



**The discovery of innovative
therapeutic approaches:**

*Under the street light is not necessarily
the right place to search.*

Dr. François Iris, Founder & C.S.O. BIO-MODELING SYSTEMS

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International Drug Discovery Science and Technology 2012
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The discovery of therapeutics.

It is first and foremost a matter of
integrating huge masses of information.

But there are first THREE problems & ONE paradox to resolve.

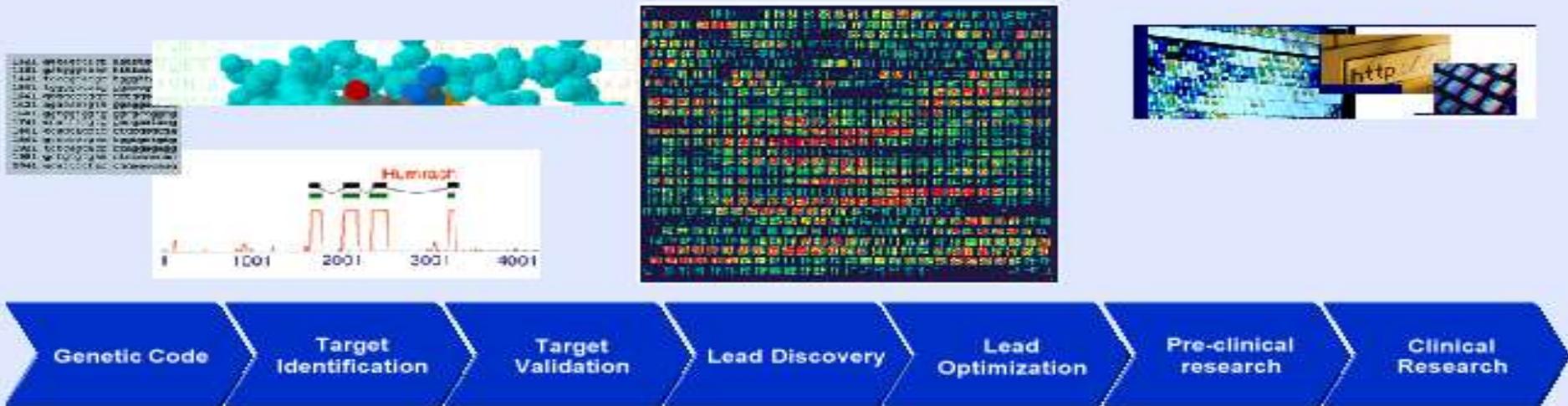
Problem 1. The nature of information

All that goes by the name « *Information* » is not necessarily
Useful and/or **Utilisable!**

In the bio-medical realm, the information available is **ALWAYS:**

- **incomplete**, to an unknown extent;
- **biased**, to an unknown extent; and
- **erroneous**, to an unknown extent.

This takes particular significance in drugs development



- ❖ Sequence analysis
 - ❖ Annotations
 - ❖ Comparative genomics
 - ❖ Pharmacogenomics
- ❖ Functional genomics
 - ❖ Expression analysis
 - ❖ Proteomics
 - ❖ Structural genomics
 - ❖ Pathway discovery
- ❖ Expression analysis (arrays)
 - ❖ Proteomics
 - ❖ Structural genomics
 - ❖ Pathway discovery
 - ❖ Pharmacogenomics
- ❖ Expression (arrays)
 - ❖ Proteomics
 - ❖ Pathway discovery
 - ❖ HTS
- ❖ Combi. chemistry
 - ❖ Expression (arrays)
 - ❖ Proteomics
 - ❖ Structural genomics
- ❖ Animal models
 - ❖ In silico simulations
 - ❖ Expression (arrays)
 - ❖ Proteomics
 - ❖ PK/PD
- ❖ Expression (arrays)
 - ❖ Pharmacogenomics
 - ❖ PK/PD

A process generating a flood of heterogeneous information

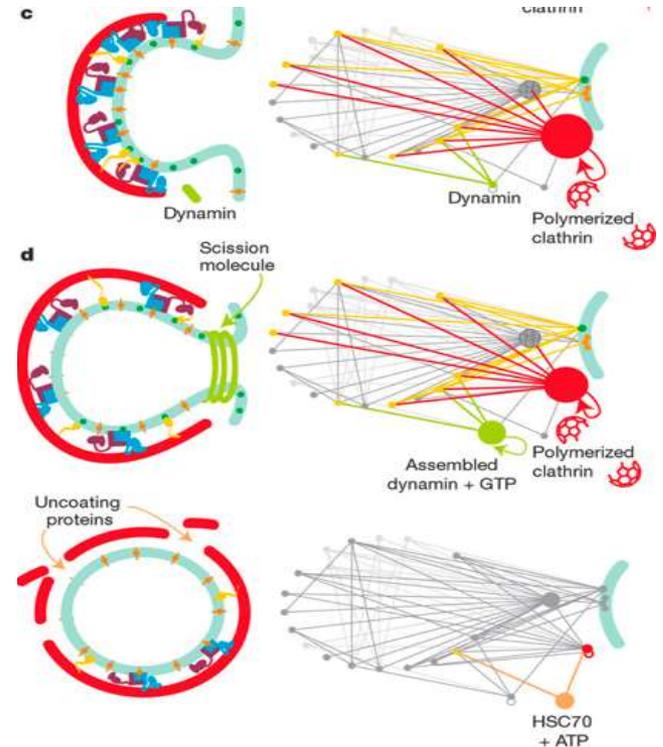
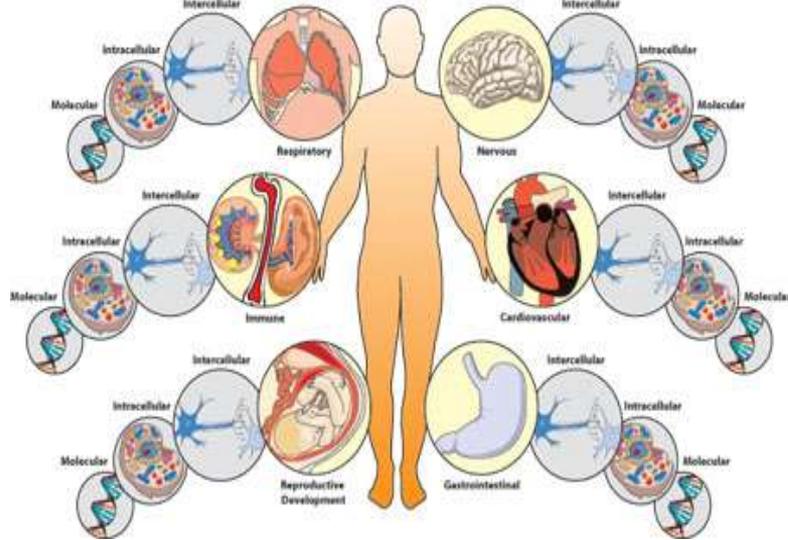
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Problem 2. Therapeutic success.

The success of a therapeutic approach largely arises from the coherent manipulation of a physiological system as a whole

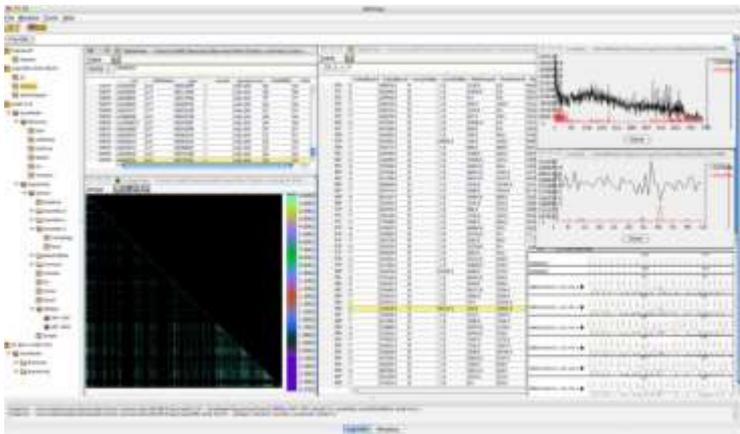


and not from that of a target in a molecular context.

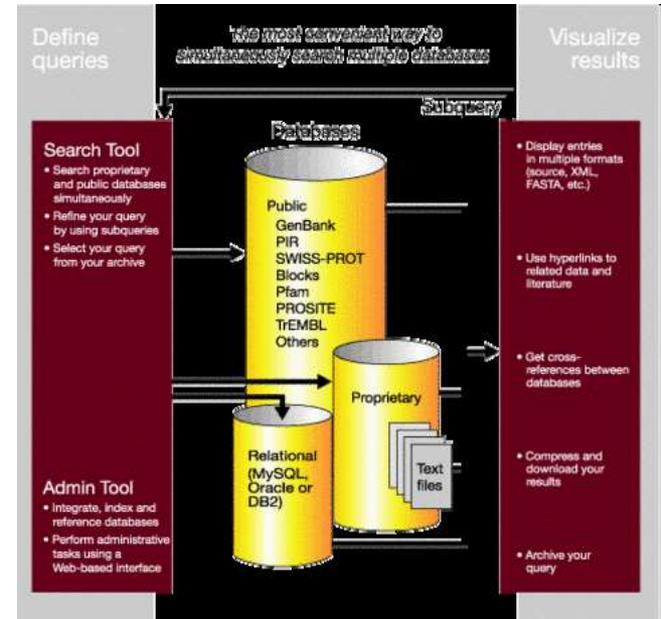


Therefore, any given medical problem must be approached from a systems standpoint.

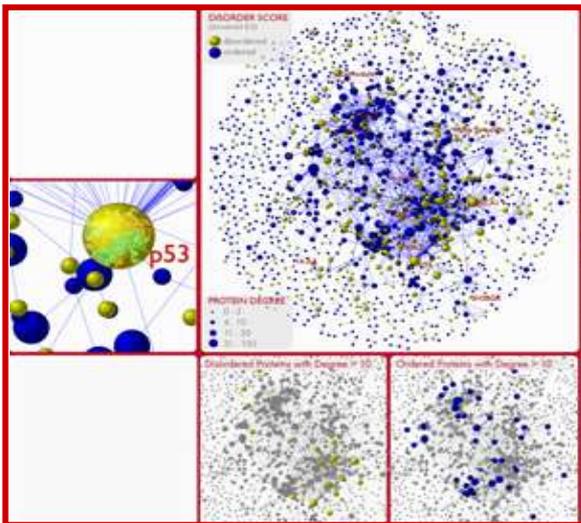
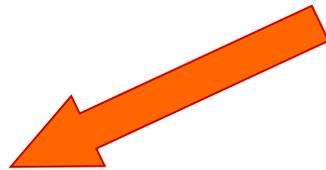
Problem 3. The data analysis & integration tools we must utilise in systems-level approaches.



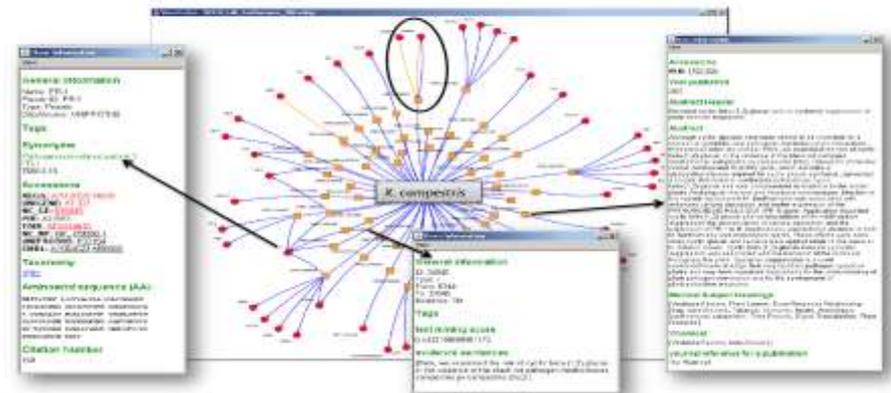
Data flat-file



Analytical WEB resources

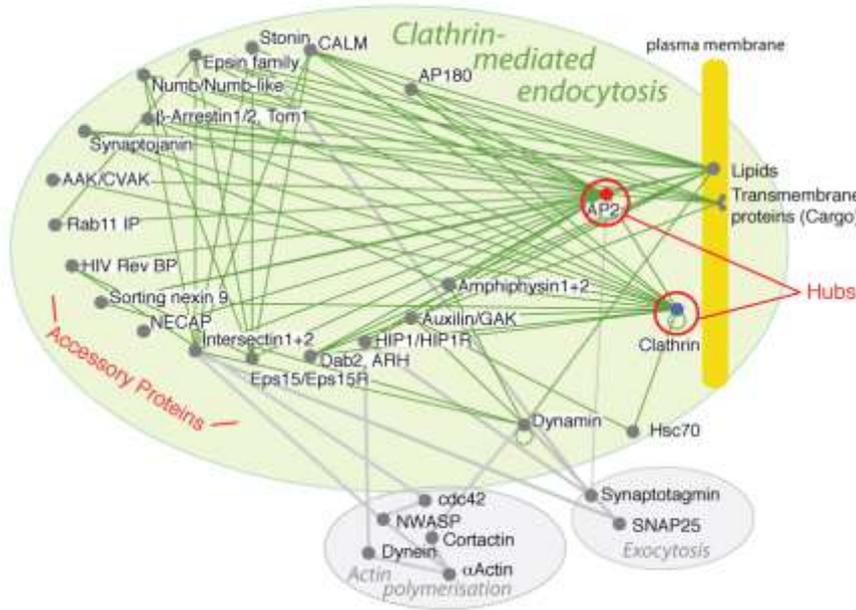


Visualisation tools



Networks construction

These approaches results in a highly misleading vision of protein interactions & networks.



How can a single hub protein bind so many different partners?

The problem is largely non-existent and resides in the construction and the representation of protein interaction networks within data-bases.

Proteins derived from a single gene, even if different, are clustered in maps into a single node.

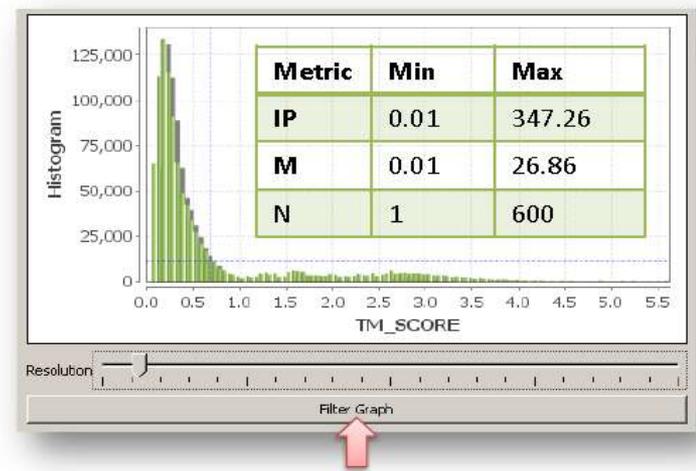
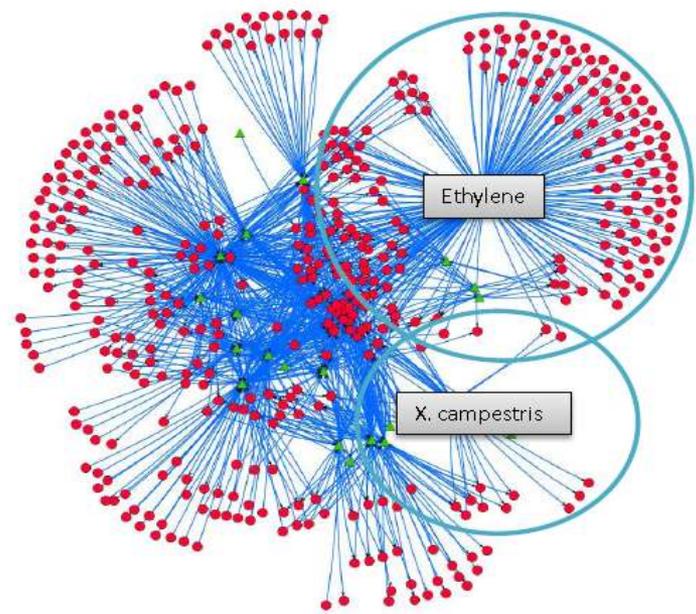
This leads to the impression that a single protein binds to a very large number of partners.

In reality, it does not.

Protein networks reflect confusions involving combinations of functional plasticity addressing a same protein together with distinct physiological roles of different proteins encoded by one gene.

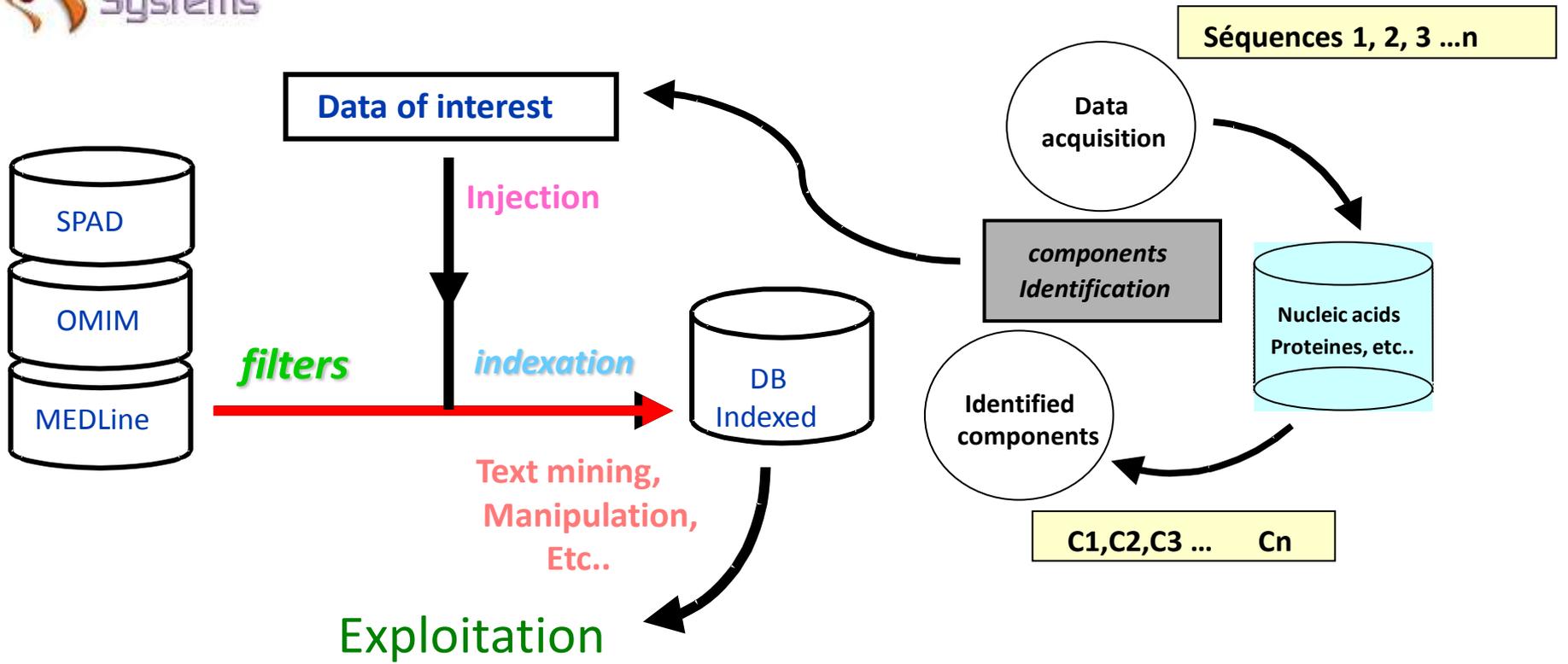
And the more complex the organism being analysed,
the worse it gets.

Protein-Stress Association Network



- 3145 proteins linked to 32 stresses by 10777 relations
- On average
 - each protein associated with 3.4 stresses
 - each stress associated with 337 proteins
- Filtering associations based on three scoring metrics IP, M and N
- **Which metric and cut-off are most suited for filtering noise?**

This significantly affects the Classical analytical Process



What constitutes a **GOOD** filter?

What constitutes a **GOOD** indexation strategy?

ALL information entered into the DB is **ALWAYS** *biased, incomplet, erroneus*, etc...

Accumulation of inconsistencies

The challenge is clearly not a question of technologies only!

The paradox that must be resolved.

If you dream to create the first operational bird model...



... a “basic” living Complex system that not only flies...

Be sure to use the appropriate modeling concepts & tools. If not...



...you get a Complicated “Cartesian” system. It does fly, but...

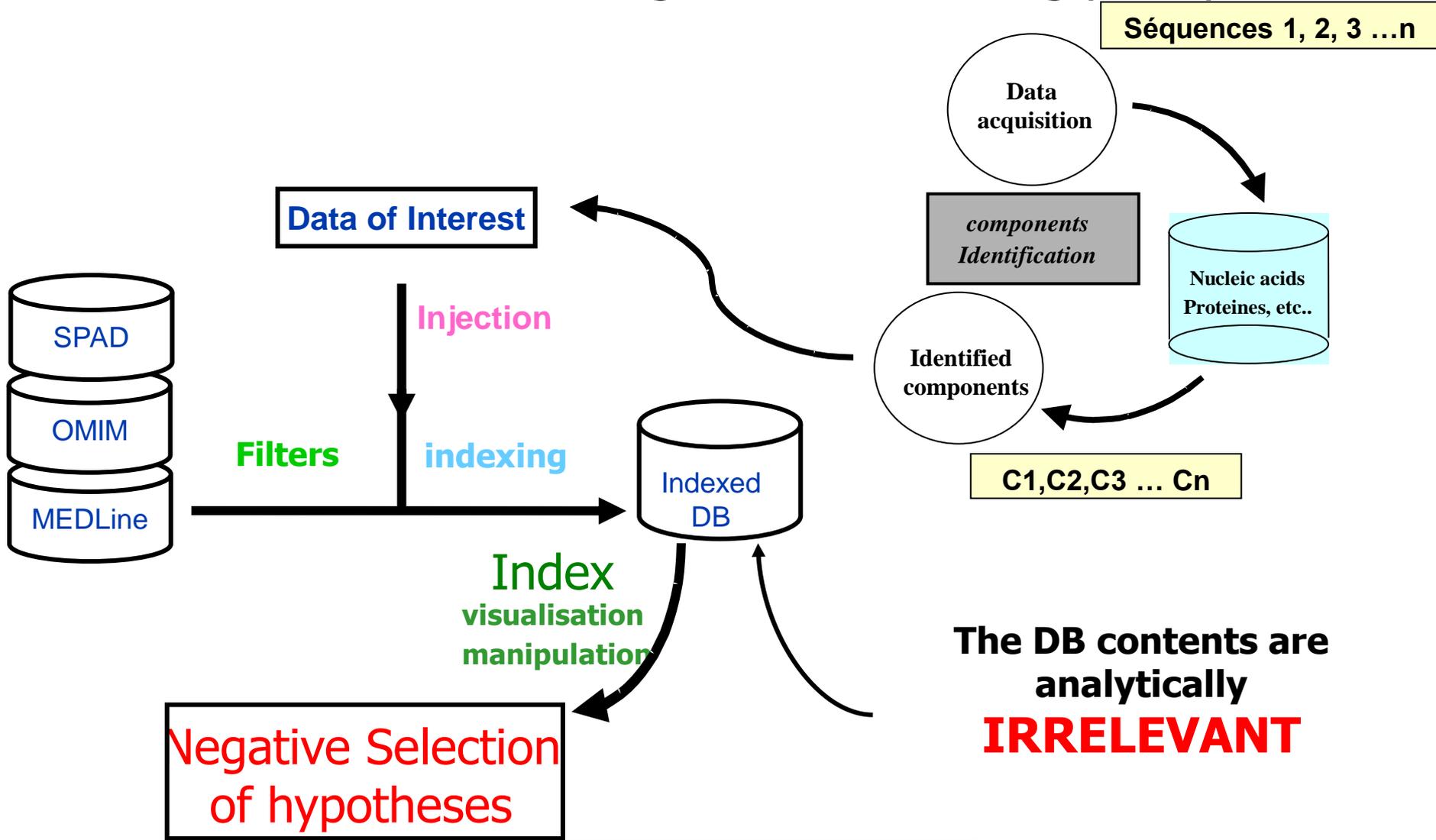


How to escape the paradox whereby we have NO OTHER CHOICE but utilise tools & approaches that CANNOT enable us to reach our goal?



By changing our intellectual approach!

Another way of thinking: The *CADI*TM Integration & Modelling principles.



This constitutes a heuristic approach!

The differences between « heuristic » and « mathematical » approaches.

Heuristics:

A problems solving approach evaluating each step in a process, searching for satisfactory solutions rather than for optimal solutions, using all available qualitative information instead of *quantitative* information.

Thus,

Heuristic modelling starts from accumulated information to produce a model capable of describing the mechanisms that generated the observed outcome / data and predict their modifications associated with a different outcome;

It plays the role of an architect

While

mathematical (Bayesian) modelling starts from quantitative data to produce models capable of reiterating this data and predict the outcome of a different experimental paradigm.

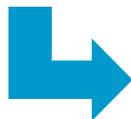
It plays the role of an engineer

and

Far from being incompatible, these two approaches can be complementary.

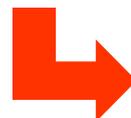
Bayesian and Heuristic approaches can be complementary, provided they are harnessed in the proper order.

Bayesian approaches are of limited usefulness when applied to poorly defined multicellular physiological systems because they cannot efficiently reveal & define the functional states within such a system (cross-talks alterations, etc...).



But heuristic approaches are very efficient at doing precisely this.

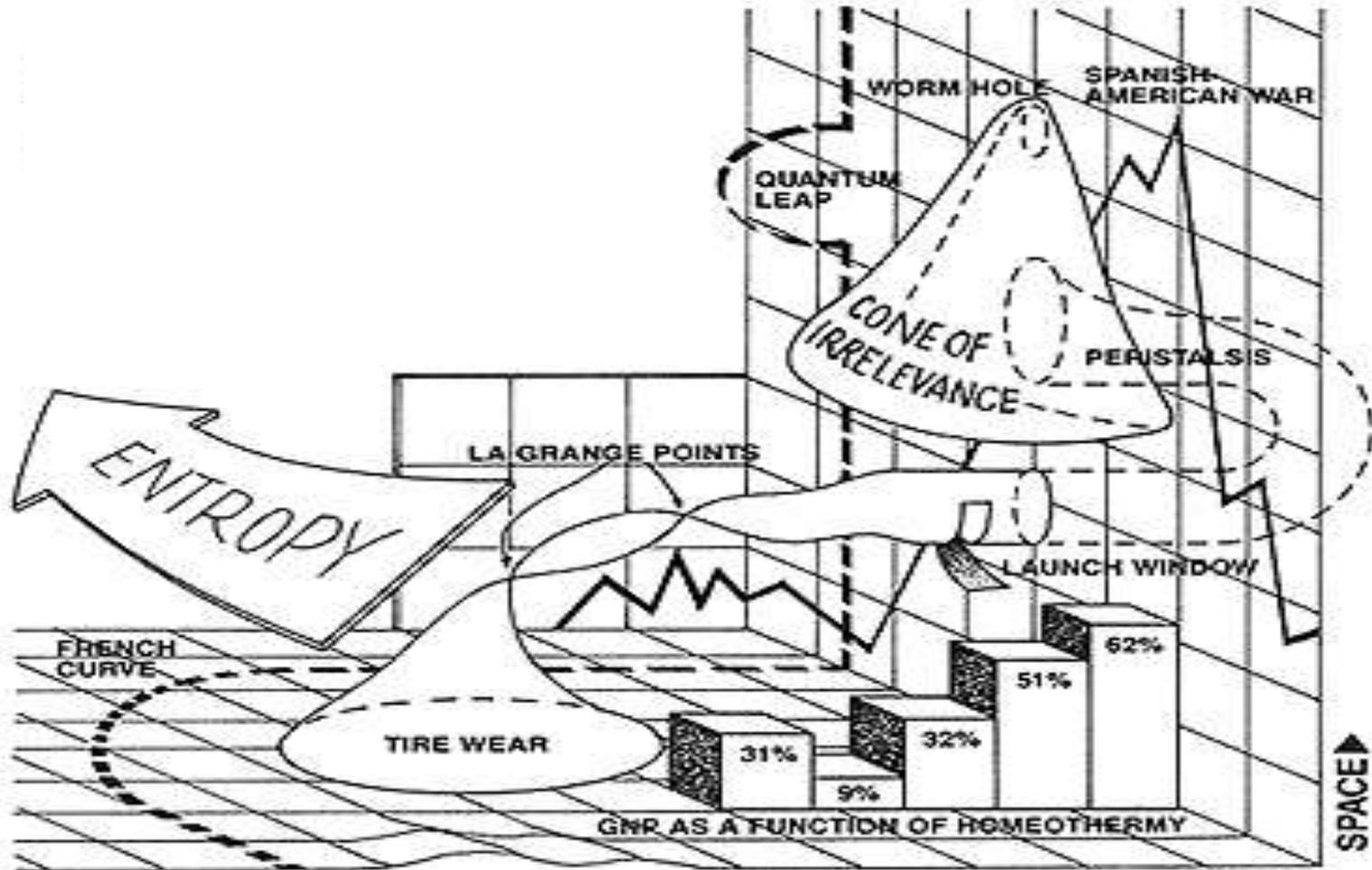
Heuristic models are of limited usefulness when addressing the dynamics of defined complex physiological pathways structures and cross-talks because they are not open to mathematical manipulations.



But Bayesian models are very efficient at doing precisely this.

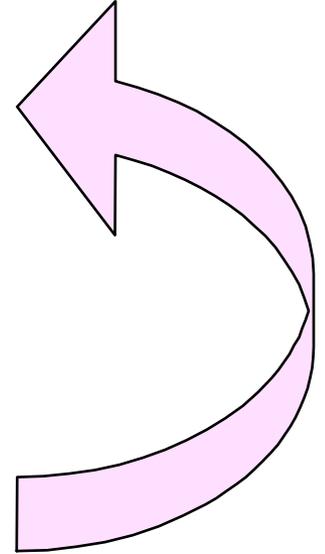
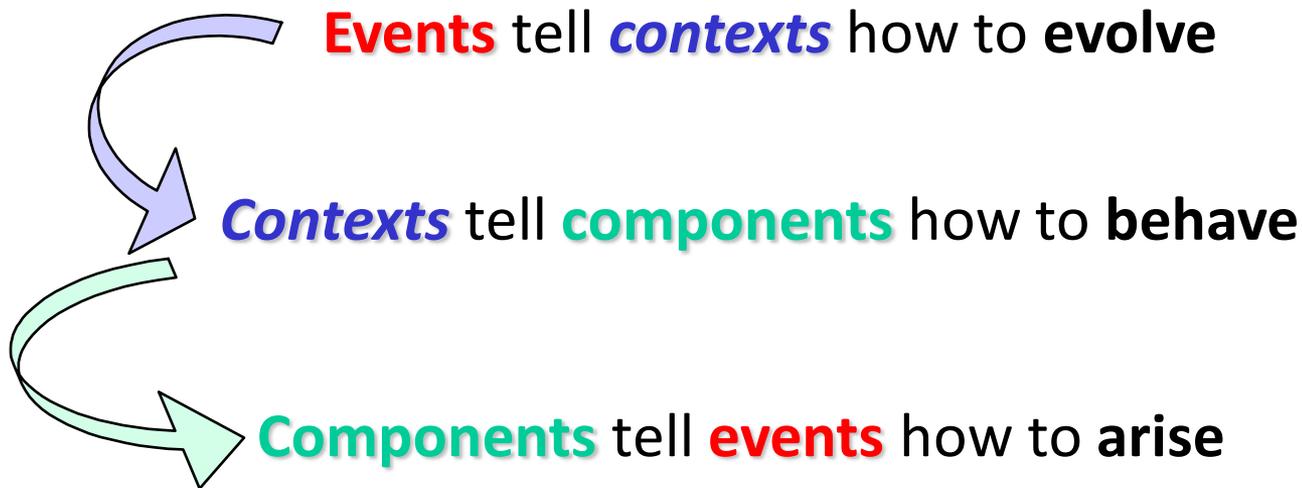
To efficiently address the translation of systems biology to clinical & medical interventions (dominated by patient's data heterogeneity and largely unstructured documents), ways to achieve synergy between Heuristic and Bayesian approaches can be effectively designed.

The heuristic analytical process must follow a « relativistic » approach.



Within this framework, *Non-linearity*, *Irrelevance*, *Wear*, *Relative weights* & *Contexts* are key concepts.

Why? Because of a very simple set of rules which imposes « relativistic » approaches.



Analyses in terms of biological components and functions are now
IRRELEVANT.

EVENT-DRIVEN (relativistic) analytical approaches become necessary.

This, in turn, imposes analytical procedures based upon the negative selection of working hypotheses.

Why “negative selection” of working hypotheses?

“While it is not always possible to demonstrate that a statement is true, it is always possible to demonstrate it to be false” Karl Popper, 1963.

Mathematical approaches are based on “positive selection”: it is assumed that every dataset/statement is actually valid.

Yet, “an estimated 85% of current published research findings are false or exaggerated”

J.P.A Joannidis, 2014 [PLoS Med. 11(10): e1001747]; F. Prinz et al., 2011 [Nat Rev Drug Discov. 10 (9):712]

Positive selection becomes a killer!

How to identify what is NOT false and/or exaggerated?

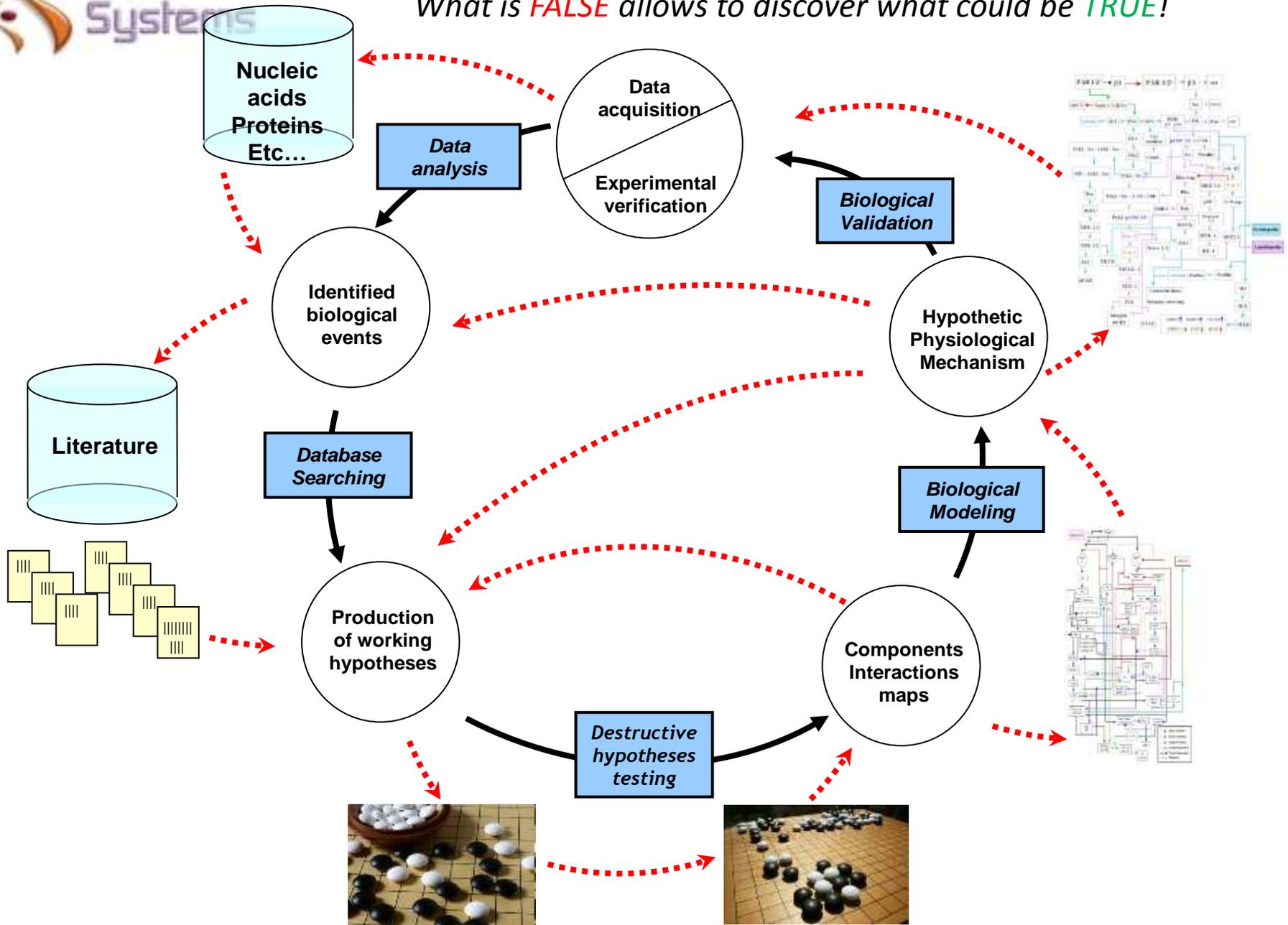
By doing every thing possible to destroy working hypotheses!

Only hypotheses that resist destruction are worth retaining.

Hence, what is demonstrated “False” can now be used to discover what could be “True”.

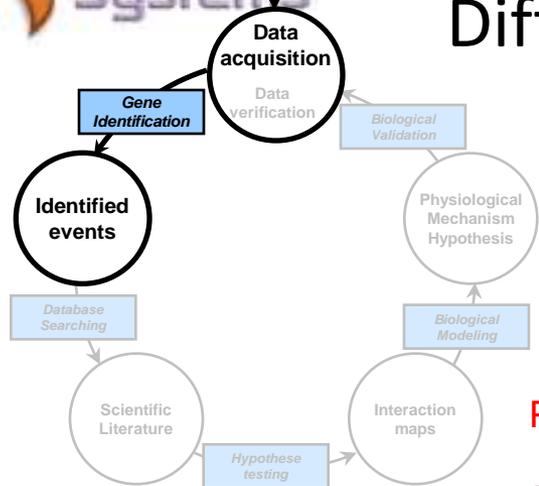
The **CADI**TM Integration workflow

What is **FALSE** allows to discover what could be **TRUE**!



MCF-7/MCF-7 ras Differentially Expressed Genes

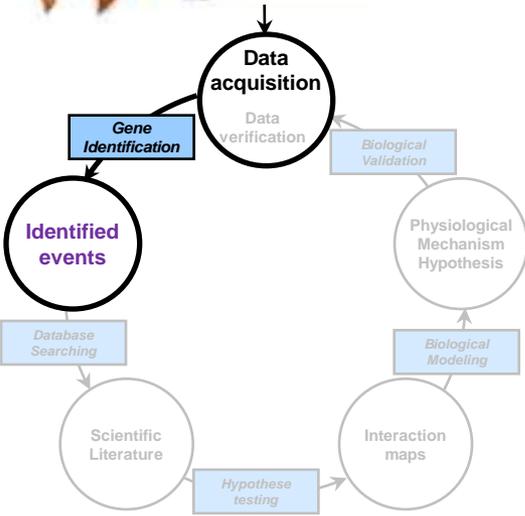
■ Over-expressed
■ Under-expressed
over 600 genes



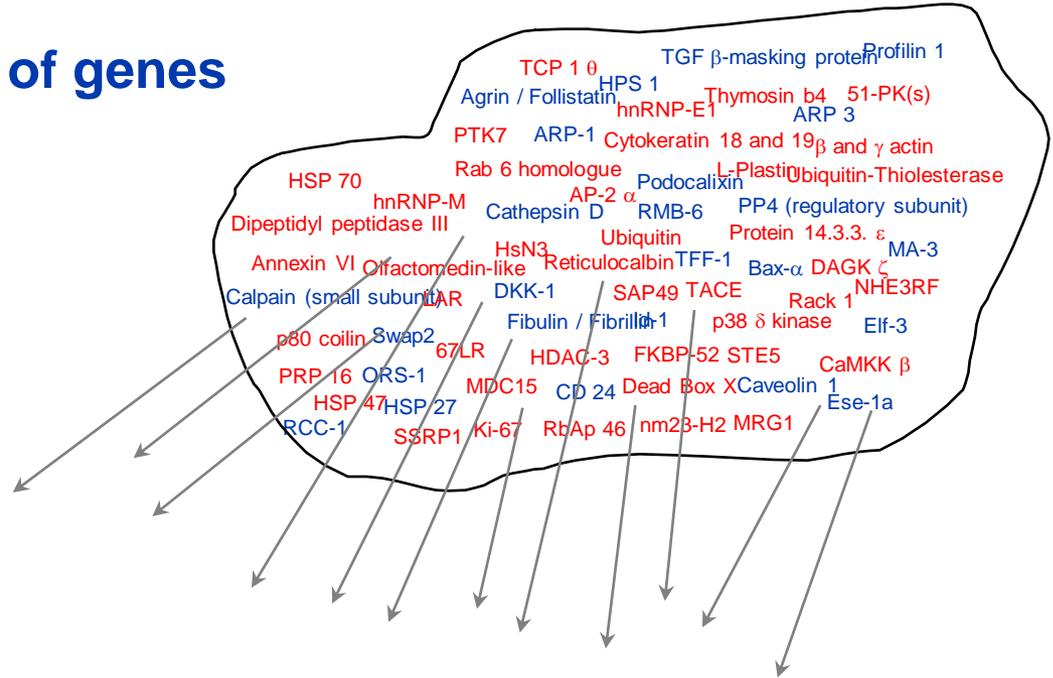
- TCP 1 θ
TGF β -masking protein
Profilin 1
- Agrin / Follistatin
HPS 1
51-PK(s)
- PTK7
hnRNP-E1
ARP 3
- ARP-1
Cytokeratin 18 and 19
 β and γ actin
- HSP 70
Rab 6 homologue
Podocalyxin
L-Plastin
Ubiquitin-Thiolesterase
- Dipeptidyl peptidase III
hnRNP-M
AP-2 α
RMB-6
PP4 (regulatory subunit)
- Annexin VI
HsN3
Ubiquitin
Protein 14.3.3. ϵ
MA-3
- Olfactomedin-like
Reticulocalbin
TFF-1
Bax- α
DAGK ζ
- Calpain (small subunit)
LAR
DKK-1
SAP49
TACE
Rack 1
NHE3RF
- p80 coilin
Fibulin / Fibrillin
Id-1
p38 δ kinase
Elf-3
- Swap2
67LR
HDAC-3
FKBP-52
STE5
CaMKK β
- PRP 16
MDC15
Dead Box X
Caveolin 1
- HSP 47
CD 24
MRG1
Ese-1a
- RCC-1
Ki-67
RbAp 46
nm23-H2
- ORS-1
HSP 27
SSRP1

Gadal F. *et al.* (2003) *Nucleic Acids Research* 19 (31): 5789-5804

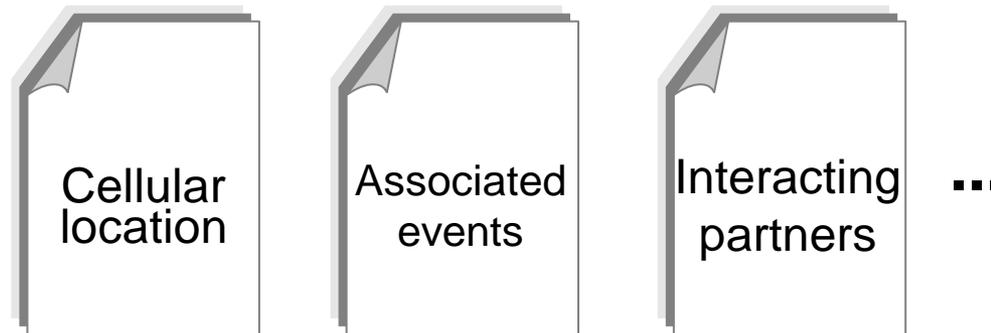
Information Retrieval & Extraction



Set of genes



Set of papers



Information MEDLINE

text only

UI - 98057316

TI - The human 37-kDa laminin receptor precursor interacts with the prion protein in eukaryotic cells.

AU - Rieger R

AU - Edenhofer F

AU - Lasmezas CI

AU - Weiss S

LA - eng

MH - Actins/metabolism

MH - Animal

MH - Binding Sites

MH - COS Cells

MH - Cell Line

MH - Eukaryotic Cells

MH - Hamsters

MH - Human

MH - Mice

MH - Mice, Inbred C57BL

MH - PrPSc Proteins/*metabolism

MH - ProteiPrecursors/chemistry/*metabolism

MH - Rabbits

MH - Laminin/chemistry/genetics/*metabolism

MH - Saccharomyces cerevisiae/metabolism

MH - Spodoptera/cytology

SO - Nat Med 1997 Dec;3(12):1383-8.

AB - Prions are thought to consist of infectious proteins that cause transmissible spongiform encephalopathies.

According to overwhelming evidence, the pathogenic prion protein PrPSc converts its host encoded isoform PrPC into insoluble aggregates of PrPSc, concomitant with pathological modifications (for review, see refs. 1-3).

Although the physiological role of PrPC is poorly understood, studies with PrP knockout mice demonstrated that PrPC is required for the development of prion diseases. Using the yeast two-hybrid technology in *Saccharomyces cerevisiae*, we identified the 37-kDa laminin receptor precursor (LRP) as interacting with the cellular prion protein PrPC. Mapping analysis of the LRP-PrP interaction site in *S. cerevisiae* revealed that PrP and laminin share the same binding domain (amino acids 161 to 180) on LRP. The LRP-PrP interaction was confirmed in vivo in insect (*Sf9*) and mammalian cells (COS-7). The LRP level was increased in scrapie-infected murine N2a cells and in brain and spleen of scrapie-infected mice. In contrast, the LRP concentration was not significantly altered in these organs from mice infected with the bovine spongiform encephalopathic agent (BSE), which have a lower PrPSc accumulation. LRP levels, however, were dramatically increased in brain and pancreas, slightly increased in the spleen and not altered in the liver of scrapie-infected hamsters. ...

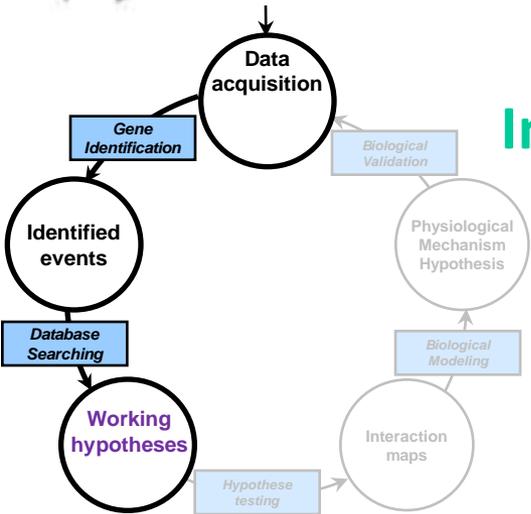
Information MEDLINE

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MH - Spodoptera/cytology
SO - Nat Med 1997 Dec;3(12):1383-8.

AB - **Prions** are thought to consist of infectious proteins that cause transmissible spongiform encephalopathies. According to overwhelming evidence, the pathogenic prion protein **PrPSc** converts its host encoded isoform **PrPC** into insoluble aggregates of **PrPSc**, concomitant with pathological modifications (for review, see refs. 1-3). Although the physiological role of **PrPC** is poorly understood, studies with **PrP** knockout mice demonstrated that **PrPC** is required for the development of prion diseases. Using the yeast two-hybrid technology in *Saccharomyces cerevisiae*, we identified the 37-kDa **laminin receptor precursor (LRP)** as **interacting** with the cellular prion protein **PrPC**. Mapping analysis of the **LRP PrP interaction** site in *S. cerevisiae* revealed that **PrP** and **laminin** share the same **binding** domain (amino acids 161 to 180) on **LRP**. The **LRP PrP interaction** was confirmed in vivo in insect (Sf9) and mammalian cells (COS-7). The **LRP** level was increased in scrapie-infected murine N2a cells and in brain and spleen of scrapie-infected mice. In contrast, the **LRP** concentration was not significantly altered in these organs from mice infected with the bovine spongiform encephalopathic agent (BSE), which have a lower **PrPSc** accumulation. **LRP** levels, however, were dramatically increased in brain and pancreas, slightly increased in the spleen and not altered in the liver of scrapie-infected hamsters. ...

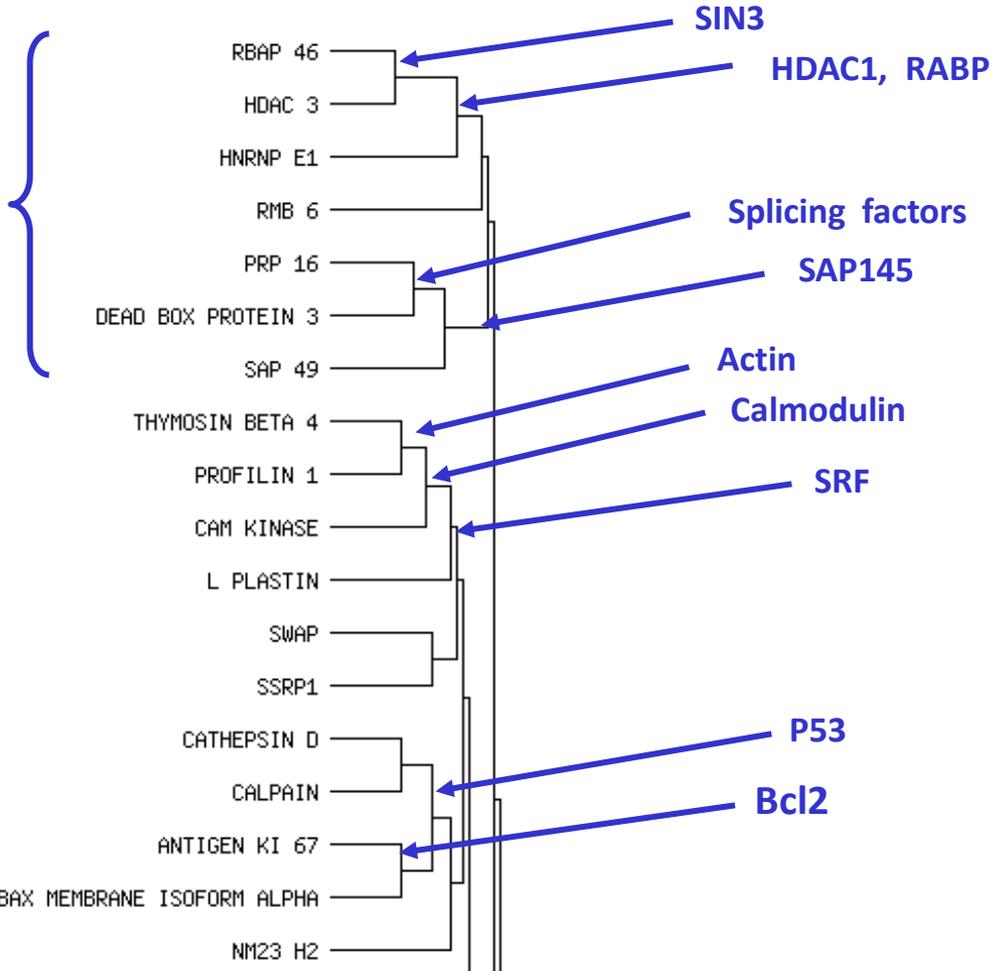
Generating hypotheses & systematic destructive testing.

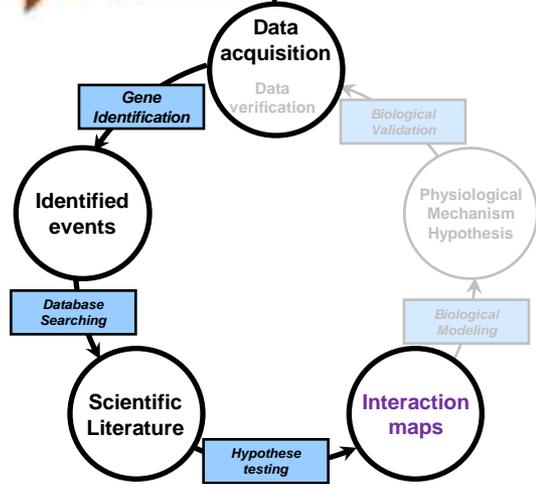


Index visualisation & manipulation

RNA Splicing & expression

Apoptosis & cell survival



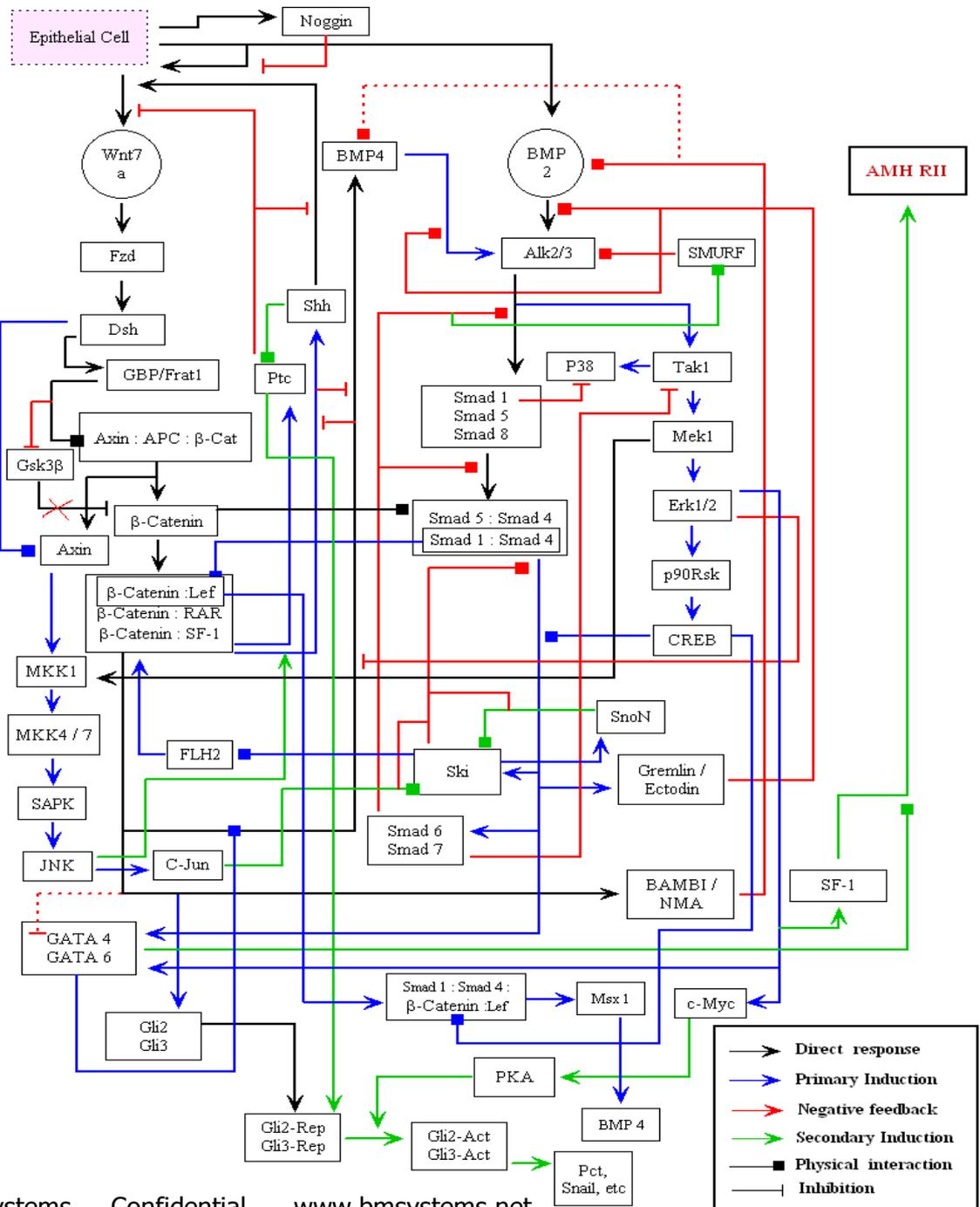


Interaction maps

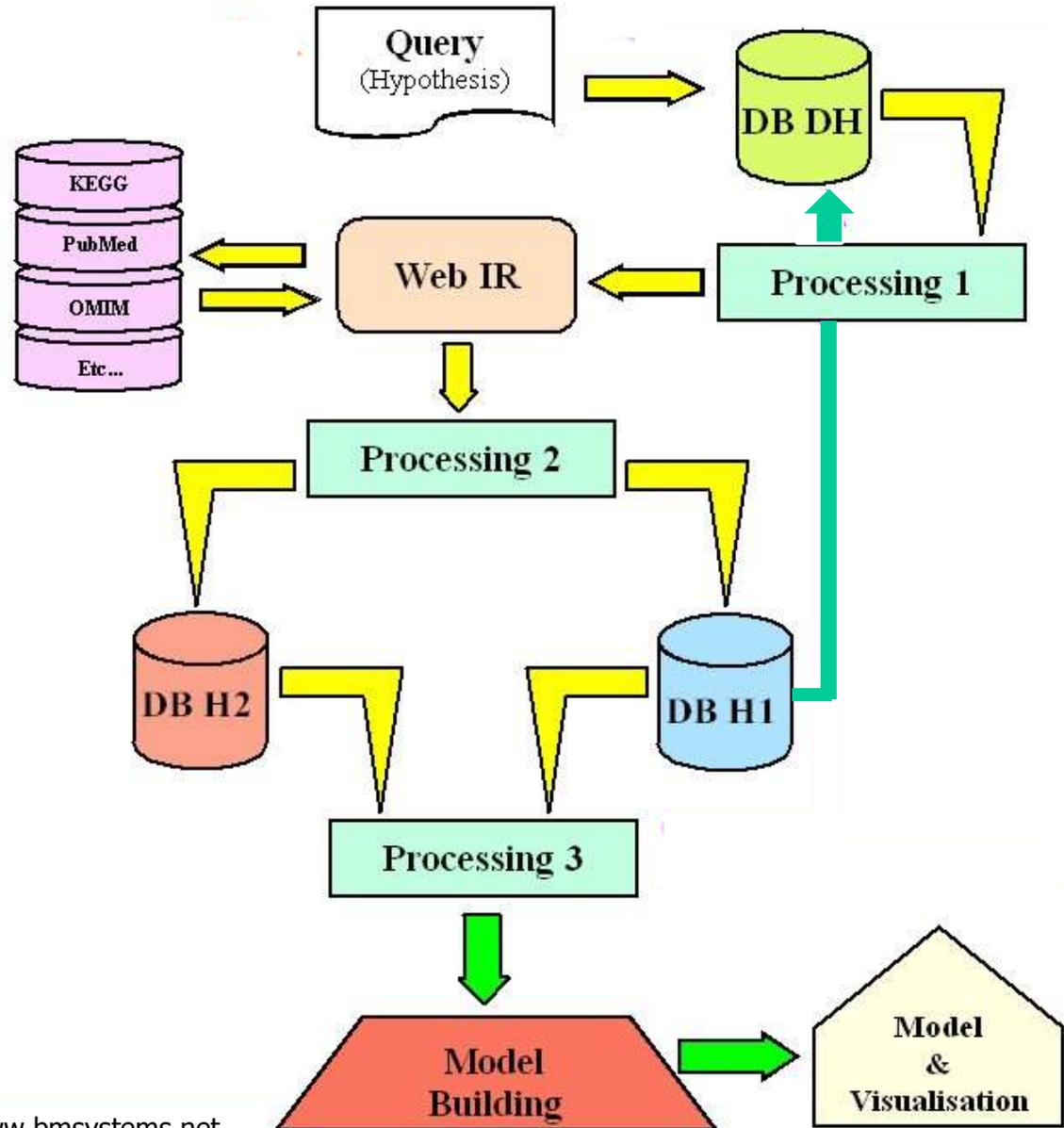
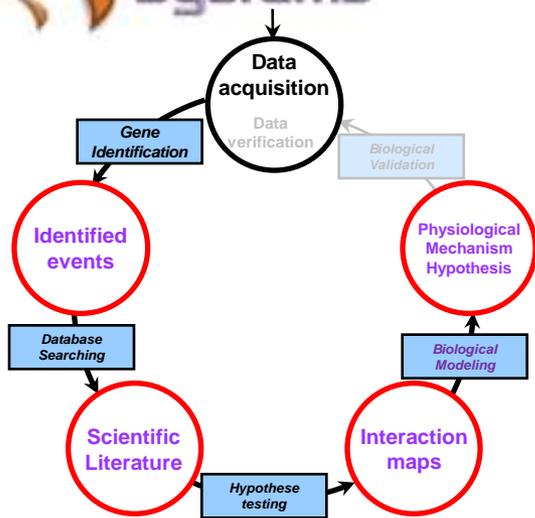
describe the pathways that have **become functional** and those that have **become forbidden** in response to local conditions imposed by the activation of defined biological mechanisms.

Specific biological events do not occur because they are fated to.

They occur because other events could not!



The CADI™ Integration & Modelling Process.



This iterative process does three things:

- It largely resolves the coherence issues attached to the classical approach;
- It reveals hitherto unknown mechanisms/processes, and
- It allows the translation of systems biology to clinical & medical interventions.

As a result,

Searching under the street lamp because that is where there is light may be much less helpful than expected.

Indeed, since it is the presence/absence of specifiable events which govern phenotypic characteristics, it follows that

The mechanisms that characterise a given phenotype (be it pathological or not) within a given biological system can be utilised as analytical tools to unravel those associated with any other phenotypic transition affecting the same biological system.

Here, symptomatology ceases to function as defining criteria to become contextual and relative functional end-products.

Therefore, the solution to a given biological problem can be efficiently obtained through entirely indirect investigations.

This is particularly true for problems resistant to direct approaches because characterised by

- High symptomatologic heterogeneity, and/or
- High functional/phenotypic uncertainty.

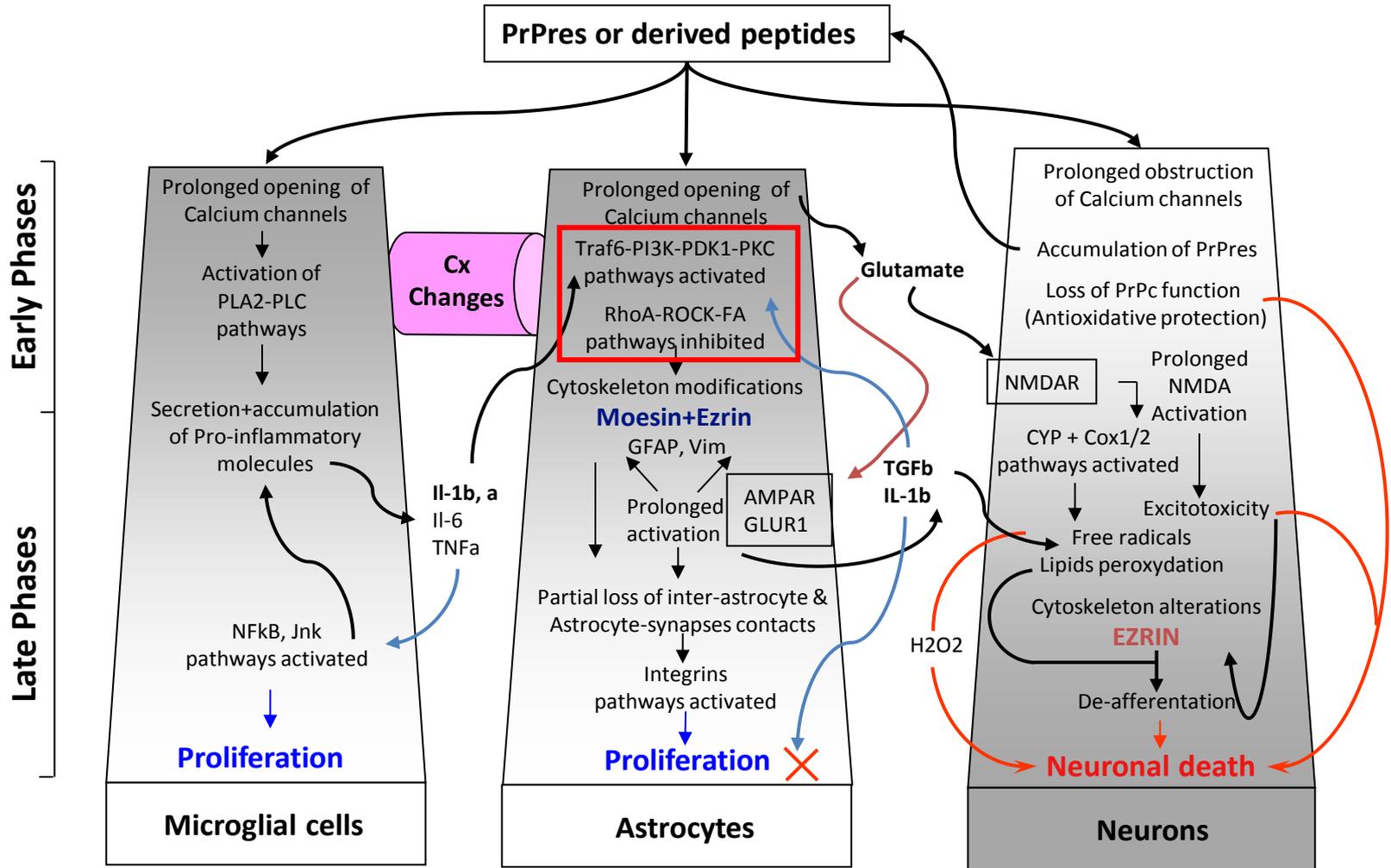
Example 1:

Understanding the *in vivo* mechanisms of Creutzfeldt-Jakob Disease pathogenesis & progression leads to the discovery of improved treatment for non-degenerative psychiatric disorders.

CJD: A few facts.

- Progressive neurodegenerative disease, invariably fatal.
- Long asymptomatic incubation phase (30 years + in man)
- Short clinical phase (death within 6 months - 2 years)
- Pathological agent: abnormally folded form of the PrP protein
- Pathological mechanisms : **Unknown**
- Clinical progression mechanisms : **Unknown**
- Mode of propagation within the CNS: **Unknown**
- Therapeutic or preventive means: **Unknown**
- Pathogenesis Biomarkers: **Clinical symptoms + CNS spongiosis** (post-mortem).

The pathogenesis & clinical progression model

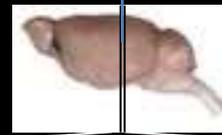


Iris F (2012); Pharmacopsych. **45** (Suppl. 1): S12-21.

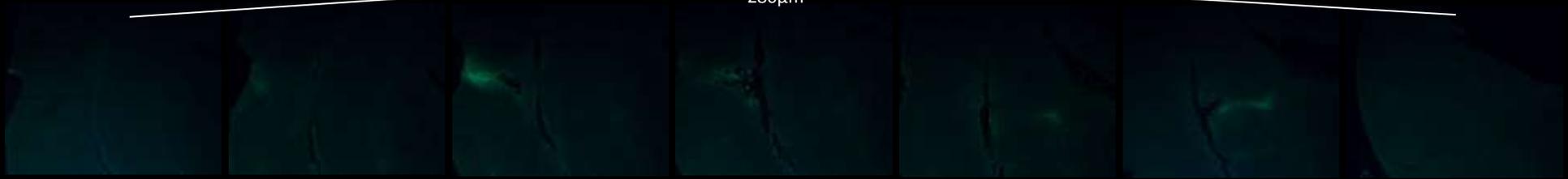
Effects of the modifications of glial connexions upon intercellular diffusion processes.

Healthy hamster

Stereotaxic Injection of 500nl fluorescent tracer < 1000d

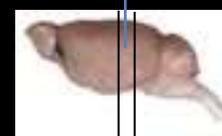


280µm



Scrapies hamster

Stereotaxic Injection of 500nl fluorescent tracer < 1000d

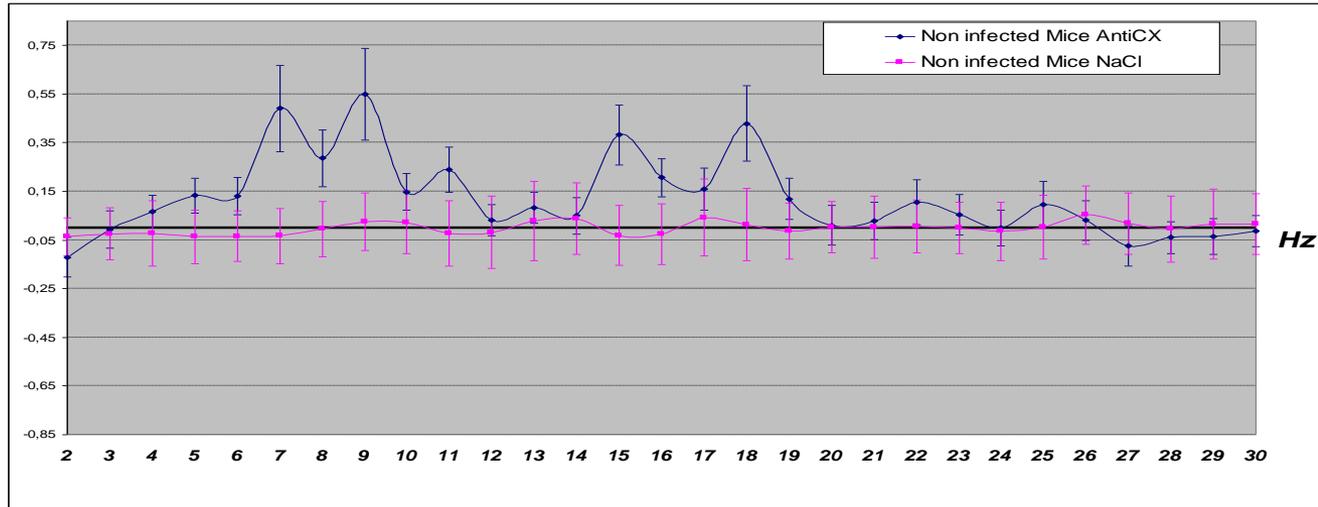


1080µm

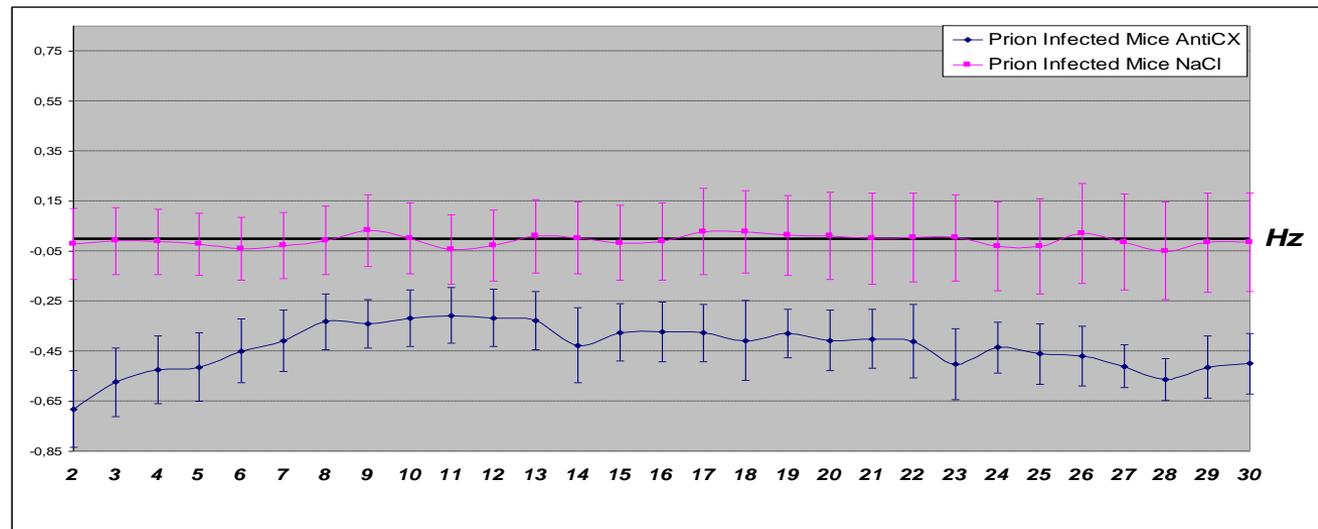


The effects are much more wide-spread than anticipated!

Functional alterations linked with modifications of glial connections.



Healthy mice

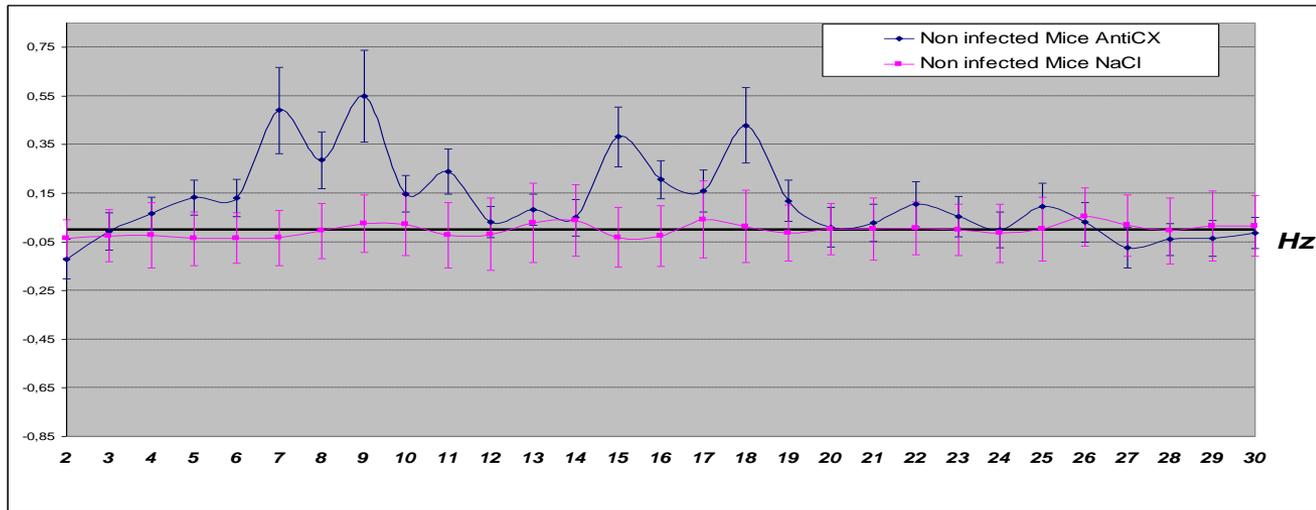


Scrapies mice (asymptomatic phase).

■ NaCl

■ Anticonnexin

One of the roles of connexins is to dampen neuronal synchronisation.



Healthy mice

■ NaCl

■ Anticonnexin

In healthy animals, pharmacological blockade of Cx activity results in quantitative EEG patterns closely resembling an epileptic crisis (frequency range-specific hyper-synchronisations).



This CEA/BMSystems collaborative research in CNS (psychiatric and neurological disorders) led to the co-owned patent WO201029131 (Use of anti-connexin agents for modulating the therapeutic effect of psychotropic drugs). Sept, 2008.

The net results.

CJD is not a neurological disease *stricto sensus*.

It is a disease that primarily affects astrocytes structures and functions which, over time, lethally affects healthy glial & neuronal cells through « bystander effects », leading to widespread CNS disorganisation (spongiosis) and functional failure.

But this model also provides an understanding of key mechanisms associated with psychiatric & neurology disorders.

An entirely new approach for their effective treatment was designed, tested in vivo and validated.



Patent covering novel therapeutics for psychiatry & neurodegenerative disorder (CEA/BMSystems).

This CEA/BMSystems [collaborative research in CNS](#) (psychiatric and neurological disorders) led to the co-owned patent [WO201029131](#) with a worldwide exclusive license to [Theranexus](#) CEA's spin-off currently in Phase II.

Neither of which have much to do with CJD *per se*...

This work received a Bio-IT World « Best Practices » award from the Cambridge HealthTech Institute (USA).



AND

Was selected as 1 of the 3 pan-European « state of the art examples of systems biology approaches of benefit to medicine » by the European Commission's DG Research, Directorate of Health (June 2010).

Example 2:

Understanding the co-evolutionary interplays between bacteria and bacteriophages leads to the discovery of the means whereby **undefined** multi-resistant bacterial pathogens can be efficiently controlled.

The questions (French Defence)

- How to rapidly (less than 30 min) and efficiently **detect** the presence of any given **LIVE** bacterial pathogen?
- How to rapidly and efficiently **destroy** any unknown bacterial pathogen or emerging strain **without using**
 - Antibiotics:** too many resistant strains, and very rapid resistance acquisition.
 - Vaccines:** much too slow to act, and small strain variations often lead to inefficacy.

In other words, what is required is a “detector-killer”.

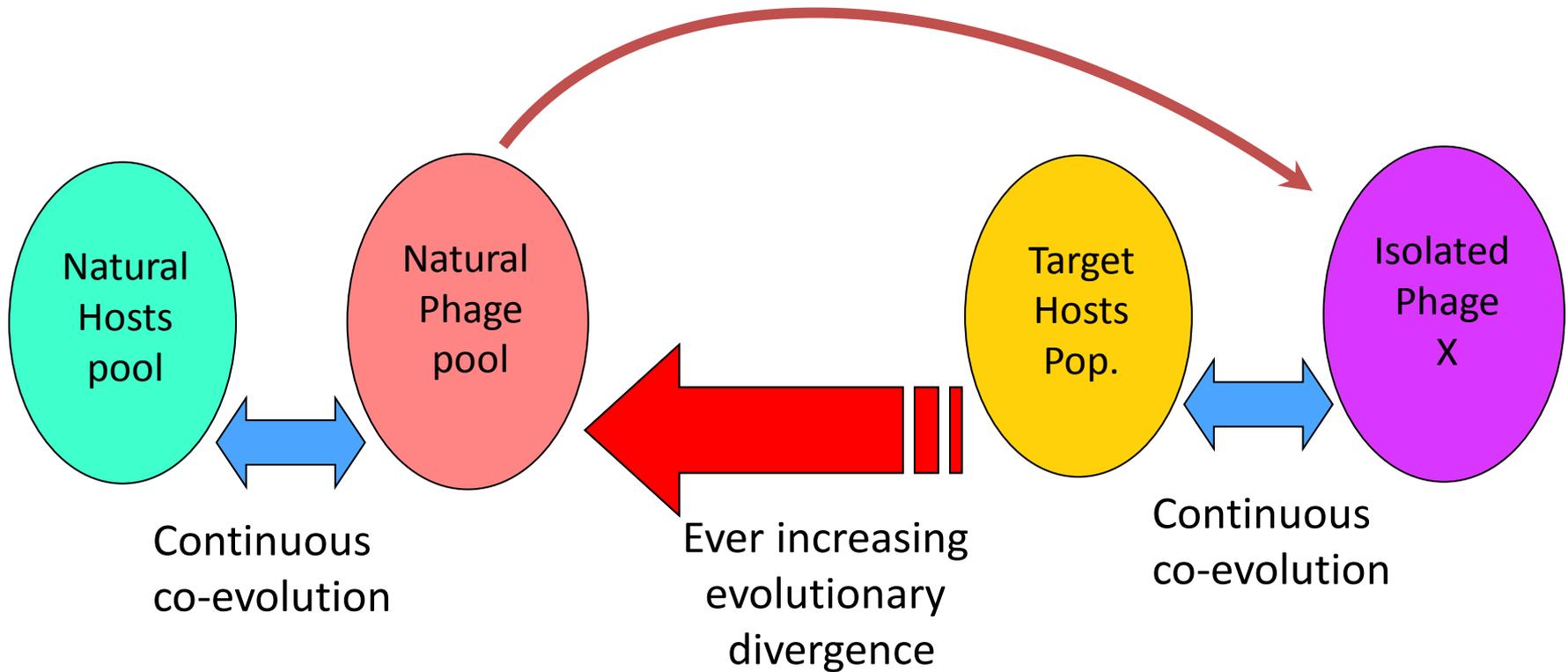
The first apparent answer

Bacteriophages, the natural predators of bacteria, could present the best potential to act as detectors-killers.

- Many are very host-specific,
- They only replicate in LIVE bacterial cells,
- Many kill the cells in which they replicate,
- As the phage progeny population increases that of the target diminishes (in a « closed » environment, few targets, if any, should escape), and
- They are extremely numerous and varied (they probably represent the most numerous « life forms » on the planet).

BUT the matter is NOT as simple as it first appears!

Co-evolution versus unidirectional predatory pressure.



+
Ever decreasing chances to
find a new efficient lytic phage.

Bacteria have existed for nearly **4 BILLION Years**. They have so far **resisted to EVERYTHING**.
And it is **certainly NOT for lack of phages!**

The model-derived solution.

- *What, in essence, is the problem?*

The bacterial targets will try anything to escape predation and we have no idea what will be the successful strategy. Furthermore, this strategy is likely to vary between locations (populations) for a same target.

- *What do we need to achieve?*

We must be capable of always preceding the targets escape strategies, no matter what they could be.

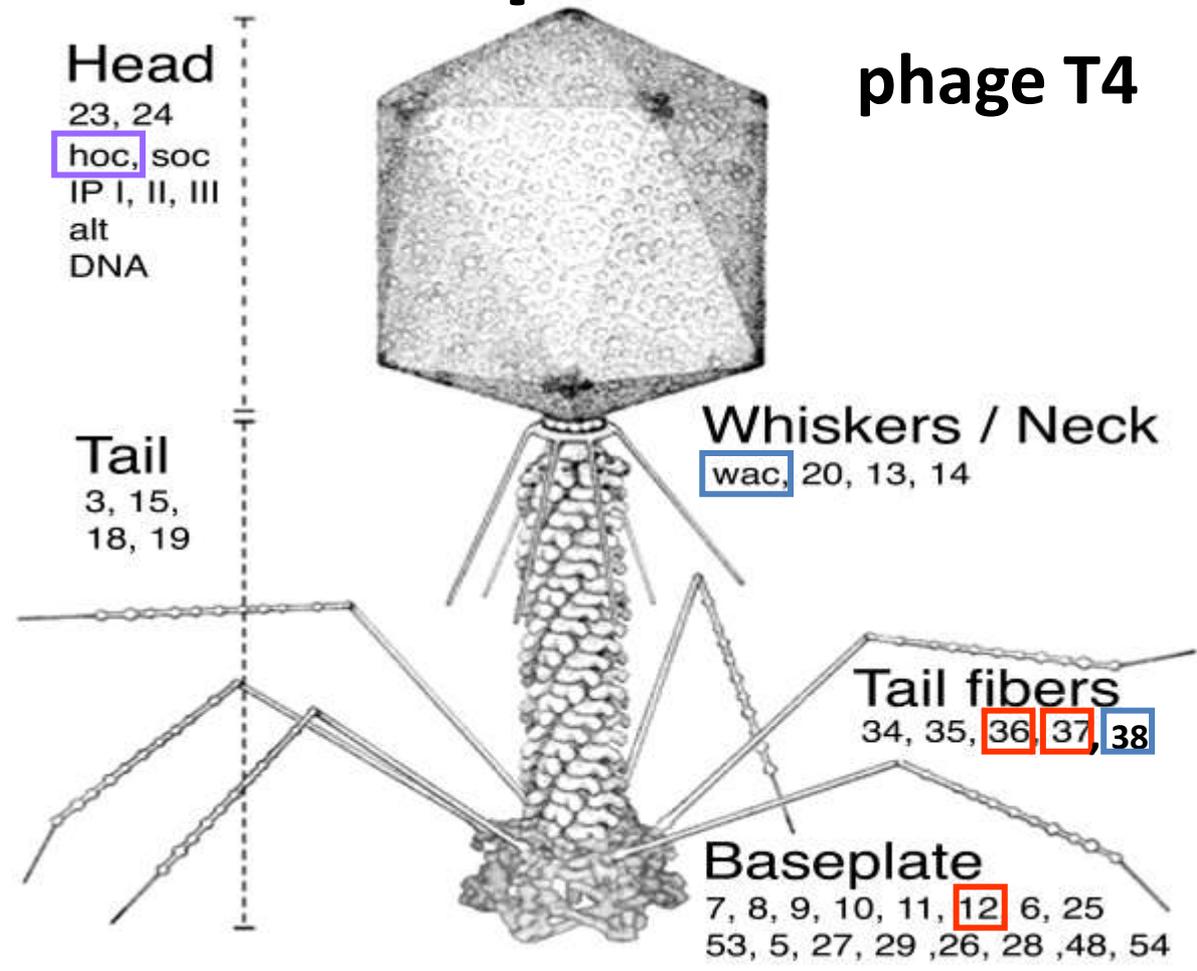
- *The best-fit solution* (model-derived):

we MUST adopt a stochastic approach.

It becomes necessary to

- abandon all idea of « natural phage pools » and,
- stochastically engineer phage banks in order to produce particles **capable of targeting anything** and **everything** while maintaining their capacity to replicate in the face of targets evasion attempts.

The problems:



How to modify any of these proteins in **N** different regions, at **X** different sites, in **Z** different manners, all this **simultaneously** and then recombine **the multitude of variants** generated in a **population of obligate lytic phages**?

The technological answers.

Three proprietary technologies (invented at BMSystems) allowing the production of stochastically engineered phage banks.

TAPETM (P) (WO 2008/093009):

A technology allowing to rapidly & simultaneously introduce defined densities of random mutations in any number of selected regions within a gene while conserving intact any number of defined coding domains in this same gene.

Applicable to any known coding sequence.

RipHTM (P) (WO 2009/090081):

A technology allowing to reversibly inactivate the genome of an obligate lytic phage within its host and carry out high efficiency homologous recombinations targeting multiple genes simultaneously without adversely affecting the host bacteria and the replicative capacity of the phage.

Ab-ACCUSTM (P) (WO 2008/093010):

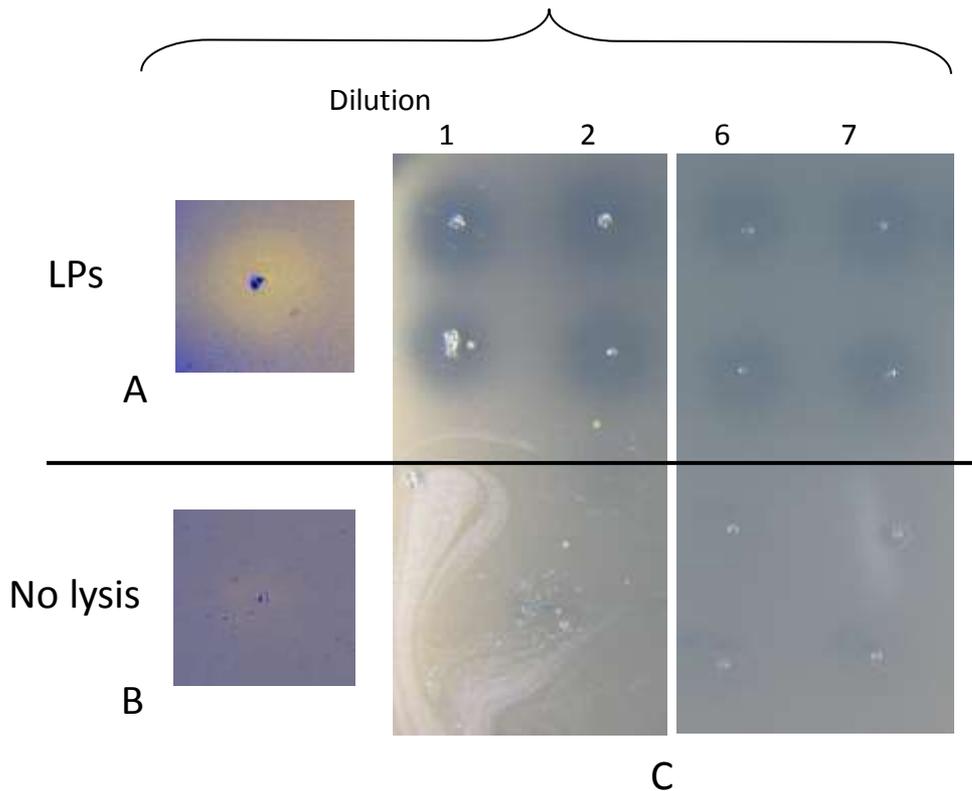
A recombination technology allowing the rapid & efficient production of lytic phage banks in which every individual differs from all others for any number of selected genes or other sequences.

Applicable to any phage and to any known sequence.

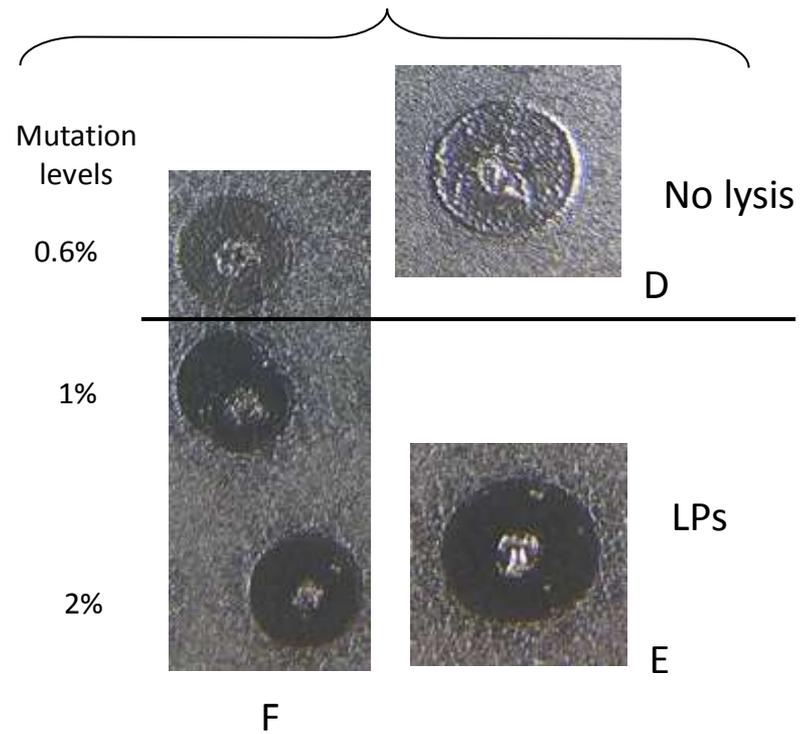
The results.

While T4 is specific to a narrow range of *E. coli* strains,
 An engineered T4 bank contains variants capable of detecting and killing
 gram⁻ bacteria far removed from *E. coli*.

Yersinia sp.



Pseudomonas sp.



Pouillot F, Blois H & Iris F (2010); *Biosecur Bioterror.* **8** (2): 155-169.

Practical consequences

(besides high-profile publications)

- Three technological patents with broad applications,
- Creation and financing of a Bio-Pharma company (Pherecydes Pharma) specialised in biodefense & biosecurity (40% owned by BM-Systems),



- Research program with French civil and defence health-services,
- Discussions with US food industry firms,
- Contract with anti-bodies producer & discussions with enzymes producers.

All this in less than 3 years.

From our point of view, under the street light is definitely not the right place to search!

Nevertheless, it **MUST** be remembered that
Models are AIDS to thought
NOT a replacement for it.

Our collaborative R&D programs & their outputs

This list excludes our contractual research programs with our clients



CEA : **"Creutzfeld-Jacob Disease CJD"** World's first in vivo validation of the mechanisms of Creutzfeldt-Jakob disease pathogenesis & progression. US, EU & French Awards; Awards (2009 and 2010) . CEA SEPIA department.

Successfully completed; **1 publication**.



CEA: **CNS disorders**. Collaborative research program that led to a [novel therapeutic strategy](#) for the treatment of psychiatric and neurological disorders. Copatent [WO/2010/029131](#)– **Use of anti-connexin agents for modulating the therapeutic effect of psychotropic drugs**. September, 2008 CEA/BMSystems,

[Pherecydes-Pharma](#) BMSystems' spin-off created in 2006, **novel M.R. anti-bacterial nano-agents biotherapies 3 patents**. Two indications: [Multi-resistant Skin infections](#) and osteo-articular infections.



Max Planck Institute (Munich): **Project "Chronic Anxiety"**.

Successfully completed; **3 publications** & a **Reference Book "Biomarkers for Psychiatric disorders"** chapter 19.



INSERM: **3 Projects "Tumoral Progression"; "Therapeutic Resistance"; "RGD 15 & Metastasis"**.

All 3 successfully completed, **3 publications**.



CNRS: **Project "Müllerian Regression"** Tissue differentiation

Successfully completed, **1 publication**.



Foundation FondaMental: **Project "Bipolar Disorders & Schizophrenia"**.

Immuno-inflammatory hypothesis. On going, **1 publication pending**



L'OREAL Arkema, Rhodia/Solvay ARD : **"Synthons"** Government funded feasibility Program at IAR cluster Industrial Biotech Feasibility study Completed 16 molecules evaluated, **2 strains built, 1 program with 1 patent (industrial partner only)**
- Skin Homeostasis: **Reference book "Computational Biophysics of Skin"** chapter 15 with Dr. Querleux (L'Oréal)



Centre of excellence in Epigenetics IISER Pune India: **Project "Etiology & Epigenetic for metabolic disorders"**
Etiology & Epigenetic for metabolic disorders, on going 1 publication pending

Useful Downloads

For more information about information quality & reliability

- ❑ [A new evidence published in Sciences](#) confirms the poor reproducibility (less than 1/3) of studies published in peer-reviewed.
- ❑ [An estimated 85% of current published research findings are false or exaggerated: How to Make More Published Research True](#). Published in PLOS Medicine by John P. A. Ioannidis Meta-Research Innovation Center at Stanford (METRICS), Stanford University.
- ❑ [Diagnosing the decline in pharmaceutical R&D efficiency](#). Published Nature Review Drug Discovery. The diagnostic is clear for our industry.
- ❑ [Believe it or not: how much can we rely on published data on potential drugs](#) targets? Their title is crystal clear. Published Nature Review Drug Discovery

Heuristic modeling principles and case studies

- ❑ [The discovery of Innovative Therapeutic Approaches: Under the street light is not the right place to search](#) BIT's 10th Annual Congress International Drug Discovery Science and Technology 2012 November 8-10, 2012, Nanjing, China
- ❑ [The Differences & Complementarities Between « Heuristic » and « Mathematical » approaches](#). The scientific presentation given by Dr. François IRIS (CSO BMSystems) during the EPA (European Psychiatric Association) conference in 2011.

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Questions



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