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New trends in the epidemiology of emerging diseases

EAGLES Food Workshop
Hangzhou
5 december 2006

Genetics of Bacterial Genomes
http://www.pasteur.fr/recherche/unites/REG/

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Take home messages

- Culture, not Nature, is the hallmark of humanity
  - Initially, humans protect Nature against humans (« *Triste tropiques* » C. Lévy-Strauss); Artifice is perceived as dangerous
  - Nature is not friendly, but needs to be tamed, hence domestication of plants and animals marks humanisation, starting the Neolithic Age
  - Animals are the reservoir of most pathogens that may adapt to humans
  - Human behaviour (including urbanisation) produces entry doors for numerous pathogens
  - What is more Natural is pre-adapted, and hence the pervasive source of pathogens
- Emerging diseases result from Human behaviour

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A few dates

- 200,000-100,000 BP Birth of *Homo sapiens* ssp. Sapiens
- 17,000-12,000 BP Domestication of dog (*Canis canis*)
- 12,000 BP Domestication of fermentation microbes (lactobacilli and fungi)
- 10,000-9,000 BP Domestication of rice (*Oryza sativa*) and wheat (*Triticum aestivum*)
- 10,000 BP Domestication of cattle (*Bos taurus*)
- 9,000 BP Domestigation of pig (*Sus scrofa*)
- 9,000 BP Domestication of maize (*Zea mays* ssp. Parviglumis)
- 6,000 BP Domestication of horse (*Equus caballus*)
- 5,000 BP Domestication of silkworm (*Bombyx mori*)

- 1796 Jenner introduces variolation
- 1809 Following Papin, Appert introduces preservation of
- 1847-1849 Semmelweiss prevents puerperal fever by ha
- 1878 Pasteur and Chamberland: sterilisation and filtratic
- 1880 Pasteur introduces the principles of non-jennerian
- 1928 Fleming discovers penicillin
- 1935 Trefouël, Nitti and Bovet use sulfonamides as antibic
- 1944 Waksman discovers streptomycin

1800 1 billion
1928 2 billion
1961 3 billion
1974 4 billion
1987 5 billion
1999 6 billion

What life is

Three processes make life:

- A programme (a “book of recipes”)
  - Information transfer => genomics decyphers the program associated to the cell

Forces coupling the genome structure to the structure of the cell (the cell factory):

- A machine putting the program into action
  - Metabolism
  - Compartmentalisation

The cell is the atom of life

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A genetic computer

- In a computer the machine is separated from the data and the program
- Data and program play the same role (*i.e.* they can be thought of as ‘ declarations ’)

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Cells and computers

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Genetics describes genomes as texts written with a four letter alphabet: do cells behave as computers?

Horizontal Gene Transfer
Viruses
Genetic engineering
Animal cloning

all points to separation between

« Machine » (the cell factory)
and
Data + program

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Information Transfer

As for building up a machine, one needs a book of recipe to build up a cell

This construction changes the text of the recipe into something concrete: this transfers « information »

In a cell, information transfer is managed by the genetic program. The cell behaves as a computer making computers.

Three different « operating systems » exist, defining Archaea, Bacteria and Eukarya, defining kingdoms with relatively impermeable borders. However viruses appear to stem from a common origin and may cross borders

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Nature and Artifice

- Biological adaptation is the easier, the closer the organism from Humans
- Coming from Humans, human blood is dangerous
- Natural processes are more difficult to control than artificial processes
- Progress in applications of biological knowledge is linked to increasing our control over the processes, i.e. getting ever more artificial, e.g. inventing efficient artificial blood would be an immense progress (cf HIV, BSE, Hepatitis, etc)

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Gene sources: what genomes projects tell us

2,208 ongoing projects, 460 completed, mainly of microbes (295 more than 1,500 genes long, more or less correctly annotated) list all the genes of an organism

More than 149,000,000,000 nucleotides at the International Nucleotide Sequence Database Collaboration (INSDC) (http://www.insdc.org)

Microbes form 50% of the Earth's protoplasm, pathogens are only a tiny proportion of those; however many of the latter's genomes have been sequenced

40-50% coding regions in DNA do not correspond to known functions; 10% correspond to the genome core (« persistent » genes)

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The first discovery of genomics and emergence of diseases

In 1991, at the EU meeting one genome projects in Elounda, in Greece, the yeast's chromosome III and the first 100 kb of the *Bacillus subtilis* genome revealed that, contrary to expectation, **at least half of the genes uncovered were totally unknown, whether in the function or the structure of their product**

This shows that our knowledge of metabolism is extremely scant, and that we do not know how new genes are created. The corresponding knowledge is essential for understanding emergence

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An unknown gene source

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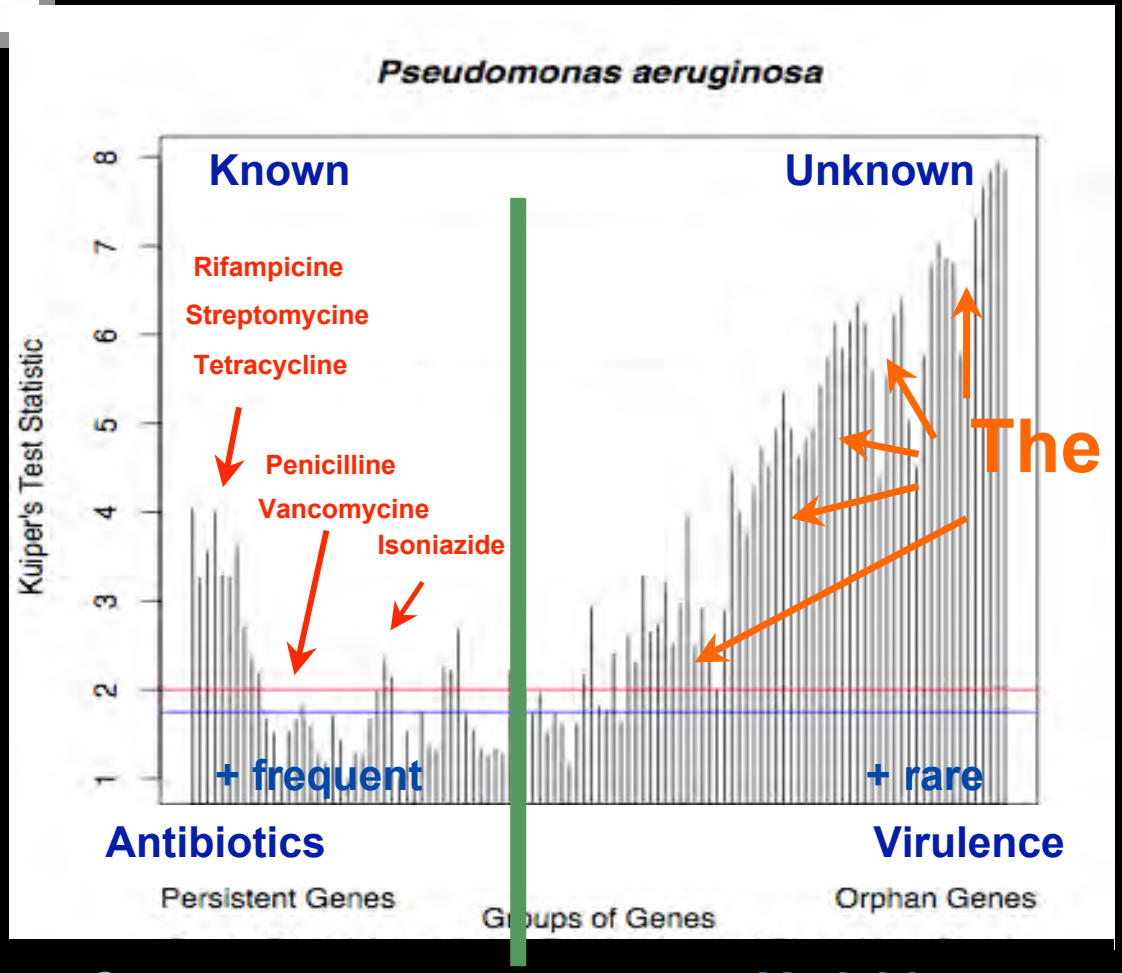
Frequency of clustering



The cenome

Frequency in genomes

Core genome
<2000 genes

Variable genes
already > 50000 genes

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From a stable niche to stressful conditions

Microbes adapt to a particular niche by recruiting or creating genes that are specific to that special environment

This means sensing chemicals, but also other biological organisms that occupy the same niche, and coping with them either through collaboration or competition

When suddenly placed in a new environment the organism has to adapt or die off, using what is immediately available

The consequence is that emerging pathogens must be pre-adapted to their new host

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A general constraint: opportunism

Variation / Selection / Amplification

Stabilisation

Evolution

creates

Fonction

capture (recruits)

Structure

codes

Sequence

Emerging viruses

The biosphere is full of viruses. In fact these organisms may have an enormous role in creating biodiversity (constant selection of resistant hosts, then virus variants attacking those hosts, etc)

The consequence is that viruses adapted to a given host will segregate variants (e.g. cow pox is becoming more virulent in some quarters, and monkey pox spread via pets in the USA)

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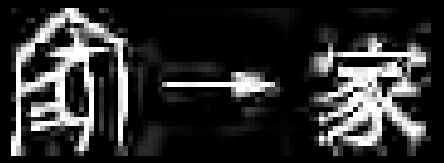
Emerging viruses (2)

A second way to create new viruses is to change the host species: this is typical of flu which is a normal virus of Anatidae (ducks, geese etc...)

Normal cycle:  =>  => 



The consequence is that viruses adapted to a given host will segregate variants that may become pathogenic to the new host (e.g. cow pox is becoming more virulent in some quarters)

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SARS and the « double epidemic » hypothesis

- The spread of the SARS-Coronavirus was highly uneven
- For example the number of cases in Beijing and Shanghai were dramatically different while the contacts with Guangdong and Hong Kong were similar

- Several hypotheses can account for this fact (including inaccurate reporting), all based on epidemiological studies
- The « double epidemic » hypothesis (i.e. that another previous epidemic by a related or unrelated pathogen would have protected against SARS-CoV) is consistent with the observations

  TW Ng, G Turinici, A Danchin A double epidemic model for the SARS propagation *BMC Infect Dis* (2003) **3:** 19

- New models should be explored, including shedding of variants by viruses during the epidemic

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Emerging bacteria

- Humans are inhabited by ten times more bacteria than the number of their own cells
- Those bacterial commensals are either innocuous or beneficial
- New life styles change the relation between the human body and its native bacterial flora (eg diet transition: new E. coli commensals are emerging...)
- Stressful conditions, when recurrent, tend to lower the immune response

- Comparative genome analyses of commensals and pathogens should not simply look for presence/absence of genes, but also for their rate of evolution

W Wei, ZW Cao, YL Zhu, XJ Wang, GH Ding, H Xu, PL Jia, D Qu, A Danchin, YX Li Conserved genes in a path from commensalism to pathogenicity: comparative phylogenetic profiles of *Staphylococcus epidermidis* RP62A and ATCC12228 *BMC Genomics* (2006) **7**: 112

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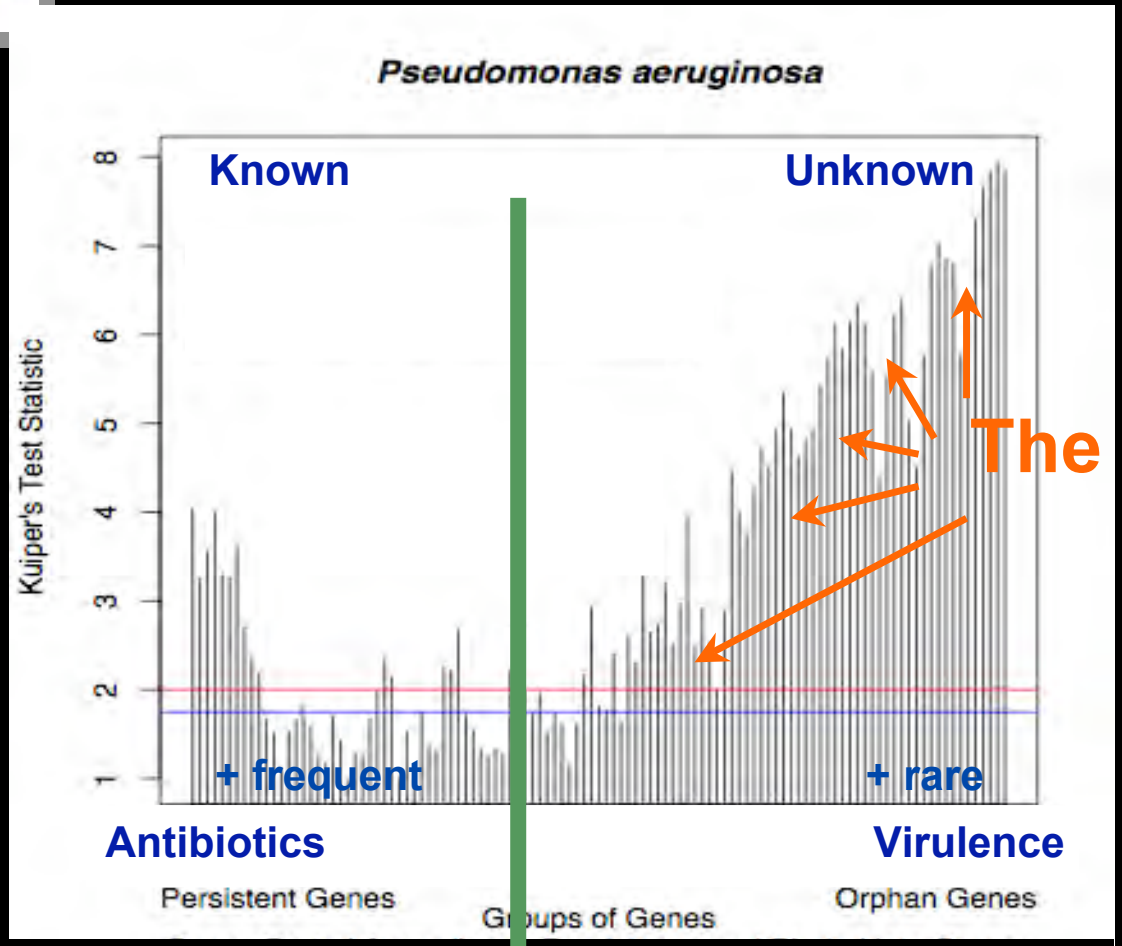
The cenome



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A danger from animal GMOs: humanisation of organs

- The initial goal of animal GMOs was similar to that of plant GMOs, improving quality of animal products, or using the animal as a factory
- Interest for health care created a new **Unmet Need**, associated to phylogenetic proximity between animals and humans: using GMOs as providing tissue substitutes
- Humanizing organs is widely accepted by the public, despite its obvious danger:
  - **Animal tissues contain retroviruses**
  - **Emerging diseases are often caused by transfer from animals to humans (eg HIV, SARS, Hantah etc)**

Nature is preadapted through evolution, it can be more dangerous in principle than Artifice => a prerequisite: make epidemiological studies of the diseases of butchers and slaughter house personnel

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Novel host-vector systems

- For a long time malaria (mal' aria: bad air) was thought to result from mephitic air in humid climates
- Discovery that the disease was transmitted by a mosquitoe vector was a revolution
- Since then many vectors were found: fleas, lice, ticks etc
- Can we think of other possible vectors?

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Transmissible Spongiform Encephalopathies

- « Scrapie » infects sheep herds in a way that is not well understood
- UK witnessed an outbreak of BSE, whose causes are not unambiguously established (contaminated food?)
- Many wild animals are the victims of TSE
- « Contaminated pastures » appear to be sources of new outbreaks

- Could the disease be transmitted by a vector?

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A vector for TSE?

- The vector has to have a form stable in time
- It must be compatible with ingestion, but needs to have access to brain tissues
- Parasites may have these features, they need to be sporulating or have similar forms

- A candidate family: Microsporidia

1. They multiply intracellularly in the brain
2. They form spores
3. They infect many tissues and can be ingested
4. Epidemiology unknown...

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An infection scenario

The epidemiological features of a parasite prion host vector would be compatible with a large outbreak in a parasite naïve population and with sporadic cases elsewhere

TW Ng, G Turinici, WK Ching, SK Chung, A Danchin A parasite vector-host epidemic model for TSE propagation *Medical Science Monitor* (2007) **13**: 000-000

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Bioterrorism

- Biological warfare has, unfortunately, been used in the past
- Rogue states, or terrorist groups may be tempted to resort to this kind of action

  - Is a scenario possible?
  - Could we have epidemiological indications of such actions?

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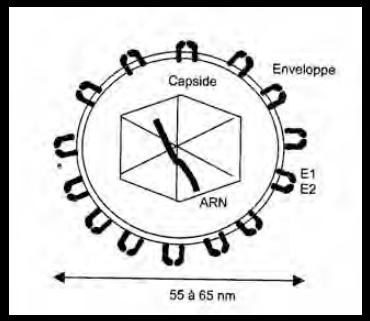
Synthetic biology

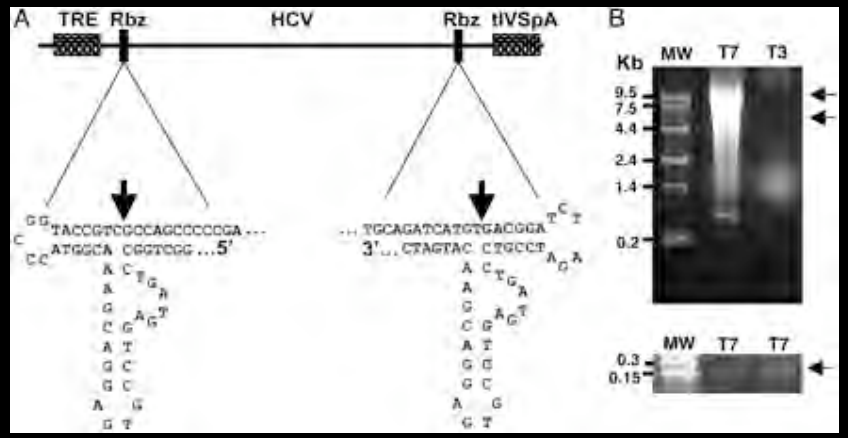
- Understanding and keeping the basic principles and components
  - Further minimising the smallest genome: towards the minimal autonomous genome (*Mycoplasma genitalium*, Smith, Venter)
  - Reconstructing what is known (repressilator, Leibler)
  - Rewrting while simplifying (software engineering) (T7, Endy ; promotors, Hwa)
  - Reprogramming: the cell factory (HCV, Liang ; carbon, Marlière)
  - Reconstructing an ancestral cell « molecular Jurassic Park » (ancestral proteins, Benner)
  - ...
- Conserving the principles of life and introducing a new chemistry
  - Changing amino acids (Cohen, Wong...)
  - Changing the genetic code (Schultz, Marlière)
  - Changing the chemistry of the support of heredity (S-2L, PNA, TNA, GNA, etc)
  - ...

Friends or foes: reprogramming viruses

- The hepatitis C virus comprises a single stranded **RNA**. It codes for a multifonctional protein, split into at least 10 late proteins. Fragile, it does not replicate well
- With genetic engineering Liang et al. made a self-replicating **DNA** coding for the virus RNA bordered by two self-cleavable regions, creating a fully active viral RNA. This artificial protection/deprotection produces continuously infectious viral particles



Pr. Amine SLIM Laboratoire de Microbiologie - CHU Charles Nicolle Tunis



Heller T et al An in vitro model of hepatitis C virion production.Proc Natl Acad Sci U S A. 2005 102:2579-2583.

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Thank you

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