

Bio-Modeling Systems implements the vision of its founders and the multi-disciplinarian experience of its co-founders

- Successful therapeutic intervention, which relieves a disease phenotype, is based on molecules that intervene upon biological mechanisms and pathways functionally associated with the expression of the phenotype.
- Therapeutic targets and modes of intervention must therefore be identified and validated in function of their actual physiological context.
- This form of identification and validation requires analytical models integrating the concepts and information embodied in the published scientific literature together with isolated sets of experimental information followed by linkage between discontinuous, non-linearly related biological processes.

Why Predictive Integrative Biology ?

- The pharmaceutical industry has been fundamentally transformed over the past five years. All international groups have undergone considerable changes.
- One reason for this is the enormous increase in accumulated information pertaining to the fields of biotechnology and genetic engineering.
- Another reason is the increasing demand for innovative and effective treatments against complex, chronic diseases pharmaceutical companies are faced with today.
- However, most biomedical research is done on a detail level using scattered approaches. Each scientist is an expert at his or her piece of the puzzle, but scientists have had to assemble those pieces in their heads. The human genome project has made available incredible quantities of genetic information, yielding thousands of potential new drug targets, but scientists have to make educated guesses about how those genes are involved in disease, how molecular-level interventions (drugs) will affect the patient as a whole, and where they should focus their research for the best success. Traditionally, these uncertainties have been resolved through years of trial-and-error research that can be slow, expensive, and prone to error. These approaches, which have been of real value in the past, are proving increasingly ineffective against complex diseases.
- As knowledge accumulates, biological mechanisms become more and more intricate to understand. Living organisms cannot be reduced to their genomes or their molecular components. Their complexity is elsewhere.
- In all eukaryotic and prokaryotic systems, proteins arising from gene transcription and translation give birth to interactions leading to intracellular events that are either structural (construction of fibres, walls, membranes, tubes, etc.), or biochemical (transformation of glucose into organic acids, alcohol, polysaccharides, etc.) in nature, consuming energy but also producing energy in latent forms (ATP/GTP, fatty acids, starch/glycogen, etc.). These events then lead to changes in the nature of local intra- and extra-cellular environments. These environmental changes in turn influence the interaction potential between proteins and therefore not only current events but also, and above all, the nature and types of events that may occur in the immediate future. Thus, the simple occurrence of a biochemical event induces a series of differential effects leading to waves of contextual modifications which in turn affect both the format and the functions of interaction complexes.
- Furthermore, all the cells and tissues of living organisms function through interconnected dynamic and synergistic networks. Every cell carries-out its tasks while communicating with its neighbours through a wide variety of means. The multiplicity and richness of these short-range and long-range interactions leads to the complexity associated with living systems that current Cartesian approaches cannot begin to decipher.

- These Cartesian approaches, whether or not they finally lead to dead-ends, have generated considerable information and knowledge which, through its modes of production and diffusion, remains widely scattered and any specialist can only use portions of this diffuse cloud.

Understanding biological mechanisms and therefore pathologies will be the major challenge of the 21st century.

Prerequisites to meeting this challenge

- **Generating new knowledge and applying it efficiently.**
- To successfully meet this challenge we shall have to abandon the classical Cartesian framework and use complexity as a tool rather than fighting against complexity.
- A better understanding of biological systems poses four major challenges:
 - The identification, classification and management of the knowledge generated by multiple research teams encompassing a wide variety of nationalities, languages and scientific specialties.
 - The development and implementation of information technologies capable of collecting, structuring and manipulating widely dispersed and heterogeneous data.
 - The capacity to integrate and extract understanding from this apparent complexity without the introduction of a-priori bias, and,
 - The mobilisation of scientific and medical multi-disciplinarian competences to directly test the biological validity of this newly generated knowledge model.
- Information is not synonymous with knowledge. However, knowledge can be generated by integrating a wide variety of information. Thus, only forms of wide spectrum analyses, capable of integrating non-linearly related complex datasets and produce biological models that provide answers sufficiently detailed to then identify credible targets and drugs will succeed.

Bio-Modeling Systems has risen to this challenge.

Predictive Integrative Biology. How ?

- Biological systems are of a non-linear and integrative nature. The path leading from genes to physiological functions is characterised by at least four series of demultiplications, each of which is associated with discontinuities.
- Experience demonstrates that, in such a context, a purely computer-driven approach is very unlikely to produce coherent exploitable results.
- Here, to generate knowledge that can then be directly exploited, a dual approach is required.
- CADI™ (Computer-Assisted Deductive Integration) is the name we have given to the suite of technologies we have developed to this effect.

The efficacy of our methodologies and their capacity to rapidly generate directly exploitable innovative therapeutic applications is demonstrated by the number of independently validated biological models of complex pathologies we have been able to generate (see “our Models”).

The CADI™ analytical platform. An original and highly efficient approach to Predictive Integrative Biology challenges

- Our approach is based upon the weighted contextual indexation of the literature, in terms of user-defined criteria, associated with the systematic destruction of hypotheses arising from the injection of data into the indexed literature databases.
- Computer-driven processes are implemented to gather and structure the information recorded in the scientific literature encompassing all known functional interactions between genes, proteins and other small molecules pertaining to cellular and physiological mechanisms in a specified context. Specialized biologists then use these data representations to generate hypotheses that can be very rapidly tested against all available information sources.
- The aim here is to invalidate the hypothesis.

- The elements that result in a hypothesis being destroyed are in turn used to generate a new hypothesis which will then be submitted to the destructive process, and so on iteratively until a hypothesis which cannot be destroyed is obtained.
- This does not mean that the hypothesis is correct; it merely means that it is supported by the existing publicly accessible information.
- Undestroyed hypotheses are then merged into 'meta-hypotheses' that are in turn subjected to the iterative destruction process. In this manner, one finally arrives at a theoretical biological model entirely supported by published information which provides directly testable explanations for as yet poorly understood mechanisms
- Should the biological data arising from these tests demonstrate that the model is largely incorrect, this new data can now be injected into the process to correct the model.
- Implementation of this process naturally requires a considerable amount of upstream programming, data-bases construction and interconnection, routines and sub-routines implementation, interface development, etc...

What is a Predictive biological model ?

- It is a detailed map of the cellular mechanisms associated with a pathological state, allowing the direct identification of
 - the pharmacological targets, and
 - the types of molecules
- Expected to produce defined therapeutic effects.

A biological model has the enormous advantage of clearly indicating to the experimenter what should be biologically tested, why, where, and how.

Constructing a biological model: an information-dependent process

- This procedure is critically dependent upon the quality and the reliability of the information utilized. The quality of the information sources must be taken into account and only well established conclusions must be retained to validate the important connections represented in the functional network.
- Nevertheless, it must be recognized that published information, of whatever source, suffers, to varying degrees, from three characteristics uncontrollable by the user:
 - the information is always
 - incomplete to an unknown extent,
 - inaccurate to an unknown extent, and
 - slanted in an unknown manner.
- For this very reason, a theoretical model built by integration of published information cannot be regarded as entirely correct.

It is merely an approximation of reality.