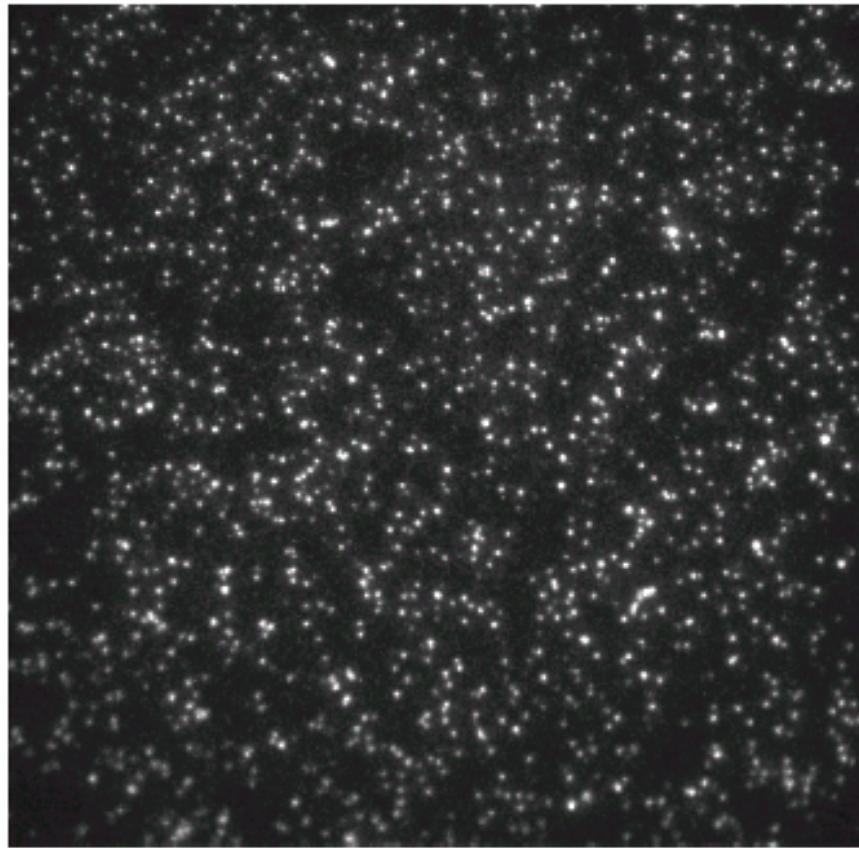
5. DENATURE THE DOUBLE-STRANDED MOLECULES

Denaturation leaves single-stranded templates anchored to the substrate.

6. COMPLETE AMPLIFICATION

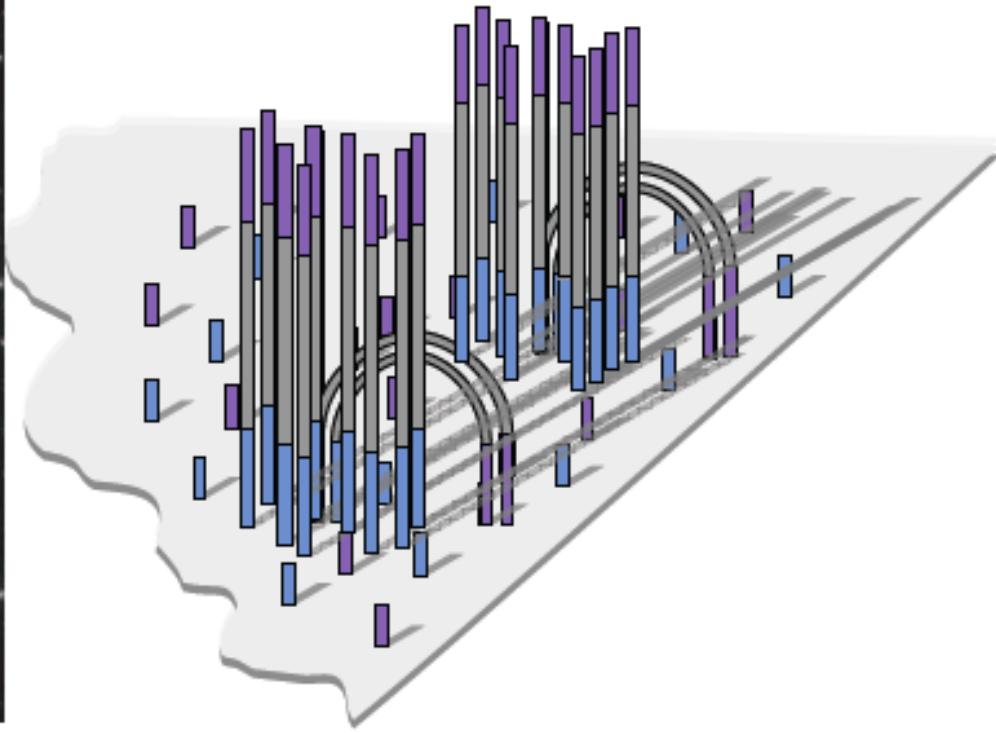
Several million dense clusters of double-stranded DNA are generated in each channel of the flow cell.

Clonal Single molecule Array



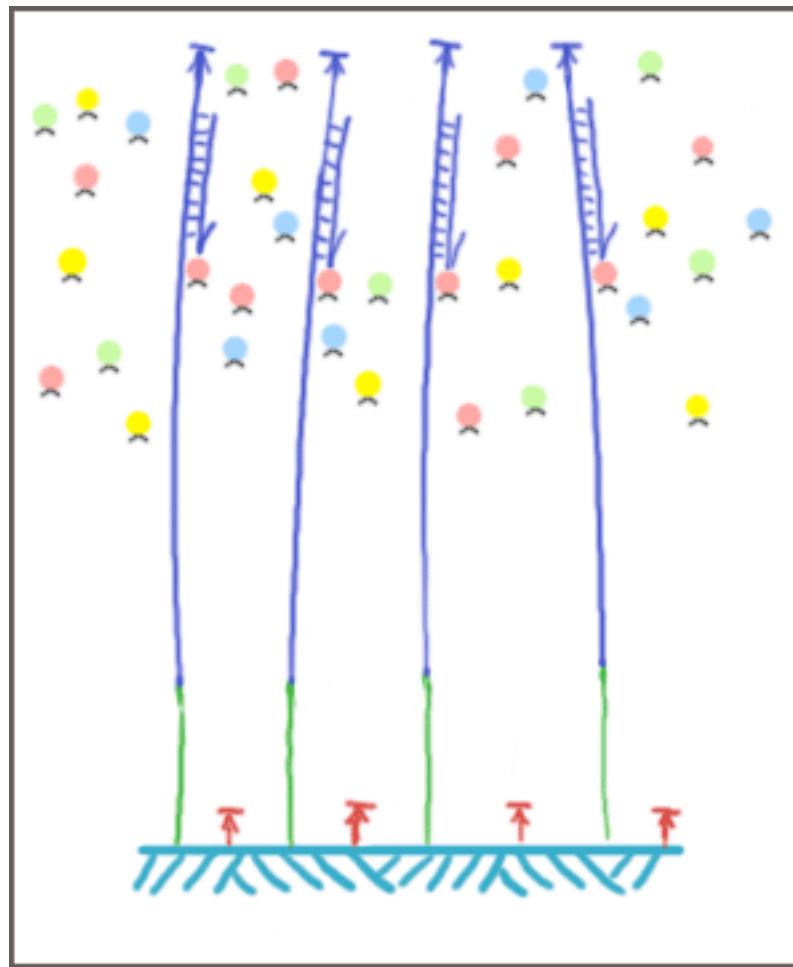
100um

Random array of clusters

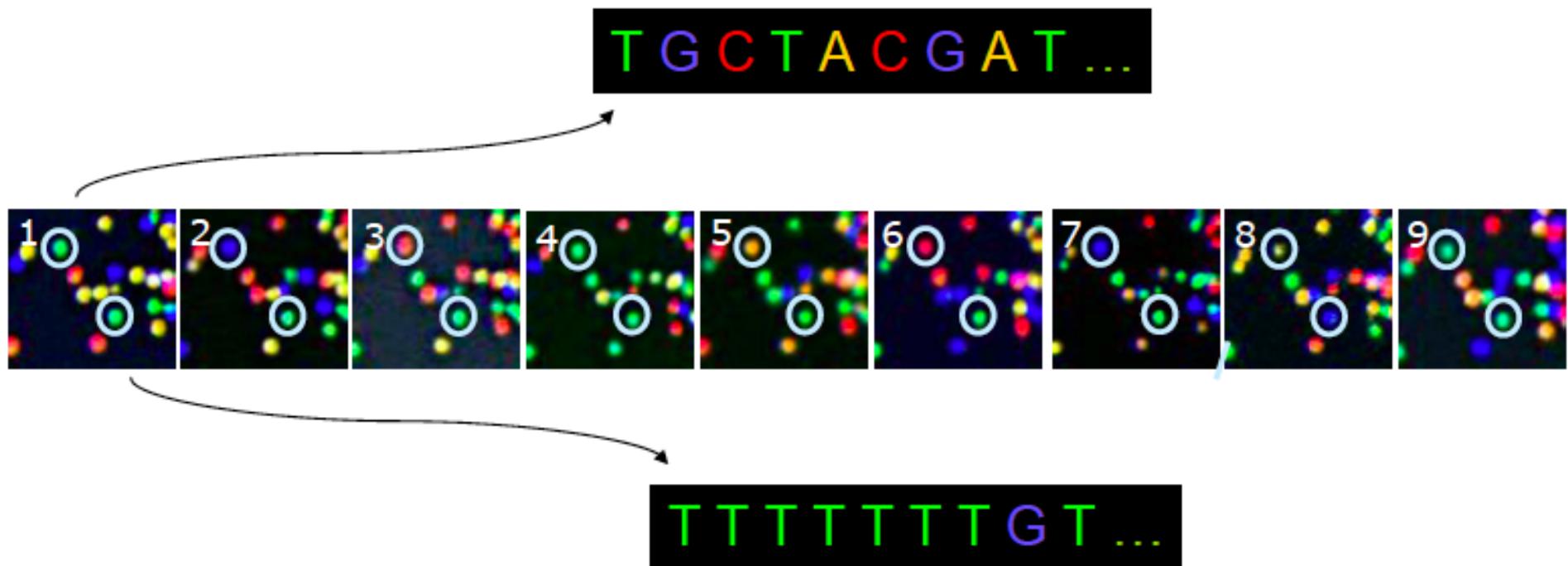


- ~1000 molecules per ~ 1 um cluster
- ~20-30,000 clusters per tile
- ~40 M clusters per flowcell

Sequencing by Synthesis (SBS)

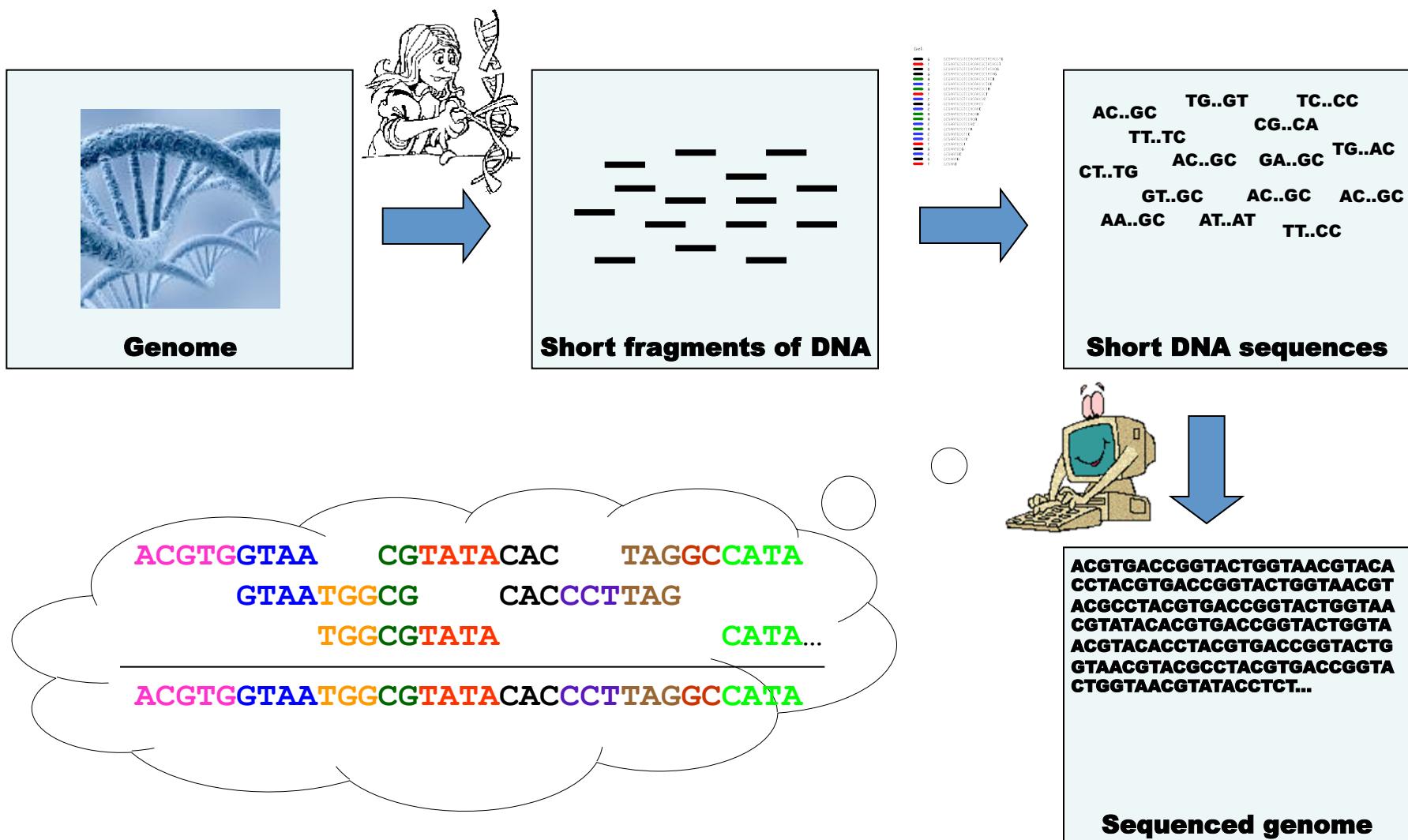


Base Calling From Images



Aplicações

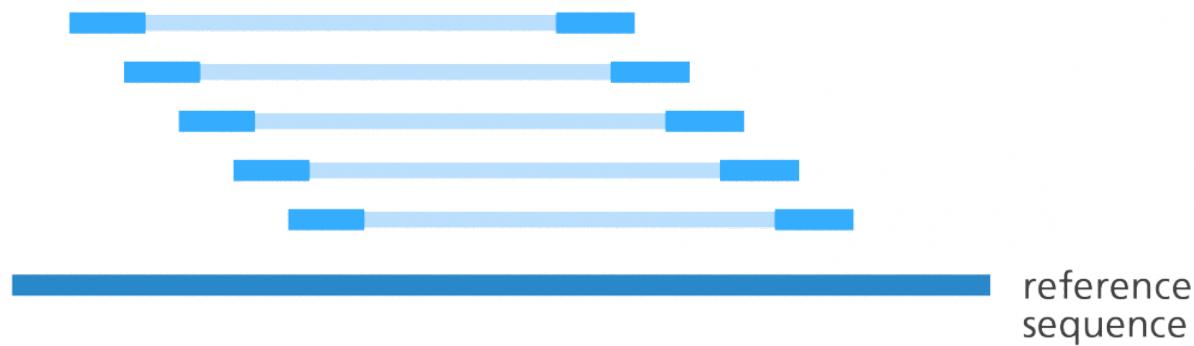
Whole-Genome Sequencing



Single-end reads



Paired-end reads



sequenced
fragment

unknown
sequence

sequenced
fragment



200 - 1000bp

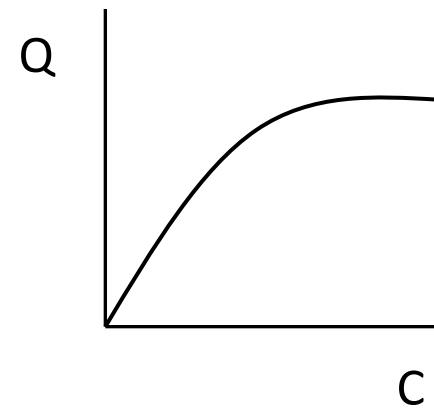
AAGTGCACCGAGATG
AGATGAAGTGCCCAGT
CCAGTCAGATCGGATGC

AAGTGCACCGAGATGAAGTGCCCAGTCAGATCCGATGC

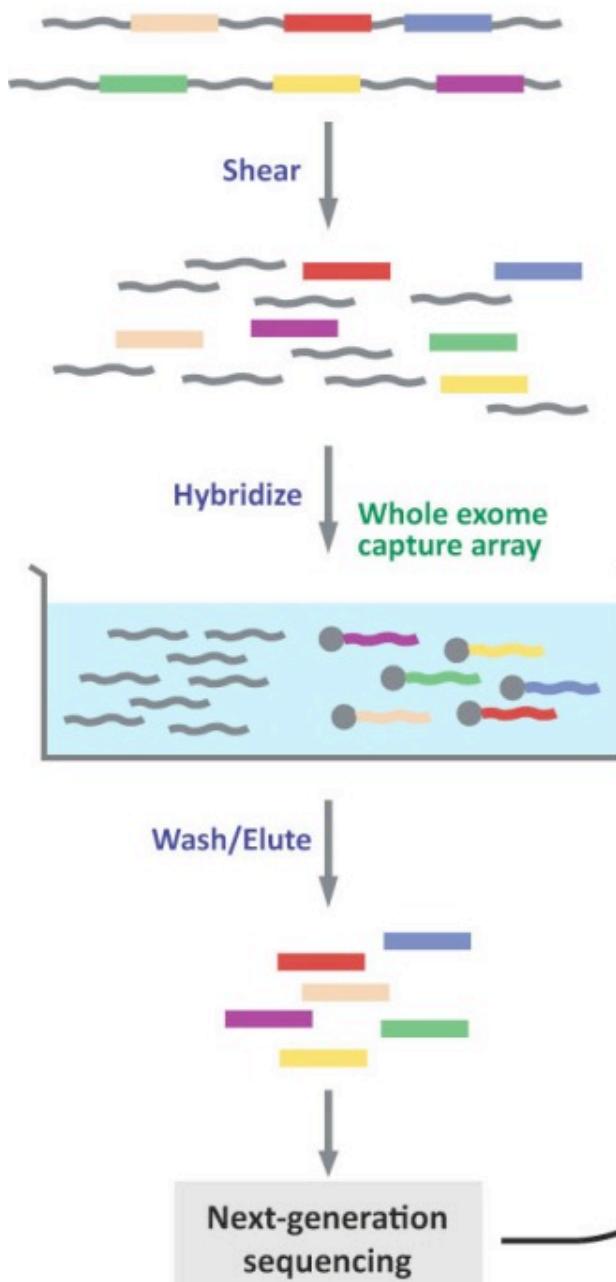
Consenso (contig) gerado a partir de alinhamentos entre todas as sequências geradas.

O método “shotgun do genoma inteiro” exige uma alta redundância entre as sequências geradas, o que define o conceito de cobertura.

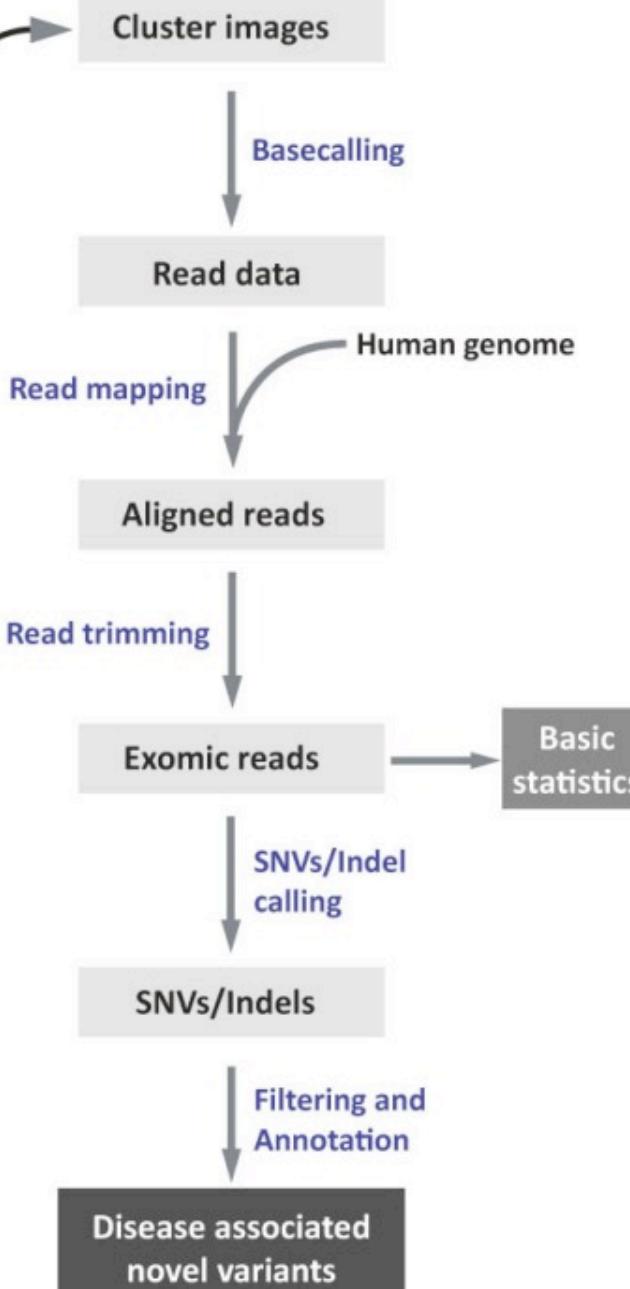
Genoma= 5MB
Sequências geradas = 50MB
Cobertura = 10X



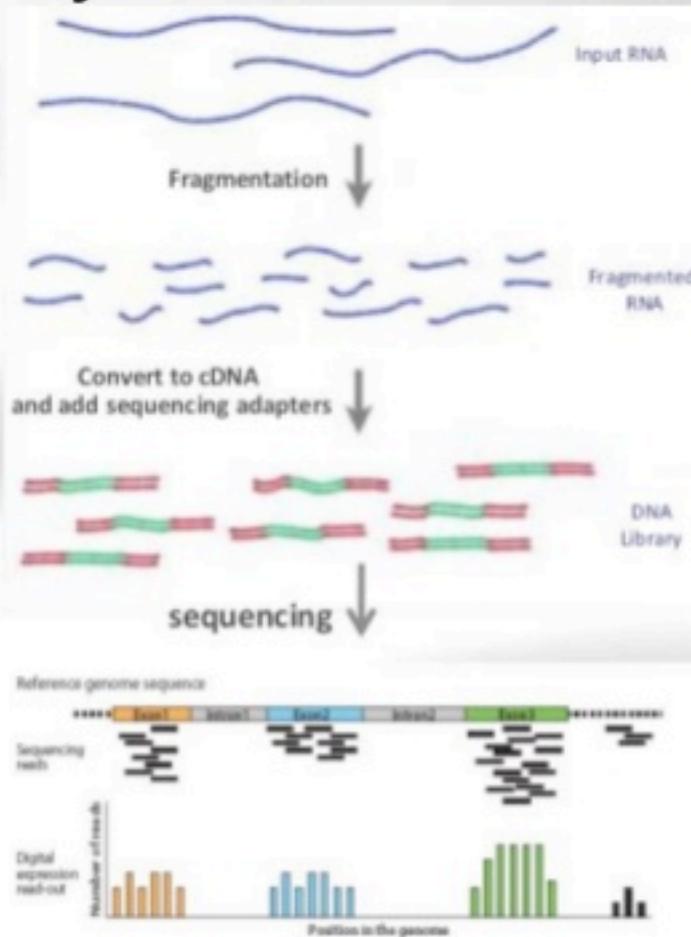
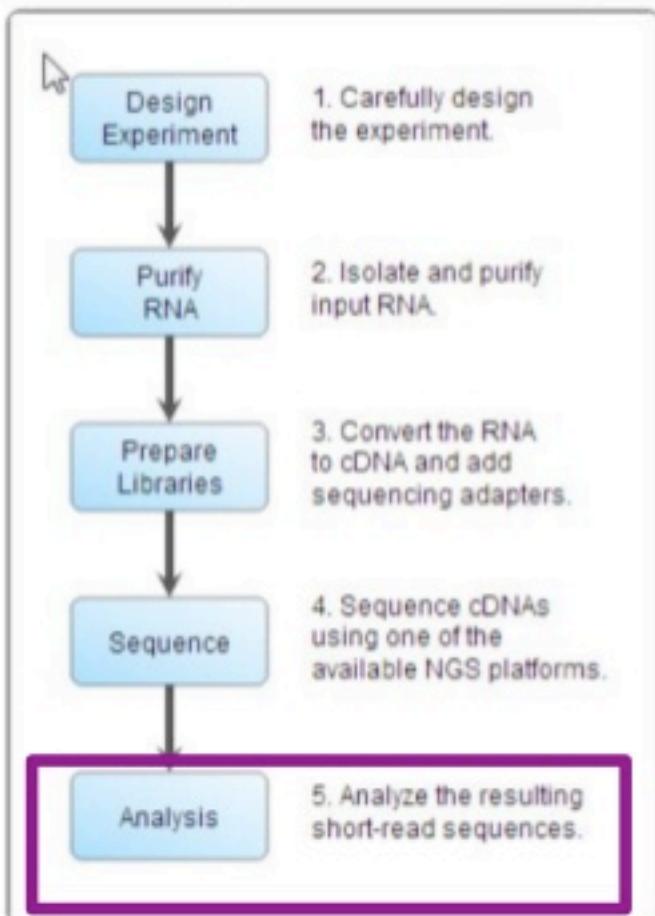
Whole exome capture/ Sequencing pipeline



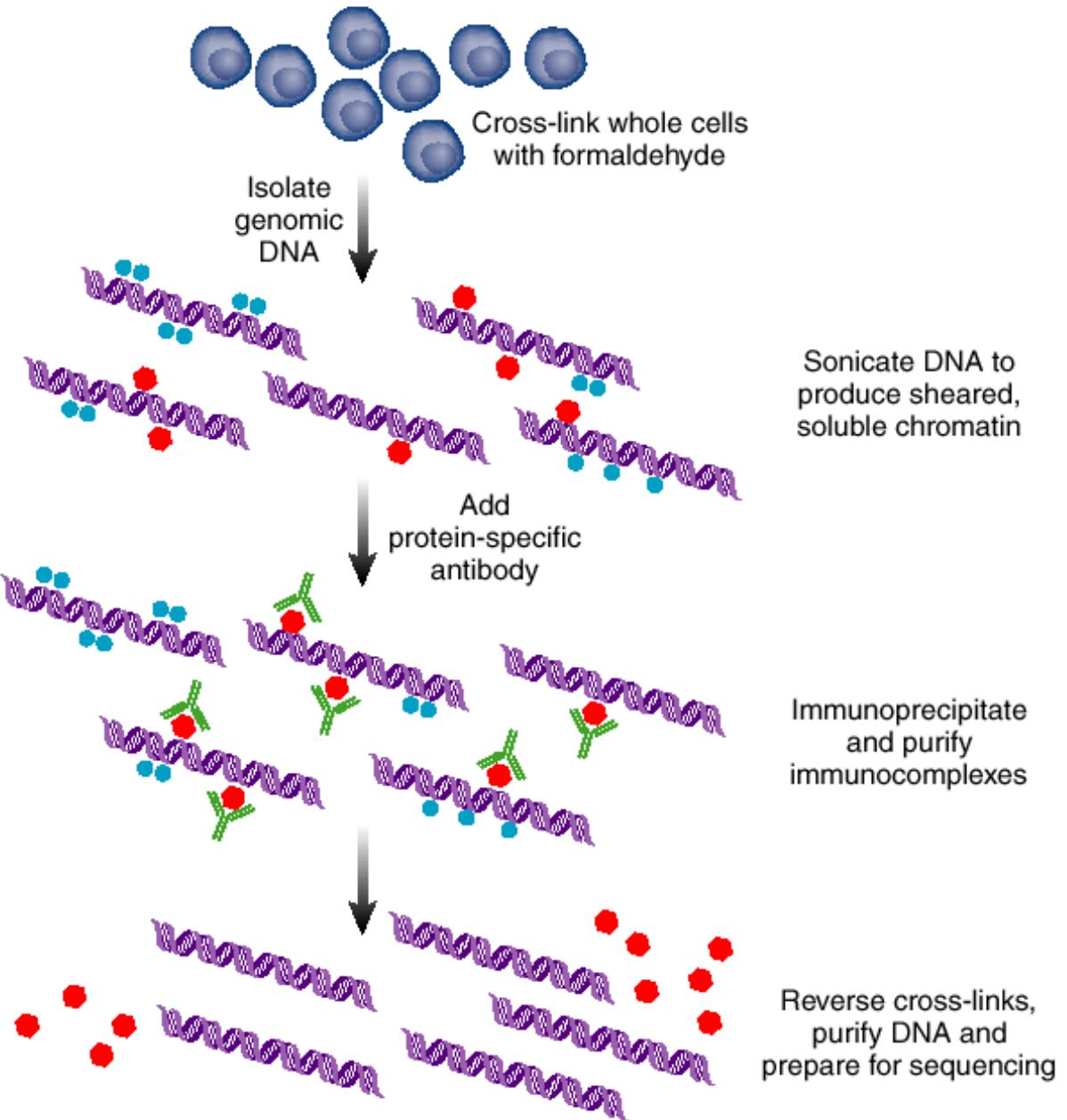
Computational pipeline



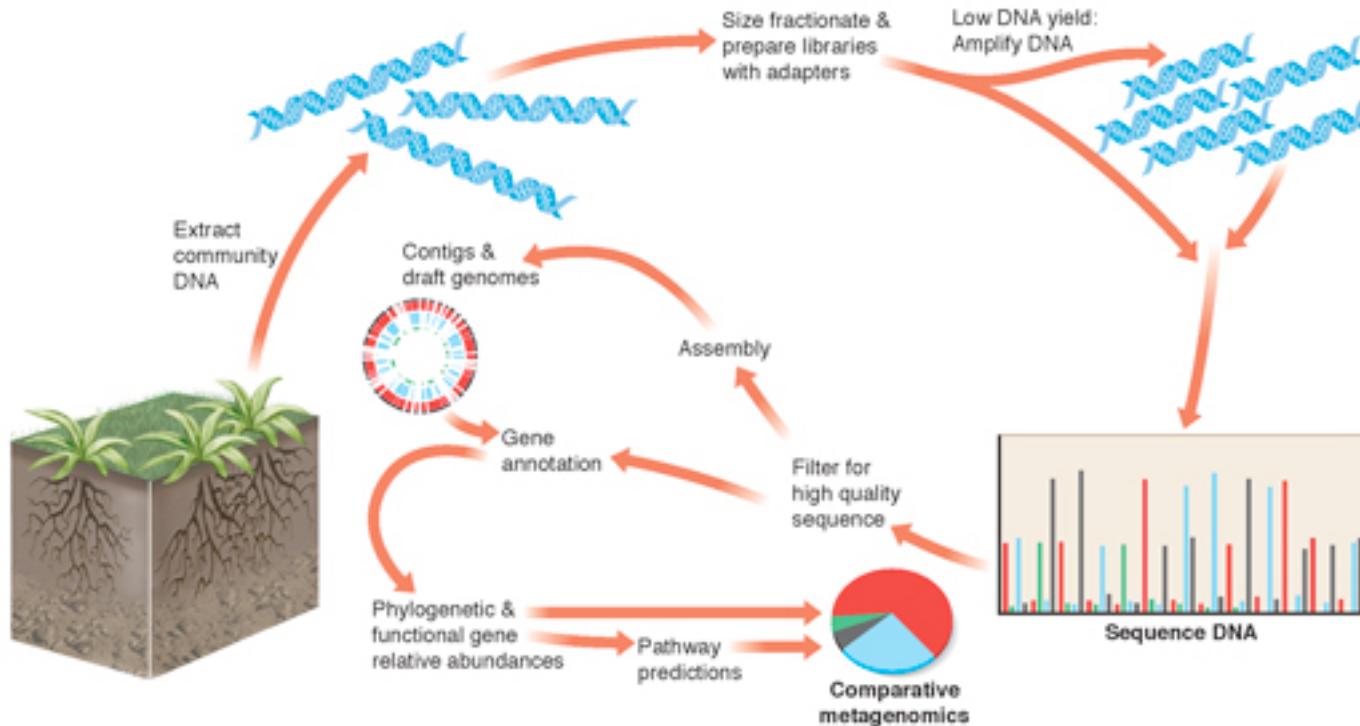
RNA-seq analysis workflow



CHIP-Seq



Metagenômica



- 16S rRNA
- Shotgun

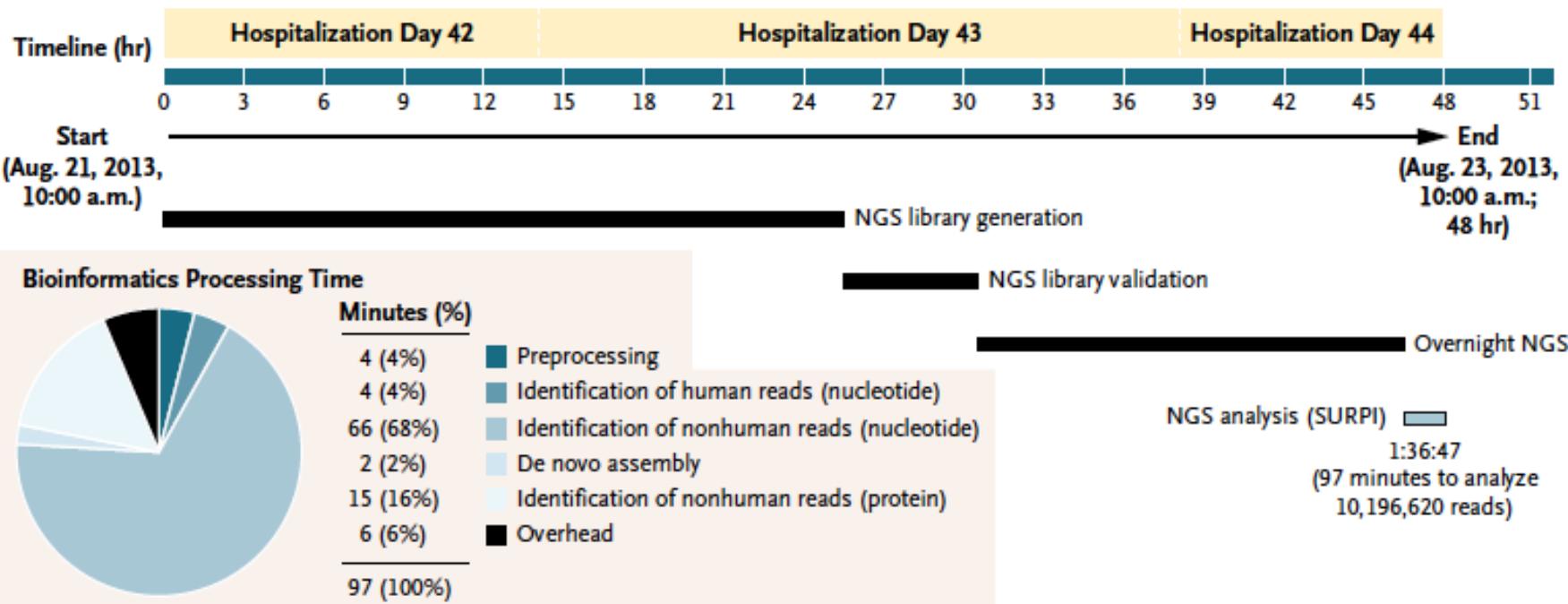
Actionable Diagnosis of Neuroleptospirosis by Next-Generation Sequencing

Michael R. Wilson, M.D., Samia Naccache, Ph.D., Erik Samayoa, B.S., C.L.S.,
Mark Biagtan, M.D., Hiba Bashir, M.D., Guixia Yu, B.S.,
Shahriar M. Salamat, M.D., Ph.D., Sneha Somasekar, B.S., Scot Federman, B.A.,
Steve Miller, M.D., Ph.D., Robert Sokolic, M.D., Elizabeth Garabedian, R.N., M.S.L.S.,
Fabio Candotti, M.D., Rebecca H. Buckley, M.D., Kurt D. Reed, M.D.,
Teresa L. Meyer, R.N., M.S., Christine M. Seroogy, M.D., Renee Galloway, M.P.H.,
Sheryl L. Henderson, M.D., Ph.D., James E. Gern, M.D., Joseph L. DeRisi, Ph.D.,
and Charles Y. Chiu, M.D., Ph.D.

SUMMARY

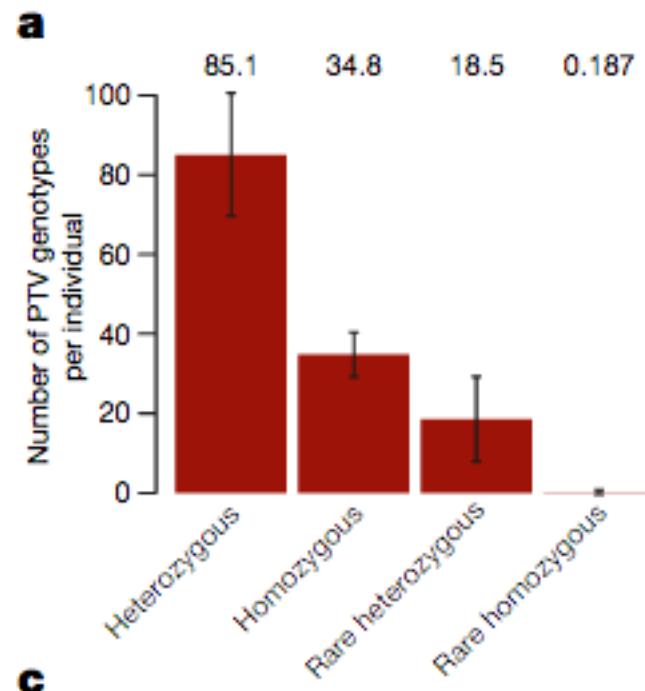
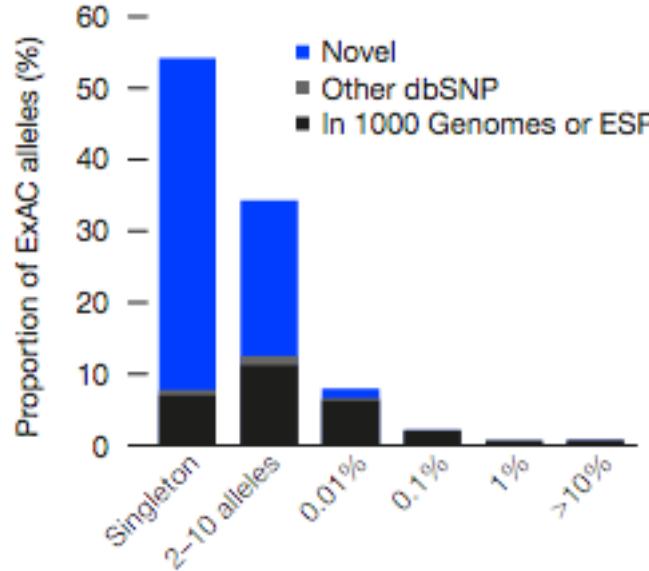
A 14-year-old boy with severe combined immunodeficiency presented three times to a medical facility over a period of 4 months with fever and headache that progressed to hydrocephalus and status epilepticus necessitating a medically induced coma. Diagnostic workup including brain biopsy was unrevealing. Unbiased next-generation sequencing of the cerebrospinal fluid identified 475 of 3,063,784 sequence reads (0.016%) corresponding to *Leptospira* infection. Clinical assays for leptospirosis were negative. Targeted antimicrobial agents were administered, and the patient was discharged home 32 days later with a status close to his premorbid condition. Polymerase-chain-reaction (PCR) and serologic testing at the Centers for Disease Control and Prevention (CDC) subsequently confirmed evidence of *Leptospira santarosai* infection.

A Clinical Laboratory Workflow for NGS



Analysis of protein-coding genetic variation in 60,706 humans

Monkol Lek^{1,2,3,4}, Konrad J. Karczewski^{1,2,*}, Eric V. Minikel^{1,2,5*}, Kaitlin E. Samocha^{1,2,5,6*}, Eric Banks², Timothy Fennell²,



Neanderthal behaviour, diet, and disease inferred from ancient DNA in dental calculus

Laura S. Weyrich¹, Sebastian Duchene², Julien Soubrier¹, Luis Arriola¹, Bastien Llamas¹, James Breen¹, Alan G. Morris³, Kurt W. Alt^{4,5,6,7}, David Caramelli⁸, Veit Dresely^{5,6}, Milly Farrell⁹, Andrew G. Farrer¹, Michael Francken¹⁰, Neville Gully¹¹, Wolfgang Haak¹, Karen Hardy^{12,13}, Katerina Harvati¹⁰, Petra Held¹⁴, Edward C. Holmes², John Kaidonis¹¹, Carles Lalueza-Fox¹⁵, Marco de la Rasilla¹⁶, Antonio Rosas¹⁷, Patrick Semal¹⁸, Arkadiusz Soltysiak¹⁹, Grant Townsend¹¹, Donatella Usai²⁰, Joachim Wahl²¹, Daniel H. Huson²², Keith Dobney^{23,24,25} & Alan Cooper¹

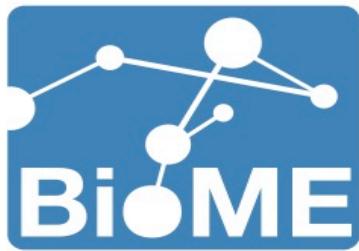
Recent genomic data have revealed multiple interactions between Neanderthals and modern humans¹, but there is currently little genetic evidence regarding Neanderthal behaviour, diet, or disease. Here we describe the shotgun-sequencing of ancient DNA from five specimens of Neanderthal calcified dental plaque (calculus) and the characterization of regional differences in Neanderthal ecology. At Spy cave, Belgium, Neanderthal diet was heavily meat based and included woolly rhinoceros and wild sheep (mouflon), characteristic of a steppe environment. In contrast, no meat was detected in the diet of Neanderthals from El Sidrón cave, Spain, and dietary components of mushrooms, pine nuts, and moss reflected forest gathering^{2,3}. Differences in diet were also linked to an overall shift in the oral bacterial community (microbiota) and suggested that meat consumption contributed to substantial variation within Neanderthal microbiota. Evidence for self-medication was detected in an El Sidrón Neanderthal with a dental abscess⁴ and a chronic gastrointestinal pathogen (*Enterocytozoon bieneusi*). Metagenomic data from this individual also contained a nearly complete genome of the archaeal commensal *Methanobrevibacter oralis* (10.2× depth of coverage)—the oldest draft microbial genome generated to date, at around 48,000 years old. DNA preserved within dental calculus represents a notable source of information about the behaviour and health of ancient hominin specimens, as well as a unique system that is useful for the study of long-term microbial evolution.

purposes⁸. As a result, Neanderthal diet remains a topic of considerable debate, with limited data on the specific animals and plants directly consumed or the potential effects on Neanderthal health and disease.

Although genomic studies continue to reveal evidence of interbreeding between anatomically modern humans and Neanderthals across Eurasia⁹, little is known about the health consequences of these interactions. The genetic analysis of Neanderthal dental calculus represents an opportunity to examine this issue and to reconstruct Neanderthal diet, behaviour, and disease¹⁰. Here, we report the first genetic analysis of dental calculus from five Neanderthals (two individuals from El Sidrón cave in Spain; two individuals from Spy cave in Belgium; and one individual from Breuil Grotta in Italy) and compare these data to a historic wild-caught chimpanzee ($n = 1$) and modern human ($n = 1$), as well as to low coverage sequencing of calculus from a wide-range of ancient humans (Supplementary Table 1). To provide increased resolution of the diseases that may have affected Neanderthals, we also deeply sequenced (>147 million reads) dental calculus from the best-preserved Neanderthal, El Sidrón 1, which suffered from a dental abscess⁴.

Size-based PCR-amplification biases can confound standard metabarcoding analyses (for example, sequencing of 16S ribosomal (r)RNA amplicons^{11,12}) of ancient dental calculus¹³. Consequently, we compared metagenomic-shotgun sequencing and 16S rRNA amplicon (V4 region) analyses of the Neanderthal dental calculus specimens—by far the oldest

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