Summary of Past Research Activity

During the earlier stage of my career, my research focused on theoretical subnuclear physics. I earned my Ph.D. in Physics from SUNY at Stony Brook in three years, I worked as postdoctoral associate at the European Centre for Theoretical Nuclear Physics and Related Areas, and I obtained a tenure position at the University of Trento at the age of 30. Over this period, I established collaborations with leading scientists in the field and I was visiting scientist at the Massachussets Institute for Technology.

In 2005, I felt the urge to devote my scientific career to an emerging, fast-growing, and experimentally driven area of Science. Therefore, I decided to start a new research line based on cross-disciplinary applications of theoretical physics to problems at the interface between physics, chemistry, and biology. This initiative eventually led to establishing the Statistical and Biological Physics Group in my Physics Department, which now includes three tenured professors and a tenure-track assistant professor[1].

A significant part of this research activity has concerned the development of enhanced path sampling schemes to simulate rare structural changes of biological molecules. These methods were derived by combining the stochastic functional integral formalism, variational approximations, and biased dynamics [40, 39, 21, 17]. They have been applied to simulate large protein conformational changes, protein folding, and misfolding and extensively validated against biophysical experiments. For example, integrating our path sampling schemes with *ab-initio* quantum mechanical calculations, we were able to validate our predictions for protein folding pathways against time-resolved *near* UV circular dichroism experiments [16]. Similarly, a direct collaboration with a world-leading laboratory in experimental biophysics enabled us to validate of our protein folding simulations against state-of-the-art time-resolved single-molecule FRET experiments [5]. Other related theoretical work in my group concerned the development and application of Renormalization Group techniques to molecular dynamics [35, 32] and molecular data analysis [20] and the calculation to quantum corrections to diffusive processes, obtaining in particular an analytic expression for the $\mathcal{O}\left(\hbar^2\right)$ semi-classical correction to the multi-dimensional Fokker-Planck equation [29].

A related on-going research direction has concerned the development of Molecular Quantum Field Theory (MQFT), a mixed quantum-classical scheme to investigate real-time dynamics of quantum electronic excitations propagating in macromolecules in solution [47, 46, 45, 44]. This approach enables opto-electronic properties to be efficiently computed, using diagrammatic techniques originally introduced in high-energy physics. The same mathematical formalism has also been applied to investigate dynamics in different ultra-hot and ultra-cold matter systems. In particular, we applied it to a gauge theory to study dissociation and recombination of heavy quarks in a quark-gluon plasma [50]. More recently, we have used it to study the stochastic dynamics of heavy impurities diffusing in a ultra-cold fermionic bath.

[1] https://sbp.physics.unitn.it

Figure 1: The official patch of the ZePrion experiment.

Technology Transfer

Some of the algorithms and approximations developed in my group make it feasible to obtain a full *in silico* physics-based characterization of the folding of many biologically relevant proteins (up to about 600 aminoacids), using state-of-the-art all-atom force fields, with explicit solvent treatment. These simulations predicted that most proteins longer than about 100 aminoacids fold by visiting at least one rather conserved on-pathway meta-stable state. This finding inspired Prof. Biasini (CIBIO) and myself to conceive and patent a completely new protocol for rational drug discovery, named **Pharmacological Protein Inactivation by Folding Intermediates Targeting** (PPI-FIT). The rationale underlying this new approach is that targeting a theoretically predicted metastable folding intermediate with small ligands could promote protein degradation by the cellular quality control machinery.

By now, the PPI-FIT technology has been validated through several cell biochemistry experiments. In particular, it was successfully applied to hamper the expression levels of the cellular prion protein [6] (that is considered undruggable using standard drug discovery protocols), leading to a second patent. Unfortunately, providing a direct biophysical evidence based on crystallographic structure of the protein-binding complex is extremely technically challenging, due to the high aggregation propensity of partially folded protein species. However, several studies have shown that microgravity conditions are ideal for carrying out particularly delicate crystallization processes, due to the absence of convective motions. This led to designing the **ZePrion Experiment** that has been approved in 2020 by the Ramon Fundation, cofounded by the Israeli Creuz-Jacob Fundation [2]. The experiment is planned to be performed in 2022 in the **International Space Station**, within the framework of an international collaboration involving academic institutions in Italy, Spain, and Israel, along with the Israeli company Space Pharma. The launch is currently scheduled in Spring 2022. I am serving as scientific spokesperson of this international collaboration.

The development of the PPI-FIT technology led to founding **Sibylla Biotech**, which in 2019

[2] https://ramonfoundation.org.il/?p=26054

Figure 2: www.sibyllabiotech.it

received a first seed investment 2.4 million EUR from venture capital VERTIS SGR. Sibylla Biotech is the exclusive licensee of PPI-FIT and operates by developing internal drug discovery pipelines as well as through services and partnerships with Pharma companies. In 2021, Sibylla Biotech was selected among the 8 world finalists of the **Nature Spin-off Prize 2021**[3] and it is now finalizing a *Class A investment*, which will be announced in the Fall 2021.

[3] "Turning transient structures into drug targets", an article about the PPI-FIT technology and Sibylla Biotech, published online by Nature Outlook: https://www.nature.com/articles/d41586-021-01668-7—

New Research Directions

In the next years, my research activity will be organized around two main avenues. On the one hand, I will work on the development of a new generation of advanced algorithms for molecular simulation, which **integrate theoretical physics methods with automated learning and quantum computation**. A second, more applicative research direction will exploit our existing computational technology to address fundamental problems at the interface between physics and molecular biology.

Molecular Simulations by Quantum Computing: The rapid acceleration of quantum computing makes it highly timely to explore new ways for directing this field towards problems of biochemical and biological interest. Indeed, to date, most of the exploratory applications of quantum computing in physics have addressed problems that are themselves quantum-related. In contrast, very few applications exist yet for soft and biological matter, despite the fact that these subjects are pervaded by computationally hard problems. Much of my current activity focuses on exploring applications to molecular simulations of different quantum computing paradigms that are applicable on Noisy Intermediate Scale Quantum (NISQ) devices, such as quantum annealing, variational quantum algorithms, and quantum simulators. A few examples of projects that are currently being pursued is in order.

1. *Enhanced path sampling by integrating AI with quantum computing.* The prize to pay for the computational advantage of many of the most efficient enhanced sampling methods is having to provide in input some prior information, such as e.g. the three-dimensional structure of the target state or the set of the system's slow collective variables. We are currently developing on a potentially ground-breaking scheme which overcomes this limitation by combining artificial intelligence (uncharted manifold exploration) and quantum computing, both within the framework of quantum annealing and gate-base quantum computers. The first results were published in Phys. Rev. Lett. [2] and focused on the calculations of the most probable transition pathways. We are currently working on extending this technology to perform transition path sampling, equilibrium sampling and to compute the system's reaction coordinate (committor function) using hybrid schemes, such as variational quantum algorithms.
2. *Polymer Physics by Quantum Computing:* Sampling equilibrium ensembles of dense polymer mixtures is a paradigmatically hard problem in computational physics, even in lattice-based models. We have recently proposed a formalism that allows for tackling this problem using quantum annealing machines. Our first results were published in Phys. Rev. Lett. [1] and showed that this scheme remains efficient even for very dense melts, where traditional approaches become exponentially inefficient. Future applications concerns the extension to different ensembles, such as e.g. semi-flexible polymers.

An additional project at an earlier stage of development concerns the development of a quantum simulator based on a 2-dimensional quantum super-solid, to investigate the dynamics of optoelectronic quantum excitations in macromolecules.

Applications of Enhanced Sampling to Molecular Biology: Along with the development of the next generation of advanced simulation methods, part of my activity will concern the application

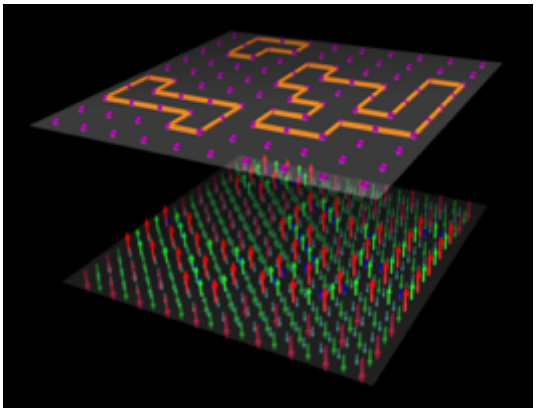

Figure 3: Illustration of the encoding on a quantum annealing machine of the problem of sampling equilibrium configurations of lattice polymers, as in Ref. [1]

of the existing algorithms in cross-disciplinary research, carried out in collaboration with molecular biologists and biochemists. The goal is to capitalize on the insight offered by physics-based modeling to address fundamental questions, which could not be tackled with conventional biochemical techniques. In particular, two high-priority projects I intend to carry out are in order.

1. *Characterization of the physicochemical mechanisms driving genetic misfolding pathologies.* In this project, we shall focus on serpin and prion misfolding, two paradigmatic pathogenic processes that are linked to a number of severe genetic diseases. Using our enhanced sampling simulation methods we can, for the first time, obtain a full reconstruction of these processes and compare wild-type and mutated (mis-)folding pathways. Our first results along this path have been published e.g. in Ref.s [9, 12]. Future studies (to be carried out in collaborations with the molecular biology laboratories led by E. Biasini (Trento) and J. Raquena (Santiago de Compostela) will focus on unveiling the physical mechanism through which genetic point mutations can promote or hamper prion protein misfolding, with the goal of envision therapeutic strategies to prevent prion related diseases.

2. *The physiological role of protein folding intermediates.* The PPI-FIT approach has shown that transient conformational states visited during protein folding can be exploited for pharmacological purposes. A natural related question is whether such folding intermediates have also a functional physiological role. Within a collaboration involving different Italian academic institutions, we are investigating their role in the post-translational regulation of protein expression levels [4]. This study integrates omics analyses, biophysical and biochemical experiments, and all-atom protein folding simulations.

Additional ongoing projects include the first all-atom simulation of RNA folding and the application of enhanced sampling algorithms to investigate target search by active particles.

[4] I am serving as national coordinator of a National Interest Research Project (PRIN) proposal on this topic, currently under evaluation.

International Collaboration Network

- *Statistical mechanics, machine learning, quantum computing and quantum technologies*: U. Paris Descartes, U. Zurich, Frankfürt Institute for Advanced Studies, ETH, IBM-Zurich, CEA-Saclay, U. Innsbruck.
- *Experimental biophysics and biochemistry*: U. Maryland at Baltimore, U. Massachussetts at Amherst, U. Santiago de Compostela, U. Zurich.
- *Protein crystallization in microgravity conditions:* U. Santiago de Compostela, U. Tel Aviv, Space Pharma.

Patents

1. "A method for identifying intermediates", E. Biasini and PF. Identification code: 10201800007535, July 2018 (IP share: 50%)
2. "Inhibitors of prion proteins", L. Berreca, E. Biasini, and PF. Identification code: 102020000006517, May 2020 (IP share: 30%)

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1. C. Micheletti, P. Hauke, and PF, Phys. Rev. Lett. 127, 080501 (2021).
2. P. Hauke, G. Mattiotti, and PF, Phys. Rev. Lett. 126, 028104 (2021).
3. L. Zanovello, M. Caraglio, T. Franosh, and PF, Phys. Rev. Lett. 126, 018001 (2021).
4. F. Dingfelder, I. Macocco, S. Benke, D. Nettels, PF, and B. Schuler, JACS Au 1, 1217 (2021).
5. G. Spagnolli et al. Comms. Biol. (Nature PG) 462 (2021) -co-corr. author-.
6. M. Bondanza, L. Cupellini, PF, and B. Mennucci. JACS 142, 21829 (2020).

Complete List of Publications

Statistical and Biological Physics

[1] "Polymer Physics by Quantum Computing", C. Micheletti, P. Hauke, and PF, Phys. Rev. Lett. 127, 080501 (2021).

[2] "Dominant Reaction Pathways by Quantum Computing", P. Hauke, G. Mattiotti, and PF, Phys. Rev. Lett.126, 028104 (2021).

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[8] "The Molecular Mechanisms of Photo-activation of Orange Carotenoid Protein Revealed by Molecular Dynamics", M. Bondanza, L. Cupellini, PF, and B. Mennucci. JACS 142, 21829 (2020).

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