ChromoGGL user manual

(authors: K.Yu. Gorbunov, V.A. Lyubetsky,

developers: R.A. Gershgorin, K.Yu. Gorbunov)

2015

Contents

Overview

ChromoGGL utilities are designed for solving the following **three** tasks:

1) Computation of the distance between the two given chromosome structures and finding a sequence of operations with the minimum total weight (distance) that transforms one structure into another. The most common definition (according to available papers) is considered as an arbitrary set of paths and cycles, representing the linear and circular chromosomes, as well as the definition of the set of allowed operations. The structures include gene paralogs, the sequence of operations permit alternate gene composition. Arbitrary weights of single operations are allowed. The task is to minimize the total weight of all operations from arbitrary sequence. The sequence, for which the minimum is reached, is called the *shortest*. The mean of the total weight of the sequence from one structure to another and vice versa is called the *distance* between them. Despite such a common task statement, our original algorithm has *linear* time and memory complexity; it has proved to be quick when performing computations on supercomputer

2) Computation of the matrix of pairwise distances for the given set of structures and generation of the tree, that matches the matrix best. These chromosome structures correspond to the leaves of the obtained tree. The algorithm with linear complexity, based on the algorithm for the first task, is used.

3) The reconstruction of the structures on the evolutionary tree defined by the structures at its leaves, usually from the section 2, not necessarily binary, on the ansestral nodes of the tree; all structures can include paralogs. The task contains the paralogs numeration, which allows to build the correspondence between paralogs at the end of edge and them at the beginning of the edge; and also to see, which paralogs have been lost and which appeared at each node of the tree. In other words, the arrangement of chromosome structures with paralogs numeration for the tree with the only structures in leaves defined (without numeration), is being searched.

The task is to minimize the total price of arrangement as the sum of the distances between the pairs of chromosomes on the ends of any edge. The difficulty of the task is that the distances are computed for the structures with fixed numerations, that is numeration of all paralogs should be searched together with arrangement. It turns out, that the solution of this problem, when using breakpoint distance between the pairs of structures at the ends of the edge, is a good initial approximation for the solution of the task 3 with the distance, described in section 1. We will refer to this distance as the *biological* distance. From now on we will refer to the problem 3 with breakpoint distance as the *task 3a.*

The task 3*a* can be restated as the integer linear programming task, so its complexity is close to linear. The package of programs for «Lomonosov» supercomputer in Moscow State University contains the appropriate program, but it is not available freely. After solving the task 3*a* the task 3 was solved. An effective algorithm of descend from different initial breakpoint positions has been applied, see [1]. Both tasks can be solved by means of this algorithm of descent from different random initial points.

Next section contains the description of the task 1. This algorithm is the key element of the solution of task 2. The solution of task 3 is described after the task 2.

The algorithm for computing the distance between two chromosome structures

The model of chromosome structure is described as the finite number of the oriented chains and cycles, including loops. This set can be thought as the oriented graph. We call this graph as *chromosome structure*. The edge of the graph is defined as the *gene*, each single chain or cycle defined as *chromosome* or *component*. We attach the name to each gene, usually it is the *number i* of this gene, the number can repeat (in case of paralogs), in this case this number becomes *i,j*. Such a model usually does not include the lengths of genes and intergenic regions, as well as the content of genes and intergenic regions. The direction of gene indicates to which chain this gene belongs. The vertex of this graph defines the “place” of connection of the neighbouring genes. Usually there are lots of chains and cycles in the structure, this leads to interaction of these components. That is why the case of multiple chromosomes differs from the case of the single chromosome.

The model includes the following *standart* operations for chromosome structures. The *double-cut-and-paste* – the cut of two pairs of ends of genes and new reconnection of these ends; *sesqui-cut-and-paste* – the cut of the pair of ends and the connection of one end with some new free end, another end stays free; *cut* of two connected ends; *join* of two free ends. If we have two chromosome structures *a* and *b*, and the gene is present in both structures, we will define this gene as the *common* gene (otherwise *special*). If the gene is present in the structure *a* and is absent in the structure *b*, we will define this gene as *a*-gene. Otherwise we define the gene as *b*-gene. The model includes two *additional* operations: the *deletion* of the region of special *a*-genes and the insertion of the region of *b*-genes.

When removing the special genes, we join the ends of common genes, which are neighbors of the removed region. Otherwise, if we insert the region of special genes inside of chromosome,

we firstly cut two ends. We do not consider the cuts of special genes regions, because such operation do not improve the solution of the task.

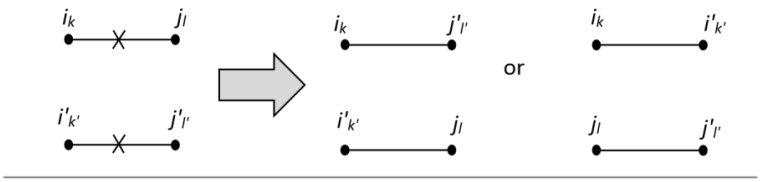
So, we have six operations and the positive rational number is defined for each operation. We define this numbers as *costs* of the operations. Including the costs of operations into the model is important difference of this model from other models.

The task is to find the *shortest* sequence of this operations; which transforms the structure *a* into the structure *b*. By "shortest"sequence we mean the sequence with the minimal total cost.

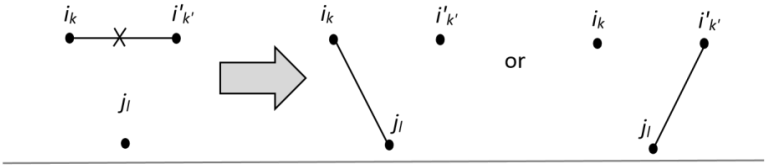
The definition of the joint graph and its final form. The vertexes of the joint graph *a*+*b* are the ends of common genes and all maximal regions of the special genes. Each end of gene is included only once. We write the name of the gene with the index 1 or 2, which indicates the the beginning of the gene or its end. The vertexes of the first type are defined as the *regular* vertexes, the vertexes of the second type – *special* vertexes. We define the border edge with the special end as the *hanging* edge. Edges are marked as *a* or *b* according to the structure, in which this vertexes are connected. Two vertexes can be connected by up to two edges. The graph may contain isolated vertexes – the regions of the special genes: if we have the cyclic region, we call it the *special* loop. We now have the undirected graph.

We apply the following analogs of defined operations to the joint graph.
(1) Delete two equally marked edges and reconnect free resulting vertexes by two new not incident edges. (2) remove the edge with some mark (say *a*) and connect one of resulting vertexes with another vertex, which is not incident to *a*-edge. (3) Delete any edge. (4). Connect two vertexes, not incident to *a*-edge by the *b*-edge (and vise versa). (5) Remove special vertex of

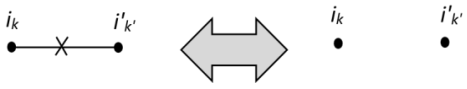
1) Double-cut-and-paste (DP). Initial edges belong to one structure



2) Sesqui-cut-and-paste (SP)



3) *a*-edge deletion or *b*-edge insertion (C) and *b*-edge deletion or *a*-edge insertion (J)



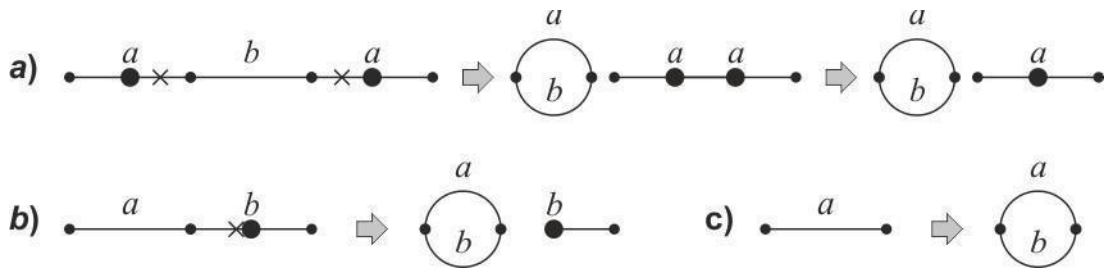
special loop. If special vertex has two regular neighboring vertexes, they are being connected by the edge.

The final form of the joint graph *a+b* is defined as the common graph that contains only isolated regular vertexes and *final 2-cycles.* It is easy to prove, that the *initial problem is equal* to the problem of transforming the graph *a+b* to the final form.

The algorithm for transforming a joint graph into the final form in case of different operation weights and extra operations of deletion and insertion

Step 1. Delete all special *a*-loops.

Step 2. Cut out a common edge not included in a 2-circle and close it into the final 2circle using a double- (internal edge) or a sesqui-cut-and-paste (extreme edge) or a join (single edge) operation. Repeat the operation if possible. If the double-cut-and-paste weight does not exceed that of sesqui-cut-and-paste, all double operations are performed first; otherwise, all sesqui operations go first.



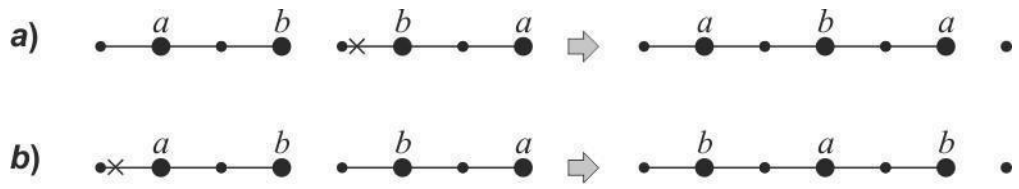
Step 3. Let us start with definitions. An *odd* (*even*) *path* is a path of an odd (even) length. An *a-path* is an odd path with extreme non-hanging edges labeled as *a*. *b-Path* is defined in a similar way. *Types* are assined to *paths or circles remaining after steps 1-2* (except the final 2circles and isolated common nodes): 2-circles containing an *a*-node but no *b*-nodes are considered as *a-circles*; opposite structures, as *b-circles*. A circle containing both *a*- and *b*-nodes belongs to the *circle* type. Special *b*-loops belong to the *loop* type.

a-Paths are assigned to the following types: *1a* if the path has a single hanging edge; *2a*, if it has two hanging edges; 2*a'* -- it is an isolated special *b*-node; *3a*, if it has no hanging edges but has both *a*- and *b*-nodes (then its length is greater than 1); and *3a'*, if there are neither hanging edges nor *b*-nodes (then its length equals 1). *b*-Path types are defined in a similar way. Note, that we split paths into types “with accent” and “without accent”, because we need to mark out paths without *b*-nodes or *a*-nodes.

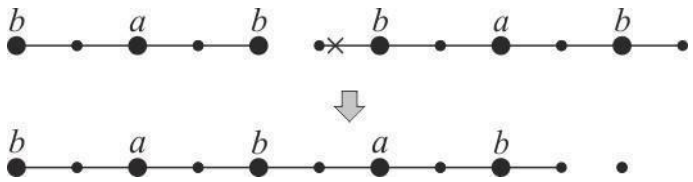
Even paths are assigned to the following types: *1*, if the path has a single hanging edge and a *b*node; *1′*, if it has one common node and one special *a*-node incident to it; *1″*, if it has one common node and one special *b*-node incident to it; *2*, if it has two hanging edges and non hanging edges; *2′*, if it has only two hanging edges; *3*, if it has at least one edge and no hanging edges. Type *1* is subdivided into types 1_a and 1_b if the path includes a hanging *a*-node and *b*-node, respectively.

The algorithm performs the actions described below; each action is applied to a set of paths (from 2 to 4) of the corresponding types (specified in the beginning of the paragraph and separated by the plus sign. Each action is repeated as long as it is applicable. For brevity we denote 2*a* и 2*a′* as 2*a*, 3*b* and 3*b′* as 3*b*, 1_b and 1″ as 1_b, 2 и 2′ as 2.

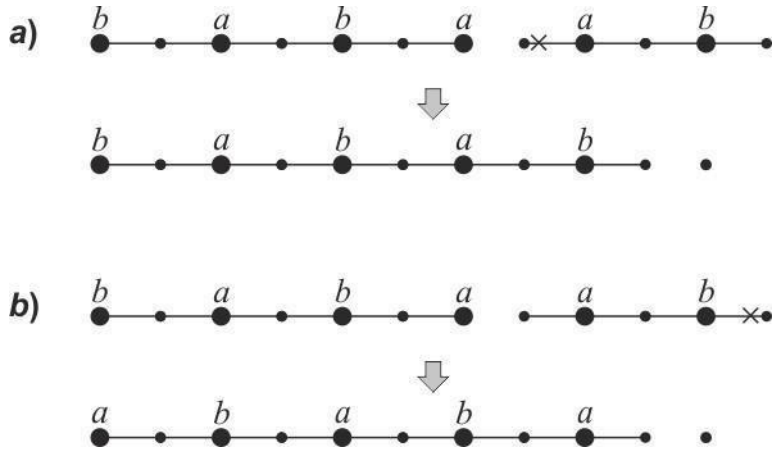
3.1. $1a+1b=1_c$. Cut an extreme non-hanging edge (such edges are called *external edges*) *in one of two paths* of types 1*a* and 1*b* and join the corresponding special node with the extreme special node of the other path (sesqui-cut-and-paste operation). The two variants (here, paths) are selected only at steps 4.15-4.23 of the algorithm. This uncertainty is a characteristic of our algorithm. Specifically, an intermediate path type 1_c corresponding to 1_a or 1_b is introduced. At these steps, *c* is set equal to either *a* or *b* for the whole chain of operations preceding this step. This trick ensures that the algorithm has no more than one branching, which emerges when the type 1_c is assigned.



3.2. $2a+3b=1_b$, $2b+3a=1_a$, $2b'+3a=1_a$, $2b+3a'=1_a$, and $2b'+3a'=1'$. Hereafter, the algorithm execution is described for the first case only (other cases are similar): cut an external edge in the 3*b*-path and join the special node with the extreme special node of the 2*a*-path.



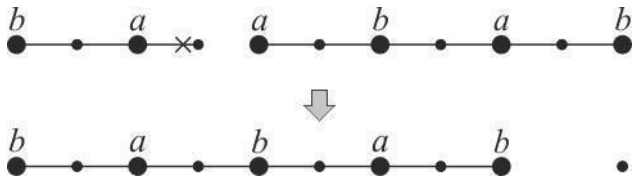
3.3. $2+3=1_c$. Cut an external edge in the 3-path and join the special node with the extreme special node of the 2-path. This results in a path of type 1_a or 1_b, i.e., of type 1_c, depending on which of two external edges was cut.



3.4. $1b+2a+3=2+3=1_c$, $1a+2b+3=2+3=1_c$, and $1a+2b'+3=2+3=1_c$. First carry out the $1b+2a=2$ operation (see below) and then the $2+3=1_c$ one.

3.5. $1a+3b+2=3+2=1_c$, $1b+3a+2=3+2=1_c$, and $1b+3a'+2=3+2=1_c$. First carry out the $1a+3b=3$ operation (see below) and then the $2+3=1_c$ one.

3.6. $1a+2=2a$ and $1b+2=2$b. Cut an external edge in the 1*a*-path and join the special node with the extreme special node of the 2-path.



3.7. $1a+3=3a$ and $1b+3=3b$. Cut an external *b*-edge in the 3-path and join the special node with the extreme special node in the 1*a*-path.

3.8. $1a+1a+2b+3b=2+3=1_c$, $1a+1a+2b'+3b=2+3=1_c$, $1b+1b+2a+3a=2+3=1_c$, and $1b+1b+2a+3a'=2+3=1_c$. First carry out the $1a+2b=2$ and $1a+3b=3$ operations; then the $2+3=1_c$ one.

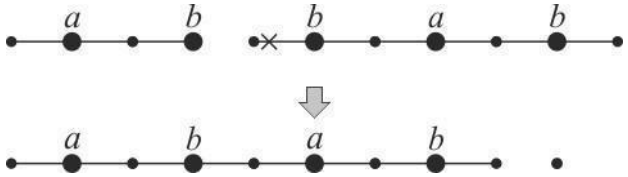
3.9. $1a+1a+2b=3a+2b=1_a$, $1a+1a+2b'=3a+2b'=1_a$, and $1b+1b+2a=3b+2a=1_b$. First carry out the $1a+1a=3a$ operation (see below); then $2b+3a=1_a$ one.

3.10. $1a+1a+3b=1a+3=3a$, $1b+1b+3a=1b+3=3b$, and $1b+1b+3a'=1b+3=3b$. First carry out the $1a+3b=3$ operation; then the $1a+3=3a$ one.

3.11. $1a+1a=3a$ and $1b+1b=3b$. Connect the extreme special nodes of two $1a$-paths.

3.12. $1a+2b=2$, $1a+2b'=2$, and $1b+2a=2$. Cut an external edge in the $1a$-path and join the special with the extreme special node of the $2b$-path.

3.13. $1a+3b=3$, $1b+3a=3$, and $1b+3a'=3$. Cut an external edge in the $3b$-path and join the special node with the extreme special node of the $1a$-path.



3.14. $2a+2b+3+3=2+3=1_c$ and $2a+2b'+3+3=2+3=1_c$. First carry out the $2a+2b+3=2$ operation (see below); then the $2+3=1_c$ one.

3.15. $3a+3b+2+2=3+2=1_c$ and $3a'+3b+2+2=3+2=1_c$. First carry out the $3a+3b+2=3$ operation (see below); then the $2+3=1_c$ one.

3.16. $2a+3+3=1a+3=3a$, $2b+3+3=1b+3=3b$, and $2b'+3+3=1b+3=3b$. First carry out the $2a+3=1a$ operation (see below); then the $1a+3=3a$ one.

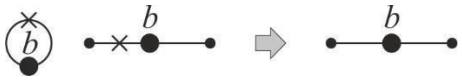
3.17. $3b+2+2=1b+2=2b$, $3a+2+2=1a+2=2a$, and $3a'+2+2=1a+2=2a$. First carry out the $3b+2=1b$ operation (see below); then the $1b+2=2b$ one.

3.18. $2a+2b+3=2a+1b=2$ and $2a+2b'+3=2a+1b=2$. First carry out the $2b+3=1b$ operation; then the $1b+2a=2$ one.

3.19. $3a+3b+2=3a+1b=3$ and $3a'+3b+2=3a'+1b=3$. First carry out the $3b+2=1b$ operation; then the $1b+3a=3$ one.

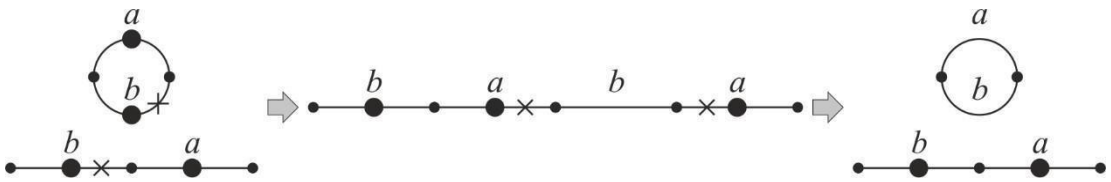
Step 4. If the weight of the double-cut-and-paste operation is greater than the weight of the sesqui-cut-and-paste, the actions 4.1–4.24 are repeated as long as they are applicable; otherwise the steps 4.1′–4.24′ are repeated analogously.

4.1. “Loop”+(“circle” or “path *K* with a *b*-node”) = “circle” or “path of the same type as *K*,” correspondingly. Join the loop node with the *b*-node by double-cut-and-paste (if *K* is not an isolated special node) or by sesqui-cut-and-paste (otherwise).



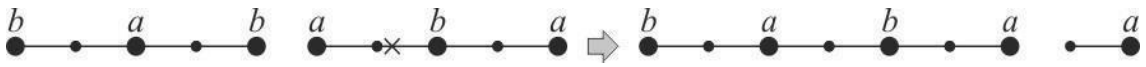
4.1′. Same as 4.1.

4.2. “Circle”+(“circle” or “path *K* with *b*- and *a*-nodes) = “circle” or “path of the same type as *K*.” Insert the circle (by double-cut-and-paste combining two *b*-nodes) near the *b*-node from *K* on the side of the *a*-node; cut out the resulting common edge.



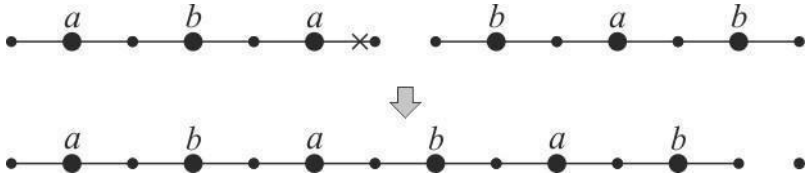
4.2′. Same as 4.2.

4.3. 2*a*+2*b*=2+1′. Cut out two 2*b*-path nodes (the extreme special *a*-node and the neighboring common node) by sesqui-cut-and-paste and join the resulting terminus with the extreme special *b*-node of the 2*a*-path.



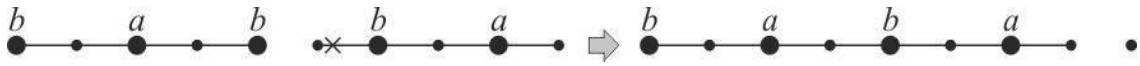
4.3′. 2*a*′+2*b*=2+1′.

4.4. 3*a*+3*b*=3. Cut an external edge in the 3*a*-path and join the special node with the extreme common node of the 3*b*-path.



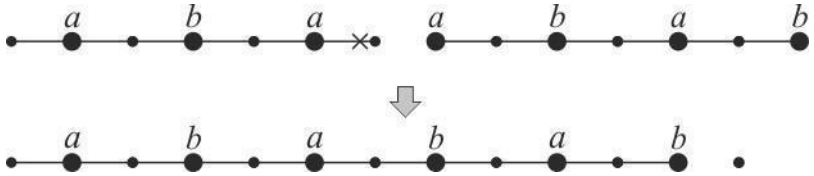
4.4′. $3a+3b'=3$.

4.5. $2a+3=1a$ and $2b+3=1b$. Cut an external b-edge in the 3-path and join the special node with the extreme special node of the $2a$-path.



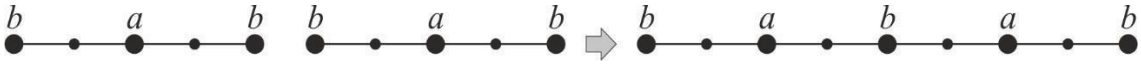
4.5′. $2a'+3=1a$.

4.6. $3a+2=1a$ and $3b+2=1b$. Cut an external edge in the $3a$-path and join the special node with the extreme special node of the 2-path.



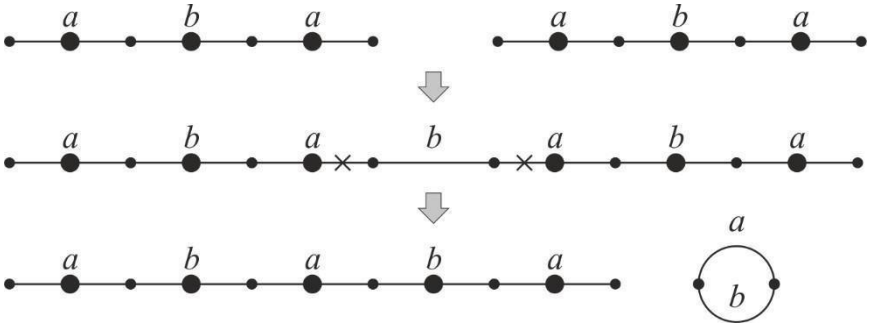
4.6′. $3a+2'=1a$, $3b'+2=1b$.

4.7. $2a+2a=2a$ and $2b+2b=2b$. Join the extreme special nodes of the two paths.



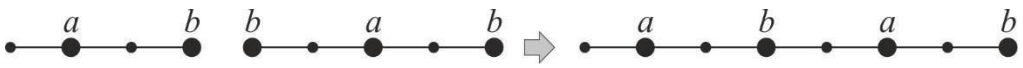
4.7′. $2a'+2a=2a$.

4.8. $3a+3a=3a$ and $3b+3b=3b$. Connect two extreme common nodes of the paths by a common edge, and then cut out this edge.



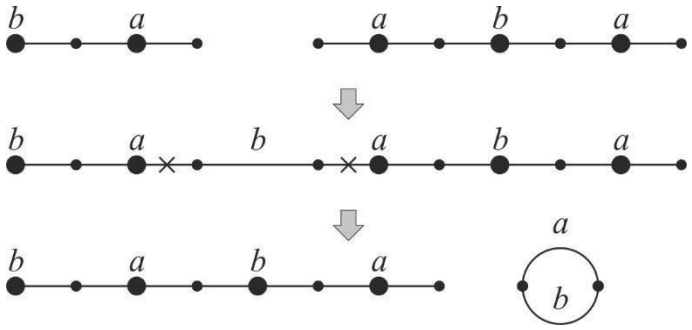
4.8′. $3b'+3b=3b$.

4.9. $1a+2a=1a$ and $1b+2b=1b$. Connect the extreme special nodes of the two paths.



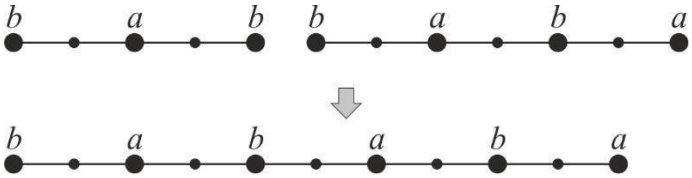
4.9′. $1a+2a'=1a$.

4.10. $1a+3a=1a$ and $1b+3b=1b$. Connect two extreme common nodes of the paths by a common edge, and then cut out this edge.



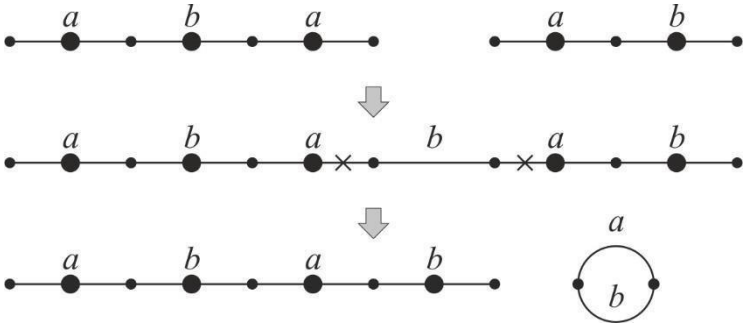
4.10′. $1b+3b'=1b$.

4.11. $2a+2=2$ and $2b+2=2$. Connect the extreme special nodes of the two paths.



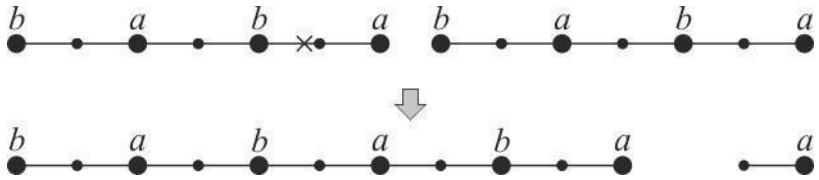
4.11′. $2a'+2=2$, $2a+2'=2$, $2b+2'=2$.

4.12. $3a+3=3$, $3b+3=3$. Connect two extreme common nodes of the paths by a common edge, and then cut out this edge.



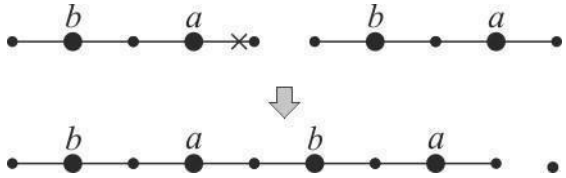
4.12′. $3b'+3=3$.

4.13. 2+2=2+1'. Perform the sesqui-cut-and-paste operation with cutting out the two nodes of the 2-path (the extreme special *a*-node and the neighbor common node) and joining the resulting terminus with the extreme special *b*-node of the other 2-path.



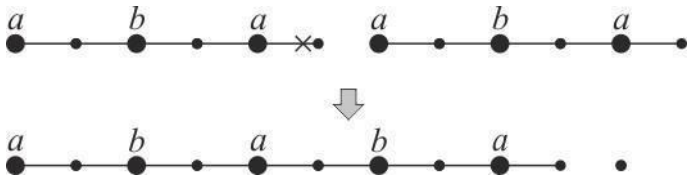
4.13′. 2′+2=2+1'.

4.14. 3+3=3. Cut an external *a*-edge in the 3-path and join the resulting terminus with the *b*terminus of the other 3-path.



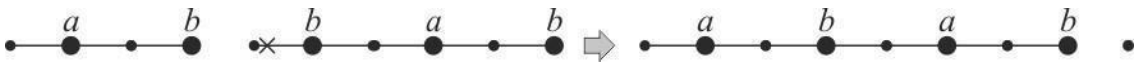
4.14′. Empty action.

4.15. $1_a+1_a=1_a$, $1_b+1_b=1_b$, and $1_b+1_c=1_b$ (set $c=b$). Cut an external edge in the 1_a-path and join the special node with the extreme special node of the other 1_a-path.



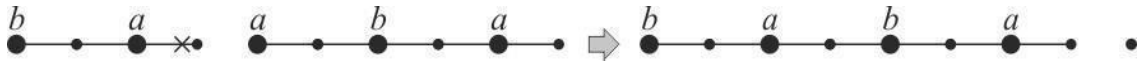
4.15′. $1''+1_b=1_b$, $1''+1_c=1_b$ (set $c=b$).

4.16. $1a+1_b=1a$, $1b+1_a=1b$, and $1a+1_c=1a$ (set $c=b$). Cut an external edge in the 1_b-path and join the special node with the extreme special node of the $1a$-path.



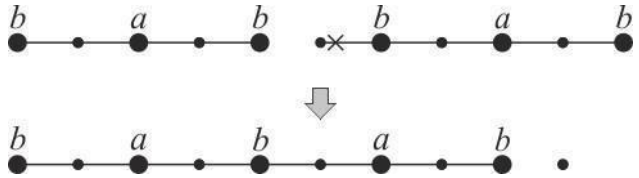
4.16′. $1a+1''=1a$.

4.17. $1a+1_a=1a$, $1b+1_b=1b$, and $1b+1_c=1b$ (set $c=b$). Cut an external edge in the $1a$-path and join the special node with the extreme special node of the 1_a-path.



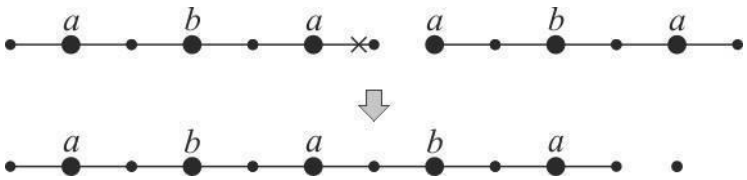
4.17′. $1b+1''=1b$.

4.18. $2a+1_b=2a$, $2b+1_a=2b$, and $2a+1_c=2a$ (set $c=b$). Cut an external edge in the 1_b-path and join the special node with the extreme special node of the $2a$-path.



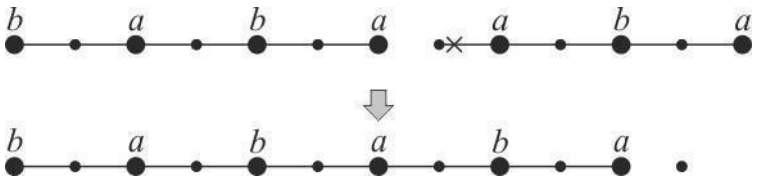
4.18′. $2a'+1_b=2a$, $2a+1''=2a$, $2a'+1_c=2a$ (set $c=b$).

4.19. $3a+1_a=3a$, $3b+1_b=3b$, and $3b+1_c=3b$ (set $c=b$). Cut an external edge in the $3a$-path and join the special node with the extreme special node of the 1_a-path.



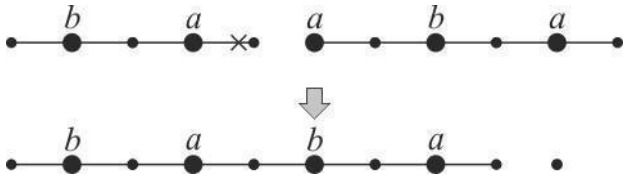
4.19′. $3b'+1_b=3b$, $3b+1''=3b$, $3b'+1_c=3b$ (set $c=b$).

4.20. $2+1_a=2$, $2+1_b=2$, and $2+1_c=2$ (set $c=b$). Cut an external edge in the 1_a-path and join the special node with the extreme special node of the 2-path.



4.20′. $2'+1_a=2$, $2'+1_b=2$, $2+1''=2$, $2'+1_c=2$ (set $c=b$).

4.21. $3+1_a=3$, $3+1_b=3$, and $3+1_c=3$ (set $c=b$). Cut an external edge in the 3-path and join the special node with the extreme special node of the 1_a-path.



4.21′. 3+1″=3.

4.22. $1_a+1_c=1_a$, $1b+1_c=1b$, $1a+1_c=1a$, $2b+1_c=2b$, and $3a+1_c=3a$. In all cases, set $c=a$.

4.22′. Empty action.

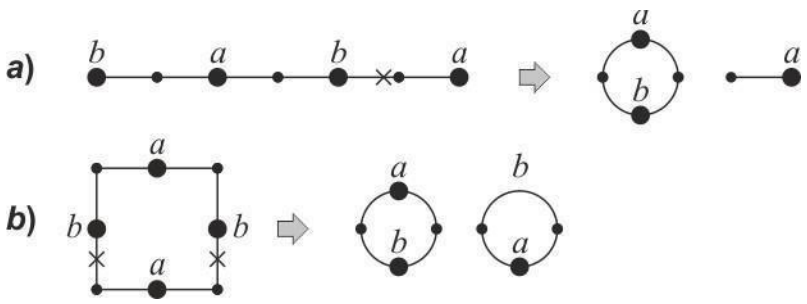
4.23. For the remaining paths of type 1_c, set $c=b$ and perform the $1_b+1_b=1_b$ operation.

4.23′. Empy action.

4.24. Paths, that have hanging edge, are being enclosed into circles by join operation (for paths $2a$, $2b$, $3a$, $3b$), by sesqui-cut-and-paste operations with joining of special nodes (paths 1_a, 1_b, 1_c, 2) or without joining (paths $1a$, $1b$, 3). When enclosing path 1_c we set $c=b$. When enclosing path 2 we choose variant when two b-nodes are joined, after that we delete a-node from 1', see Fig. *a* below. We also cut out the common edge from circles, that were produced by $3a$ or $3b$ closure, then we apply step 4.2 to these circles again.

4.24′. Same as 4.24.

Step 5. Remove isolated special nodes and loops. Cut out 2-circles (using double-cut-and-paste) from circles without common edges to combine two b-nodes (accordingly, the a-node is included into the 2-circle), fig. b. Delete special nodes from the 2-circles.



The end of algorithm description.

Algorithm of generation of the evolutionary tree of chromosome structures

The generation of the optimal evolutionary tree for matrix of pairwise distances between the given chromosome structures uses UPGMA algorithm, http://en.wikipedia.org/wiki/UPGMA.

Algorithm “gradient descent” from multiple random initial points for task 3

On each step of the algorithm we iterate over all inner vertexes of the tree and try to transform the structures by means of all possible operations. We then choose the pair vertex-operation, which delivers minimum to the total cost of structures arrangement and by replacing the structure in the optimal vertex with the new one we get next structures arrangement on the tree. We repeat this step till we can’t decrease the total cost of structures arrangement.

Note that this algorithm is fast and effective when the initial arrangement is chosen correctly. The problem of initialization was briefly described as task 3a. Even approximate solution of task 3a let us to limit the set of possible initial points.

Installation and execution of ChromoGGL utilities on Windows

Chromo

Chromo command line utility is implemented using C++. 32-bit version of executable module is available for download. Utility does not require installation.

Several steps are required to start use utility:

download archive *chromo.zip* and unpack it to any directory (for example, f:/Chromo); run console Windows (Start > Run > cmd) and enter the directory with archive content:

f: cd f:/Chromo; run command:

chromo –h.

In case of successful execution short instruction should appear on the screen. Otherwise the information about the error will be printed. It is recommended to test utility with run_example_1.bat on the short example.

hrom_reconstruction

hrom_reconstruction utility is implemented as 32-bit executable module. It does not require installation.

Several steps are required to start use utility:

download archive *hrom_reconstruction.zip* and unpack it to any directory (for example, f:/hrom_reconstruction); run console Windows (Start > Run > cmd) and enter the directory with archive content: f: cd f:/hrom_reconstruction

Input data

Chromo input data

The **input data** consists of one file – string with the following data: the *number* of chromosome structures, *name* of specie/culture; the number of chromosome, included to the structure from

this specie, that is, the *number* of paths and cycles in the chromosome; *label L* if chromosome is linear, and *C* if cyclic; the *number* of genes in the chromosome; *sequence* of genes in the chromosome, it consists of gene names. If gene is located on the minus-strand, «–» is written in front of its name (it is possible to mark such genes with «*» as well). For example, the file for thwo structures from Fig. 1 is presented below.

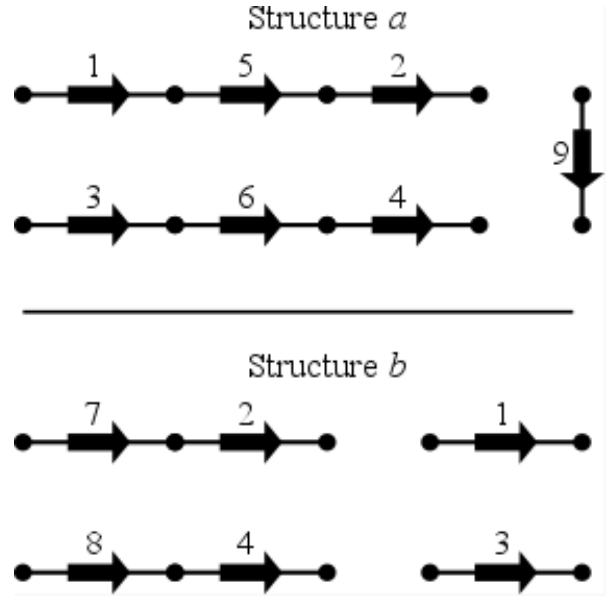


Fig. 1

File with structures, shown on Fig. 1:
2; Structure_*a*; 3; *L*3: +1+5+2; *L*3: +3+6+4; *L*1: +9; Structure_*b*; 4; *L*2: +7+2; *L*2: +8+4; *L*1: +1; *L*1: +3

Joint graph of two given on the Fig. 1 structures, where the special nodes are represented as circles of bigger size, other nodes are circles of smaller size:

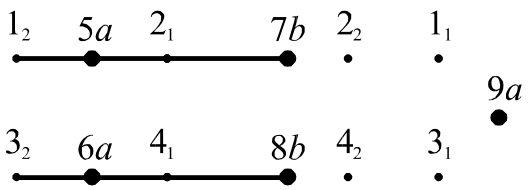


Fig. 2

hrom_reconstruction input data

hrom_reconstruction utility requires two input files: *input.tre* and *input.chrom.* input.tre contains one single line: the tree in Newick format. The leaves of the tree are being enumerated left to

right by numbers 1, 2, 3. input.chromo contains chromosome structures assigned to the leaves of the tree. The structures in this file should be listed in accordance with their number in the tree. The descriptions of the structures are separated by the line, containing multiple symbols "*". The content of each chromosome should start from the new line. Chromosomes are described as the sequence of the names of the genes together with signs "–" or "+". The sign "–" indicates the position of the gene on the complement (-minus) strand. Each chromosome has the *mark* (C), if chromosome is cyclic and (L) otherwise.

Example for artificial data:

File *input.tre* contains one line ((1,2),(3,4),(5,6));

File *input.chrom* contains initial chromosome structures for six leaves:

+g2+g3+g4+g5+g6 (*C*)
+g7 (*C*)
+g8+g9 (*C*)
****
+g1+g3+g4+g5+g6 (*C*)
+g7 (*C*)
+g8–g9 (*C*)
****
+g1+g2+g4+g5+g6 (*C*)
+g8 (*C*)
+g7+g9 (*C*)
****
+g1+g2+g3+g5+g6 (*C*)
+g8 (*C*)
+g7–g9 (*C*)
****
+g1+g2+g3+g4+g6 (*C*)
+g9 (*C*)
+g7+g8 (*C*)
****
+g1+g2+g3+g4+g5 (*C*)
+g9 (*C*)
+g7–g8 (*C*)
###

Here each structure contains three cycles, formed by five, one and two genes each. The structures differ by the content of the genes and by the order of the genes in chromosomes. Second, forth and sixth leaf contain genes from complement strand.

ChromoGGL parameters

Chromo parameters

The utility requires several parameters for execution, the meaning of these parameters is revealed below. Also the file with string – weights of single operations is required.

Command line parameters

- -m – execution mode, it equals dist, if task 1 is being solved; tree, if task 2 is being solved;
- -c – path to the file with chromosome structures;
- -o – path to the file with operations weights;
- -r – path to the directory with the results of utility execution.

File with operations costs

Weights are placed one by one in the single string, all of them are represented by one positive double number:

DP = …, SP = …, J = …, C = …, *a*D = …, *b*D = ….

Example of the file – string with operations weights:

DP = 1.2, SP = 1.1, J = 1, C = 0.9, *a*D = 0.8, *b*D = 1.5

hrom_reconstruction parameters

hrom_reconstruction does not require commandline parameters or additional files.

Output data

In task 1 two files are being created: *joint_graph* – the description of the joint graph and *shortest_sequence* – the description of the shortest sequence of transformations. The *first file* has: heading *joint_graph*, heading cycles (…), which includes the number of cycles in the joint graph, then they are listed; heading paths (…) indicates the number of paths, then they are listed. Each cycle is represented as the sequence of its nodes: common node is represented as a gene name, followed by the number 1 if it is the start of gene, and 2 if it is the end. Special node consists of the names of special genes from the block, it is followed by the name of structure, to which this

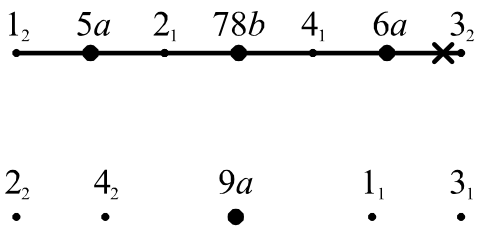
edge belongs. The edge between common nodes is represented as «_», after it the name of structure, to which this edge belongs, is printed. The edge to the special node is represented by the same symbol, the name of the structure is not printed. At the end of file the number of special a- and b- nodes in the joint graph is printed. It is represented as “spnodes”. If the gene partition is not well-defined, it is enclosed in the brackets.

Example of the first file for the joint graph from Fig. 2:
Joint_graph cycles (0): paths (7):1.1; 2.2; 3.1; 4.2; 9*a*; 1.2_5*a*_ 2.1_7*b*;
3.2_6*a*_4.1_8*b* *a*-spnodes: 3, *b*-spnodes: 2

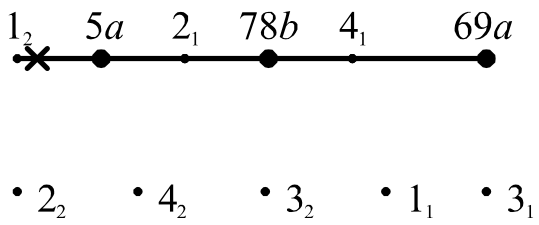
The second file contains the shortest sequence of operations, transforming the joint graph to its final form. Its first line contains: the *number* of operations in the sequence; its total *weight*. Then operations are listed. Each operation contains: component, to which one or several operations are being applied, short names of operations; result.

Example of the second file for the joint graph from Fig. 2:

5; 5.4;
[1.2_5*a*_2.1_7*b* (*L*); 3.2_6*a*_4.1_8*b* (*L*)] C [1.2_5*a*_2.1_78*b*_4.1_6*a*_3.2 (*L*)]
Here special nodes 7*b* and 8*b* from two paths are being united into special node 78*b* at one path. Labels (*L*) and (*C*) mean «path» and «cycle». The result can be seen on the figure below.

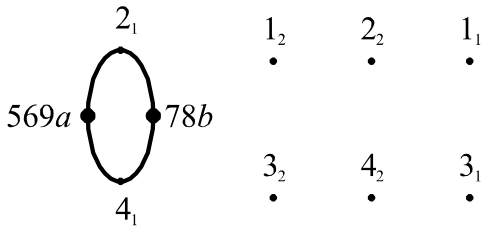


[1.2_5*a*_2.1_78*b*_4.1_6*a*_3.2 (*L*); 9*a* (*L*)] SP [3.2; 1.2_5*a*_2.1_78*b*_4.1_6*a* (*L*)]
Cut of the node 3.2 and union of special nodes 6*a* and 9*a* into one node 69*a*. The result is on the figure below.



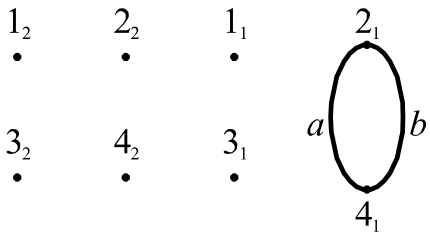
[1.2_5*a*_2.1_78*b*_4.1_6*a* (*L*)] SP [2.1_78*b*_4.1_569*a*_2.1 (*C*); 1.2]

Cut of the node 1.2 and union of the special nodes 5*a* and 69*a* into one node 569*a*. See the result below.



[2.1_78*b*_4.1_569*a*_2.1 (*C*)] *a*D, *b*D [2.1_*a*4.1_*b*2.1 (*C*)]

Deletion of the special nodes 569*a* и 78*b*. See the result below.



Now graph is reduced to the final form, algorithm is over.

Examples of task 1 solutions

The archive *chromo.zip* contains several examples of task 1 solutions. Example – the pair of structures from Fig.1, and the pair of structures from chromosome *Salmonella enterica* to chromosome *Escherichia coli.*

Input data can be found in *artificial* and *Salmonella_Escherichia*, the joint graphs can be found in *artificial* and *Salmonella_Escherichia*, the shortest sequences are described in *artificial* and *Salmonella_Escherichia*. To run the utility on these examples it is necessary to run the following scripts from the archive: *run_example_1.bat* и *run_example_2.bat*.

Also the program was tested using the following 8 sets of artificial data: *artificial1*, *artificial2*, *artificial3*, *artificial4*, *artificial5*, *artificial6*, *artificial7*, *artificial8*. The joint graphs are described in *artificial1*, *artificial2*, *artificial3*, *artificial4*, *artificial5*, *artificial6*, *artificial7*, *artificial8*. The shortest sequences for three variants of weights are described in *artificial1*, *artificial2*, *artificial3*, *artificial4*, *artificial5*, *artificial6*, *artificial7*, *artificial8*. The variants are separated from each other by empty line.

The **task 2** solution contains two files: *distance* – matrix of pairwise distances between chromosome structures; *tree* – the evolutionary tree of chromosome structures, that matches best to the matrix.

Exampels of task 2 solutions

The first example of the set of chromosome structures contains 66 plastids from rhodophytic branch. All chromosomes are circular.

The second example of the set of chromosome structures contains 18 mitochondrion of class *Aconoidasida*. There are both circular and linear chromosomes in this set.

Input chromosome structures can be found in *rhodophytic_branch* and *mitochondria*, matrixes of pairwise distances are in *rhodophytic_branch* and *mitochondria*, the evolutionary trees are described in *rhodophytic_branch* and *mitochondria*. The archive also contains all this data, suitable for Microsoft Excel.

To run utility on these examples it is necessary to run the following scripts from the archive: *run_example_3.bat* and *run_example_4.bat*.

hrom reconstruction output

The inner vertexes of the tree in output are enumerated in order they are being visited by DFS algorithm, which starts from the root of the tree and visits the leaves in accordance with their numbers. The resulting structure is being printed for every inner vertex.

Example of output:

File *output*:

#leaves 6, #species 6, #genes 9

assignment cost 9

assignment itself:

node 1 with the composition of 9 genes:

+g1+g2+g3+g4+g5+g6 (*C*)

+g9–g8+g7 (*C*)

node 2 with the composition of 9 genes:

+g1+g2+g3+g4+g5+g6 (*C*)

+g9–g8 (*C*)

+g7 (*C*)

node 3 with the composition of 9 genes:

+g1+g2+g3+g4+g5+g6 (*C*)

+g9+g7 (*C*)

+g8 (*C*)

node 4 with the composition of 9 genes:

+g1+g2+g3+g4+g5+g6 (*C*)

+g9 (*C*)

+g8–g7 (*C*)

Here the root is vertex 1, vertex 2 is ancestral for the leaves 1 and 2, vertex 2 is ancestral for the leaves 3 and 4, 4 is ancestral for the leaves 5 and 6.

Biological examples for task 3

The archive *hrom_reconstruction.zip* contains two biological examples. First example contains tree *tree*, structures description *chromosomes* and optimal arrangement *arrangement*. The second example contains tree *tree*, structures description *chromosomes* chromosomes and optimal arrangement *arrangement*.

Recommended standart programs

To work with output data it is recommended to used the following standart programs: Microsoft Excel to work with matrixes. They are printed using tab separated values format (tsv). The dot is used as the separator in numbers. It is necessary to set the correct separator for numbers, it can be done through the menu: File>Options>Additional>Use system separators.

TreeViewX to visualize trees in the Newick format.

Any text editor to work with the joint graphs and the shortest secuences.

Reference

[1] K.Yu. Gorbunov, R.A. Gershgorin, V.A. Lyubetsky. Rearrangement and Inference of Chromosome Structures. *Molecular Biology*, 2015, Vol. 49, No. 3, pp. 327–338