Topics of today:

1. NP-hardness of unichromosomal breakpoint median
2. Double-cut-and-join (DCJ) model
3. General DCJ halving

NP-hardness of unichromosomal breakpoint median

A unichromosomal circular genome $\mathbb{C}$ can be represented as a simple directed cycle graph:

Ex: $\mathbb{C} = (1\,\bar{2}\,3)$

Assume that the genes in three canonical circular genomes $\mathbb{C}_1$, $\mathbb{C}_2$ and $\mathbb{C}_3$ have the same relative orientation and represent these three genomes in the same directed cycle graph:

Ex: $\mathbb{C}_1 = (1\,2\,3\,4)$, $\mathbb{C}_2 = (2\,4\,1\,3)$, $\mathbb{C}_3 = (2\,3\,1\,4)$

NP-hardness of unichromosomal breakpoint median

The Problem of determining whether a directed graph G has a hamiltonian cycle is NP-complete, even if G has maximum indegree and maximum outdegree equal to 3.

Reduction of this problem to the problem of computing a breakpoint median of three canonical circular genomes $\mathbf{A}$, $\mathbf{B}$ and $\mathbf{C}$ that have the same relative orientation:

> We need to transform G into another directed graph G'', such that G'' is the union of three hamiltonian cycles (each one representing one input genome of the median problem)

NP-hardness of unichromosomal breakpoint median

Build a modified directed graph G'', such that G'' is the union of three hamiltonian cycles (each one representing one genome among $\mathbf{A}$, $\mathbf{B}$ and $\mathbf{C}$)

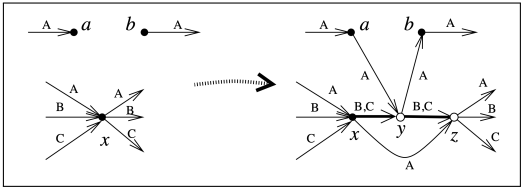
G'' has only adjacencies that occur in one or in two genomes

Let $\mathbb{M}$ be a solution to the circular breakpoint median of $\mathbf{A}$, $\mathbf{B}$ and $\mathbf{C}$:

$\mathbb{M}$ contains all adjacencies common to two input genomes and no "new" adjacency

$\updownarrow$

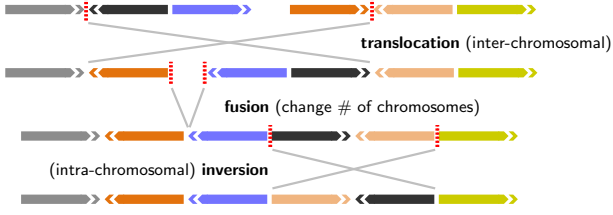
Initial graph G has an hamiltonian cycle



Double-cut-and-join (DCJ) model

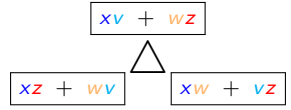
Double-cut-and-join (DCJ) operation: two cuts + two joins

- Cuts the genome twice and rejoins loose ends in a different way.
- Represents most large-scale genome rearrangements (inversions, translocations, fusions, fissions...)



DCJ model

DCJ operation involving two adjacencies



two possibilities of rejoining in a different way

Cases:

A. Each adjacency is in a distinct linear chromosome:

$[1\ x\ v\ 2\ 3]\quad [4\ w\ z\ 5\ 6]$

reciprocal translocation / reciprocal translocation

$[1\ x\ z\ 5\ 6]\quad [4\ w\ v\ 2\ 3]$ reciprocal translocation $[1\ x\ w\ \bar{4}]\quad [\bar{3}\ \bar{2}\ v\ z\ 5\ 6]$

B. Both adjacencies are in the same chromosome, or one is in a circular chromosome:

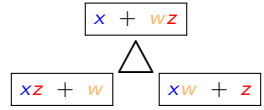
$([1\ x\ v\ 2\ 3\ 4\ z\ w\ 5\ 6])$

inversion / excision/integration

$([1\ x\ z\ \bar{4}\ \bar{3}\ \bar{2}\ v\ w\ 5\ 6])$ excision/integration $([1\ x\ w\ 5\ 6])\quad (3\ 4\ z\ v\ 2)$

DCJ model

DCJ operation involving one adjacency and one telomere



two possibilities of rejoining in a different way

Cases:

A. The adjacency and the telomere are in distinct linear chromosomes:

$$[\,1\ 2\ 3\ x\,] \quad [\,4\ w\ z\ 5\ 6\,]$$

translocation translocation

$$[\,1\ 2\ 3\ x\ z\ 5\ 6\,] \quad [\,4\ w\,] \quad \text{translocation} \quad [\,1\ 2\ 3\ x\ w\ \bar{4}\,] \quad [\,z\ 5\ 6\,]$$

B. The adjacency is in the same linear chromosome, or in a circular chromosome:

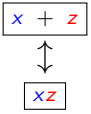
$$[\,1\ 2\ 3\ 4\ z\ w\ 5\ 6\ x\,]$$

inversion excision/ integration

$$[\,1\ 2\ 3\ 4\ z\ x\ \bar{6}\ \bar{5}\ w\,] \quad \text{excision/ integration} \quad [\,1\ 2\ 3\ 4\ z\,] \quad (\,6\ x\ w\ 5\,)$$

DCJ model

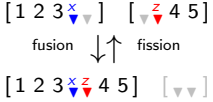
DCJ operation involving one adjacency or two telomeres



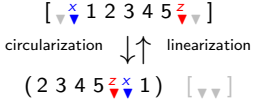
one possibility of rejoining in a different way

Cases:

A. The adjacency is in a linear chromosome / the telomeres are in two distinct chromosomes:



B. The adjacency is in a circular chromosome / the telomeres are in the same chromosome:



DCJ halving

DCJ Halving Distance Problem:

Compute the minimum number of DCJ operations required to transform
a (rearranged) duplicated genome $\mathbb{D}$ into a perfectly duplicated genome $2 \cdot \mathbb{H}$.

Denote by $h_{DCJ}(\mathbb{D})$ the DCJ halving distance of $\mathbb{D}$.

DCJ Halving Problem:

Find a sequence of $h_{DCJ}(\mathbb{D})$ DCJ operations that transform
a (rearranged) duplicated genome $\mathbb{D}$ into a perfectly duplicated genome $2 \cdot \mathbb{H}$.

Natural graph $NG(\mathbb{D}) = (V, E)$ of a duplicated genome $\mathbb{D}$:

1. $V = \alpha(\mathbb{D}) \cup \gamma(\mathbb{D})$ (each adjacency or telomere of $\mathbb{D}$ is a vertex of $NG(\mathbb{D})$)
2. For each family $f \in \mathcal{F}(\mathbb{D})$, each pair of paralogous extremities is connected by an edge in $NG(\mathbb{D})$, i.e.:
   - there is an edge connecting the vertex u that contain f_1^h and the vertex v that contain f_2^h
   - there is an edge connecting the vertex u' that contain f_1^t and the vertex v that contain f_2^t

Note that:

- There can be adjacencies/vertices of type $f_1^h f_2^h$ and/or $f_1^t f_2^t$ ($NG(\mathbb{D})$ can contain 1-cycles)
- Let $n = |\mathcal{F}(\mathbb{D})| = \frac{|\mathcal{G}(\mathbb{D})|}{2}$. The number of edges in $NG(\mathbb{D}) = 2n$ (two edges per element of $\mathcal{F}(\mathbb{D})$).

Natural graph of a duplicated genome

Ex: $\mathbb{D} = [\bar{4}\ 1\ \bar{4}\ \bar{3}\ 2] \quad [\bar{2}\ 3\ 1] \quad [5\ \bar{5}]$

$\alpha(\mathbb{D}) \cup \gamma(\mathbb{D}) = \{\, 4_1^h\,,\ 4_1^t 1_1^t\,,\ 1_1^h 4_2^h\,,\ 4_2^t 3_1^h\,,\ 3_1^t 2_1^t\,,\ 2_1^h\,,\ 2_2^h\,,\ 2_2^t 3_2^t\,,\ 3_2^h 1_2^t\,,\ 1_2^h\,,\ 5_1^t\,,\ 5_1^h 5_2^h\,,\ 5_2^t\,\}$

$n = |\mathcal{F}(\mathbb{D})| = 5$ and $\kappa(\mathbb{D}) = 3$

Every vertex has degree one or two:
$NG(\mathbb{D})$ is a collection of paths and cycles

cycle with k edges: k-cycle or c_k
path with k edges: k-path or p_k

$$\begin{cases} \mathcal{C}_e = \{c_k : k \text{ is even}\} & : \text{ set of even cycles} \\ \mathcal{P}_e = \{p_k : k \text{ is even}\} & : \text{ set of even paths} \\ \mathcal{C}_o = \{c_k : k \text{ is odd}\} & : \text{ set of odd cycles} \\ \mathcal{P}_o = \{p_k : k \text{ is odd}\} & : \text{ set of odd paths} \end{cases}$$

$|\mathcal{C}_o| + |\mathcal{P}_o|$ is even (NG has $2n$ edges)
$|\mathcal{P}_e| + |\mathcal{P}_o| = \kappa(\mathbb{D})$

For a perfectly duplicated genome $2{\cdot}\mathbb{H}$,
$NG(2{\cdot}\mathbb{H})$ has only 2-cycles and 1-paths:

$$2n = 2|\mathcal{C}_e| + |\mathcal{P}_o| \quad \Rightarrow \quad n = |\mathcal{C}_e| + \frac{|\mathcal{P}_o|}{2}$$

Otherwise, if a duplicated genome $\mathbb{D}$
is not perfectly duplicated:

$$n > |\mathcal{C}_e| + \left\lfloor \frac{|\mathcal{P}_o|}{2} \right\rfloor$$

Types of DCJ operation

Let a DCJ operation transform a duplicated genome $\mathbb{D}_1$ into another duplicated genome $\mathbb{D}_2$:

$$\left.\begin{array}{l} m_1 : \#\text{ of components in } NG(\mathbb{D}_1) \\ m_2 : \#\text{ of components in } NG(\mathbb{D}_2) \end{array}\right\} \quad 0 \leq |m_2 - m_1| \leq 1$$

Goal: increase the number of even cycles ($|\mathcal{C}_e|$) and/or the number of odd paths ($|\mathcal{P}_o|$) in NG

Types of DCJ operation

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DCJ Halving & Distance

Recall that, if the genome is perfectly duplicated, we have $n = |\mathcal{C}_e| + \frac{|\mathcal{P}_o|}{2}$, otherwise $n > |\mathcal{C}_e| + \left\lfloor \frac{|\mathcal{P}_o|}{2} \right\rfloor$

A DCJ operation ρ is called **optimal** if

- ρ increases the number of even cycles by one, or
- ρ increases the number of odd paths by two, or
- the number of odd paths is odd and
  - ρ increases the number of odd paths by one
  - (can occur at most once)

Given a duplicated genome $\mathbb{D}$, it is possible to find an optimal DCJ operation at each sorting step. Therefore:

$$\mathsf{h}_{\mathrm{DCJ}}(\mathbb{D}) = n - |\mathcal{C}_e| - \left\lfloor \frac{|\mathcal{P}_o|}{2} \right\rfloor$$

DCJ Halving

Given a duplicated genome $\mathbb{D}$,

with natural graph $NG(\mathbb{D})$,

and DCJ halving distance $h = \mathrm{h}_{\mathrm{DCJ}}(\mathbb{D}) = n - |\mathcal{C}_e| - \left\lfloor \frac{|\mathcal{P}_o|}{2} \right\rfloor$:

1. For $i = 1$ to h :
   - Find and apply one optimal DCJ operation.

2. NG is now a simple collection of 2-cycles and 1-paths.
   Reconstruct the perfectly duplicated genome $2 \cdot \mathbb{H}$ from NG.

References

The complexity of the breakpoint median problem

(David Bryant)

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Genome Halving under DCJ Revisited

(Julia Mixtacki)

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