ScaffHiC – Genome Scaffolding by Modelling Distributions of HiC Paired End Reads

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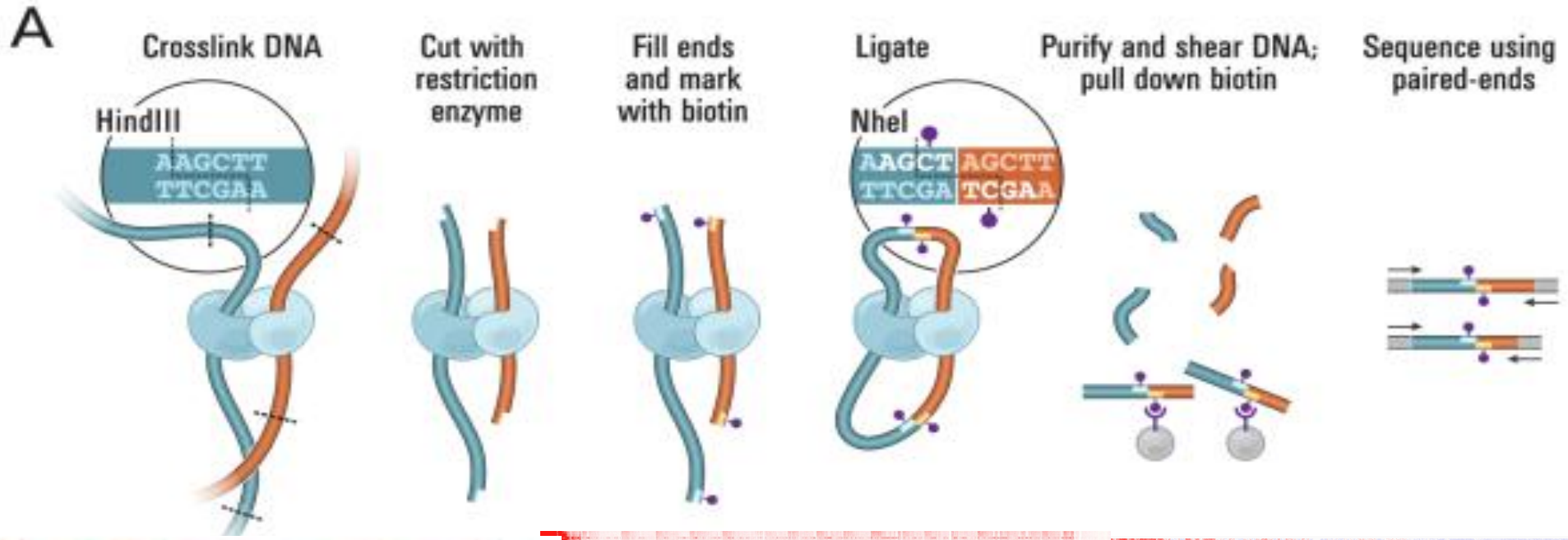
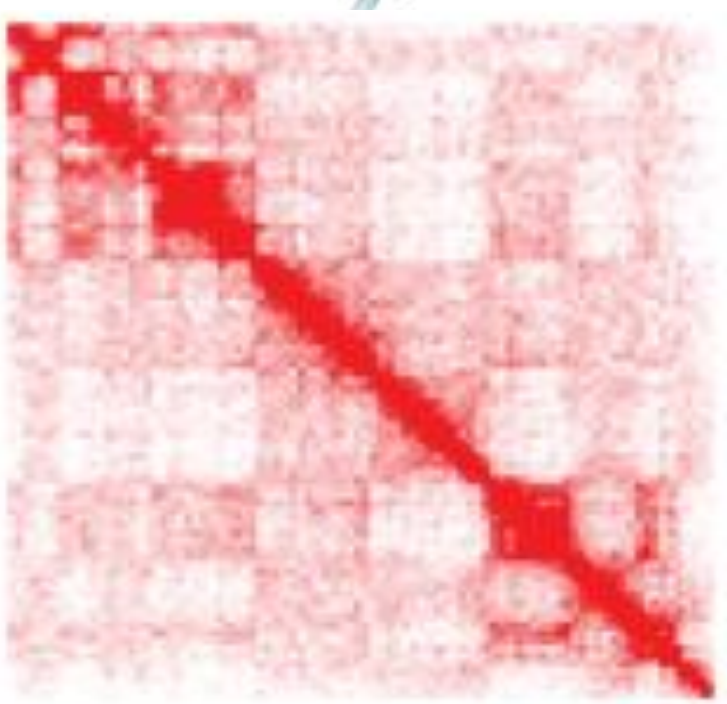
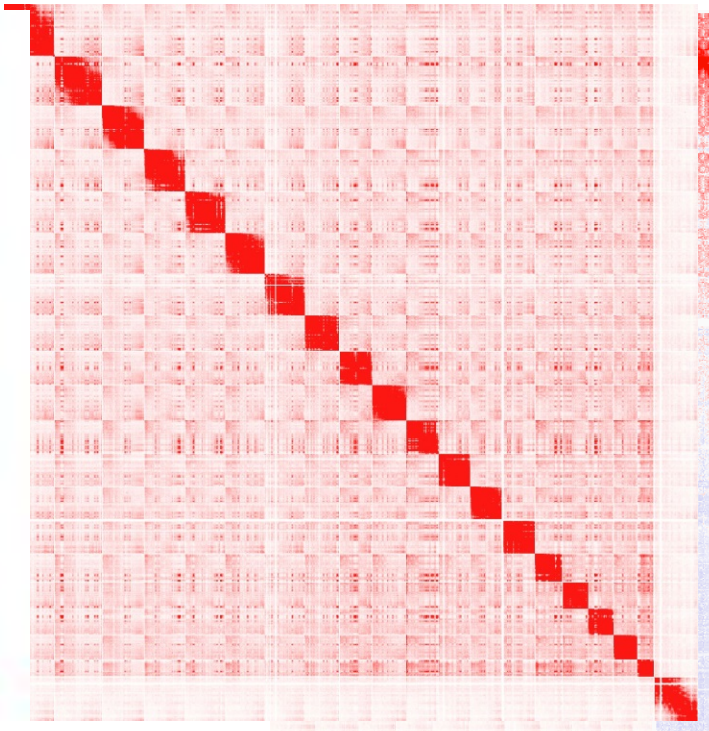
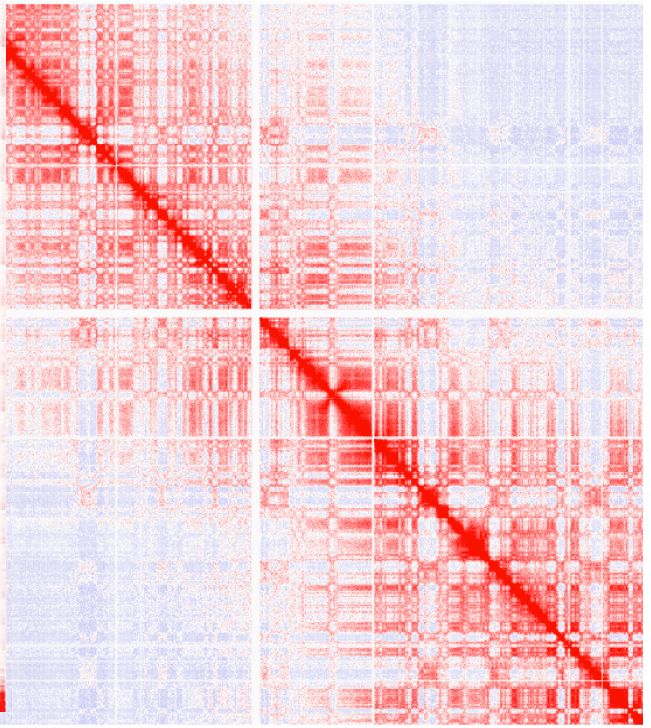
HiC – 3D Genomics

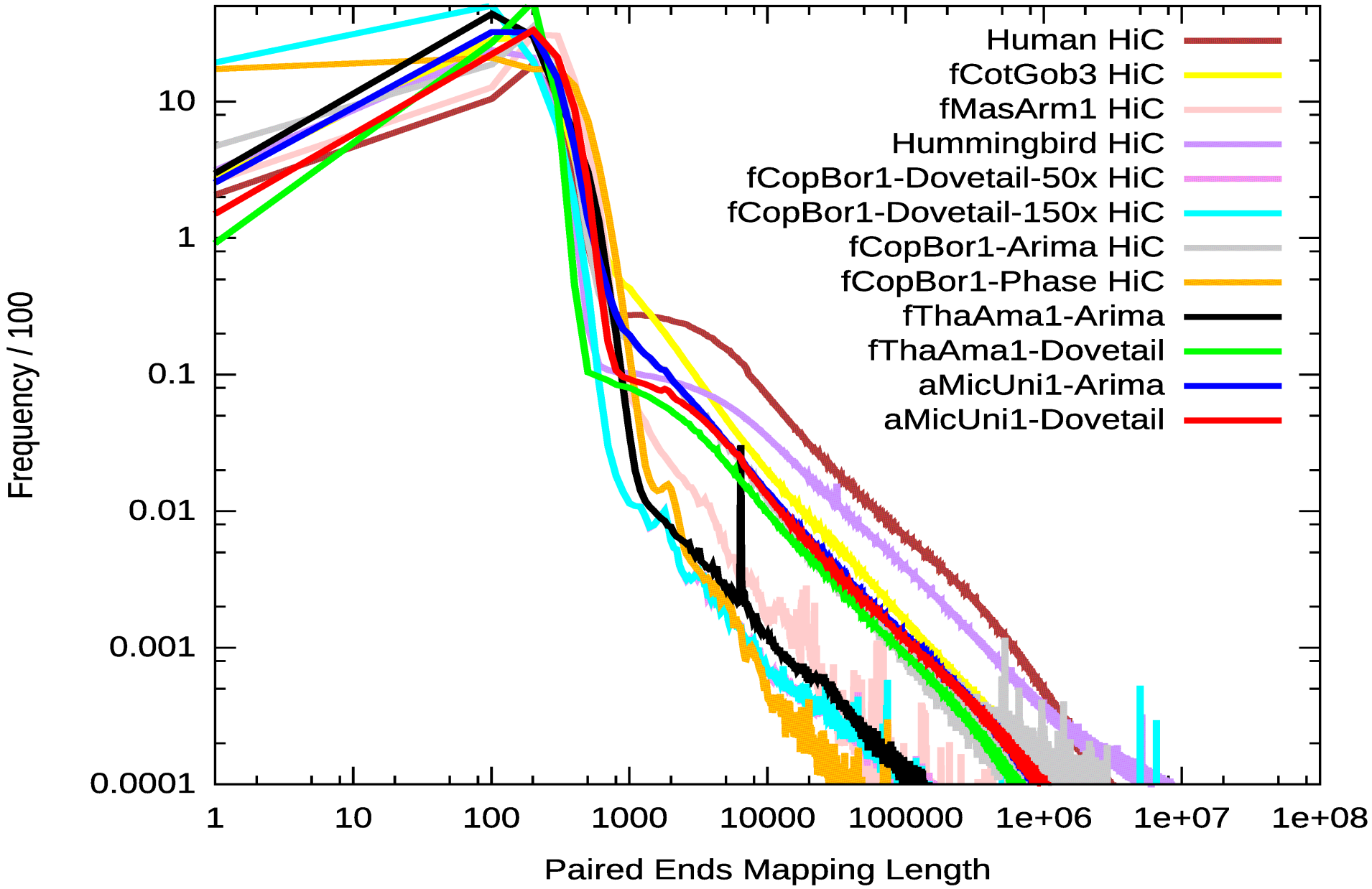




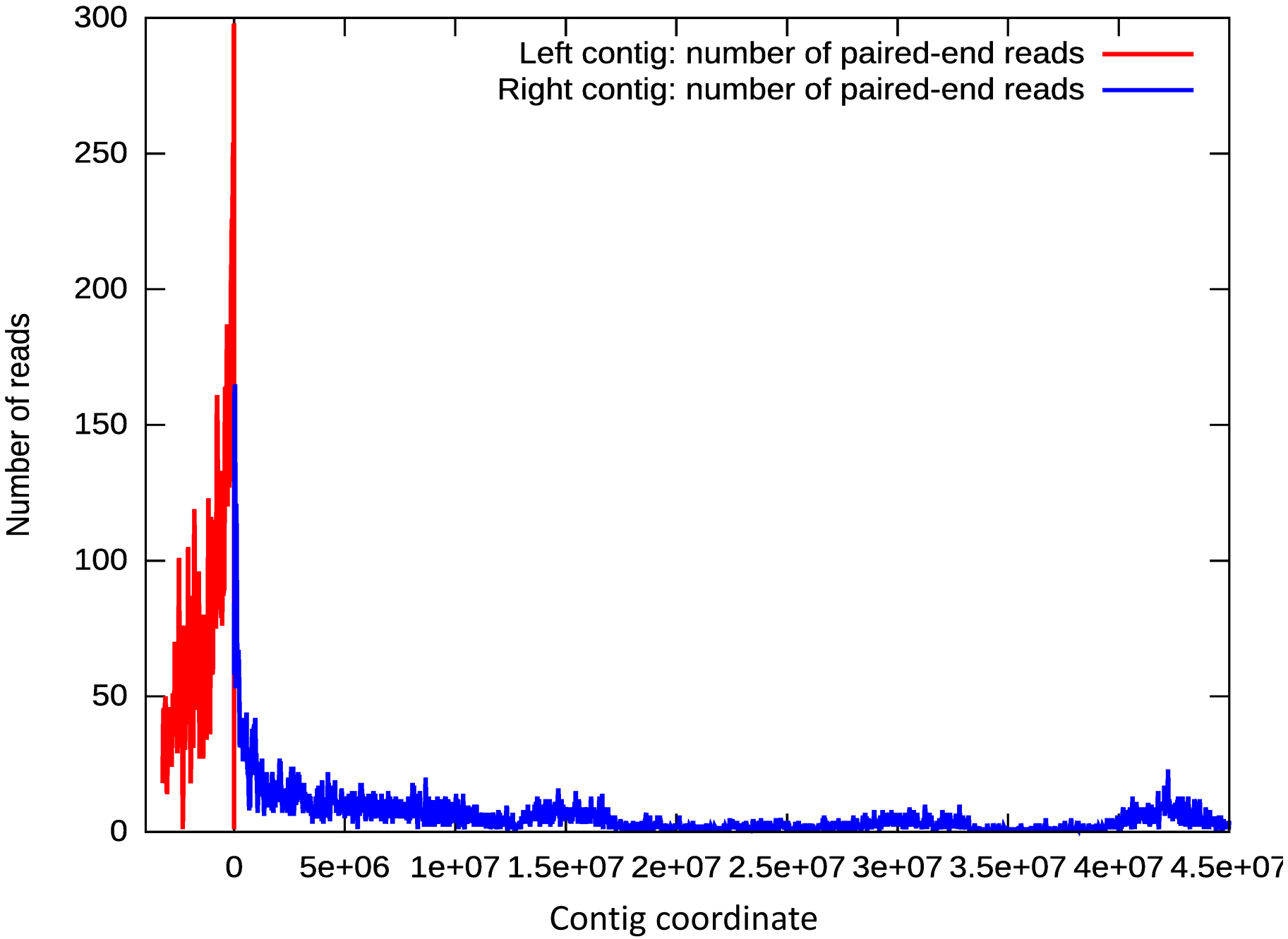




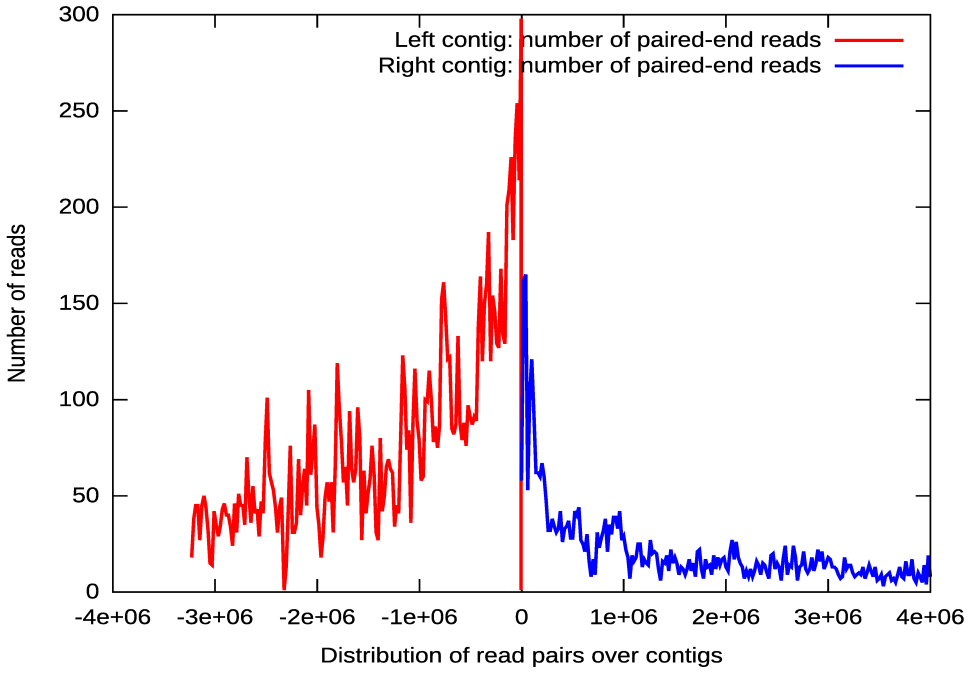
	In_Pairs	Different_Chr	No_hits
Human:	86.0%	13.9%	<0.3 %

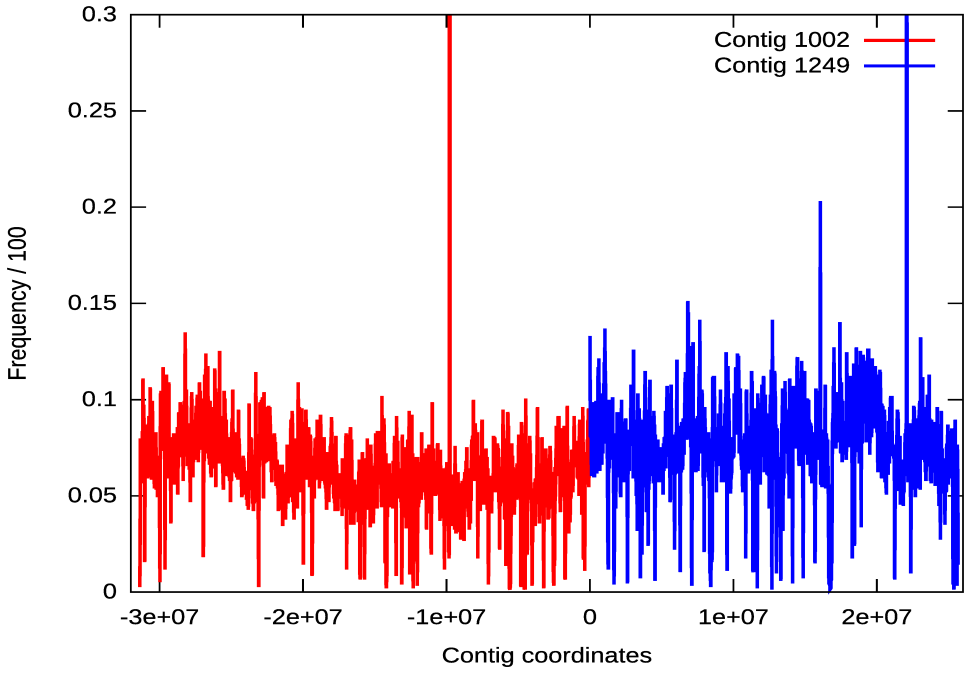


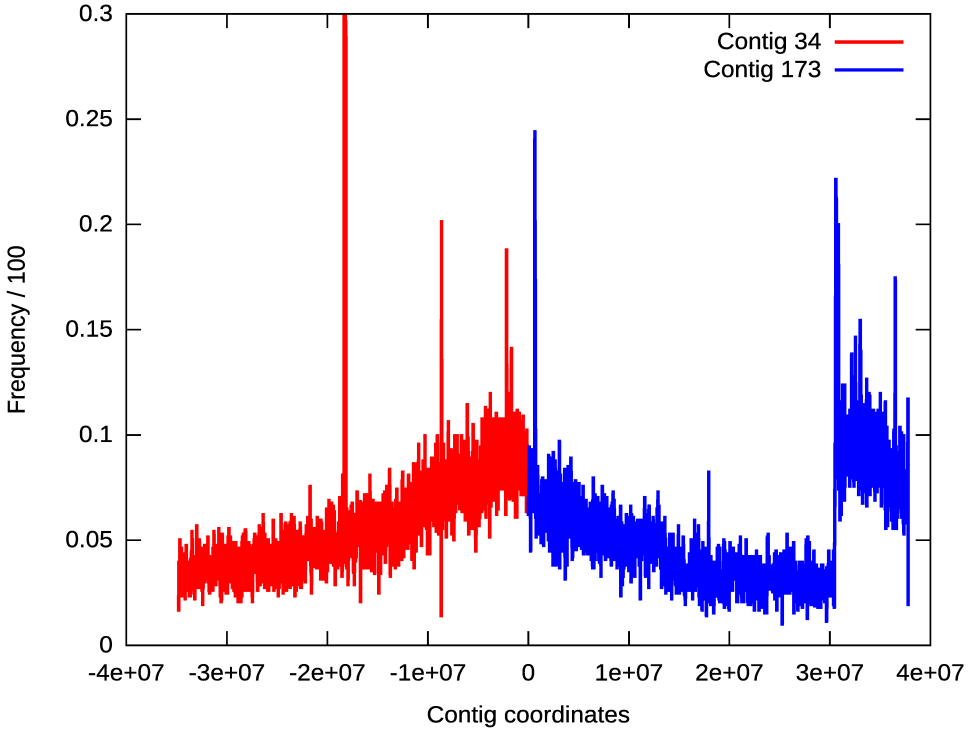
Pair-end Reads Distributions over Contig i and j

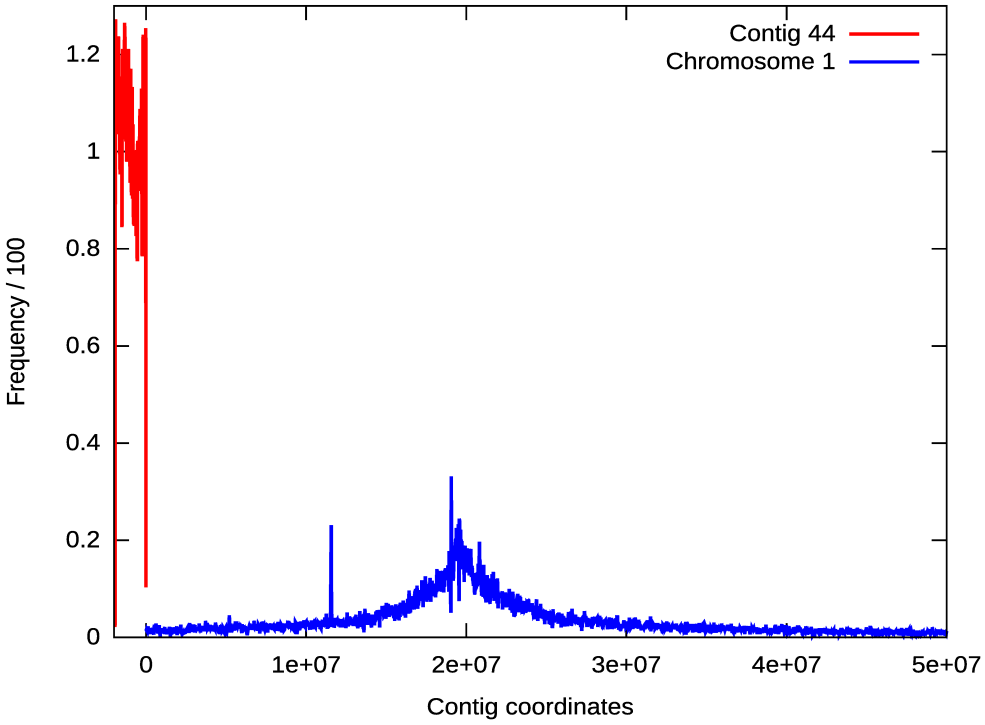


Distribution, Distribution and Distribution



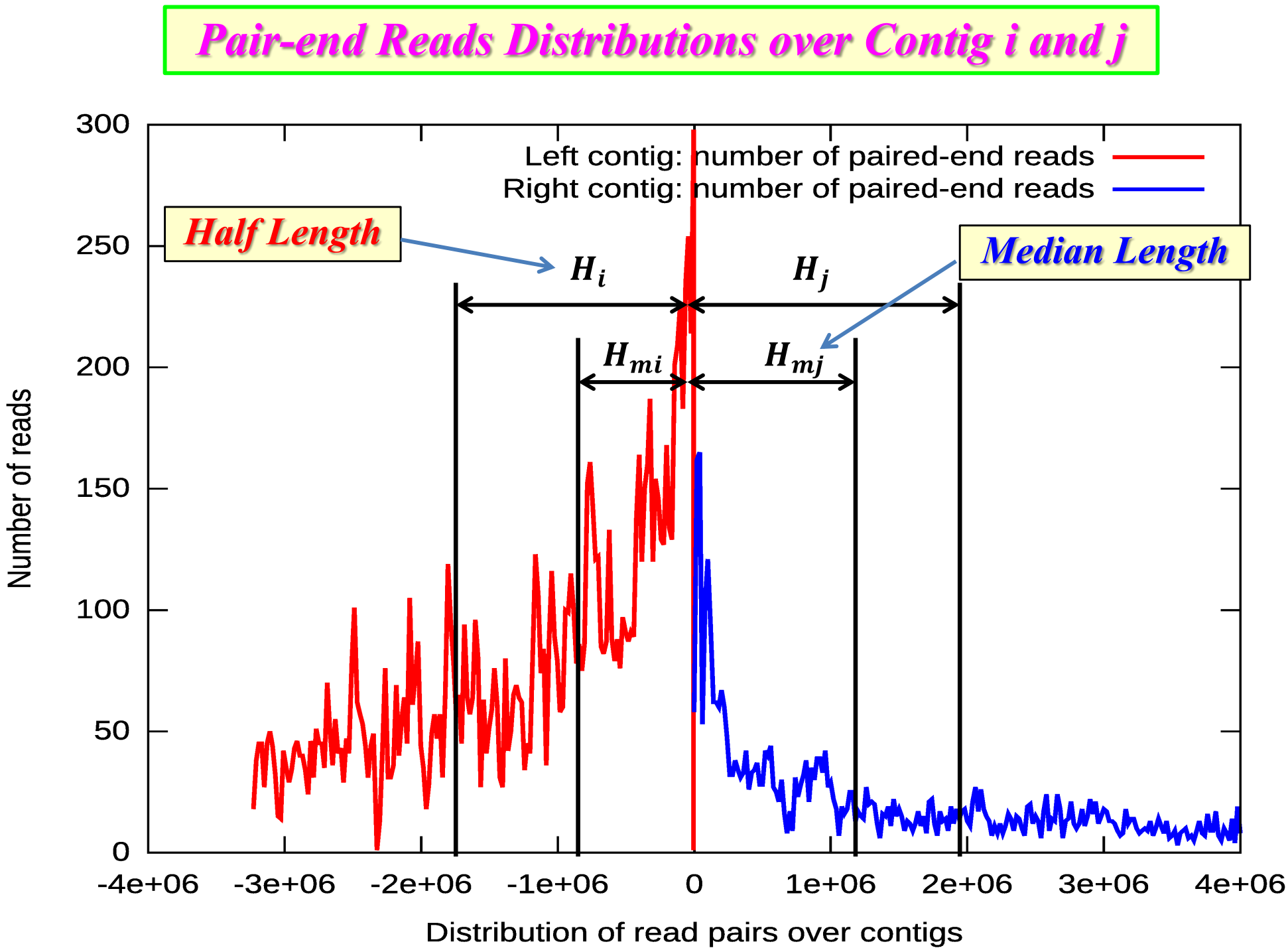






Contact Matrix: C(i,j) – number of paired-end reads between contig i and contig j

	1	2	3	4	5	6	… j …	N
1		4005	200	0	3000	0		
2	4005		870	0	0	0		
3	200	870		0	7400	0		
4	0	0	0		0	13560		
5	3000	0	7400	0			0	
6	0	0	0	13560	0			
i								
N							C(i,j)	


Pair-end Reads Distributions over Contig i and j
Left contig: number of paired-end reads
Right contig: number of paired-end reads
Half Length
Median Length
H_i
H_j
H_{mi}
H_{mj}
Number of reads
Distribution of read pairs over contigs
300
250
200
150
100
50
0
-4e+06
-3e+06
-2e+06
-1e+06
0
1e+06
2e+06
3e+06
4e+06

I_{CD} - Index of Contig Distance i and j

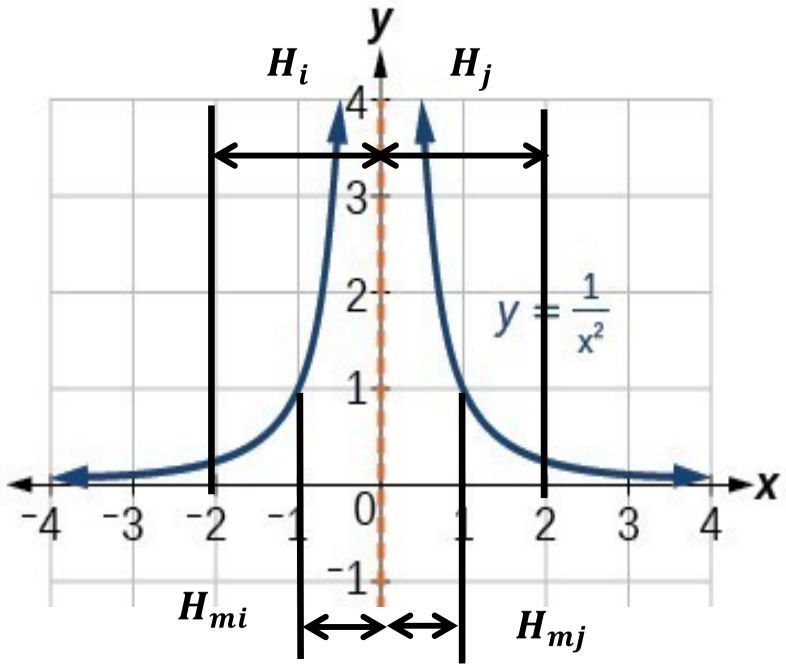
$$I_{CD} = \frac{GN_i}{N_T H_{mi}}\left(\frac{H_i}{H_{mi}} - 1\right) * \frac{GN_j}{N_T H_{mj}}\left(\frac{H_j}{H_{mj}} - 1\right)$$

Where

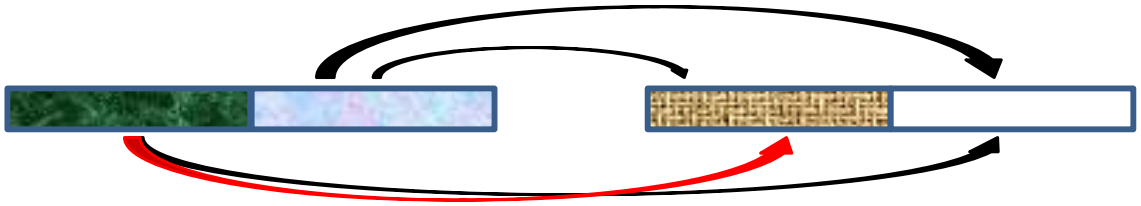
$G - Genome\ size;$
$N_T - Total\ number\ of\ read\ pairs;$
$N_i - Number\ of\ paired\ ends\ on\ Contig\ i;$
$N_j - Number\ of\ paired\ ends\ on\ Contig\ j;$
$H_i - Half\ length\ of\ Contig\ i;$
$H_j - Half\ length\ of\ Contig\ j;$
$H_{mi} - Median\ length\ of\ Contig\ i;$
$H_{mj} - Median\ length\ of Contig\ j;$

$\frac{H_i}{H_{mi}}\ and \frac{H_j}{H_{mj}} - length\ distribution\ ratio$

When
$H_i \to H_{mi}\ or\ H_j \to H_{mj}\ ,\quad I_{CD} -> 0$
$H_i \gg H_{mi}\ or H_j \gg H_{mj}\ ,\quad I_{CD} -> \infty$



Contig Order and Orientation



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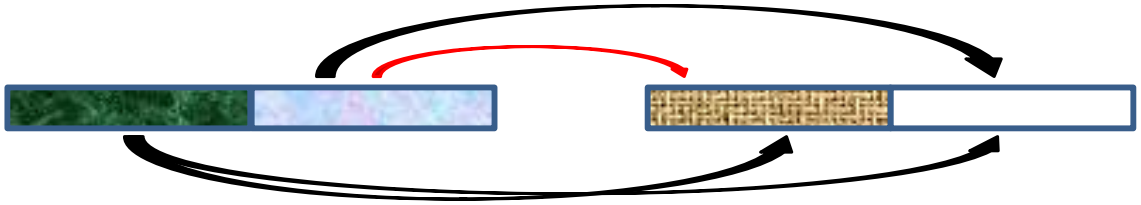

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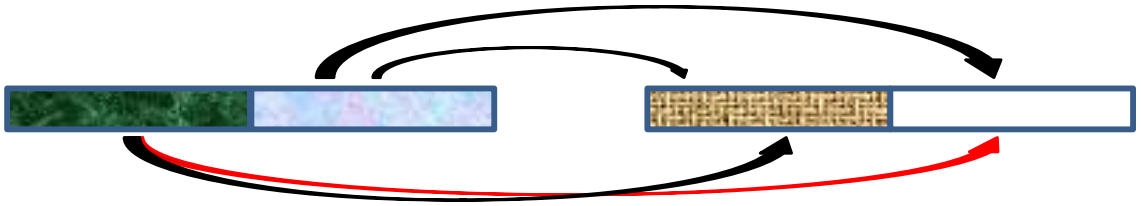

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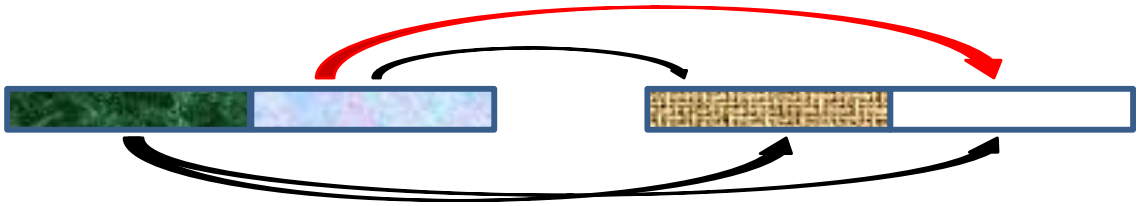

0: 1F-2C

Contig Distance Index Identifies Best Partners

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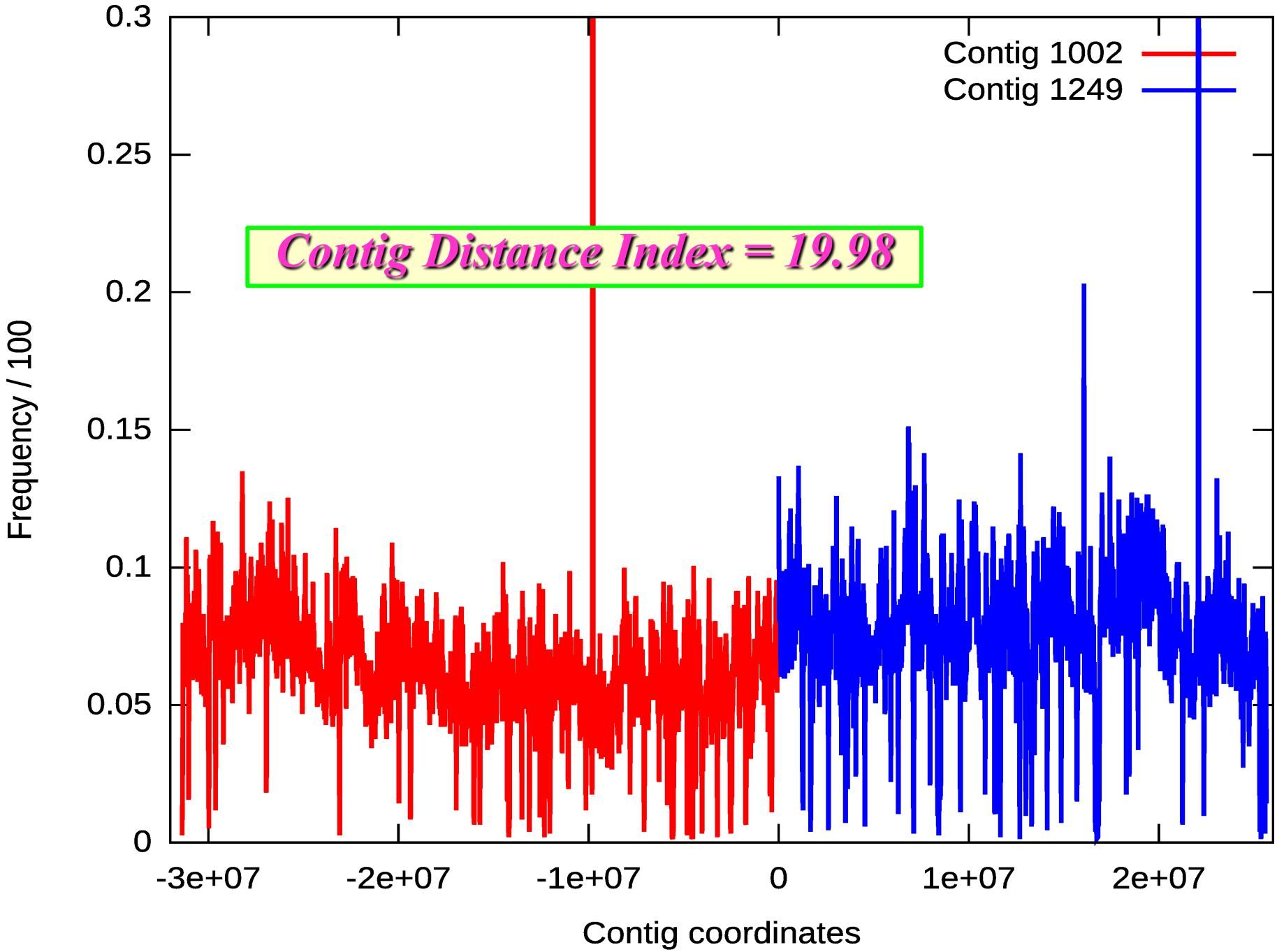
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Contig coordinates

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2926209 |  4288 1297 0 | 2493551 1414241 1.236541 1.034551 | 2.840282 0.874307 2.483277  866 1199  881 1342
2470652 |  3782 1457 1 | 2461134 1185057 1.252828 1.042419 | 2.677610 1.121318 3.002453  780 1206  777 1019
3944518 |  3761 1063 3 | 2880049 1775042 1.070599 1.111106 | 0.743536 1.829376 1.360207 1125 1008  878  750
2516334 |  3447 2 0 | 3066901 1226064 1.005372 1.026184 | 0.051855 0.619390 0.032119  872  807  844  924
3044807 |  3260 1222 3 | 2805927 1301318 1.098880 1.169893 | 0.902666 3.141171 2.835427 1040  898  740  582
2438354 |  3196 272 0 | 2615448 1086565 1.178910 1.122047 | 1.601185 2.762451 4.423197  595  812  801  988
2404967 |  3172 1285 2 | 3065329 1154190 1.005888 1.041842 | 0.052298 0.952992 0.049839  747  790  847  788
2425694 |  3160 420 1 | 3068889 1096689 1.004721 1.105917 | 0.041775 2.382728 0.099538  840  871  734  715
2828887 |  3092 1087 3 | 3073616 1338280 1.003176 1.056911 | 0.027497 1.074184 0.029537  820  810  734  728
1904542 |  2875 433 1 | 2805822 894892 1.098921 1.064118 | 0.796394 1.671428 1.331114  748  819  591  717
2202572 |  2824 408 1 | 2899636 1027032 1.063367 1.072300 | 0.501104 1.600767 0.802151  707  795  632  690
2351542 |  2767 1359 0 | 2503130 1032689 1.231809 1.138553 | 1.796138 2.815333 5.056726  511  669  601  986
mapp: 1 1124 518 20736 || 3458.791504 1 0 1.651331 1.349721
mapp: 2 1124 940 116654 || 2254.821777 2 0 1.231467 1.221592
```

Partners and Partnership

(1) A partnership is unique;

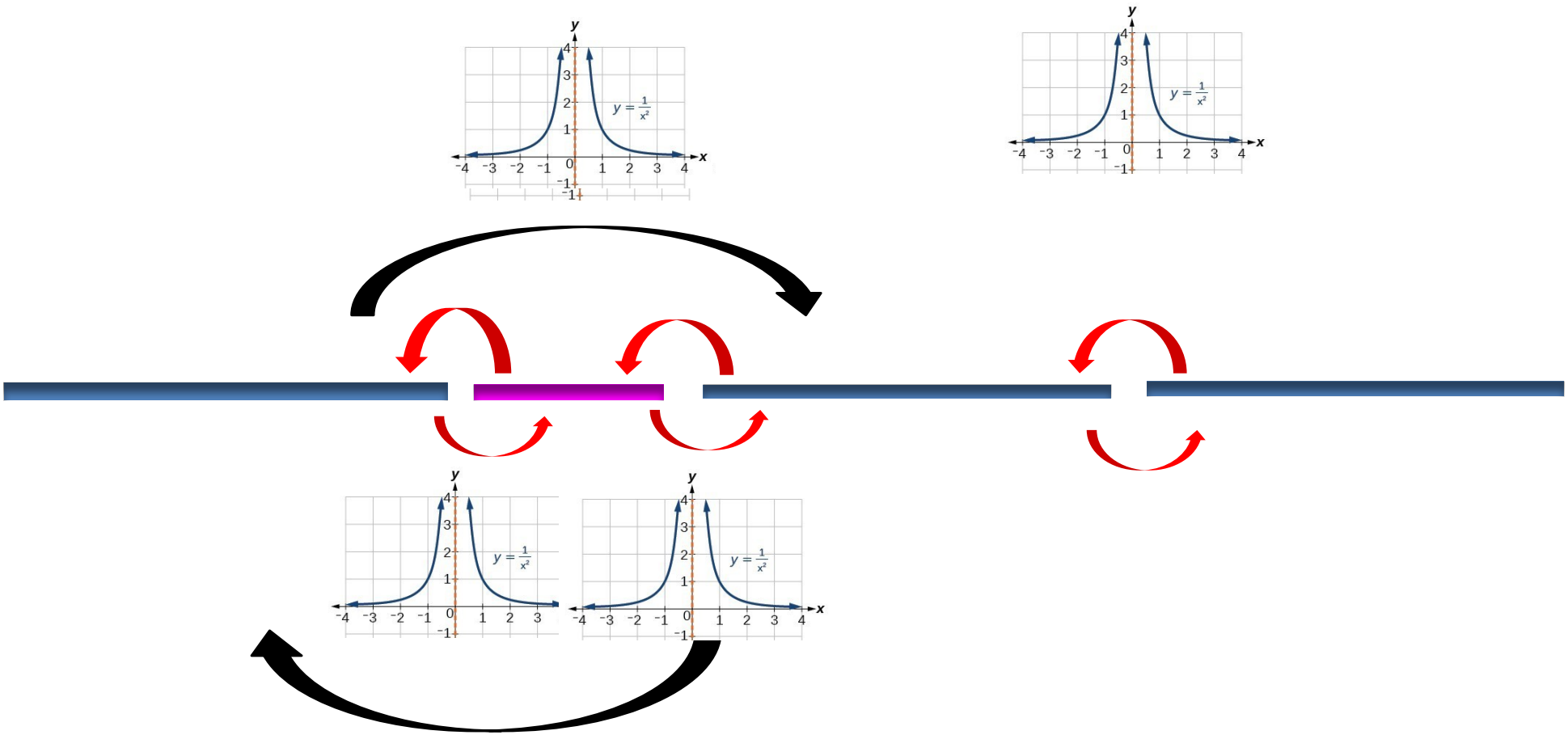
(2) Each partner is independent;

(3) Establishment of a partnership is determined by the willingness of both sides:

(a) Unique mutual best partner

(b) Select partner with a criteria when there are choices

Re-adjust the Best Partner



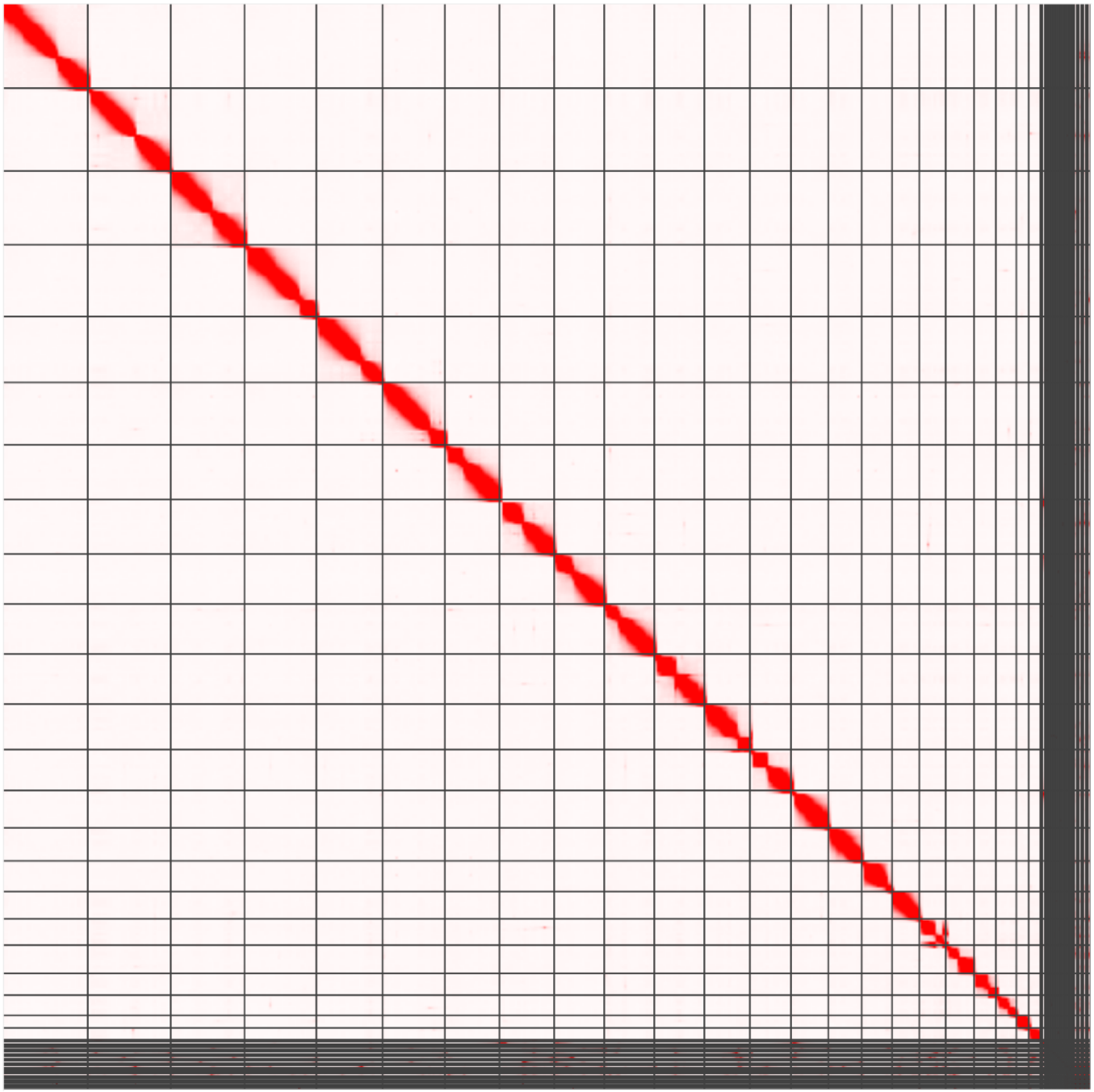
1 2 3 4

Partner Matrix: P(i,j) – number of paired-end reads between contig i and contig j

	1	2	3	4	5	6	… j …	N
1		$P_{1,2}$	0	0	0	0		
2	$P_{2,1}$		$P_{2,3}$	0	0	0		
3	0	$P_{3,2}$		0	$P_{3,5}$	0		
4	0	0	0		0	$P_{4,6}$		
5	0	0	$P_{5,3}$	0		0		
6	0	0	0	$P_{6,4}$	0			
i								
N								

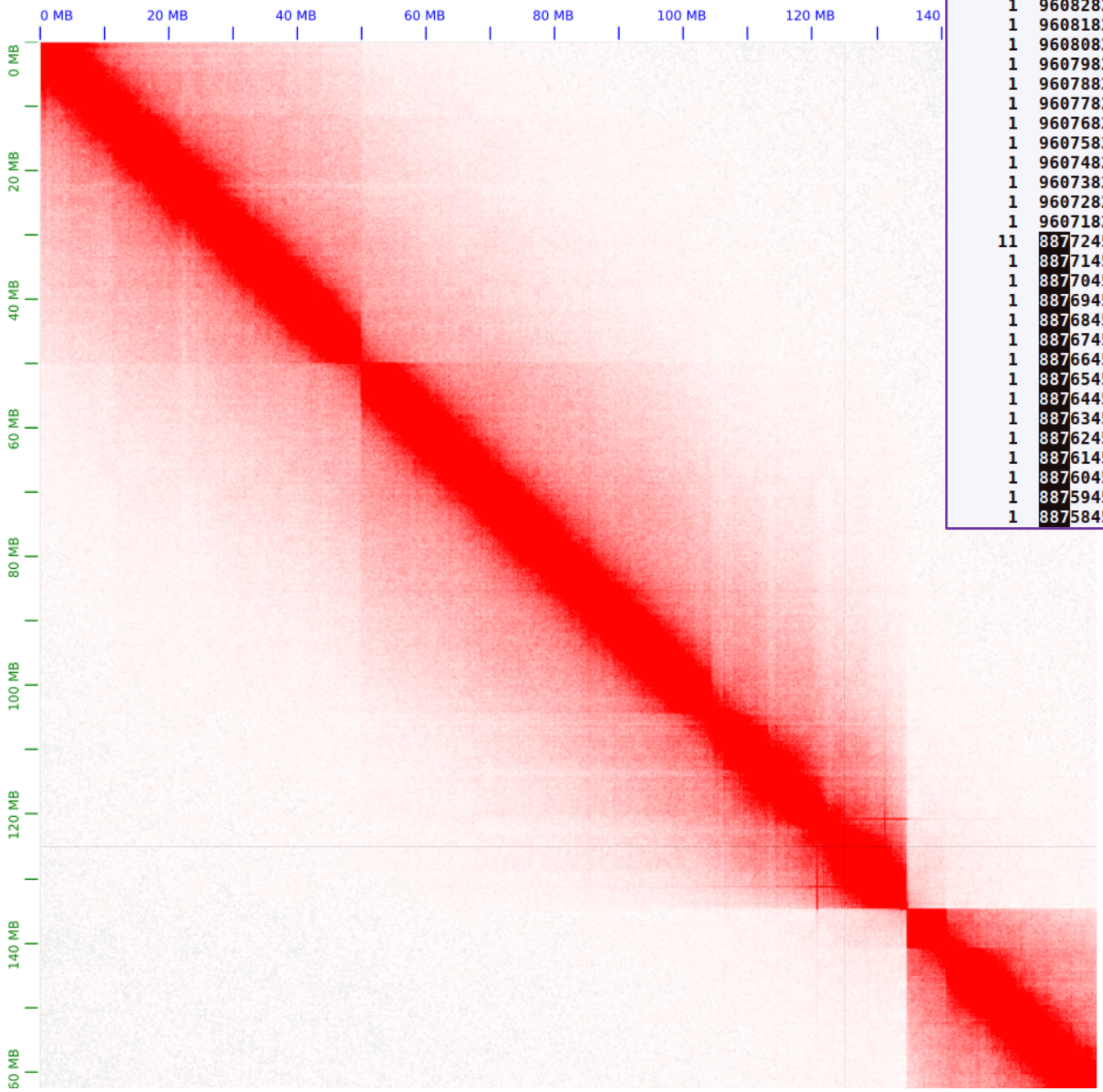
P(i,j)

Human HG002 Assembly



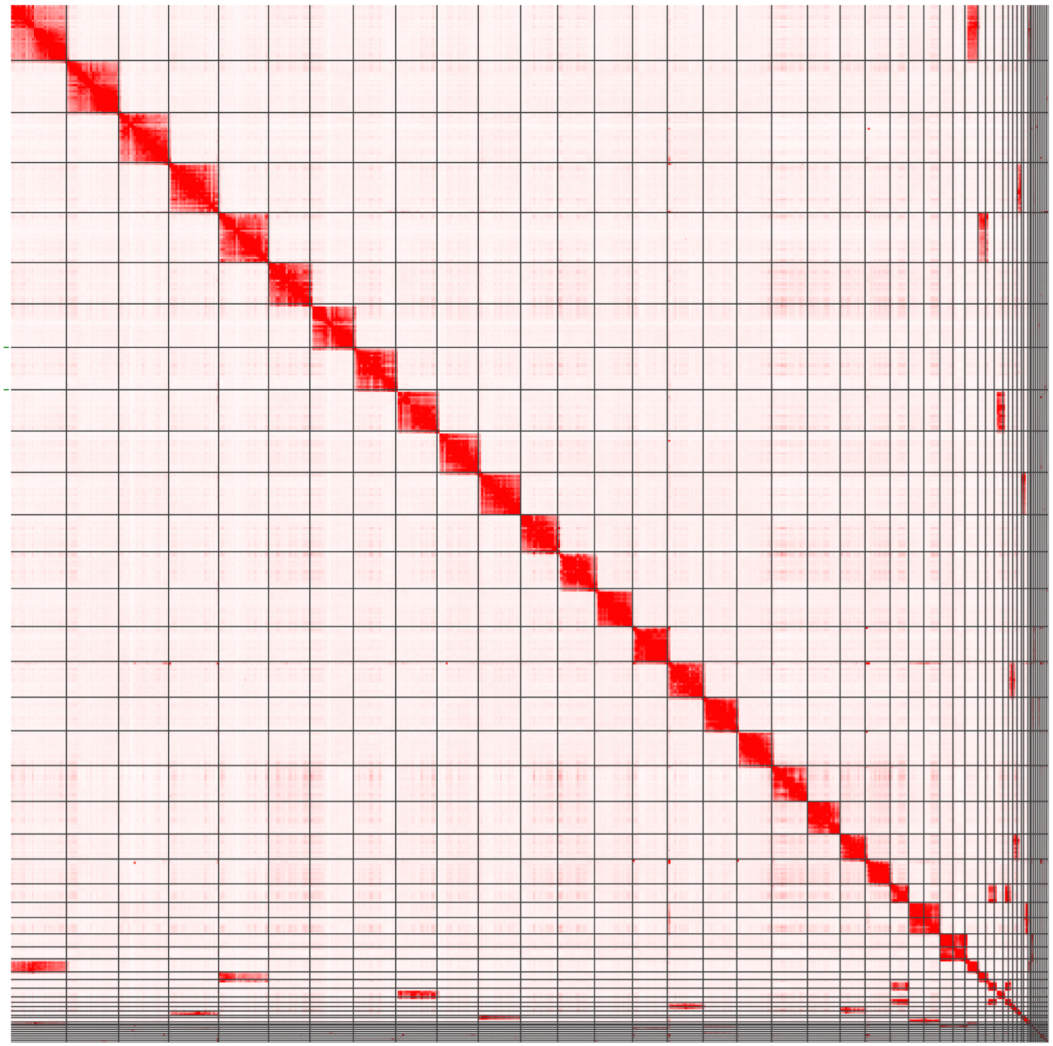
	WTdbg	*ScaffHiC*
Bases (Mb)	2732	2732
Number scaffolds	2213	1762
Scaffold N50 (Mb)	11.2	134
Scaffold N90 (Mb)	1.4	58
Max scaffold (Mb)	71.7	218

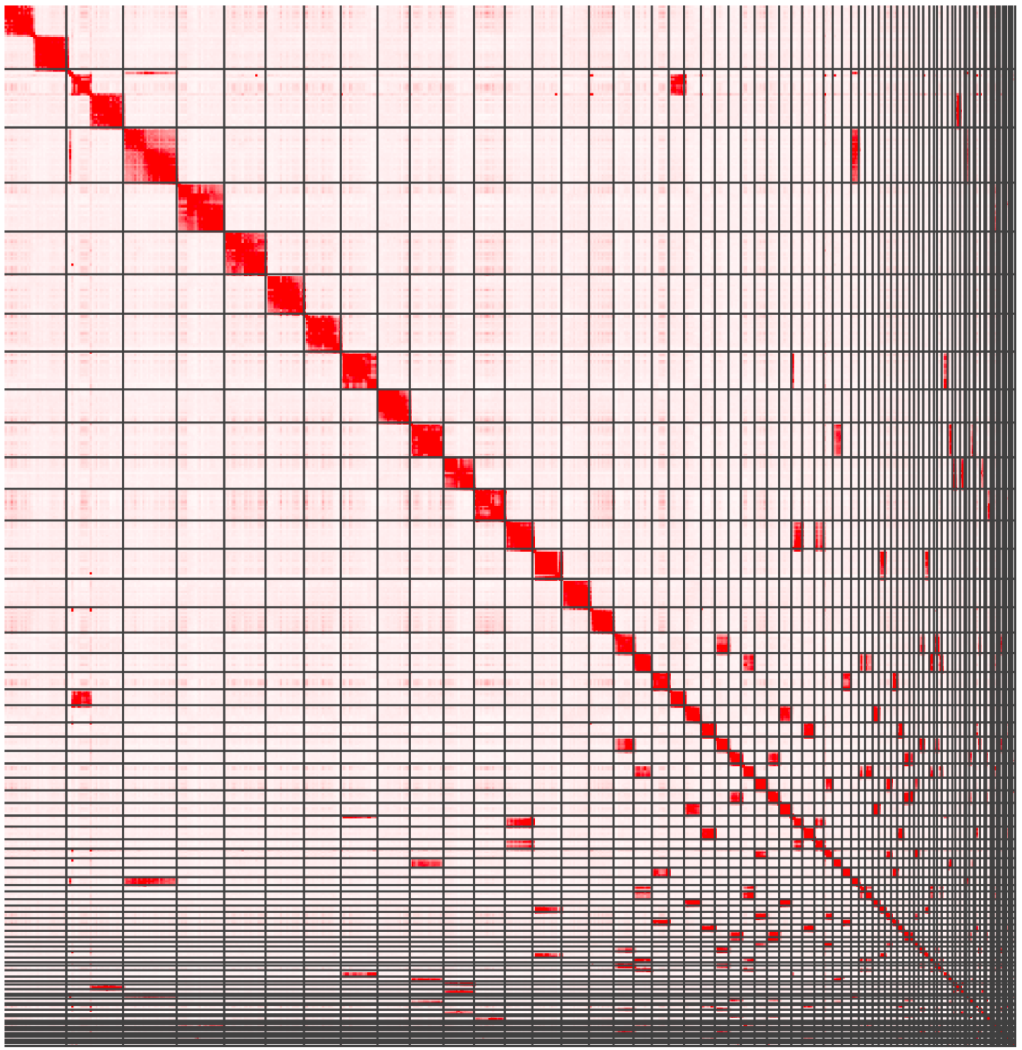
Chromosome 2



1	96086954	96087969	C	999	98.33	1000 242193529
1	96085954	96086953	C	1000	100.00	1000 242193529
1	96085250	96085953	C	704	100.00	1000 242193529
1	96083823	96084822	C	1000	100.00	1000 242193529
1	96082823	96083822	C	1000	100.00	1000 242193529
1	96081823	96082822	C	1000	100.00	1000 242193529
1	96080823	96081822	C	1000	100.00	1000 242193529
1	96079823	96080822	C	1000	100.00	1000 242193529
1	96078823	96079822	C	1000	100.00	1000 242193529
1	96077823	96078822	C	999	99.90	1000 242193529
1	96076823	96077822	C	1000	100.00	1000 242193529
1	96075823	96076822	C	1000	100.00	1000 242193529
1	96074823	96075822	C	1000	100.00	1000 242193529
1	96073823	96074822	C	1000	100.00	1000 242193529
1	96072823	96073822	C	999	99.90	1000 242193529
1	96071823	96072822	C	1000	100.00	1000 242193529
11	88772456	88773445	C	789	79.70	1000 242193529
1	88771456	88772455	C	1000	100.00	1000 242193529
1	88770455	88771455	C	1000	99.90	1000 242193529
1	88769455	88770454	C	1000	100.00	1000 242193529
1	88768455	88769454	C	999	99.90	1000 242193529
1	88767455	88768454	C	1000	100.00	1000 242193529
1	88766455	88767454	C	1000	100.00	1000 242193529
1	88765455	88766454	C	1000	100.00	1000 242193529
1	88764455	88765454	C	1000	100.00	1000 242193529
1	88763455	88764454	C	1000	100.00	1000 242193529
1	88762455	88763454	C	999	99.90	1000 242193529
1	88761455	88762454	C	1000	100.00	1000 242193529
1	88760455	88761454	C	1000	100.00	1000 242193529
1	88759455	88760454	C	1000	100.00	1000 242193529
1	88758454	88759454	C	1000	99.90	1000 242193529

fSclFor1: ScaffHiC vs Salsa2

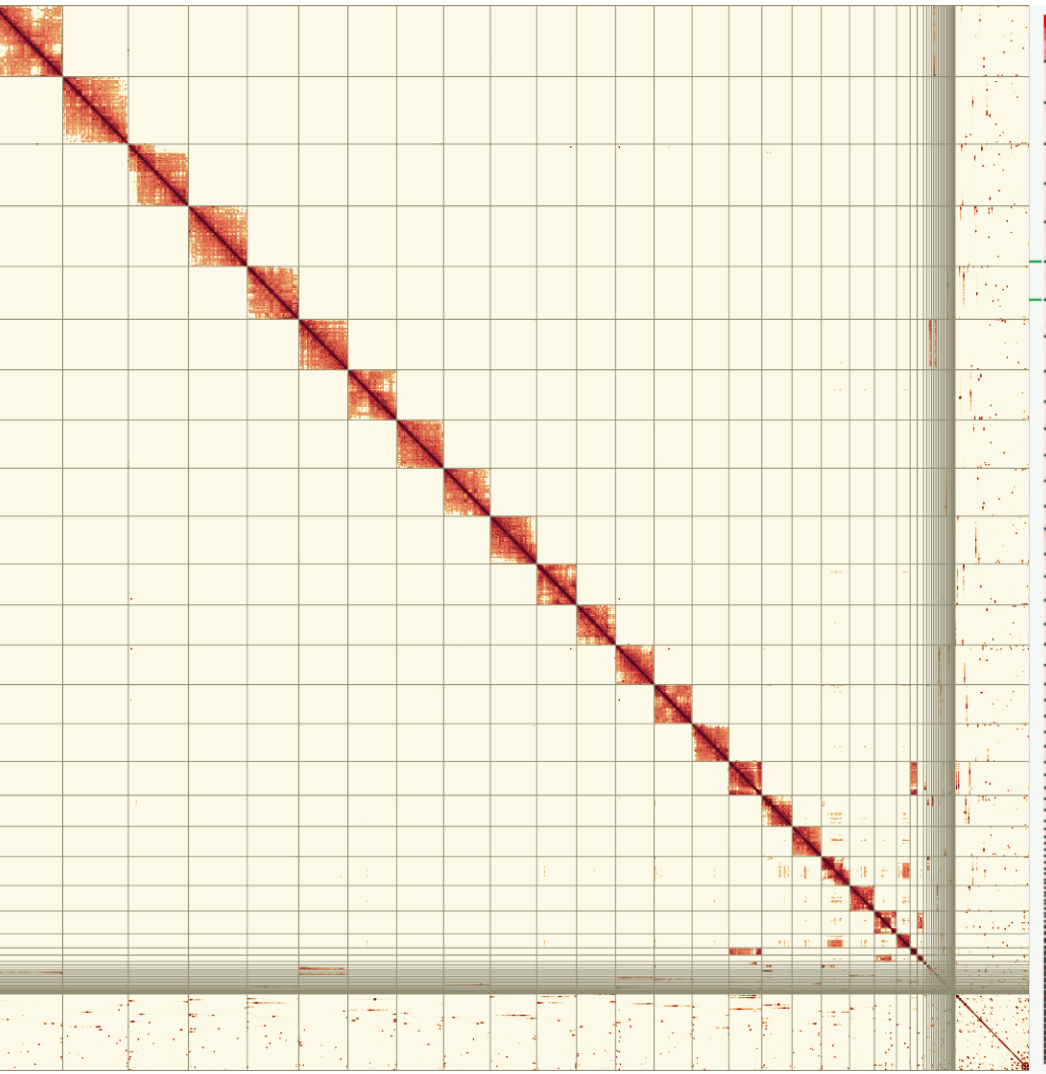


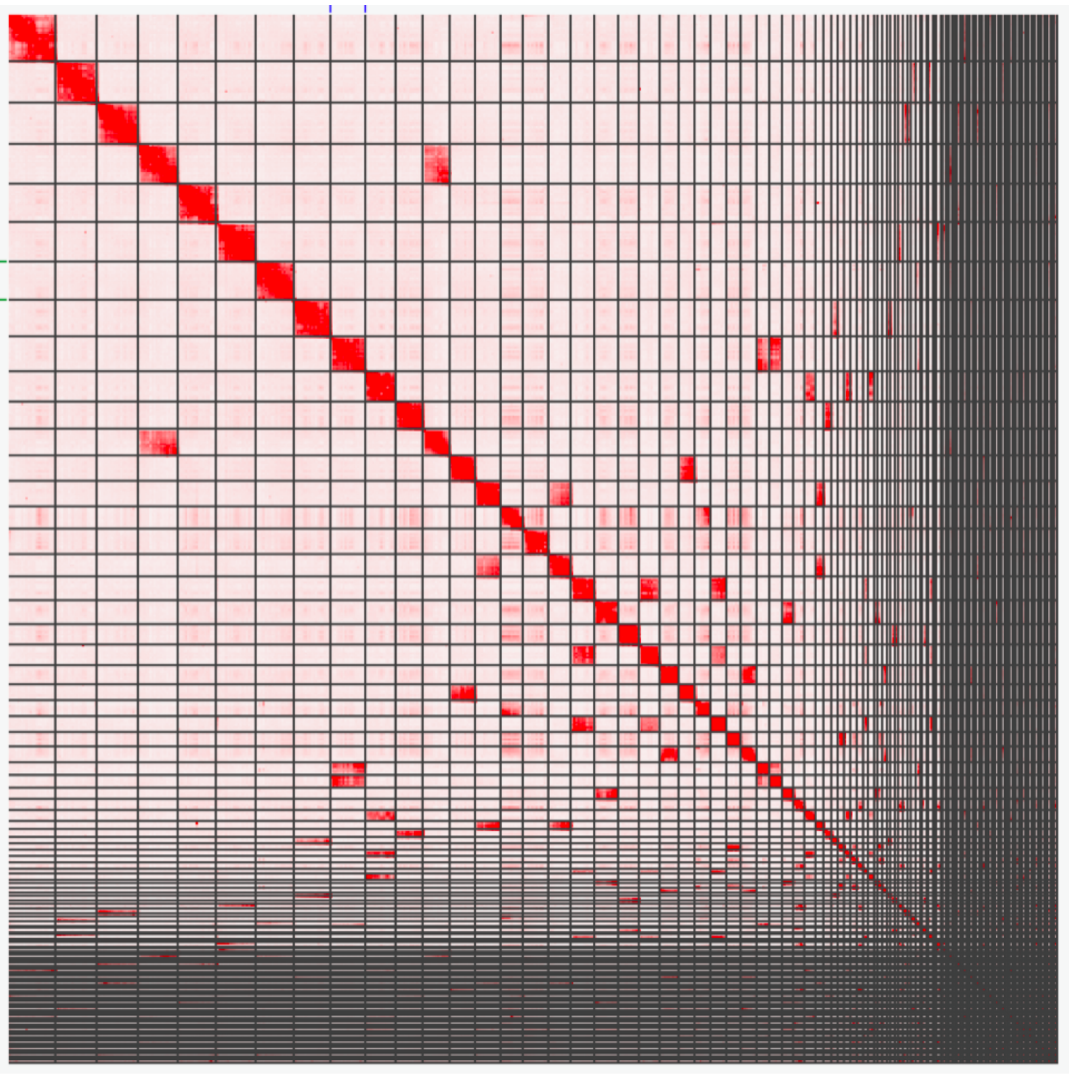


```
========
ScaffHiC
========
sum = 785500277, n = 123, ave = 6386181
      largest = 43024501
N50 = 29668867, n = 12
N60 = 27165132, n = 15
N70 = 25967964, n = 18
N80 = 19888780, n = 21
N90 = 10321926, n = 26
N100 = 2021, n = 123
```

```
======
SALSA2
======
sum = 785521263, n = 123, ave = 6386351
      largest = 50076388
N50 = 22561231, n = 13
N60 = 18658253, n = 16
N70 = 11901779, n = 22
N80 = 8474493, n = 31
N90 = 4017783, n = 45
N100 = 23590, n = 123
```

fThaAma1: ScaffHiC vs Salsa2





Summary

- ***The Contig Distance Index based on empirical mathematical modelling works well and there are hardly any trans-chromosome errors***
- ***It is possible to generate chromosome level and error free human genome assemblies***
- ***More work is need to sort out intra-chromosome rearrangements***
- ***PacBio, 10X, Bionano and HiC:***

Do we need all 4 data types?

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Phase Genomics