

A Perspective: Genomics and Bioinformatics

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A Brief History



Sequencing Platforms

- 1986 - Dye terminator Sanger sequencing, peaking at about 900kb/day in early 2000s



'Next' Generation

- 2005 – 'Next Generation Sequencing' as Massively parallel sequencing, both throughput and speed advances. The first was the Genome Sequencer (GS) instrument developed by 454 life Sciences (later acquired by Roche), Pyrosequencing 1.5Gb/day

Discontinued



Illumina (Solexa)

- 2006 – The second ‘Next Generation Sequencing’ platform. Now the dominant platform with 75% market share of sequencer and an estimated >90% of all bases sequenced are from an Illumina machine, Sequencing by Synthesis > 1600Gb/day.

NovaSeq



HiSeq



Complete Genomics

- 2006 – Using DNA nanoball sequencing, has been a leader in Human genome resequencing, having sequenced over 20,000 genomes to date. In 2013 purchased by BGI and is now set to release their first commercial sequencer, the Revolocity. Throughput on par with HiSeq

DEFUNCT

Human genome/exomes only.

10,000 Human Genomes per year



Bench top Sequencers

❖ Life Technologies

- Ion Torrent
- Ion Proton
- Gene Studio S5



❖ Illumina

- MiSeq
- MiniSeq
- iSeq 100



The 'Next, Next' Generation Sequencers (3rd Generation)

- 2009 – Single Molecule Read Time sequencing by Pacific Biosystems, most successful third generation sequencing platforms, RSII ~2Gb/day, newer Pac Bio Sequel ~14Gb/day, near 100Kb reads.

[SMRT Sequencing](#)



Iso-seq on Pac Bio possible, transcriptome without 'assembly'

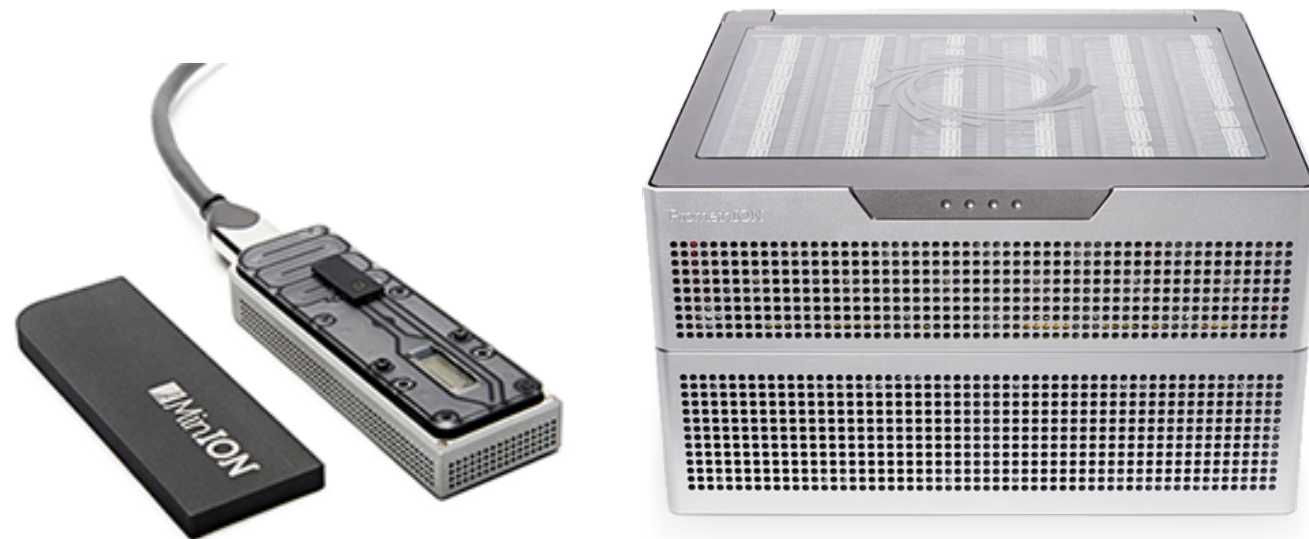
Oxford Nanopore



- 2015 – Another 3rd generation sequencer, founded in 2005 and currently in beta testing. The sequencer uses nanopore technology developed in the 90's to sequence single molecules. Throughput is about 500Mb per flowcell, capable of near 200kb reads.

Fun to play with but results are highly variable

[Nanopore Sequencing](#)



FYI: 4th generation sequencing is being described as In-situ sequencing

Bioinformatics

Old Way of
thinking about
Bioinformatics

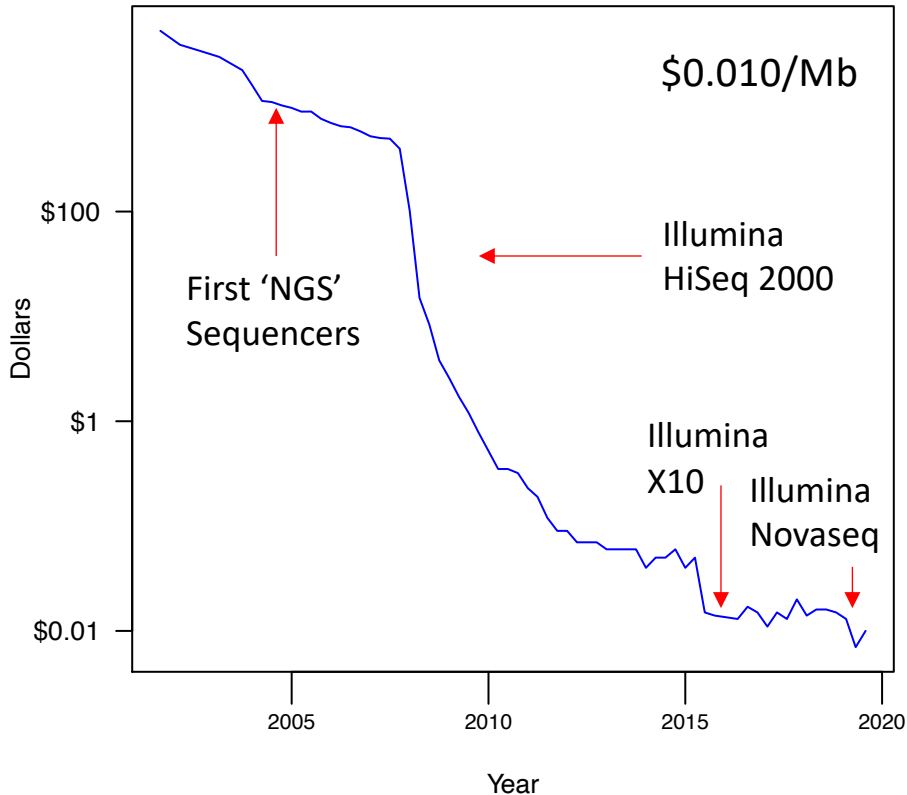


Appro Cluster

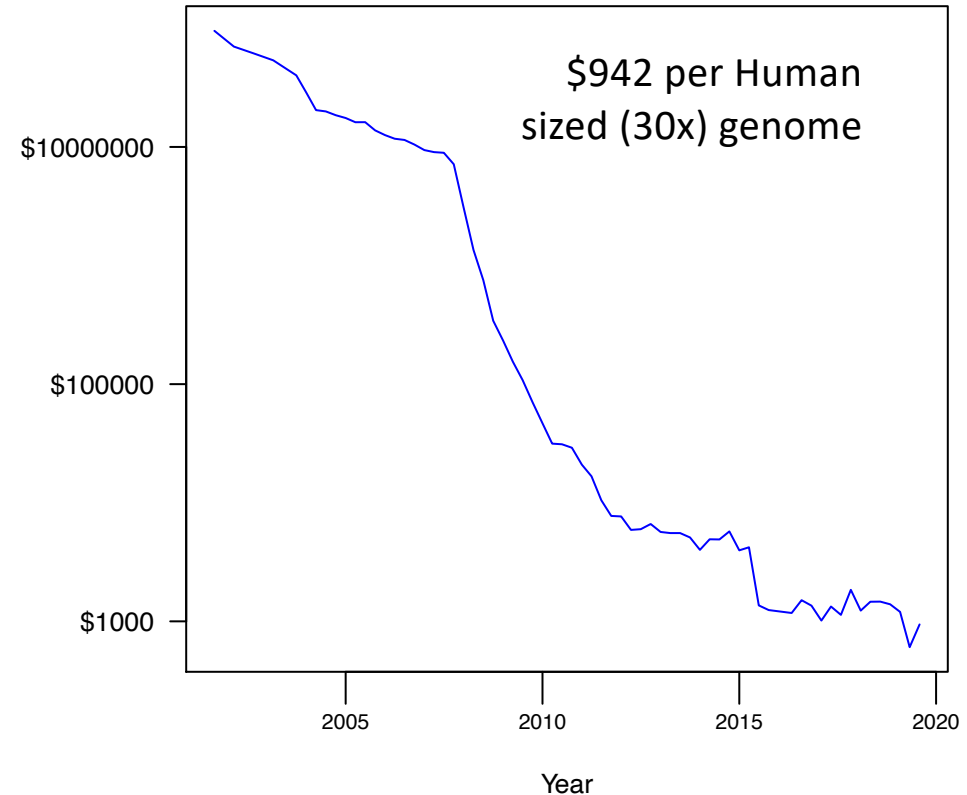
Sequencing Costs

August 2019

Cost per Megabase of Sequence



Cost per Human Sized Genome @ 30x (Illumina)

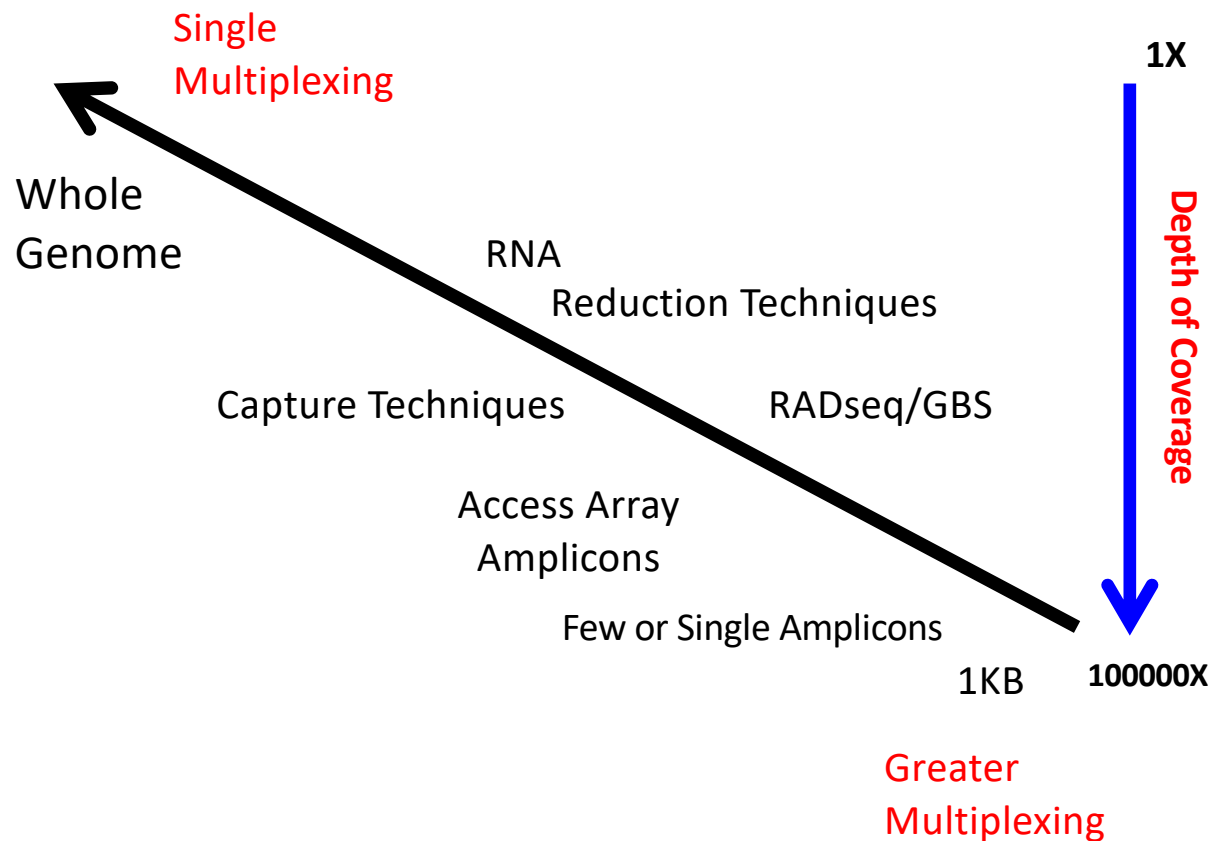


- Includes: labor, administration, management, utilities, reagents, consumables, instruments (amortized over 3 years), informatics related to sequence productions, submission, indirect costs.
- <http://www.genome.gov/sequencingcosts/>

Flexibility

Genomic reduction allows for greater coverage and multiplexing of samples.

You can fine tune your depth of coverage needs and sample size with the reduction technique



Sequencing Libraries:

DNA-seq	DNase-seq	tagRNA-seq	EnD-seq
RNA-seq	ATAC-seq	PAT-seq	Pool-seq
Amplicons	MNase-seq	Structure-seq	G&T-seq
CHiP-seq	FAIRE-seq	MPE-seq	Tn-Seq
MeDiP-seq	Ribose-seq	STARR-seq	BrAD-seq
RAD-seq	smRNA-seq	Mod-seq	SLAF-seq
ddRAD-seq			

MLA-seq is my favorite seq

The data deluge



- Plucking the biology from the Noise

Reality



- Its much more difficult than we may first think

Data Science

Data science is the process of formulating a quantitative question that can be answered with data, collecting and cleaning the data, analyzing the data, and communicating the answer to the question to a relevant audience.

7 Stages to Data Science

1. Define the question of interest
2. Get the data
3. Clean the data
4. Explore the data
5. Fit statistical models
6. Communicate the results
7. Make your analysis reproducible

1. Define the question of interest

Begin with the end in mind!

what is the question

how are we to know we are successful

what are our expectations

dictates

the data that should be collected

the features being analyzed

which algorithms should be use

2. Get the data
3. Clean the data
4. Explore the data

Know your data!

know what the source was
technical processing in producing
data (bias, artifacts, etc.)
“Data Profiling”

Data are never perfect but love your data anyway!

the collection of massive data sets often leads to unusual ,
surprising, unexpected and even outrageous.

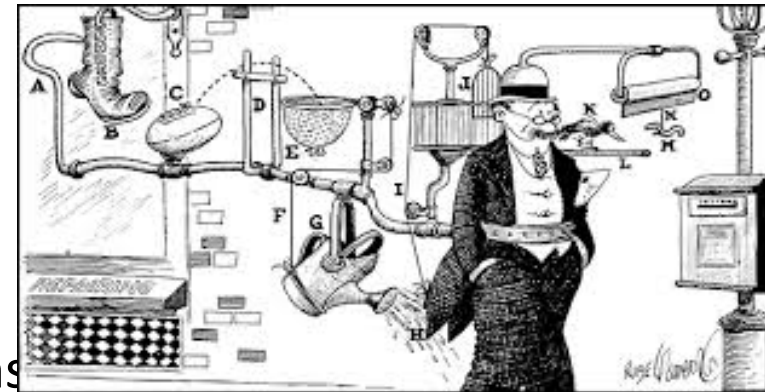


5. Fit statistical models Machine Learning

Over fitting is a sin against data science!

Model's should not be over-complicated

- If the data scientist has done their job correctly the statistical models don't need to be incredibly complicated to identify important relationships
- In fact, if a complicated statistical model seems necessary, it often means that you don't have the right data to answer the question you really want to answer.



6. Communicate the results
7. Make your analysis reproducible

Remember that this is 'science'!

We are experimenting with data selections, processing, algorithms, ensembles of algorithms, measurements, models. At some point these ***must all be tested for validity and applicability*** to the problem you are trying to solve.



**Data science done well looks easy – and
that's a big problem for data scientists**

**simplystatistics.org
March 3, 2015 by Jeff Leek**

Bad data science (bioinformatics) also looks easy

The Data Science in Bioinformatics

Bioinformatics is not something you are taught,
it's a way of life

*“The best bioinformaticians I know are **problem solvers** – they start the day not knowing something, and they enjoy finding out (themselves) how to do it. It’s a great skill to have, but for most, it’s not even a skill – it’s a passion, it’s a way of life, it’s a thrill. It’s what these people would do at the weekend (if their families let them).”*

Mick Watson – Rosland Institute

Substrate

Cloud
Computing



Cluster
Computing



BAS™

LINUX

Laptop & Desktop



Environment

“Command Line” and “Programming Languages”



vs

Bioinformatics Software Suite



Prerequisites for doing Bioinformatics

- Access to a multi-core (24 cpu or greater), 'high' memory 64Gb or greater Linux server.
- Familiarity with the 'command line' and at least one programming language.
- Basic knowledge of how to install software
- Basic knowledge of R (or equivalent) and statistical programming
- Basic knowledge of Statistics and model building

Training - Models

- Workshops
 - Often enrolled too late
- Collaborations
 - More experience persons
- Apprenticeships
 - Previous lab personnel to young personnel
- Formal Education
 - Most programs are graduate level
 - Few Undergraduate

Genomics and Bioinformatics

Following data science principles, 2 stages in bioinformatics

- **Data reduction**

Sequence data (raw data) to summarized form.

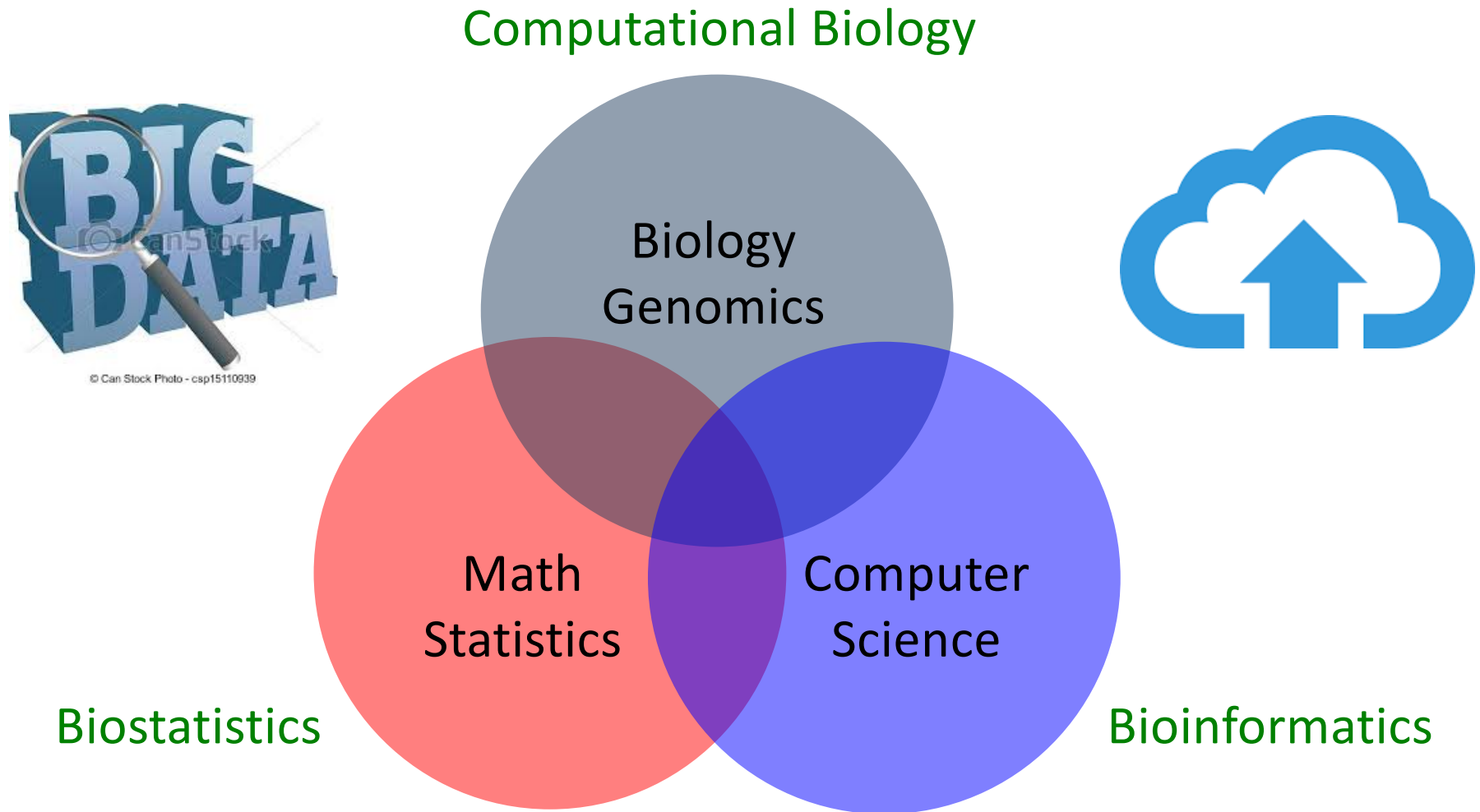
- * Command line, shell scripting, and programming.
- * Requires an understanding of the technology, molecular biology.
- * Removing technical noise from data.

- **Data analysis**

Summarized data to biological interpretation

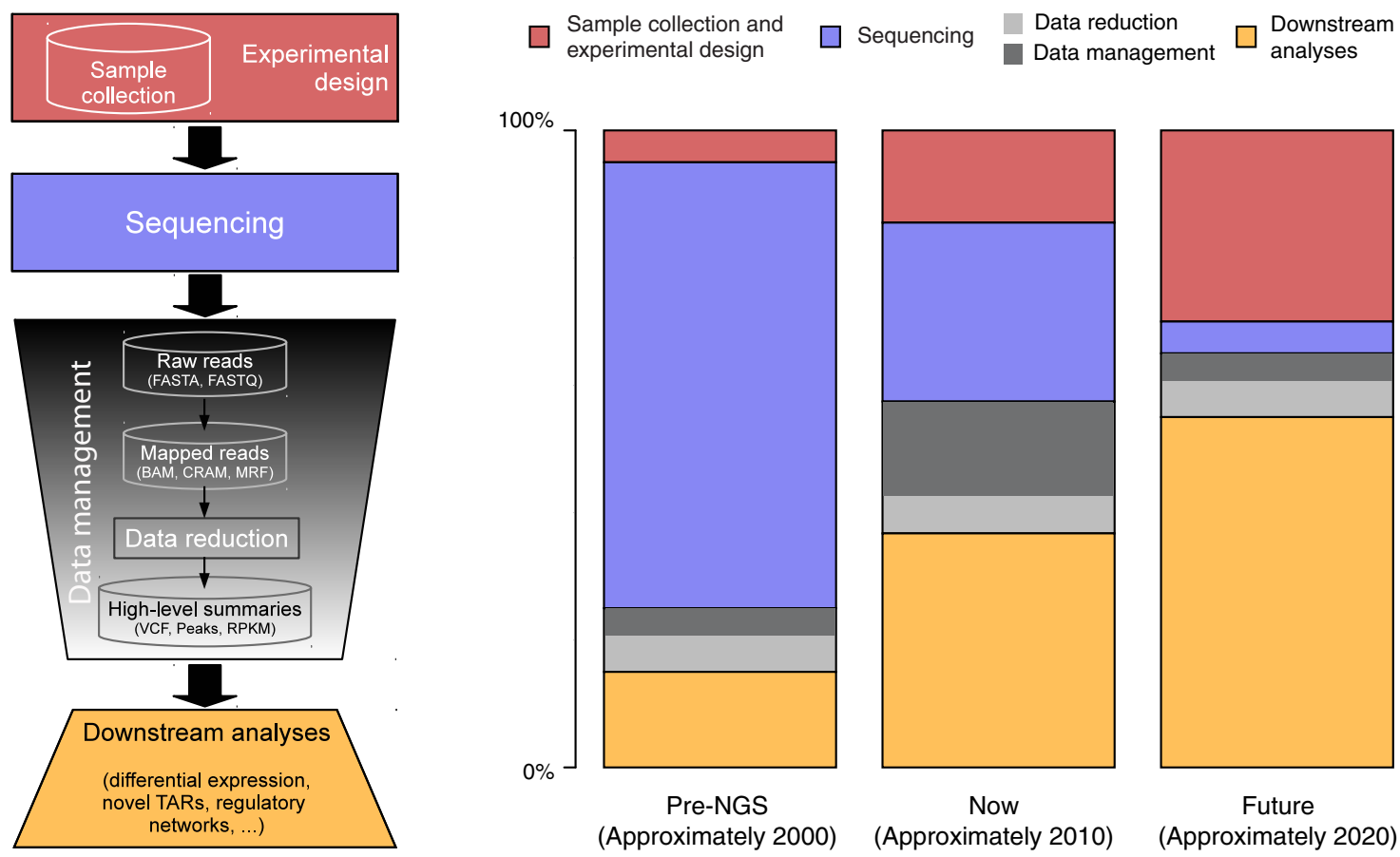
- * R/Python statistical programming
- * Requires an understanding of the biological question, statistics.

Bioinformatician as Genomics Data Scientist



‘The data scientist role has been described as “part analyst, part artist.”’
Anjul Bhambhri, vice president of big data products at IBM

“The real cost of sequencing”



The last mile



<http://www.bikeblanket.com/blog/suisse>

The Bottom Line: In Genomics

Spend the time (and money) planning and producing **good quality, accurate and sufficient data.**

Get to know the data, develop and test expectations, explore and identify patterns.

Result, **spend much less time** (and less money) extracting biological significance and results with fewer failures and reproducible research.