Fine-Grained Parallel Genomic Computation

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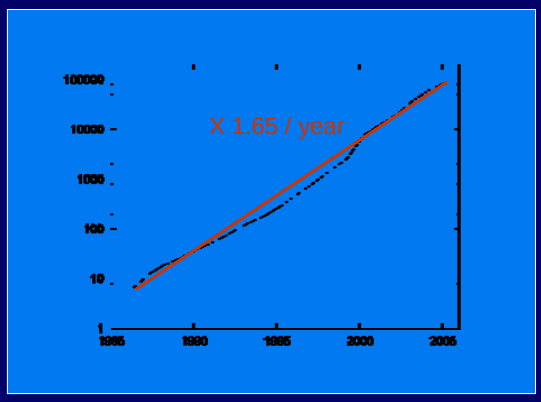
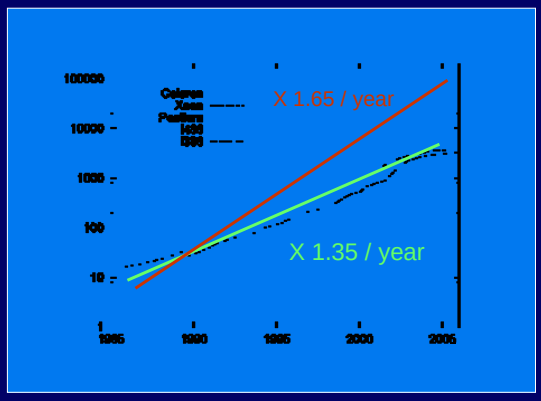
GenBank
nucleotide database



Microprocessor Performances



Data vs proc. performances

2006 : GenBank 120 Gbp
computational power: 12 Gbp/sec
→ time: 10s

2010 : GenBank 900 Gbp
computational power: 40 Gbp/sec
→ time: 25s

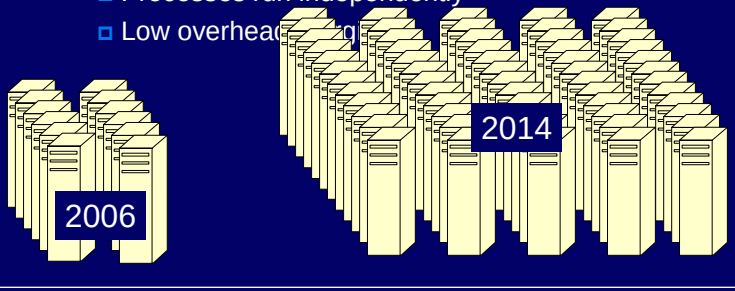
2014 : Genbank 6.6 Tbp
computational power: 130 Gbp/sec
→ time : 50s

1.65^4
7.4x

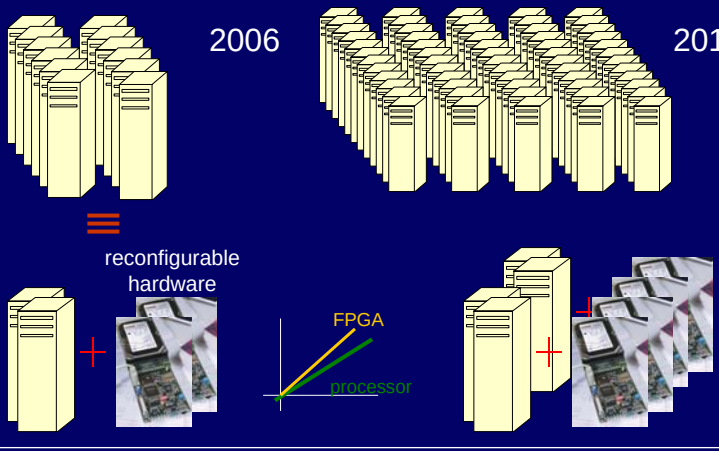
1.35^4
3.3x

Genomic processing

- High potential parallelism
  - Very efficient on large clusters
    - Data are dispatched on the nodes
    - Processes run independently
    - Low overhead



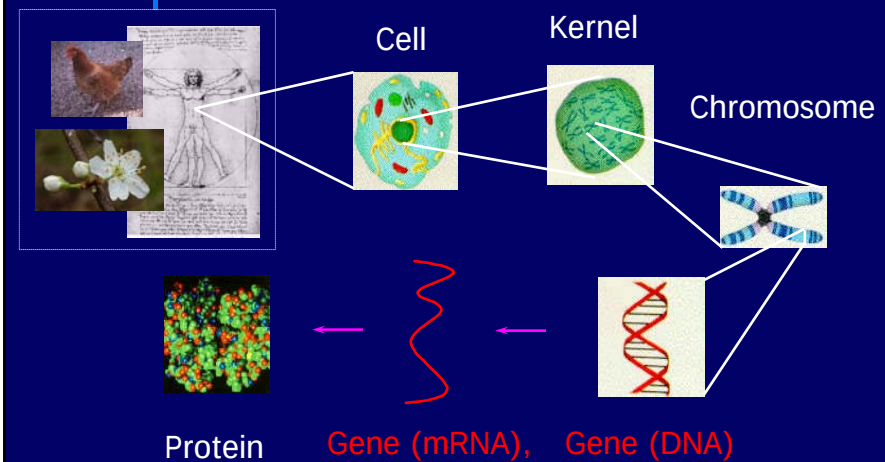
Fine-grained processing



Content

- Molecular biology
- Genomic processing examples
- Algorithms
  - Dynamic programming
  - Seed-based
- Hardware

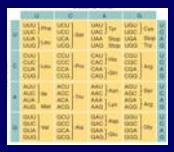
Organism → molecule



DNA → Protein

Nucleotide (nt) Base pair (bp)

TTTCGGAGAGAGGCCCCCCATGGACCAGGTTGAGACATGGACCAGGTTGATGCCAGGGATTAGGAGATGGACCTAAGGT — genome



Genetic code

ATG CCA GGG ATT AGG AGA TGG ACC TAA — gene

stop

M P G I R R W T — protein

amino acid (aa)

folding

function

Gene : text / function relationship

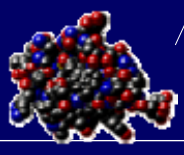
Gene A → Protein A →  → function

attaggtggaccaccattaccctta

g*tgga*caccat*acc

30% identity → same 3D structure

gcctgctggatcaccatgaccgagt

Gene X → Protein A' → 

Content

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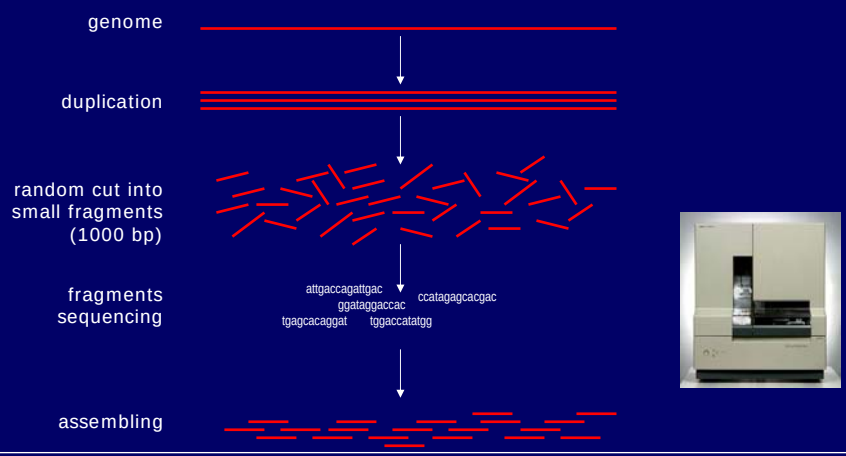
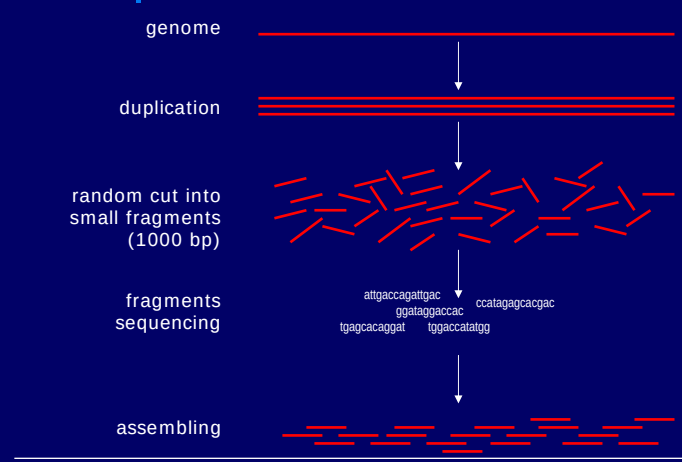
  - Shotgun sequencing
  - Content-based search
  - Motif detection
- Algorithms
- Hardware

Example 1
Shotgun sequencing



Example 1
Shotgun sequencing



Human

3×10^9 genome size

10 X coverage

3×10^7 number of fragments

5×10^{15} pairwise comparisons

Pairwise comparison

substitution error

insertion/deletion error

AGGACCAGGATGAGCCAGGGAT.AGGACCCAGAT

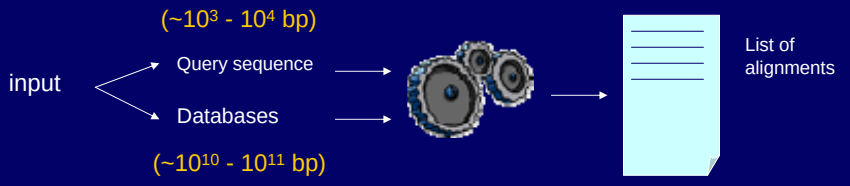
GCCTGGGATTAGGACCCAATTTGACCATATGAGCAC

errors:
- sequencing machines are not perfect
- polymorphism (when a few individuals are sequenced together)

Example 2
Content-based search

unknown gene ?

find in the genomic databases genes having similar text



Alignments

Sequence #1

ATTAGAGACACGATATAGAGCACACGAGTTAGGACCAGGGATTAGGGAGAGGACTAAATATAGAGCATATAGGAGGTAGGATCCAGGGATTAG

Sequence #2

TGGACCAGATTAGAGCCAGGATATTAGAGGATATAGGAAGGTAGGACCGGTAGACCAGTTAGACCAGGGATTTAGGGGGGATTTAGGAGTTAAA

Finding a local alignment
we don't know:
- *its length*
- *its position in both sequence*

```
TAGAGCATATAGGA.GGTAGGATCC
|||||  ||||||| |||||||  ||
TAGAGCATATAGGAAGGTAGGA.CC
```

Alignment scoring

Score = 21x1 -2x3 – 2x2

= 11

```
TAGAGCATATAGGA.GGTAGAATCC
|||||  ||||||||  |||||  |  ||
TAGAGGATATAGGAAGGTAGGA.CC
```

Score = $\sum$ elementary cost

- match +1
- mismatch -3
- gap -2

Necessary to compare alignments → extract the best ones

Content-based search

- Activity #1
  - May represent more than 70 % of bioinformatics computation
- NCBI (*National Center for Bioinformatics*)
  - Handle more than 100,000 queries each day
- Have to deal with
  - The exponential growth of the databases
  - The increasing user needs

Example 3
Motif detection

- Gene families may contain specific signatures
- A signature is a pattern of amino acids (aa)
- Example :
  - M x(1-3) K P L [I V L] x(2-4) [R S] L

M T E K P L V S T R L is valid

R or S

2 to 4 aa

- Can be expressed by regular expressions

Complex motifs

- 2 D structure

A A
T C
A – T
C – G
G – C
A – T

A T G C T G C T G A T G C T G A A C

- Can be expressed by string variable grammars
- Example
  - ATGCTGCTGATAGCATAACTGCTGCTGAAC

bio-palindrome

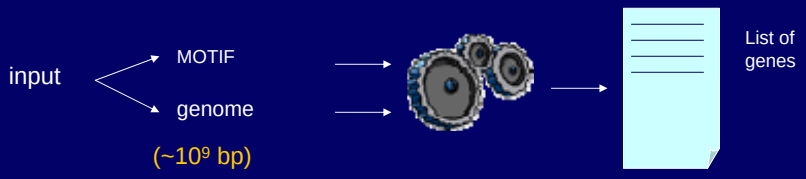
repeat

Y:3 Y x(2-6) X:4 x(3-6) $\overline{X}$ x(4) AA

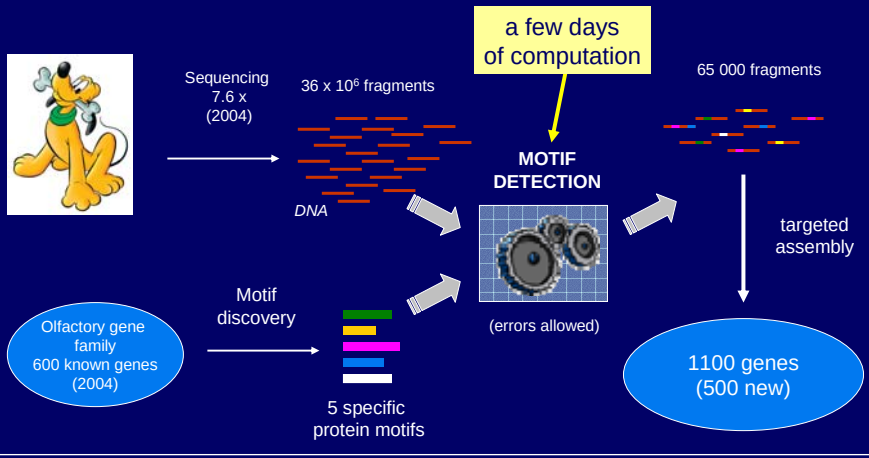
Motif search

signature

find in the genomic databases genes having this signature



Dog olfactory gene discovery



Genomic Processing features

- Data
  - Sequences
    - DNA (4 letters) – protein (20 letters)
  - Size : 10-100 Gbp (*1 Tbp → 2010*)
- Algorithms
  - Mostly string processing
    - approximate sequence comparison
  - Integer operation
  - Reduced arithmetic (8 – 16 bits)

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  - Seed-based
- Hardware

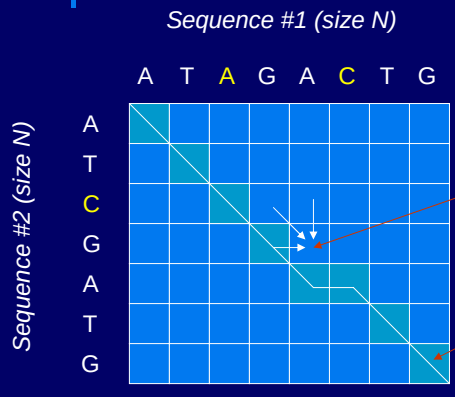
Dynamic programming

- Input : 2 (text) sequences
- Output : 1 alignment
- Idea:
  - Find the minimal number of operations to move from sequence #1 to sequence #2
- Needleman & Wunsh (1970)
  - Global alignment
- Smith & Waterman (1981)
  - Local alignment

```
GLOBAL
GLOCAL   substitution
.LOCAL   omission
LOCAL
```


Dynamic programming

Needleman & Wunsh – Global alignment



Complexity : N^2
(N = sequence length)

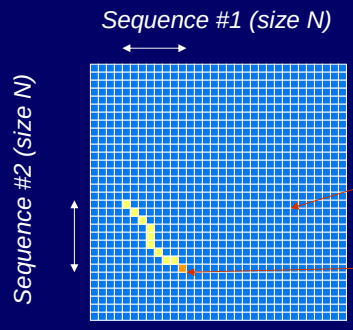
$F_{Global}(M_{i,j-1}, M_{i-1,j-1}, M_{i-1,j})$

Score of the alignment

```
A T A G A C T G
| |   | |   | |
A T C G A . T G
```

Dynamic programming

Smith & Waterman – Local alignment



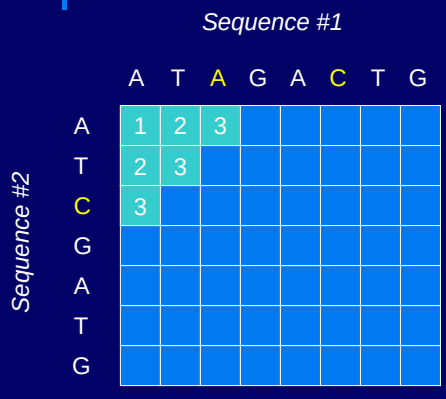
Complexity : N^2
(N = sequence length)

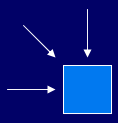
$F_{Local}\ (M_{i,j-1}, M_{i-1,j-1}, M_{i-1,j})$

Best score

```
A T A G A C T G
| |   | |   | |
A T C G A . T G
```


Data dependencies



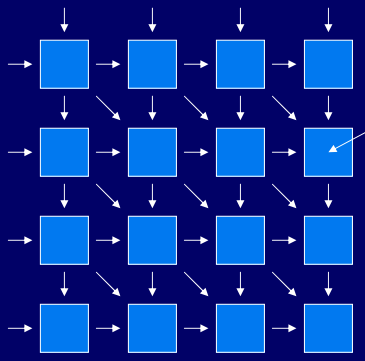


step 3

Computation requires
2N -1 steps

Possible speed-up : $N^2/2N-1 = N/2$

2D systolic architecture



1 systolic cell performs

$F(M_{i,j-1}, M_{i-1,j-1}, M_{i-1,j})$

N^2 cells → speed-up $\frac{N^2}{2N-1}$ ~ N/2

Bad efficiency

1D systolic architecture

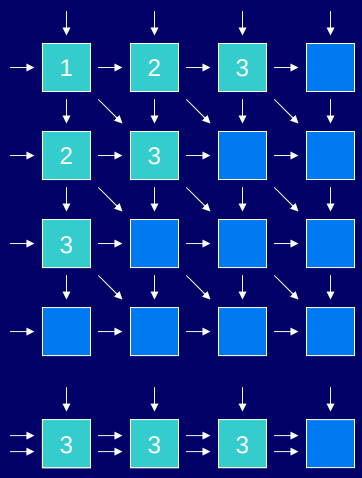
2D array :
- only one diagonal active at each step

1D array
- one cell emulates one column

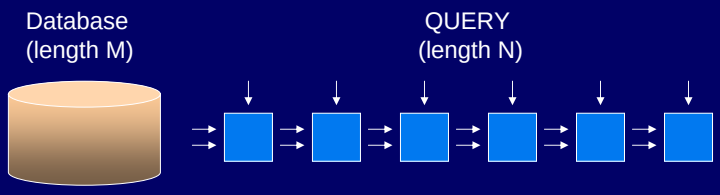
step 3

N cells → speed-up ~ N/2

better efficiency than 2D structure



Database scanning

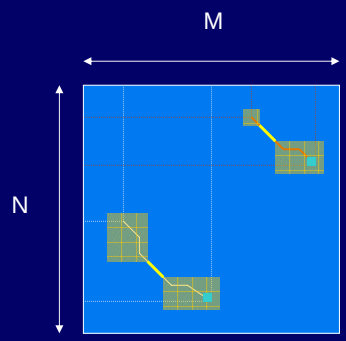


$$\text{Speed-up} = \frac{N \times M}{N + M - 1} = \sim N \quad (N << M)$$

Dynamic Programming *Conclusion*

- Advantages
  - Gives the exact solution
  - Efficient parallelization on 1D systolic architecture
- Drawback
  - Too high complexity (N^2) to handle large databases with sequential machines
    - Scan of GenBank can take a few hours
- Need of heuristic to decrease computation time
  - FASTA (*Pearson, Lipman 1988*)
  - BLAST (*Altschul et al. 1990*)

Seed-based algorithm *idea*



Local Alignments

Programming dynamic:

1. *Full matrix computation*
2. *Highest scores detection*
3. *Trace-back*

Seed-based idea:

1. *find "high similarity" regions from seeds*
2. *limit the search space near these regions*

Seeds ?

- A common word of K characters includes in both sequence

ATTAGGACCATTAGGCAGGACCTCCAGGATAGGACCCAGGAGTTAGAC

TTTAGGACACGAGGATATGGACCAGGCCCTTAGGCTGGACCGTGGTTAG

Seed ?

- A common word of K characters includes in both sequence

ATTAGGACCATTAGGCAGGACCTCCAGGATAGGACCCAGGAGTTAGAC

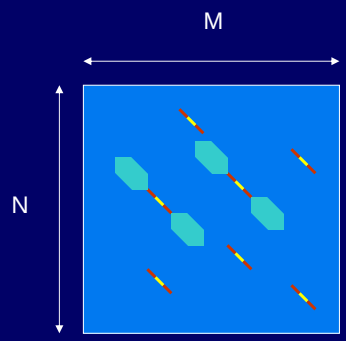
TTTAGGACACGAGGATATGGACCAGGCCCTTAGGCTGGACCGTGGTTAG

```
GACCATTAGGCAGGACC.T
|  ||  ||||||  ||||| |
G.CCCTTAGGCTGGACCGT
```


Seed based algorithm efficiency

- 100X – 1000X time faster than Programming Dynamic
  - Space search is drastically reduced
    → default k-word size = 11
- Large databases can be scanned in a few seconds
- Is there still room for fine-grained parallelism ?

Seed based algorithms



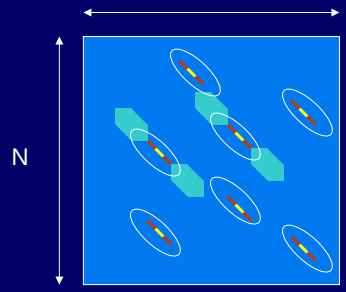
- k-word hit
- Ungapped alignment

if score > threshold

- gapped alignment

Profiling
~ 85 %
~ 12 %

Parallelization of seed based algorithms



2 sub levels of parallelism

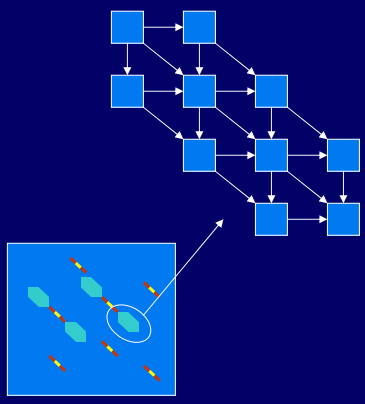
1 multiple gapped/ungapped alignments can be performed simultaneously

→ high data throughput

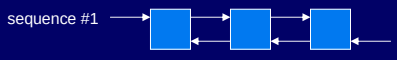
2 alignment computation

→ DP on a restricted area

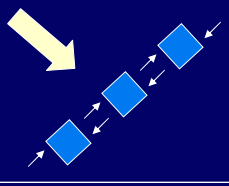
Dynamic programming on a restricted area



1D systolic architecture



Search space around D diagonals
→ D cells



Seed-based algorithms *Conclusion*

- Very powerful heuristic
  - *BLAST software can compute hundred of Mbp/sec*
- Adopted by the scientific community
  - *BLAST is the reference software*
- High potential for fine-grained parallelism
  - However: more complicated than dynamic programming (data access)

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2 main classes of applications

- Intensive computation
  - Shotgun
  - Genome structure analysis
    - Ex: Repeat sequences
  - Genome comparison
    - Ex: Human ←→ mouse
- Database querying
  - One (small) query against the databases

must be done as fast as possible

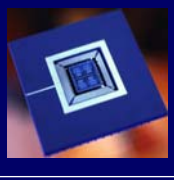
must be done in a few secondes

Clusters

- Coarse grained parallelism
- Well suited for intensive computation
  - Large tasks can run independently
  - Limited I/O operations : data are intensively re-used
- Database querying:
  - Data access can be a bottleneck

VLSI Accelerators

- A few realizations essentially for speeding up DP algorithm (systolic array)
- Advantage
  - Very fast: 50X – 100X
- Drawback
  - Chip need to be periodically redesigned
    - Expensive, niche market
  - Lake of flexibility
    - S&W algorithm



FPGA Accelerators

- Suppress the VLSI drawback
  - Standard components
  - Can be reconfigured indefinitely
- Commercial products available
  - Ex: Decypher Engine from TimeLogic Inc.
    - S&W algorithm
    - BLAST-like algorithm
    - HMM motif search
    - . . .
- Performances: 50X – 100X

Hardware accelerators General *conclusion*

- Fine-grained parallelization
- Speed-up: 50 to 100 compared to microprocessors
- Can be mixed with clusters
  - *i.e. node = 1 processor + 1 accelerator*
- Well suited for intensive computation
- Database querying
  - Do not solve the data access problem

Querying databases

- First bioinformatics activity
- Genomic databases grow faster than
  - processor performances
  - data access time (disks!)
- Solutions
  - Keep the data in main memory and parallelized the accesses
    - → *Databases are dispatched on memory cluster nodes*
  - Design a large parallel fast access memory