

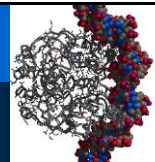
Exemple of Fast Translation Algorithm

Object-oriented modeling and post-genomic
biology : Programming Analogies

David Hill

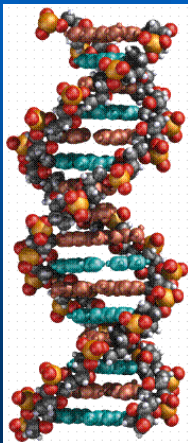
Former Blaise Pascal University > UCA)
Université Clermont Auvergne
UMR CNRS 6158 : LIMOS
France

Key points

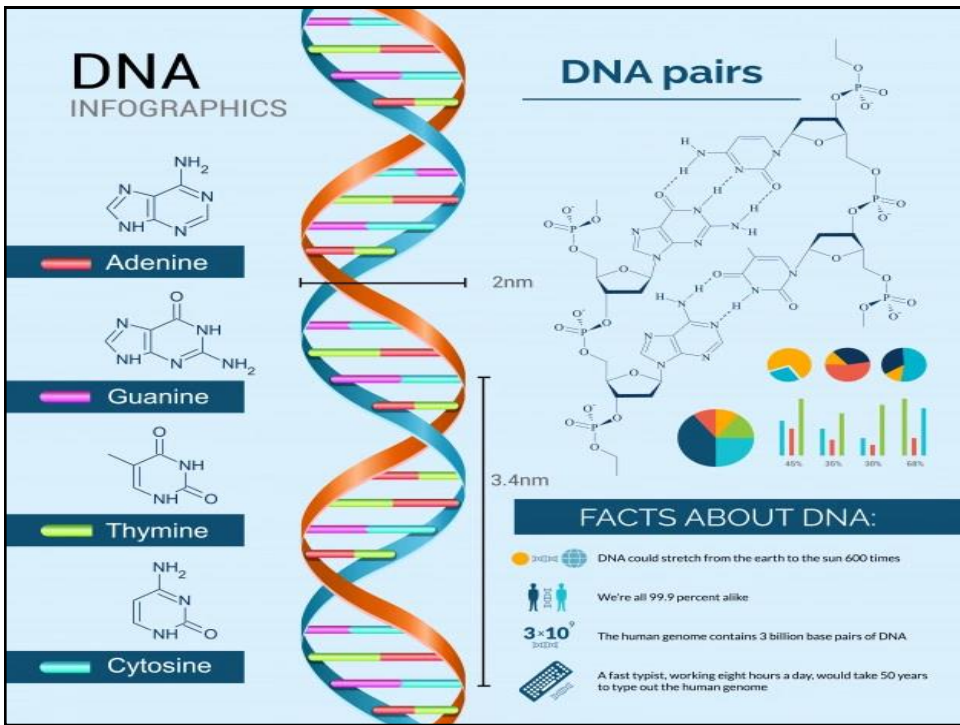


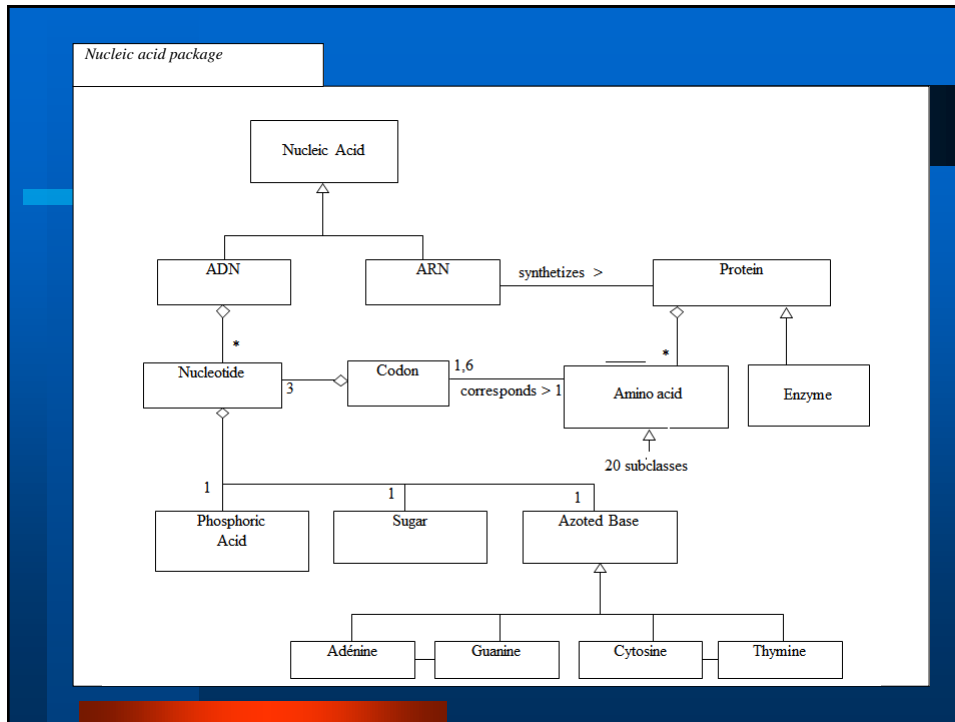
- **Molecular Biology basics**
- **Corresponding Classes in UML**
- **A translation algorithm**
- **Programming analogies**
- **Perspectives & Applications**

Molecular Biology basics

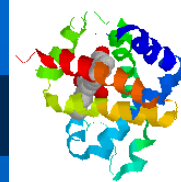


- DNA is made up of 4 individual chemical units called nucleic bases (A,C,G,T)
- DNA can act not only as a template for making copies of itself, but also as a blueprint for mRNA (messenger RiboNucleic Acid (repro. plan détaillé))
- The translation of mRNA into protein is the final major step in putting the information in the genome to work in a cell (in RNA Uracil U, replaces Thymine T)
- This kind of knowledge can be formalized by UML models and ontologies

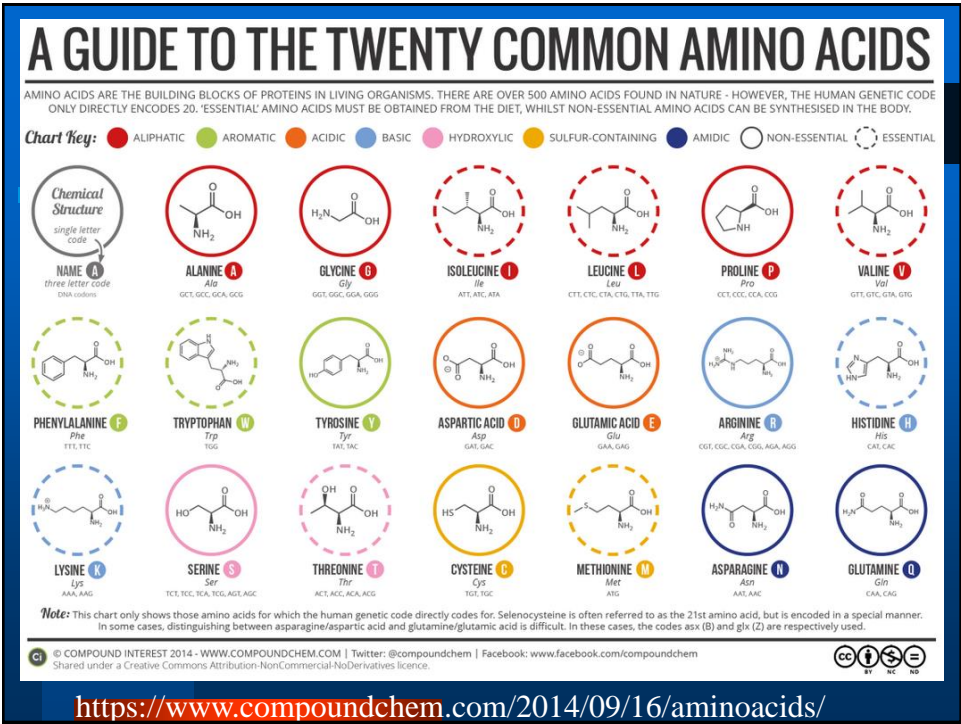




mRNA Translation process



- A group of 3 bases is called a **codon**
- To each codon corresponds an amino acid
- There are 20 different amino acids
- We have coding redundancies since different codons give the same amino acid.
64 codons => 20 amino acids
- The amino acid sequence specifies a protein (with start & stop sequences) or the enzymes.



From Amino Acids to proteins

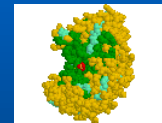
- All the proteins that make up living organisms are huge molecules, but they're composed of tinier building blocks, known as amino acids.
- There are over 500 amino acids found in nature, yet, of these, the human genetic code only directly codes for 20.
- Every protein in your body is made up of some linked combination of these amino acids
- The previous graphic shows the structure of each, as well as giving a little information on the notation used to represent them.

Essentials or not ? (Covid again ?)

- Broadly, these twenty amino acids can be sorted into two groups: essential and non-essential.
- Non-essential amino acids are those which the human body is capable of synthesising, whereas essential amino acids must be obtained from the diet.
- Some can also be termed 'conditionally essential', meaning that they may be needed from the diet during illness or as a result of health problems. This sub-category includes arginine, glycine, cysteine, tyrosine, proline, and glutamine.
- The essential amino acids are histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine.

Start & stop codons...

- Usual START codon : ATG (AUG)
- 3 STOP codons : TAG, TGA, TAA
- Sequences between 2 stop codons are called open reading frames (ORFs), they are potentially coding for a protein
- With codons of 3 bases there are potentially 6 reading frames (3 on each complementary strands)



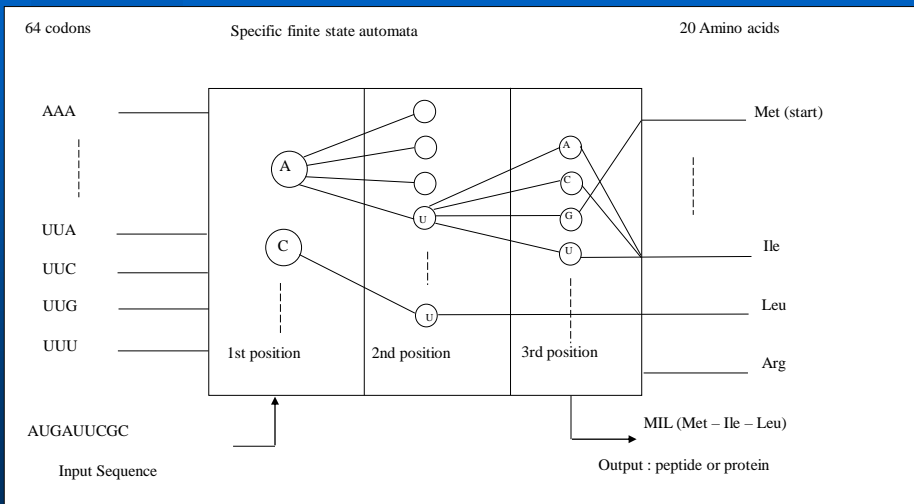
The « genetic code »...

1st	2nd				3rd
	T	C	A	G	
T	F Phe	S Ser	Y Tyr	C Cys	T
	F Phe	S Ser	Y Tyr	C Cys	C
	L Leu	S Ser	Ter	Ter	A
	L Leu	S Ser	Ter	W Trp	G
C	L Leu	P Pro	H His	R Arg	T
	L Leu	P Pro	H His	R Arg	C
	L Leu	P Pro	Q Gln	R Arg	A
	L Leu	P Pro	Q Gln	R Arg	G
A	I Ile	T Thr	N Asn	S Ser	T
	I Ile	T Thr	N Asn	S Ser	C
	I Ile	T Thr	K Lys	R Arg	A
	M Met	T Thr	K Lys	R Arg	G
G	V Val	A Ala	D Asp	G Gly	T
	V Val	A Ala	D Asp	G Gly	C
	V Val	A Ala	E Glu	G Gly	A
	V Val	A Ala	E Glu	G Gly	G

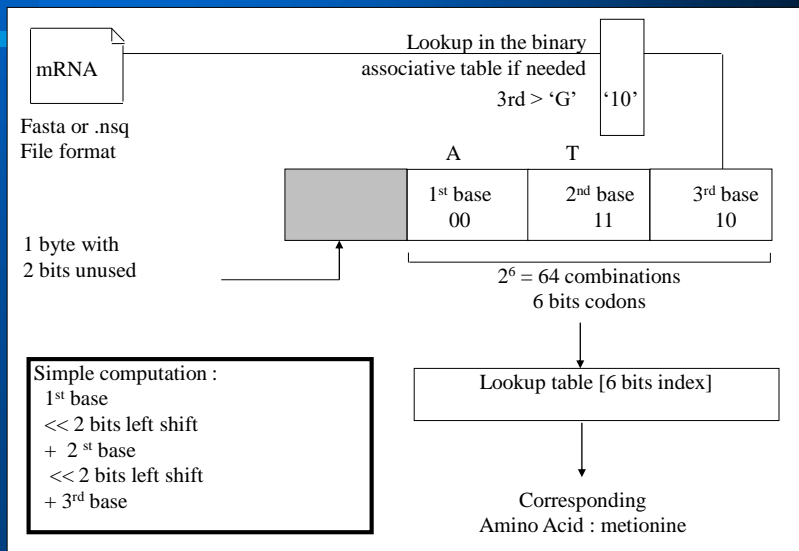
Translation algorithms

- Bioinformaticians intensively use Translation of mRNA sequences and it is a very simple process compared to the sequence alignment problems (were the famous BLAST and FASTA programs are used)
- A fast translation process is modelled and implemented using :
 - Translation automata
 - (or even) Lockup tables
- Translation routines exist in every Bioinformatic package and library (GCG Translate, Bioperl translate,...)

A translation automata exploiting the genetic coding redundancies



A very fast translation model



Main translation code (C or C++)

```
// The following code supposes the initialization
// lookup tables. Thus majority of the code is composed of
// array initialisation + a simple computation of the
// binary index (given below for one codon)

index = Binary_Lkup   [ Bases[ i++ ] ];    // 1st base
index <=<= 2;
index += Binaire_Lkup [ Bases[ i++ ] ];    // 2nd base
index <=<= 2;
index += Binaire_Lkup [ Bases[ i++ ] ];    // Last base
                                           // for codon

// Look up of the corresponding Amino Acid
result = AminoAcid[index]
```

Some translation times

Linux Athlon 1.5 Ghz	CODING APPROACHES					
File size	Library routine	Better coding	Lookup tables		Fastest algorithm	
# of input bases			Without opt.	With optimization	Without opt.	With opt.
1 016 684	8,0	2,8	1,1	0,52	0,1	0,09
2 033 351	16	5,4	2,0	1,0	0,2	0,2
4 066 684	32	11	4,1	2	0,4	0,37
8 133 351	63	22	8,3	4,1	1	0,6
16 266 684	126	43	17	8	1,9	1,2
32 533 351	251	86	33	16	3,2	2,5
64 066 684			66	32	6,6	5
130 133 351			132	65	12,6	9,5
260 266 684					25	19

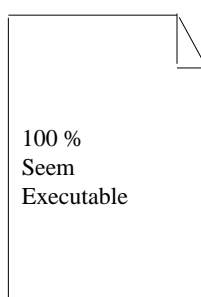
Translation times in seconds in 2002 !

Test at genome scale... on a basic PC and 2 Giga bases

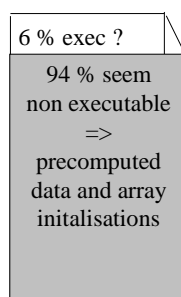
- On simple PC, the whole translation takes 3mins & 15 seconds (Including the reading of a 2Gb file (fasta format) and output of 670 Mb file (in 2002!)
- The translation in itself takes 14 seconds for 2 Giga bases.
- Input / outputs now take 94% of the global response time
- => if possible optimize input/ouputs with the Unix mmap function and specific HW (see code).

Program models & representations

Finite automata



Fastest implementation



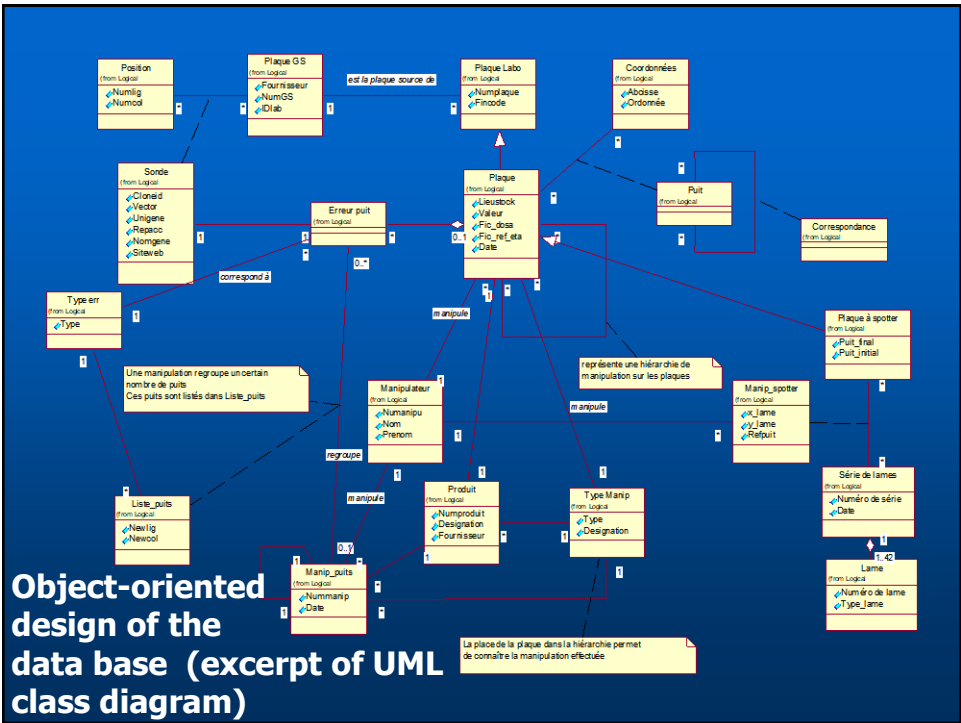
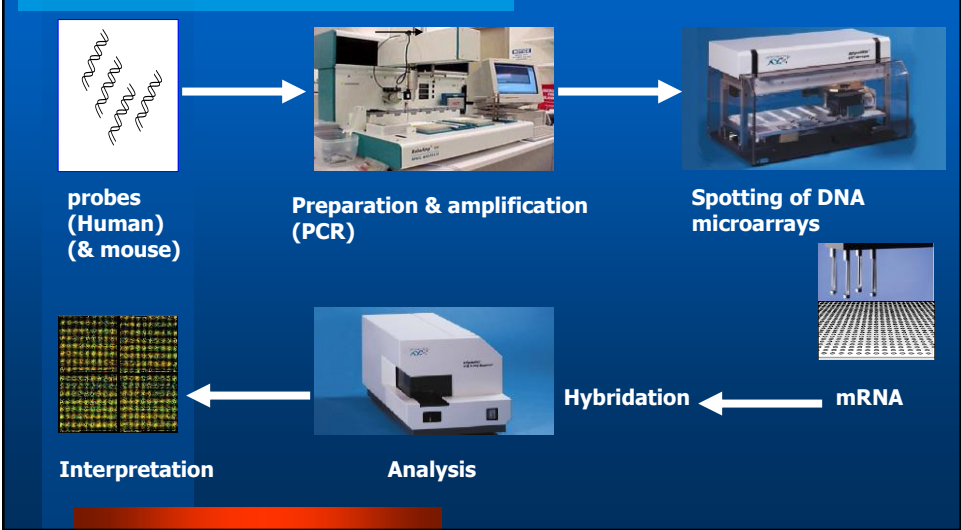
Analogy between genetic « data » and optimized computer programs ?

- The draft of the human genome sequence announces that only 1.1% of the genome is spanned by exons (coding regions), 24% in introns (non coding region) and 75% being (unknown) intergenic DNA
- Advances showed that some introns area could be coding in specific tissues
- What about the role of intergenic DNA, could it be used as data by the rest of the code ?

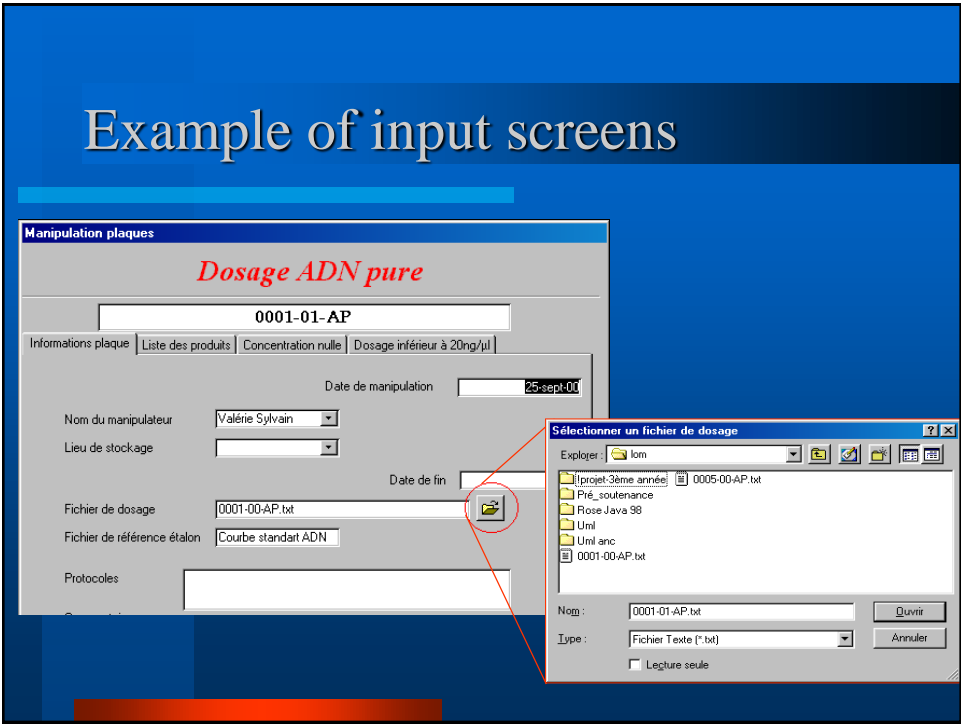
Applications @ LIMOS

- Breast Cancer Research
- Design of oligonucleotides for DNA chips and microarrays
- *Study of the Encephalitozoon cuniculi parasite (smallest Eucaryote genome, sequenced at Blaise Pascal University)*
- Bioremediation : design biological depollutant with Micro-arrays

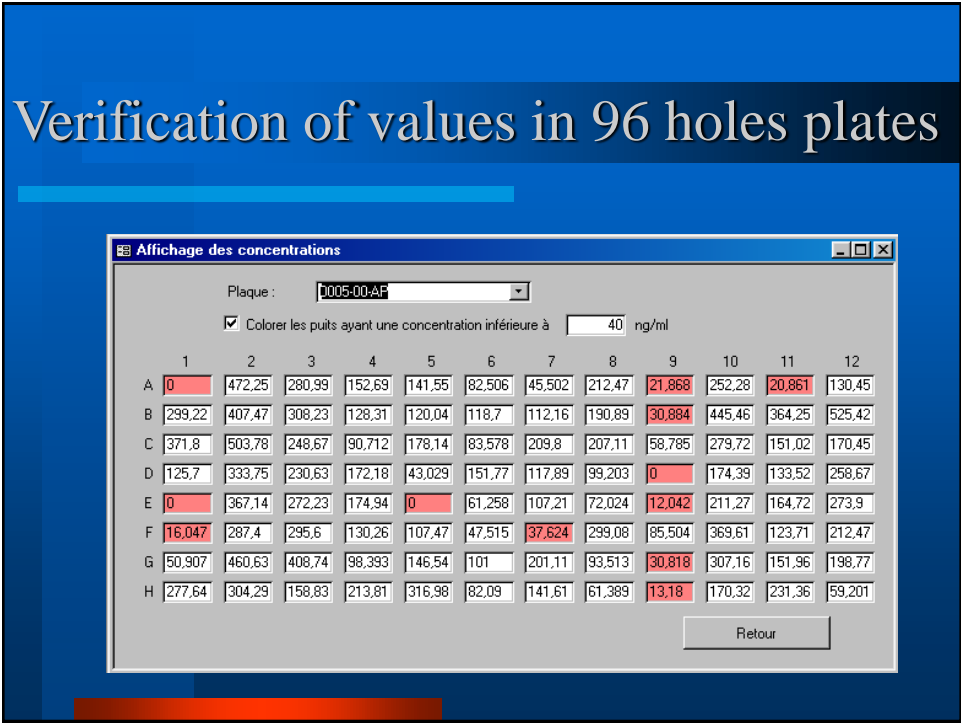
Research platform for DNA chips & microarrays.



Example of input screens



Verification of values in 96 holes plates



Holes Tracability

Selection_plaques_et_puits : Formulaire

Historique des puits

0007 - 00AP-1-1-003-G
0008 - 00
0008 - 00AP
0008 - 01
0008 - 01AP
0008 - 00AP-1
0009 - 00AP-1-1
0009 - 00AP-1-1-001
0009 - 00AP-1-1-001-G
0008 - 00AP-1-1-002
0008 - 00AP-1-1-002-G
0014 - 00
0014 - 00AP
0014 - 00AP-1
0014 - 00AP-1-1
0014 - 00AP-1-2
0014 - 00AP-1-1-001
0014 - 00AP-1-1-001-G
0014 - 00AP-1-1-010

Selection puits de

Selection_plaques_et_puits : Formulaire

Historique des puits

0014 - 00AP-1-1-001-G

Valider la sélection pour toutes les plaques

Annuler

Plaques

	1	2	3	4	5	6	7	8	9	10	11	12
A	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
B	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
C	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
D	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
E	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
F	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
G	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
H	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Oligonucleotide design

Criteria :

- Melting Temperature
- Secondary Structure
- Distance from 3' end

>INPUT_CDS
ATGCTTGCT...
ATGCTTGCTTCCGATAGCGTA

>Selected oligo
CTTCCGATAGCGTA

BLAST

BLAST DATABASE
>CDS_1
ATGCAATAGC...
>CDS_2
ATGCAGGTAACC...
...
>CDS_N
ATGTAAGCTT...

OligoArray

File data

Select Sequence file

Save As :

Run Cancel Exit

Oligonucleotide data

Oligonucleotide length : 50 nt

Distance 5'- Stop : 1000 nt

Tm range : 88 +/- 5 °C

Max Tm for structure : 63 °C

Max number of oligo : 1

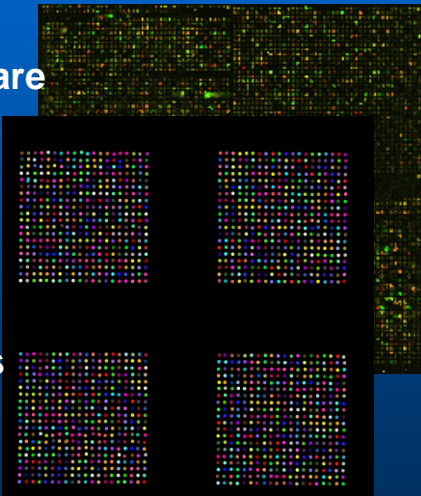
5' Tag :

3' Tag :

Prohibited sequences :

DNA Microarray Image Analysis

- **Study of existing software**
 - Scanalyze
 - Arrayvision
 - Genepix
 - Dapple
 - Jaguar
 - ...
- **Specific developments**

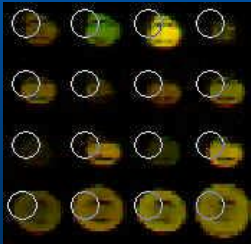


Automatic Alignment

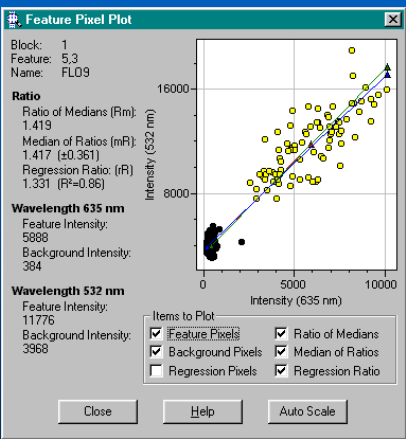
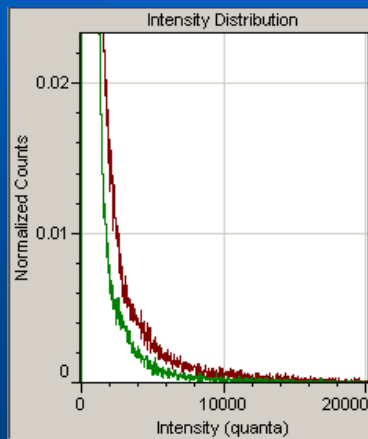
Two algorithms are used :

The first giving a rough alignment

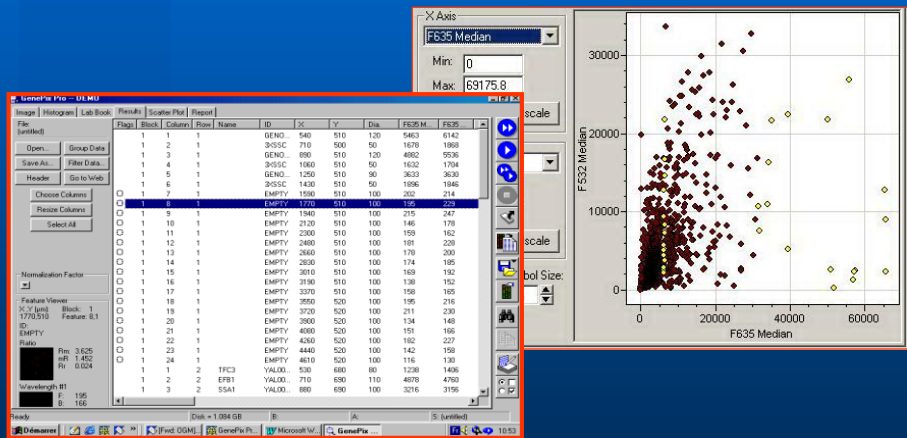
A second which will refine the first results



Study of pixels distribution



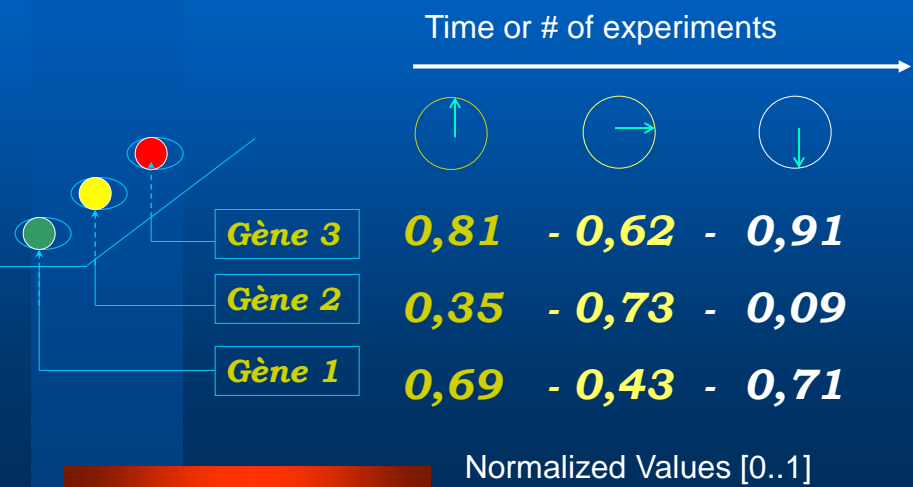
Assignment of results enabling the characterization of genes expression



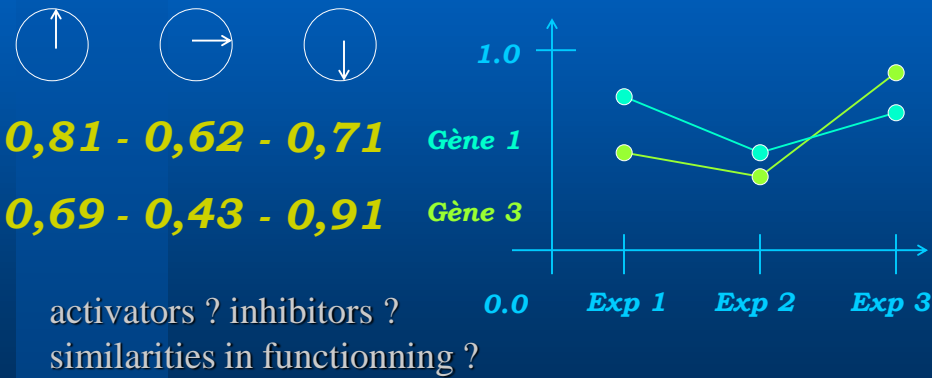
Classification & data-mining

- Supervised & non supervised techniques :
 - Hierarchical clustering,
 - K-Mean and variants,
 - Aggregation algorithms
 - Self-Organizing Maps : SOM
 - Decision Trees (C5 & Classification with Regression Trees :CART)
 - Neural networks
 - Genetic algorithms
 - Information theory
 - Fuzzy logic,
 - Support Vector Machines (SVM)
- Data base techniques
 - Association rules (Apriori algorithm & its optimizations, LIMOS)
 - Functional dependencies (DepMiner, LIMOS)

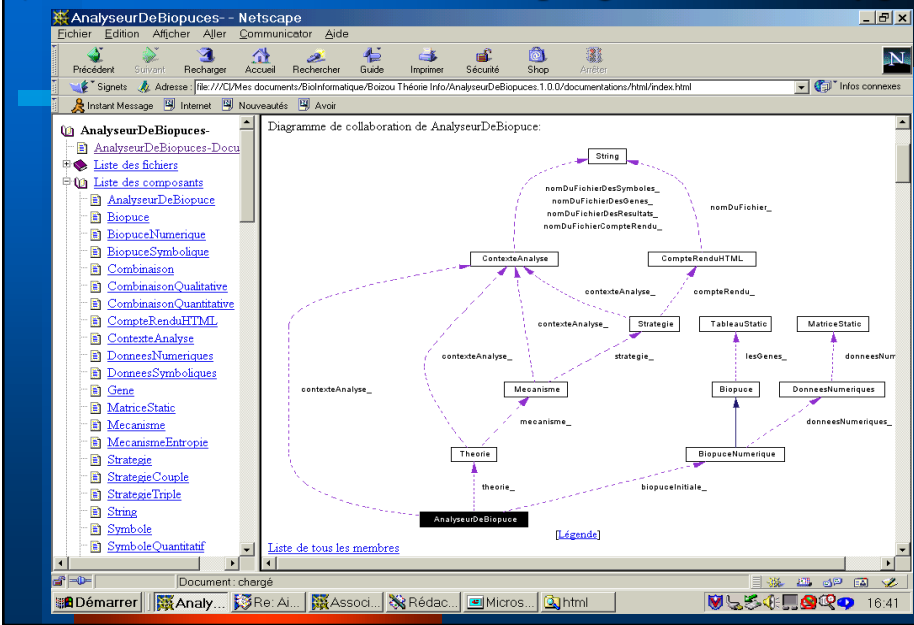
Resulting matrix to explore



Research of similar or opposite behaviours

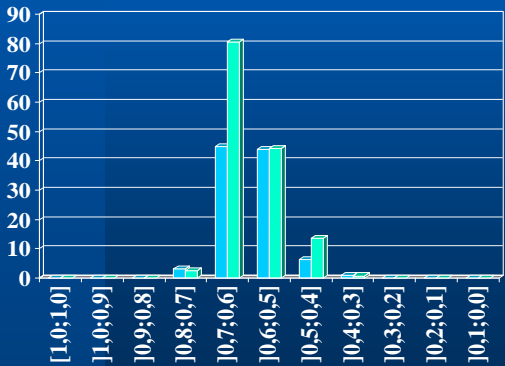


OO Modeling and development (UML Documentation of C++ program with Doxygen)



Study of the impact of noise in the observed results ...

Sensibility to the number of experiments and to the number of classes



Example for :
100 random genes
10 Classes
20 Experiments

■ Moyenne
■ Variance



Main partners

- Computer Science & Modelling Laboratory (L.I.M.O.S) at Blaise Pascal University
UMR CNRS 6158 – Now @ UCA & Clermont INP
- L.O.M. : Laboratoire d'Oncologie Moléculaire du Centre Jean-Perrin (Clermont-Ferrand)
- Cellular & Molecular Nutrition Unit at INRA (National Agronomy Research Institute)
- Old Protists Biology Laboratory (LBP) at Blaise Pascal University UMR CNRS

Perspectives

- Study of SNP surprises ! (Single Nucleotide Polymorphism) and developement of simulations
- Study of the bioremediation process thanks to reverse transcription
- Development of gene prediction models at genome scale, based on the fast algorithm presented (discovering ORFs)
- Evaluation of classification techniques

accueil

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informations pratiques

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00 jours

00 heures

Mardi 20 septembre 2022 - ...

Consultez le planning des conférences et des ateliers !

Cliquez sur une conférence pour la visionner

> Consultez le replay du Salon 2022

SALLE IGN	SALLE INETUM	SALLE DATAGALAXY	SALLE ACSSI	SALLE ALTAIR	SALLE NANTES MÉTROPOLE	ATELIER DÉMO 1	ATELIER DÉMO 2	AUTRE ATELIER
PROGRAMME DU MATIN								
<div>9h-9h50</div> <div>La charte de la donnée de Nantes, quelles actions conduites ?</div>	<div>9h-9h25</div> <div>Vulgariser les concepts de protection des données personnelles et des conditions d'utilisation pour mieux communiquer</div>	<div>9h-9h25</div> <div>Talan - CNIIEG - Accompagner les métiers dans la mise en place d'une solution décisionnelle</div>	<div>9h-9h25</div> <div>Les données d'intelligence artificielle au service de l'occupation du sol</div>	<div>9h-9h50</div> <div>L'Intelligence Artificielle Générale : fiction ou possibilité de conscience synthétique</div>	<div>9h00-9h25</div> <div>"Collectivités locales : De la donnée énergétique à la planification territoriale"</div>	<div>9h30-9h55</div> <div>Atelier démonstration Insee site de cartes et rapports dynamiques Statistiques locales</div>	<div>10h-10h50</div> <div>Choisir entre Excel et Power BI ? Atelier Démo par ASI</div>	<div>9h-10h30</div> <div>Atelier : Construisez votre patrimoine numérique en engageant vos lab</div>
<div>10h-10h50</div> <div>IGN : A la rencontre de la Fabrique des géo-communs</div>	<div>9h30-9h55</div> <div>De la fiabilité mathématique</div>	<div>9h30-10h20</div> <div>Prévoyance, Santé et Retraite : Le Data Catalogue, clé</div>	<div>9h30-9h55</div> <div>La Culture Data du Top Management est-elle essentielle pour réussir ?</div>	<div>10h-10h50</div> <div>Témoignages "rapido-presto-pratico", Deux responsables de la data sur</div>	<div>9h30-9h55</div> <div>Comment trouver des diamants dans Minecraft</div>	<div>10h-10h45</div> <div>Retailers - PXM/DXM - l'expérience Produit au</div>	<div>11h-11h50</div> <div>d'usage - Atelier démo par Jems</div>	

Chottez avec nous

From Web developer... Salon de la DATA ...to Bioinformatics

https://www.youtube.com/watch?v=ocvSY74narw&ab_channel=SalonData



Another possible optimization technique

- Among the programming optimization techniques the unrolling technique is sometimes used
- Meta-programming can exploit this directly within the C++ language
- It helps in the coding of programs that will be unrolled at compilation time.

Unrolling with a C++ metaprogram

```
template<bool> void IF(int tab[], int n)    { }
inline void IF<true>(int tab[], int n)     { tab[n] *= -1; }
inline void IF<false>(int tab[], int n)    { tab[n] = 0; }

template<int N>
inline void FOR(int tab[])
{
    IF<N%2>(tab,N);
    FOR(N-1)(tab);
}
inline void FOR<-1>(int tab[])            { }

const int N = 10;
void main()
{
    int * tab, i ;

    tab = new int[N];
    for(i = 0 ; i < N ; i++) cin >> tab[i];
    FOR<N-1>(tab);
    for(i = 0 ; i < N ; i++) cout << tab[i];
}
```

THANKS FOR YOUR ATTENTION

More to come
Invitation to C++ TMP ZZ3