Haplotype assembly in dipSPAdes

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dipSPAdes

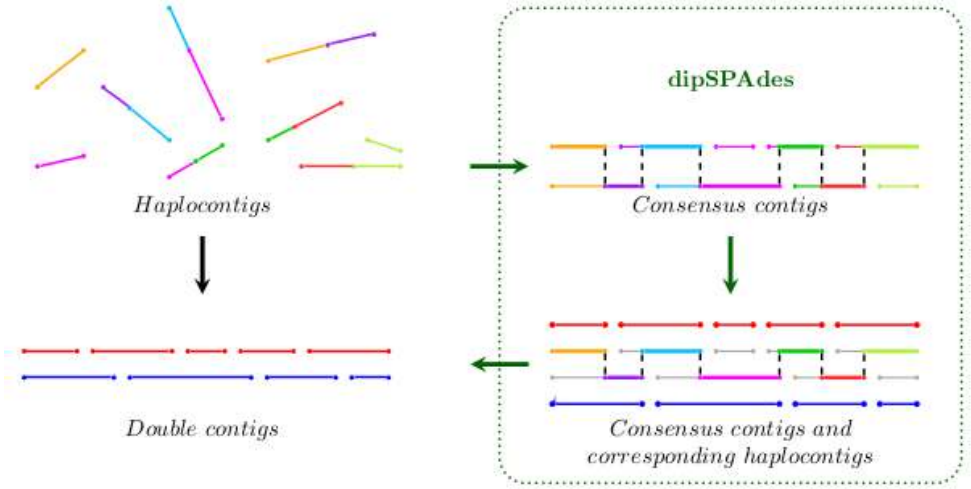
dipSPAdes is a new algorithm (and a tool) for assembling HP genomes that was developed at the Algorithmic Biology Lab (St. Petersburg University of the RAS).

It generates both consensus contigs and haplocontigs using de Bruijn graph.

http://bioinf.spbau.ru

Yana Safonova, Anton Bankevich, Pavel A. Pevzner. dipSPAdes: an assembler for highly polymorphic diploid genomes. In Sharan, Roded (eds.) RECOMB 2014, LNCS (8394), pp. 265–279. Springer, Heidelberg (2014). http://link.springer.com/chapter/10.1007/978-3-319-05269-4_21

dipSPAdes pipeline



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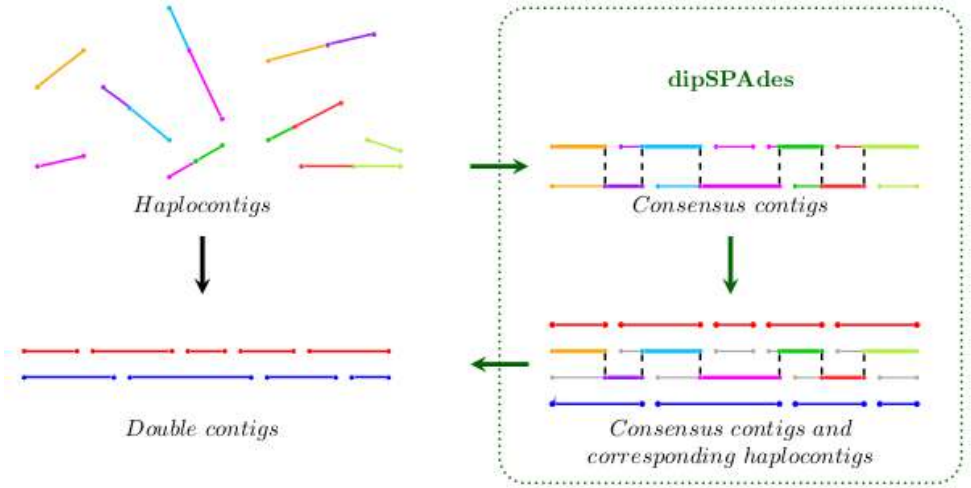

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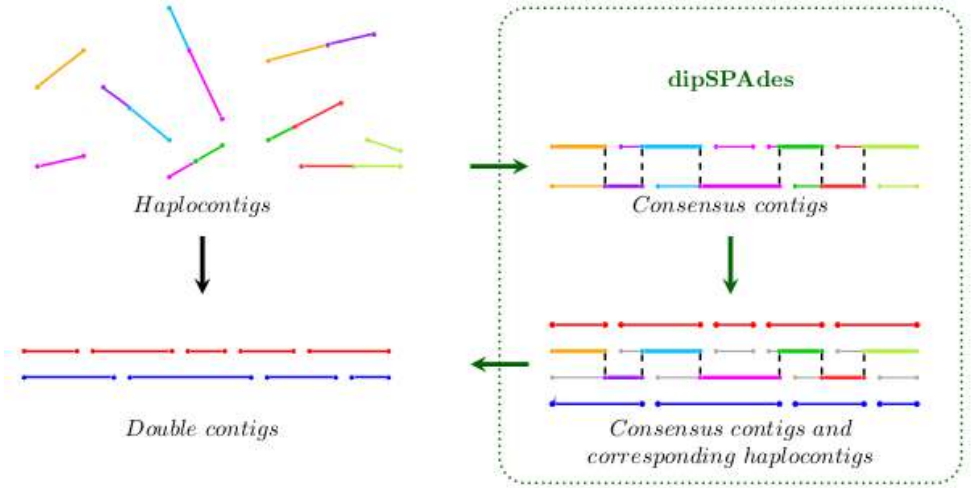

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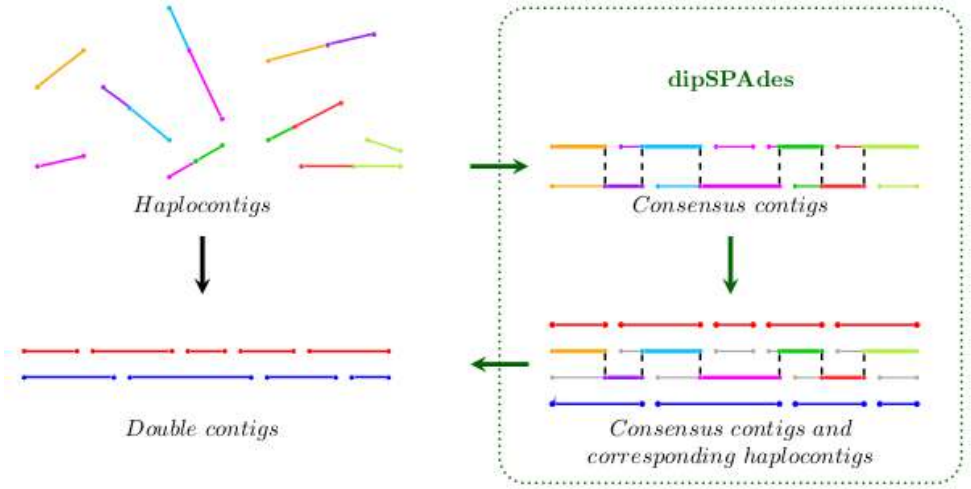

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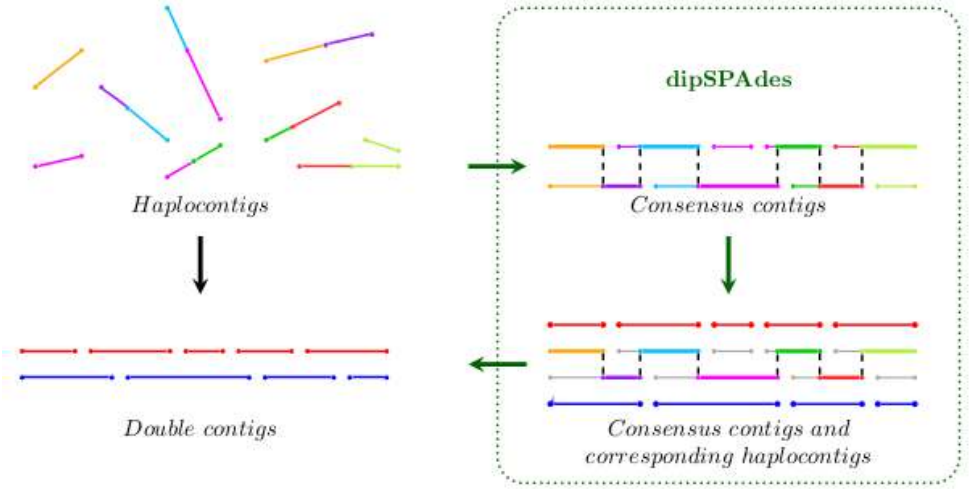

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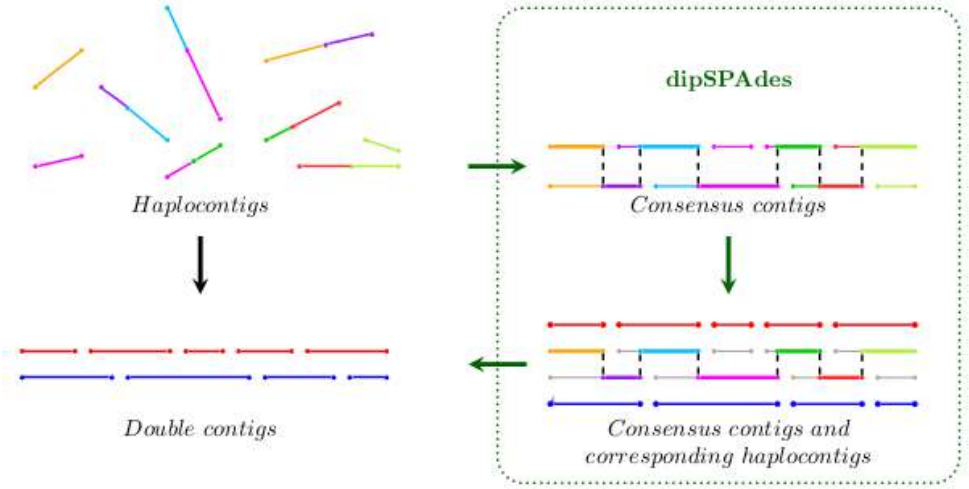

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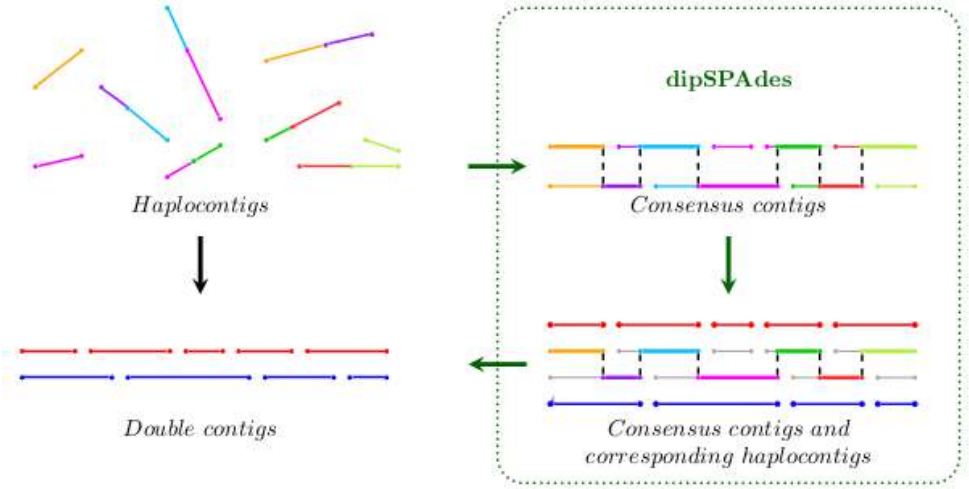
5. Haplocontigs resolutions.



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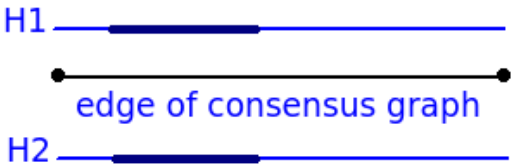
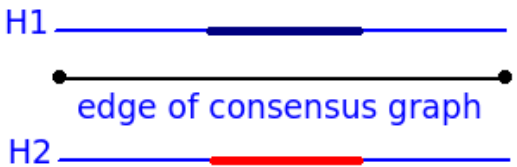
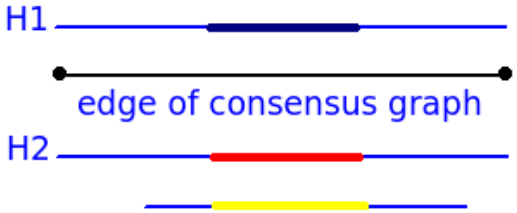
Problem (with haplotype assembly)



(conservative region)



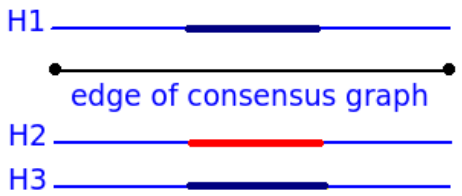
(H1 and H2 are from different haplomes)



(repeat?)

Project goals

1. Find out what mistakes dipSPAdes makes during the haplotype assembly.
2. Improve haplocontigs resolution and filtrate short haplocontigs with repeats.
3. Design a method for assembly of haplomes from resolved homologous haplocontigs.



(H1 and H3 are from the same haplome)

Result 1

Pipeline for simulation of diploid datasets with known haplomes (based on a bunch of Python scripts):

- haplomes: first 100 Kbp from *E. coli* reference genome (GenBank: U00096.2) and its copy with 10 % of nucleotides randomly changed;
- from the two haplomes paired-end reads 100 bp long were ‘cutted’ with 50x average coverage and 250 bp insert size;
- reads obtained were assembled into haplocontigs with SPAdes (*-k 15 --diploid --only-assembler* options).

Reads from different haplomes can be stored in different FASTA files or in the same FASTA file.

Result 2

Detection of SPAdes erroneous behavior: it may produce not only haplocontigs (as expected) but *chimeric contigs* too (contigs that contain polymorphic regions from both haplomes).

So we proceed to simulation of an ‘ideal’ haplocontigs assembly (we assembled reads from each haplome separately).

Result 3

An idea of haplocontigs resolution improvement and filtration of haplocontigs with repeats:

- construct a bipartite *conflict graph* where vertices are haplocontigs, and they’re connected iff dipSPAdes says that they belong to different haplomes;
- so, for every connected component of the conflict graph we know what haplome each haplocontig belongs to.

Conflict graph

How to construct *bipartite* conflict graph*?*

Algorithm sketch:

- dipSPAdes can provide us with individual edges of the conflict graph;
- we should assign some weight to each edge so that it's big if two haplocontigs belong to different haplomes and small if they belong to one and the same haplome;
- keep adding edges with max weight to the graph until it ceases to be bipartite.

Conflict graph

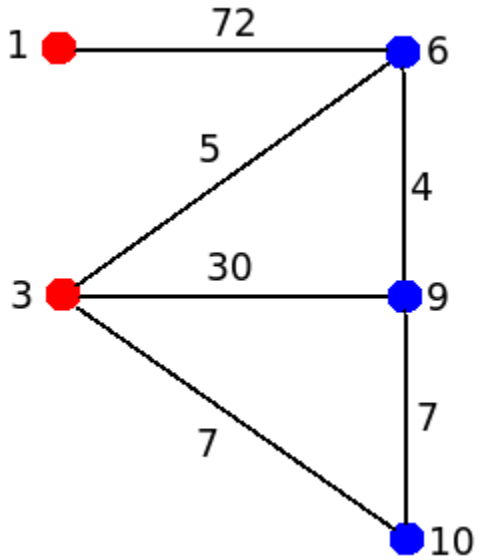
How to assign weights to edges?

The weight is (ideas we tested):

- a number of consensus graph edges on which two haplocontigs have a subsequence in common;
- a total length of consensus graph edges on which two haplocontigs have a subsequence in common;
- a number of bulges and shared edges in diploid graph that two subsequences have in common.

Edge weight

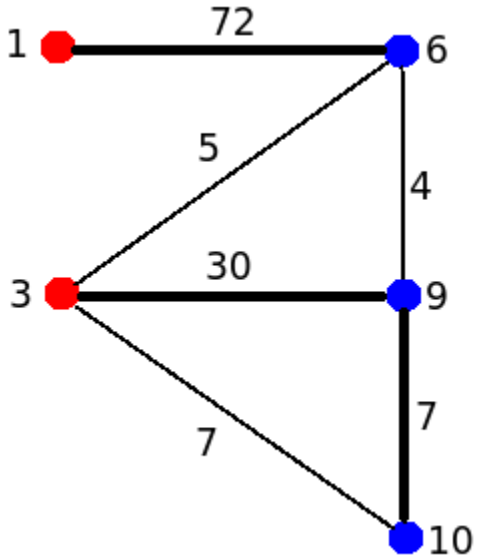
Idea 1: weight is a number of consensus graph edges on which two haplocontigs have a subsequence in common.



Edge weight

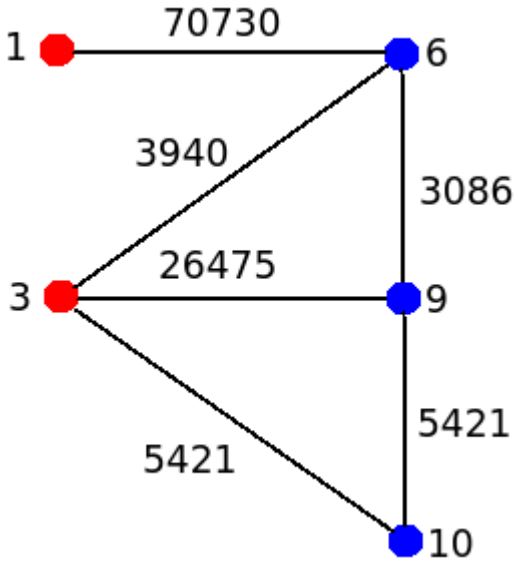
Idea 1: weight is a number of consensus graph edges on which two haplocontigs have a subsequence in common.

When the graph was constructed we lost the right edge {3, 6} but got the wrong edge {9, 10}.



Edge weight

Idea 2: weight is a total length of consensus graph edges on which two haplocontigs have a subsequence in common.



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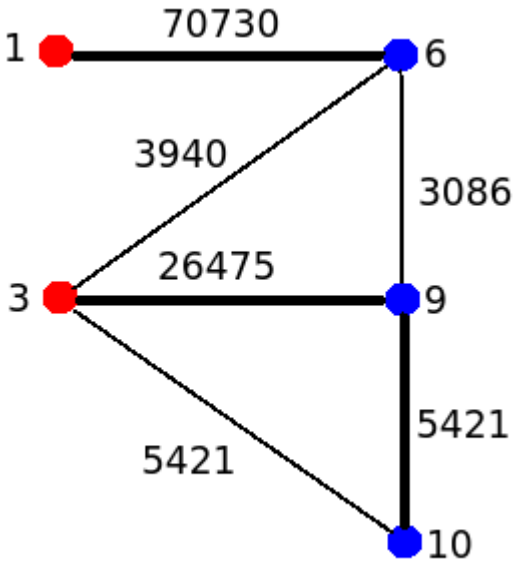
The same story...



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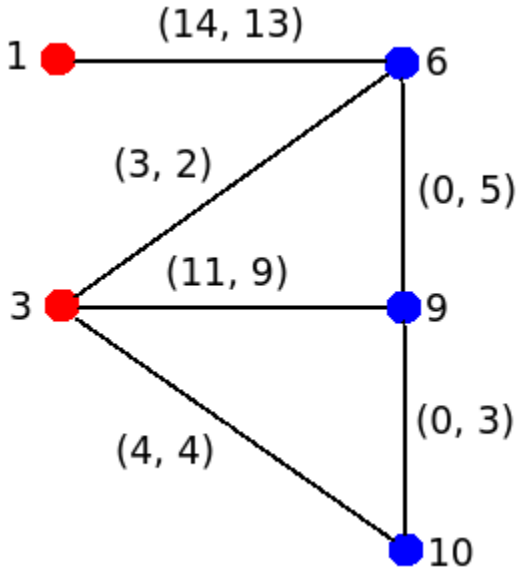
Idea 3: weight is a number of bulges and shared edges in diploid graph that two subsequences have in common.



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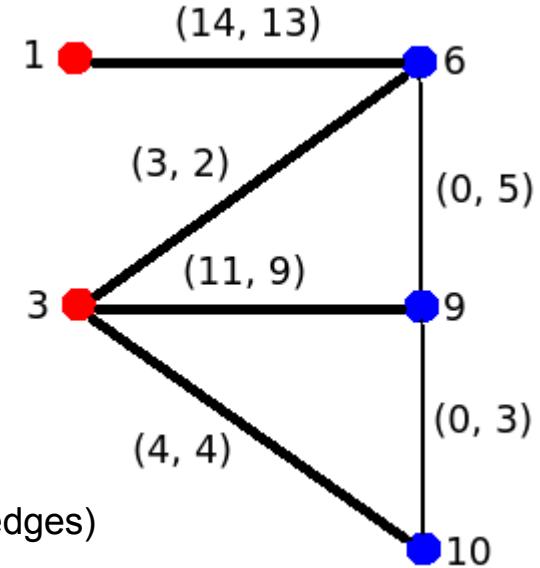
Idea 3: weight is a number of bulges and shared edges in diploid graph that two subsequences have in common.

There are only right edges in the conflict graph.



weight = (# of bulges, # of shared edges)

Results

- pipeline for simulation of diploid datasets with known haplomes was developed (a bunch of Python scripts were written);
- SPAdes erroneous behavior was detected: it may produce not only haplocontigs (as expected) but chimeric contigs;
- **algorithm for haplotype assembly and haplocontigs filtration was developed and partially implemented in dipSPAdes**.

Thank you!

Clavelina moluccensis, a tunicate. Tunicates are diploids with high polymorphism rate.

Nick Hobgood. http://en.wikipedia.org/wiki/File:Bluebell_tunicates_Nick_Hobgood.jpg