Chromosome scale de novo assembly of genomes using chromatin interaction data

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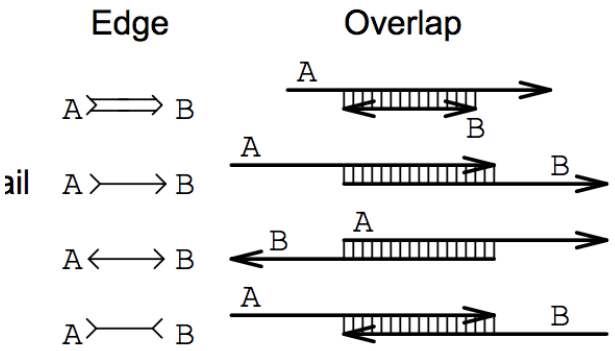
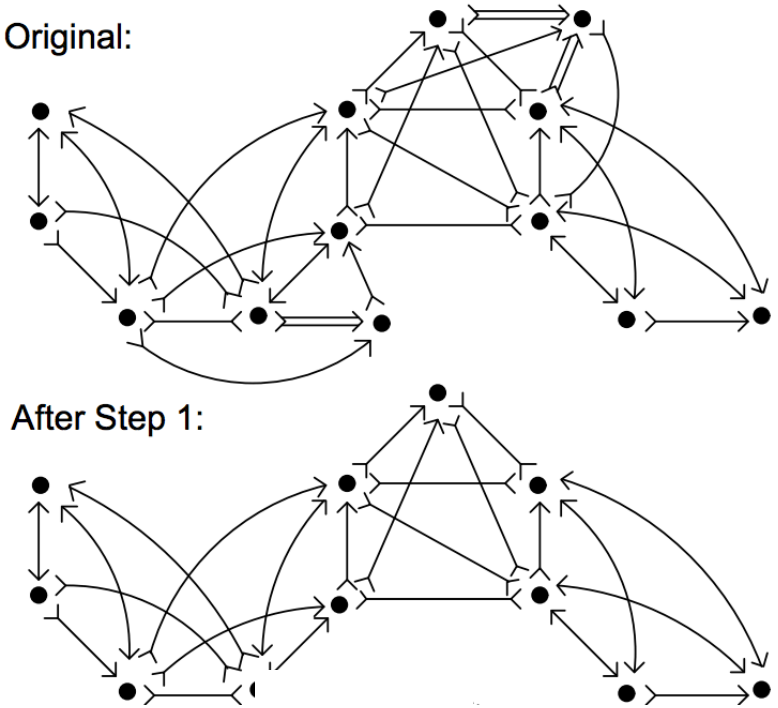
Genome assembly is a big puzzle!

Genome assembly overview

Find overlaps



Construct overlap graph

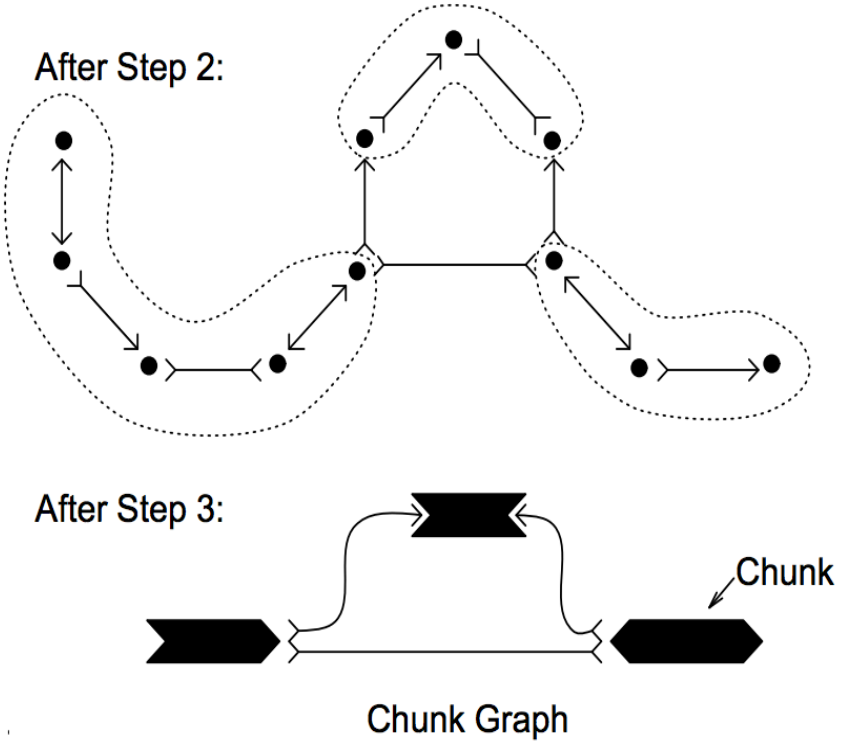


Remove contained edges

Myers, E. W. (1995). Toward simplifying and accurately formulating fragment assembly. *Journal of Computational Biology*, *2*(2), 275-290.

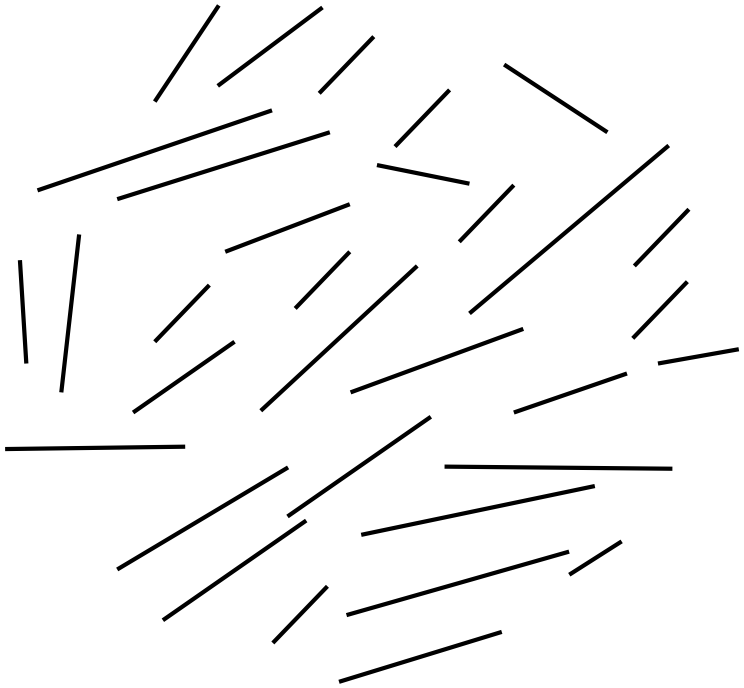
Genome assembly overview

- Remove transitive edges
- Collapse unitigs
- Output unitigs



Myers, E. W. (1995). Toward simplifying and accurately formulating fragment assembly. *Journal of Computational Biology*, *2*(2), 275-290.

Contigs



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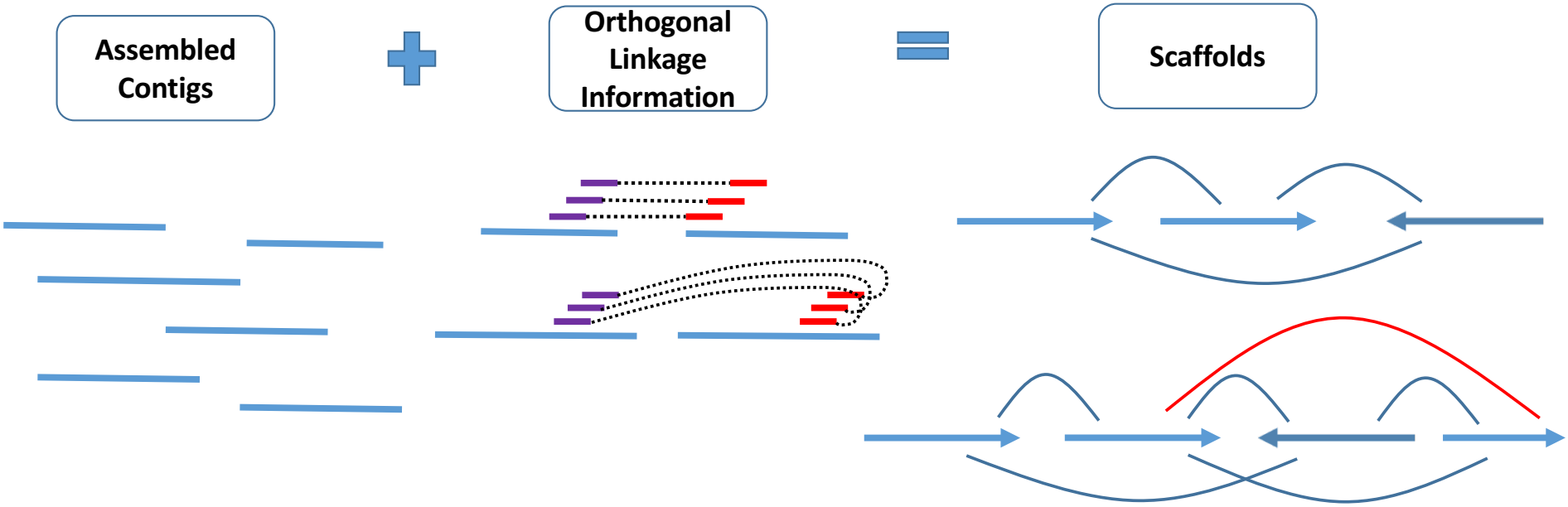
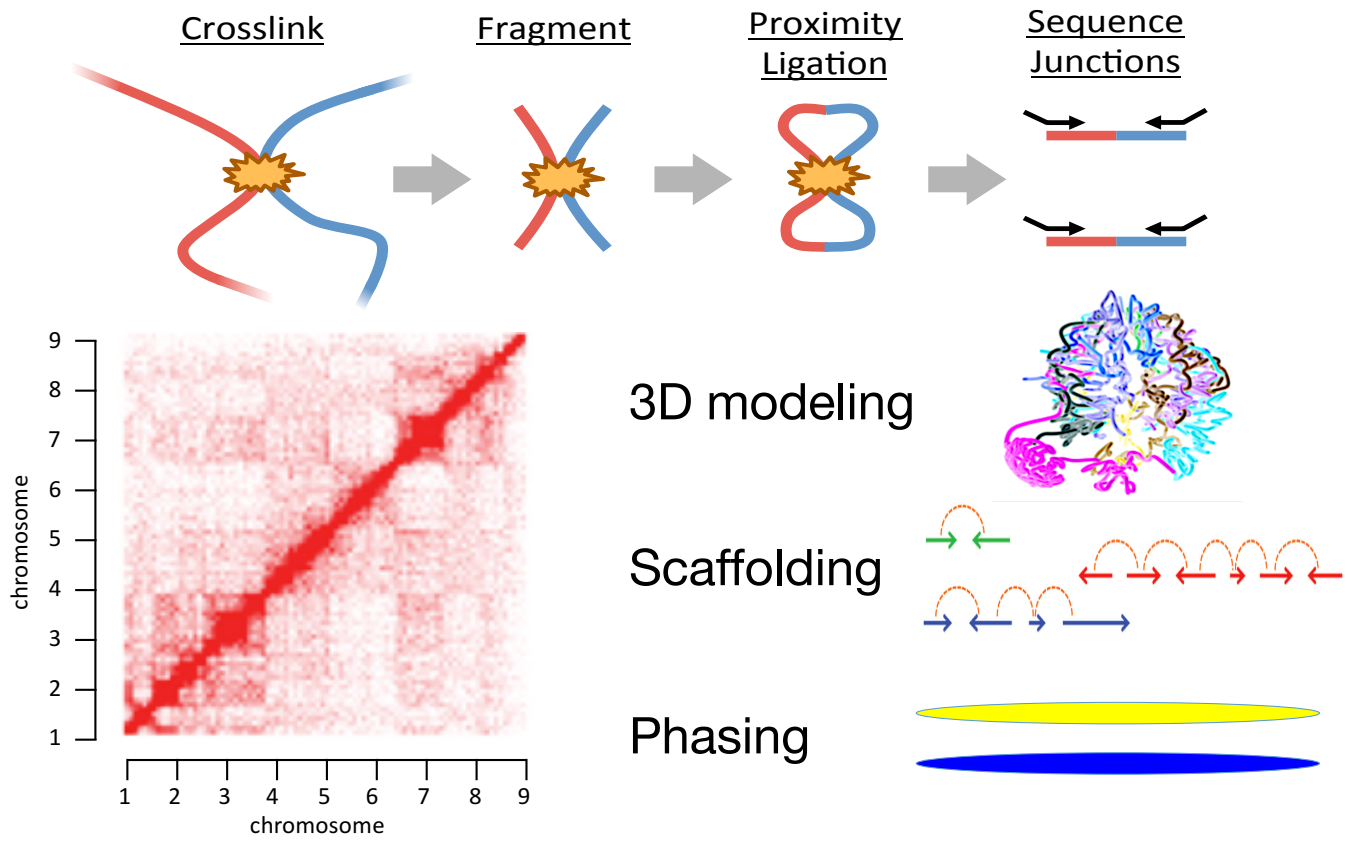
Chromosomes

Genome scaffolding



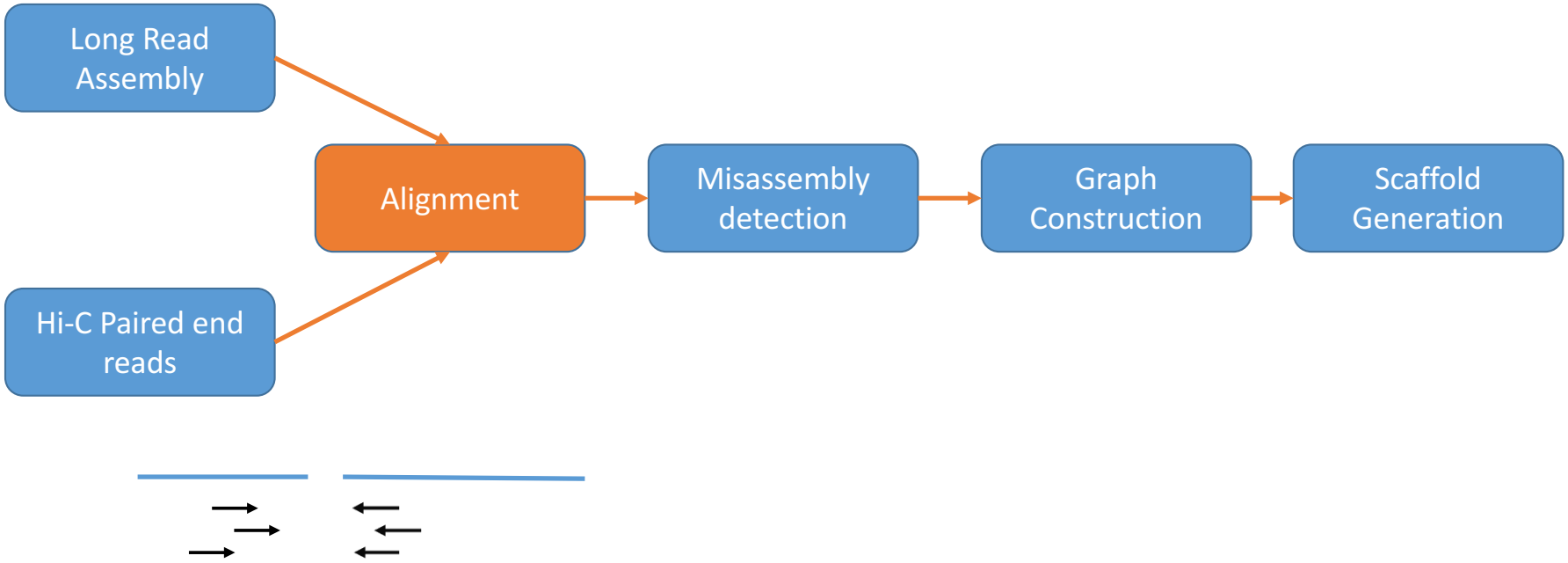
Hi-C chromatin conformation capture



- Duan *Nature* 2010, Burton *Nat Biotech* 2013, Kaplan *Nat Biotech 2013*, Selvaraj *Nat Biotech* 2013

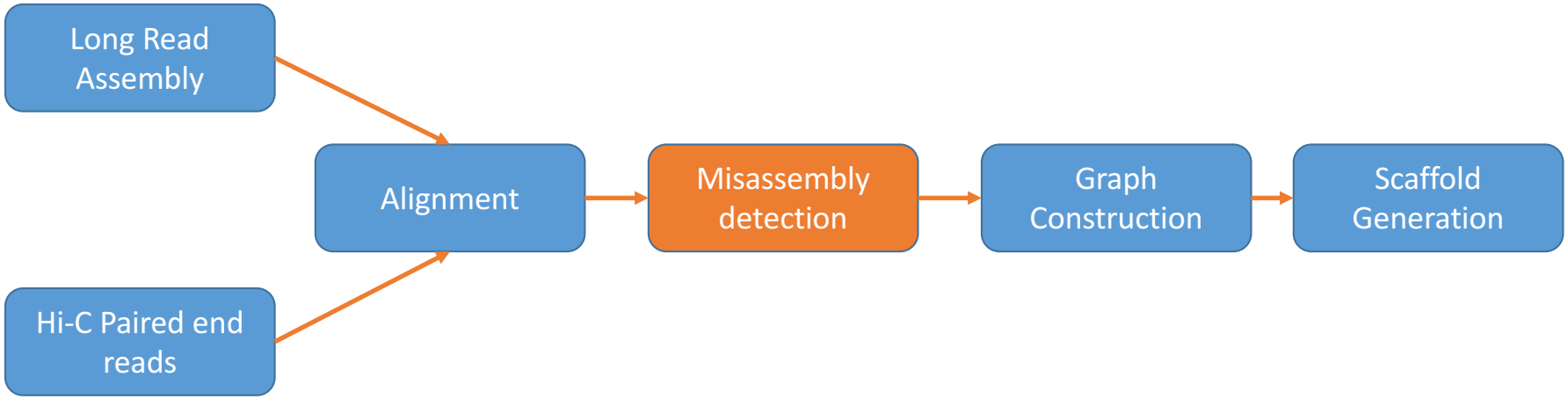
Ivan Liachko, Phase Genomics; Sid Selvaraj, Arima Genomics

SALSA - **S**imple **A**assembL**L**y **S**c**A**ffolder

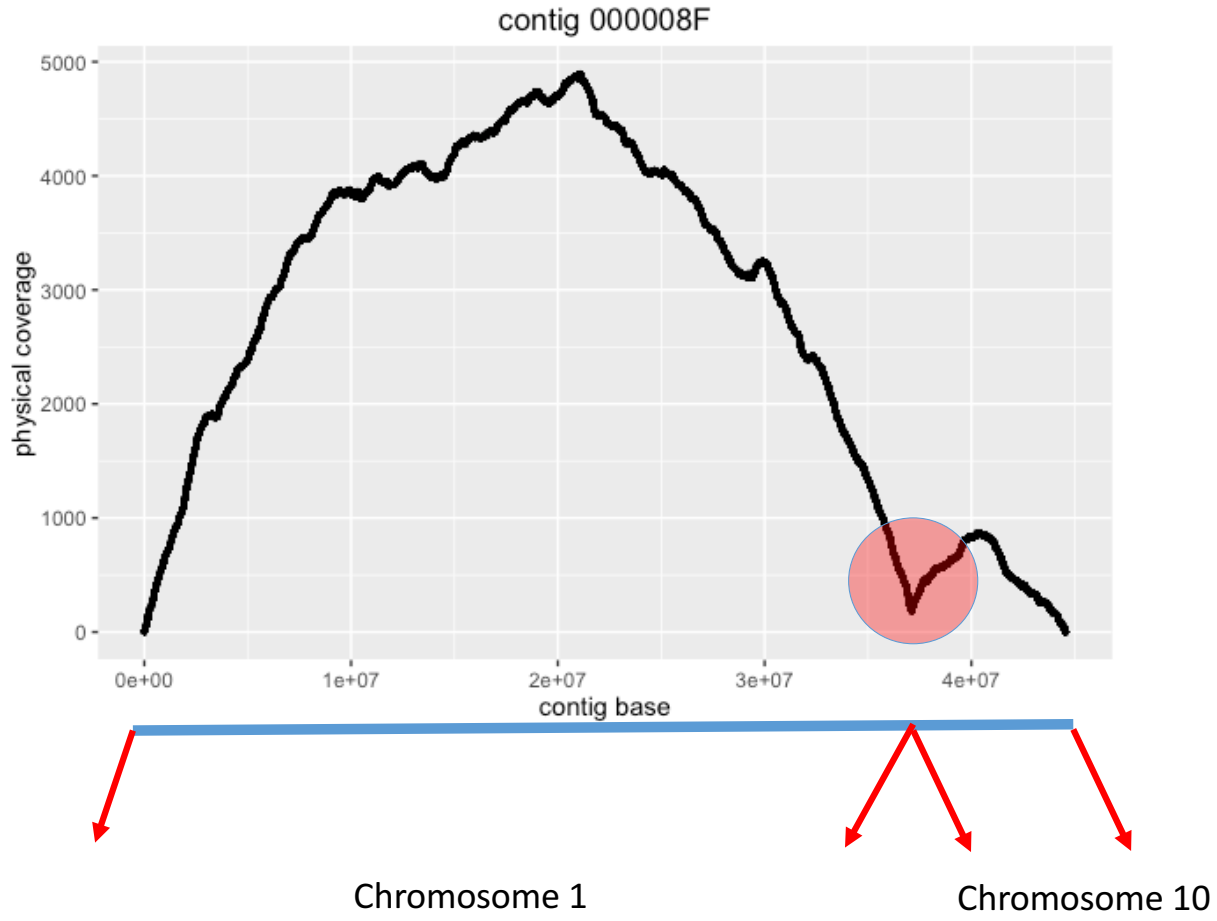


Ghurye, Jay, et al. "Scaffolding of long read assemblies using long range contact information.'' BMC Genomics

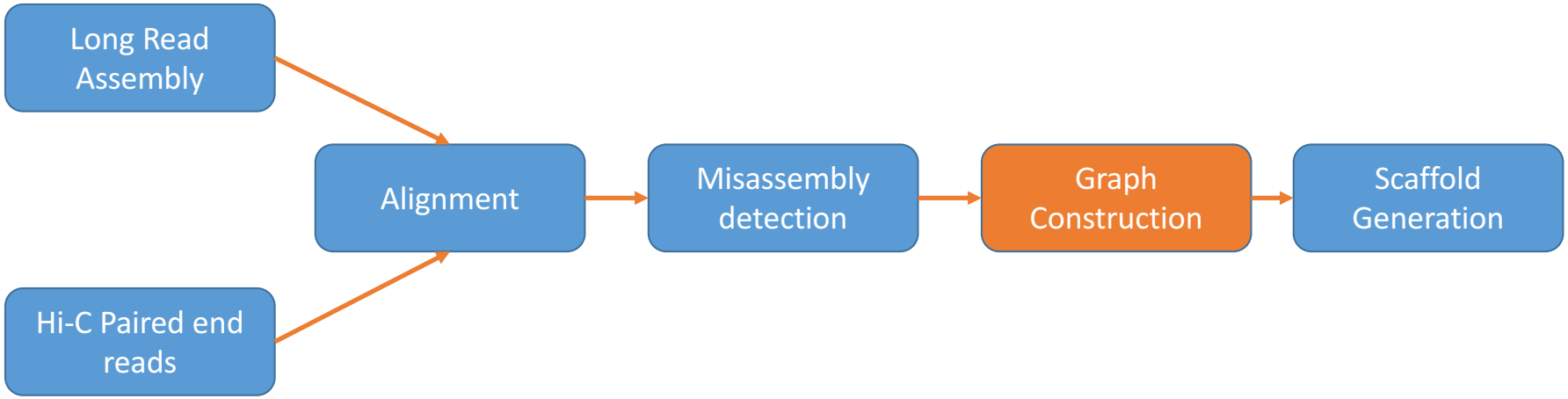
SALSA - **S**imple **A**ssembb**L**y **S**c**A**ffolder



Ghurye, Jay, et al. "Scaffolding of long read assemblies using long range contact information.'' BMC Genomics


contig 000008F
physical coverage
5000
4000
3000
2000
1000
0
0e+00
1e+07
2e+07
3e+07
4e+07
contig base
Chromosome 1
Chromosome 10

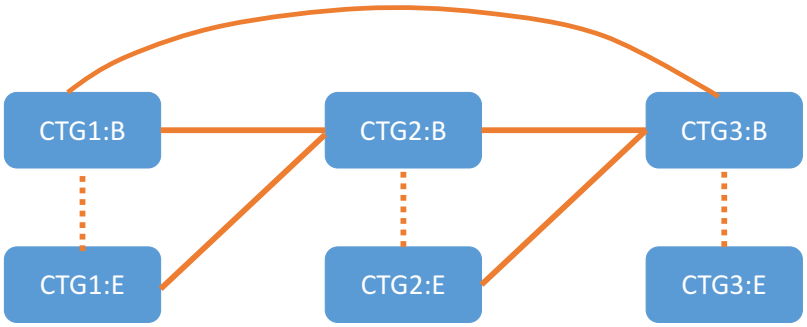
SALSA - **S**imple **A**ssembl**L**y **S**c**A**ffolder

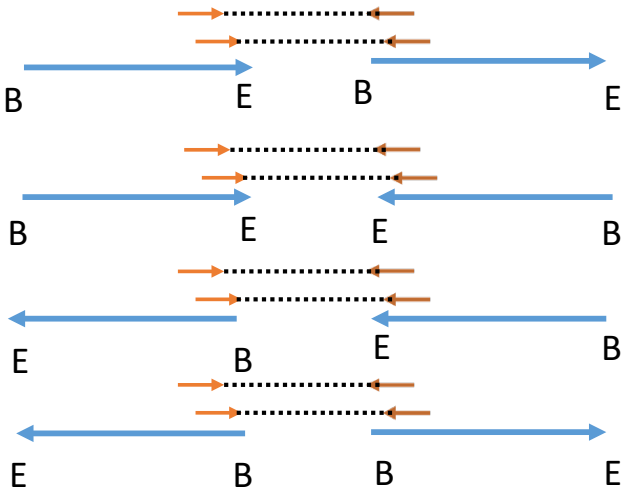


Ghurye, Jay, et al. "Scaffolding of long read assemblies using long range contact information.'' BMC Genomics

Scaffold graph

- Nodes are contig ends (Begin and End)
- Edges imply HiC read linkage





- Number of sites where restriction enzyme reduce length bias
- Find # cut sites for each contig
- Score for particular orientation = # read pairs / #restriction sites

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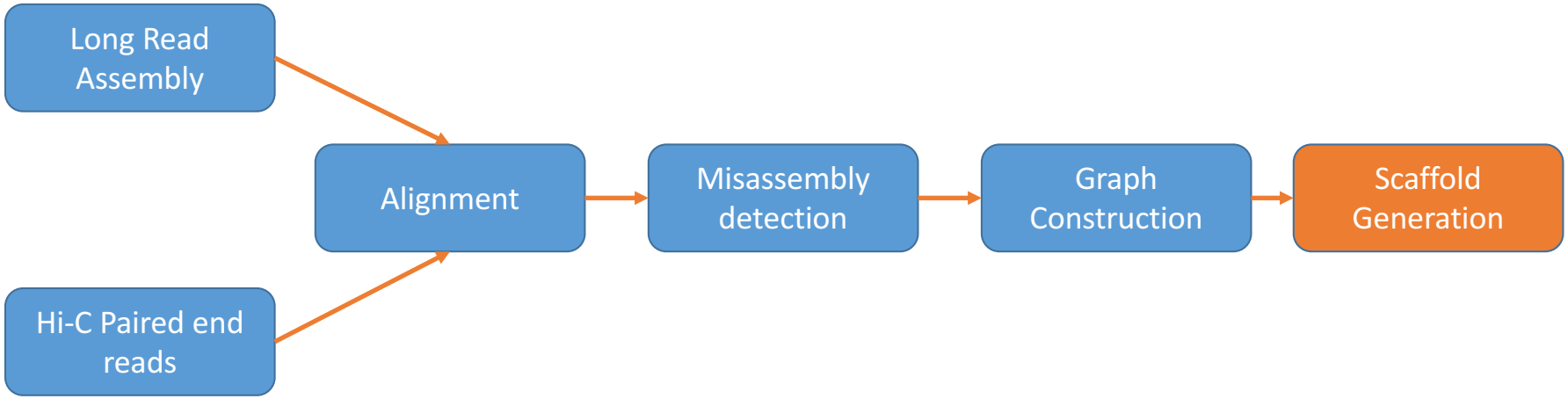
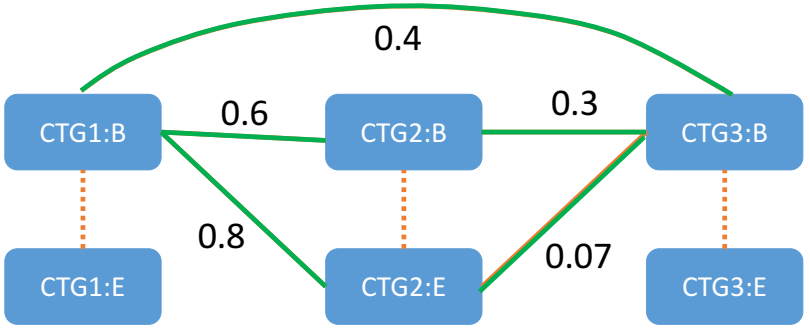
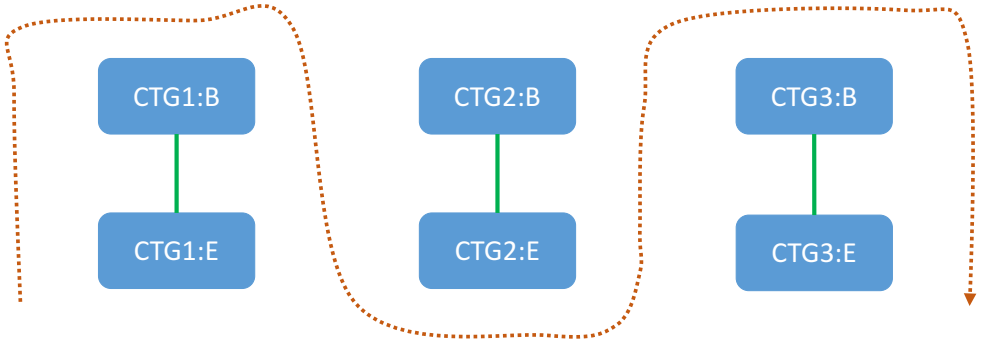


Ghurye, Jay, et al. "Scaffolding of long read assemblies using long range contact information.'' BMC Genomics

Scaffold construction





Consider edges in decreasing order of weights

Traversal of this graph gives scaffold

[CTG1:E, CTG1:B, CTG2:E, CTG2:B, CTG3:B, CTG3:E]

Reverse Reverse Forward

NA12878 assembly evaluation

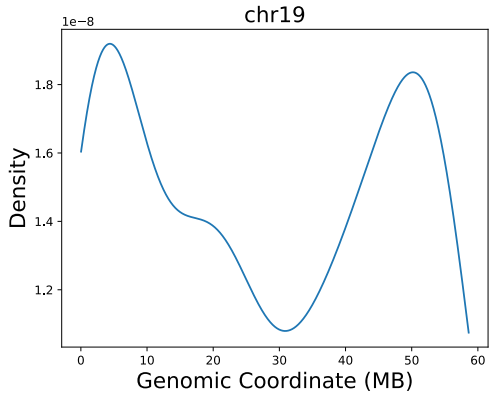
Metric
#Scaffolds
Total Bases
Aligned bases
Breakpoints
Relocations
Translocations
Inversions

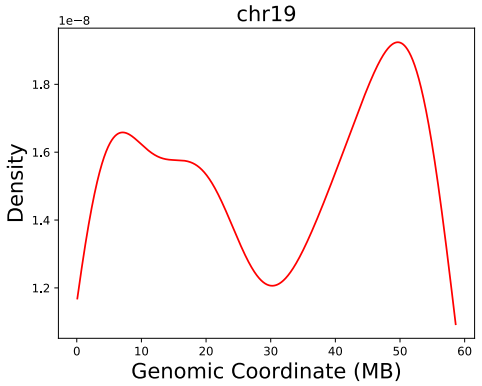
Some errors are common in both scaffolds due to structural variations between GRCh38 and NA12878 Genome

NA12878 Error Distribution

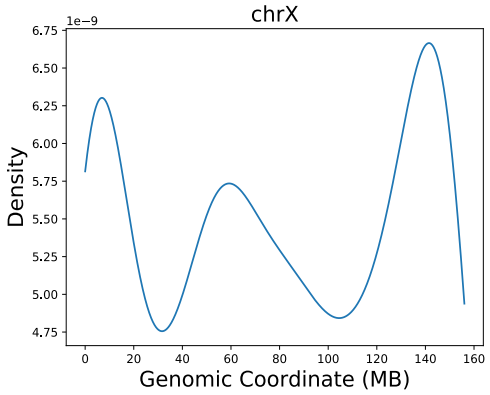
SALSA **LACHESIS**

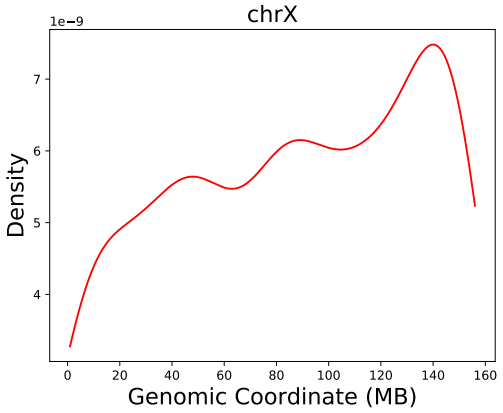
(A)





(B)





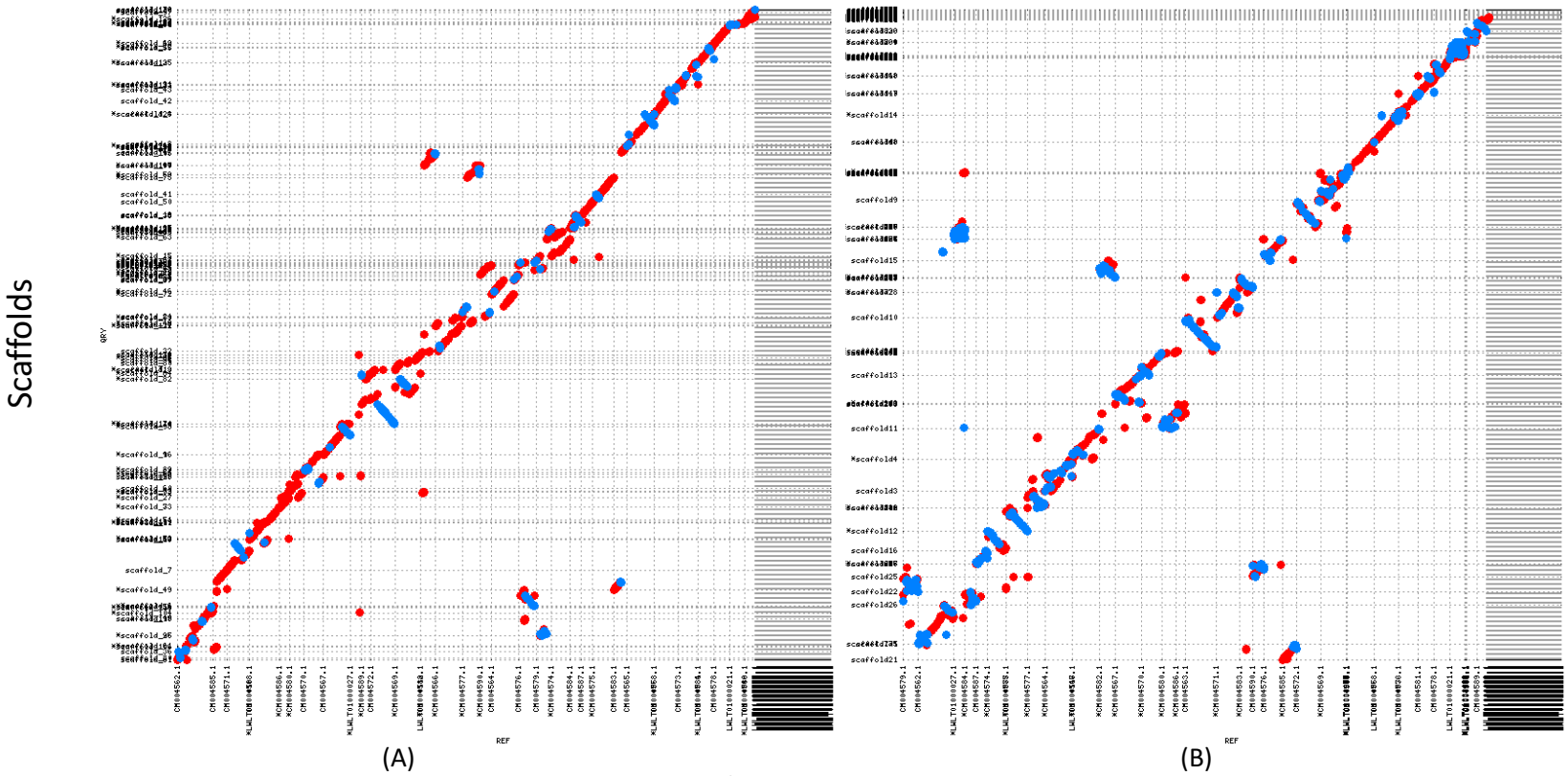
Result – NA19240 : Pacbio + HiC

Feature	Value
#Contigs	3242
Contig NG50	23.98 Mb
# Scaffolds	118
Scaffold NG50	69.49 Mb
Number of Bases	2789088362 (2.78 Gb)
# chr arms (p and q) covered by single scaffold	26
# chr arms covered by 2 scaffolds	14

Result: Goat – Pacbio + HiC

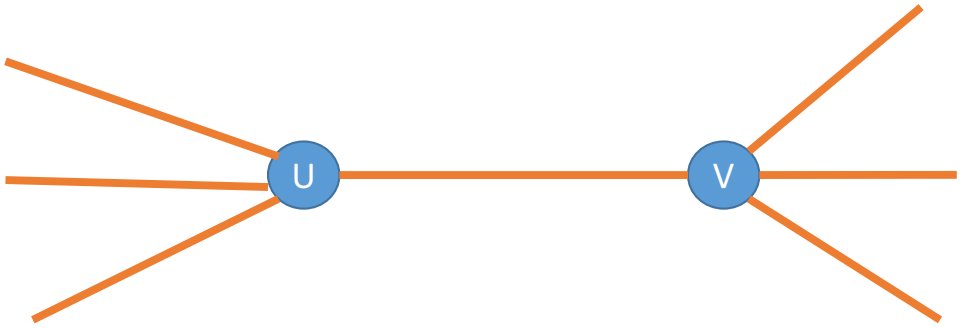
SALSA
365 errors

LACHESIS
1414 errors



SALSA – New Improvements

- Edge weighing Scheme



W(u,v) = RE normalized edge score for edge u,v

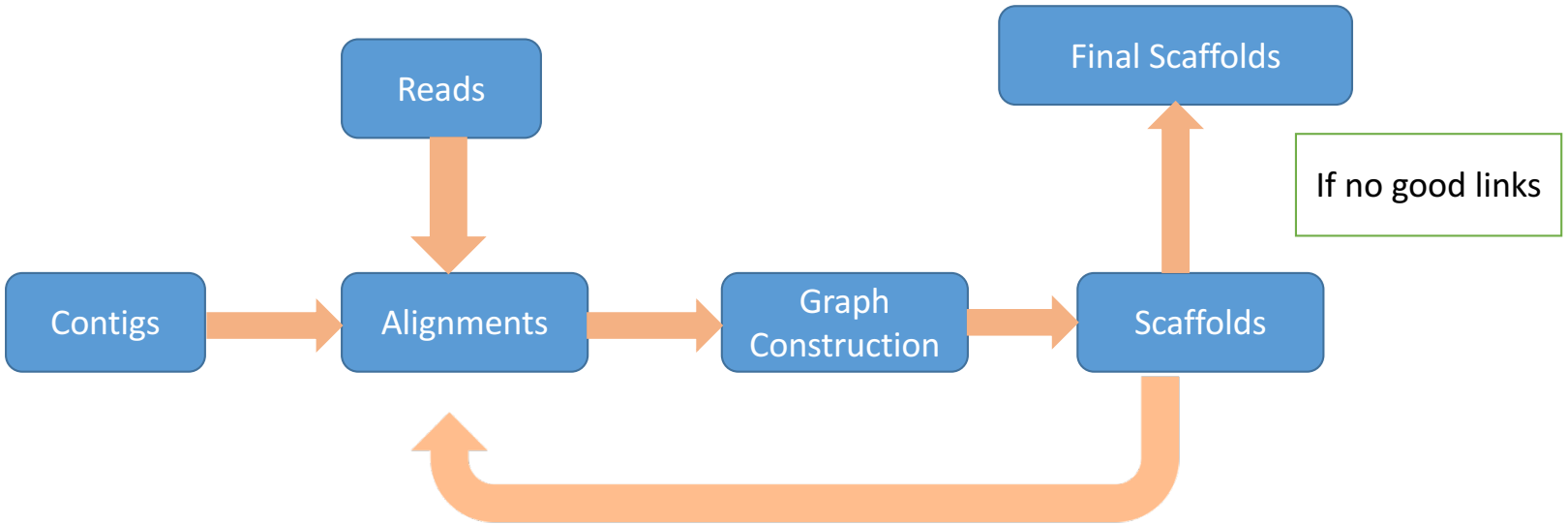
W(u,u1) = max weighted incident edge on u

W(v,v2) = max weighted incident edge on v

W'(u,v) = W(u,v)/ max(W(u,u1), W(v,v2))

SALSA – New Improvements

- Iterative pipeline



Credits: Adam Phillippy

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- Jason Chin
- Sergey Koren
- Adam Phillippy
- Arang Rhie
- Derek Bickhart
- Mihai Pop

SALSA: https://github.com/machinegun/hi-c-scaffold