CoCoGen meeting

Accuracy of the anchor-based strategy for genome alignment

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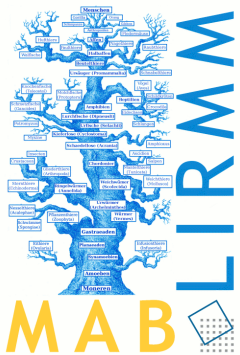

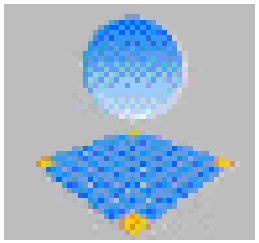

Summary

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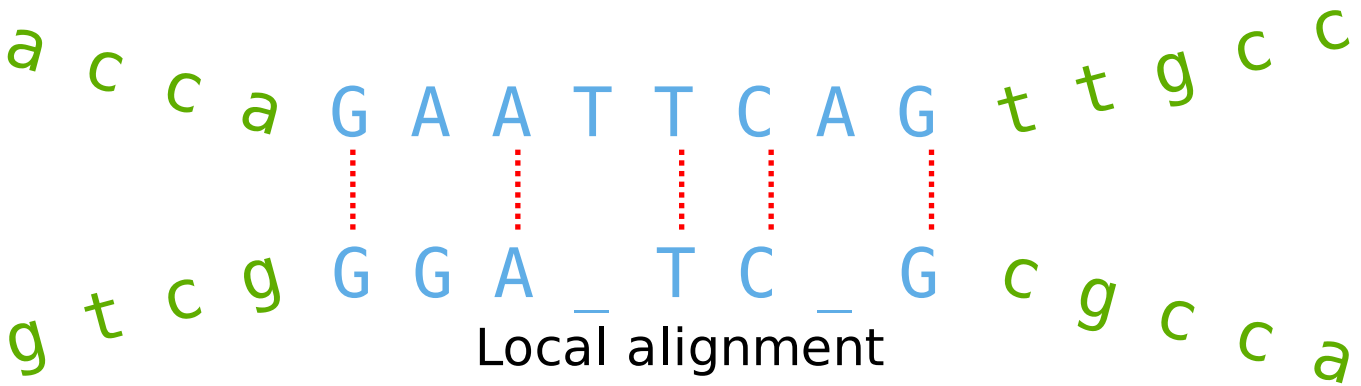
Motivation

Do I really have to explain this to YOU ?

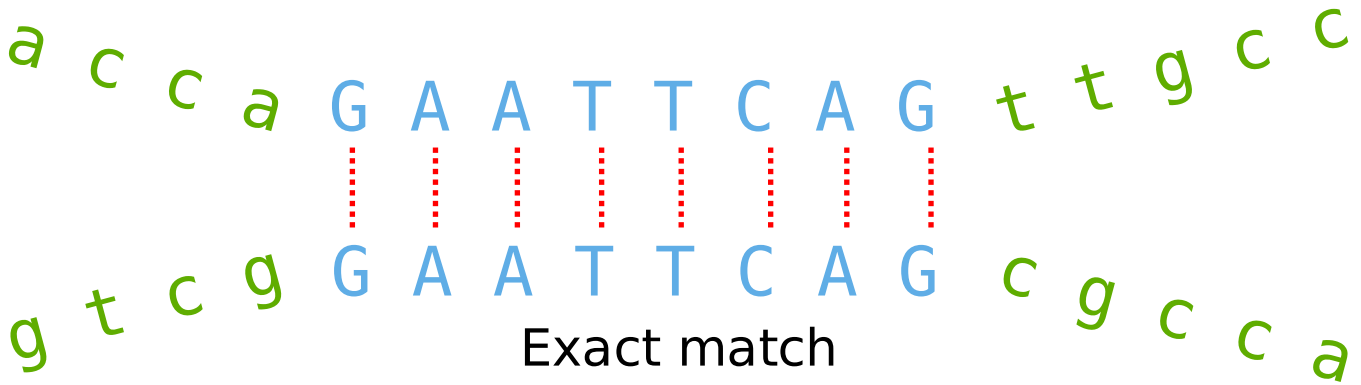
We are working along with the people from the

MOSAIC project
segmentation of bacterial genomes :
backbone & **variable segments**

Local alignments vs exact matches



Local alignment



Exact match

Genome alignment approaches

Local alignment

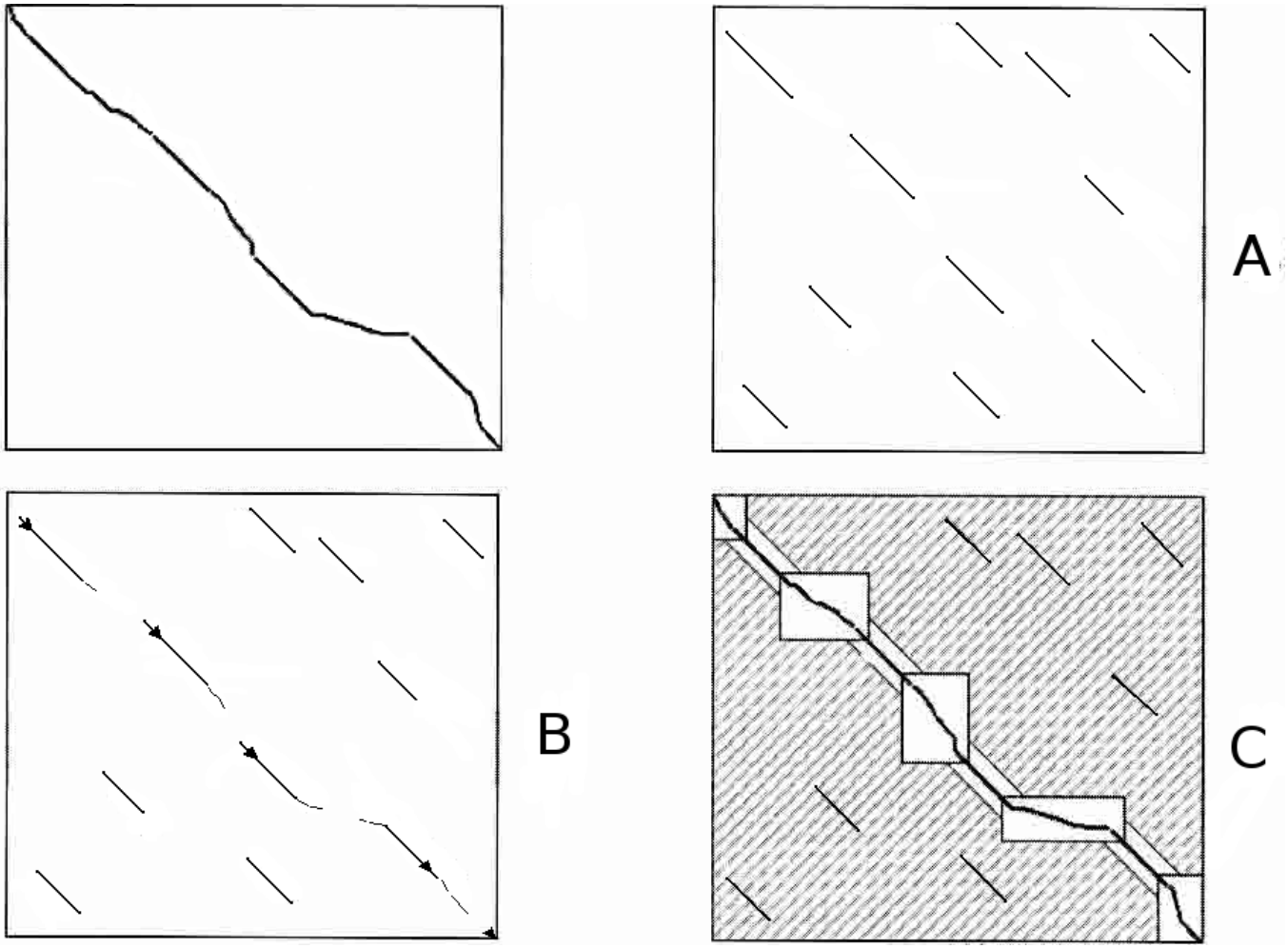
- in case of **genomic rearrangements**
- align common regions instead of the entire genomes
- for big, distant, rearranged genomes (e.g. *eukaryotes*)

Global alignment

- in case of collinear genomes
- technique : anchor-based, 3-phase method
- for closely related, non-rearranged genomes (e.g. *bacteria*)

Summary

Anchor-based, 3-phase method



Anchor-based, 3-phase method (2)

1. Computation of fragments
   pairwise similarity regions

2. Anchors computation (*chaining phase*)
   - *basis of the alignment*
   - *subset of non-overlapping fragments forming an optimal scoring, global chain*

3.
   - Recursive anchoring
     for each pair of yet unaligned regions between the anchors
   - "last chance align." with **ClustalW** [J.D. Thompson et al., 1994]

Global alignment (GA) programs

Present global alignment programs are heuristic variations on the **anchor based strategy**

- **MGA** [M. Hohl et al., 2002] (*does not deal with rearrangements*)
  1. compute **M**aximal **E**xact **M**atches (VMatch [S. Kurtz, 2003])
  2. select the set of anchors (Chainer [M.I. Abouelhoda et al., 2005])
     subset of non-overlapping MEMs forming the maximal scoring **consistent chain**

     consistent chain = increasing on both genomes
  3. recursive anchoring
     "last chance alignment"

Global alignment programs (2)

- **MAUVE** [A.C.E. Darling et al., 2004] (*handles rearrangements*)

  1. search for approximate matches using **spaced seeds**
  2. select a subset of non-overlapping anchors
     without imposing the consistency property

     use a heuristic consisting in finding a minimum partition in **L***ongest* **C***ollinear* **B***locks*
  3. *recursive anchoring*
     “last chance alignment”

Global alignment programs (3)

Non investigated questions on the *anchor based strategy*

Lack of evalution for :

- global accuracy
  benchmark, evaluation criteria & significance measure
- the influence of exact & approximate matches
- the impact of $\neq$ types of matches on chaining

1. Does the *anchor based strategy* produce satisfactory results on non-rearranged genomes ?
2. How can one deal with rearrangements ?

2 initial prototypes

To address the 1st previous question, we designed 2 prototypes for pairwise genome alignment without rearrangements

1. **VMatch + Chainer** (VC)

   simulate the first 2 phases of **MGA**

2. **Yass + Chainer** (YC)

   same outline as **MGA**
   replace **VMatch** by **Yass** [L. Noe et al., 2005]

   Yass = *fast similarity search tool based on spaced seeds*

   use local alignments instead of MEMs

Comments on the 2 prototypes

- frequent overlaps due to the use of local alignments (2^{nd} prot.)
  - overlaps should be taken into account in the chaining
  - proposed solution : "hierarchical chaining method" (3^{rd} prot.)
- not dealing with rearrangements may generate poor results :
  - singular inversions, complementary strands (all 3 prot.)
  - circularity (3^{rd} prot.)
  - other rearrangement events :
    successive inversions, translocations, duplications, . . .

    need chaining without consistency property : NP-complete prob ?

the 3rd prototype

3. **Yass + Hierarchical** (YH)

   replace the first 2 phases of **MGA** :

   - *use local alignments instead of MEMs*
   - *replace Chainer by* **greedy, hierarchical chaining method**

   Hierarchical method

   - *keep stronger simil. regardless of their conflicts with weaker ones*
   - *multiple level chaining heuristic, dealing with overlaps*

Summary

Benchmark

MOSAIC [H. Chiapello et al., 2005]

- public curated database of backbone alignments for intra species bacterial genomes
- 42 species from Genome Reviews [P. Sterk, 2006], except 5

  Buchnera aph., *Prochl. marinus*, *Synechococcus sp*, *Pseudomonas fluor.*, *Rhodopseudomonas pal.*

  excluded due to not satisfactory alignments
- alignments are made with :
  MAUVE (rearranged) & **MGA** (non-rearranged)
- parameters calibrated on *E-coli*
- backbone alignments were post-processed
  keep aligned gaps $\geq$ 76% *id%*

Global evaluation criteria

- complexity of the anchor chain
  number of anchors in the chain
- coverage
  total length of regions common to both sequences
  filtered cov. = cov. without aligned gaps <76% id%
- identity percentage (id%)
  ratio of identical bp in the segm. from the cov., over gen. len.
  filtered id%. = id% without aligned gaps <76% id%

Comparison protocol

- 42 bacterial species (236 intra-species genome pairs)
  - close, moderately divergent, rearranged genomes

  ⋆ *for exceptions, see the 5 species excluded from MOSAIC*
  - 94 collinear pairs, 142 rearranged pairs
  - existence of benchmark (**MOSAIC**)
- compare alignments obtained with **MGA**, **MAUVE**, **VC**, **YC** & **YH**
- 3 evaluation criteria (*see prev. slide*)
- tested several parameters and options, kept the best ones

Present achievements (MOSAIC)

MGA and MAUVE

- species with average good coverages
  Staphylococcus aureus : >90% both **MGA** and **MAUVE**
- coverage differences in different species
  Streptococcus thermophilus : 97% both **MGA** and **MAUVE**
  Synechococcus sp : <10% both **MGA** and **MAUVE**
- coverage differences inside a species
  Prochlorococcus marinus : [0, 78]% **MGA**, [6, 96]% **MAUVE**

Programs succeed in aligning some pairs and fail in others

Causes :

high level of divergence, rearrangements

Local similarities vs MEMs

YC/YH vs VC

YC vs VC

- compute the difference in cov. **YC**-**VC**
- $[-69, 81]$%, positive in 89 (over 236) cases
- unexpected bad results for close genome cases

  Cause : large overlaps of local align.
  Solution : **YH**

YH vs VC

- **YH** improves the cov. over **VC** : 11% in avg
- **YH** improves the cov. over **YC** : 19% in avg
- Example CP000046 vs BA000018 (*Staphylococcus aureus*)
  YC 64%, **VC** 88%, **YH** 99%

Hierarchical method vs MOSAIC

YH vs MGA/MAUVE

YH vs MGA on the 94 collinear pairs

- compute the difference in cov/id% **YH-MGA**
- cov : $[-4, 45]$%, 3% in avg
- positive in 52 cases, <-2% in 3 cases
- id% : $[1, 45]$%, 9% in avg

YH vs MAUVE on the 142 rearranged pairs

- **MAUVE** covers 21% more nucleotides than that of **YH**
- **MAUVE** has 18% more identities than **YH**

Summary

Discussion : evaluation of the anchor-based strategy

- we do not solve rearrangements and we do not do recursion steps
  However, we obtain
- gain in cov, id% and simplicity of chain complexity
  of **YH** over **MGA** and **VC**

  nb of anchors : <150 **YH**, >3000 **MAUVE**, >13000 **MGA**

Discussion : evaluation of the anchor-based strategy (2)

- in terms of filtered coverage and id%, **YH** improves **MGA** . . .
- and **MAUVE**, only in the case of

  divergent genomes (thanks to spaced seeds ?)
  what is happening with the aligned gaps ?

  Example (*Buchnera aphidicola* - 3 genome pairs)
  filtered coverage : **YH** improves **MGA**/**MAUVE** by 69%
  filtered id% : **YH** improves **MGA**/**MAUVE** by 47%

Conclusion

- pairwise alignment is incompletely solved nowadays
- heuristic anchor methods can be improved :
- quantitatively
  - local similarities
  - chaining with overlaps
- qualitatively : E-values for local similarities
  - improved backbone alignment
  - avoid alignment post-processing
- in terms of chain complexity
  - computationally less expensive
  - easy to biologically interpret

Short time perspectives

- recursive anchoring
  - successively search for similarities in non-aligned regions
  - "chained spaced seeds"

    knowing that the spaced seed (set) A is not found on step i, compute the best spaced seed (set) B for step i + 1
- dealing with rearrangements :
  method for non-consistent global alignment allowing overlaps

Short time perspectives (2)

- biological validation

  global, average values are not entirely relevant
- reinforce (test) the gain from using spaced seeds

  compare to BLAST
- use negative filters

  detect unique regions
  - validation method on the non-aligned regions
  - pre-processing step

Bibliography

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OMICS, 2006

- Support :

  CocoGEN
  http://www.lirmm.fr/~rivals/

  PlasmoExplore
  http://www.lirmm.fr/~brehelin/PlasmoExplore/

- Supplementary material available at :
  www.lirmm.fr/~uricaru/Appendix_RecombCG.html

Thank you for your attention !

Questions ?