Trapezoid Graphs, Independent Sets, and Whole Genome Comparisons

Raluca Uricaru, Eric Rivals

LIRMM, CNRS Université de Montpellier 2

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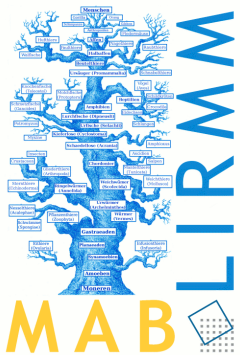

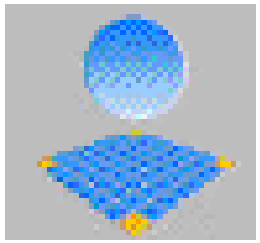

Summary

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Problem and Motivation

Align two or several genomic sequences to determine resemblances between them ;

- infer knowledge from one sequence to other highly similar sequences ;
- identify the conserved parts between sequences indicating common biological components ;
- identify differences between sequences responsible for what distinguishes them (e.g., virulence, pathogenicity).

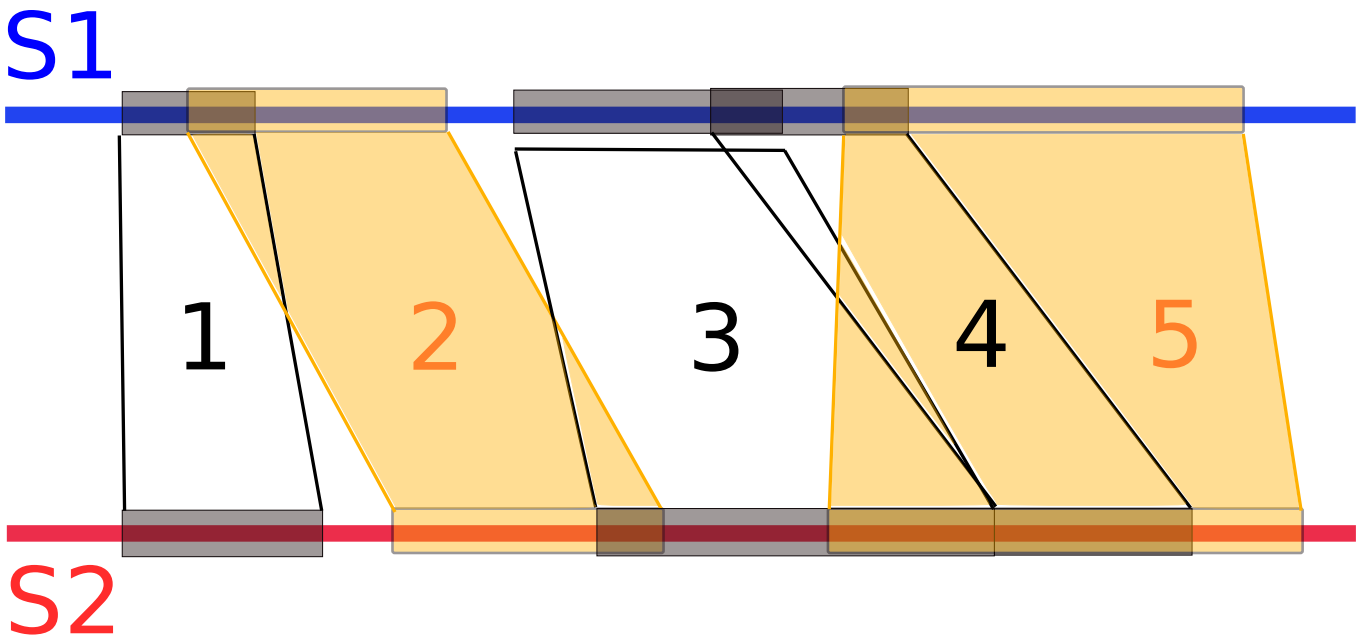
General Method for Pairwise Alignment

- complex problem due to the sizes of the genomic sequences ;
- 3-phase heuristic called the "anchor based strategy" :
  1. computation of local similarities (fragments) between sequences ; *using an external method* ;
  2. fragment chaining phase : selects a subset of non-overlapping, collinear anchors giving a maximum weighted chain ; *non-collinear anchors* $\longrightarrow$ *NP-complete problem* ;
  3. apply recursively the first 2 phases on yet not aligned regions ;

Summary

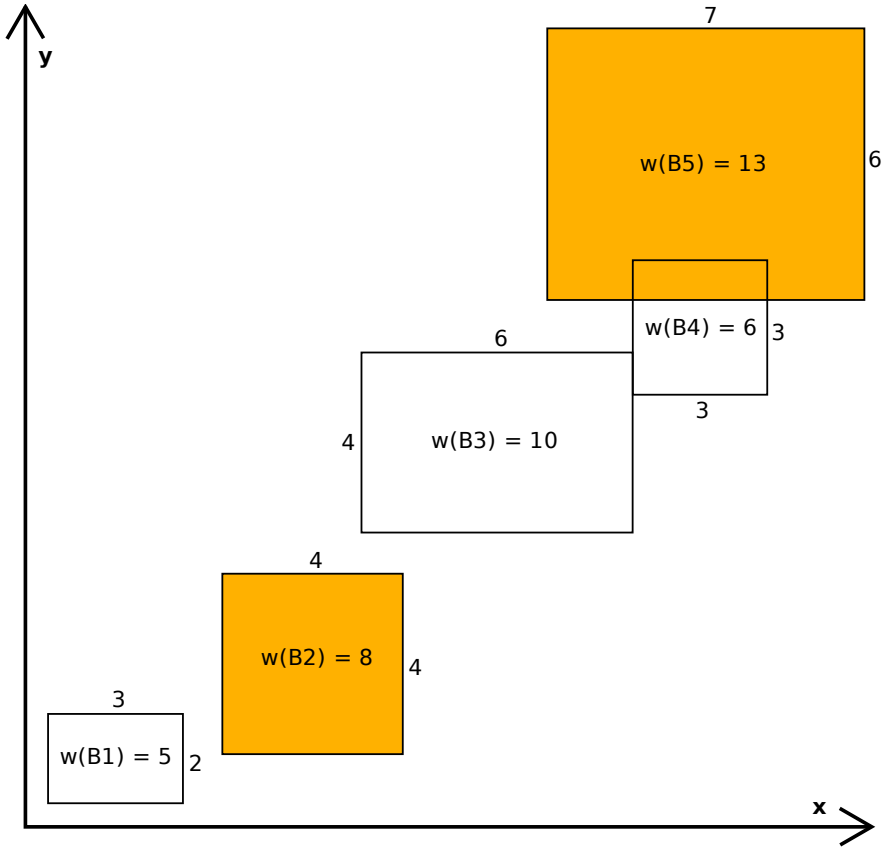
Fragment Chaining

Trapezoid Representation



Fragment Chaining

Box Representation



$$W[C_{max}] = w(B_2) + w(B_5) = 8 + 13 = 21$$

Fragment Chaining Definition

- n fragments represented as boxes in a dotplot : $\{B_1, \ldots, B_n\}$;
- lower corner of $B_i = l(B_i)$, upper corner of $B_i = u(B_i)$;
- if $u(B_i) < l(B_j)$ then $B_i \ll B_j$;
- the weight of a box B_i : $w(B_i) = \mid P_x(B_i) \mid + \mid P_y(B_i) \mid$
  P_x and P_y are the projections on the 2 axis ;

$\{B_{i_1}, B_{i_2}, \ldots B_{i_k}\}$ forms a chain C if $B_{i_j} \ll B_{i_{j+1}}$ $\forall j, 1 \leq j \leq k$, with $W[C] = \sum_{j=1}^{k} w(B_{i_j})$.

We are looking for the chain C_{max} giving the maximum weight.

Fragment Chaining

- equivalent to the maximum weighted independent set in the trapezoid graph corresponding to the trapezoid/box representations above ;

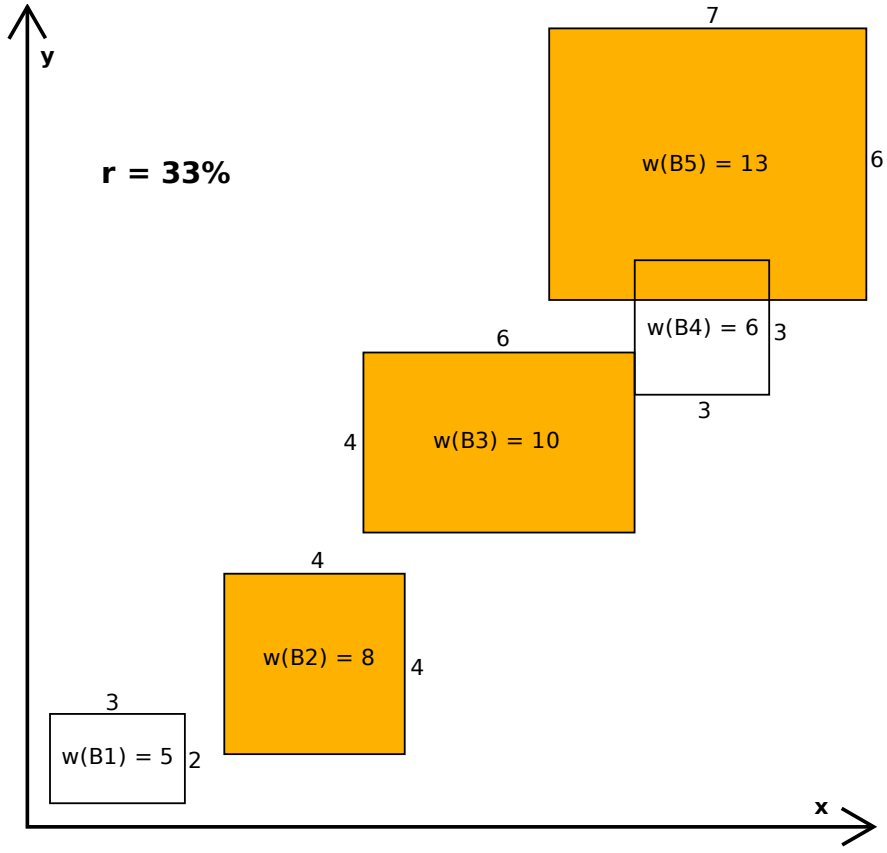
  [S. Felsner et al, *Trapezoid graphs and generalizations, geometry and algorithms*, 1995.]

- dynamic programming algorithm in $O(n \log(n))$, using the sweep line paradigm ;

Summary

Chaining with Overlaps

Box Representation



$$W[C_{max}] = w(B_2) + w(B_3) + w(B_5) - O_x(B_2, B_3) - O_x(B_3, B_5) = 28$$

Chaining with Overlaps

- overlap between B_i, B_j boxes on x-axis : $O_x(B_i, B_j) = \mid P_x(B_i) \cap P_x(B_j) \mid$
- maximum allowed overlap on x-axis : $r * min(\mid P_x(B_i) \mid, \mid P_x(B_j) \mid)$
- if $l(B_i) < l(B_j)$ and $O_x(B_i, B_j) \leq r * min(\mid P_x(B_i) \mid, \mid P_x(B_j) \mid)$ or $B_i \ll B_j$ then $B_i \ll_{r,x} B_j$. *Similarly on y-axis . . .*
- if $B_i \ll_{r,x} B_j$ and $B_i \ll_{r,y} B_j$ then $B_i \ll_r B_j$
- total overlap between B_i, B_j boxes : $O(B_i, B_j) = O_x(B_i, B_j) + O_y(B_i, B_j)$

$\{B_{i_1}, B_{i_2}, \ldots B_{i_k}\}$ forms a chain C if $B_{i_j} \ll_r B_{i_{j+1}}$ $\forall j, 1 \leq j \leq k$, with $W[C] = \sum_{j=1}^{k} w(B_{i_j}) - \sum_{j=1}^{k-1} O(B_{i_j}, B_{i_{j+1}})$.

We are looking for the chain C_{max} giving the maximum weight.

Remarks on Chaining With Overlaps

- adapted to all types of fragments ;
- makes sense from a biological point of view ;
- a straightforward but non-practical dynamic programming algorithm in $O(n^2)$, n = *number of fragments* ;
- partial order on boxes $\ll_r$ with the sweep line paradigm : novel algorithm in $O(n \log n + nm)$, where $m \leq r\% \max(\mid P_y \mid)$

Algorithm for Chaining With Overlaps

Algorithm 1: Maximum Weighted Chain with Overlaps

Data: $\mathcal{P}$ a set of points corresponding to the $2n + 4$ box corners
n boxes + 2 additional boxes corresponding to $\perp, \top$
Result: *Prev* a vector of previous boxes in the maximum weighted chain
begin
  foreach $p \in \mathcal{P}$ **in ascending order on** x**-coordinate do**
    if $\exists$ **a box** B_i**, with p the lower corner of** B_i **then**
      Case 1 *Compute* B_j*, the best previous box ending before* B_i ;
        /* B_j may overlap B_i on y-axis */
    else /* $\exists$ a box B_i, with p the upper corner of B_i */
      Case 2 *Update the weight and the predecessor of opened boxes* ;
        /* deal with overlaps on x-axis */
      Update the list of potential predecessors ;
  traceback(*Prev*[$\top$]);
end

Algorithm for Chaining With Overlaps

Algorithm 2: Maximum Weighted Chain with Overlaps

Data: $\mathcal{P}$ a set of points corresponding to the $2n + 4$ box corners
n boxes + 2 additional boxes corresponding to $\perp, \top$
Result: *Prev* a vector of previous boxes in the maximum weighted chain
begin
  foreach $p \in \mathcal{P}$ **in ascending order on** x**-coordinate do**
    if $\exists$ **a box** B_i**, with p the lower corner of** B_i **then**
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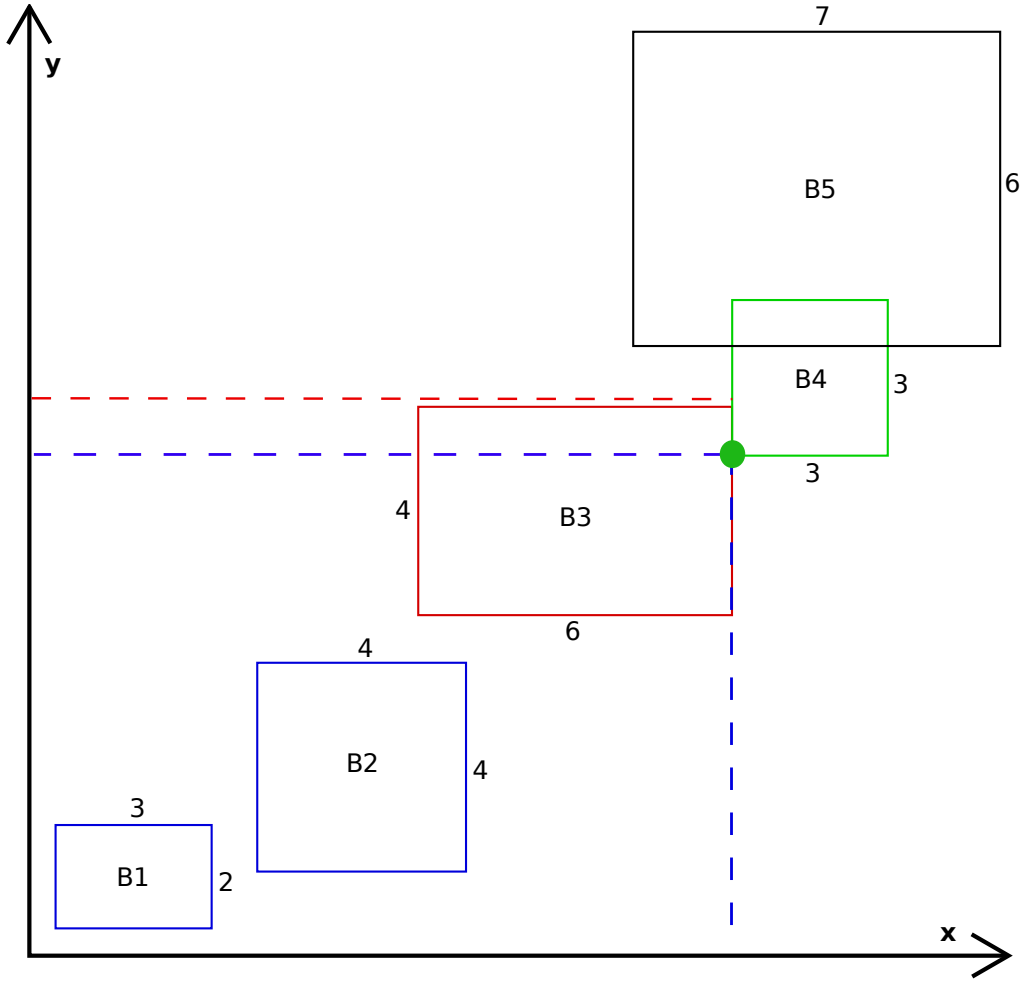
        /* B_j may overlap B_i on y-axis */
    else /* $\exists$ a box B_i, with p the upper corner of B_i */
      Case 2 *Update the weight and the predecessor of opened boxes* ;
        /* deal with overlaps on x-axis */
        Update the list of potential predecessors ;
  traceback(*Prev*[$\top$]);
end

Case 1

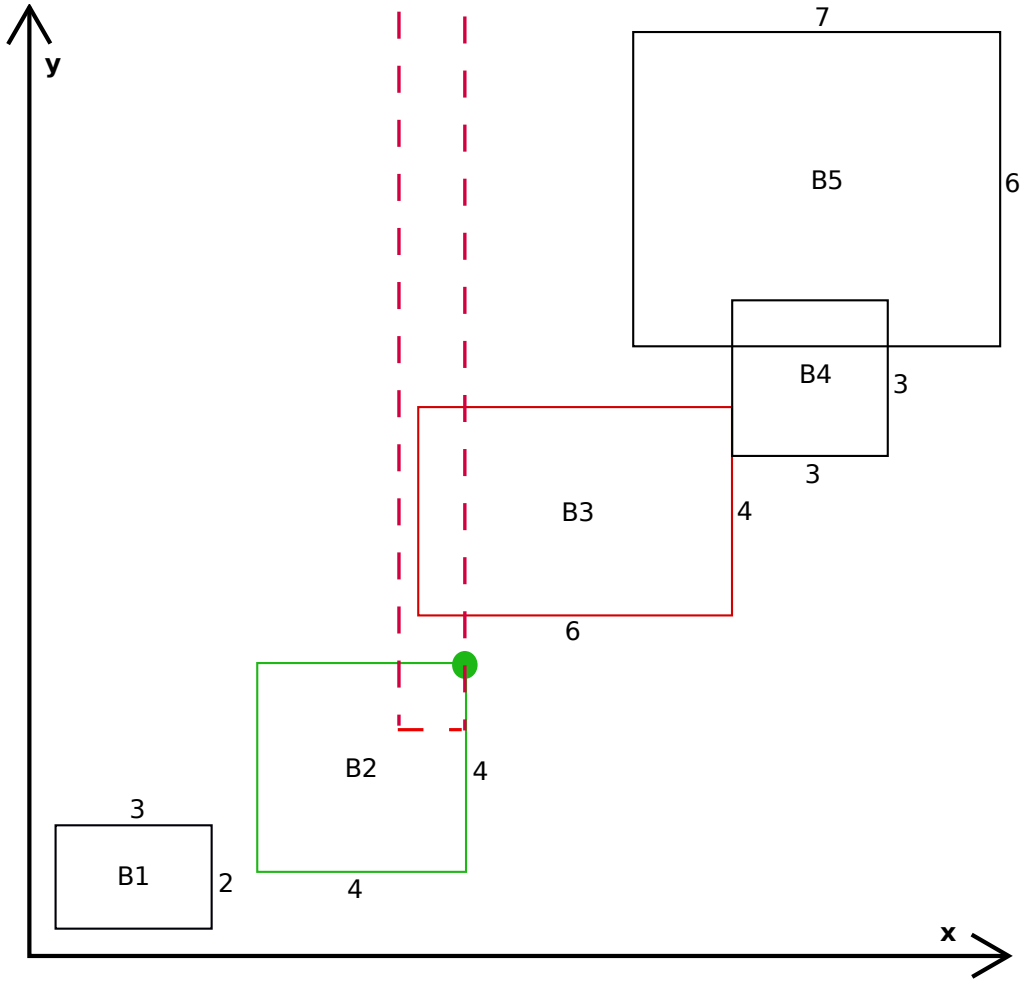
Compute B_j, the best previous box ending before B_i . . .



▸ Algorithm

Case 2

Update the weight and the predecessor of opened boxes . . .



Summary

Conclusion

- the chaining with proportional overlaps corresponds to an extended definition of a maximum weighted independent set including a tolerance notion ;
- the algorithm in $O(n \log n + nm)$ is very efficient in practice ;

  e.g., on a real case composed of 190000 fragments :
  $O(n^2)$ algorithm : $34 min$
  $O(n \log n + nm)$ algorithm : $< 2 min$;

- Support :

  CoCoGEN project
  http://www.lirmm.fr/~uricaru/CoCoGEN

Thank you for your attention !

Questions ?