# Sorting by TDRL and iTDRL 

Bruno Schmidt, Tom Hartmann, Peter Stadler

## Genome Rearrangements

## Genome Rearrangements

- Not only genes undergo mutation
$\rightarrow$ Genome mutations, or genome rearrangements


## Genome Rearrangements

- Not only genes undergo mutation
$\rightarrow$ Genome mutations, or genome rearrangements
- Many rearrangement types have been considered
$\rightarrow$ Inversion, Transposition, inverse Transposition, Cut and Join, ...


## Genome Rearrangements

- Not only genes undergo mutation
$\rightarrow$ Genome mutations, or genome rearrangements
- Many rearrangement types have been considered $\rightarrow$ Inversion, Transposition, inverse Transposition, Cut and Join, ...
- Sorting Problem: Given a set of rearrangement types, what is the shortest sequence of those operations to transform one genome into another?


## Genome Rearrangements

- Not only genes undergo mutation
$\rightarrow$ Genome mutations, or genome rearrangements
- Many rearrangement types have been considered $\rightarrow$ Inversion, Transposition, inverse Transposition, Cut and Join, ...
- Sorting Problem: Given a set of rearrangement types, what is the shortest sequence of those operations to transform one genome into another?
- Many rearrangement models have been considered
$\rightarrow$ Inversion + Transposition, Transposition + inverse Transposition, ...
$\rightarrow$ Depending on rearrangement types considered, sorting problem is NP-hard


## Genome Rearrangements

- Not only genes undergo mutation
$\rightarrow$ Genome mutations, or genome rearrangements
- Many rearrangement types have been considered
$\rightarrow$ Inversion, Transposition, inverse Transposition, Cut and Join, ...
- Sorting Problem: Given a set of rearrangement types, what is the shortest sequence of those operations to transform one genome into another?
- Many rearrangement models have been considered
$\rightarrow$ Inversion + Transposition, Transposition + inverse Transposition, ...
$\rightarrow$ Depending on rearrangement types considered, sorting problem is NP-hard
- The Tandem Duplication Random Loss/inverse Tandem Duplication Random Loss model can mimic most "popular" rearrangements, and we developed a polynomial time algorithm for the sorting problem with TDRL/iTDRL


## Genome Model

## Genome Model

- Unichromosomal Genomes can be modelled by permutations


## Genome Model

- Unichromosomal Genomes can be modelled by permutations



## Genome Model

- Unichromosomal Genomes can be modelled by permutations



## Genome Model

- Unichromosomal Genomes can be modelled by permutations
- "Strandedness" can be modelled by signed permutations $\rightarrow$ Important when considering inversion-like mutations



## Genome Model

- Unichromosomal Genomes can be modelled by permutations
- "Strandedness" can be modelled by signed permutations $\rightarrow$ Important when considering inversion-like mutations



## TDRL and iTDRL?

- Tandem Duplication Random Loss (TDRL) and inverse Tandem Duplication Random Loss (iTDRL)
$\rightarrow$ Duplication of genome/permutation (inverted for iTDRL)
$\rightarrow$ Followed by random loss of one copy for each gene


## TDRL and iTDRL?

- Tandem Duplication Random Loss (TDRL) and inverse Tandem Duplication Random Loss (iTDRL)
$\rightarrow$ Duplication of genome/permutation (inverted for iTDRL)
$\rightarrow$ Followed by random loss of one copy for each gene


TDRL

## TDRL and iTDRL?

- Tandem Duplication Random Loss (TDRL) and inverse Tandem Duplication Random Loss (iTDRL)
$\rightarrow$ Duplication of genome/permutation (inverted for iTDRL)
$\rightarrow$ Followed by random loss of one copy for each gene


TDRL
liTDRL

## TDRL and iTDRL?

- Tandem Duplication Random Loss (TDRL) and inverse Tandem Duplication Random Loss (iTDRL)
$\rightarrow$ Duplication of genome/permutation (inverted for iTDRL)
$\rightarrow$ Followed by random loss of one copy for each gene


TDRL
liTDRL
riTDRL

## Maximal Increasing Sign-Consistent Substrings (MISC)

## Maximal Increasing Sign-Consistent Substrings (MISC)

- "maximal increasing sign-consistent substrings" of a permutation:


## Maximal Increasing Sign-Consistent Substrings (MISC)

- "maximal increasing sign-consistent substrings" of a permutation:
$\rightarrow$ Substring: Appear as substring of the permutation


## Maximal Increasing Sign-Consistent Substrings (MISC)

- "maximal increasing sign-consistent substrings" of a permutation:
$\rightarrow$ Substring: Appear as substring of the permutation
$\rightarrow$ Increasing: Elements of appear in increasing/ascending order


## Maximal Increasing Sign-Consistent Substrings (MISC)

- "maximal increasing sign-consistent substrings" of a permutation:
$\rightarrow$ Substring: Appear as substring of the permutation
$\rightarrow$ Increasing: Elements of appear in increasing/ascending order
$\rightarrow$ Maximal: Cannot be extended (to left or right) in permutation


## Maximal Increasing Sign-Consistent Substrings (MISC)

- "maximal increasing sign-consistent substrings" of a permutation:
$\rightarrow$ Substring: Appear as substring of the permutation
$\rightarrow$ Increasing: Elements of appear in increasing/ascending order
$\rightarrow$ Maximal: Cannot be extended (to left or right) in permutation
$\rightarrow$ Sign-Consistent: Contain only positive or negative elements


## Maximal Increasing Sign-Consistent Substrings (MISC)

- "maximal increasing sign-consistent substrings" of a permutation:
$\rightarrow$ Substring: Appear as substring of the permutation
$\rightarrow$ Increasing: Elements of appear in increasing/ascending order
$\rightarrow$ Maximal: Cannot be extended (to left or right) in permutation
$\rightarrow$ Sign-Consistent: Contain only positive or negative elements

$$
\pi=\left(\begin{array}{cccccccc}
3 & 7 & -6 & -2 & -1 & 5 & -8
\end{array}\right)
$$

## Maximal Increasing Sign-Consistent Substrings (MISC)

- "maximal increasing sign-consistent substrings" of a permutation:
$\rightarrow$ Substring: Appear as substring of the permutation
$\rightarrow$ Increasing: Elements of appear in increasing/ascending order
$\rightarrow$ Maximal: Cannot be extended (to left or right) in permutation
$\rightarrow$ Sign-Consistent: Contain only positive or negative elements

$$
\pi=(37-6-2-145-8)
$$

## Maximal Increasing Sign-Consistent Substrings (MISC)

- "maximal increasing sign-consistent substrings" of a permutation:
$\rightarrow$ Substring: Appear as substring of the permutation
$\rightarrow$ Increasing: Elements of appear in increasing/ascending order
$\rightarrow$ Maximal: Cannot be extended (to left or right) in permutation
$\rightarrow$ Sign-Consistent: Contain only positive or negative elements

$$
\pi=(37-6-2-145-8)
$$

## Maximal Increasing Sign-Consistent Substrings (MISC)

- "maximal increasing sign-consistent substrings" of a permutation:
$\rightarrow$ Substring: Appear as substring of the permutation
$\rightarrow$ Increasing: Elements of appear in increasing/ascending order
$\rightarrow$ Maximal: Cannot be extended (to left or right) in permutation
$\rightarrow$ Sign-Consistent: Contain only positive or negative elements

$$
\pi=(37-6-2-145-8)
$$

## Maximal Increasing Sign-Consistent Substrings (MISC)

- "maximal increasing sign-consistent substrings" of a permutation:
$\rightarrow$ Substring: Appear as substring of the permutation
$\rightarrow$ Increasing: Elements of appear in increasing/ascending order
$\rightarrow$ Maximal: Cannot be extended (to left or right) in permutation
$\rightarrow$ Sign-Consistent: Contain only positive or negative elements

$$
\pi=(37-6-2-145-8)
$$

## Maximal Increasing Sign-Consistent Substrings (MISC)

- "maximal increasing sign-consistent substrings" of a permutation:
$\rightarrow$ Substring: Appear as substring of the permutation
$\rightarrow$ Increasing: Elements of appear in increasing/ascending order
$\rightarrow$ Maximal: Cannot be extended (to left or right) in permutation
$\rightarrow$ Sign-Consistent: Contain only positive or negative elements

$$
\pi=(37-6-2-145-8)
$$

- MISC-Encoding einer Permutation:


## Maximal Increasing Sign-Consistent Substrings (MISC)

- "maximal increasing sign-consistent substrings" of a permutation:
$\rightarrow$ Substring: Appear as substring of the permutation
$\rightarrow$ Increasing: Elements of appear in increasing/ascending order
$\rightarrow$ Maximal: Cannot be extended (to left or right) in permutation
$\rightarrow$ Sign-Consistent: Contain only positive or negative elements

$$
\pi=(37-6-2-145-8)
$$

- MISC-Encoding einer Permutation:
- Each MISC-substring is assigned a letter ( $p$ or $n$ )


## Maximal Increasing Sign-Consistent Substrings (MISC)

- "maximal increasing sign-consistent substrings" of a permutation:
$\rightarrow$ Substring: Appear as substring of the permutation
$\rightarrow$ Increasing: Elements of appear in increasing/ascending order
$\rightarrow$ Maximal: Cannot be extended (to left or right) in permutation
$\rightarrow$ Sign-Consistent: Contain only positive or negative elements

$$
\pi=(37-6-2-145-8)
$$

- MISC-Encoding einer Permutation:
- Each MISC-substring is assigned a letter ( $p$ or $n$ )
- Capture number, and structure of MISC-substrings


## Maximal Increasing Sign-Consistent Substrings (MISC)

- "maximal increasing sign-consistent substrings" of a permutation:
$\rightarrow$ Substring: Appear as substring of the permutation
$\rightarrow$ Increasing: Elements of appear in increasing/ascending order
$\rightarrow$ Maximal: Cannot be extended (to left or right) in permutation
$\rightarrow$ Sign-Consistent: Contain only positive or negative elements

$$
\pi=\left(\begin{array}{llll}
3 & 7 & -6-2 & -1
\end{array} 45-8\right)
$$

- MISC-Encoding einer Permutation:
- Each MISC-substring is assigned a letter ( $p$ or $n$ )
- Capture number, and structure of MISC-substrings
- Allow us to ignore pesky integers


## Maximal Increasing Sign-Consistent Substrings (MISC)

- "maximal increasing sign-consistent substrings" of a permutation:
$\rightarrow$ Substring: Appear as substring of the permutation
$\rightarrow$ Increasing: Elements of appear in increasing/ascending order
$\rightarrow$ Maximal: Cannot be extended (to left or right) in permutation
$\rightarrow$ Sign-Consistent: Contain only positive or negative elements
- MISC-Encoding einer Permutation:
- Each MISC-substring is assigned a letter ( $p$ or $n$ )
- Capture number, and structure of MISC-substrings
- Allow us to ignore pesky integers



## TDRL, iTDRL, and MISC-substrings



## TDRL, iTDRL, and MISC-substrings



## TDRL, iTDRL, and MISC-substrings



## TDRL, iTDRL, and MISC-substrings



## MISC-Substring Patterns

## MISC-Substring Patterns



- MISC-encoding of permutation after applying TDRL/iTDRL continuously follows a pattern $\rightarrow$ different orders of applying TDRL/iTDRL yields different MISC-Substring Patterns


## MISC-Substring Patterns



## MISC-Substring Patterns



## An Algorithm

## Algorithm - Sketch:



## An Algorithm

## Algorithm - Sketch:

1. Greedy matching to fitting pattern.


## An Algorithm

## Algorithm - Sketch:

1. Greedy matching to fitting pattern.
2. Use pattern as "sorting guide".


## An Algorithm

## Algorithm - Sketch:

1. Greedy matching to fitting pattern.
2. Use pattern as "sorting guide".
3. Sort matching intervals sequentially.


## An Algorithm

## Algorithm - Sketch:

1. Greedy matching to fitting pattern.
2. Use pattern as "sorting guide".
3. Sort matching intervals sequentially.
4. Derive a TDRL/iTDRL corresponding to sorting step.


## An Algorithm

## Algorithm - Sketch:

1. Greedy matching to fitting pattern.
2. Use pattern as "sorting guide".
3. Sort matching intervals sequentially.
4. Derive a TDRL/iTDRL corresponding to sorting step.
5. Repeat 1-4, until sorted.


## An Algorithm

## Algorithm - Sketch:

1. Greedy matching to fitting pattern.
2. Use pattern as "sorting guide".
3. Sort matching intervals sequentially.
4. Derive a TDRL/iTDRL corresponding to sorting step.
5. Repeat 1-4, until sorted.


## An Algorithm

## Algorithm - Sketch:

$$
n \cap p p n p
$$

1. Greedy matching to fitting pattern.
2. Use pattern as "sorting guide".
3. Sort matching intervals sequentially.
4. Derive a TDRL/iTDRL corresponding to sorting step.

прпр $п p n p$
5. Repeat 1-4, until sorted.


## An Algorithm

## Algorithm - Sketch:

1. Greedy matching to fitting pattern.
2. Use pattern as "sorting guide".
3. Sort matching intervals sequentially.
4. Derive a TDRL/iTDRL corresponding to sorting step.
5. Repeat 1-4, until sorted.


## An Algorithm

## Algorithm - Sketch:

1. Greedy matching to fitting pattern.
2. Use pattern as "sorting guide".
3. Sort matching intervals sequentially.
4. Derive a TDRL/iTDRL corresponding to sorting step.
5. Repeat 1-4, until sorted.


## An Algorithm

## Algorithm - Sketch:

1. Greedy matching to fitting pattern.
2. Use pattern as "sorting guide".
3. Sort matching intervals sequentially.
4. Derive a TDRL/iTDRL corresponding to sorting step.
5. Repeat 1-4, until sorted.


## An Algorithm

## Algorithm - Sketch:

1. Greedy matching to fitting pattern.
2. Use pattern as "sorting guide".
3. Sort matching intervals sequentially.
4. Derive a TDRL/iTDRL corresponding to sorting step.
5. Repeat 1-4, until sorted.


## An Algorithm

## Algorithm - Sketch:

1. Greedy matching to fitting pattern.
2. Use pattern as "sorting guide".
3. Sort matching intervals sequentially.
4. Derive a TDRL/iTDRL corresponding to sorting step.
5. Repeat 1-4, until sorted.


## An Algorithm

## Algorithm - Sketch:

1. Greedy matching to fitting pattern.
2. Use pattern as "sorting guide".
3. Sort matching intervals sequentially.
4. Derive a TDRL/iTDRL corresponding to sorting step.
5. Repeat 1-4, until sorted.


## An Algorithm

## Algorithm - Sketch:

1. Greedy matching to fitting pattern.
2. Use pattern as "sorting guide".
3. Sort matching intervals sequentially.
4. Derive a TDRL/iTDRL corresponding to sorting step.
5. Repeat 1-4, until sorted.


## An Algorithm

## Algorithm - Sketch:

1. Greedy matching to fitting pattern.
2. Use pattern as "sorting guide".
3. Sort matching intervals sequentially.
4. Derive a TDRL/iTDRL corresponding to sorting step.
5. Repeat 1-4, until sorted.


## An Algorithm

## Algorithm - Sketch:

1. Greedy matching to fitting pattern.
2. Use pattern as "sorting guide".
3. Sort matching intervals sequentially.
4. Derive a TDRL/iTDRL corresponding to sorting step.
5. Repeat 1-4, until sorted.

$n p n p$

## An Algorithm

## Algorithm - Sketch:

1. Greedy matching to fitting pattern.
2. Use pattern as "sorting guide".
3. Sort matching intervals sequentially.
4. Derive a TDRL/iTDRL corresponding to sorting step.
5. Repeat 1-4, until sorted.


## An Algorithm

## Algorithm - Sketch:

1. Greedy matching to fitting pattern.
2. Use pattern as "sorting guide".
3. Sort matching intervals sequentially.
4. Derive a TDRL/iTDRL corresponding to sorting step.
5. Repeat 1-4, until sorted.

$n p n p$

## An Algorithm

## Algorithm - Sketch:

1. Greedy matching to fitting pattern.
2. Use pattern as "sorting guide".
3. Sort matching intervals sequentially.
4. Derive a TDRL/iTDRL corresponding to sorting step.
5. Repeat 1-4, until sorted.


## An Algorithm

## Algorithm - Sketch:

1. Greedy matching to fitting pattern.
2. Use pattern as "sorting guide".
3. Sort matching intervals sequentially.
4. Derive a TDRL/iTDRL corresponding to sorting step.
5. Repeat 1-4, until sorted.

$n p n p$

## An Algorithm

## Algorithm - Sketch:

1. Greedy matching to fitting pattern.
2. Use pattern as "sorting guide".
3. Sort matching intervals sequentially.
4. Derive a TDRL/iTDRL corresponding to sorting step.
5. Repeat 1-4, until sorted.


## An Algorithm

## Algorithm - Sketch:

1. Greedy matching to fitting pattern.
2. Use pattern as "sorting guide".
3. Sort matching intervals sequentially.
4. Derive a TDRL/iTDRL corresponding to sorting step.
5. Repeat 1-4, until sorted.

$n p n p$

## An Algorithm

## Algorithm - Sketch:

1. Greedy matching to fitting pattern.
2. Use pattern as "sorting guide".
3. Sort matching intervals sequentially.
4. Derive a TDRL/iTDRL corresponding to sorting step.
5. Repeat 1-4, until sorted.


## An Algorithm

## Algorithm - Sketch:

1. Greedy matching to fitting pattern.
2. Use pattern as "sorting guide".
3. Sort matching intervals sequentially.
4. Derive a TDRL/iTDRL corresponding to sorting step.
5. Repeat 1-4, until sorted.

$n p n p$

## An Algorithm

## Algorithm - Sketch:

1. Greedy matching to fitting pattern.
2. Use pattern as "sorting guide".
3. Sort matching intervals sequentially.
4. Derive a TDRL/iTDRL corresponding to sorting step.
5. Repeat 1-4, until sorted.


## Sorting by TDRL and iTDRL

## Sorting by TDRL and iTDRL



## Complexity



## Complexity



## Complexity

- Number of characters in MISC-encoding: $\mathcal{O}(n)$

- Number of characters in matching MISC-pattern: $\mathcal{O}(n)$


## Complexity

- Number of characters in MISC-encoding: $\mathcal{O}(n)$

- Number of characters in matching MISC-pattern: $\mathcal{O}(n)$
- Number of patterns to check: $\mathcal{O}(\log n)$


## Complexity

- Number of characters in MISC-encoding: $\mathcal{O}(n)$

- Number of characters in matching MISC-pattern: $\mathcal{O}(n)$
- Number of patterns to check: $\mathcal{O}(\log n)$
- Check which pattern MISC-encoding is subsequence of: $\mathcal{O}(n)$


## Complexity

- Number of characters in MISC-encoding: $\mathcal{O}(n)$

- Number of characters in matching MISC-pattern: $\mathcal{O}(n)$
- Number of patterns to check: $\mathcal{O}(\log n)$
- Check which pattern MISC-encoding is subsequence of: $\mathcal{O}(n)$
- Sorting of permutation: $\mathcal{O}(\log n)$ sorting steps with $\mathcal{O}(n)$ cost


## Complexity

- Number of characters in MISC-encoding: $\mathcal{O}(n)$

- Number of characters in matching MISC-pattern: $\mathcal{O}(n)$
- Number of patterns to check: $\mathcal{O}(\log n)$
- Check which pattern MISC-encoding is subsequence of: $\mathcal{O}(n)$
- Sorting of permutation: $\mathcal{O}(\log n)$ sorting steps with $\mathcal{O}(n)$ cost


## Conclusion



## Conclusion

- TDRL/iTDRL distance between the identity, and any other permutation $\pi$ is bounded by the number of characters in $\pi$ 's MISCencoding (logarithmic).
$\rightarrow$ The sorting scenario can be computed in $\mathcal{O}(n \log n)$.


## Conclusion



- TDRL/iTDRL distance between the identity, and any other permutation $\pi$ is bounded by the number of characters in $\pi$ 's MISCencoding (logarithmic).
$\rightarrow$ The sorting scenario can be computed in $\mathcal{O}(n \log n)$.
- Powerful model as, for example for metazoan mitochondria, at most 7 TDRLs/iTDRLs are necessary to rearrange any of their gene orders into another.


## Conclusion



- TDRL/iTDRL distance between the identity, and any other permutation $\pi$ is bounded by the number of characters in $\pi$ 's MISCencoding (logarithmic).
$\rightarrow$ The sorting scenario can be computed in $\mathcal{O}(n \log n)$.
- Powerful model as, for example for metazoan mitochondria, at most 7 TDRLs/iTDRLs are necessary to rearrange any of their gene orders into another.
- Biological constraints need to be considered
$\rightarrow$ Keep common gene clusters at each sorting step
$\rightarrow$ restrict number of genes on which a TDRL/iTDRL can act on

