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Special Issue Preface

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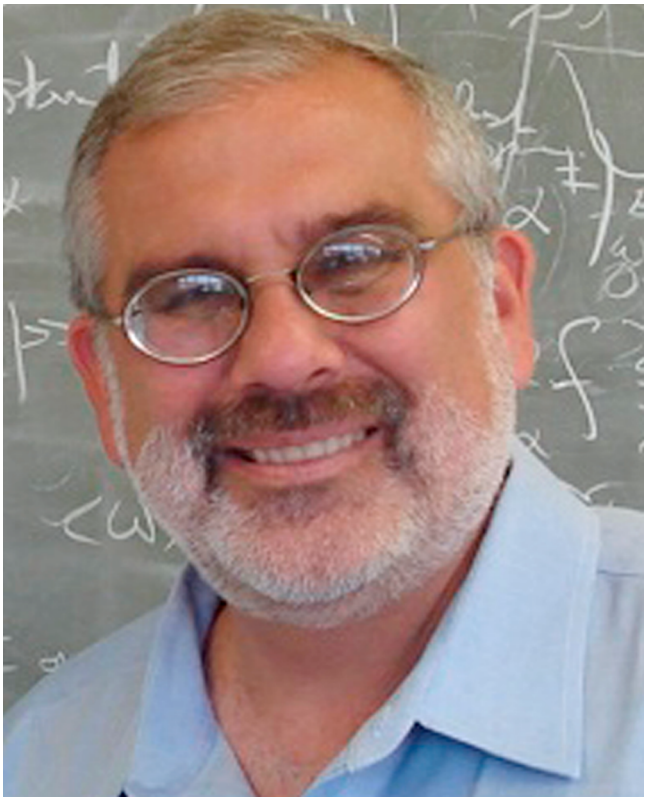
Tribute to Peter G. Wolynes



Photograph courtesy of Brandi Powell-Espiritu

It is our great privilege to co-edit this special issue of *The Journal of Physical Chemistry B* in honor of our friend and colleague, Professor Peter Wolynes, on the occasion of his 60th birthday. Peter's work, with its numerous brilliant and piercing insights, has changed the thinking and direction of modern experimental, theoretical, and computational research in many different fields, including protein folding and dynamics, the glass transition, energy flow within molecules, gene regulation, binding of proteins, cell motility, and reaction dynamics. His work covers an unprecedented range of topics, yet there is one unifying feature of Peter's efforts. He develops *new* conceptual—and subsequently quantitative—frameworks to attack complex problems that had been approached largely by trial and error.

It is fun and instructive to recount those breakthroughs. Peter was the first to understand quantum-mechanically how the environment-induced frictional forces affect chemistry in the condensed phase. It was work by Peter that made it clear yet in the early 1980s that the key to the structural glass transition is the emergence of metastable aperiodic crystals. This approach, in which the thermodynamics and kinetics go hand in hand, has flourished over the years and produced a constructive, quantitative theory of the structural glass transition. In the equally controversial protein folding area, it was Peter who first developed a conceptual framework which was not system-specific but instead was grounded in the theory of phase transitions: To fold into that special native state, a protein molecule must be able to bypass a continuum of glassy states. Upon the recognition of the limited utility of early force-field-based approaches to protein structure prediction, the associative memory Hamiltonian method was born, which can handle cases where little or no homology information is available. These and other conceptual breakthroughs generated in the Wolynes lab have led to quantitative answers to many dozens of specific problems in chemical and biological physics and materials science.

Let us now delve into only three distinct areas of Peter's research in more detail: protein folding and dynamics, glasses, and quantum phenomena.

PROTEIN FOLDING AND DYNAMICS

Prior to Peter's theoretical work, mechanistic descriptions of protein folding were primarily heuristic and pictorial, and mainly concerned with whether or not intermediates could be detected, an approach not unlike that of classical organic chemistry. There was no theoretical framework for providing a coherent and quantitative description of the wide variation in experimental observations. This situation changed dramatically with Peter's introduction of his statistical energy landscape theory, the first analytical theory of protein folding. In this theory, protein folding kinetics and dynamics turned out to be described as diffusion on a low-dimensional free-energy surface, while mis-folding was understood as a frictional effect using spin glass ideas.[69,85,90] (Reference numbers in this piece refer to Wolynes' full bibliography accompanying his autobiographical essay.) The coordinates of the surface are order parameters, such as the fraction of native contacts or the number of residues ordered in their native conformation. The depths and shapes of the free energy minima and the heights of the free energy barriers are determined by a trade-off between the destabilizing loss of conformational entropy and the stabilizing enthalpic interactions. The latter are dominated by native interactions, resulting in a protein folding "funnel".[141,143,190,204] This idea, developed with José Onuchic, Peter's close collaborator for many years, that proteins have been selected by evolution to have "minimally frustrated" interactions and thus to have funnel-like energy landscapes, has been the key to most recent theoretical work on the folding problem. The minimum frustration principle has been used by many successful workers in *ab initio* structure prediction, and indeed, Peter's own implementations of the idea have achieved significant successes in structure prediction.[106,115,161,223,362] Further predictions include the explanation of fractional Φ-values,[166] the description of both equilibria and kinetics with a few order parameters as reaction coordinates, and the appearance of different "folding scenarios".[135] All of these predictions have not only been confirmed by both experiments and simulations but have changed the way experiments are being interpreted and have motivated totally new kinds of experiments.

Peter's proposal that the kinetics of folding could be described by diffusion on a low-dimensional free energy surface with an

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order parameter as a reaction coordinate has been dramatically confirmed in Monte Carlo simulations of lattice models[155] and by both molecular dynamics simulations of simplified off-lattice representations and atomically detailed models of others. This was done by showing that the rate of folding could be obtained with great accuracy by using the free energy barrier height ($\Delta G^{\dagger}$) for the surface obtained from the simulation (i.e., the relative population of each structure with the same value of the order parameter, such as the fraction of native contacts), together with the diffusion coefficient (D) using the simple Kramers relation: $k \sim D \exp(-\Delta G^{\dagger}/RT)$. Additional confirmation came with the demonstration that the conformations at the free energy barrier top in these simulations are indeed transition state structures, as judged by their folding probability near 1/2 (i.e., an equal probability of proceeding to the denatured and native states—the rigorous definition of a transition state structure). Peter's free energy landscape approach to protein folding kinetics, together with the explicit consideration of native-only interactions (the funnel concept), has had an enormous impact on all theoretical and computational work and is a key ingredient in his subsequent theoretical studies[137,171,179,184,225,226] and just about every statistical mechanics folding model developed by the community.

Peter's description of protein folding scenarios immediately produced a beautiful grand synthesis and coherent picture of the origin of variability and numerous previously unexplained phenomena in protein folding kinetics—multiple pathways, rates limited by the escape from misfolded traps, low free energy barriers, non-exponential kinetics, internal friction, and so on.[135,160,255,285] One of the most interesting predictions, again resulting from small free energy differences among conformations, is that for the fastest-folding proteins folding can be "downhill", with no barrier separating the folded and unfolded states. Downhill folding on the microsecond time scale has now been observed in several laboratories using nanosecond laser T-jump, P-jump, or continuous flow to measure these ultrafast rates.[316]

Peter's principle of minimal frustration, made quantitative with spin-glass theory, posits that both the native protein structure and the evolution of the native structure from the unfolded state occur with the involvement of only a minimum of unfavorable residue−residue interactions, and has had wide-reaching applications in protein studies. A particularly interesting application of this principle is the identification of functionally active parts of proteins, such as binding sites, as regions in which frustration occurs, i.e., in which unfavorable as well as favorable interactions occur.[314,315,354,366] It has also provided a very important ingredient to Peter's success in predicting protein three-dimensional structures from amino acid sequences, an approach that is being increasingly adopted by the full-time structure predictors. He has also extended his protein folding work to multisubunit proteins and to address other important issues in protein physical chemistry, such as protein recognition and binding[252] and the mechanism of conformational changes responsible for allostery. He has shown, for example, how binding of an unfolded protein to a target followed by folding can accelerate the binding rate ("fly casting" mechanism[218]), and has applied similar novel ideas to explain the role of folding in protein−protein binding mechanisms.[276] He has also introduced a totally new concept in understanding allosteric conformational changes by showing how partial unfolding, which he calls "cracking", can be a key part of the mechanism.[249]

Overall, Peter's work has also had a tremendous influence on protein science by attracting a whole generation of both experimental and theoretical physicists and physical chemists to the field.

GLASSES

Starting in the 1980s, Wolynes and his collaborators developed a unified theory of structural glasses and supercooled liquids. This theory has passed, so far, all experimental tests. Today, it qualifies as "The Theory of Glasses" from a thermodynamic−structural point of view. Peter's theory describes a glassy liquid as a mosaic of aperiodic crystal structures which locally are minimum free energy configurations connected by less stable regions near saddle points on the free energy landscape.[87,215] The theory shows that the glass transition is a dynamical manifestation of a "random first order transition" (RFOT) that, at mean-field level, exhibits one-step replica symmetry breaking.[72] This symmetry breaking amounts to an exponential proliferation of free energy minima which decrease in number upon cooling. The theory naturally explains the previously mysterious Kauzmann entropy crisis in which the configurational entropy appears to vanish just at the same low temperature where viscosity diverges. The RFOT theory gives a simple formula[215] that makes no use of adjustable parameters but that quantitatively links the thermodynamics of supercooled liquids (accessible to static experiments) to the free energy barriers slowing their relaxation in dynamics.

The RFOT theory of Wolynes and co-workers is a beautiful synthesis of Peter's early results on the density-driven emergence of aperiodic crystals—based on the density functional[49] and self-consistent phonon theory[45,67]—and the kinetic catastrophe predicted by the mode-coupling theory. Wolynes and Kirkpatrick[62] showed the two descriptions merge in the mean-field limit. These authors[72] discovered a mean-field glass that exhibits entropy-driven kinetic arrest at a finite value of the temperature, much as appears true for real liquids! The mosaic picture, in which the activated dynamics in glassy fluids are driven by the multiplicity of the aperiodic structures, was developed subsequently,[87] still in the 1980s, and showed how the kinetic slowing down in supercooled liquids results from the scarcity of configurations at low temperatures.

It was the early 2000s that brought a quantitative clarity to these ideas in the form of many testable predictions, after Xia and Wolynes[215] quantitatively showed how to estimate the free energy cost for individual activated events. The key microscopic prediction of the theory is the size of the cooperative rearrangements, which has been confirmed by nonlinear spectroscopy, and recently seen in direct observations using scanning tunneling microscopy. The RFOT theory has directly shown that the following dynamical signatures of glassy dynamics are determined by the rate of growth of the configurational entropy with temperature: the non-Arrhenius character of the relaxation rates,[215] the non-exponentiality of relaxation rate,[227] the violations of the Stokes−Einstein relation in supercooled liquids,[230] and the apparent activation energy for moderate aging.[257] With regard to aging, several qualitatively new phenomena have been predicted by Peter such as the propagation of fronts in the "melting" of glasses[334] which has been observed in the laboratory by Ediger. Recently, Peter showed how new mechanisms of the crystal nucleation and growth take over from the classical Zeldovich−Frankel theory in supercooled liquids at and below the conventional laboratory glass transition temperature.[351] High surface mobility and ultrastable glass surfaces also naturally follow from the microscopic picture advanced by the RFOT theory.[327]

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Much progress has been achieved in Wolynes' lab in the difficult regime of the onset of the activated transport, where the mode-coupling effects are significant. A picture of compact activated droplets accompanied by string-like excitations has emerged from the analysis, which predicts the temperature of the onset,[284] reveals a universal contributor to the β relaxations,[340] and, very recently, quantitatively predicts the strength of glasses.[365]

By quantizing the RFOT theory, Peter has shown that universal low temperature properties of glasses ascribed to the so-called "two-level systems" are quantitatively accounted for by multiparticle tunneling motions that are quantized remnants of the classical activated events that occur near the glass transition.[232] This establishes a new kind of elementary excitation in quantum many body systems. The "two-level systems" turn out to be actually high-lying resonances, not traditional harmonic excitations or strongly interacting quasi-particles. The RFOT theory identifies the Boson peak excitations as vibrational excitations of the strained regions corresponding to the saddle-point configurations forming the mosaic;[239] these vibrational excitations exclusively accompany those multiparticle tunneling motions, which are strongly anharmonic.

QUANTUM PHENOMENA AND REACTION DYNAMICS

Long before he turned his attention to biomolecules and glasses, Peter was active in the field of molecular quantum phenomena, an area that still attracts his attention. As Peter discusses in his autobiography, quantum mechanics, the Copenhagen interpretation, and all that, puzzled and interested him from an early age. As a theorist, he became very practical about it—perhaps some of his father's influence did rub off, after all.

Starting in the late 1970s, Peter was one of the leaders who developed the current picture of how a condensed phase environment affects chemical reaction dynamics.[31] Chemical reactions are often rate-limited by barriers between products and reactants that have to be climbed by thermal excitation before reaction occurs. Peter showed how friction from a molecule's environment modifies tunneling, whereby a chemical reaction can occur without having to be excited above the barrier. He also resurrected classical barrier crossing theories, such as the ones based on Kramer's model, and illuminated the theory of non-adiabatic curve crossing and coherent resonance phenomena long before they became the popular objects of study that they are today.[46,56,79] These are important foundational models for reactions of biomolecules, in liquids, as well as for electron and proton transfer. His introduction with Chandler of the tools of path integral quantum mechanics exploiting their isomorphism with polymer physics undergirds most of today's simulation-based approaches to the quantum aspects of reactions in liquids and biomolecules.[28] This work also formed the basis for many computational forays into quantum phenomena of chemical systems, such as the solvated electron.

Peter's work on fluctuations in reaction dynamics (so-called "intermittency") motivated much experimental and theoretical work in single molecule spectroscopy.[139] Most recently, he has shown how molecular level fluctuations are not just laboratory curiosities but play a role in gene regulation, allowing the single molecule behavior of protein−DNA binding to lead to stochastic outcomes for individual cellular decisions.[325] Thus, the condensed phase reaction dynamics studies deeply touch modern single cell experiments and systems biology.

At the smallest end of the size spectrum of chemical physics, Peter brought new insights to the old problem of how vibrational energy flows in organic molecules. By the late 1980s, it was becoming clear that a simple Golden Rule description for energy flow was not sufficient: the average coupling matrix elements derived from such a model had no connection with the real cubic and higher order couplings vibrational spectroscopists were using to discuss their spectra. By introducing the "local random matrix" model for intramolecular vibrations in 1990, Peter was one of the pioneers who could explain how vibrating molecules make the transition to "quantum chaos" when enough vibrational energy is deposited in them.[92] Subsequent studies showed that energy flows very slowly once it is diluted into ever smaller packets among different vibrational degrees of freedom. The model has been confirmed in the laboratory, as has Peter's microscopic explanation of why energy-flow-limited non-RRKM behavior occurs in low barrier gas phase reactions.[251] As an offshoot, Peter recently studied how such "weak quantum chaos" in molecules affects their controllability: Stanislaw Ulam conjectured in 1956 that classical chaos can be used to speed up a body's motion from origin to target enormously with very little energy expenditure. Peter showed that this feature is retained in quantum mechanical systems such as highly excited molecules.[310]

We could go on with further discoveries, but this cross section of Peter's work should suffice to illustrate his versatility as a theorist, and how deeply relevant Peter's work is not only for theorists but also for experimentalists in many fields, including two of the authors of this piece! Peter is a great mentor who teaches how to identify and attack important problems. He is an outstanding colleague whose insight and erudition have been a guiding light to many of us. Above all, he is an extraordinary scientist and tireless learner who will not hesitate to tackle the most difficult problem, even if it requires learning the Latin. Happy Birthday, Peter!

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