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PROF. YVES BRUN  
Systems Biology/Microbiology Faculty Search  
Department of Biology  
Indiana University  
Jordan Hall 142,  
1001 E 3rd St  
Bloomington IN 47405-7005

Dear Professor Brun,

Please find enclosed my application package for the announced tenure track position in computational systems biology at the Department of Biology.

I am currently a Director Funded Postdoctoral Fellow at Los Alamos National Laboratory. This is a fellowship awarded based on Laboratory-wide competition that allows for independent research and includes extra funding for research program development (such as hiring graduate and undergraduate summer students and organizing conferences).

My first exposure to research during my undergraduate studies was a study of synchronization of rhythmic clapping in theaters (*Nature* **403**, 850, 2000). As a graduate student in the group lead by Prof. Barabási I focused on topological aspects of the cellular metabolic network. I showed that metabolic networks are structured in a hierarchically modular fashion, and the nested modules are related to functional organization known in biology (*Science* **297**, 1551, 2002). I also found that hierarchical organization is generic to many real networks such as the World Wide Web, coauthorship networks or the language (synonym) network (*Phys. Rev. E* **67**, 026112, 2003).

The research I would pursue at Indiana University involves the application of network concepts in modeling energy landscapes of proteins, as well as the dynamics of information spreading on complex networks. Both projects are under development and would benefit greatly from undergraduate as well as graduate student participation.

For better than half of my undergraduate and Masters years I have lead and graded problem sessions in undergraduate courses. It was during this time that I have developed a great appreciation for the challenge of teaching, which I see as an integral part of my career. For graduate and advanced undergraduate courses I would prefer to teach courses related to the biology of complex systems, thus taking advantage of my research experience.

Please find enclosed a description of my research plans and interests, teaching philosophy, and curriculum vitae, as well as five of my most cited publications. I

have asked that five letters of recommendation be sent to you on my behalf. The writers are Zoltán Toroczkai (postdoctoral advisor), Albert-László Barabási (Ph.D. advisor), Zoltán Nédá (undergraduate research advisor), Eivind Almaas (research staff at Lawrence Livermore National Laboratory) and Zoltán Oltvai, a collaborator during my Ph.D. years. Their addresses appear in my curriculum vitae.

Please let me know if I can provide you with any additional information to support my application.

Sincerely,

A handwritten signature in black ink that reads "Erzsébet Ravasz". The script is cursive and fluid.

Erzsébet Ravasz, Ph.D.,  
Director Funded Fellow  
Los Alamos National Laboratory

# Research Interests and Experience

ERZSÉBET RAVASZ

My general research interests focus on the applications of modern network concepts to physical and biological systems. The simple idea of describing complex systems as networks lead to new ways of understanding a wide variety of physical, biological and sociological systems under a single framework. Moreover, this approach has opened the door for interdisciplinary research in fields where the behavior of the system as a whole is the central question. My current research rests on two central topics, which I plan to pursue in the future: (1) using network concepts to model energy landscapes underlying protein folding dynamics and (2) the dynamics of information spreading on networks. My main research experience is in statistical mechanics with applications in (3) complex networks including biological networks, (4) synchronization and (5) stochastic resonance.

**1. Energy landscapes in protein folding.** Virtually all biological processes in a living cell are performed by proteins. The functionality of these amino-acid chains is strongly tied to their three dimensional structure. Fast and reliable folding to a unique three dimensional shape is crucial for protein functionality. In 1969, C. Levinthal made the point that a protein of 150 amino-acids would need more than the age of the universe to find it's lowest energy state by randomly sampling it's conformation space. The consensus in protein folding today is that most functional proteins evolved to have free energy landscapes with a funnel structure. If one were to design proteins by randomly selecting the side-chains from the pool of amino acids one would get, in general, structures that do not fold, or do not fold reliably under physiological conditions. The main questions therefore are: what general conditions must the amino-acid sequence obey in order to produce a fast and reliably folding protein? Moreover, by what mechanism have these structures evolved? Sampling all possible amino-acid sequences in search of the ones capable of fast and reliable folding poses similar problems to Levinthal's original paradox, only stretched out to evolutionary time-scales. The central thrust of my research is to develop a framework for investigating both of these questions, along with a new set of tools — namely that of complex networks research — to study these spaces in their entirety.

I began working on this problem at the start of my postdoctoral fellowship at Los Alamos National Laboratory. I first developed a basic understanding of the topology of configuration networks as well as simple mechanisms that can lead to funneled energy landscapes. I am currently working on a bead-chain model system much less complex than real proteins, but which allows me to separately control the topological and steric aspects influencing foldability. I also have an ongoing collaboration with a molecular dynamics expert at Los Alamos National Laboratory, Gnana Gnanakaran, who provides data on real proteins to verify my modeling assumptions. While my model generates valuable data about the topology of energy landscapes, a visiting graduate student, Andrea Asztalos is working on the dynamical aspects of the problem, simulating the behavior of a system on different model configuration landscapes.

Understanding the mechanisms by which funnels form would be a fundamental contribution to our understanding of proteins. The network approach to configuration spaces could lead to

the design of fast methods for deciding, for a given artificial amino-acid sequence, whether it is a good folder. This would be a useful tool for biotechnology. Ultimately, the design of synthetic proteins in pharmaceutical research would be greatly enhanced by a deep understanding of folding dynamics.

I would also like to explore the possibility of applying the ideas developed for protein landscapes to different optimization problems. Many of these problems (such as K-SAT or error correcting codes) have been mapped onto a spin-glass system, much like protein folding. Understanding more about the difference between foldable and non-foldable protein landscapes could be of great help in studying the hard phase of problems like K-SAT. If successful, this would pinpoint the characteristics that sets apart the particularly hard (computationally demanding) realizations of the problem.

**2. Information processing in complex networks.** Developing tools to quantify the way communication networks (WWW, Internet, social systems, gene- or neuron networks) process information could be an important contribution to our understanding of complex systems, impacting many areas, from biology to communication and sociological networks.

I recently began investigating the information processing capabilities of gene regulatory networks. Using regulatory network topologies known from real-world datasets, I would like to link the characteristics of functions performed by regulatory genes to the overall behavior of the genetic network. There is a wide body of knowledge about the biological properties of the regulatory network in single celled organisms such as *E. coli* and in *S. cerevisiae* (yeast). However, these systems are still largely incomplete and not well understood due to the absence of data about the combinatorial rules that govern the individual genes. In pursuit of this, Boolean network models of small regulatory systems have been successful at reproducing biologically observed behavior but larger scale studies of Boolean networks have been mostly done on non-biological network architectures. According to the known genetic regulatory interaction network of *E. coli*, there are no directed closed loops in this system. The acyclic nature of the network suggests a model characterized by layers of Boolean functions. I expect the cellular network to be built such that it is sensitive to external signals (adaptability) but also filters useless information quite efficiently (a type of robustness). If we succeed in categorizing or even restricting the possible internal architectures the cell can have, we could perform a study of robustness against random function failure in the regulatory network, aiming to find the most vulnerable parts of the system. This understanding could also lead the way to more realistic constraint-based modeling of cellular metabolism (such as flux-balance analysis), incorporating the influence of the regulatory system.

**3. Topology of Complex Networks.** Natural and social systems possess characteristics that are fundamentally determined by their organization, displaying emergent phenomena created by the interaction of their constituents. A complex system as a whole is made up of an assemblage of generic elements and connections which can be described in the language of graphs or networks. For example, a cells metabolism is maintained by a biochemical network, whose nodes and links are substrates and chemical reactions. But equally complex webs describe human societies, the Internet, World Wide Web or scientific collaborations. The recognition of generic organizational principles and order behind the apparent randomness of these different systems lead to significant advances in many disciplines, including molecular biology, computer science, ecology and the social sciences. In the following I will describe two different

topics in complex networks research which I have been involved in.

*Hierarchy in complex networks.* Many real networks are fundamentally modular, where each module performs an identifiable task or function. A central question is whether the topological modules of the *network* representing this system reflect this functional modularity. Before this can be answered, one needs to find these topological modules. However, the scale-free topology of most networks (the existence of high-connectivity hubs signaled by a fat-tail connectivity distribution) makes finding a separable grouping of nodes difficult. The scale-free and modular character of networks can be reconciled in a most natural way by assuming a hierarchical organization of the modules (*Physica A* **299**, 559, 2001). A hierarchical scale-free network is made of small groups of nodes embedded into increasingly large groups, while the connections between these modules give rise to hubs at all scales, and thus a scale-free degree distribution. I have developed a method that identifies these hierarchically ordered clusters in the topology of networks. By applying my method to the metabolic network of *Escherichia coli* I found a direct correspondence between the obtained network modules and the functional modules of the metabolism (*Science* **297**, 1551, 2002). Moreover, I showed that the metabolic networks of 43 distinct organisms are organized in a hierarchical fashion. As part of a study of individual gene essentiality in *Escherichia coli* I examined the essentiality of metabolic modules (*J.Bact.* **185**, 5673, 2003). I found that essential enzymes tend to group according to the modules of the metabolic network. While many modules are almost entirely nonessential, at the lowest hierarchical level several small topological modules (like parts of the pyrimidine and coenzyme metabolism) appear to be catalyzed by predominantly essential enzymes.

Hierarchical organization is also present in several non-biological networks such as the World Wide Web, actor network, the Internet at the domain level and the semantic web (*Phys.Rev.E* **67**, 026112, 2003).

*Co-authorship networks.* The co-authorship network of scientists, made of researchers linked via co-authored papers, offers one of the most extensive databases to date on social networks. By mapping the electronic database containing all relevant journals in mathematics and neuroscience for an 8-year period, we uncovered the dynamic and structural mechanisms that governed the evolution and topology of this complex system (*Physica A* **311**, 590, 2002). Our measurements indicate that the network is scale-free in its degree distribution. Thanks to the time-resolution of our data, we were able to show that the network's evolution is governed by preferential attachment, affecting both internal and external links (an external link being a paper between an extant and novel author, while a new internal link is a paper between two previously unaffiliated authors). In contrast with most model predictions, the average degree increases in time and the node separation decreases. We proposed a simple model to capture the network's time evolution. In some limits the model can be solved analytically, predicting a two-regime scaling in agreement with the measurements. Both our analytical and numerical results underline the important role internal links play in determining the observed scaling behavior and network topology.

**4. Synchronization.** An audience expresses appreciation for a good performance by the strength and nature of its applause. The initial thunder of applause often turns, quite suddenly, into synchronized clapping. This synchronization can disappear and reappear several times during the applause. The phenomenon is an expression of social self-organization that provides an example on a human scale of the synchronization processes that occur in numer-

ous natural systems, ranging from flashing Asian fireflies to oscillating chemical reactions. I performed a series of measurements aimed at characterizing the development and dynamics of this synchronization (*Nature* **403**, 850, 2000). These measurements demonstrate that the mechanism lying at the heart of the synchronization process is period doubling in the rhythm of the clapping. The characteristic interplay between synchronized and unsynchronized regimes during applause is the result of frustration in the system. Thunderous applause is fast and thus loud, but the relatively wide spread of the frequency forbids synchronization. Skipping every other beat allows the audience to reduce the natural spread of frequencies and the clapping achieves synchrony when most of the audience switches to the slower mode. However, this rhythmic applause is quieter and naturally accelerates until synchronization is lost.

**5. Spatial Stochastic Resonance.** An Ising system placed in a magnetic field that is periodic in time is known to demonstrate stochastic resonance. We explored the behavior of an Ising chain in a *spatially* periodic magnetic field (*Phys.Rev.E* **60**, R3463, 1999). The system has an analytic solution, via the transfer-matrix method. When the external field is not strong enough to align the spins to its spatial profile, the temperature of the system becomes a critical factor. In this situation, there exists an optimal temperature at which the correlation between the spin orientation and magnetic field is maximal. This phenomenon can be interpreted as a resonance induced by the stochastic heat bath. Spatial stochastic resonance is realized in the equilibrium state and not as a dynamical response to a time-periodic driving.

Naturally, the research topics detailed above are not exclusive and cover only part of my interests in statistical mechanics and its application to biological systems. I enjoy thinking about social systems and ways to model and test their behavior, or problems in language evolution. On a different note, the possibility of connecting knowledge in optimization problems to the organization of biological systems offers another promising line of investigation. As my interests have always been wide, I am open to the exploration of research projects where my expertise could be put to good use.

# Teaching Philosophy and Experience

ERZSÉBET RAVASZ

Science education is unique in its potential to develop critical thinking and logical reasoning crucial to solving problems in every environment. Indeed, science majors are appreciated in quite a broad set of jobs; researchers with a science undergraduate education are usually able to cross fields of study later in their carrier. It also enhances one's ability to make connections between very different phenomena governed by the same underlying principle. These rather general skills prepare the students to be adaptable and deal with problems they encounter in ways that go well beyond the specific technical skills developed by their area of major. Mastering these skills, however, is also an important part of a thorough scientific education. Using the language of mathematics to describe and solve a problem analytically, as well as efficient use of a computer for simulations or numerical calculations is often indispensable for students going into research or teaching. These skills are not unique to research, but are required on a broad range of career paths.

Different levels of scientific education require the teacher to adapt his or her methods to the underlying goal of the particular course in question. While teaching the basic concepts and fundamental principles is always central to any class, the level of technical skills taught varies greatly. Humanities majors should develop a basic understanding of how the scientific method works and in what ways is it different from their field of focus. Science majors need to acquire a broad set of technical skills, achieved best through a well-designed homework load as an integral part of their final grade. Understanding after a course fades quickly unless the student applies theoretical knowledge across a broad range of concrete problems and irons out small details and misconceptions. At yet a higher level, teaching research skills means teaching the students to learn and explore on their own. I believe undergraduate research is an important first step in a scientist's development; where strong guidance is often required for the development of certain specific skills. At the same time, encouragement and room to freely explore an idea is also necessary. A research topic allows the student to learn how the process of research works, and how it is different from difficult course-work. Instead of a well-posed question with an answer that almost certainly exists and is possible to find with the student's body of knowledge, in research this safety-net is missing. Instead, one has the satisfaction of exploring a new idea and the surprise that comes along with any discovery. I believe it is important to make the student aware of this difference as early as possible.

Enthusiasm both about the topic in question but also the act of teaching itself is crucial in keeping students involved in the process. I have seen the most exciting topics presented such that everyone in the audience would rather watch grass grow than be there. Fascination with an idea or a phenomenon is largely contagious. Paired with a clear explanation that draws students in and keeps them curious about the outcome, these are priceless ingredients of an exceptional course. More than just helping with the learning process itself, the enthusiasm of the teacher is often the determining factor in sparking interest in research as a career choice in future scientists. The best teachers are never just good sources of information, they offer an attitude towards science and often towards life that students respect. This can have a

great impact on the motivation of students. Also, personal advice and attention to those who struggle in class is a responsibility of a good teacher. The use of mathematics in solving scientific problems often comes hard for many students, especially ones used to more memory-based learning. Encouragement and help with the shift to problem-solving based learning can make all the difference in a student's future development.

Clarity of explanation is indispensable for teaching science. Whether an explanation or demonstration has a natural flow that students can follow is quite sensitive to the actual group of individuals one has to work with. Instant feedback from students can significantly assist this process. I have often found that asking simple questions about the next logical step can keep students involved, as well as indicate their understanding of the material presented so far. Regardless of the level of a class, a teacher will always encounter students with very different ways and paces of learning. I believe one of the best ways to benefit them all is to always attempt to explain a concept or solve a problem in more than one way. Some students will follow a particular route of reasoning much better, but even students who can grasp all of the explanations will benefit from this approach, as it will teach them to cast the same problem in different lights.

Concrete everyday examples and small experiments or computer-aided demonstrations are often remembered much more vividly than a beautiful set of equations. It also gives students a more solid, almost intuitive feel for the phenomena in question. For more advanced science majors, a good feel for the phenomena in question is necessary in order to see into the math describing the problem and spotting unreal results from erroneous equations. Often, referring to applications of a principle or a phenomenon in everyday life can help students understand the importance of science in the modern world.

My teaching experience goes back to my undergraduate and Masters years at Babeş-Bolyai University. The physics major curriculum includes optional courses that are effectively a minor in Physics Education, which qualified us to teach physics at a high-school level. It involved us teaching 6 hours in various courses at a local high-school, while the teacher of the class as well as our undergraduate instructor analyzed and improved our methods. Right after my first Quantum Mechanics course at the middle of my junior year I was asked by the course instructor to be his TA for that course (leading problem sessions and grading homework), offered the coming semester for the mathematics-physics double majors. I continued to be the TA of this course for physics students throughout my senior and Masters years. Leading these sessions was a very engaging experience, since physics majors at Babeş-Bolyai were spread over a wide range of ability. I had to balance between explaining basic concepts and simple algebra to some, while the few exceptional students in the class were busy solving complex or conceptually challenging problems. I was also responsible for grading the students on their performance during these sessions, as well as their homework. Thus I needed to have a transparent grading system which made sure that the highest grade was a challenge even for the best students, while a medium grade was accessible for the average student of the class.