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Workshop Report

Spin Glass theory and High-Dimensional Landscapes in Biology

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Topic Introduction and Workshop Goals

The main goal of this workshop was to bring together mathematicians, physicists, and biologists to develop a shared language, identify connections between spin glass theory and biological systems, and foster new interdisciplinary collaborations. This objective is motivated by the growing complexity of modern biology, where high-dimensional systems of interacting components often give rise to rugged landscapes with numerous competing states. Spin glass theory, originally developed in statistical physics to study systems characterized by disorder and frustration, provides a natural theoretical framework for investigating such biological phenomena.

Tutorials

With these goals in mind, the workshop was initiated by three 75-minute tutorial talks covering the main themes of the workshop. More specifically, the main contents include:

- *Generative Models for Proteins (by R. Ranganathan)*: The talk focused on how generative models learned from evolutionary protein sequences can be used both to understand natural proteins and to design new functional ones. He emphasized how proteins combine precise three-dimensional structure and complex functions such as binding, catalysis, and information transmission with the flexibility to evolve under changing selective pressures. Statistical analysis of large families of homologous sequences reveals constraints ranging from direct structural contacts to collective patterns related to biological function. Generative models encode these constraints and generate new sequences for experimental testing, allowing researchers to explore regions of sequence space far from naturally occurring proteins. More broadly, such models can help uncover the principles linking protein structure, function, robustness, and evolvability.

- *Complexity of High-Dimensional Random Landscapes (by G. Ben Arous)*: The talk gave an introductory overview of the mathematics of high-dimensional random landscapes, using spin glasses as a paradigm for systems with disorder, frustration, and many competing states. He discussed how these landscapes can contain large numbers of critical points, local minima, and barriers, and how probability and random matrix theory can be used to study their structure and phase transitions. A central theme was the connection between landscape geometry and dynamics: rugged landscapes can lead to trapping, slow relaxation, and other glassy behavior. The talk also showed how ideas from spin glass theory provide a framework for studying complex high-dimensional systems beyond physics, including biological systems.

- *Structure and Navigability of Fitness Landscapes: From Models to Data (by J. Krug)*: He discussed the structure and navigability of high-dimensional fitness landscapes and how mathematical models can be related to empirical observations in evolutionary biology. Genotype spaces were represented as Hamming graphs, with evolutionary accessibility characterized through fitness-increasing mutational paths. He compared these ideas with empirical fitness landscapes and discussed two models closely related to spin glass theory: the House-of-Cards, or Random Energy, model and a genotype-based version of Fisher's geometric model, which can be formulated as an antiferromagnetic Hopfield model. The talk showed how probability and statistical physics can help characterize fitness landscapes and the constraints on evolutionary adaptation.

We believe that the ordering of the three tutorials worked particularly well and was appreciated by the audience, as the talks complemented one another in both perspective and accessibility. R. Ranganathan opened with a highly accessible presentation on protein evolution and generative models, making a special effort to connect recent developments in evolutionary biology with ideas and tools from random matrix theory and high-dimensional probability. G. Ben Arous then developed the mathematical perspective more systematically, introducing high-dimensional random landscapes through concepts from spin glass theory, random matrices, and the geometry of complex energy landscapes. J. Krug's tutorial complemented these viewpoints by discussing evolutionary fitness landscapes and highlighting important gaps between current theoretical models and the richer, more realistic biological landscapes presented by Ranganathan. Together, the three lectures provided a coherent progression from biological motivation to mathematical structure and open theoretical challenges.

Research Talks and Points of Discussion

Following the tutorials, the workshop featured sixteen 30-minute research talks organized into three broad groups. The talks were mostly well received and sparked many thoughtful discussions among participants.

- *Biology talks (by S. Cocco, K. Crona, S. Kuehn, L. Mazzucato, V. Ros, S. Solla, M. Tikhonov, and J. Thornton)*: Several fields were covered, ranging from proteins to ecology and to neuroscience. On the ecology side, M. Tikhonov and V. Ros addressed the existence of multiple stationary points of ecological dynamics, which may largely differ in structural properties (very different compositions in terms of species, of stability to perturbations), and yet show similarity in terms of metabolic function and pathways. Concerning the protein evolution, J. Thornton presented fascinating results on the reconstruction of ancestral proteins from the knowledge of current protein sequences, and on the history of mutations along the evolutionary paths joining those proteins. For the neuroscience, we had two talks by S. Solla and L. Mazzucato and a discussion session on neuroscience and glassy systems hosted by the latter. Neuroscience is especially interesting as it offers the vision of high-dimensional landscapes controlling the activity of large neural populations, which evolves under plasticity (learning) mechanisms. The talks explained how the fast dynamics of neural activity slowly reshapes the landscape and future dynamical trajectories. Additionally, three complemented topics were delivered. S. Cocco reported on mutational paths in sequence landscapes inferred from biological data, showing how statistical models can be used to characterize the accessibility and organization of evolutionary trajectories. K. Crona studied high-dimensional fitness landscapes, focusing on evolutionary accessibility, reversibility, and recombination. Finally, S. Kuehn examined how interactions in microbial communities can reflect higher-order

effects and shared ecological constraints rather than simple pairwise relationships. Overall these talks unveil fundamental processes of evolution, not only at the sequence level, but also at the functional one, in particular on the appearance of specificity as a speciation process at the molecular level.

- *Math talks (by A. El Alaoui, D. Gamarnik, V. Gayrard, and S. P. Li):* Several mathematically oriented talks developed rigorous approaches to problems arising from disordered systems and high-dimensional landscapes. S. P. Li addressed the algorithmic geometry of the binary perceptron, showing that stable algorithms cannot reliably find strongly isolated solutions, thereby connecting landscape structure with computational hardness. In a related direction, V. Gayrard studied spurious local minima in classical, dense, and modern Hopfield networks, constructing "mixed memories" and identifying regimes in which they become exact minima of the energy landscape. A. El Alaoui studied a random matrix discrepancy problem, introducing an iterative algorithm whose asymptotic behavior is described through free probability and a correlated Gaussian–semicircular process. D. Gamarnik presented a rigorous computation of the high- temperature partition function of the quantum Sachdev–Ye–Kitaev model using sparse random graph and large-deviation methods, providing a mathematical validation of predictions previously obtained through non-rigorous physics techniques. Together, these talks illustrated how probability, random matrices, free probability, and rigorous methods for disordered systems can clarify both the geometry and computational properties of complex high-dimensional models.

- *Physics talks (by P. Charbonneau, P. Urbani, V. Vitelli, and P. Mehta)*: The physics talks approached high-dimensional complexity from several distinct directions. P. Charbonneau examined how active motion changes caging and critical behavior in the random Lorentz gas, while P. Urbani used dynamical mean-field theory to study learning dynamics in neural networks and the emergence of different training timescales. V. Vitelli focused on asynchronous computation in interacting systems, showing how nonequilibrium mechanisms can support reliable collective behavior without centralized timing. P. Mehta turned to biological networks, asking how low- dimensional functional dynamics can be embedded within much larger systems in a way that remains robust to perturbations. Despite their different settings, the talks shared a common concern with how collective structure and function emerge from many interacting degrees of freedom.

In addition, several discussion sessions were organized during the workshop to cover complementary issues, in particular on Boltzmann machines, high-dimensional modeling of ecological systems, glassy dynamics in neural activity data. These sessions were rather informal and allow participants to ask questions, exchange opinions, emphasize open questions. The highlight of the workshop was Daniel Fisher's colloquium on the last day of the program, "Beyond landscapes: ecological and evolutionary chaos". He emphasized that evolution in complex biological systems cannot always be understood through a static fitness landscape, since ecological interactions can continually reshape the environment and produce chaotic dynamics.

Participant Feedback

We close this report by noting that the stimulating environment at NITMB played an important role in the success of the workshop. Participants were highly engaged throughout the program, and many discussions continued informally beyond the scheduled sessions, including after the final program on the last day. This was particularly valuable given the diverse backgrounds of the

participants. These exchanges created opportunities for new connections across mathematics, physics, and biology and may lead to longer-term interdisciplinary collaborations. The participant survey provides further evidence that these interdisciplinary goals were achieved. Ninety-five percent of respondents reported that the workshop helped them better understand unfamiliar scientific language, 93% felt better equipped to apply mathematical tools or concepts to biological questions, and 93% reported increased confidence in interdisciplinary communication. Participants also reported an average of 2.3 new connections per person, while 95% agreed that the workshop provided opportunities for meaningful network-building that would continue beyond the event. More broadly, all survey respondents agreed that the workshop was worth their time, would consider attending a future NITMB workshop, and would recommend future NITMB events to colleagues. The organizers are very grateful to NITMB for providing this valuable opportunity and for creating such a welcoming setting for scientific exchange.