Honoris Causa

Universitat de Lleida

Michael A. Savageau

Honoris Causa

Investidura com a doctor *Honoris Causa* del senyor

Michael A. Savageau

Universitat de Lleida

Recull de les intervencions i lliçons pronunciades en l'acte d'investidura com a doctor *Honoris Causa* de la Universitat de Lleida del senyor Michael A. Savageau, que es va fer a l'església vella de Sant Martí de Lleida el dia 9 de maig de 2011.

Disseny i maquetació: cat & cas / Edicions i Publicacions de la UdL

Fotografia de portada: Xavier Goñi. Servei de Reproducció d'Imatge de la UdL

Dipòsit Legal: L-1188-2011

Per a més informació, visiteu la web de la Universitat de Lleida.

Índex

Salutació

Dr. Joan Viñas Salas 5

Laudatio

Dr. Albert Sorribas i Tello 8

Acte de doctorat *Honoris Causa*

Dr. Michael A. Savageau 15

Discurs de cloenda

Dr. Joan Viñas Salas 30

Salutació

Dr. Joan Viñas Salas

Bona tarda, Good evening

Secretària general de la Universitat de Lleida, vicerectores, vicerectors, degans, directors de centre, Dr. Savageau's family, digníssimes autoritats,

Benvinguts i benvingudes a l'acte d'investidura del Professor Michael Savageau com a doctor *Honoris Causa* per la Universitat de Lleida. Welcome to the investment ceremony of Professor Michael A. Savageau as Doctor Honoris Causa of Lleida University.

És un reconeixement de la seva trajectòria professional i humana, alhora que posem de manifest el compromís de la nostra universitat amb la recerca i la docència, ja que a l'honorar la seva trajectòria universitària ens obliguem a tenir en consideració el seu exemple.

Tot això fa que la universitat reservi per a aquest acte un ritual solemne, de sabor antic i d'un alt valor simbòlic, virtuts que en aquest marc històric tenen un notable valor i significat, ja que —com vostès saben— aquesta església de Sant Martí era la seu dels actes més solemnes de l'Estudi General de Lleida, i és l'únic vestigi que resta en peu d'aquella venerable institució universitària.

Gràcies al conveni recentment signat amb el Bisbat de Lleida i el Consorci del Museu de Lleida Diocesà i Comarcal, la nostra universitat recupera avui la que havia estat seu universitària, compartida, és clar, amb els usos litúrgics i culturals. Aquest és, per tant, un dia molt assenyalat per a la Universitat de Lleida, ja que establim un llaç d'un gran valor històric i simbòlic amb el nostre passat.

Aquest murs venerables, doncs, evoquen el nostre passat, la tradició, alhora que aquest acte és, en canvi, un homenatge a un investigador innovador, a l'avantguarda de la ciència mèdica. Tradició i innovació, com la nostra mateixa història.

Em plau també posar de manifest que aquesta investidura es fa en el marc del XII International Congress on Molecular Systems Biology. Vull saludar, doncs, tots els congressistes que ens acompanyen i que ens fan l'honor de sumar-se a l'homenatge al Dr. Savageau. Sigueu benvinguts a aquesta vella església de Sant Martí, testimoni històric de l'antic Estudi General de Lleida.

I would like to greet all the conference attendants who are with us today, honoring us by their presence at this event that has been organized as a tribute to Professor Savageau. Please be welcome to this old Saint Martin's Church, a historical witness of the former General Study of Lleida.

La Universitat de Lleida sap que, a l'honorar el Dr. Michael Savageau incorporant-lo al nostre claustre de doctors i doctores, ens enriquim, ja que ens beneficiarem del seu prestigi, de la seva saviesa i de la seva humanitat.

Laudatio

Dr. Albert Sorribas i Tello

Rector Magnífic,

Dignissimes autoritats i claustrals,

Dear colleagues,

Senyores i senyors,

It is an honor for me to deliver this citation to you for the work of Professor Michael Savageau as a candidate to the honorary degree of Doctor *Honoris Causa* from our University. The Department of Basic Medical Sciences is grateful to the members of the Governing Council of the University of Lleida for recognizing his merits and for accepting the proposal for this degree. I will start by introducing Professor Savageau's scientific background and major scientific contributions, and finish with a personal appraisal of his impact on the scientific community.

Professor Savageau was born some years ago in Fargo, North Dakota. After studying engineering and physiology at the University of Minneapolis and the University of Iowa, he obtained his PhD in Cell Physiology and Systems Engineering at Stanford University in 1967. His research interests, right from the beginning, focused on problems related to the integrated behavior of biological systems, mainly gene regulatory networks and metabolic pathways. At that time, it must be remembered that almost no computer facilities were available to the scientific community, which forced its members to search for tools and methods to address systemic complexity in biology at the molecular level.

In this context, one of the first questions Professor Savageau addressed was how to represent the different processes within a cell using mathematical models. This is a

basic step that still drives the research efforts of many groups, including our own here at the University of Lleida. The right choice of a mathematical representation makes possible and, at the same time, constrains subsequent analysis. An incorrect choice can prevent researchers from obtaining any new insight into a system. An appropriate choice facilitates the understanding of fundamental questions. Starting with methods related to engineering analysis and the theory of the approximation of functions, he proposed the **power-law formalism** as a mathematical tool for obtaining useful models for biological networks. These models, which are relatively simple, capture the essential properties of the constitutive processes of cell biology. This was as early as 1969, right after he obtained his PhD.

The power-law formalism, as I shall discuss in a moment, was a fruitful idea that opened many new possibilities for the analysis of biological networks. Its use, beginning in the 1970s, allowed Savageau and others to postulate **design principles** in molecular biology. Such principles provide objective reasons for why there are, for instance, different modes of regulation for a gene circuit and predict which type of regulatory structure is to be expected in a given situation. Within the domain of gene regulation, the meticulous and extensive analyses of the designs of gene circuitry ultimately led to the creation of the **demand theory**, a theory that explains and has correctly predicted regulatory patterns for gene circuits whose regulation was unknown. Design principles for metabolic pathways have not yet yielded a comparable, comprehensive theory, but numerous valuable insights have been gained into the hardwiring of representative, simply structured biochemical systems.

While working on this class of problems, he also developed a whole set of analytical tools that can be applied to relate a system's behavior to the properties of the underlying processes. The different methods are now globally known as the **biochemical systems theory** and can be considered the first serious attempt to devise a new field of research that should bring together experiments and theory to better understand the evolution of biological systems and their adaptive responses. At this point, I should highlight that no analytical methods for the large scale analysis of living beings at the molecular level were

yet available. Such analysis was done on a gene-by-gene, protein-by-protein succession of individual experiments involving enzyme isolation and in vitro mechanistic assays.

Also, and I'm talking about the 1970s, the role of mathematics in biochemistry was not widely accepted. Savageau's work stressed the already classical idea that **the system is more than the sum of its parts** and that the appropriate way to approach such problems was through mathematical methods.

Many of the ideas that Professor Savageau introduced went unnoticed by many people for different reasons: (1) The lack of appropriate data that could be applied to their system of interest; (2) the lack of computational tools that would facilitate such an application; and (3) the dominant vision in the field: reductionism was thought to be the only way to understand cell biology.

While he was working on different analyses of gene circuits and their organizational principles, Professor Savageau continued the methodological developments of the power-law formalism as a modeling tool for biological systems. Together with Professor Eberhard Voit, he demonstrated that nonlinear models can be recast as power-law models. This provides a canonical mathematical representation that we can use to tackle different questions. For instance, highly efficient computational algorithms were developed for S-system models, which are one of the two possible mathematical variants for representing a system using the power-law formalism by focusing on their regular structure. I still remember my surprise when he showed me the ESSYNS program running on a rudimentary PC and simulating the dynamic behavior of a quite complex model. This was in 1986 when I moved to the University of Michigan for a post-doctoral stay. To give you an idea of the importance of ESSYNS and how much ahead of his time Professor Savageau was, I should remind you that at that time we were not yet able to connect two computers to a network in order to share a printer. I'm not sure if Professor Savageau remembers this, but we spent almost a week working in his laboratory on this problem with an expert from Apple without succeeding.

Power-law models have provided a very fruitful way of representing cellular networks, and many of the colleagues present here have contributed in one way or another to developing new methods and computational solutions to biological problems. These include optimization, computer simulation, parameter estimation, biotechnological applications, etc.

The implications of Professor Savageau's work underwent a sudden change with the development of what is now known as systems biology. The success of the human genome project, the development of new high-throughput techniques for gene expression, and the sequencing of genomes bring forth the need for tackling cell complexity in a new way. The rediscovery of the idea of the system as central to biology stressed the need for computational and mathematical methods. Bioinformatics contributed to put some order in the big-bang of new data that suddenly appeared, but mathematical models were required to integrate them and develop new knowledge.

At this point, the early ideas of Professor Savageau appear as premonitory of the new paradigm. Many of us have witnessed the spectacular change in biology that has occurred over the last few years. Today, mathematical models and computational methods are common in many research papers and they appear in almost any high impact journal. The search for design principles in biological networks is now one of the hottest topics in biology. Although some of us were expecting this development, the rate at which this change in paradigm is occurring throughout biology still surprises us.

And yet, Michael Savageau is right there with new ideas and proposals to keep us busy. On the one hand, he has been working side by side with experimental groups to develop artificially engineered cells with modified gene circuits that help demonstrate some of his all time ideas. On the other, he keeps pushing the theory further with the proposal of **design spaces** as a way of understanding the operation of cellular networks.

The presence of many colleagues from all over the world to attend this ceremony and the meeting we are holding here at the University of Lleida is proof of the success of his work and the many fruitful ideas this has generated. Many of us have forged a

whole scientific career by developing new methods, applications, and models based on Professor Savageau's work. And we all have benefited from his vision, intellectual rigor and friendship.

Nowadays, scientific activity has changed a great deal. The pressure for publication, the need for quick results, the lack of funds, etc., constrains, in one way or another, our scientific activity. Because of these pressures, and the sudden interest in systems biology, we have witnessed an astonishing increase in the number of new proposals in the field of modeling and the analysis of complex systems. As a result, I must say that we have experienced a certain degree of confusion about what is new and useful in this field. In these confusing times, Professor Savageau has managed to maintain his activity focused on quality, intellectual rigor, independence and creativity. I would like to highlight his independence and intellectual rigor as his principal qualities. Because of this, he has always stressed the need for developing good scientific results that will speak for themselves, whatever the circumstances. Although such recognition is taking more time in some cases than in others, he still holds on to these principles, which he had right from the beginning.

Professor Savageau has been an active member of the universities where he has worked, mainly the University of Michigan at Ann Arbor, and the University of California at Davis. He has been chair of the Department of Microbiology and Immunology at the University of Michigan Medical School and of the Department of Biomedical Engineering at the University of California, Davis. He was the director of the Bioinformatics program in Michigan and member of different advisory boards in other universities. He is, or has been, a member of the editorial board of the most relevant journals in the field of mathematical biology, including ten years as a chief editor of Mathematical Biosciences.

The list of his honors and awards includes being made a fellow of the American Association for the Advancement of Science, the Nicolas Rashevsky Distinguished University Professor by the University of Michigan, the membership of the National Academies of Science, the Moore Distinguished Scholar by the California Institute of Technology,

the Stanislaw Ulam Distinguished Scholar Award, Center for Non-Linear Studies, Los Alamos National Laboratory, and many others.

From a broad perspective, the work of Professor Savageau has contributed to understanding the emergence of systems' properties from the interaction of their constitutive elements. This is a fundamental question for understanding the evolution of molecular circuits. In this sense, Savageau's work has provided tools and perspectives for dealing with evolutive questions in this field. I would like to point out that these methods make it possible to solve these questions in a way that cannot be addressed experimentally. In this sense, his work is fundamental as a contribution of what can be achieved with mathematical models. More than just reproducing a given system, by focusing on a class of systems we are now able to understand complex properties and the emergence of design. This may seem simple now that many groups have entered the race for solving these kinds of questions, but you need to be clever to recognize this necessity when almost no one is still addressing them. And Michael Savageau is one of those clever men.

Així doncs, considerats i exposats tots aquests fets, Rector Magnífic, dignísimes autoritats i membres del claustre, sol·licito amb tota la consideració i prego encaridament, d'acord amb la resolució aprovada pel Consell del Departament de Ciències Mèdiques Bàsiques, que s'atorgui al professor Michael A. Savageau el grau de doctor *Honoris Causa* per la Universitat de Lleida.

Acte de doctorat *Honoris Causa*

Dr. Michael A. Savageau

Challenges in the Development of Molecular Systems Biology

Introduction

There are many commonalities between my university and yours that suggest they could be sister institutions. There are also intellectual links between our universities in my particular field, molecular systems biology, which is the subject of the International Conference currently being hosted by the University of Lleida. I will allude to the importance of these links in the following personal account that focuses on three fundamental challenges in the development of molecular systems biology. But first let me make a few observations about our commonalities.

The cities of Lleida and Davis

I quote from one of your publications: "The city of Lleida, with 120,000 inhabitants, [...] enjoys a privileged strategic position. It is only two hours' drive to the ski runs in the Pyrenees and an hour to the beaches of the Mediterranean. Lleida is located in the centre of a rich agricultural region, on the banks of the river Segre."

If I loosely paraphrase from this publication: "The city of Davis, with 70,000 inhabitants, [...] enjoys a privileged strategic position. It is only one and a half hours' drive to the ski runs in the Sierras and two hours to the beaches of the Pacific. Davis is located in the centre of a rich agricultural region, near the banks of the river Sacramento."

The Universities of Lleida and California Davis

Again, from your website: "[In 1968] university studies in Lleida were effectively re-established and consolidated as extensions to various universities in Barcelona: Law was introduced in 1968, Agricultural Engineering in 1972, Arts and Philosophy in 1975, and Medicine in 1977. On 12 December 1991, the Catalan Parliament passed an act for the creation of the University of Lleida. [...] Today, it is recognized for its growing prestige and the greatly increased number of degrees offered."

A rough paraphrase: "In 1908 university studies in Davis were effectively established and consolidated as extensions to the University of California Berkeley: Engineering was introduced in 1962, Law in 1963, and Medicine in 1965. On 23 October 1959, the California Regents designated UC Davis as a full-spectrum university. [...] Today, it is the fastest growing of the UC's campuses, and it leads the nation in the number of PhDs awarded in the biological sciences."

There also are significant differences. "The University of Lleida has its roots in the Estudi General de Lleida, which was created in 1300 by virtue of a charter granted to the city of Lleida by King Jaume II of Aragon. He based his decision on a papal bull issued in Rome on 1 April 1297, by Pope Boniface VIII. The University recently celebrated its 700-year history." "The University of California Davis has its roots in the UC Berkeley's College of Agriculture, which was chartered in 1868 as a land-grant university by an Act of the US Congress. The University recently celebrated its 100-year history." As you can see, we could be considered your younger sibling with only 600 years difference in age!

Three fundamental challenges in the development of molecular systems biology

There are undoubtedly many challenges in any field that deals with complex systems —physical, chemical, biological, sociological, technological. In addressing the development of molecular systems biology, I will select just three fundamental challenges from amongst those that my colleagues and I have confronted. There have been numerous investigators whose work we have built upon, and there are numerous investigators

who have built upon our work and extended it in significant ways as well. The numbers preclude any balanced acknowledgement in this short account, and for this I must apologize in advance. In any event, I trust that there will be sufficient context that will allow for a search of the relevant references and citations.

Representation

As early as the mid-1900s, the challenge of representing complex biological systems was well recognized. It was clear that it had to involve mathematics. However, the existing approaches were largely unsuccessful. First, there were many attempts to use well-established linear mathematics, but this proved of limited value since most, if not all, of the interesting properties exhibited by biological systems arise from their nonlinearities. Indeed, it has been said that memory (a nonlinear phenomenon) is the essence of human identity. A second approach was based on the principles of mass action adopted from physical chemistry. This too proved of limited value when confronted with the phenomena of adaptation that proved to involve the newly discovered mechanisms of gene control and allostery, not to mention the intractability of the nonlinearities and the issues of parameter estimation in large systems. Yet a third approach attempted to incorporate the nonlinearities associated with these newly recognized mechanisms and to build on an analogy between concepts like temperature in the statistical mechanics of physics. However, this approach also proved to be relatively fruitless.

This was the state of affairs when I entered the field in the mid-sixties, and of course I was influenced by all these approaches. However, it eventually became clear to me that the existing approaches were not meeting the fundamental, often conflicting, requirements for an effective representation of biological systems. On the one hand, the mathematics had to be *tractable* if it were ever to be really useful in the analysis of complex biological systems; on the other hand, it had to *faithfully reflect the fundamental nonlinear character* of biological phenomena. After many unsuccessful attempts at such a representation, I discovered the analogy between the rational functions of biochemical kinetics and the transfer functions of electrical circuits, which ultimately proved fruitful.

The explosive growth of molecular biology that occurred in the latter half of the 20th century is often referred to as "The Biological Revolution". The focus of this reductionist period was on the discovery and characterization of the basic components of organisms; interest in the integrated system was on the periphery. Not surprisingly, biochemical kinetics during this period was focused on the rate laws of isolated enzymes and steady states, and there were no generic tools for extending these approaches to larger systems of reactions relevant to biology. By contrast, the theory of electronic circuits was already well developed by the 1950s, and intellectual giants such as Hendrik W. Bode had developed rigorous tools for the analysis, synthesis and control of large complex circuits. One of his more practical discoveries was the importance of decomposing systems into modules and treating their dynamics in the frequency domain using log-log graphs known today as Bode plots.

By building on this analogy, I discovered that biochemical rate laws could be represented in a logarithmic coordinate system and then approximated by the leading terms of their Taylor series to produce a local nonlinear representation. All of this was rigorously justified by the theorems of classical mathematical analysis, which also give bounds on the size of the valid region. When the representation in logarithmic coordinates is transformed into Cartesian coordinates, the result is a set of equations involving products of power-law functions. This representation, now referred to as the *power law formalism*, was the first that allowed one to quantitatively relate the behavior of an intact biological system to the properties of its underlying molecular determinants.

It was recognized from the beginning that this formalism could be considered a canonical nonlinear representation from three different perspectives. From the *fundamental* perspective, it provides a generalized mass action representation within which traditional mass action is a special case when the exponential parameters are restricted to small positive integers. From the *local* perspective, it provides a general representation in logarithmic space that is guaranteed by Taylor's theory to be accurate within a well-defined neighborhood about a nominal operating state. This representation is the most tractable and appropriate for systems in a well-regulated homeostasis. From the *piecewise power-law* perspective, it provides a global representation constructed from

a set of local descriptions that can be made as accurate as desired, again according to Taylor's theory.

Subsequently, my colleagues and I discovered that the power law formalism could be considered a canonical nonlinear representation from a fourth perspective. Namely, the *recast* perspective, which provides an exact global representation for an enormous scope of nonlinear equations. Thus, the power law formalism provides a nonlinear representation that is sufficiently general to describe biochemical models composed of rate laws having essentially any form of biological interest. Later, in discussing the issue of biological design, I will have occasion to describe how one makes use of all four of these different perspectives.

The appropriateness of any representation is ultimately determined by its ability to make specific predictions that are confirmed by experiment. There is now a wealth of examples for which this formalism has been used to predict the function, design and evolution of biological systems and for which there is confirmatory experimental evidence. Many colleagues participating in the conference this week have enormously expanded this activity with research programs on biological systems at various scales, from the molecular and cellular to the organismal and ecological. Indeed, the generic character of these methods has led to applications in areas beyond biology as well.

When this work first came to the attention of others, there were some who criticized our methods for their lack of applicability and inaccuracy compared to subsequently developed methods. One of the first to recognize the fallacy of these claims was Albert Sorribas, professor and researcher in the Biostatistics and Biomathematics Research Group here at the University of Lleida and organizer of the International Conference on Molecular Systems Biology being held here this week. Professor Sorribas, my first intellectual link to the University of Lleida, addressed this issue directly by making a detailed comparison of the alternative methods in the context of a metabolic pathway involving protein-protein interaction, an issue of some metabolic interest at the time that has since become a major focus of genomic systems biology. His results demonstrated that our methods were not only applicable to this phenomenon, but that they

were capable of representing it more accurately than subsequently developed methods. Professor Sorribas has since been an active contributor to this field. By exploiting the generality of the methods, he helped develop and extend them into entirely new areas such as computational statistics and genomics.

Comparison

Comparison plays a central role in scientific research. Hypotheses that make alternative predictions are tested in experiments; the hypothesis that provides the best agreement with reality is refined and subjected to further tests and comparisons. This is the textbook description of the scientific method. In practice things are never so simple, particularly in dealing with complex biological systems.

There is a story told by Paul Tillich, a prominent theologian in the 1960s, in which his son asks him a question that stimulated Tillich to do some of his most productive work: "Why is there something and not nothing?" A number of philosophers and cosmologists also are interested in this question. A less philosophical, but equally profound question of interest to biologists is: "Why is there something and not something else?" It asks why in nature only certain molecular components, biochemical systems and organisms have been selected rather than others.

In the mid-20th century this was a particularly difficult problem for evolutionary biologists. At that time, one could not really conduct evolutionary experiments and the notion of making a well-controlled comparison of alternatives did not exist. As a result many explanations in evolutionary biology involved long, often eloquent, arguments that were essentially circular. When stripped to their essentials, they went something like the following: "Why did X evolve?" ... "Because it had a selective advantage!" ... "How do you know it had a selective advantage?" ... "Because it evolved!" With such arguments, one could produce a superficially satisfying narrative for almost anything; eventually these were rightly criticized as "Just So Stories", in reference to the delightful children's tales of Rudyard Kipling. This changed when evolutionary biologists realized the potential of bacteria as a model system for the experimental study of evolution

and the intellectual gulf between molecular and evolutionary biology began to narrow. However, answers to the profound questions remained elusive.

In most cases the experimental approach of directly comparing alternative mechanisms in otherwise identical organisms is not a practical option because selection has operated and the alternatives no longer exist. Furthermore, there is equal ambiguity in the task of mimicking the local environments to which such alternatives were exposed in the remote past. There are, of course, rare exceptions —"experiments of nature" or mutants selected in the laboratory— that manifest certain alternatives. These are but a minute fraction of the possibilities that have been tried in the course of evolution. Even if precision genetic engineering allows us in principle to construct the alternatives, there is still the practical impossibility of producing and examining the overwhelming number of alternatives. There are millions of possibilities to consider even for relatively simple mechanisms. Thus, the experimental approach of direct comparison cannot be used to answer the question of why certain mechanisms have been selected in nature. This absence of a direct experimental approach is undoubtedly responsible for the tautological nature of many explanations for selection. The fact of selection must be explained without presupposing it.

This intellectual milieu provided the stimulus for me to propose basic attributes that should be possessed by any theory of alternative designs for biological systems. Such a theory should provide explanations for universal (or nearly universal) designs relative to hypothetical alternatives, as well as explanations for existing alternative designs in terms of conditions that might promote their selection or maintenance. Moreover, an adequate theoretical framework for understanding alternative designs of biochemical systems should provide three fundamental capabilities. First, it should provide an appropriate language or formalism for describing alternatives. Since many of the alternatives no longer exist, generic methods of accurately representing their behavior are required so that comparisons can be made in principle just as if the alternatives did exist. Second, it should provide methods for relating system behavior to changes in elements of the design. These methods must be tractable, systematic procedures so that an arbitrary number of possibilities can in principle be examined. Third, it should provide methods

for critically comparing the behavior of the alternatives according to objective criteria that can be quantified. Although a general theory that would possess these attributes and provide such understanding for alternative biological designs has yet to be formulated, my colleagues and I have developed the rudiments of such a theory and applied it successfully in a number of instances.

The first of the above capabilities, a generic representation, is provided by the power law formalism, as I noted above. The second capability, relating system behavior to changes in elements of the design, has also been developed within the power law formalism by building on well-established theory from engineering systems.

The third capability, critically comparing the behavior of the alternatives according to objective criteria that can be quantified, is no trivial matter for complex systems. Various approaches to this problem have developed in different disciplines (e.g., engineering, physics and experimental biology), but none of these has proved to be very satisfactory for complex biological systems. To address this last capability, I proposed a method called *mathematically controlled comparison* that combines aspects from several of these existing approaches. Its characteristic features can be summarized in very abbreviated form as follows. (1) The two designs being compared are restricted to having differences in a single specific process that remains embedded within its natural milieu. This is equivalent to a single mutational difference in an otherwise isogenic background. (2) The values for the parameters that characterize the unaltered processes of the alternative are assumed to be strictly identical to the values for the corresponding parameters of the reference system. This equivalence of parameter values from a perspective within the systems is called *internal equivalence*. It provides a means of nullifying or diminishing the influence of the background, which in complex systems is largely unknown. Again this is analogous to the isogenic control in an experimental comparison. (3) The two systems are required to be as nearly equivalent as possible in their interactions with the outside environment, i.e., from a perspective external to the system. This is called *external equivalence*. The one altered process will in general have a different set of values for all of its parameters. This introduces extra "degrees of freedom" that must be constrained; otherwise arbitrary differences

will arise in the comparison. The constraints imposed by external equivalence fix the values of the parameters for the altered process in such a way that arbitrary differences in system behavior are largely eliminated. Functional differences that remain between the two systems with maximum internal and external equivalence represent inherent functional differences for the designs in question.

The method of mathematically controlled comparison has been used for some time to determine which of two alternative regulatory designs is better according to specific quantitative criteria for functional effectiveness. In some cases, the results obtained are general and qualitatively clear-cut; i.e., one design is always better than another, regardless of parameter values. In contrast, an ambiguous result is obtained when either of the alternatives can be better, depending on the specific values of the parameters.

This issue was addressed by Rui Alves, associate professor and researcher in the Biostatistics and Biomathematics Research Group at the University of Lleida and the other organizer of the International Conference on Molecular Systems Biology. Professor Alves, my second intellectual link to the University of Lleida, developed a numerical approach to this problem by combining the method of mathematically controlled comparison with novel statistical techniques to yield numerical results that are general in a statistical sense. This approach retains some of the generality that makes mathematically controlled comparison so attractive, and at the same time provides quantitative results that are lacking in the symbolic approach. For example, the symbolic approach may well prove that one design is always better than another, but the numerical approach might show that the difference is miniscule. For those cases in which the symbolic approach shows that one design is superior under one set of conditions and inferior under another set of conditions, the numerical approach might resolve the issue by demonstrating that only the first set of conditions leads to a statistically significant difference between the systems. Professor Alves has gone on to address alternative designs for signal transduction cascades, as well as other classes of mechanisms, using bioinformatic and structural genomic approaches.

Design

For a long time the issue of design in biology was not a legitimate consideration, and in some quarters it remains a taboo subject. This is a legacy of its misuse in arguments against evolution and in the "Just So Stories" of early evolutionary biologists. However, the term design has a rich and well-established meaning, and when used in the context of rigorous analysis and objective performance criteria, provides a deep understanding of the function and evolution of biological systems. This is now more widely accepted, as is evident in books being published on biological design principles, the establishment of new journals with this focus, and conferences such as the current one being devoted to the subject.

Any discussion of design raises the question: Are there design principles or rules that govern the patterns observed among biological systems? The answer depends upon whom one asks. There are some biologists who would answer: "Of course there are rules, and it is the business of science to discover them!" This structuralist view has a long tradition embedded in positivist philosophy —the collection of empirical data, induction of rules and synthesis of general laws. Brahe, Kepler and Newton provide the paradigm. On the other hand, there are some biologists who would answer: "No, there are no rules! Anything is possible. There is only what exists to be discovered and history". This historical view is part of the Darwinian legacy and, according to some, it has become the dominant view in modern biology. In the mid-eighties, Gerry Webster and Brian C. Goodwin provided an extensive account of these contrasting philosophies in the context of developmental biology.

In the realm of molecular genetics, the latter view has often been expressed explicitly by leaders in the field. One prominent pioneer in the study of gene regulation has stated that the rich variety of mechanisms governing gene expression is the result of historical accident. Nature is a tinker who haphazardly draws upon what already exists; she is not an engineer seeking optimal performance. Another well-known molecular geneticist has said that this rich variety shows that "the only rule is that there are no rules". Yet another authority has said, in addressing the question of why there are positive and negative regulators, "God only knows".

In 1989 I reviewed a few simple rules governing the patterns of gene regulation that suggest how these two philosophies or views can be reconciled in specific cases. A recently acquired function may not agree with some proposed rule. Such discrepancies can reflect historical contingencies associated with the origins of a mechanism. While such discrepancies may be evident initially, they are not expected to survive long-term selective pressures that enforce the rule. Differences may also be seen in the detailed molecular mechanisms by which a given type of system is realized. Such differences might be the result of historical accidents that are functionally neutral, or they might be governed by additional rules that have yet to be determined. One can always assume that certain differences are the result of historical accident, but such an explanation has no predictive power and tends to stifle the search for alternative hypotheses. It generally tends to be more productive if one starts with the working hypothesis that there are rules. One may end up attributing differences to historical accident, but in my opinion it is a mistake to start there.

Modern systems and synthetic biology face two major challenges involving the issue of design. How can one elucidate the relationship between the information encoded in the genome and the context-dependent expression of that information as manifested in the phenotypic repertoire of an organism? The first is the fundamental unsolved problem of relating the digital representation of the genotype to the analog representation of the parameters for the molecular components. For example, knowing the DNA sequence for an enzyme does not allow one to determine its kinetic parameters. The second is the fundamental unsolved problem of relating the parameters of the components and the environment to the phenotype of the global system. For example, knowing the parameters does not tell one how many qualitatively distinct phenotypes are in the organism's repertoire, nor does it reveal their relative fitness. These also are challenges for clinicians trying to develop therapeutic strategies for treating pathology or biomedical engineers attempting to redirect normal cellular functions for biotechnological purposes. Although astonishing advances in addressing the first of these fundamental unsolved problems have been made, and many more are sure to come, there has been by comparison a conspicuous absence of advances related to the second.

If we are to relate genotype to phenotype, we must start with a clear idea of what it is we are attempting to relate. Although we now have a good idea of what is meant by the genotype, given the complete DNA sequence for the genome of numerous organisms including humans, it is less clear what is meant by the phenotype. At the level of the organism, we have a sampling of phenotypes such as hair color of cats, shape and size of flowers, height and weight of livestock, not to mention disease states in humans. The difficulty in relating these two levels of biological organization and function is hard to over-estimate. Moreover, between the levels of genotype and phenotype of the organism there are many intervening levels that form a rich hierarchy of cell and molecular sub-systems. Although there are some intuitive notions of what is meant by phenotype at the level of the organism, it is far from clear what the term phenotype means at the level of the intervening systems and what the phenotypic repertoire of any given system might be.

To address this challenge my colleagues and I have recently introduced the concept of a *system design space* in which qualitatively distinct *phenotypes* of a model can be identified and counted, their fitness analyzed and compared, and their tolerance to change measured. The application of this theory to a number of simple well-characterized systems, such as the lactose operon and bacteriophage lambda, has provided "proof-of-principle". Each of the design spaces constructed to date is unique, representing a "fingerprint" of the system.

The construction of a system design space is based on the power law formalism and makes use of all four of the perspectives mentioned earlier. In outline, the steps in the construction are the following. First, either one starts with a model of interest already in the *fundamental representation*, or one transforms the model of interest into the *recast representation*. The result in either case is a set of generalized mass action equations, each with a number of positive and negative terms. This is exactly equivalent to the original model and in general it is complex and intractable. Second, one selects a "dominant" positive and negative term from each equation to form a sub-model, which by comparison is tractable. The sub-model has a unique analytical steady-state solution in the logarithms of the independent variables and rate cons-

tants. The dominance constraints, which ensure that the selected terms are in fact dominant, constitute a set of linear inequalities in a logarithmic coordinate system. Third, inserting the analytical solution into the system of inequalities generates a set of boundary conditions, again involving the independent variables and rate constants, within which the solution is a valid *local representation*. The number of ways in which one can select dominant terms gives a bound on the total number of sub-models. The actual number is less because sub-models whose solution does not satisfy the dominance conditions are invalid. The result of this construction, which has been automated, is a partitioning of the design space into a *piecewise power law representation* of regions that exhibit qualitatively distinct behavior; thus, these regions provide an unambiguous definition of molecular phenotypes for the original system.

The parameters of the original system define landmarks in its design space that consist of the slopes and intercepts of the linear hyperplanes separating the phenotypic regions. The particular constellation of parameters that define these landmarks often reveal important system design principles that are not at all obvious and would otherwise be difficult to discover. For example, the system design space that has been constructed for lambda, a bacterial virus with a biphasic life style, reveals such system design principles. This virus can infect a cell and rapidly replicate, eventually killing its host, and releasing virus particles to infect other cells; this is its lytic phase of growth. Alternatively, upon entering the cell it can insert its DNA into the chromosome of the host cell and become quiescent, and simply reproduce along with its unharmed host cell; this is its lysogenic phase of growth. The system design space of lambda reveals the following design principle: There is a "band" within which a constellation of its parameters must fall in order to maintain the long-term survival of its biphasic life style. If the constellation of parameter values lies above this band, then the phage would be locked into the lytic life style (like that of a different type of virus, T4); on the other hand if it falls below this band, then the virus would be locked into the host's chromosome and could no longer become lytic. Similar design principles have been found for other systems as well.

Conclusion

Although my colleagues and I have contributed to other aspects of molecular systems biology, I consider the three that have been emphasize here to be among the most significant. This undoubtedly reflects my own interests, talents and limitations, as would any such account. It also reflects a set of scientific values and experiences that have formed my perspective. When I began my career there were few individuals with the interdisciplinary training that I received in systems engineering and cell biology at a premier university. Thus, I brought a nearly unique perspective to the field that has since become molecular systems biology. Today the investigation of design principles in molecular systems is becoming increasingly important for the understanding of complex biological systems. Although there are a number of successes that have legitimized this effort, this is a rich and relatively unexplored domain. The rise of a new generation of investigators addressing these issues with a focus on the interface between biology and the other quantitative sciences bodes well for the future of this endeavor.

Finally, it is a great honor to receive this doctorate and a very humbling experience to be in the company of the luminaries that have previously received this honor from the University of Lleida. It is also a particularly pleasant occasion because so many are present with whom I have had the privilege of collaborating over the years. I have already mentioned Albert Sorribas and Rui Alves because of the special connection to Lleida. I also have had the good fortune of working with my other talented colleagues Eberhard Voit, Masahiro Okamoto, Fumihide Shiraishi, Armindo Salvador, Oleg Igoshin, Michael Wall, Pedro Coelho, Dean Tolla, Rick Fasani, and Jason Lomnitz who are here, and many others from around the world who could not be here. I am indebted to all of them for their intellectual support and the sharing of ideas. In the interest of full disclosure, I should also acknowledge my wife Ann who is a professor of Design at UC Davis and who claims to have had a major influence on my interest in design. I thank the University of Lleida for this wonderful event, and the many colleagues and friends for coming to share their passion for furthering the development of molecular systems biology.

Discurs de cloenda

Dr. Joan Viñas Salas

We are celebrating this academic event in the ancient Romanesque church of Sant Martí. Built in the 13th century by King James II and Pope Boniface VIII, it was our University's first church. The rectors and presidents of our University have been appointed to office in this church since the early 18th century.

The University regained independence in 1991 following its dependence on the University of Barcelona since the 19th century. In recent years, we have built new buildings and we now have many modern facilities.

We have gained prestige and thanks to the work of our lecturers and researchers, the University of Lleida was ranked among the top Spanish universities in the life sciences in 2010.

We have extended our international relations year after year and have agreements with hundreds of other universities all around the world, as a result of which hundreds of foreign students come here to study.

It is an honor and a great pleasure for us to include you, Professor Savageau, in our senate of doctors. We heard an excellent citation from Professor Sorribas. He is one of our great lecturers and researchers. He has demonstrated his knowledge to us, which does not surprise me, as I am well aware of his great qualities. I would like to thank him for proposing Professor Savageau as doctor *Honoris Causa*. I will not repeat your merits, Professor Savageau; I would just like to highlight the quality, intellectual rigor, independence and creativity put to use in developing good scientific results that will speak for themselves, even if this takes some years. In Catalonia we have a saying: "A job well done has no obstacles or borders, bad work has no future" ("la feina ben feta no té destorb ni fronteres, la feina mal feta no té futur").

Your research subjects and topics are very important for human health and for improving our quality of life. Today, good research is interdisciplinary; it involves mathematics, physics, chemistry, bioinformatics, biology, medicine, surgery, bioethics, philosophy, etc. New technologies have had a great impact on all scientific research and have become absolutely necessary. In the near future, we will be able to practice medicine adapted to the specific needs of each patient; give him or her exact doses that can be better metabolized and help his or her rapid recovery. This is thanks, to a large extent, as Professor Sorribas said before, to mathematical modeling, particularly yours.

To advance medicine and basic research it is essential to know about cellular cycles, cellular stress, molecular functioning and genetic expression, for instance, which is all far removed from the operating theater, but thanks to all this research, we surgeons can operate on patients in better conditions and ensure better and faster postoperative recovery. We must continue to learn from the way that the science is organized in the US; I confirmed this on my internship at Minnesota University, one of the universities where you have worked, and on my visit to Davis University, which forms part of the University of California system.

Another important aspect that I wish to highlight is that in many research studies, and especially in Professor Savageau's research, there is a major component of the philosophy of science, in addition to ethical and bioethical considerations. Thomas Kuhn, in his book "The Structure of Scientific Revolutions" studied these aspects in the behavior of the scientific community. A scientist is able to look at nature and study a problem in a new light —take new approaches based on a well established knowledge of the scientific community. Professor Savageau proposed new theories, such as the demand theory, that allowed him to move forward, to open new doors to science, to formulate new paradigms that were rejected for a long time, but that were finally accepted by the scientific community. He has set us all a good example. Thank you, professor Savageau, for a life fully dedicated to producing good science.

I shall now continue in my own language, the language of my country, Catalan.

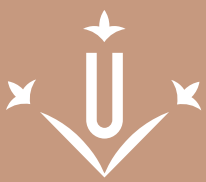
La ciència fa grans salts quan un investigador és capaç de mirar amb ulls nous; és el que permet descobrir coses noves a la natura de cada dia. En el nostre cas, una nova teoria, la de la demanda, ha permès al professor Savageau anar molt lluny, obrir noves portes a la ciència, creant nous paradigmes que no han estat acceptats immediatament, però davant dels quals la comunitat científica ha acabat rendint-se a les seves teories i recerca. Tot un exemple.

Com ha esmentat el professor Sorribes, gràcies al seu treball sobre models matemàtics, el professor Savageau avança ràpidament vers una medicina a la carta. Podrem saber la dosi més exacta per a cada malalt, el que li convé més menjar, els riscos que té per a la seva salut. Ja no servirà allò d'un comprimit cada vuit hores, sinó la dosi específica que metabolitzarà millor i el portarà a la curació al més ràpidament possible i amb menys efectes secundaris. També ajudarà a fer la millor cirurgia personalitzada. I tot això, gràcies als models matemàtics, que estan tan lluny de les sales d'hospitalització i les sales d'operacions.

Personalment, he fet una estada a la Universitat de Minneapolis, i he comprovat com és una gran universitat, i he après molta cirurgia i gestió. També he visitat la Universitat de Califòrnia a Davis —on treballa el professor Savageau. Estem aprenent molt dels Estats Units, i encara ens queda molt per aprendre'n. Veiem que en una ciutat petita inverteixen per convertir la seva universitat en referent mundial en una especialitat, però excel·lent en moltes altres disciplines. No se'ls acut concentrar en grans capitals tota la ciència i la indústria, ans el contrari, porten la ciència especialitzada on hi ha l'interès i les possibilitats de l'entorn. Ni la capital de Califòrnia, Sacramento, és la més habitada, sinó que és més aviat petita; ni porten ni concentren la ciència a San Francisco, la ciutat més gran de Califòrnia, ni el sistema públic universitari californià es menja les universitats que en formen part, que llueixen per si soles i prestigien el conjunt, com Berkeley o Davis, estiguin en una capital o en un poble.

Per tant, per acord per unanimitat del Consell de Govern de la UdL, a proposta del Departament de Ciències Mèdiques Bàsiques, m'ha plagut atorgar aquest títol de doctor *Honoris Causa* i incloure en el claustre de professors i professores el professor Savageau, i a més fer-ho a l'església de Sant Martí, recuperada per a actes acadèmics al segle XXI, com es feia des del segle XIV, en el que és el meu darrer acte com a rector de la UdL.

Moltes gràcies a tothom.



Universitat de Lleida