

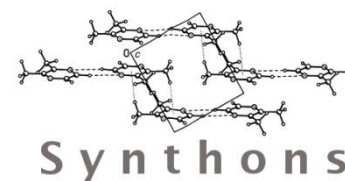
Bio-Modeling Systems

Manuel GEA, Co-founder & CEO,

BIO-MODELING SYSTEMS:

A leading Integrative Systems Biology SME.

New collaborative R&D paradigm deciphered. Set-up background
First operational successes in CNS, biodefense/biosecurity and
Green Industrial Biotech.



INTERNATIONAL EXPERIENCED TEAM CHALLENGES IN 2004

- **Global challenge: Create the first Integrative Systems Biology company based on a disruptive “*negative selection process*”,**
- **A concept contrary to “dominant” thinking.**

Two main proofs of concept to succeed:

- **Scientific: Create the 1st *in-silico* model of a complex human disease to be validated *in-vivo*;**
- **Business: Set up a 1st spin-off company created from an internal integrative systems biology program.**

Global critical issue: *Where to set up our company?*



5 countries short listed to set up a business:
1 - CAN, 2 - CH, 3 - UK, 4 - SG, 5 - Fr. (*not the favorite country*)

BMSystems: A fully international Co. in Paris.

2004 - BMSystems' team decides to set up its Co. in France for 4 reasons:

- **Young Innovative Enterprise Status, and R&D tax credit**
- **Key academic scientific teams identified & willing to collaborate**
- **Creation of clusters of interest**
- ***And finally, France is a nice place to live in!***

While taking advantage of its founders' international networks:

- **Scientific Committee of the Cambridge Healthtech Institute USA (2005-)**
- **Welcome Trust's Board of Experts, Systems Biology. U. K. (2001-)**
- **Human Genome Organization (HUGO); (USA) (1994-)**
- **Medical Research Council (MRC); U.K. (1989-)**
- **Max Planck Munich Germany (2006-)**
- **Medical Systems Biology- MedSys"ministry of Research; Berlin (2008-)**
- **Etc ...**

BMSystems: a collaborative biotech company focused on its core know-how to optimize time to market & R.O.I.

- Independent Private Company incorporated in 2004.
- Young Innovative Enterprise status since creation.
- *100% owned by its founders* (no search for external investors)
- A “*Biology*” driven company that intensively uses I.T. resources.
- Inventor and exclusive owner of all its technologies.
- All non-strategic functions and resources are externalized.
- FTE*: 9 scientists/professionals only focused on CADI™ research.
- Over 100 professionals are working on BMSystems’ related programs.
- Member of BiO (USA), MEDICEN, IAR (Industrial biotech) clusters.
- Controls 40% of its biopharmaceutical spin-off: Pherecydes-Pharma.



Building CADI™ models and validating them/developing outputs do not require the same competences and resources.
We prefer to share costs and profits with complementary partners.

New collaborative R&D paradigm deciphered and its first operational successes in CNS, biodefense/biosecurity and Green Industrial Biotech.

The Life-modeling issue

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...

The challenge is clearly not a question of technologies only

The Life science modeling dilemma

1. The mechanisms of life are *complex, non-linear and integrative*
2. In “living complex” systems, the functions of *biological components and mechanisms are event and context-dependent*. The same components/networks can produce different biological effects
3. Classical “Cartesian” modeling concepts & approaches, valid for the majority of man-made artifacts, imply the concept of a “blue-print”. Components are “function-specific” and their assembly pattern determines the final function of the structure they constitute. *But this concept is at the opposite of biological reality*
4. ... While “Cartesian” Bioinformatics and *Mathematical tools have proven to be efficient to* collect, structure, analyze, simulate specific functions to test or to generate innovative hypotheses, yet...
5. ...The *“garbage in, garbage out” reality*, tells us that the information produced and published (even in leading scientific journals) is necessarily *ALWAYS incomplete, biased and erroneous to unknown extents*

Despite increasing investments in Technology &I.T., major drugs products submissions to FDA are constantly declining

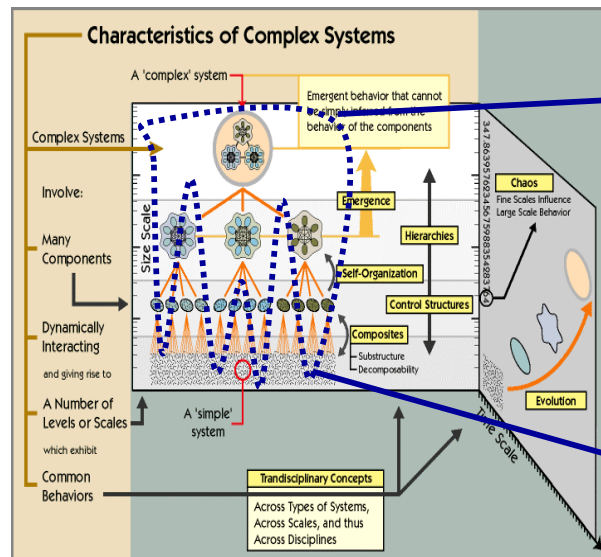


We need to change our point of view

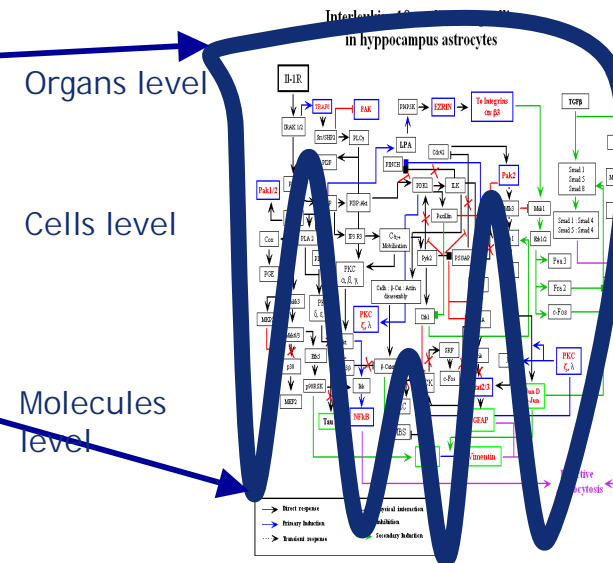
We invented CADI*™ “non-mathematical” modeling, successfully applying its 5 principles

1. An **“Architectural Principles”** Approach
2. Our **“Negative Selection”** Process
3. Our **“4 steps validation”** Process
4. Our **“Broad life sciences & IT”** Expertise
5. Our **“synergic collaboration”** with classical IT partners

A complex system to study



A CADI™ model representing the system in a specific context

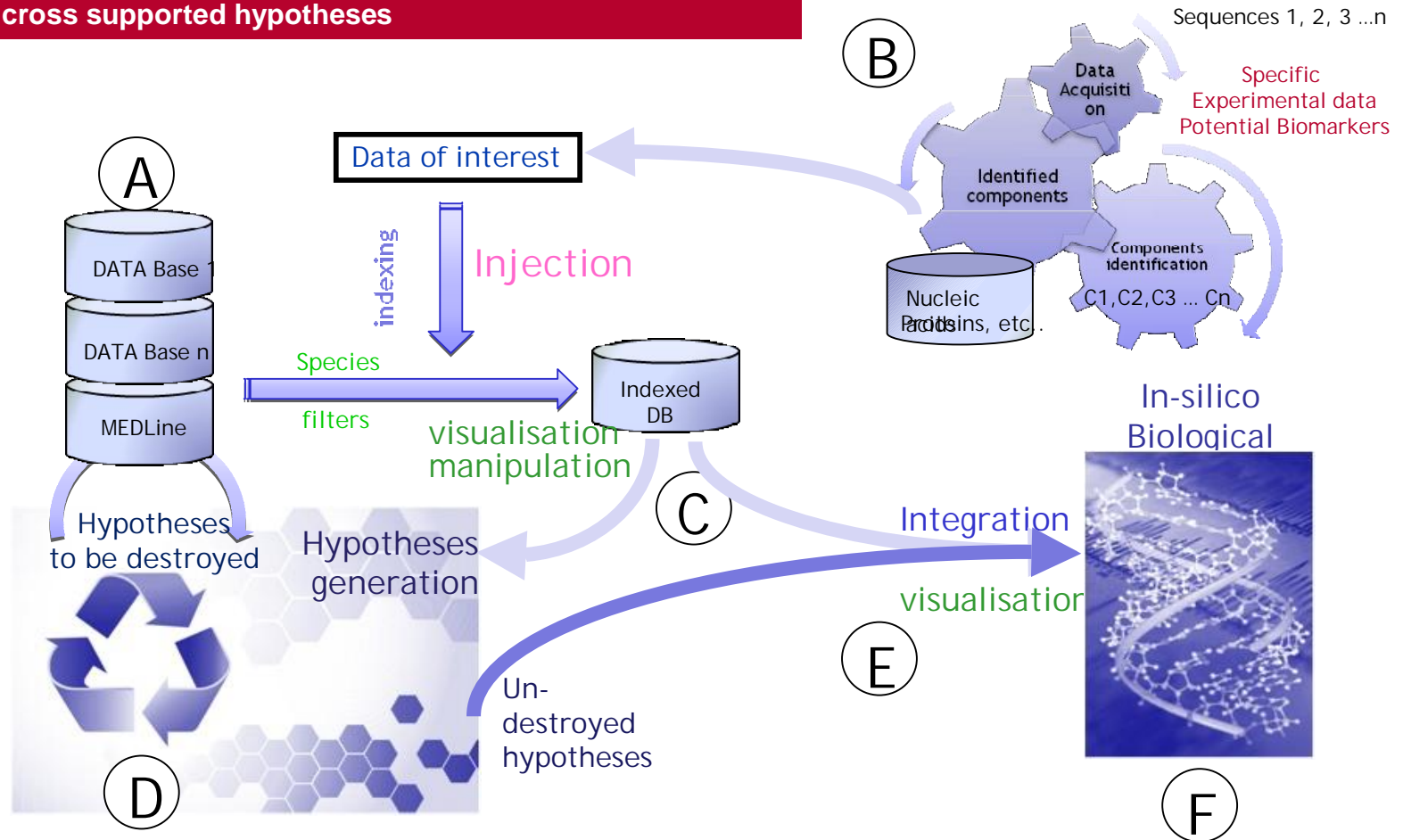


*Computer Assisted Deductive Integration

CADI™ negative selection process

The first operational application of the negative selection concept

CADI™ original concept is an operative answer to “the garbage in garbage out issue”, and a disruptive innovative way to generate new knowledge from new cross supported hypotheses



Synergic collaboration with classical IT partners

The first operational application of the negative selection concept

Let's go a step beyond with partners.

The pharmaceutical industry now requires its *scientists and clinicians* to harness & explain the mechanisms of health and diseases.

But they need *adapted systems and tools to help them work*.

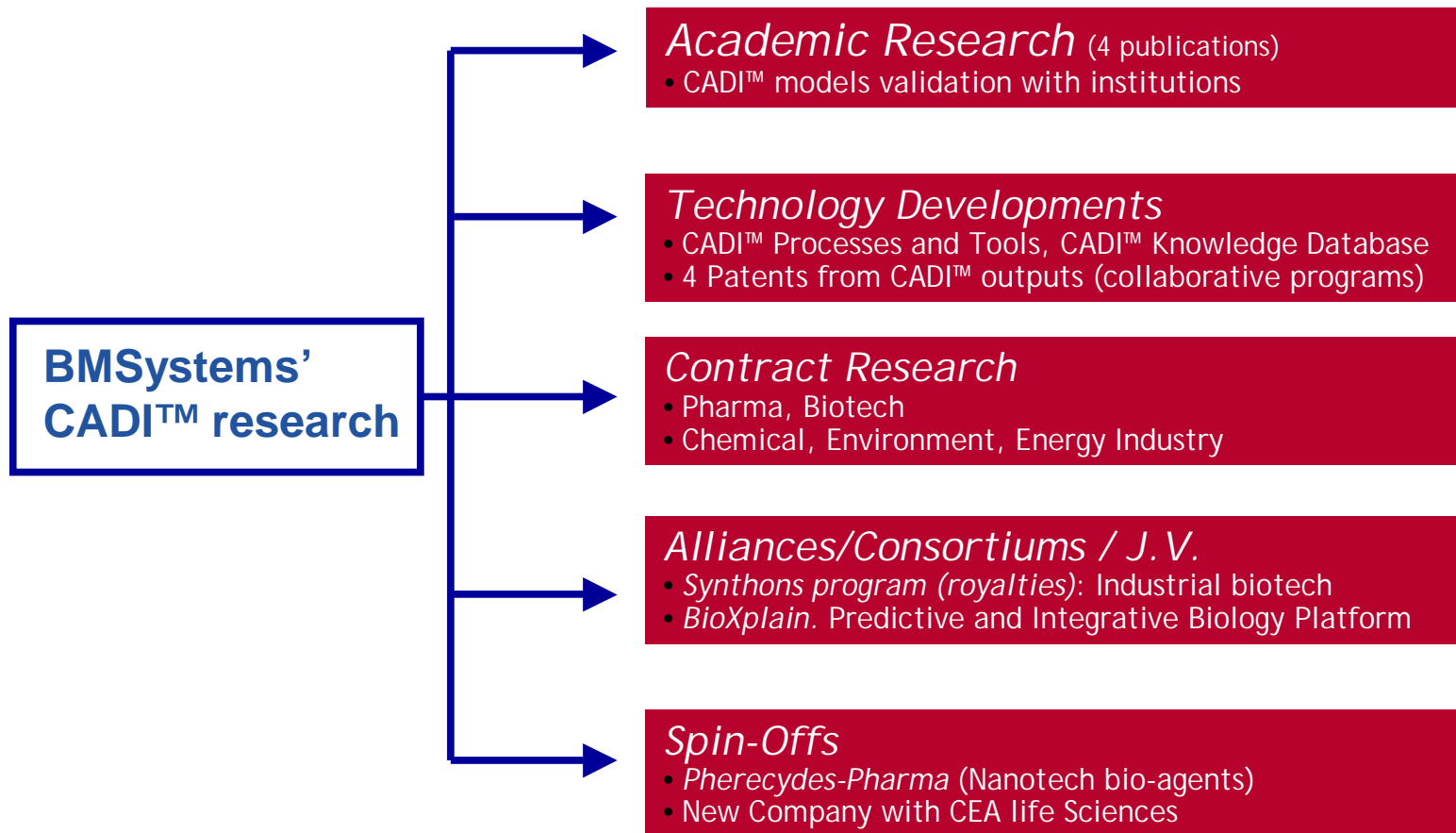
Three complementary, cutting edge life sciences companies decided to collaborate to address this challenge:

- *Bio-Modeling Systems*: The inventor of CADI™ methodologies and tools, including the collaborative iterative validation process.
- *BioXpr*: The most diversified provider of Software solutions built from a versatile library of modules to create real-added value from "OMICS" datasets.
- *Kayentis*: The provider of the first "Digital Pen and Paper technology 2.0", the universal platform delivering "contextualized" information .



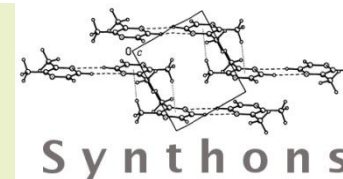
**BioXplain: The first Open Platform
for Iterative Predictive and Integrative Systems Biology.**

A collaborative strategy to optimize capital investments and time to market



BMSystems' CADI™ programs to date

Program Name	Validation / Business Partner(s)	Feasib. study	CADI™ vers. 0	Ind. Valid.	Patents / Publi.	First Proof of Concept (POC)	Mid scale or preclinic. P.O.C.	Ready for Business
Nano-Bioagents	Pherecydes							
TAPE	Pherecydes							
Chronic Fatigue Syndrome	Open							
Ebola virus ecology	Open							
Hepatitis C	Open							
CNS-Psychiatry	CEA Life Sciences							
CNS-Neurodegenerative	CEA Life Sciences							
Fibromyalgia	Open							
Pain	Open							
Migraine	Open							
Multiple Sclerosis	Open							
Psychiatric disorders	Open							
Program Synthons	ARD-IBT-L'Oréal							
Program Synthons	ARD-IBT-Rhodia							
Program Synthons	ARD-IBT-Arkema							
Breast cancer-Hras	INSERM							
Tamoxifen resistance	INSERM							
Metastasis mechanism	INSERM							
Müllerian regression	CNRS							
Adipocytes growth control	Open							
Hypercholestemia	Open							
Metabolic Syndrome	Open							



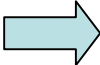
Synthons program, major collaborative industrial biotech research platform in the IAR world-class cluster

A complementary collaborative team:

- **A.R.D.:** Leading Industrial Biotech research company with experimental capacities, pilot scale-up, pilot plant (2000 Tons), etc.
- **I.B.T.:** One of France's leading Technology Transfer Institutes.
- **BMSystems:** integrative Biology & metabolic engineering expertise.
- **C.V.G.:** "green chemical" sourcing research institute.

3 EU chemical companies proposing their molecules to the platform:

- **L'Oréal:** (world leader in cosmetics)
- **Rhodia:** (ex Sanofi Aventis fine chemical entity)
- **Arkema:** (ex Total chemical entity)



2 engineered strains generated are under evaluation and a finalized process under mid-scale validation. The program is funded by the ministry of Industry and supported by IAR world-class cluster



The double take win-win collaborative programs

1. 2008: **World's first in-vivo validation of a CADI™ in-silico model of a complex human disease (Creutzfeldt-Jakob/prion disease) with CEA SEPIA***, coordinator of the European NeuroPrion Network of Excellence. Discovery of a new regulation system in the brain. (publi. Pending)



The program received a prestigious US Industry Award:
Bio-IT World 2009 Best Practice Award
The only EU team rewarded in 2009

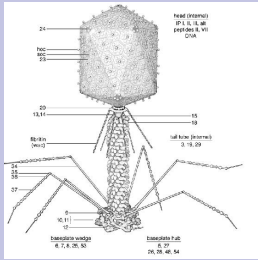


2. 2009: **New industrial application:** A 2nd CADI™ model with the same research team, exploiting one discovery of the 1st CADI™ model, led to the discovery of novel therapeutic approaches in the treatment of poorly served psychiatric diseases (patent filed Sept 2008).



In 2009, BMSystems and CEA Life Sciences decided to support a spin-off research team to develop the patent.

*CEA (Atomic Research Council) Department of prion and atypical infections research (SEPIA) A department of the CEA IMETI Institute. Jean-Philippe Deslys, Franck Mouthon and Pierre Chagvardieff.



PHERECYDES-PHARMA: Less that 5 years from concept to industrial proof in the field of biodefense /biosecurity.

- *World's 1st company created from an integrative systems biology program*
- Creation of the *first operational large-scale engineered bacteriophage bank* to fight against *“unknown multi-resistant” bacterial infections.*
- *Outstanding support from CEA Fontenay-aux Roses* (founding member of Medicen cluster), including IMETI* Institute’s scientific team.
- Creation Dec. 2006: *1.15 Million € raised*, from ACE management funds.
- *500 k € Innovation Program grant* from Oséo Innovation Agency.
- Rapid international recognition in the USA (*4 invitations to present*).
- *3 fully owned international patents* invented by BMSystems.
- *Industrial proof of concept: Sept. 2009.*
- April 2010: signs its *first international collaboration with BAC (Bio Affinity Company) BV* to develop improved antibodies and is negotiating 2 others in N. America.
- Pherecydes Pharma is member of Medicen and is also supported by the Lyon Biopôle cluster.



Clearly, the outstanding collaboration & support from CEA life Sciences Fontenay-aux-Roses, led to Pherecydes-Pharma being located in France

Clients & Partners of BioXplain founders

Diversified complementary network



Conclusions / Questions



For more information:

- www.bmsystems.net
- www.pherecydes-pharma.com
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To meet us during BiO:

- Booth 3712 UBI FRANCE-MEDICEN
- BiO Partnering Forum