Genome Sequencing & Assembly

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March 30, 2015

CSHL Genome Access

Outline

1. Assembly theory
    1. Assembly by analogy
    2. De Bruijn and Overlap graph
    3. Coverage, read length, errors, and repeats
2. Whole Genome Alignment
    1. Aligning & visualizing with MUMmer
3. Genome assemblers
    1. ALLPATHS-LG: recommended for Illumina-only projects
    2. Celera Assembler: recommended for PacBio/ONT projects

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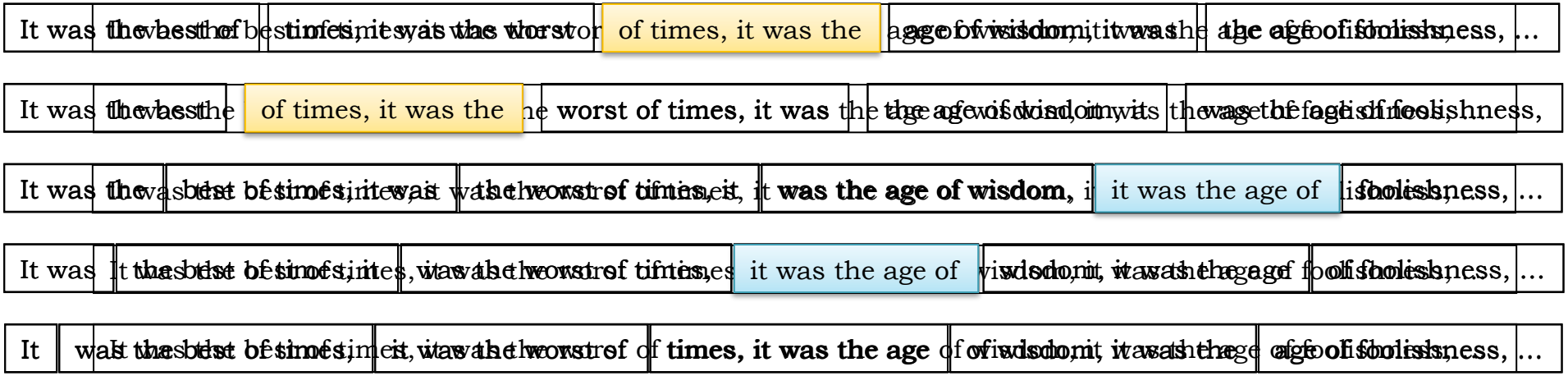
Shredded Book Reconstruction

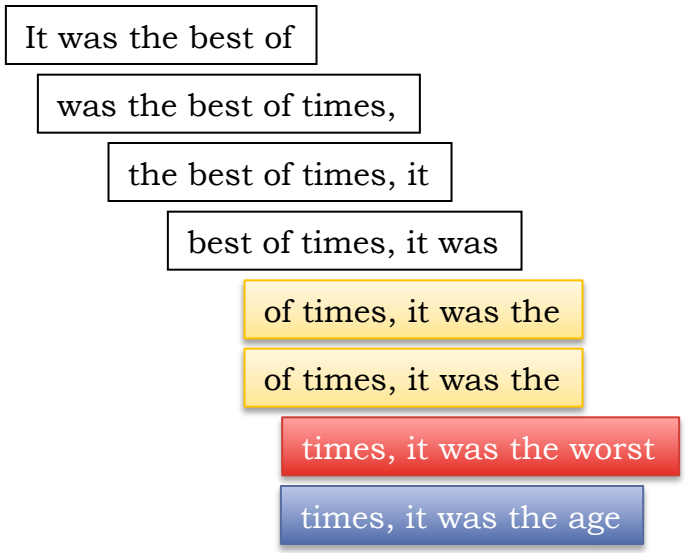
- Dickens accidentally shreds the first printing of A Tale of Two Cities
  - Text printed on 5 long spools



- How can he reconstruct the text?
  - 5 copies x 138, 656 words / 5 words per fragment = 138k fragments
  - The short fragments from every copy are mixed together
  - Some fragments are identical

Greedy Reconstruction

It was the best of
age of wisdom, it was
best of times, it was
it was the age of
it was the age of
it was the worst of
of times, it was the
of times, it was the
of wisdom, it was the
the age of wisdom, it
the best of times, it
the worst of times, it
times, it was the age
times, it was the worst
was the age of wisdom,
was the age of foolishness,
was the best of times,
was the worst of times,
wisdom, it was the age
worst of times, it was



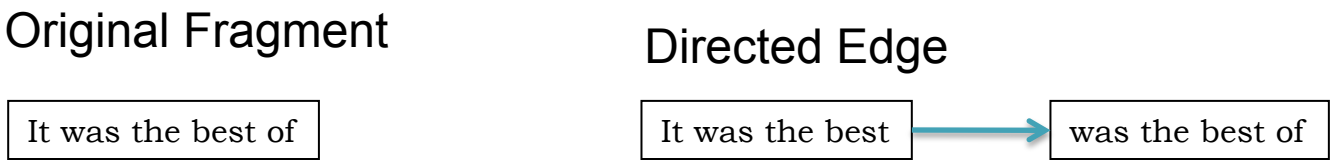
The repeated sequence make the correct reconstruction ambiguous

- It was the best of times, it was the [worst/age]

Model the assembly problem as a graph problem

de Bruijn Graph Construction

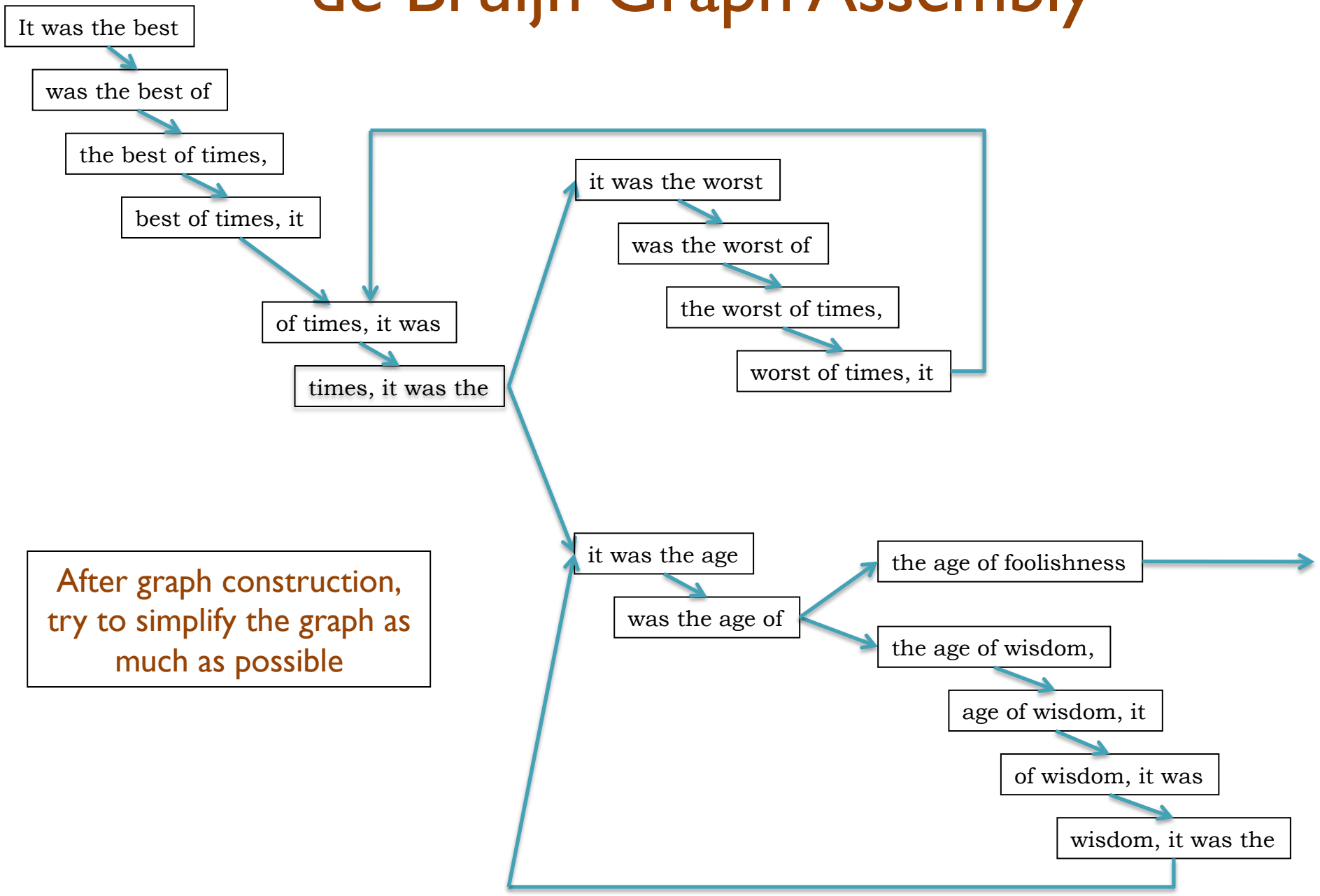
- $D_k = (V,E)$
  - V = All length-k subfragments (k < l)
  - E = Directed edges between consecutive subfragments
    - Nodes overlap by k-1 words



- Locally constructed graph reveals the global sequence structure
  - Overlaps between sequences implicitly computed

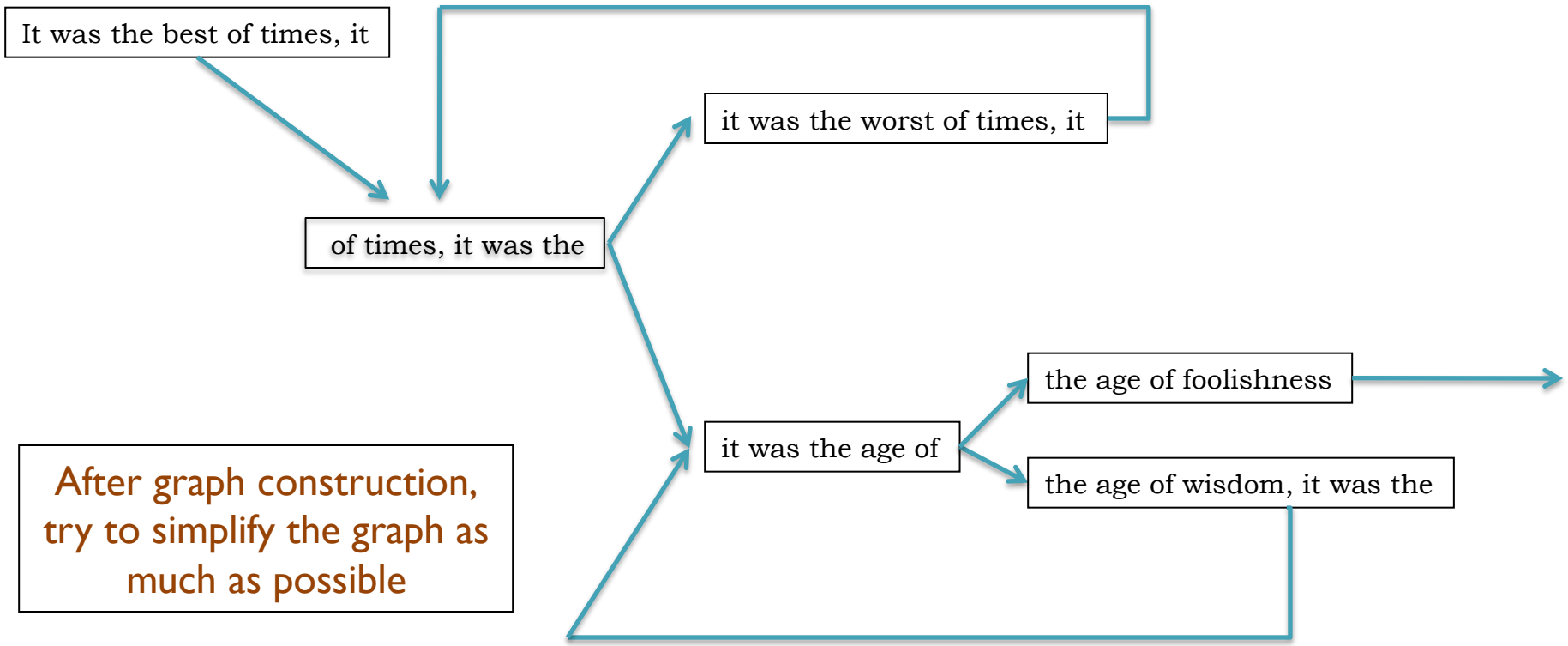
de Bruijn, 1946
Idury and Waterman, 1995
Pevzner, Tang, Waterman, 2001

de Bruijn Graph Assembly



After graph construction, try to simplify the graph as much as possible

de Bruijn Graph Assembly



After graph construction, try to simplify the graph as much as possible

The full tale

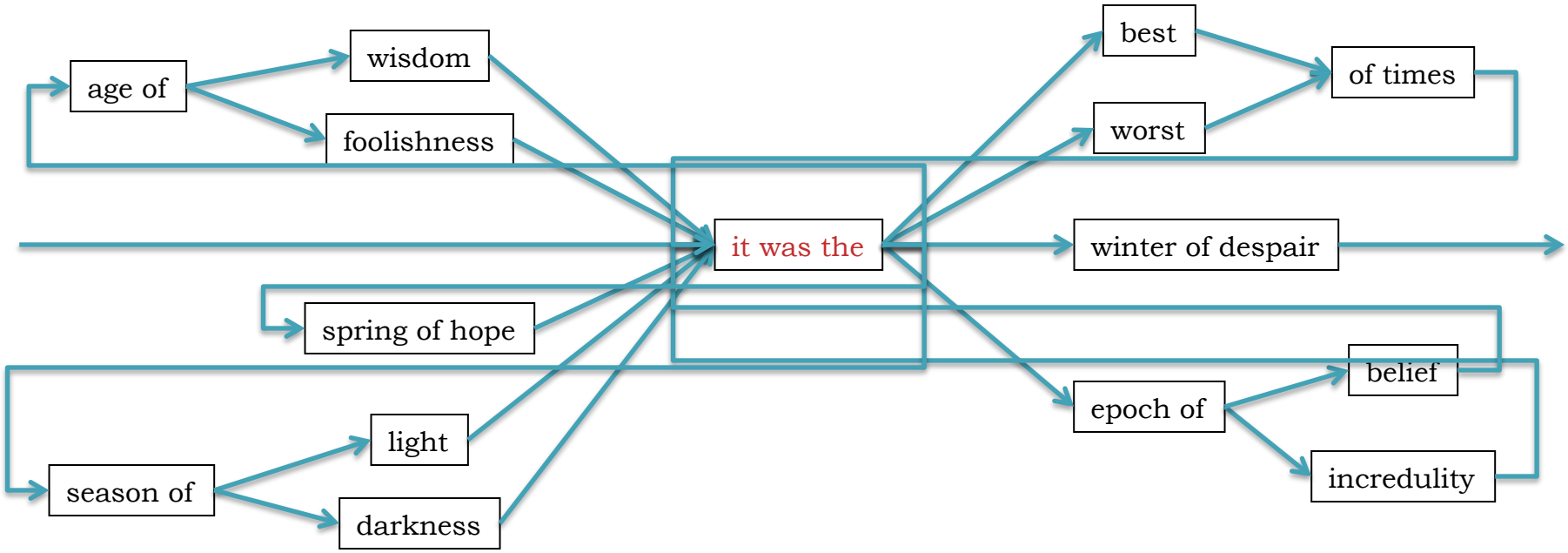
… it was the best of times it was the worst of times …

… it was the age of wisdom it was the age of foolishness …

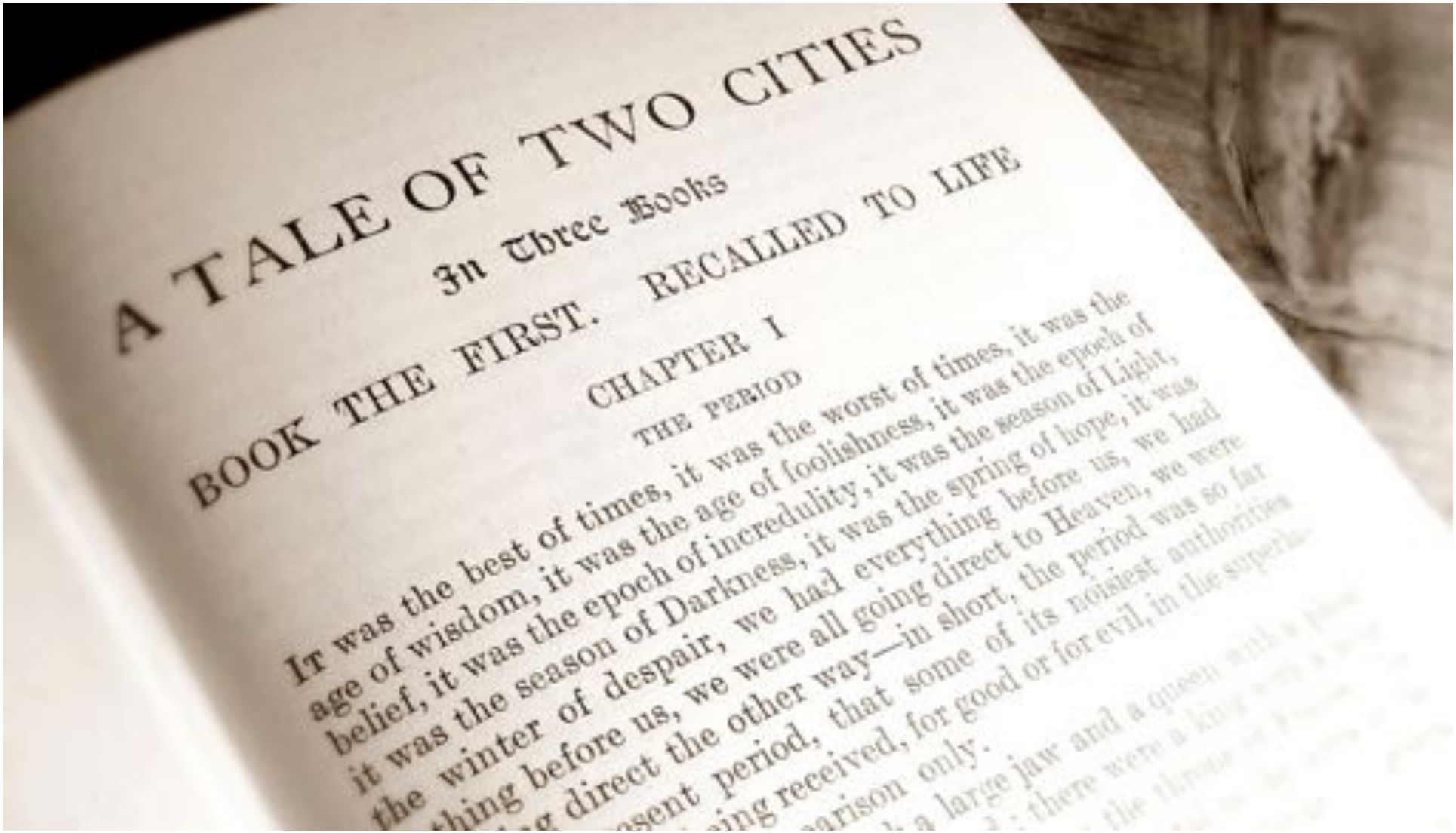
… it was the epoch of belief it was the epoch of incredulity …

… it was the season of light it was the season of darkness …

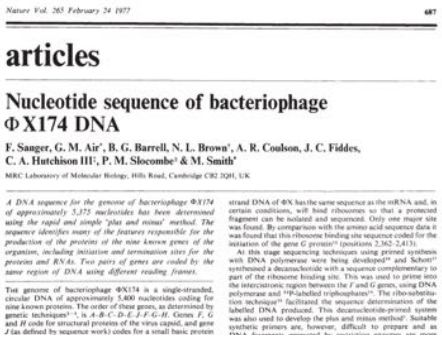
… it was the spring of hope it was the winder of despair …



The full tale



Milestones in Genome Assembly



articles

Nucleotide sequence of bacteriophage ΦX174 DNA

F. Sanger, G. M. Air*, B. G. Barrell, N. L. Brown†, A. R. Coulson, J. C. Fiddes, C. A. Hutchison III‡, P. M. Slocombe§ & M. Smith*

MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH, UK

1977. Sanger *et al.*
1st Complete Organism
5375 bp

1995. Fleischmann *et al.*
1st Free Living Organism
TIGR Assembler. 1.8Mbp

1998. C.elegans SC
1st Multicellular Organism
BAC-by-BAC Phrap. 97Mbp

2000. Myers *et al.*
1st Large WGS Assembly.
Celera Assembler. 116 Mbp

2001. Venter *et al.*, IHGSC
Human Genome
Celera Assembler/GigaAssembler. 2.9 Gbp

2010. Li *et al.*
1st Large SGS Assembly.
SOAPdenovo 2.2 Gbp

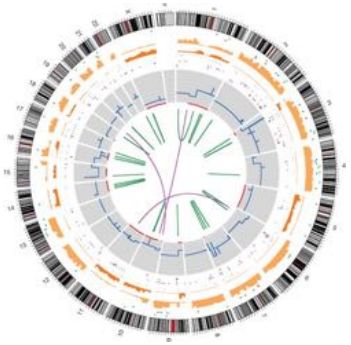
Like Dickens, we must computationally reconstruct a genome from short fragments

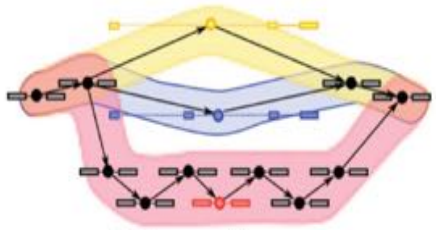
Assembly Applications

- Novel genomes

- Metagenomes

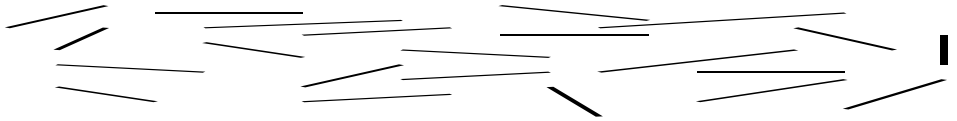
- Sequencing assays
  - Structural variations
  - Transcript assembly
  - …





Assembling a Genome

1. Shear & Sequence DNA



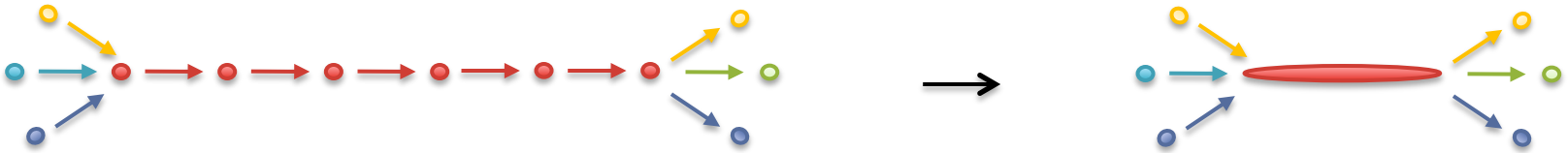
2. Construct assembly graph from overlapping reads

...AGCCTAGGGATGCGCGACACGT

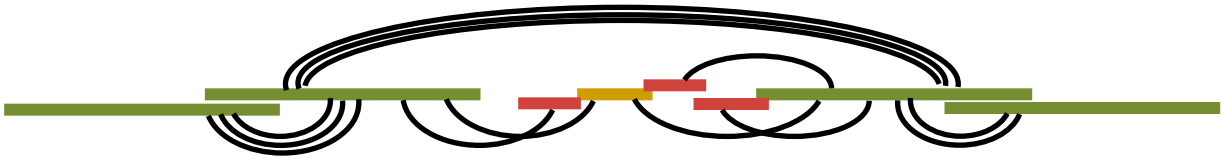
GGATGCGCGACACGTCGCATATCCGGTTTGGTCAACCTCGGACGGAC

CAACCTCGGACGGACCTCAGCGAA...

3. Simplify assembly graph



4. Detangle graph with long reads, mates, and other links



Why are genomes hard to assemble?

1. ***Biological***:
   - (Very) High ploidy, heterozygosity, repeat content

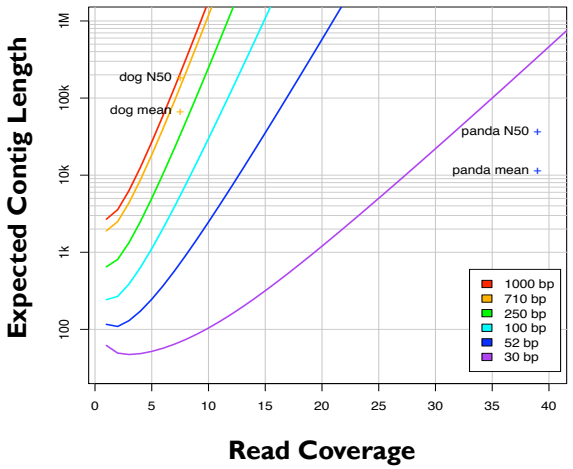
2. ***Sequencing***:
   - (Very) large genomes, imperfect sequencing

3. ***Computational***:
   - (Very) Large genomes, complex structure

4. ***Accuracy***:
   - (Very) Hard to assess correctness

Ingredients for a good assembly

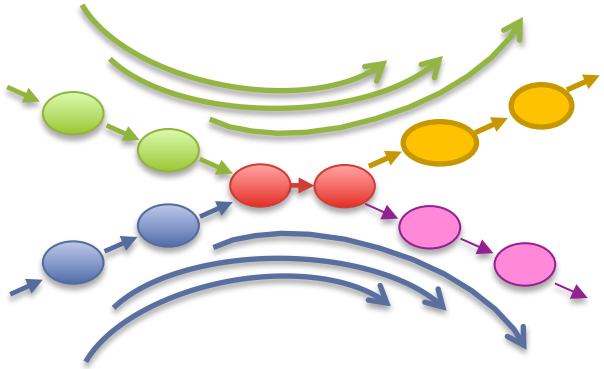
Coverage



High coverage is required

- Oversample the genome to ensure every base is sequenced with long overlaps between reads
- Biased coverage will also fragment assembly

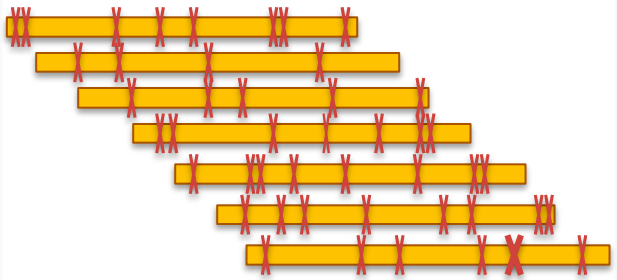
Read Length



Reads & mates must be longer than the repeats

- Short reads will have ***false overlaps*** forming hairball assembly graphs
- With long enough reads, assemble entire chromosomes into contigs

Quality

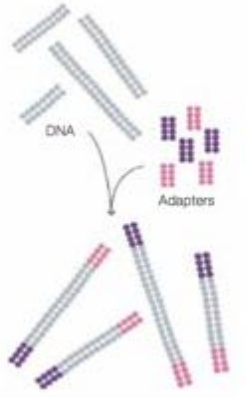


Errors obscure overlaps

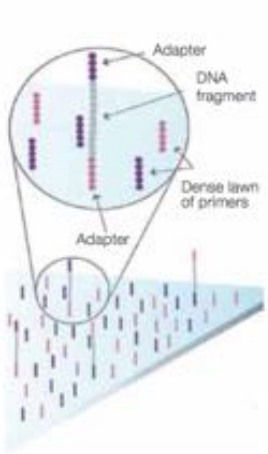
- Reads are assembled by finding kmers shared in pair of reads
- High error rate requires very short seeds, increasing complexity and forming assembly hairballs

Current challenges in *de novo* plant genome sequencing and assembly
Schatz MC, Witkowski, McCombie, WR (2012) *Genome Biology*. 12:243

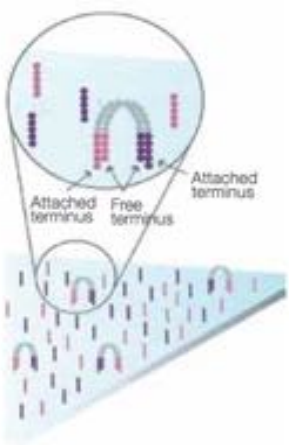
Illumina Sequencing by Synthesis



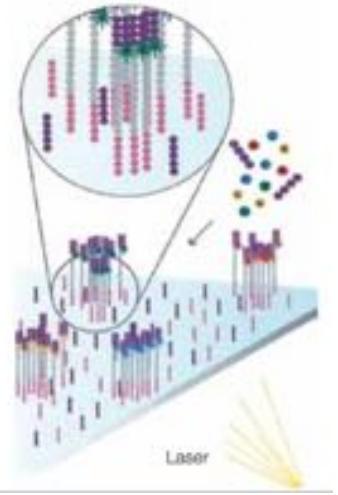
1. Prepare



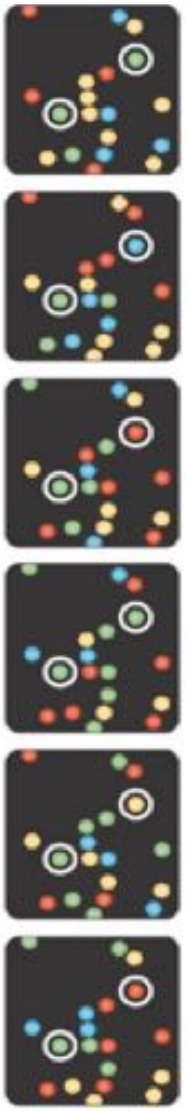
2. Attach



3. Amplify



4. Image

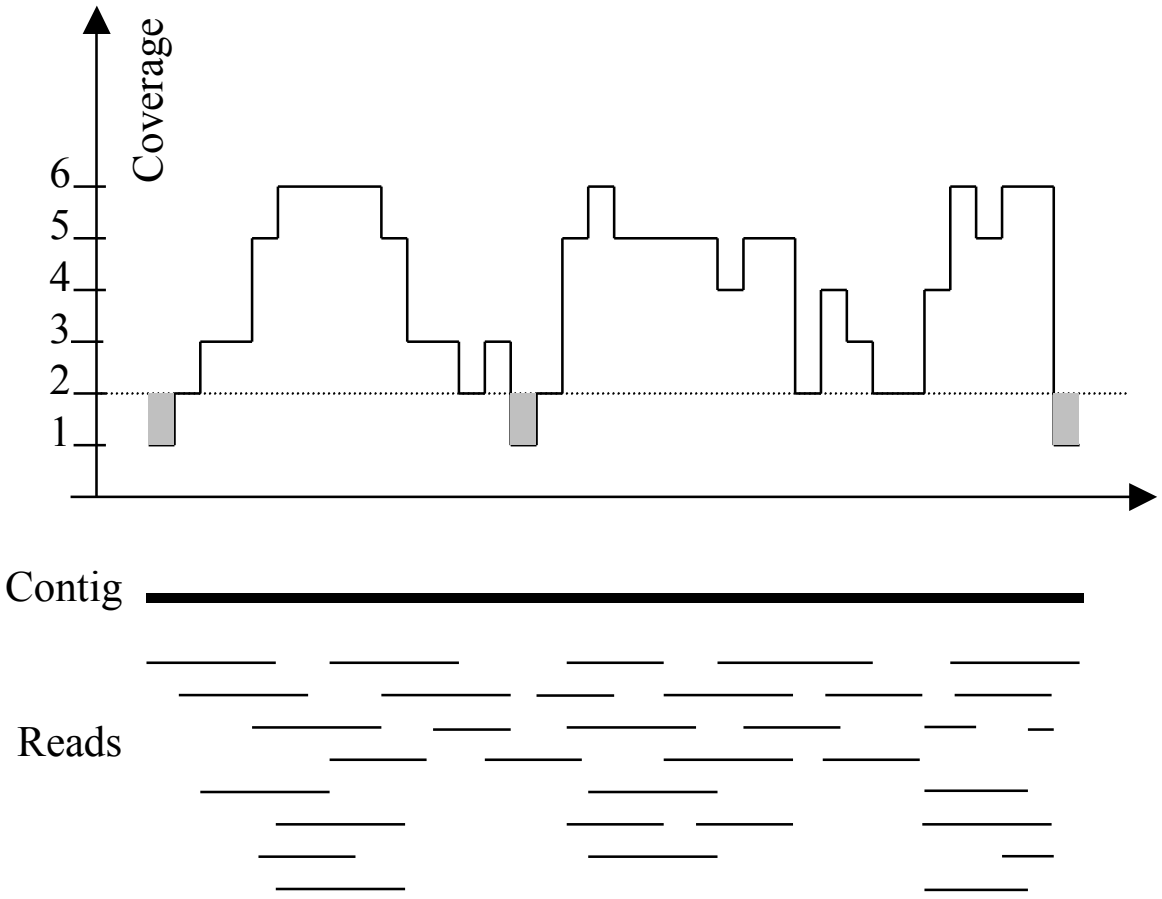


5. Basecall

Metzker (2010) Nature Reviews Genetics 11:31-46

http://www.youtube.com/watch?v=l99aKKHcxC4

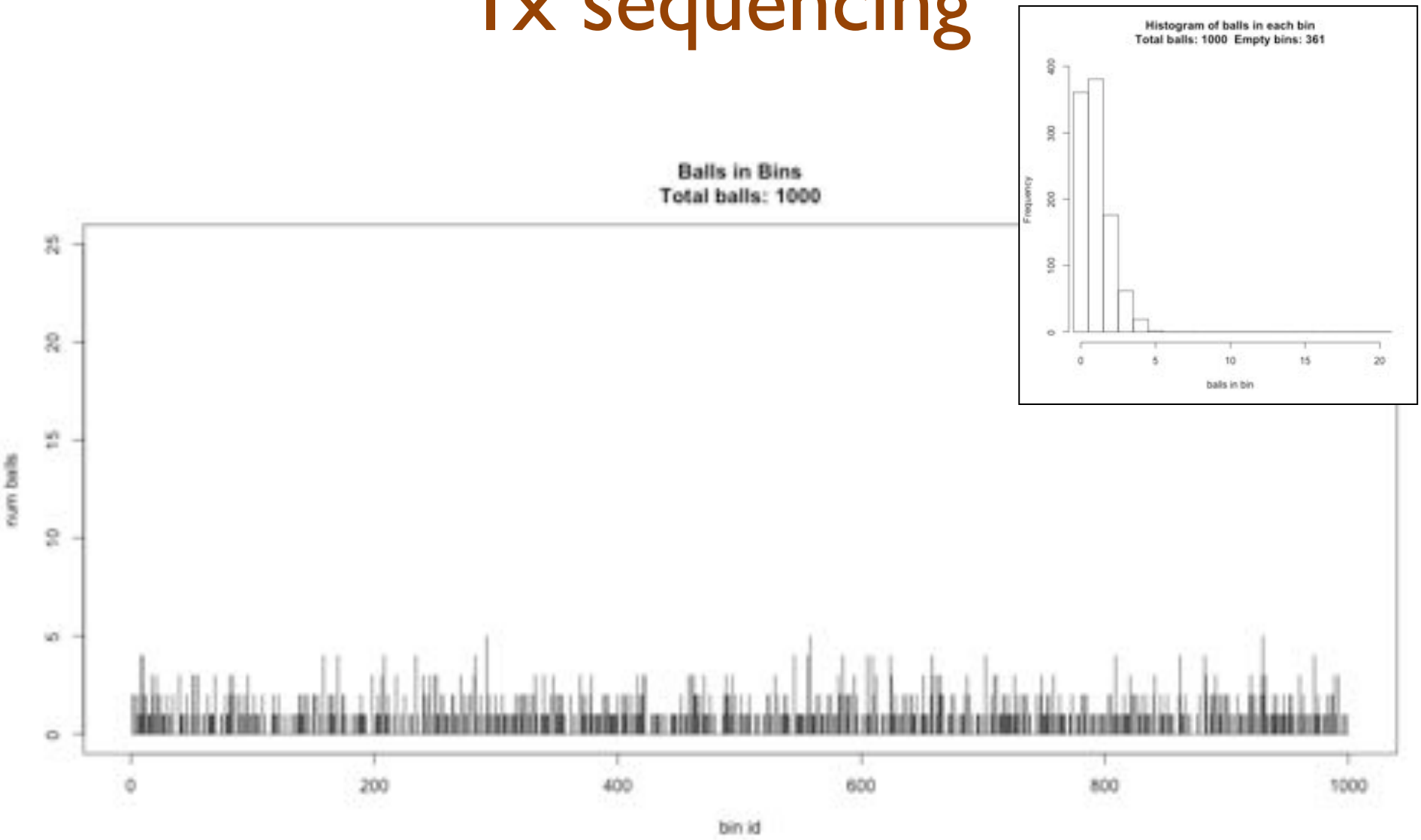
Typical sequencing coverage



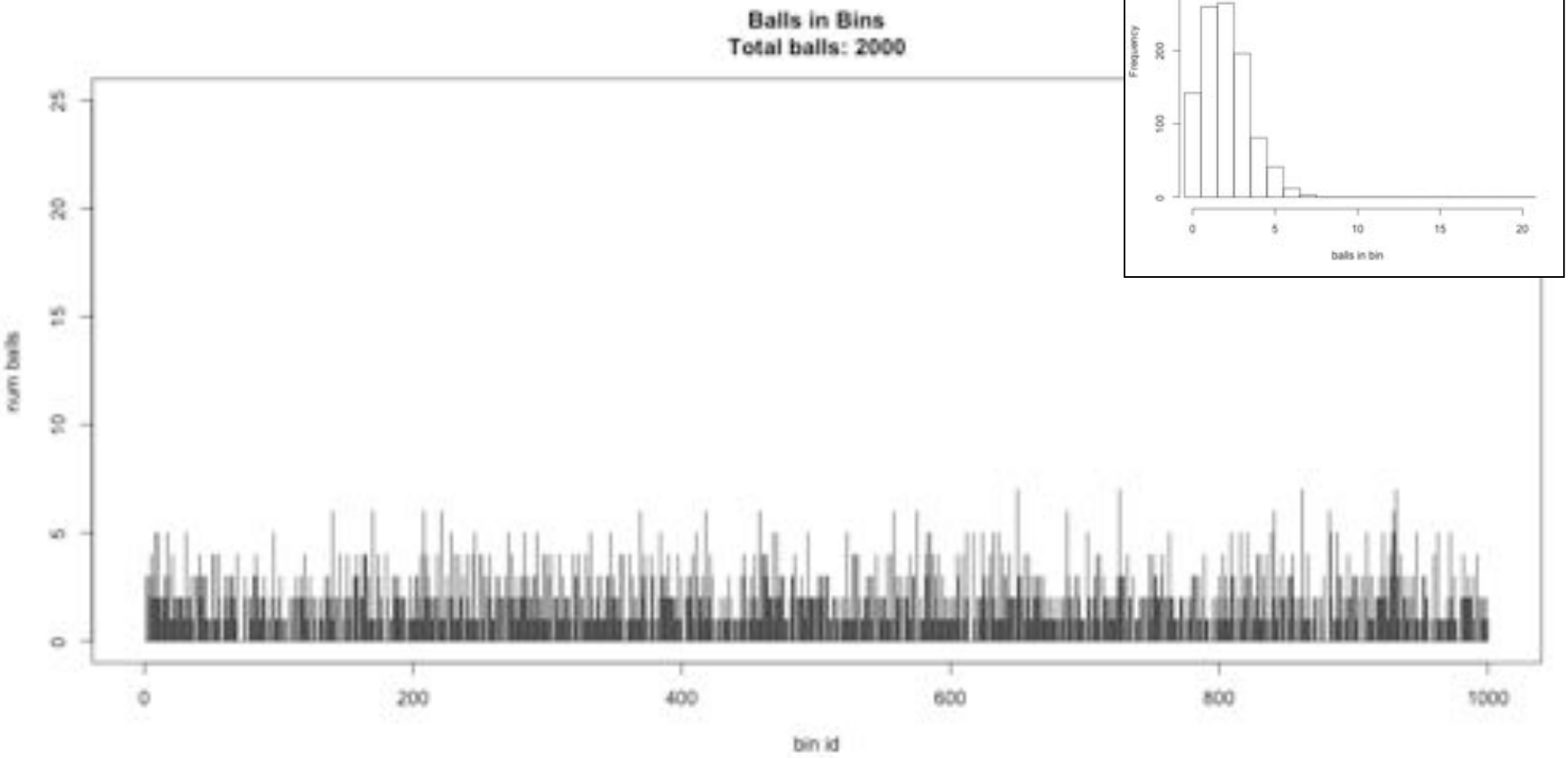
Imagine raindrops on a sidewalk

We want to cover the entire sidewalk but each drop costs $1

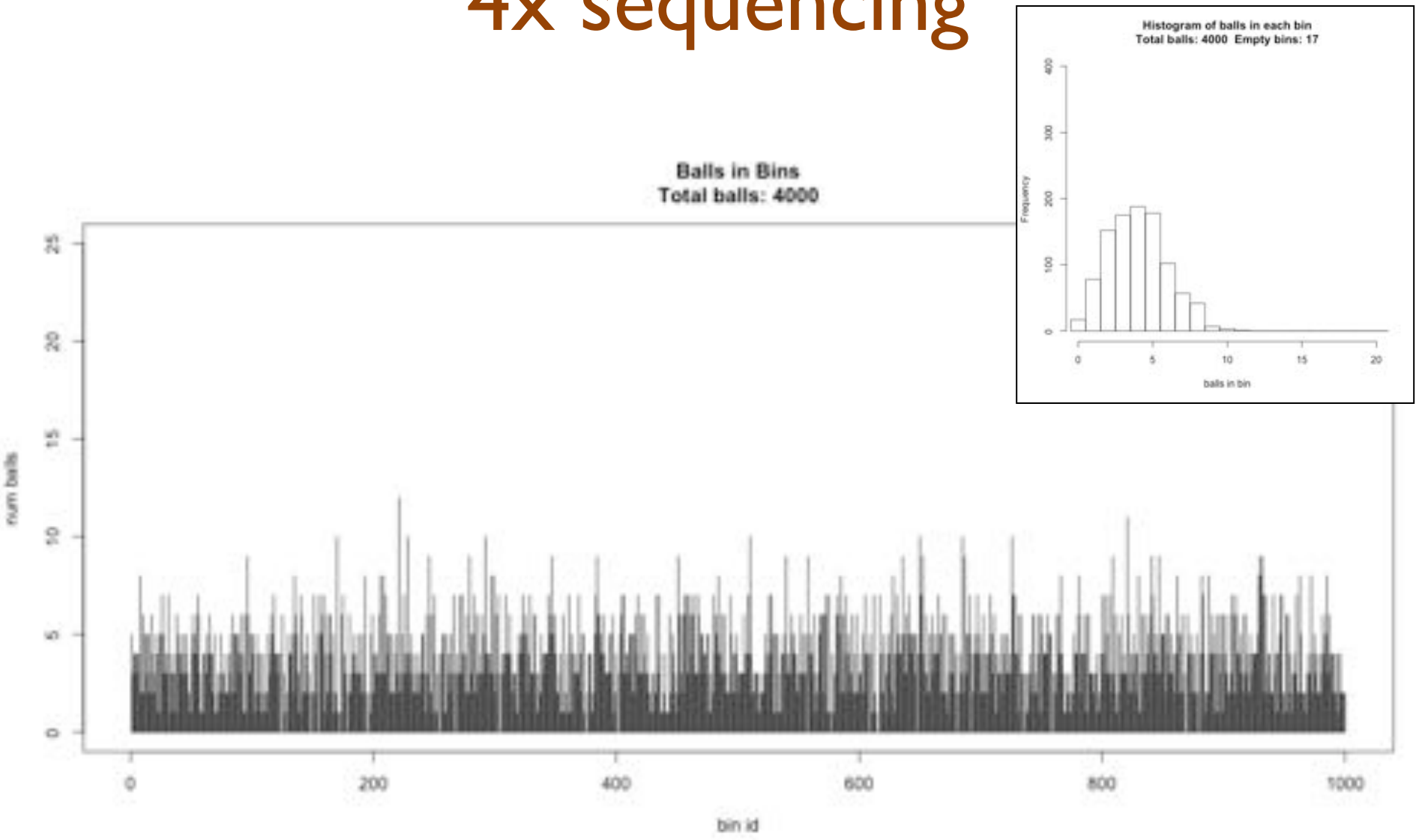
1x sequencing



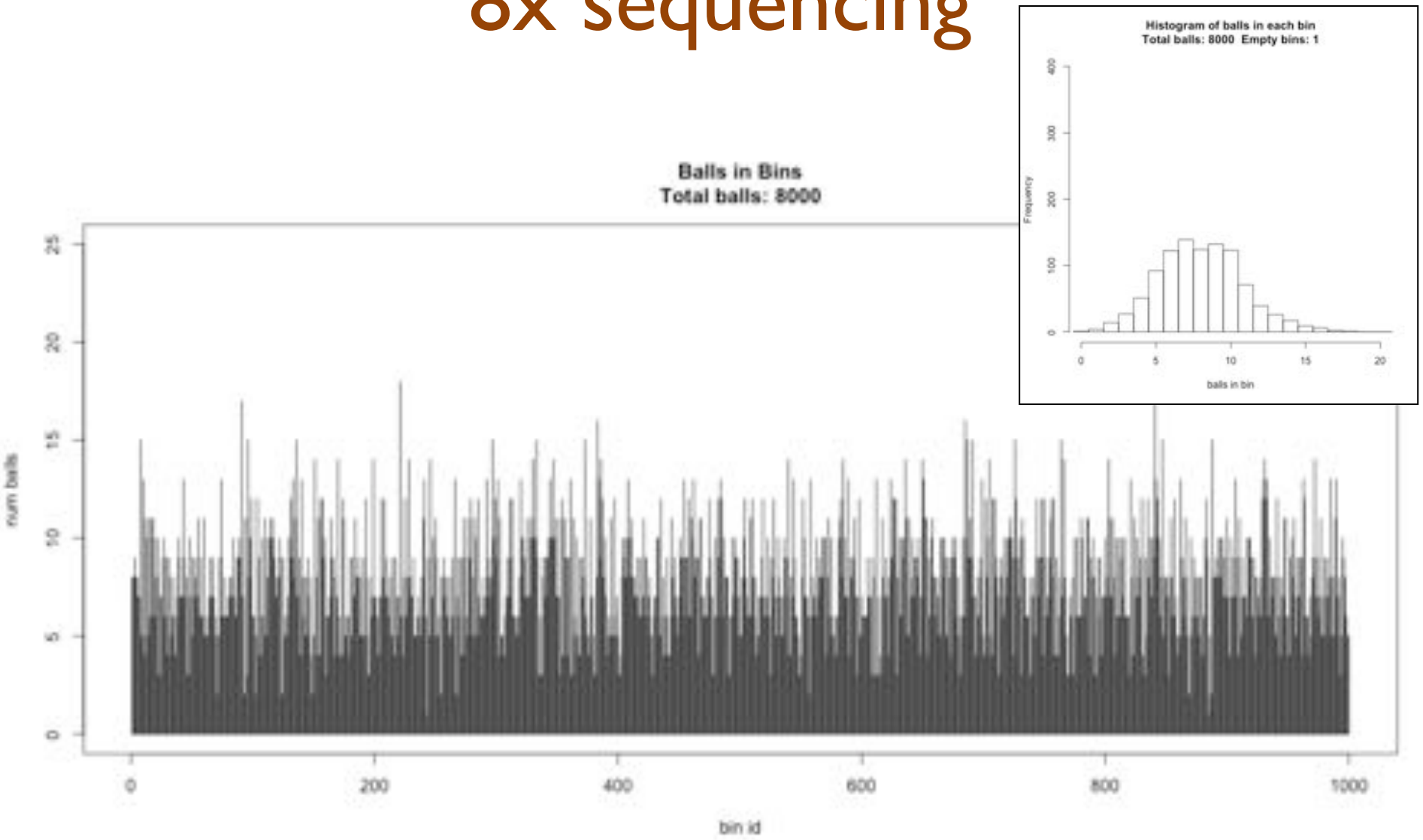
2x sequencing



4x sequencing



8x sequencing



Poisson Distribution

The probability of a given number of events occurring in a fixed interval of time and/or space if these events occur with a known average rate and independently of the time since the last event.

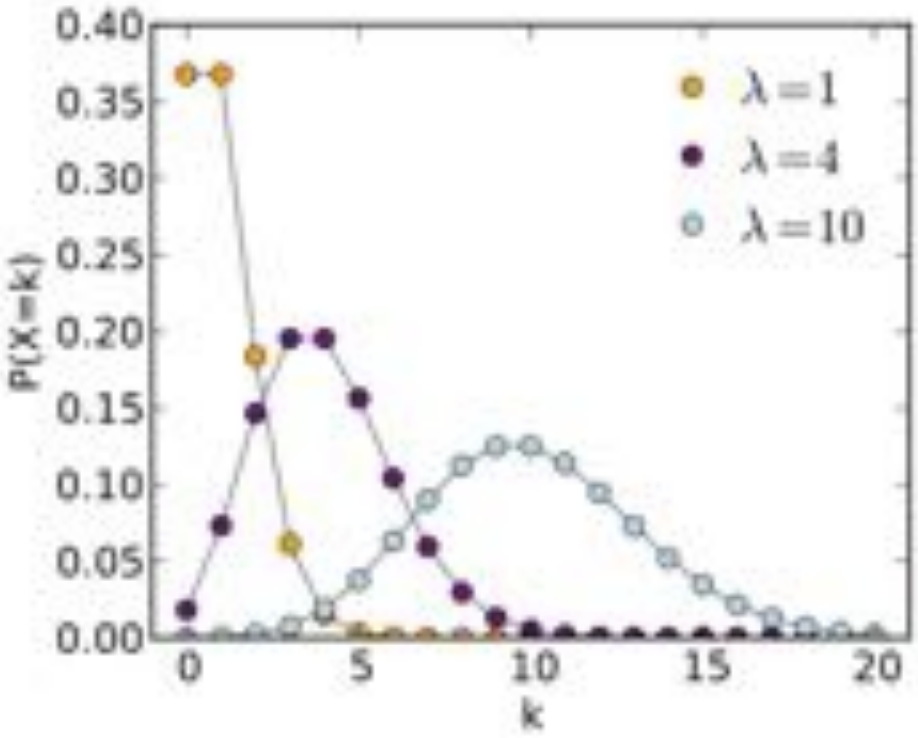
$$P(k) = \frac{\lambda^k}{k!} e^{-\lambda}$$

Formulation comes from the limit of the binomial equation

Resembles a normal distribution, but over the positive values, and with only a single parameter.

Key property:

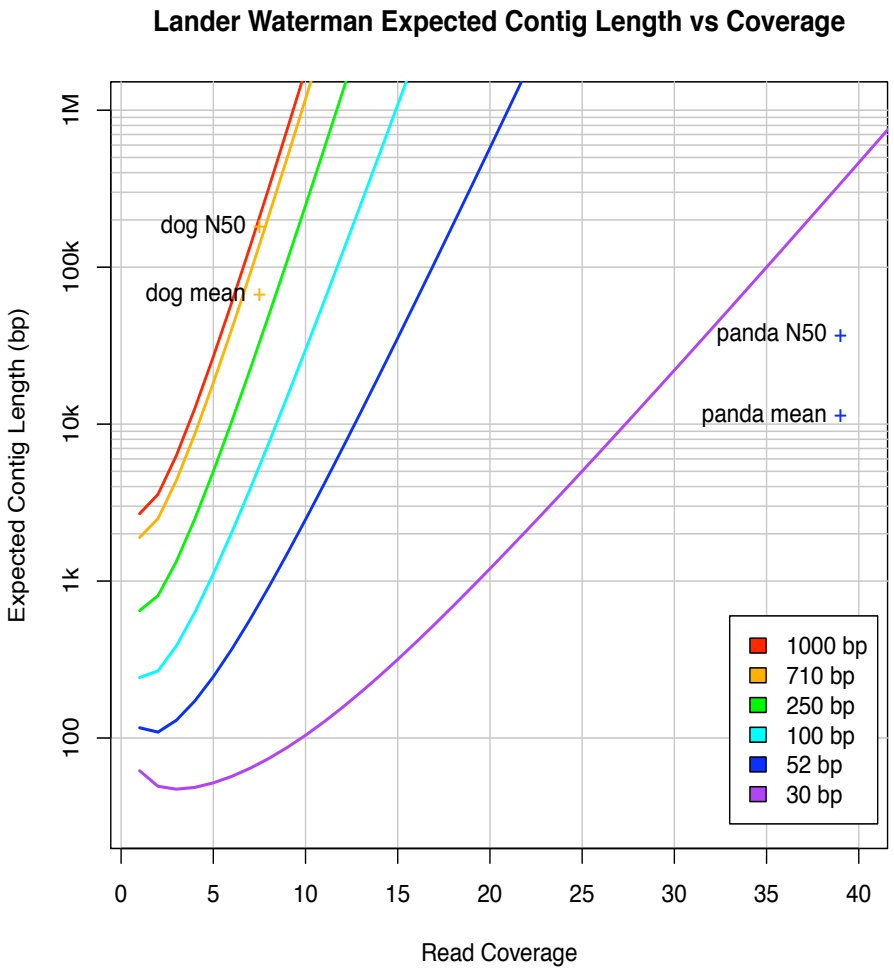
- ***The standard deviation is the square root of the mean.***



Coverage and Read Length

Idealized Lander-Waterman model

- Reads start at perfectly random positions
- Contig length is a function of coverage and read length
  - Short reads require much higher coverage to reach same expected contig length
- Need even high coverage for higher ploidy, sequencing errors, sequencing biases
  - Recommend 100x coverage

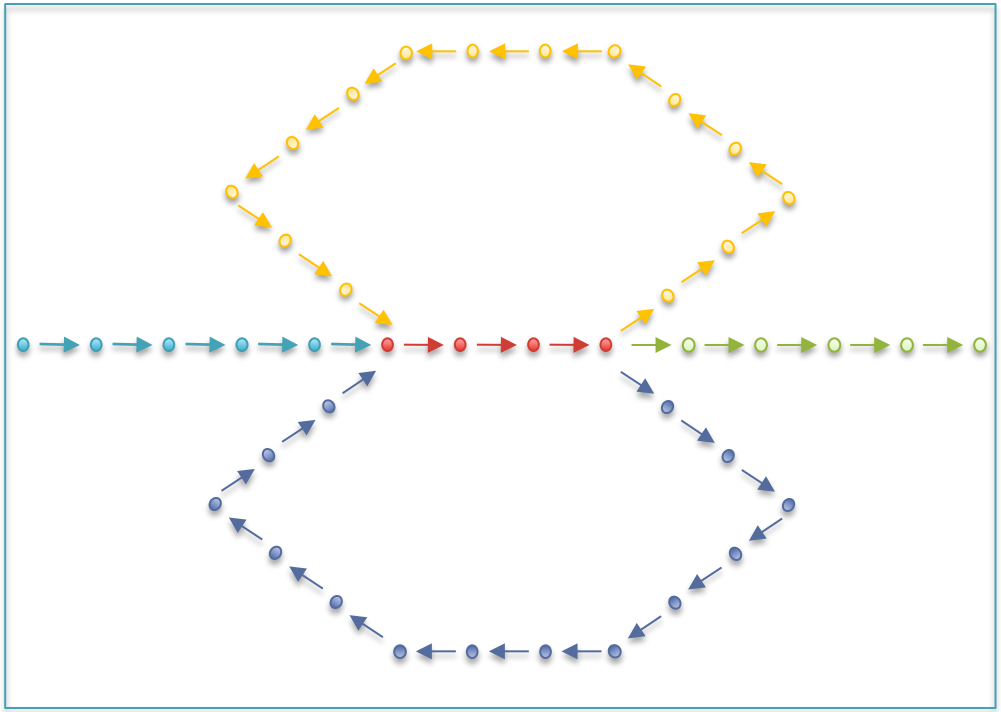


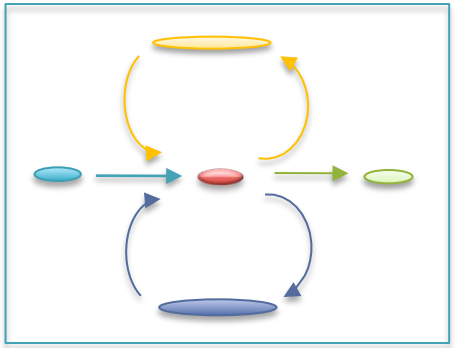
Assembly of Large Genomes using Second Generation Sequencing
Schatz MC, Delcher AL, Salzberg SL (2010) *Genome Research.* 20:1165-1173.

Errors

Unitigging / Unipathing

- After simplification and correction, compress graph down to its non-branching initial contigs
  - Aka "unitigs", "unipaths"
  - Unitigs end because of (1) lack of coverage, (2) errors, and (3) repeats





Errors in the graph

(Chaisson, 2009)

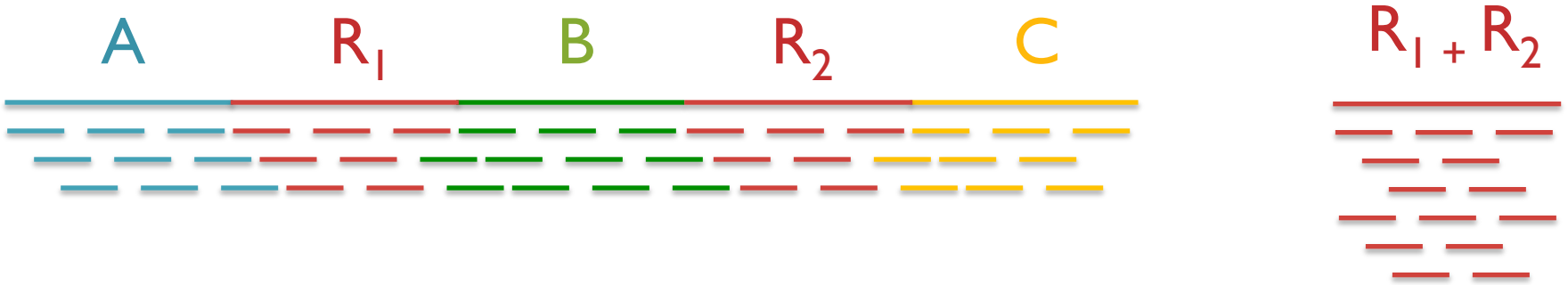
Clip Tips	Pop Bubbles
was the worst of times, was the worst of t**y**mes, the worst of times, it	was the worst of times, was the worst of t**y**mes, times, it was the age t**y**mes, it was the age
the worst of t**y**mes, was the worst of the worst of times, worst of times, it	t**y**mes, was the worst of it was the age times,

Repetitive regions

Repeat Type	Definition / Example	Prevalence
Low-complexity DNA / Microsatellites	$(b_1b_2\ldots b_k)^N$ where $1 \leq k \leq 6$ CACACACACACACACACAC A	2%
SINEs (Short Interspersed Nuclear Elements)	*Alu* sequence (~280 bp) Mariner elements (~80 bp)	13%
LINEs (Long Interspersed Nuclear Elements)	~500 – 5,000 bp	21%
LTR (long terminal repeat) retrotransposons	Ty1-copia, Ty3-gypsy, Pao-BEL (~100 – 5,000 bp)	8%
Other DNA transposons		3%
Gene families & segmental duplications		4%

- Large plant genomes tend to be even worse
- Wheat: 16 Gbp; Pine: 24 Gbp

Repeats and Coverage Statistics



- If *n* reads are a uniform random sample of the genome of length *G*, we expect $k=n\Delta/G$ reads to start in a region of length Δ.
  - If we see many more reads than k (if the arrival rate is > A) , it is likely to be a collapsed repeat

$$\Pr(X-copy)=\binom{n}{k}\left(\frac{X\Delta}{G}\right)^{k}\left(\frac{G-X\Delta}{G}\right)^{n-k}$$

$$A(\Delta,k)=\ln\left(\frac{\Pr(1-copy)}{\Pr(2-copy)}\right)=\ln\left(\frac{\frac{(\Delta n/G)^{k}}{k!}e^{\frac{-\Delta n}{G}}}{\frac{(2\Delta n/G)^{k}}{k!}e^{\frac{-2\Delta n}{G}}}\right)=\frac{n\Delta}{G}-k\ln 2$$

The fragment assembly string graph
Myers, EW (2005) Bioinformatics. 21(suppl 2): ii79-85.

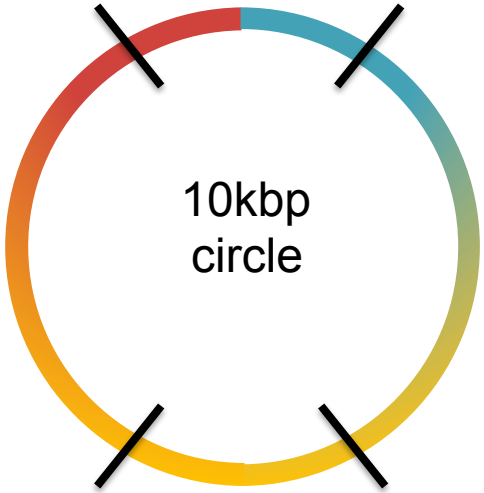
Paired-end and Mate-pairs

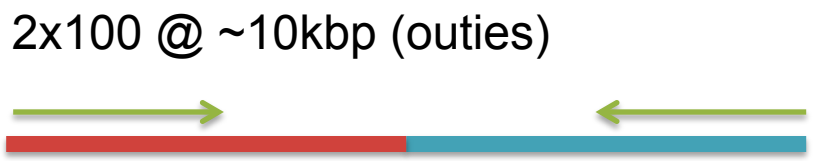
Paired-end sequencing

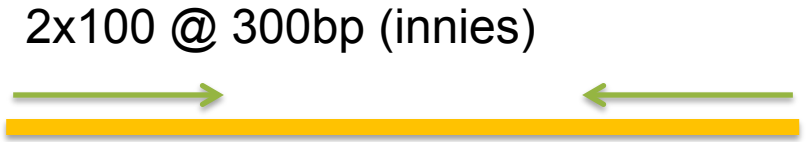
- Read one end of the molecule, flip, and read the other end
- Generate pair of reads separated by up to 500bp with inward orientation

Mate-pair sequencing

- Circularize long molecules (1-10kbp), shear into fragments, & sequence
- Mate failures create short paired-end reads

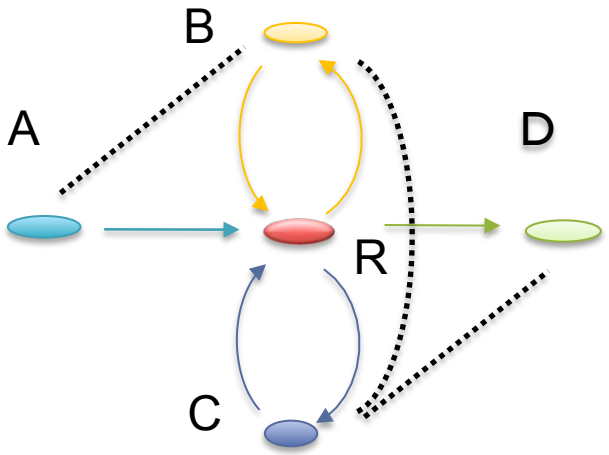




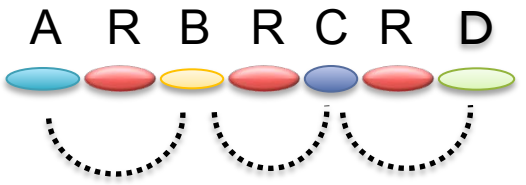


Scaffolding

- Initial contigs (*aka* unipaths, unitigs) terminate at
  - *Coverage gaps*: especially extreme GC
  - *Conflicts*: errors, repeat boundaries



- Use mate-pairs to resolve correct order through assembly graph
  - Place sequence to satisfy the mate constraints
  - Mates through repeat nodes are tangled

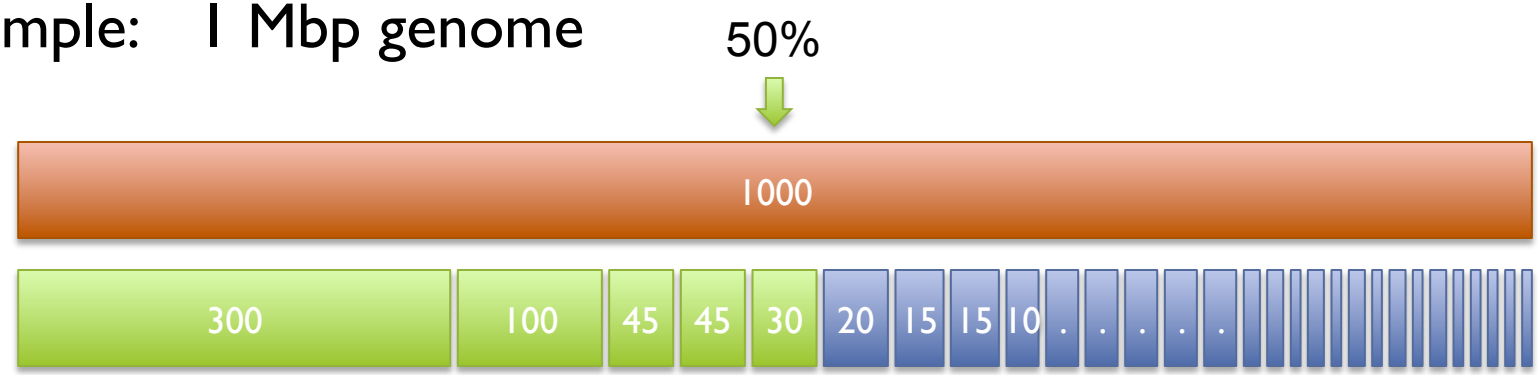


- Final scaffold may have internal gaps called sequencing gaps
  - We know the order, orientation, and spacing, but just not the bases. Fill with Ns instead

N50 size

Def: 50% of the genome is in contigs as large as the N50 value

Example: 1 Mbp genome



N50 size = 30 kbp

(300k+100k+45k+45k+30k = 520k >= 500kbp)

Note:

N50 values are only meaningful to compare when base genome size is the same in all cases

Outline

1. Assembly theory
    1. Assembly by analogy
    2. De Bruijn and Overlap graph
    3. Coverage, read length, errors, and repeats

2. Whole Genome Alignment
    1. Aligning & visualizing with MUMmer

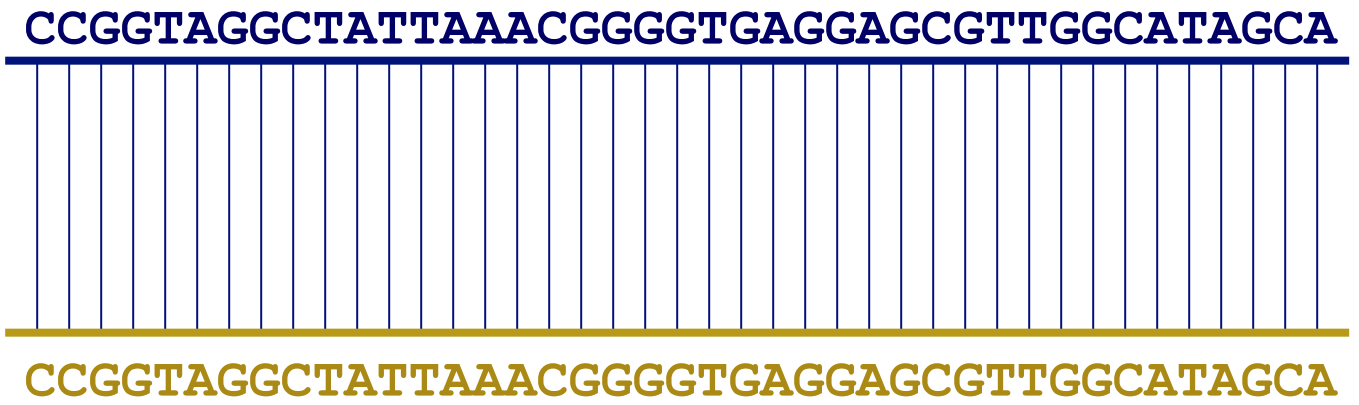
3. Genome assemblers
    1. ALLPATHS-LG: recommended for Illumina-only projects
    2. Celera Assembler: recommended for PacBio projects

Whole Genome Alignment with MUMmer

Slides Courtesy of Adam M. Phillippy
University of Maryland

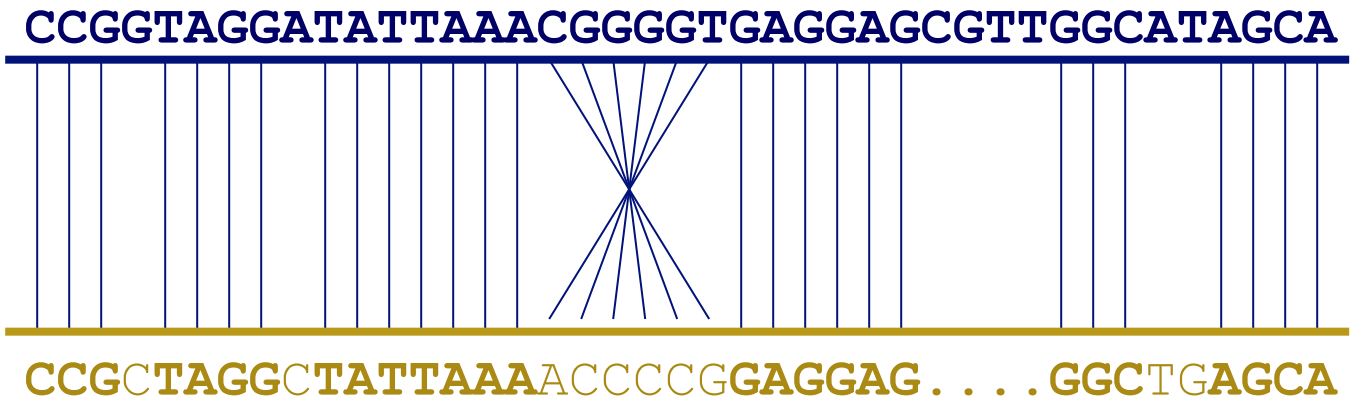
Goal of WGA

- For two genomes, *A* and *B*, find a mapping from each position in *A* to its corresponding position in *B*



Not so fast...

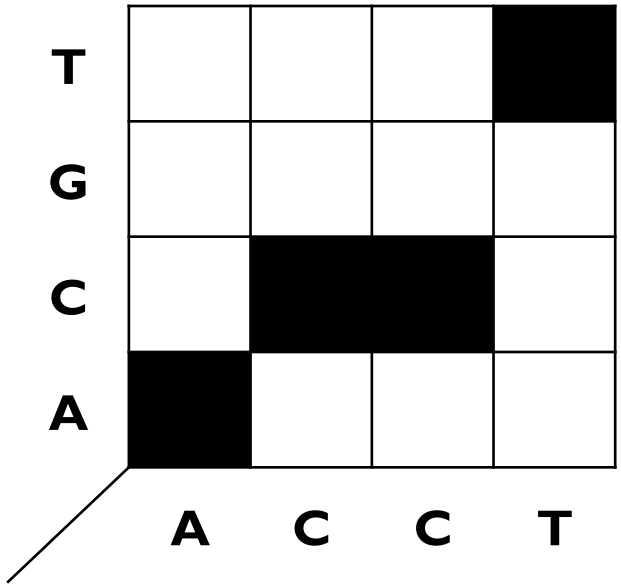
- Genome *A* may have insertions, deletions, translocations, inversions, duplications or SNPs with respect to *B* (sometimes all of the above)



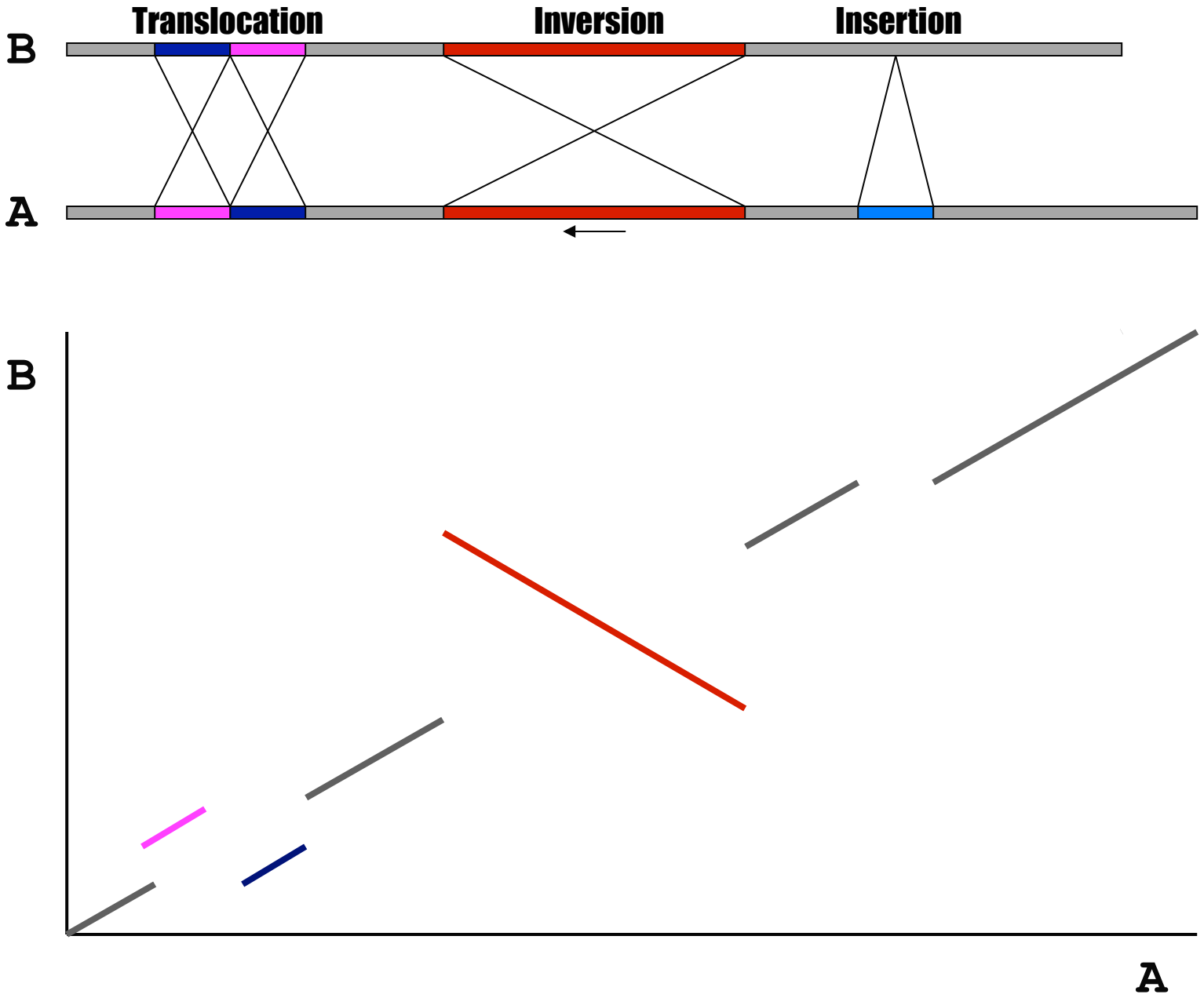
WGA visualization

- How can we visualize *whole* genome alignments?

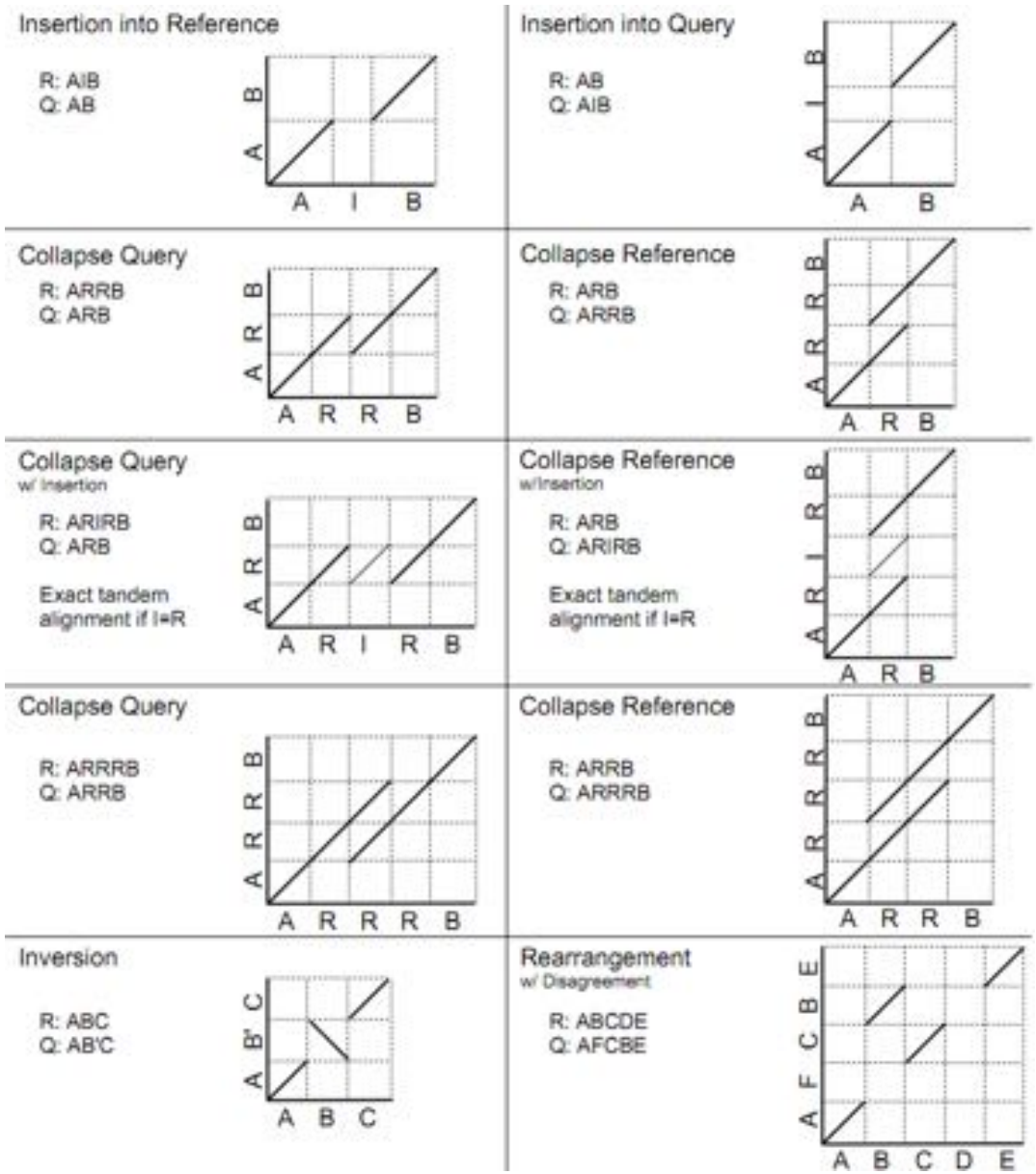
- With an alignment dot plot
  - *N* x *M* matrix
    - Let *i* = position in genome *A*
    - Let *j* = position in genome *B*
    - Fill cell *(i,j)* if A_i shows similarity to B_j



  - A perfect alignment between *A* and *B* would completely fill the positive diagonal

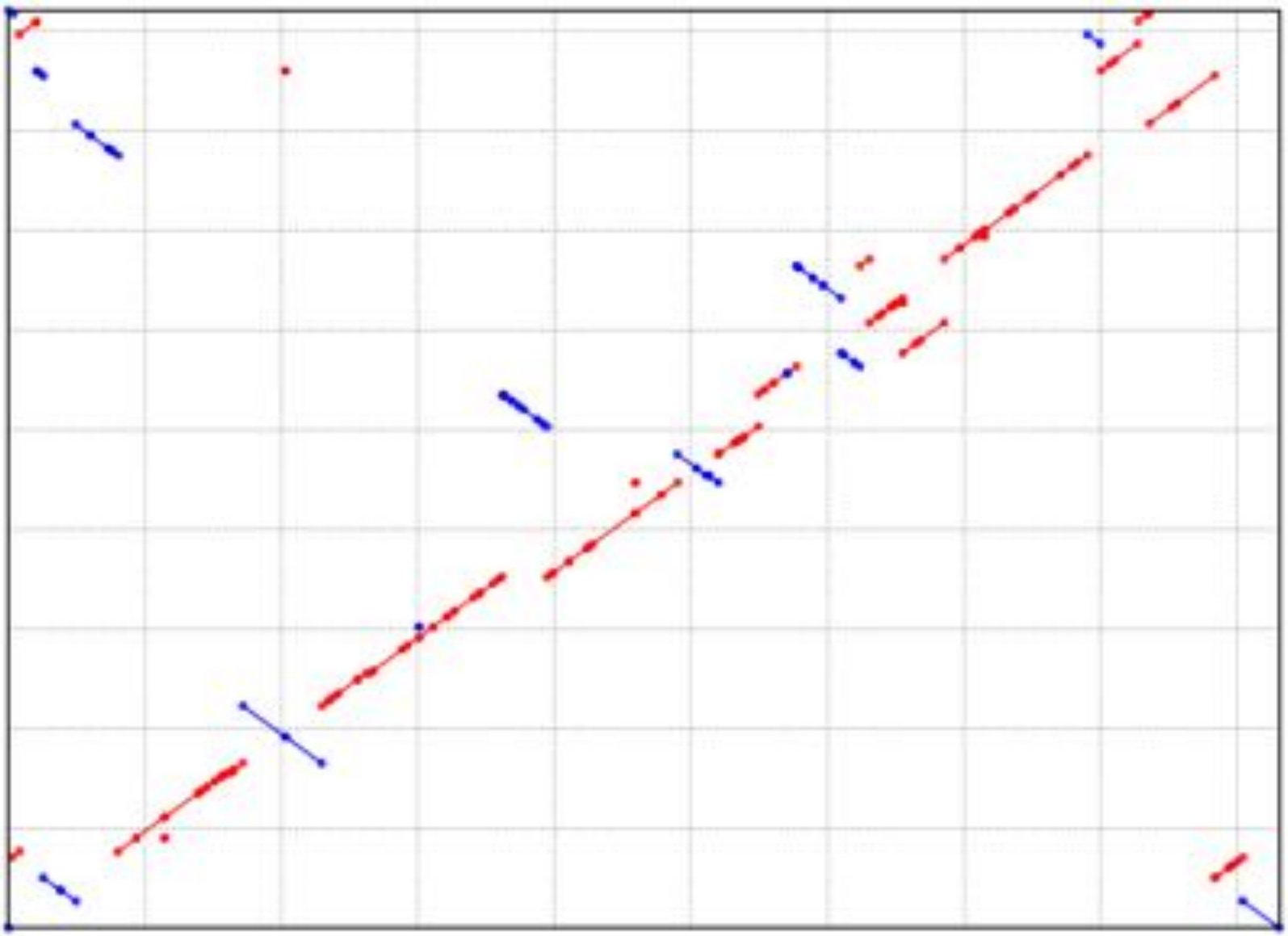

Translocation
Inversion
Insertion
B
A
B
A

SV Types



- Different structural variation types / misassemblies will be apparent by their pattern of breakpoints
- Most breakpoints will be at or near repeats
- Things quickly get complicated in real genomes

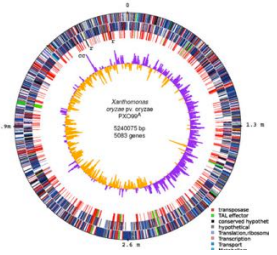
http://mummer.sf.net/manual/AlignmentTypes.pdf



Alignment of 2 strains of *Y. pestis*

http://mummer.sourceforge.net/manual/

Assembly Summary



Assembly quality depends on

1. ***Coverage***: low coverage is mathematically hopeless
2. ***Repeat composition***: high repeat content is challenging
3. ***Read length***: longer reads help resolve repeats
4. ***Error rate***: errors reduce coverage, obscure true overlaps

- Assembly is a hierarchical, starting from individual reads, build high confidence contigs/unitigs, incorporate the mates to build scaffolds
  - Extensive error correction is the key to getting the best assembly possible from a given data set

- Watch out for collapsed repeats & other misassemblies
  - Globally/Locally reassemble data from scratch with better parameters & stitch the 2 assemblies together

Break


PHASE TWO: INTERPRETATION
I THINK I FOUND A CORNER PIECE.
3 BILLION PIECES
GENOME

Outline

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    1. ALLPATHS-LG: recommended for Illumina-only projects
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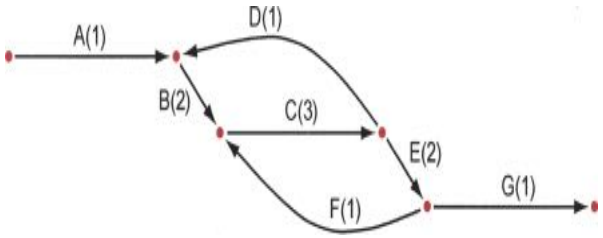
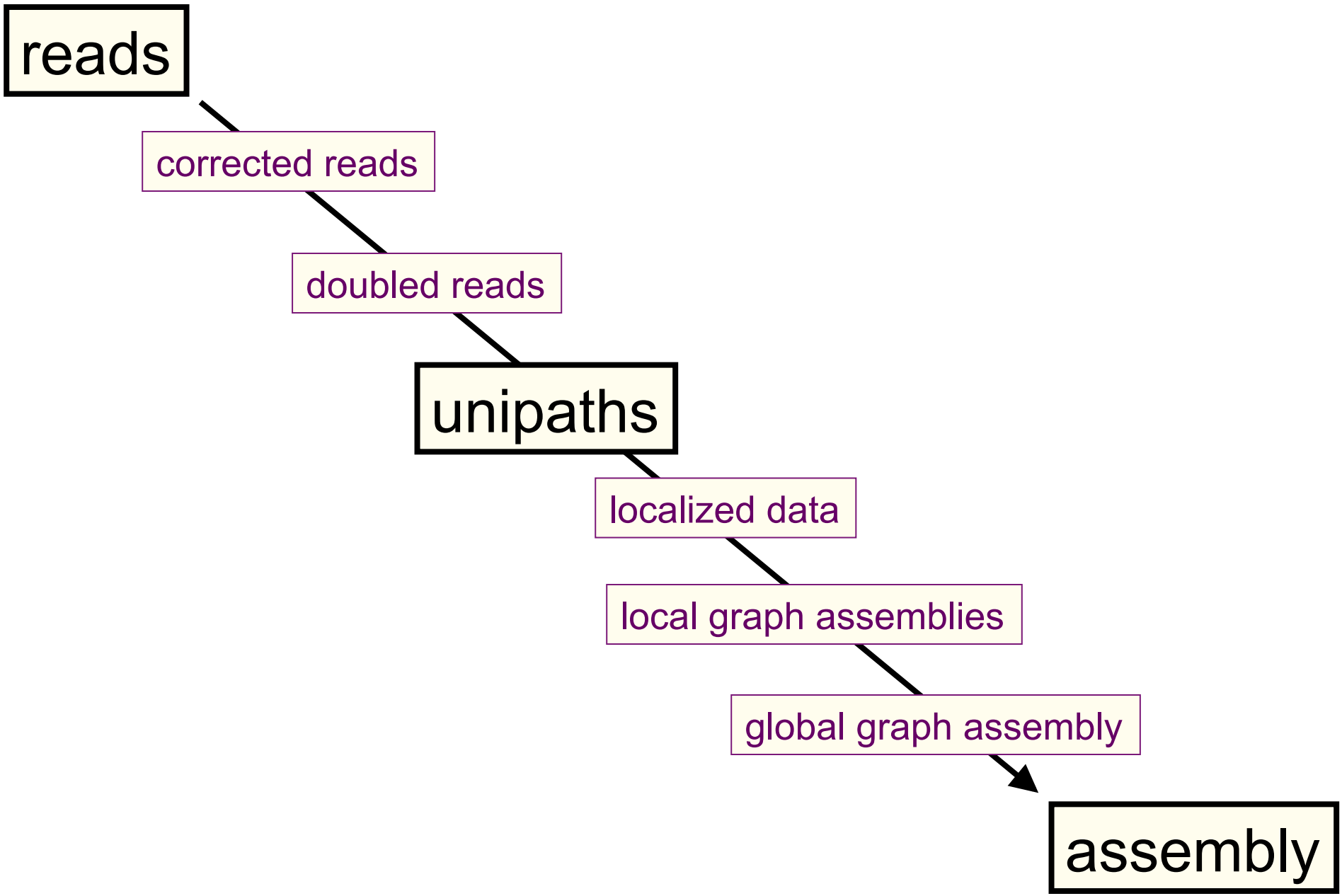


Genome assembly with ALLPATHS-LG

Iain MacCallum

BROAD INSTITUTE

How ALLPATHS-LG works



ALLPATHS-LG sequencing model

Libraries (insert types)	Fragment size (bp)	Read length (bases)	Sequence coverage (x)	Required
Fragment	180*	≥ 100	45	yes
Short jump	3,000	≥ 100 preferable	45	yes
Long jump	6,000	≥ 100 preferable	5	no**
Fosmid jump	40,000	≥ 26	1	no**

*See next slide.

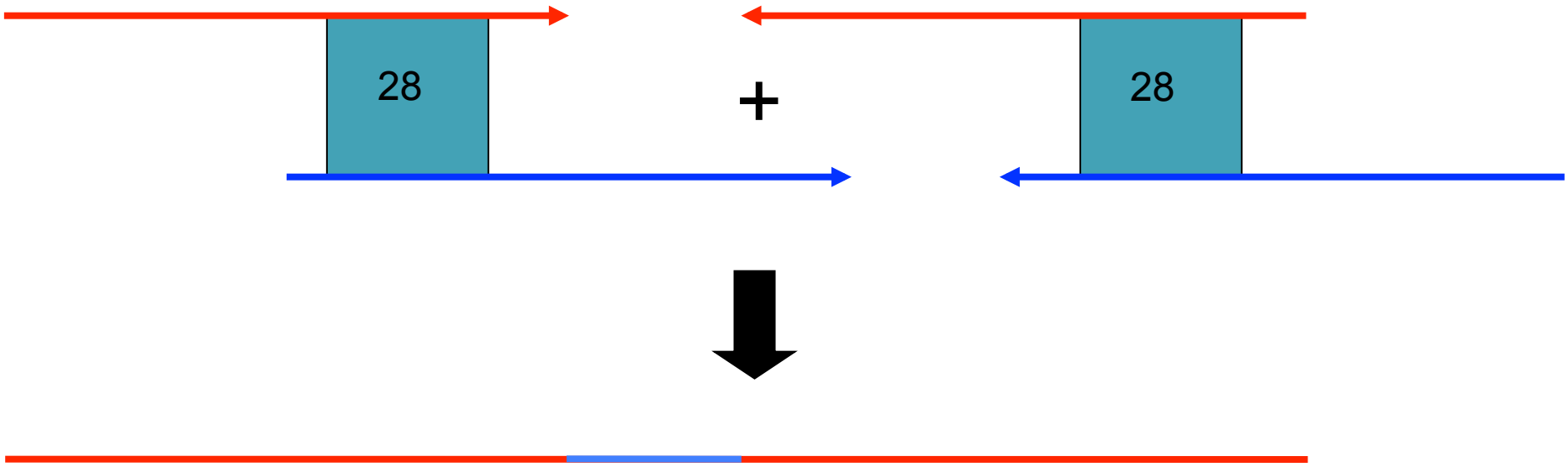
**For best results. Normally not used for small genomes.
However essential to assemble long repeats or duplications.

Cutting coverage in half still works, with some reduction in quality of results.

All: protocols are either available, or in progress.

Read doubling

To close a read pair (red), we require the existence of another read pair (blue), overlapping perfectly like this:

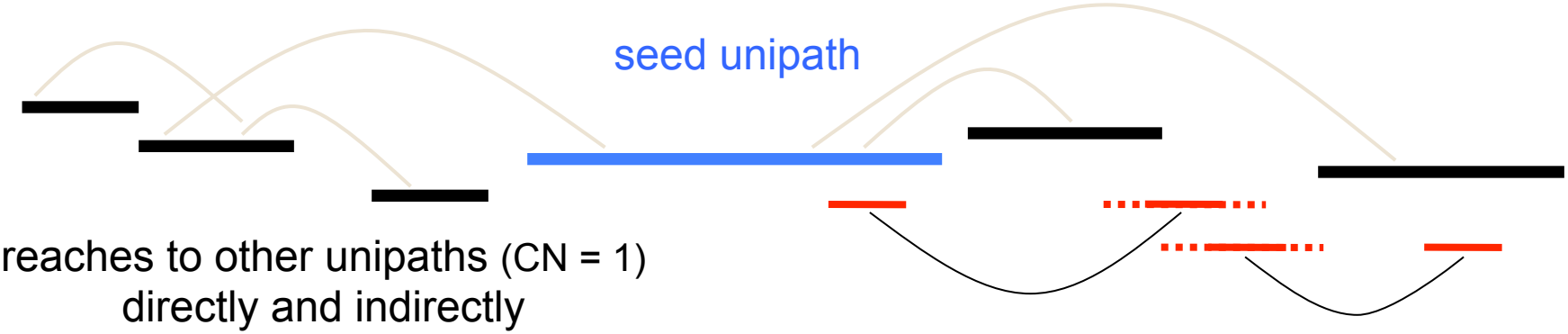


More than one closure allowed (but rare).

Localization

I. Find 'seed' unipaths, evenly spaced across genome
(ideally long, of copy number CN = 1)

II. Form neighborhood around each seed

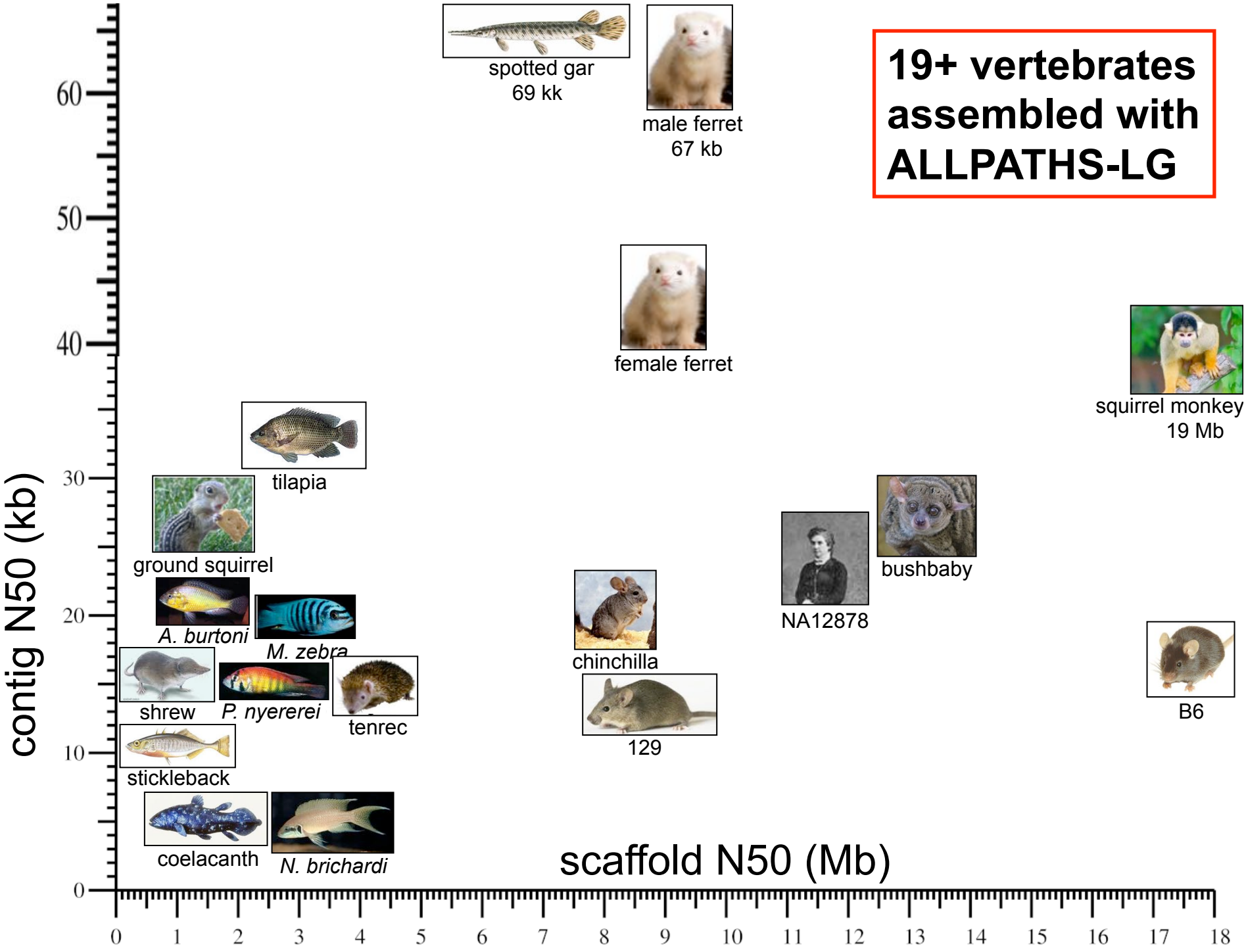


reaches to other unipaths (CN = 1)
directly and indirectly

read pairs reach into repeats

and are extended by other unipaths

.....


19+ vertebrates assembled with ALLPATHS-LG
spotted gar
69 kk
male ferret
67 kb
female ferret
squirrel monkey
19 Mb
tilapia
ground squirrel
A. burtoni
M. zebra
shrew
P. nyererei
tenrec
stickleback
coelacanth
N. brichardi
chinchilla
129
NA12878
bushbaby
B6
contig N50 (kb)
scaffold N50 (Mb)
0
10
20
30
40
50
60
0
1
2
3
4
5
6
7
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11
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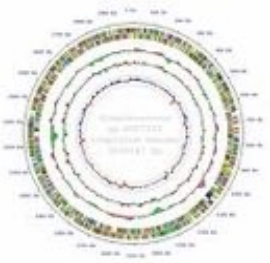
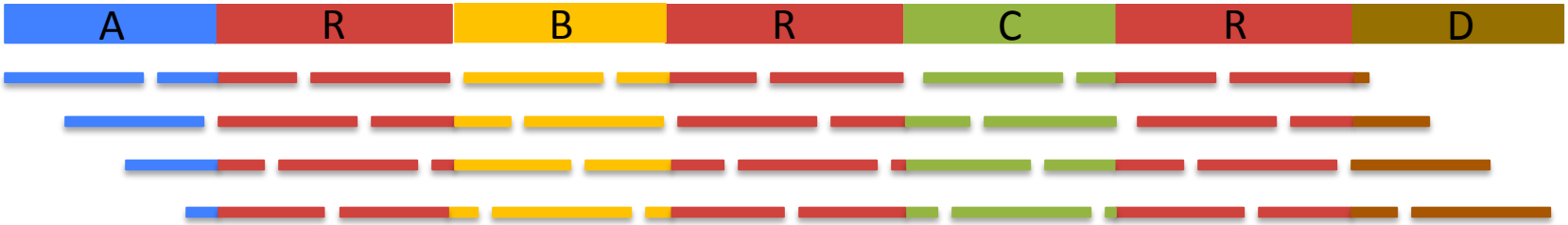
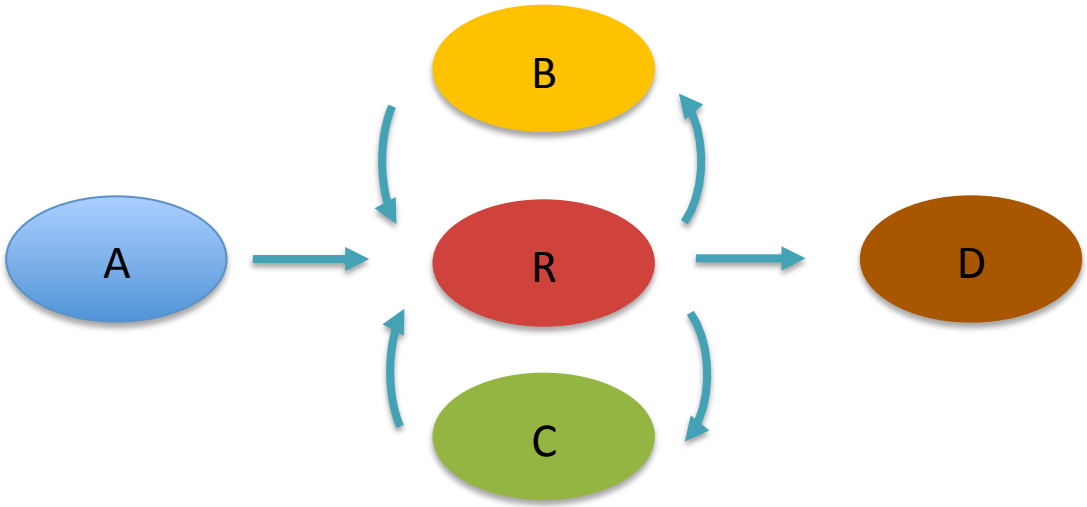
18



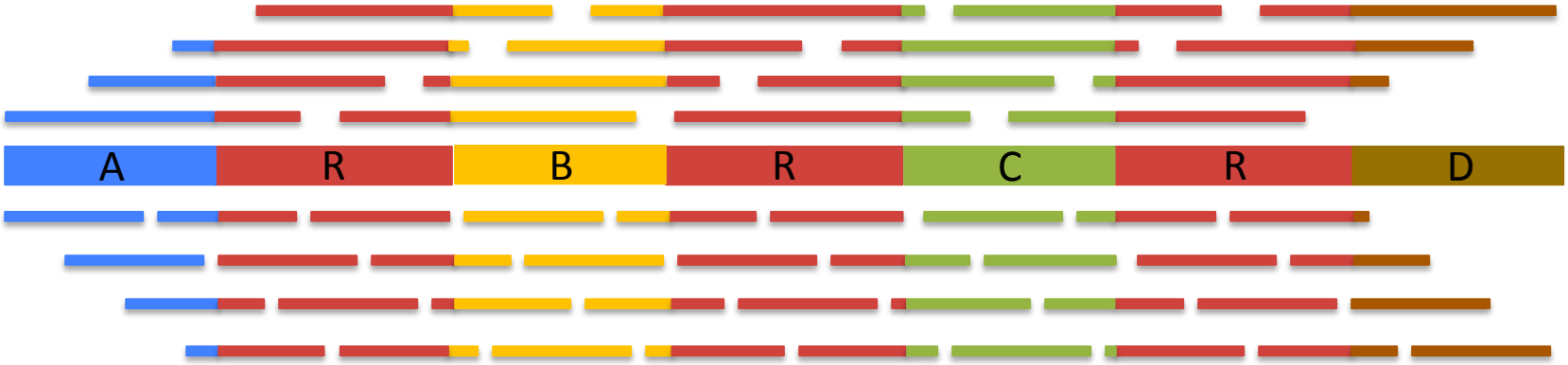
Genome assembly with the Celera Assembler

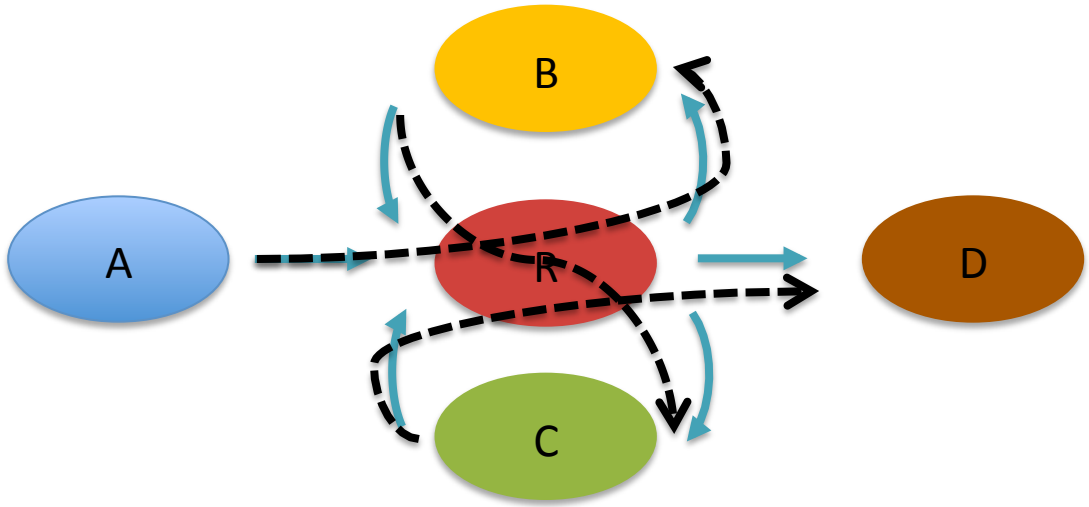
Assembly Complexity



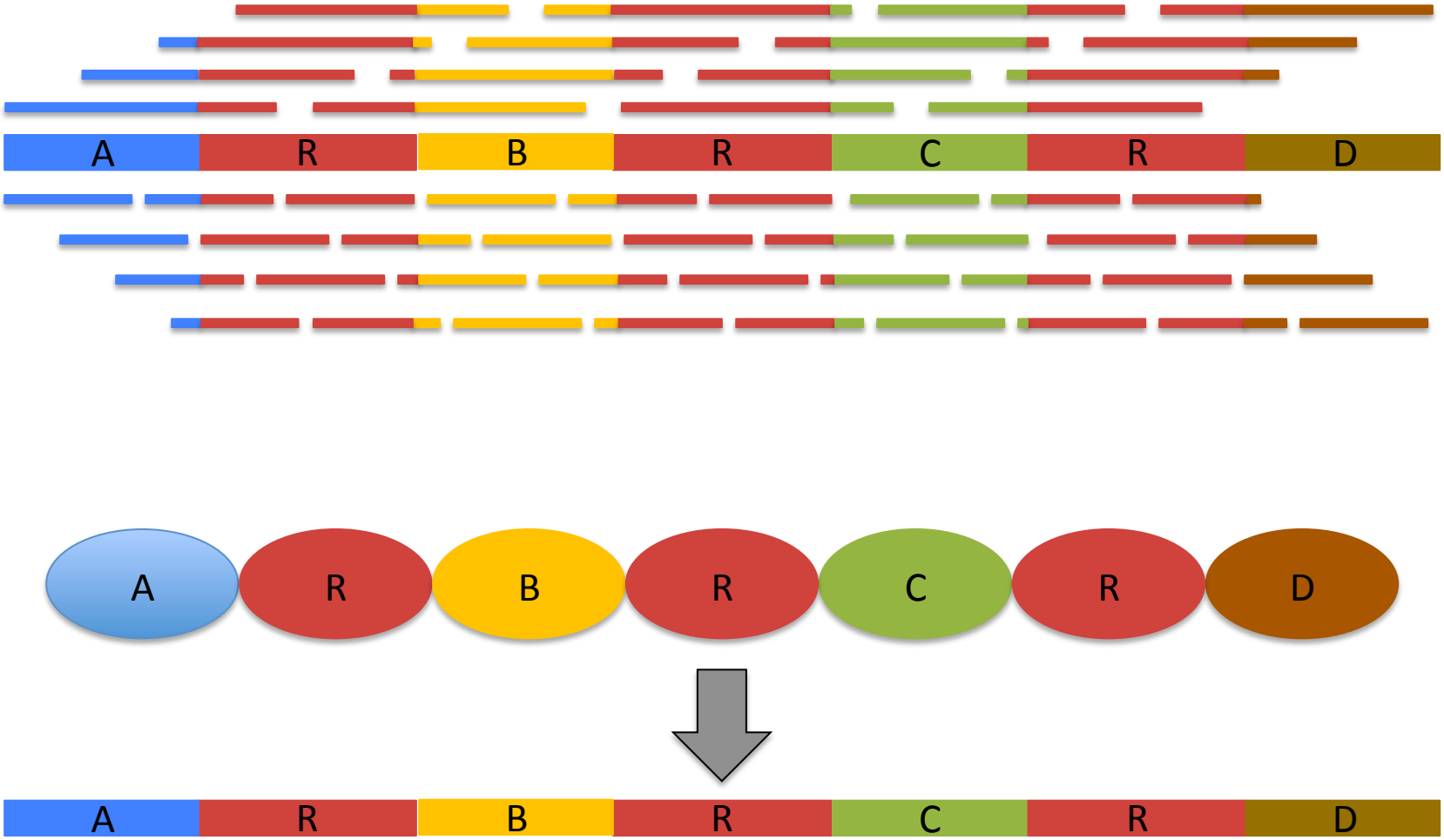


Assembly Complexity





Assembly Complexity



The advantages of SMRT sequencing
Roberts, RJ, Carneiro, MO, Schatz, MC (2013) *Genome Biology.* 14:405

Long Read Sequencing Technology

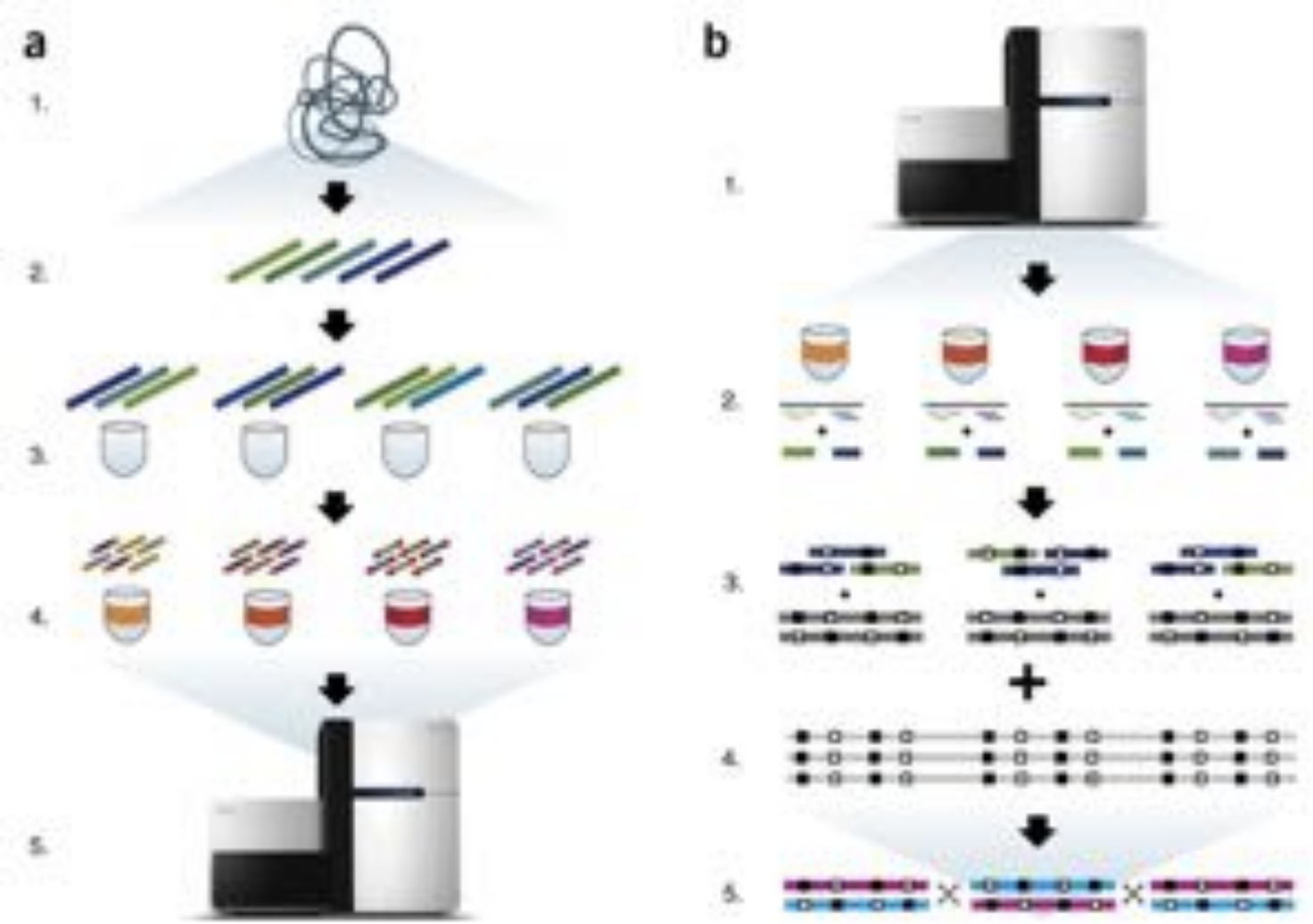
Moleculo

PacBio RS II

Oxford Nanopore

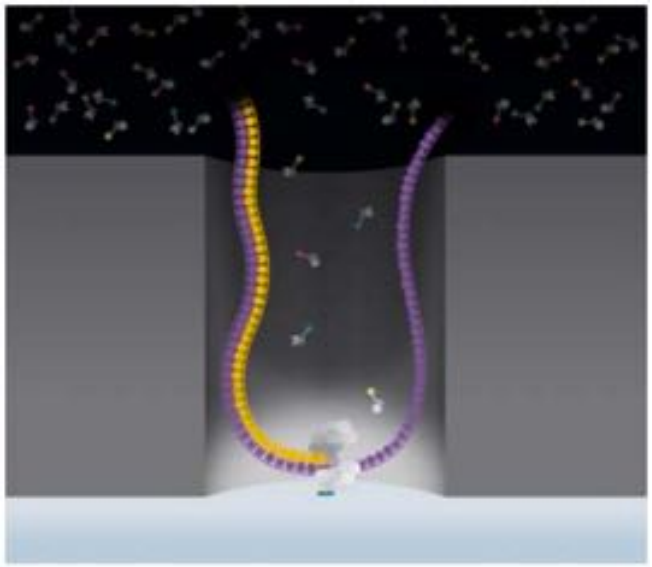
Moleculo Sequencing

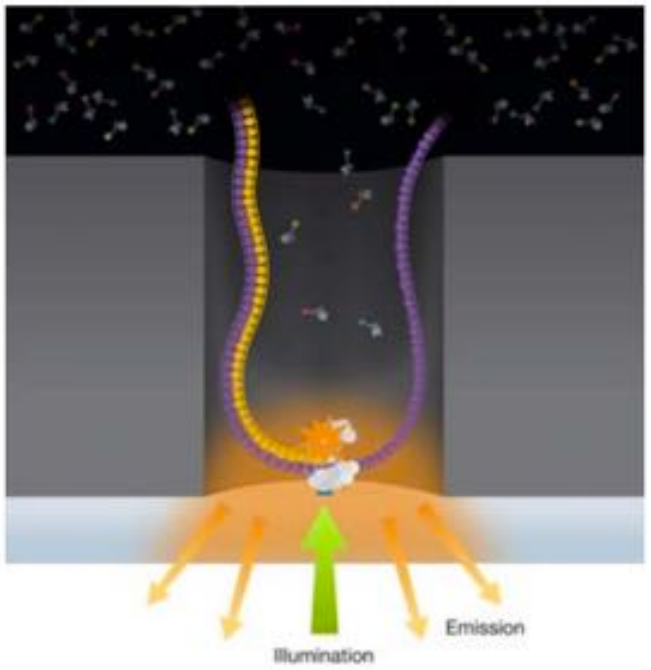
Clever library preparation technique to turn a short read sequencer into a quazi-long read sequencer

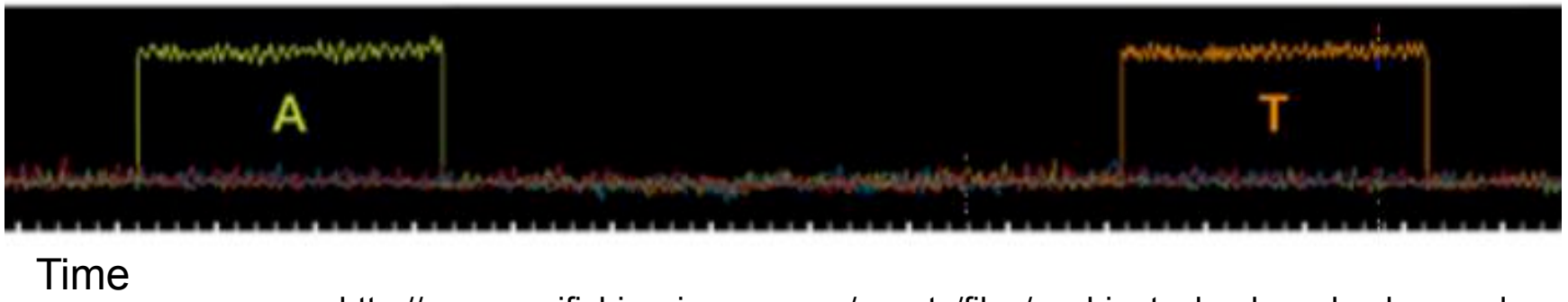


PacBio SMRT Sequencing

Imaging of fluorescently phospholinked labeled nucleotides as they are incorporated by a polymerase anchored to a Zero-Mode Waveguide (ZMW).



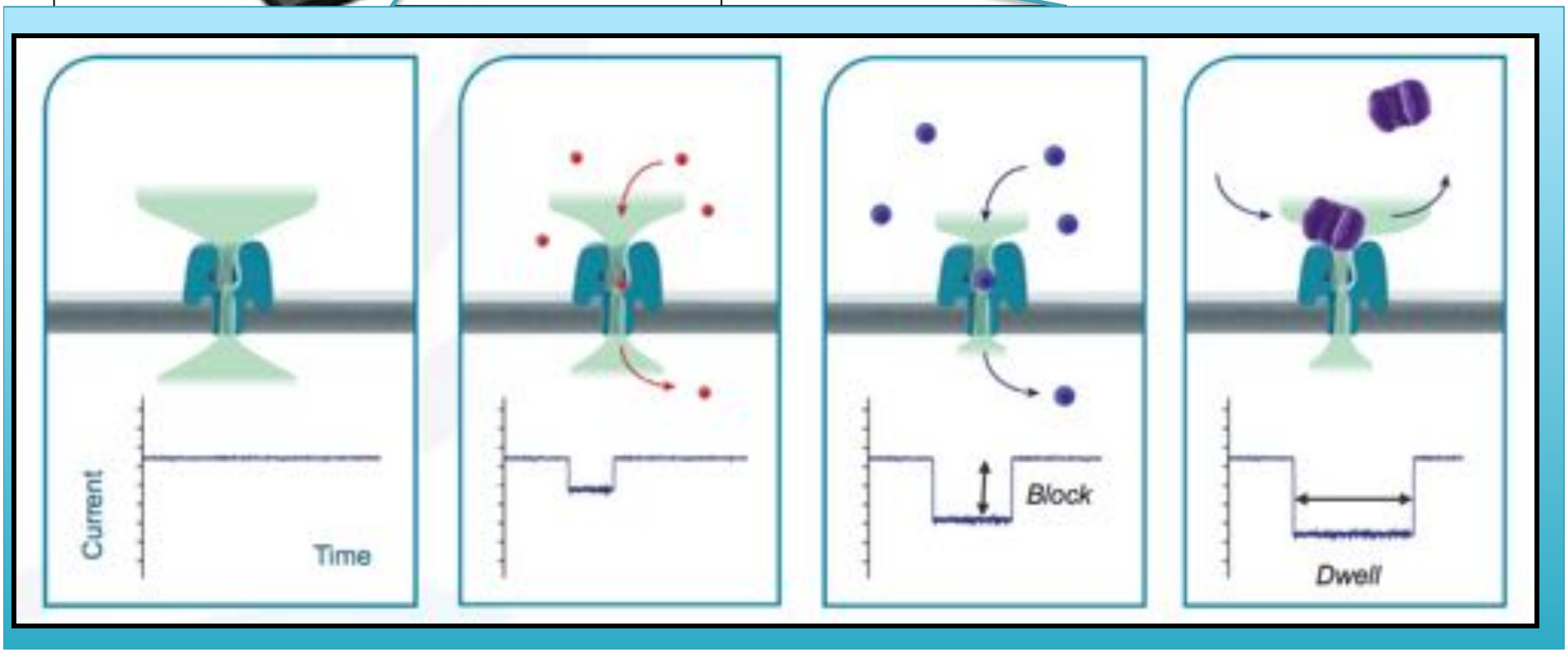




http://www.pacificbiosciences.com/assets/files/pacbio_technology_backgrounder.pdf

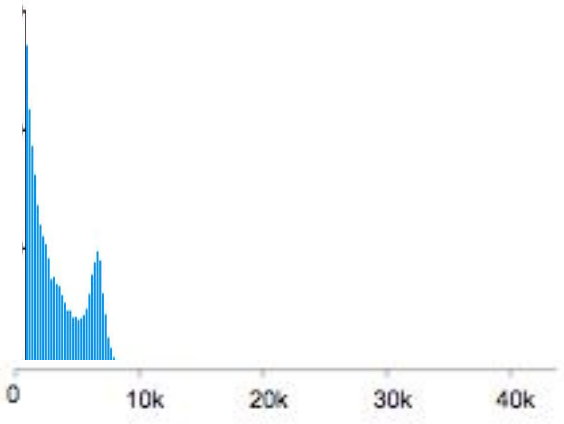
Oxford Nanopore MinION

- Thumb drive sized sequencer powered over USB
- Capacity for 512 reads at once
- Senses DNA by measuring changes to ion flow



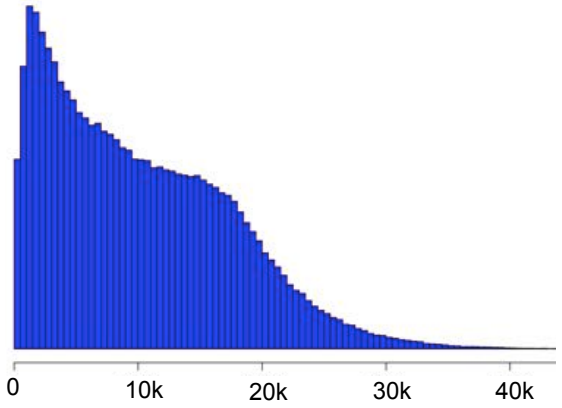
Long Read Sequencing Technology

Moleculo



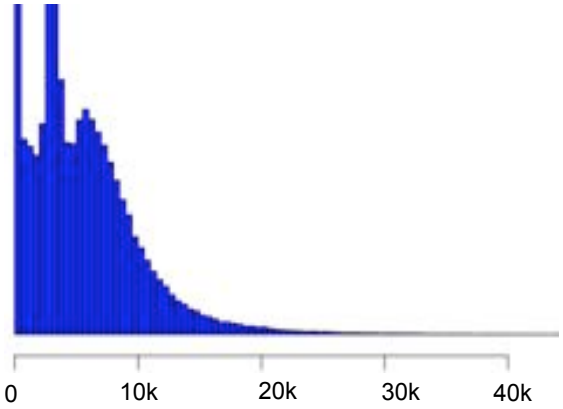
(Voskoboynik et al. 2013)

PacBio RS II



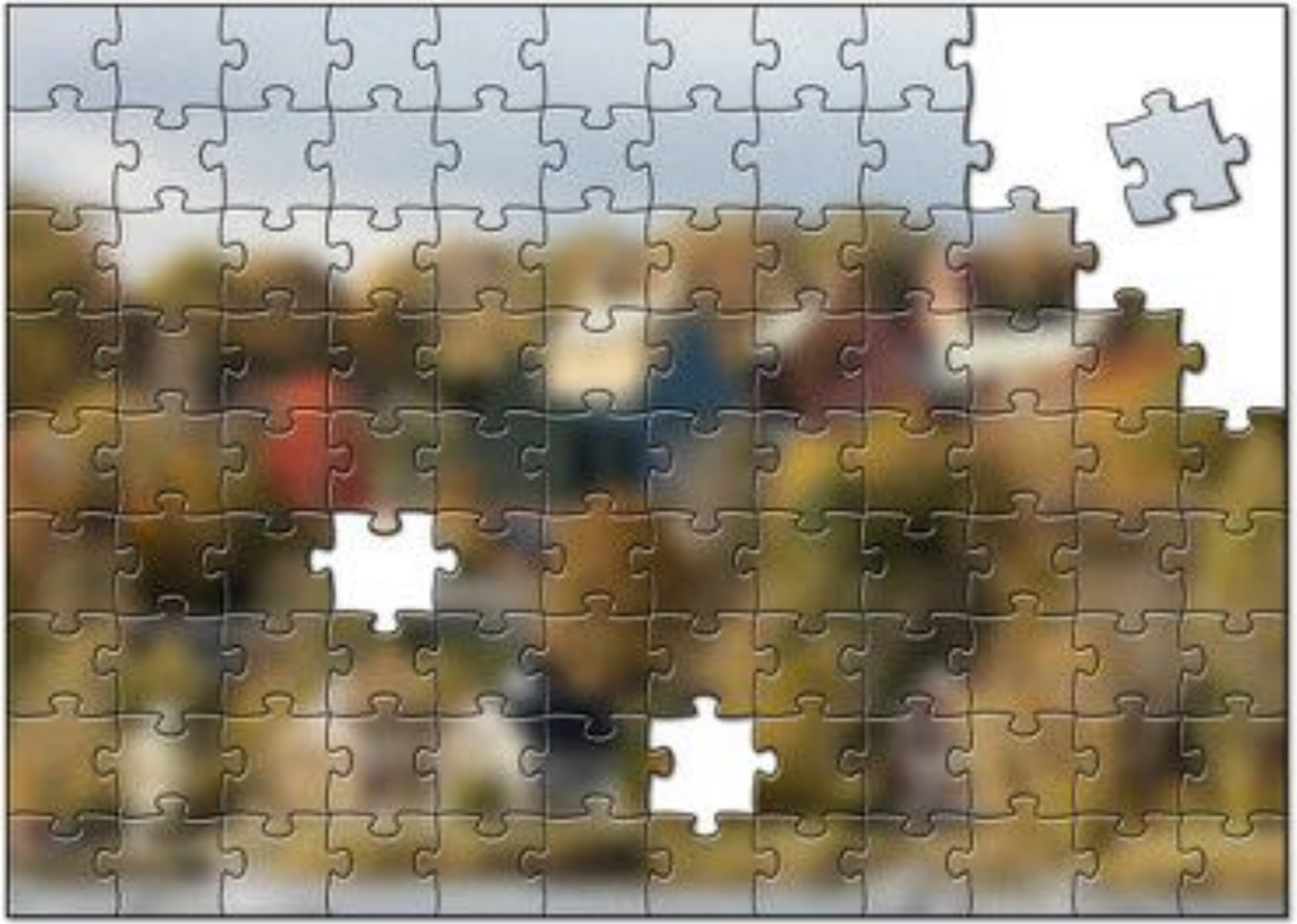
CSHL/PacBio

Oxford Nanopore

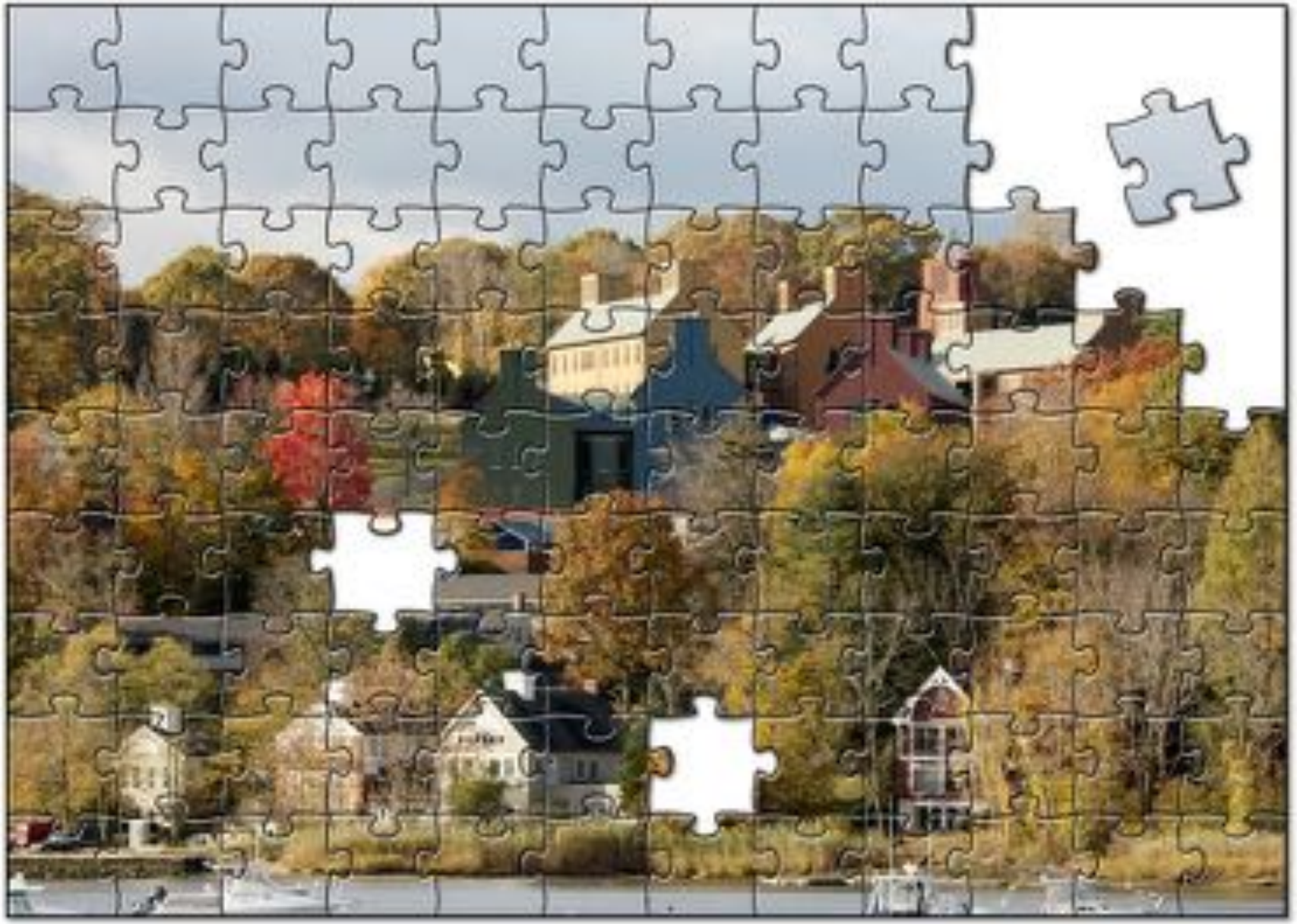


CSHL/ONT

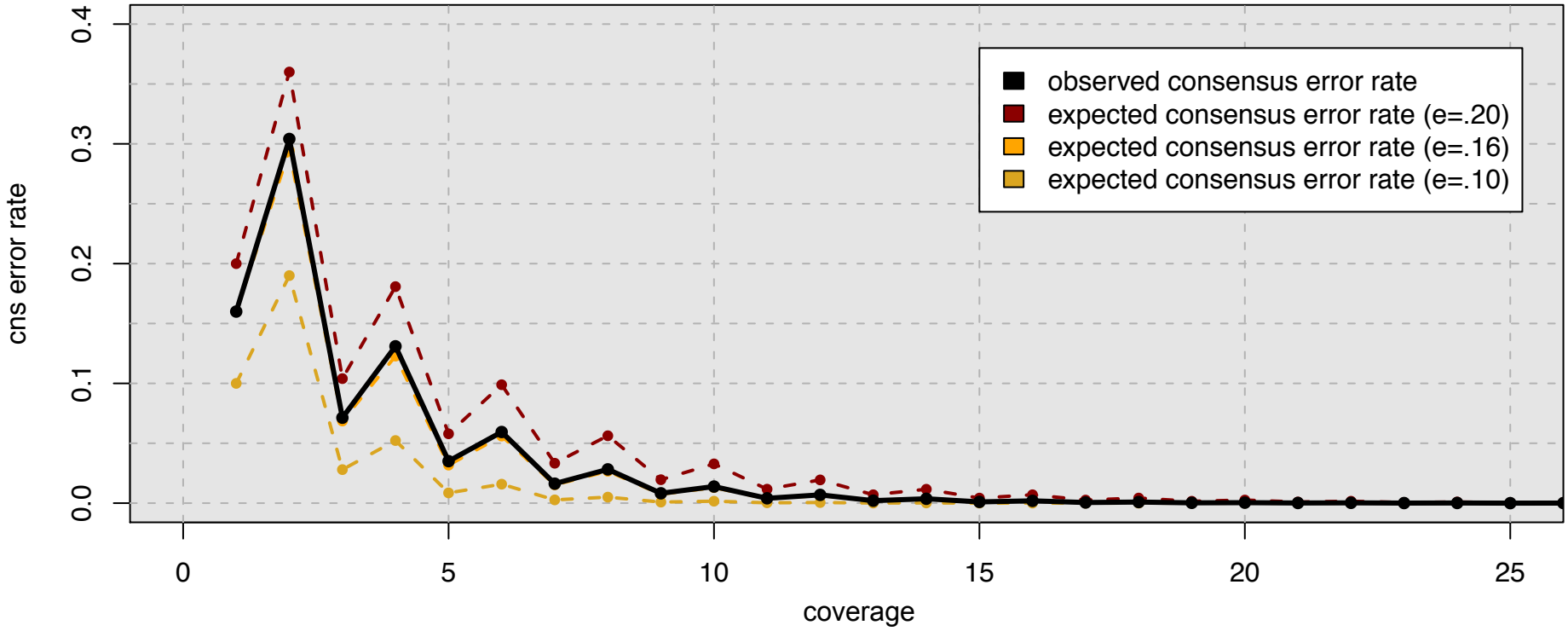
Single Molecule Sequences



“Corrective Lens” for Sequencing



Consensus Accuracy and Coverage



Coverage can overcome random errors

- Dashed: error model from binomial sampling
- Solid: observed accuracy

$$CNS\ Error = \sum_{i=\lceil c/2 \rceil}^{c} \binom{c}{i} (e)^{i} (1-e)^{n-i}$$

Koren, Schatz, *et al* (2012)
Nature Biotechnology. 30:693–700

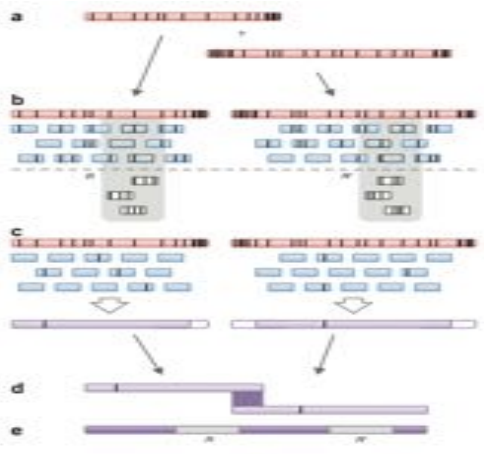
PacBio Assembly Algorithms

PBJelly

Gap Filling and Assembly Upgrade

English *et al* (2012)
PLOS One. 7(11): e47768

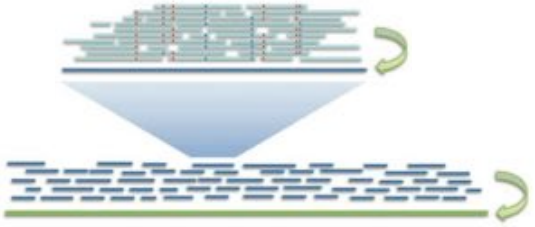
PacBioToCA & ECTools



Hybrid/PB-only Error Correction

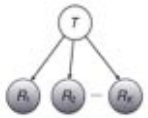
Koren, Schatz, *et al* (2012)
Nature Biotechnology. 30:693–700

HGAP & Quiver



$$\Pr(\mathbf{R} \mid T)$$

$$\Pr(\mathbf{R} \mid T) = \prod_k \Pr(R_k \mid T)$$



Quiver Performance Results
Comparison to Reference Genome
(M. ruber ; 3.1 MB ; SMRT® Cells)

	Initial Assembly	Quiver Consensus
QV	43.4	54.5
Accuracy	99.99540%	99.99964%
Differences	141	11

PB-only Correction & Polishing

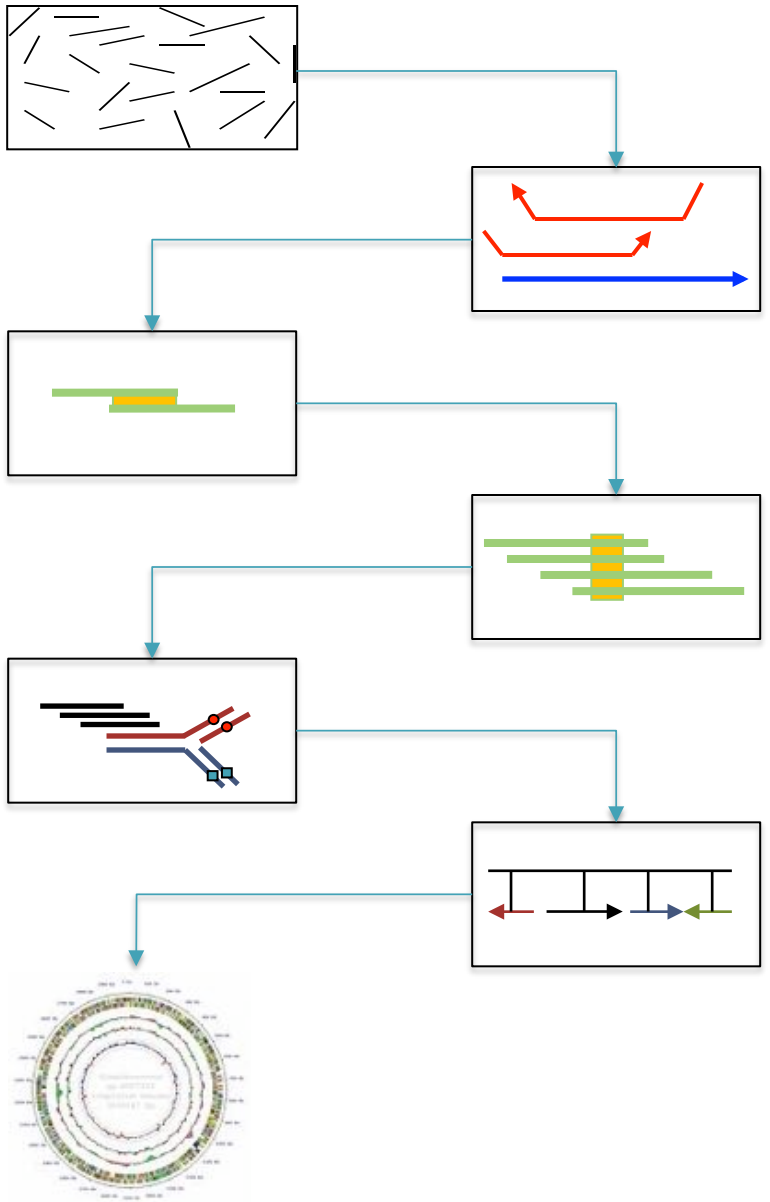
Chin *et al* (2013)
Nature Methods. 10:563–569

< 5x PacBio Coverage > 50x

Celera Assembler

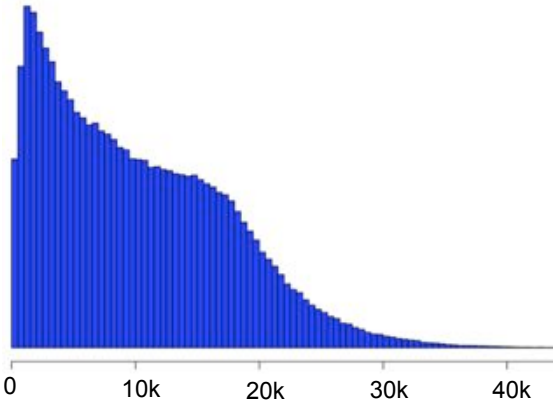
http://wgs-assembler.sf.net

1. Pre-overlap
   - Consistency checks
2. Trimming
   - Quality trimming & partial overlaps
3. Compute Overlaps
   - Find high quality overlaps
4. Error Correction
   - Evaluate difference in context of overlapping reads
5. Unitigging
   - Merge consistent reads
6. Scaffolding
   - Bundle mates, Order & Orient
7. Finalize Data
   - Build final consensus sequences

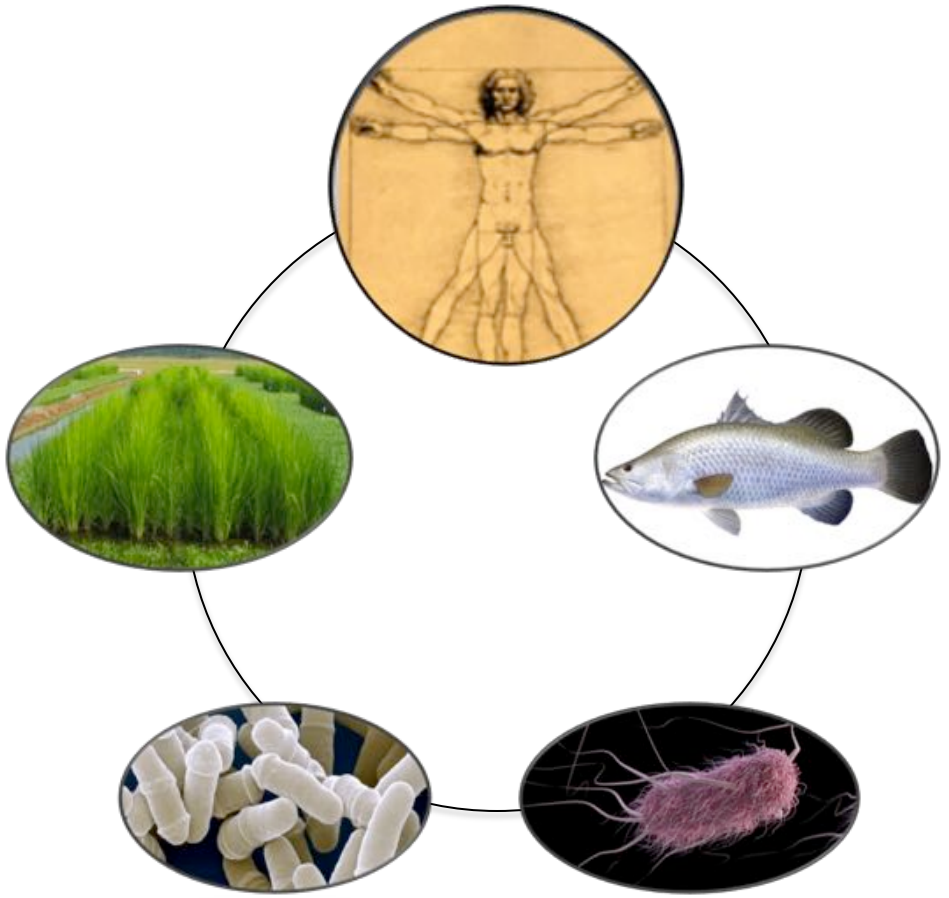


3rd Gen Long Read Sequencing

PacBio RS II

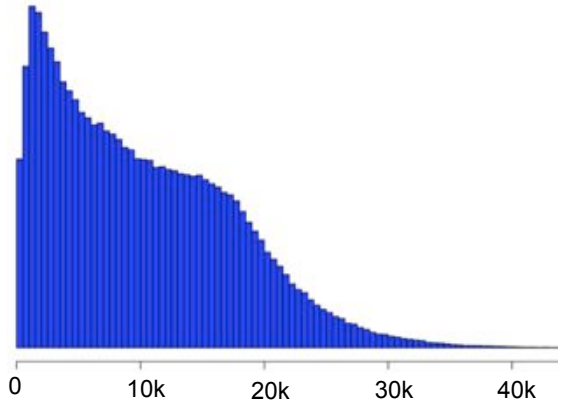


CSHL/PacBio

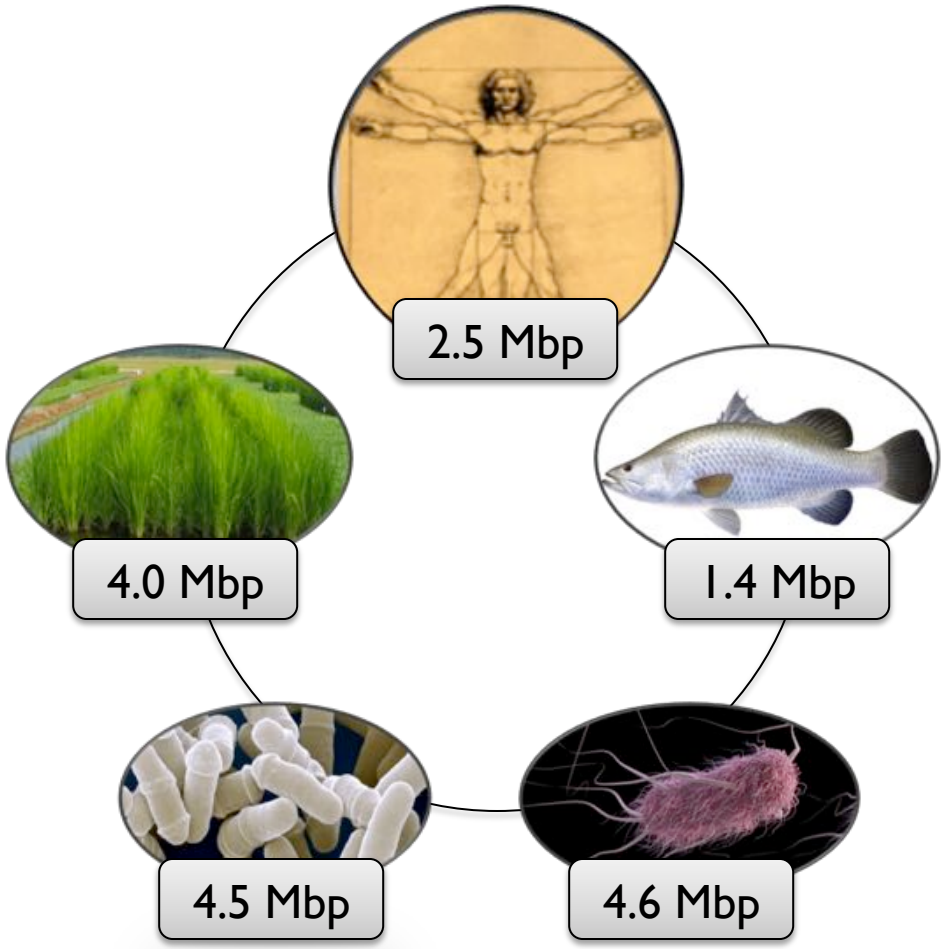


3rd Gen Long Read Sequencing

PacBio RS II



CSHL/PacBio



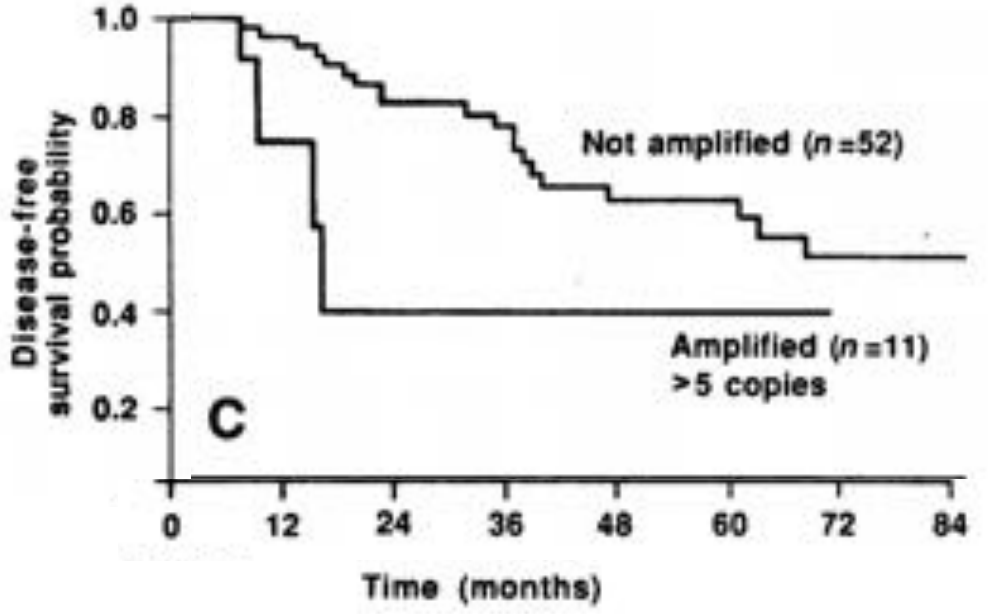
Her2 amplified breast cancer

Breast cancer

- About 12% of women will develop breast cancer during their lifetimes
- ~230,000 new cases every year (US)
- ~40,000 deaths every year (US)

Her2+ breast cancer

- 20% of breast cancers
- 2-3X recurrence risk
- 5X metastasis risk



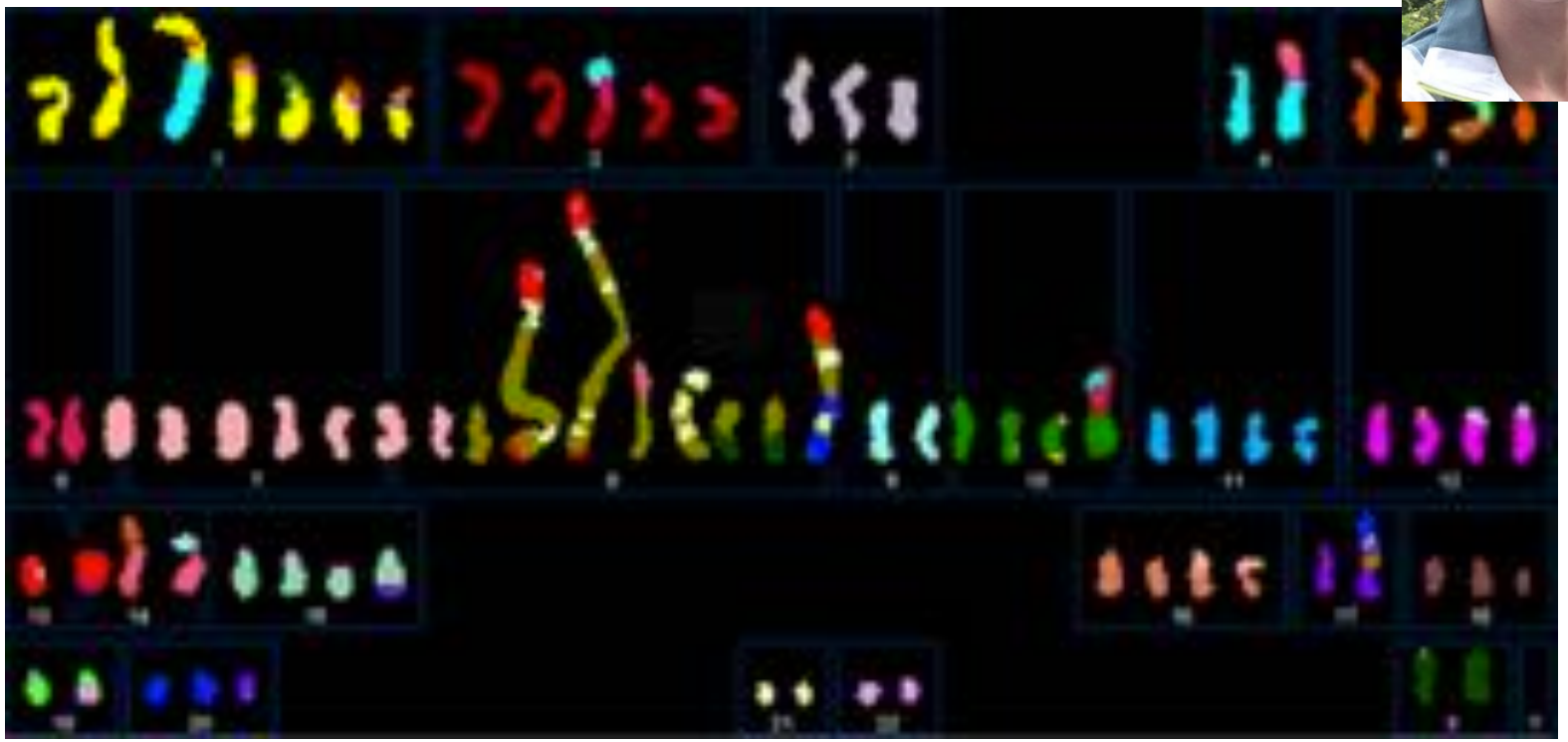
(Adapted from Slamon et al, 1987)

Statistics from American Cancer Society and Mayo Clinic.

Recurrence and metastasis from Gonzalez-Angulo, et al, 2009.

SK-BR-3

Most commonly used Her2-amplified breast cancer ce

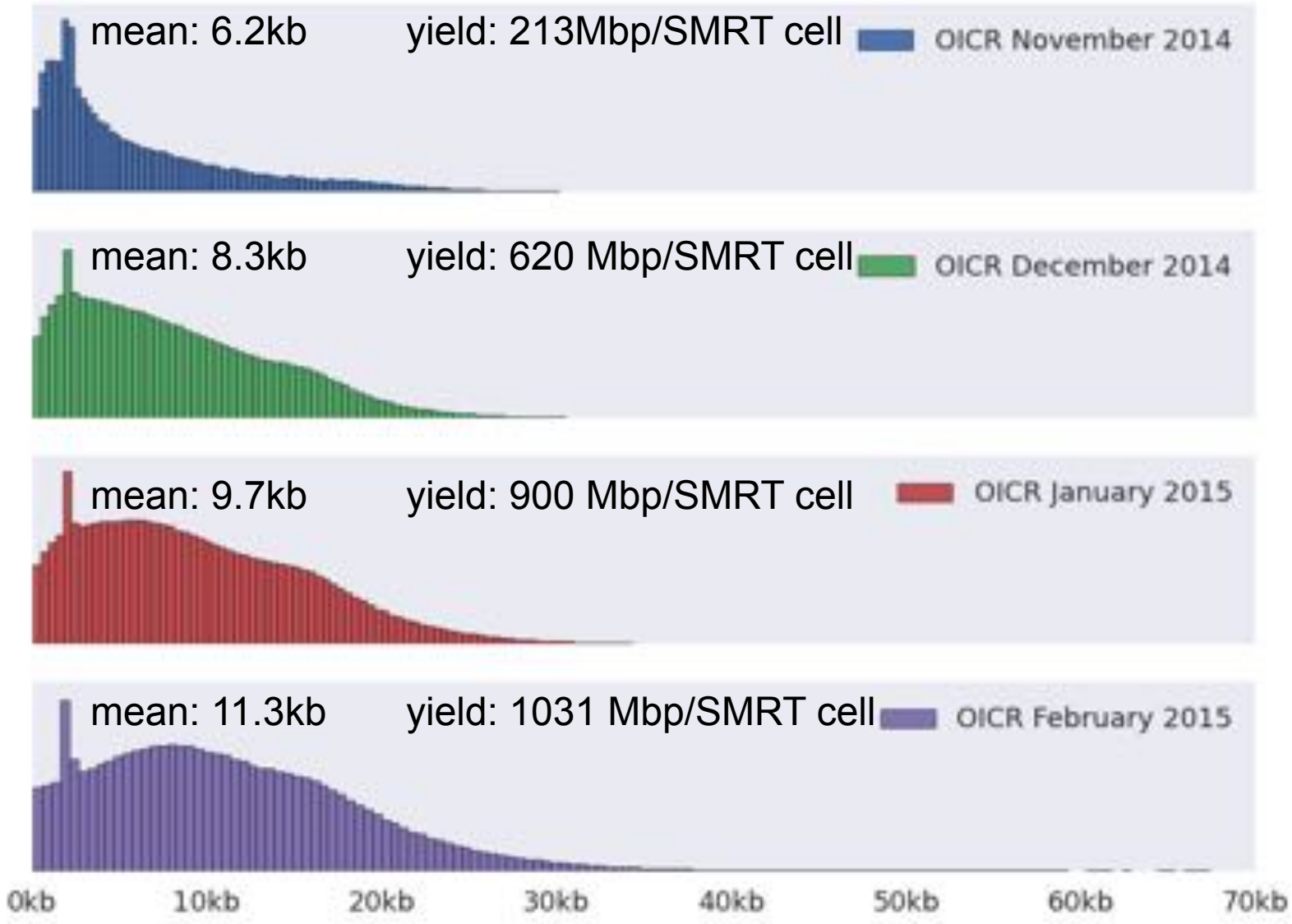


(Davidson et al, 2000)

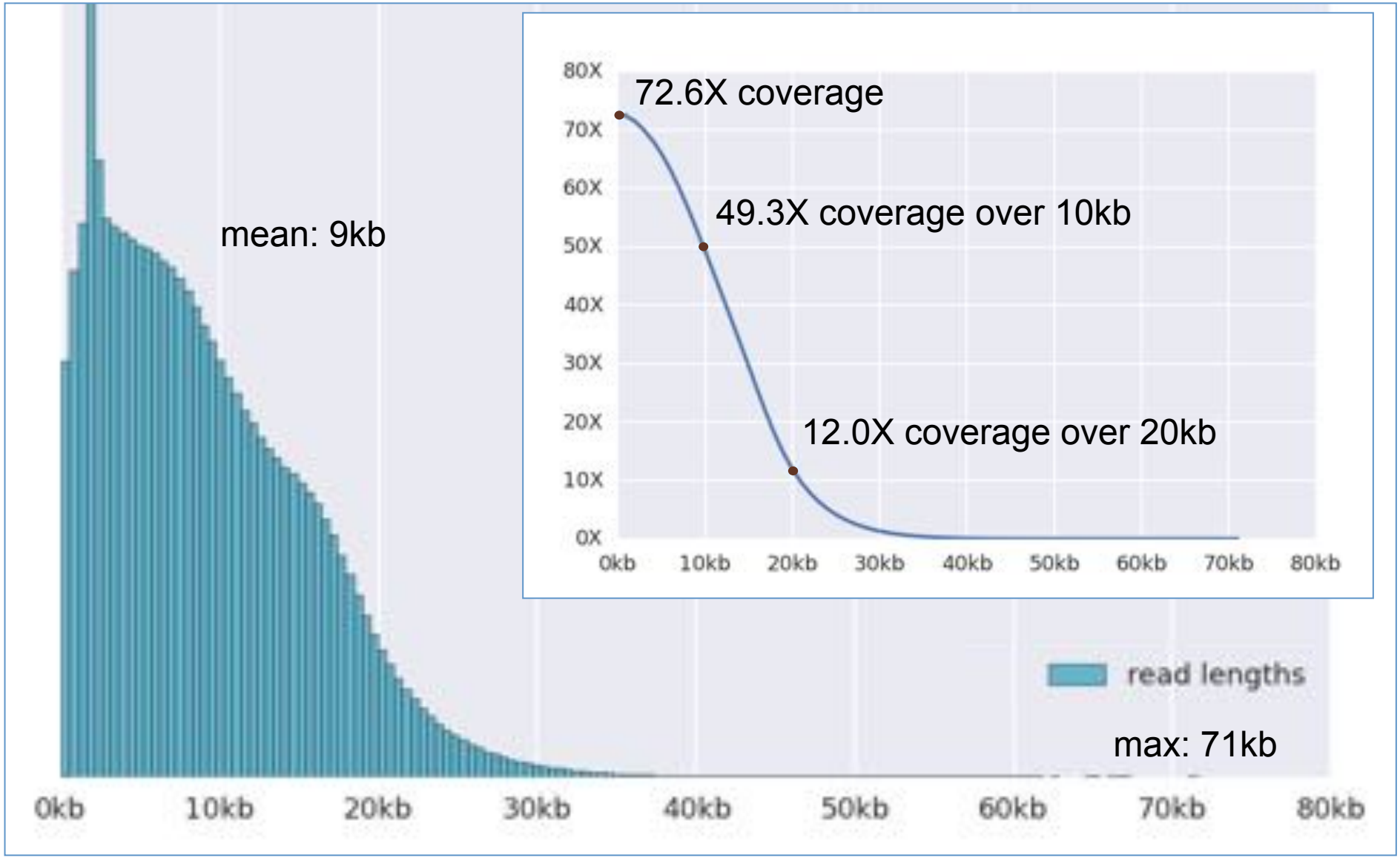
Can we resolve the complex structural variations, especially around Her2?

Ongoing collaboration between CSHL and OICR to *de novo* assemble the complete cell line genome with PacBio long reads

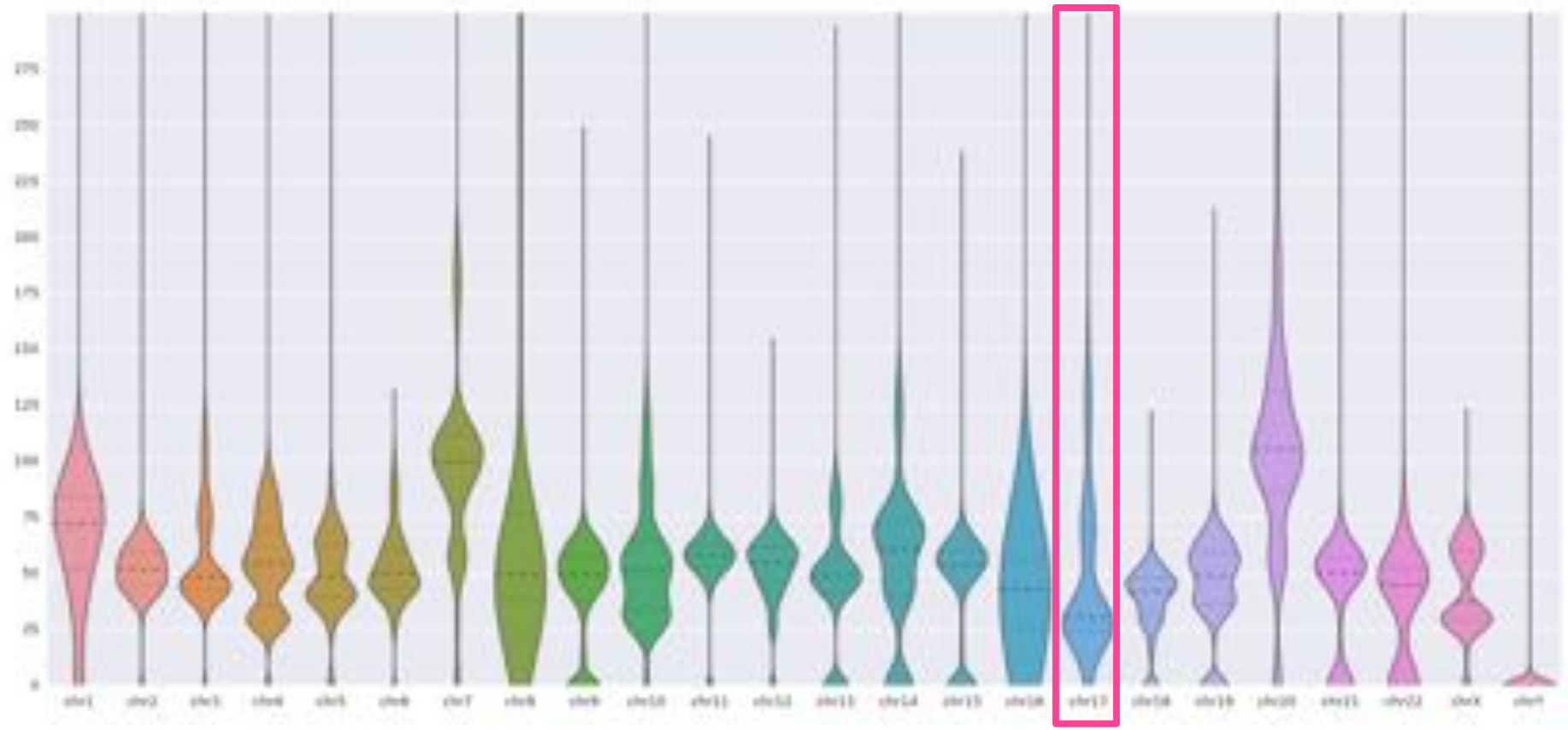
Improving SMRTcell Performance



PacBio read length distribution

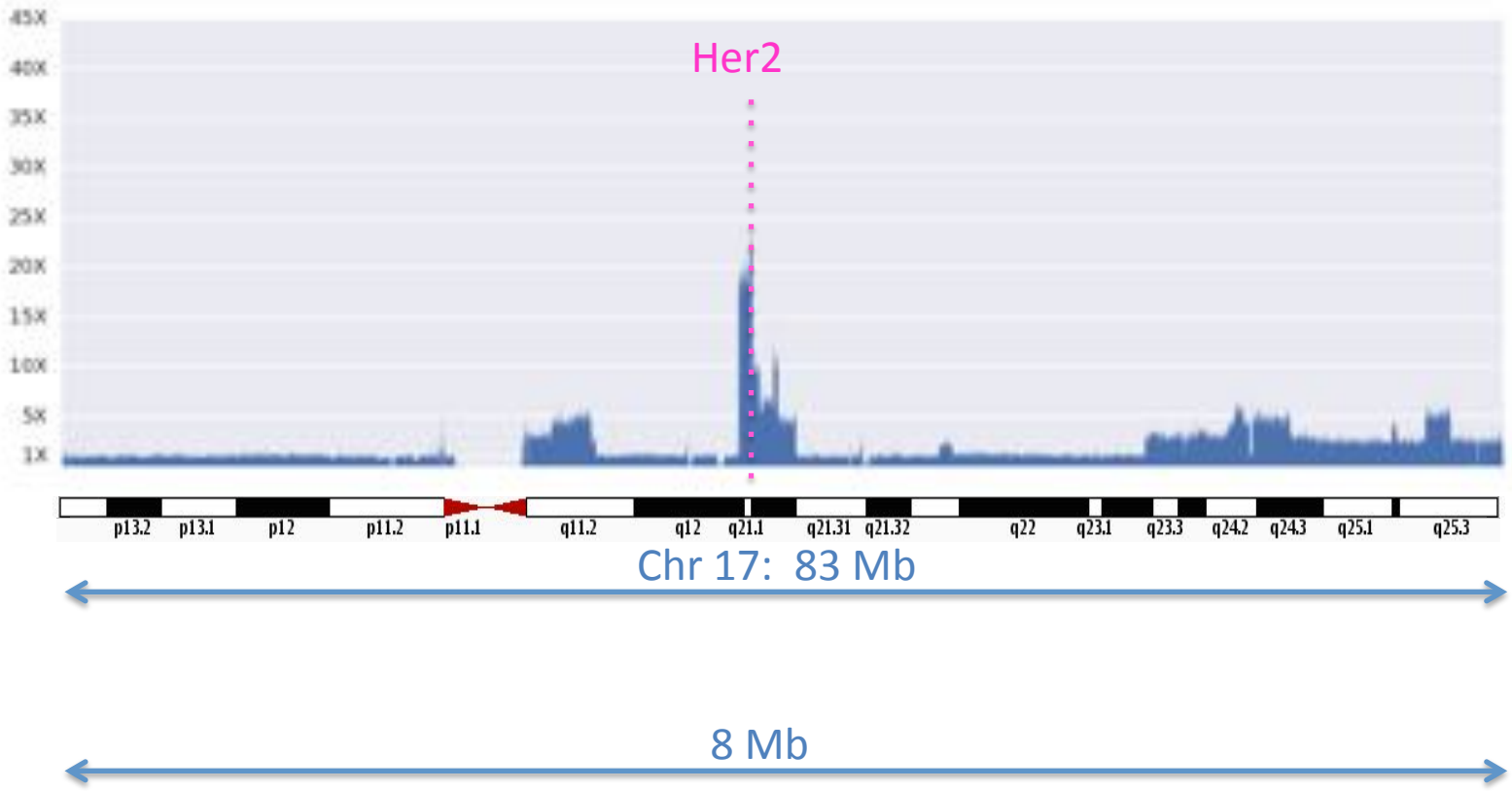


Genome-wide alignment coverage

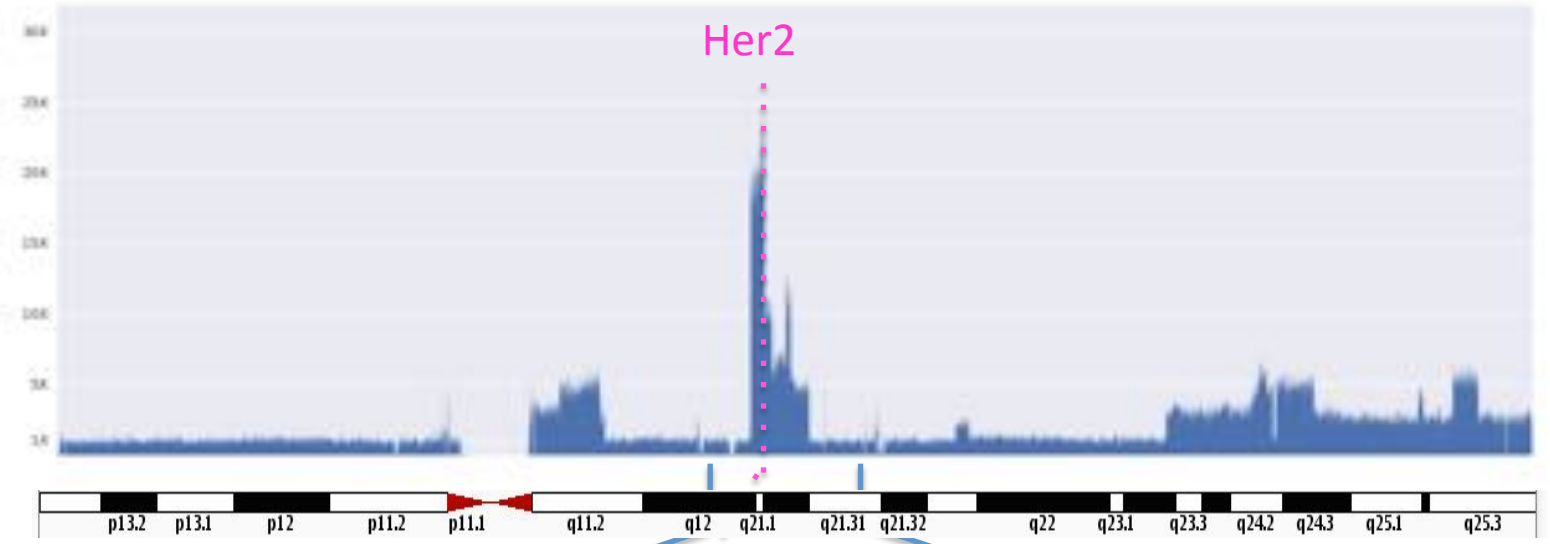


Genome-wide coverage averages around 54X
Coverage per chromosome varies greatly as expected from previous karyotyping results

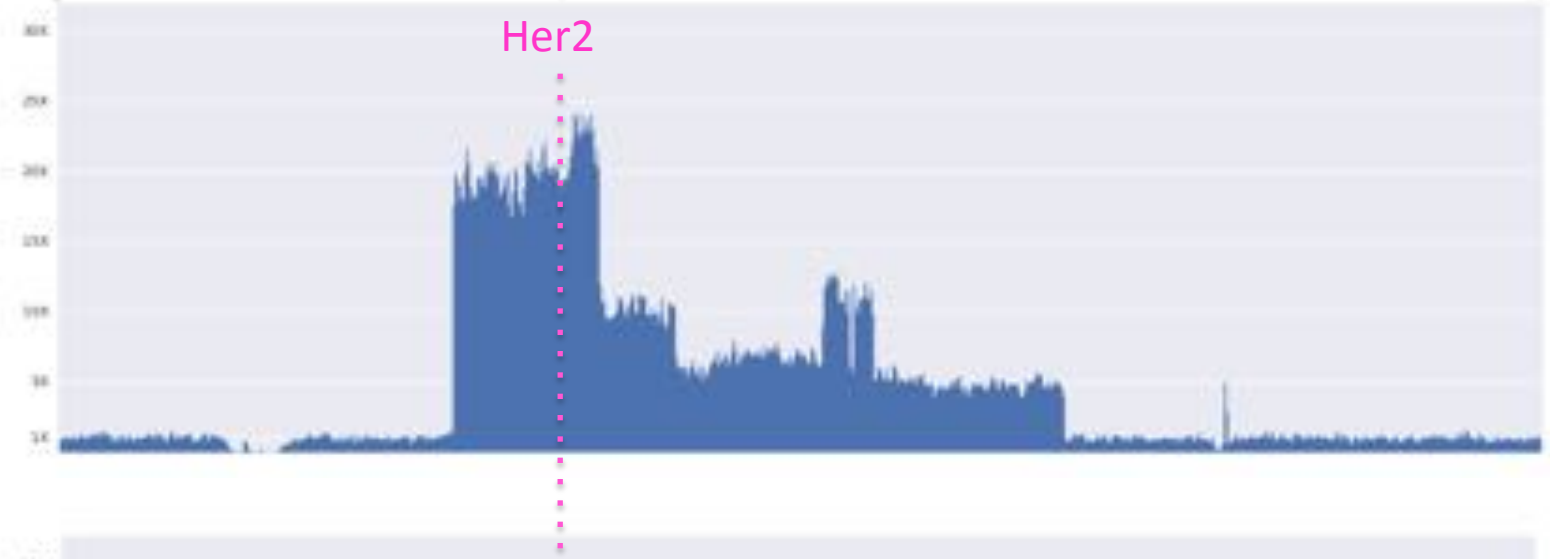
PacBio

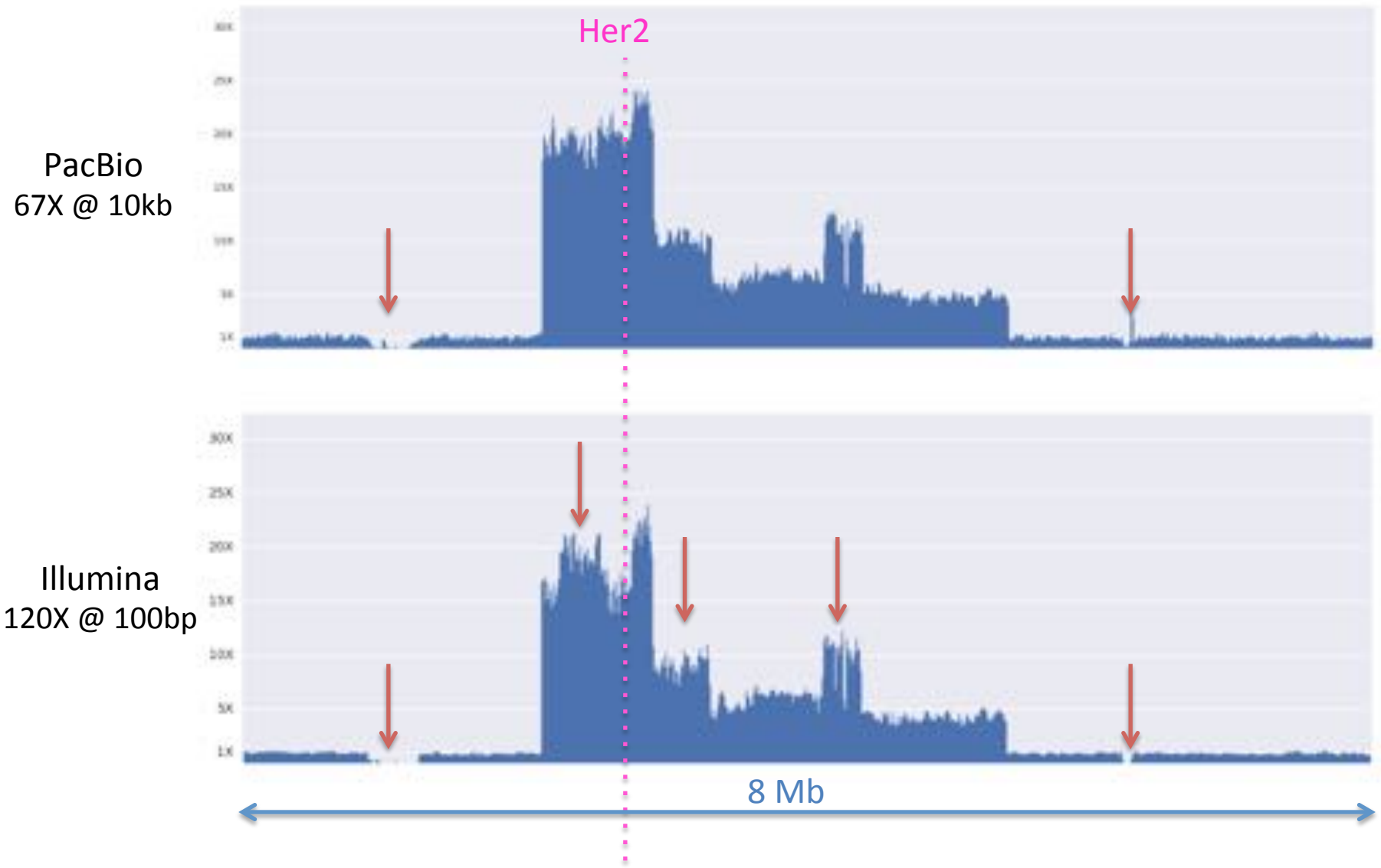

Her2
45X
40X
35X
30X
25X
20X
15X
10X
5X
1X
p13.2
p13.1
p12
p11.2
p11.1
q11.2
q12
q21.1
q21.31
q21.32
q22
q23.1
q23.3
q24.2
q24.3
q25.1
q25.3
Chr 17: 83 Mb
8 Mb

PacBio

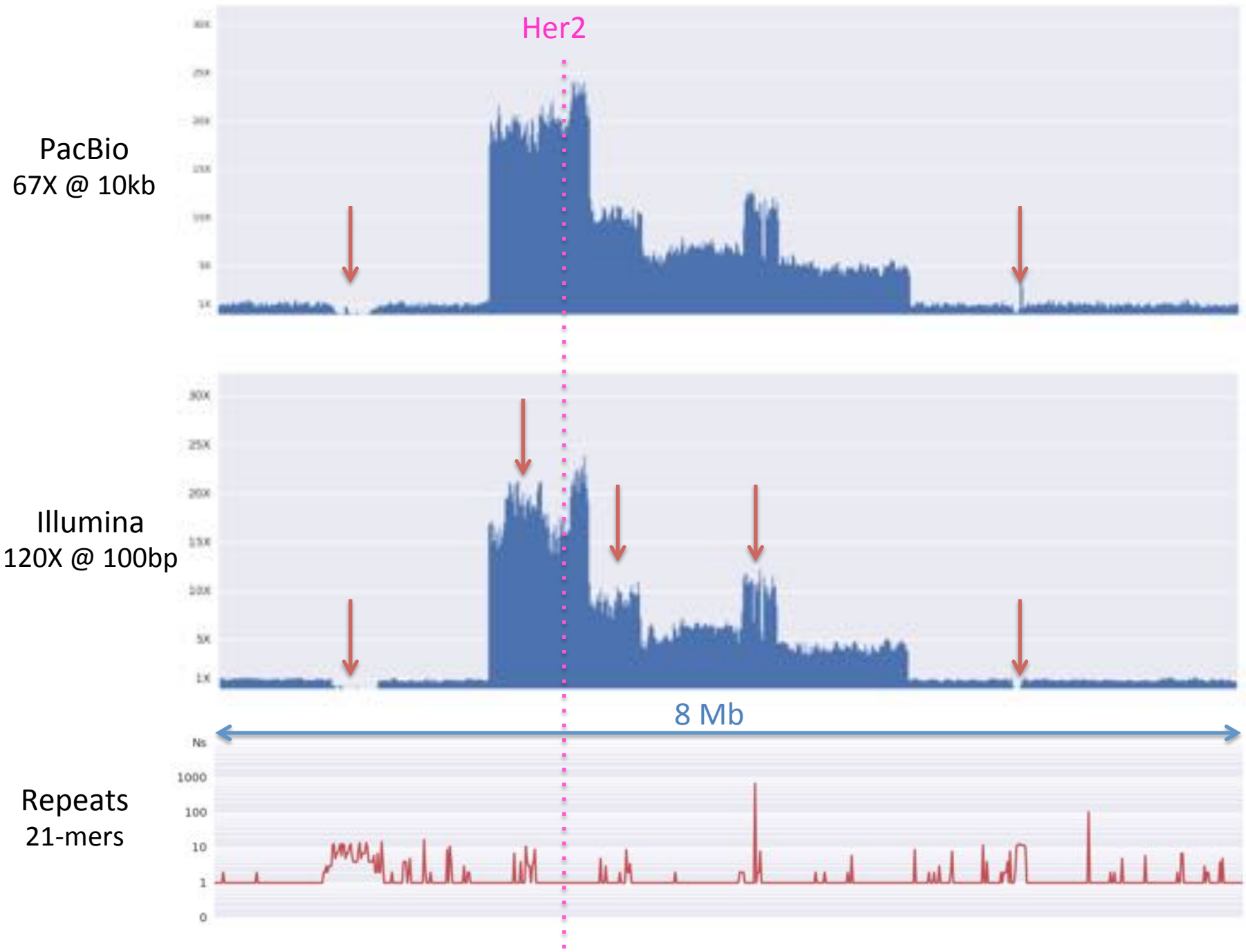


PacBio

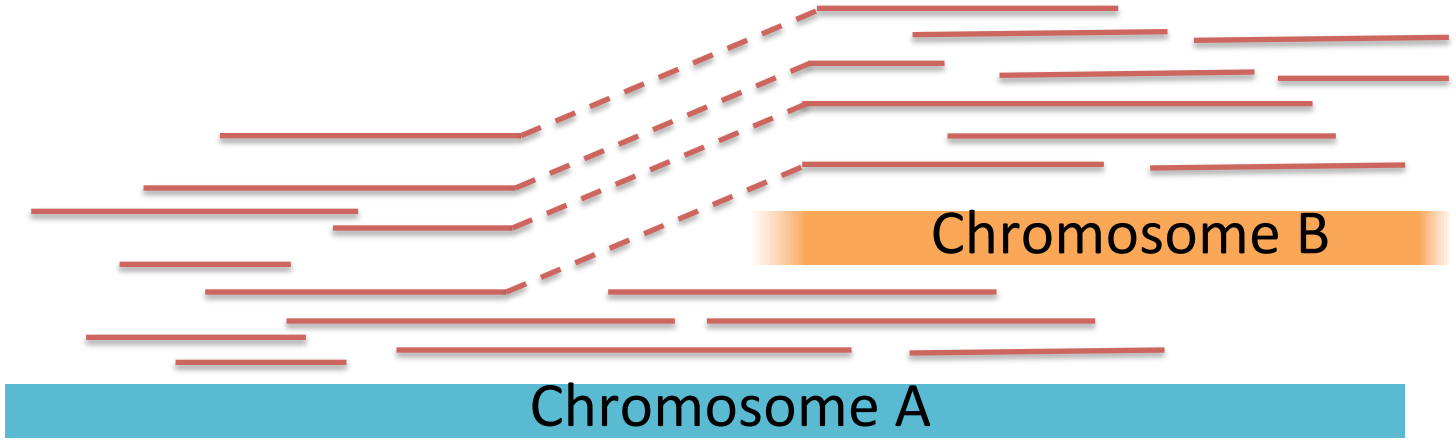




PacBio and Illumina coverage values are highly correlated
but Illumina shows greater variance because of poorly mapping reads


PacBio
67X @ 10kb
Her2
Illumina
120X @ 100bp
8 Mb
Repeats
21-mers
Ns
1000
100
10
1
0

Structural variant discovery with long reads



1. Alignment-based split read analysis: Efficient capture of most events

BWA-MEM + Lumpy

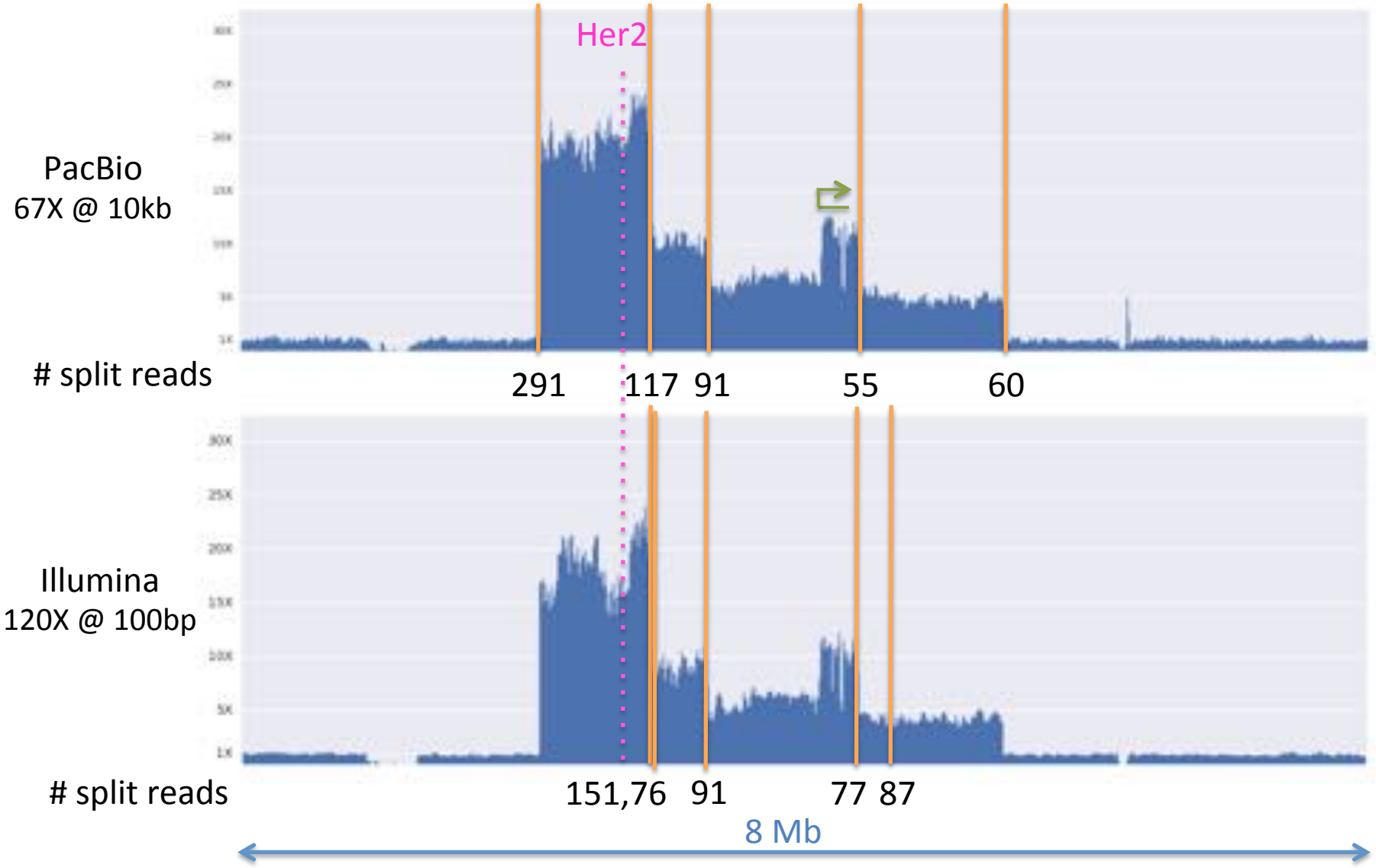
2. Local assembly of regions of interest: In-depth analysis with *base-pair precision*

Localized HGAP + Celera Assembler + MUMmer

3. Whole genome assembly: In-depth analysis including *novel sequences*

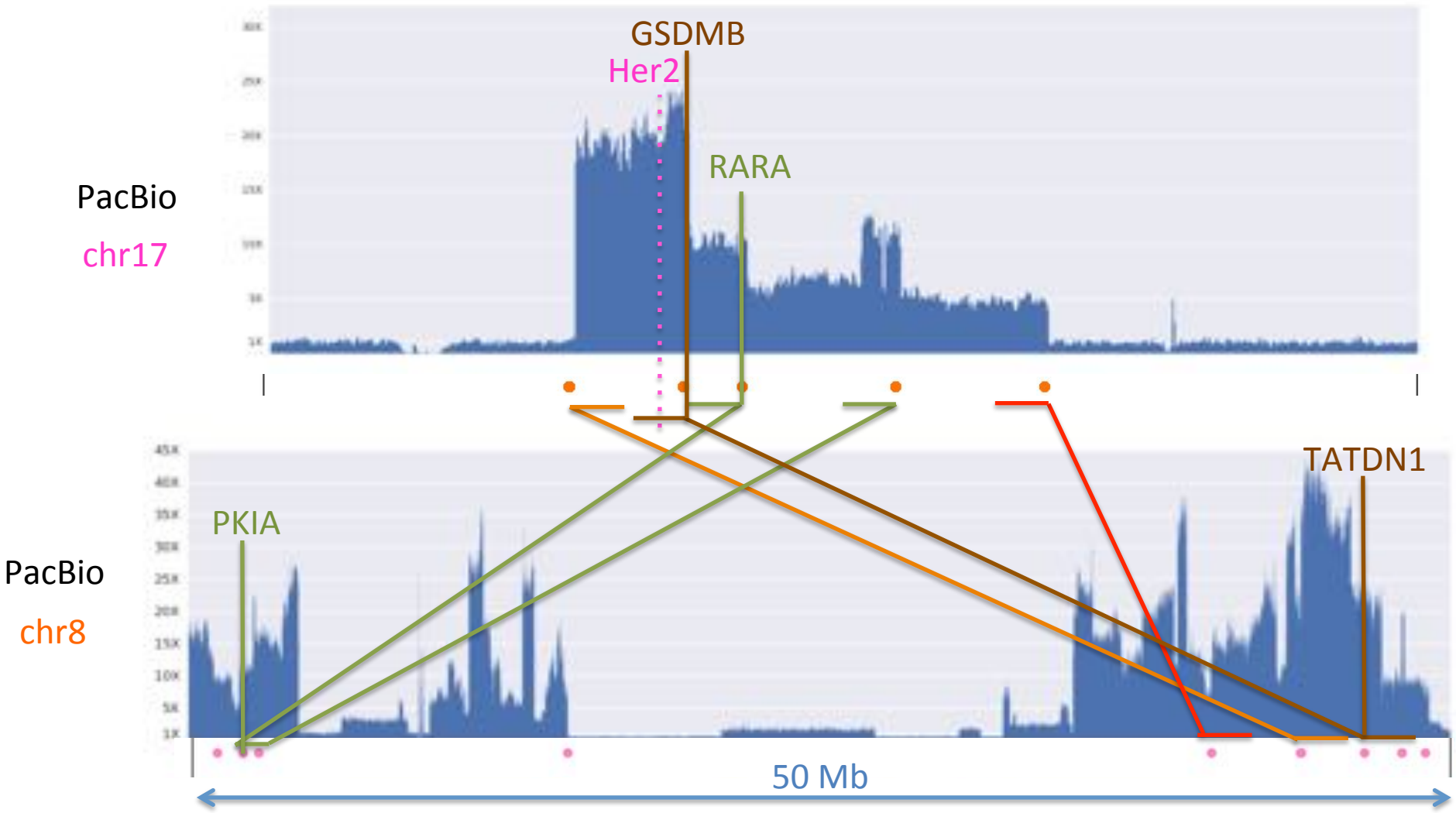
DNAnexus-enabled version of Falcon

Total Assembly: 2.64Gbp **Contig N50: 2.56 Mbp** **Max Contig: 23.5Mbp**

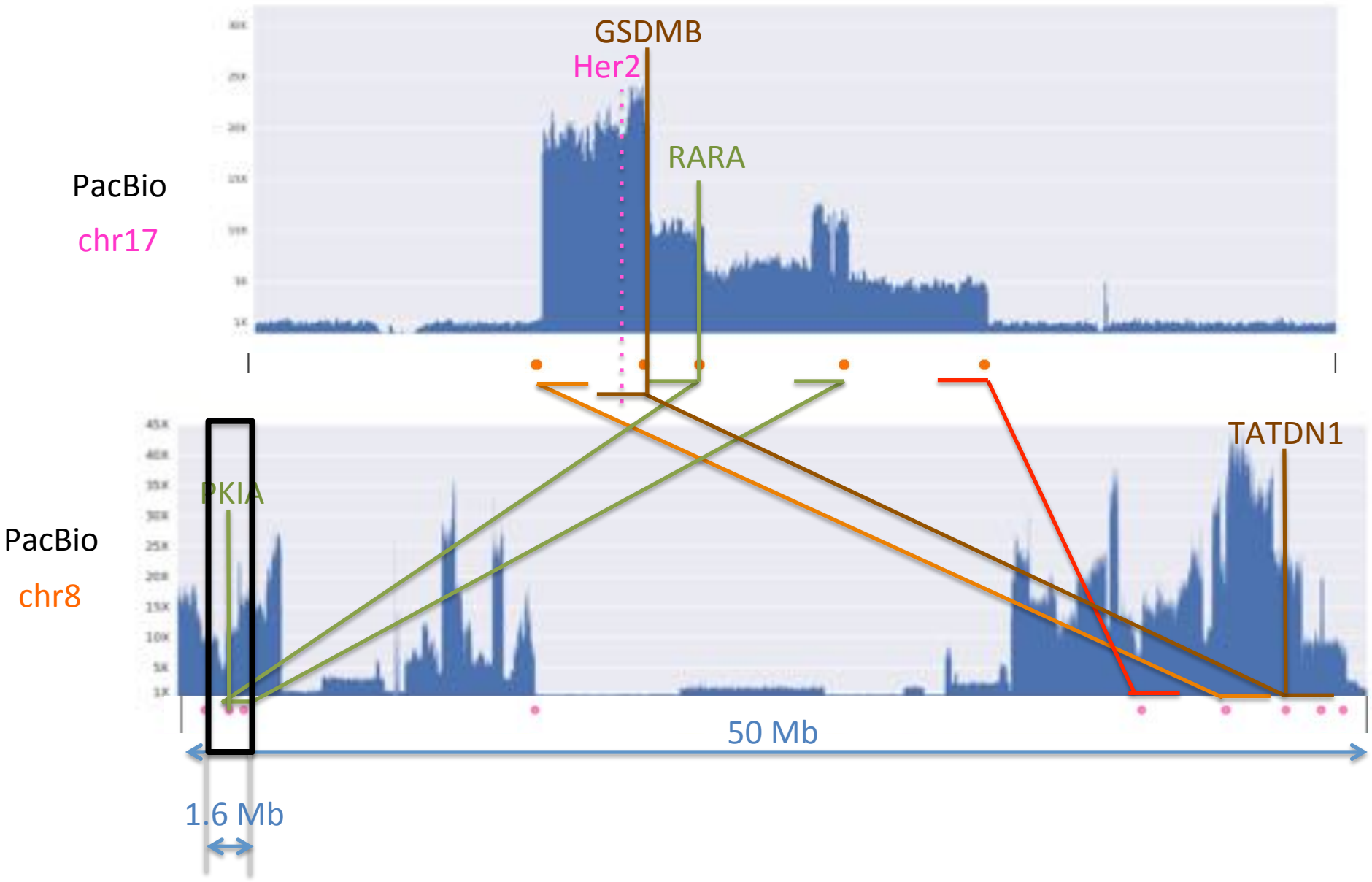


Green arrow indicates an inverted duplication.

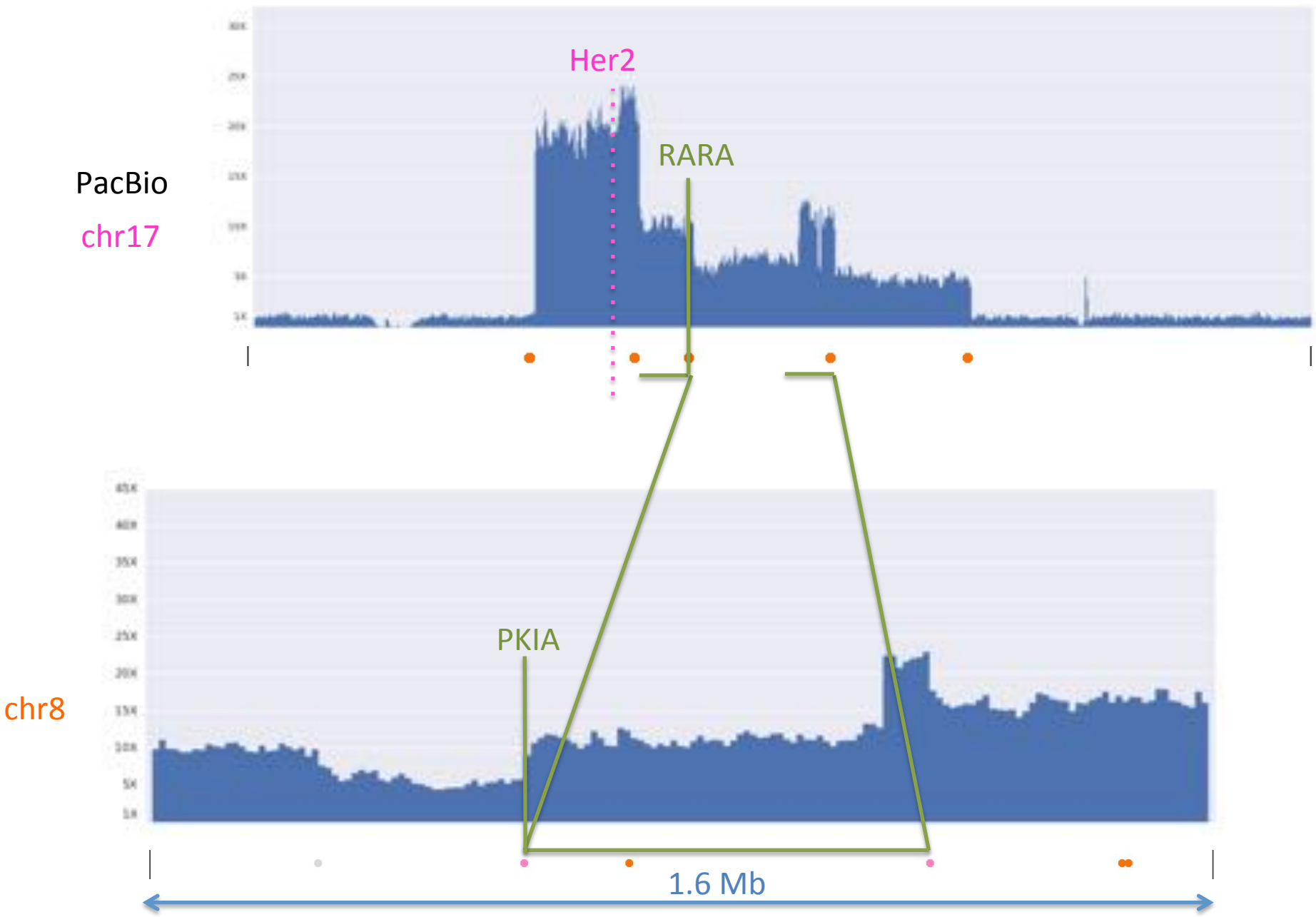
False positive and missing Illumina calls due to mis-mapped reads (especially low complexity).



Confirmed both known gene fusions in this region



Confirmed both known gene fusions in this region

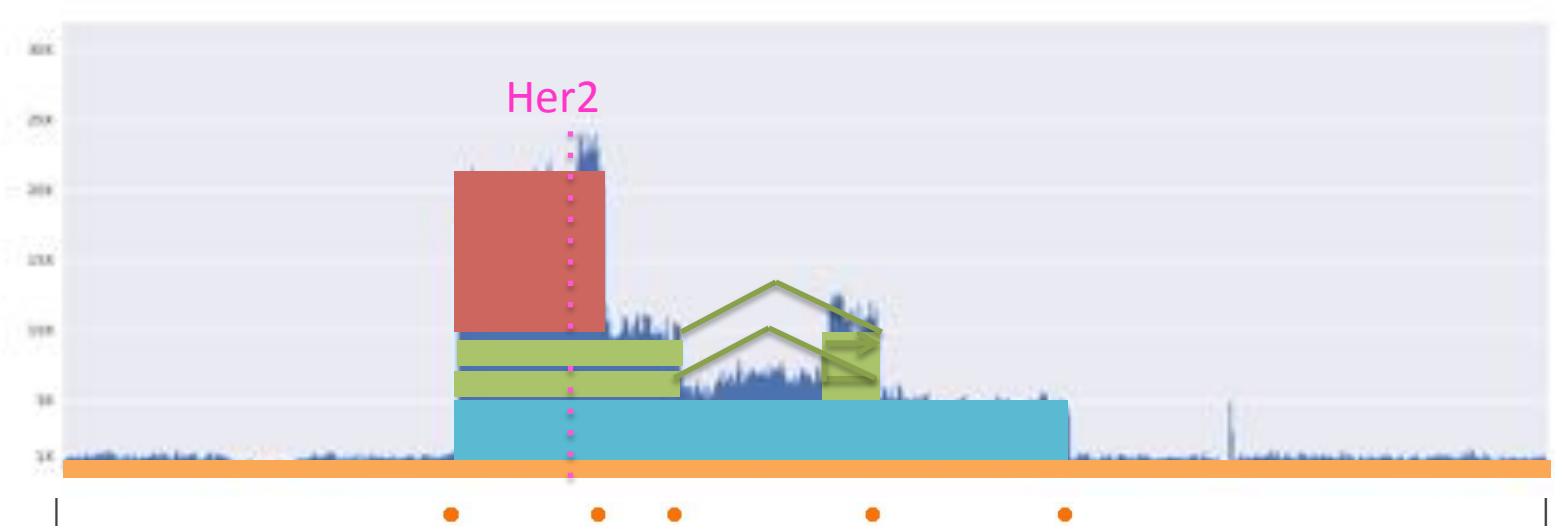


Joint coverage and breakpoint analysis to discover underlying events

Cancer lesion Reconstruction

PacBio

chr17



By comparing the proportion of reads that are spanning or split at breakpoints we can begin to infer the history of the genetic lesions.

1. Healthy diploid genome
2. Original translocation into chromosome 8
3. Duplication, inversion, and inverted duplication within chromosome 8
4. Final duplication from within chromosome 8

SKBR3 Oncogene Analysis

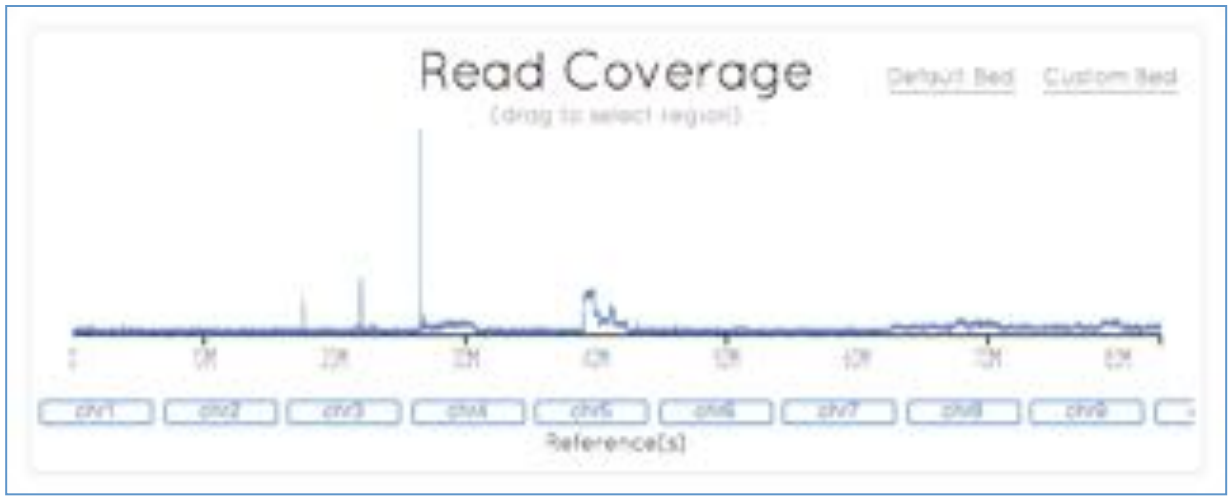
Known missense mutation in p53: **R175H**

Oncogene amplifications	
ErbB2 (Her2/neu)	≈20X
MYC	≈27X
MET	≈8X

Genetic Lesion History Analysis Underway

Known Gene fusions		Confirmed by PacBio reads?
TATDN1	GSDMB	**Yes**
RARA	PKIA	**Yes**
ANKHD1	PCDH1	**Yes**
CCDC85C	SETD3	**Yes**
SUMF1	LRRFIP2	**Yes**
WDR67 (TBC1D31)	ZNF704	**Yes**
DHX35	ITCH	**Yes**
NFS1	PREX1	**Yes *read-through transcription**
CYTH1	EIF3H	**Yes *nested inside 2 translocations**

Her2+ Breast Cancer Reference Genome



Available *today* under the Toronto Agreement:

- Fastq & BAM files of aligned reads
- Interactive Coverage Analysis with BAM.IOBIO
- Whole genome assembly

Available soon

- Whole genome methylation analysis
- Full length cDNA transciptome analysis
- Comparison to single cell analysis of >100 individual cells

http://schatzlab.cshl.edu/data/skbr3/

What should we expect from an assembly?

The resurgence of reference quality genomes

Summary & Recommendations

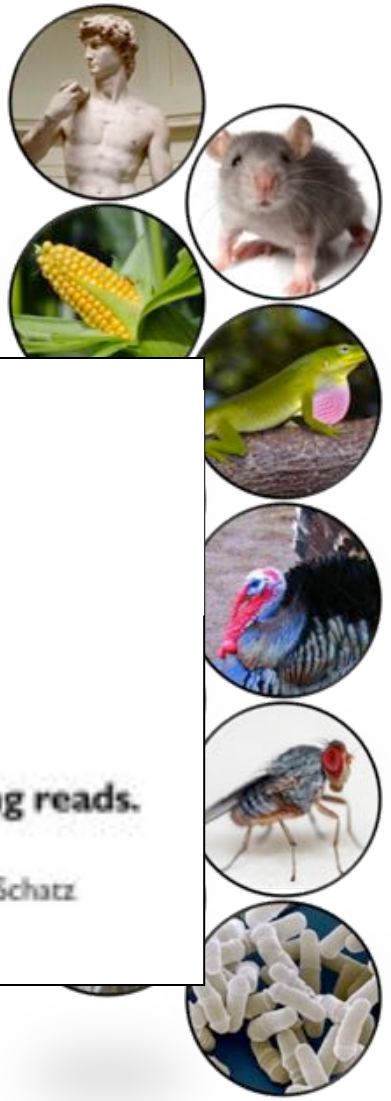
< 100 Mbp: HGAP/PacBio2CA @ 100x PB C3-P5

expect near perfect chromosome arms

< 1GE

> 1GE

> 5GE



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New Results

Error correction and assembly complexity of single molecule sequencing reads.

Hayan Lee , James Gurtowski , Shinjae Yoo , Shoshana Marcus , W. Richard McCombie , Michael Schatz

doi: http://dx.doi.org/10.1101/006395

Caveats

Model only as good as the available references (esp. haploid sequences)

Technologies are quickly improving, exciting new scaffolding technologies

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Levy Lab
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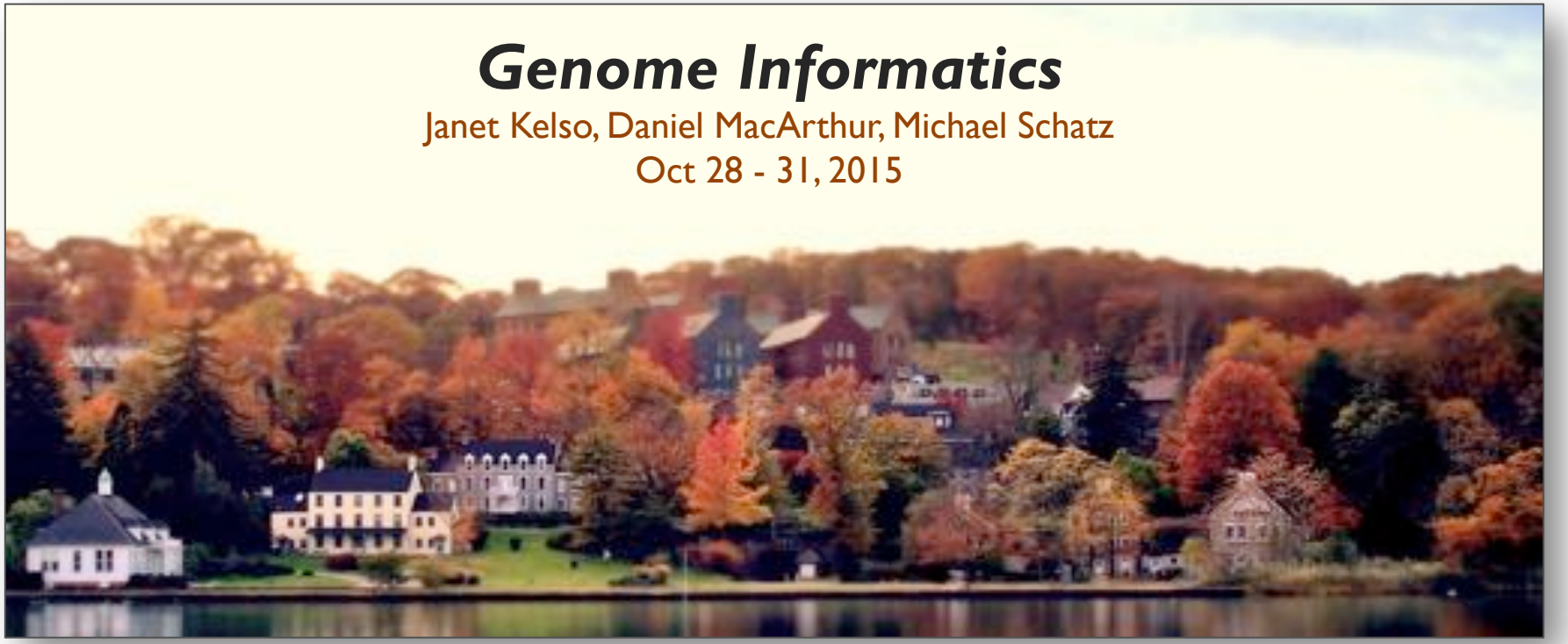

Thank you

http://schatzlab.cshl.edu

@mike_schatz