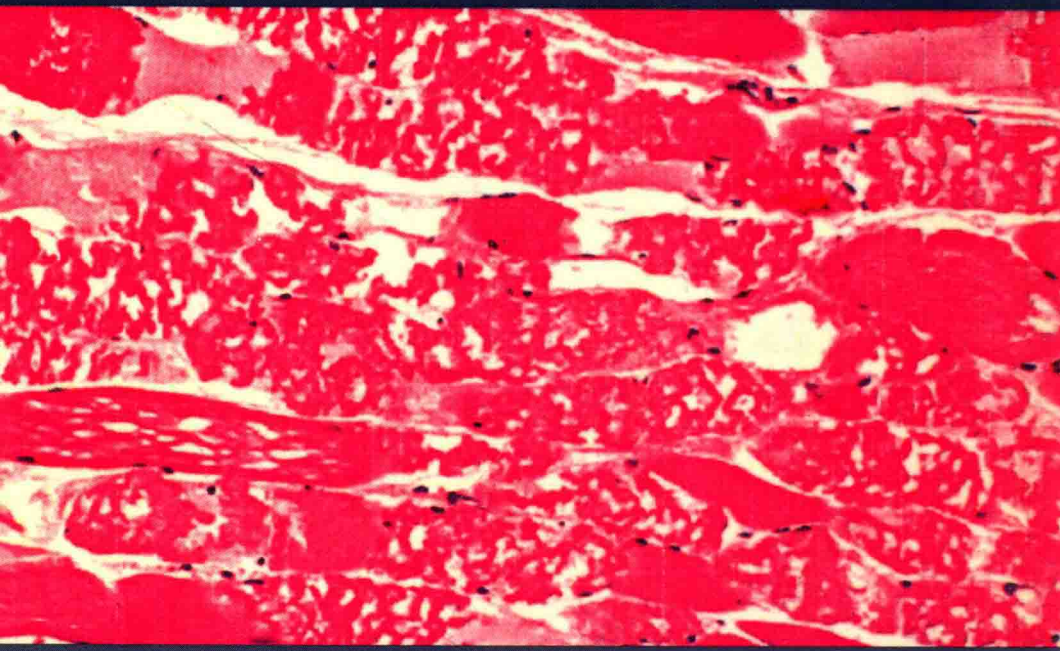
CELL INJURY

Mechanisms, Responses, and Repair



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Edited by Raphael C. Lee, Florin Despa, and Kimm J. Hamann

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CELL INJURY

MECHANISMS, RESPONSES, AND REPAIR

Foreword

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At the time my obsession with wound healing began 40 years ago, collagen, epithelization, and a little angiogenesis were the whole field. I tried to visualize how individual cells might react to injuries. Do they recover or do they die? If they recover, do they regenerate or do they bear scars as tissues do? On searching the literature, I found little and, lacking the courage to answer such questions, I stayed on the beaten path. Surely, though, I thought, when I smashed my thumb with a hammer, cells must suffer as much as connective tissue. Do hammered cells just collapse like oversqueezed balloons? Can they recover at all or do they die at the slightest trauma? Is there a patch for punctured cell membranes? (This book says that there may be one.) Aside from inflammation, do injured cells influence healing? Can injured cells incite unwanted scar directly, or is inflammation a necessary intermediary? For a number of good and bad reasons, wound healers have skipped past those questions in the rush to clarify the issue of growth factors arising from coagulation and inflammation. The diversity and subtleties of injuries were overlooked. This book attends to a number of overlooked opportunities.

Unfortunately, the course we took, though a productive one, tended to isolate the injury-induced deposition of vascularized connective tissue ("wound healing") from the rest of its genre (arteriosclerosis, diabetic retinopathy, ischemic injury, and so on). The more we see of wound healing, the more we must concede that vascularized scar is the final common pathway of many human diseases and has many origins, many of which are not preceded by injuries in the usual sense.

Diabetic retinopathy is an instructive case. It is scar tissue in the retina in which the vascular element is more than usually apparent, probably because, as opposed to other scars, we can see it through an ophthalmoscope. There is no mechanical damage. Clearly, there is loss (death?) of normal cells and replacement of the normal stroma due to scar. Where or what is the injury? Is it the result of normal cells taking another phenotype, that is to say, being misdirected to producing scar by their environment? Inflammation is minimal, so what is the origin of the signals that induce angiogenesis and connective tissue deposition? It seems to me that injury must have occurred.

We have almost forgotten the diversity of injury and we do not know how much mechanical, electrical, or "metabolic" injury is necessary to make an individual cell complain enough to incite its surrounding tissues to do something about it. Does the

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"complaint" arise from hypoxia, as some will say, or from lactate accumulation, as I believe? There is no evidence that hypoxia precedes the scar. We have ignored the fact that non-inflammatory cells release angiogenic factors and cytokines that stimulate collagen and proteoglycan deposition! Are injured but still viable cells the source of unwanted connective tissue deposition?

On the one hand, we need to know how to save cells that, though injured, have reparative capacities or will resume their original functions. On the other hand, we need to know how sick a cell has to be in order to incite the deposition of vascularized scar in the course of trying to save itself. Is the scar just the result of normal attrition and replacement in the diabetic environment?

At the time my interest began, only a few brave souls puzzled over the fate and functions of pre-existing, presumably injured, cells in wound sites. During many, but not all, of those years, were it not for Raphael Lee, I would scarcely have thought of how injured cells repair themselves, much less of how cells are injured absent an obvious trauma. Finally, he has got the concept on paper and in one place! To my knowledge, this is the first compendium on repair of injured cells, and he has put it together in a context in which "injury" and "repair" can be seen in their broader contexts.

I like the first sentence from Agarwal, Walsh, and Lee: "Biologists commonly consider a wound to be an acquired defect in the structural integrity of tissues." It is true. We are careless about that, and have tended to see wounds as an anatomic "fracture" of connective tissue that needs to be stuck together again as rapidly as possible. We see the glue as deposition of coagulation proteins and later the deposition of new, "connective" tissue. Though it may be a fine point, this view makes the tacit assumption that the hallmark of an injury is what happens after mechanical trauma, rather than as a protean process that pervades multicellular life and follows the inevitable injuries that also afflict individual cells. I suspect that in time, we will strip off layer after layer of inflammatory stimuli, metabolic events, and mechanical or electrochemical influences in search of the lowest common denominator that we hope will be the quintessence of "injury." I suspect, however, that there is no such point.

After all, there is no point in evolution at which " healing" became possible. Rather, repair of life's weak and often broken spots has always borrowed from already existing normal life processes. Cells were re-adhering to each other on the way to multi-cellular life before collagen even evolved. As long as life creates substance, there will be collisions and exchanges of mechanical forces. As long as life depends upon oxygen, carbohydrate, and, minerals there will be electrons that will go astray and injure the inner workings of cells. Fridlyand and Philipson have described that process in a remarkably brief and informative chapter. The consequences of such subtle injuries as a localized rupture of the cell membrane are discussed, and evidence for the possibility that a lipid patch may limit the extent of injury is summarized. This is truly a new idea! Can cells be given a head start on repair?

While the authors have sought to deal mainly with repair, they have by necessity also examined "injury." They have expanded the scope of injury from simple mechanical or electrical wounds all the way to incineration in the fire of carbohydrate metabolism. If you want to know how much rough handling a cell can stand, you would do well to read on. If you are brave enough to attempt an understanding of the full spectrum of injury and repair, you really *must* read on!

Introduction

RAPHAEL C. LEE, FLORIN DESPA, AND KIMM J. HAMANN

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When the subject of responses to injury or wound healing arises, the discussion usually pertains to reparative processes at the tissue or organ system level. Until recently, relatively little attention has been paid to the healing of wounded cells. Although much is known about the responses of individual cells to injury, and about their repair processes, there has not been a collective synthesis published that integrates the interdisciplinary aspects of the cellular healing responses. This *Annals* volume represents the first endeavor to bring this subject into focus.

Each of the many and various molecular processes involved in cell repair are the subject of active research efforts scattered over numerous biomedical science research fields. When viewed collectively, it becomes clear that cellular wound-healing activities are highly organized and complex. By comparison, the reparative processes involved in tissue wound-healing reflects the outcome of complex coordinated events involving many cells and cell types. Reparative processes at the cell level are also complex and coordinated, involving highly orchestrated series of molecular events designed to detect and repair injured components of the cell. As opposed to healing of tissue injury, which often occurs by replacement of damaged tissue with scar, cellular wound-healing processes are more regenerative and, when successful, the repair is more precise.

Cell Injury: Mechanisms and Repair is concerned chiefly with describing the processes of injury and healing at the molecular level. In the spring of 2004, a conference was organized at The University of Chicago to bring together experts on the various aspects of cell injury and repair, to share information and consider each aspect of the healing response in light of all the other processes that are simultaneously occurring in cells while they are healing and responding to injury. The symposium has since evolved into a graduate-level core course in molecular medicine and pathology at The University of Chicago. Like the original symposium, this book is organized in four sections, which progress from basic structure and physical integrity of the mammalian cell to modes of cell injury and cellular responses to ways in which we may be able to utilize our understanding of these types of injury and subsequent responses for therapeutic strategies that limit injury or enhance repair.

Part I of this *Annals* volume focuses on the structural factors which are deterministic of cell integrity and the physicochemical modes of cell injury. It is essentially a materials-science approach to cell injury. The chapters review basic aspects of mammalian cell structure, including not only the biophysical nature and responses

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of specific cell components such as the plasma membrane but also interactions with the extracellular and intracellular "matrix of life," water. This pertains to basic determinants of protein stability, protein assemblies and organelles. Thus, information about the energetics of passage through intermediate steps leading to aggregation of unfolded proteins and about the role of the biological solvent (water) as an active player in all these molecular events is discussed in the context of their role in the pathogenesis of cell injury. Physical and chemical aspects of interactions within and between proteins are reviewed and the effects of temperature and molecular crowding on these interactions are discussed.

In Part II, several different biophysical modes of cell injury are reviewed in a series of chapters that examine electrical injury to cells such as electroporation of the lipid bilayer and electrical denaturation of membrane proteins, as well as the effects of temperature extremes on cells. In these latter chapters, effects of excessive heat on individual cells and their components, as well as the effects of freezing and thawing on cells in both cryo-injury and biopreservation attempts are considered. Thus, the chapters in this section give the reader an overview of the types of direct cell injury which promote cellular responses and for which we are currently seeking and testing therapeutic strategies.

Part III of this volume is devoted to the healing responses of cells. In the opening chapter of this section, a tutorial overview of endogenous and therapeutic mechanisms of cell membrane repair is presented, giving the reader an introduction to key experiments in the elucidation of these concepts. Subsequent chapters in this section review the roles of endogenous substances, including calcium and heat shock proteins, in responses to cell injury. Molecular mechanisms involved in the induction of and the cellular response to DNA damage are also detailed in this section. Considerations of genetic syndromes and the clinical phenotypes resulting from aberrations in DNA repair are included. This part of the text concludes with a treatise on autophagy, a relative newcomer to the spectrum of endogenous protective responses to injury and stress, and discusses the pathological implications of deregulation of the autophagic response in mammalian cells.

The final components of the text deal with therapeutic strategies to rescue injured cells by augmenting the cell's natural healing responses. Many of the strategies discussed are those we considered when resuscitating damaged tissues and organs. These include inhibition of injurious factors such as reactive oxygen species, as well as direct repair of membranes through the use of specific polymers or through stimulated enhancement of endogenous repair mechanisms. By distinguishing cellular wound-healing process from tissue and organ wound-healing processes, it is hoped that the therapeutic goals will be better defined, and that this will result in more effective clinical resuscitation efforts.

The editors would like to thank Sandra Marijan for her enormous help coordinating the development of the seminar series and the text. We would also like to thank Dr. Julian Solway, the Chairman of the Committee of Molecular Medicine at the University of Chicago, for his support and for making this effort possible.

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CELL INJURY

MECHANISMS, RESPONSES, AND REPAIR

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RAPHAEL C. LEE, FLORIN DESPA, AND
KIMM J. HAMANN

This volume is the result of a seminar series entitled **Cell Injury: Responses and Repair** held between March 31st and June 2nd, 2004 at the University of Chicago, Chicago, Illinois.

CONTENTS

Part III. Cellular Responses to Injury

Part IV. Therapeutics for Cell Injury

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Biological Water

Its Vital Role in Macromolecular Structure and Function

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ABSTRACT: **Water in tissues and cells is confined by intervening cellular components and is subject to structural effects that are not present in its bulk counterpart. The structuring effects lower the dielectric susceptibility of water molecules and induce a "red shift" of their relaxation frequency. This is also a source of polarization fields that contribute to the effective interactions between macromolecules. The behavior of water molecules at hydrophilic sites is different from that at hydrophobic sites, and this dissimilar behavior promotes the anisotropy of the hydration shell of proteins. The anisotropy of the hydration shell is essential for the enzyme function, but it is also important in detecting denaturation of the protein (i.e., proteins expose their hydrophobic parts to water during unfolding). The most significant differences between biological and ordinary water will be presented along with how this information can be used to decipher patterns in dynamical behavior of biological water and to detect possible structural changes of the cellular components.**

KEYWORDS: **biological water; protein dynamics; injuries**

INTRODUCTION

Water is the critical substance for production of biochemical energy (photosynthesis) and the most common product of the metabolic processes as well. Water represents the matrix of life on Earth. Because life on Earth is so tightly connected with water, many human achievements based on water and aqueous solutions became a matter of fact. "As the fish forgets the water in the ocean." we often neglect the essential role of water in our life. The water content of the living cell (TABLE 1) is about 70%, making the molarity of the human body less than 1 mole (for an average molecular weight < 10 kDa).

However, the water control in a human body is rigorous. On one hand, a deficiency in hydration of less than 5% is usually fatal. On the other hand, an increase of the water content in cells and tissues over the physiological limit changes the protein activity and may trigger also cell malfunctioning and death.

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TABLE 1. The composites of a mammalian cell

Cell Component		% Weight
Water		70
Inorganic ions (Na^+, K^+, Cl^-, Ca^{2+}, Mg^{2+}, etc.)		1
Metabolites		3
Macromolecules	Proteins	18
	RNA	1.1
	DNA	0.25
	Polysaccharides	2
Lipid bilayer	Phospholipids	3
	Glycolipids plus cholesterol	2

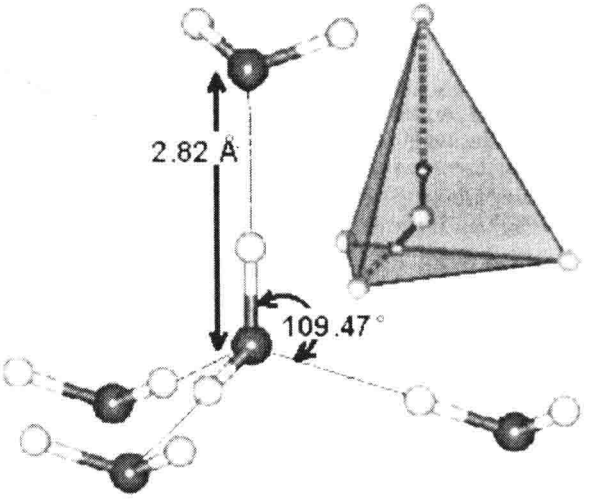

FIGURE 1. Three-dimensional structure of bulk water.

From a chemical point of view, water has a very simple structure (FIG. 1) in comparison to the complicated architectures of other biological molecules, such as the amino acids.

Despite its simplicity, water has unusual thermodynamic parameters (melting and boiling points, vaporization, and fusion heat), higher than expected for liquids composed of hydrogen and oxygen. In addition, water shows abnormal structural properties: maximal density at 4°C decreases its viscosity with a pressure up to about 1,000 atm.

Water in tissues and cells (biological water) rarely is thicker than a few molecular layers and mostly confined by intervening cellular components. This water is markedly different from the bulk counterpart. Although our knowledge about biological water is incomplete, all theories of cell biochemistry have explicit or implicit as-

TABLE 2. The energy (E) of common bonds in vacuum and water

Bond	E (vacuum) [kcal/mole]	E (water) [kcal/mole]
Covalent	90	90
Ionic	80	1
Dipolar	4	1
van der Waals	1	1

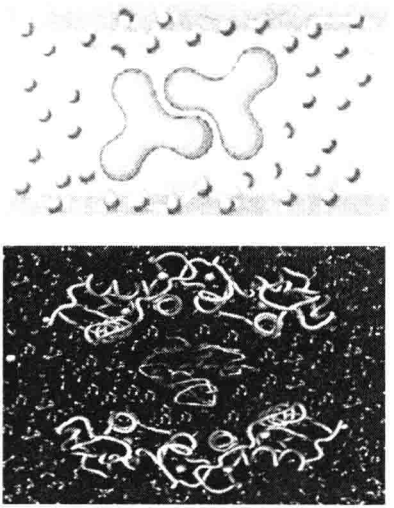

FIGURE 2. Water mediates nonspecific interactions in biological systems, such as interactions between hydrophobic molecules (*top*) and crowding effects (*bottom*). Crowding effects are manifest on the dynamics of the protein in the center, which is obstructed by the surrounding proteins.

sumptions about the physical properties of this water.[1] Most of them consider biological water as a solvent which rescales the strength of Coulomb interactions (ionic and dipolar) between macromolecules with respect to vacuum (TABLE 2). Also, it is admitted that this solvent mediates the hydrophobic interactions and plays a role in setting the level of cellular crowding (FIG. 2).

STRUCTURAL EFFECTS IN BIOLOGICAL WATER: PAIR CORRELATION APPROXIMATION

Water at a macromolecular interface is subject to structural effects which are not present in its bulk counterpart.[2] Jacobson,[3] more than fifty years ago, suggested in a general manner that these structuring effects actually expand beyond the first hydration layer and may give rise to long-range hydration structures; the details of his explanation can now be formulated in a more quantitative manner.[2] At the interface

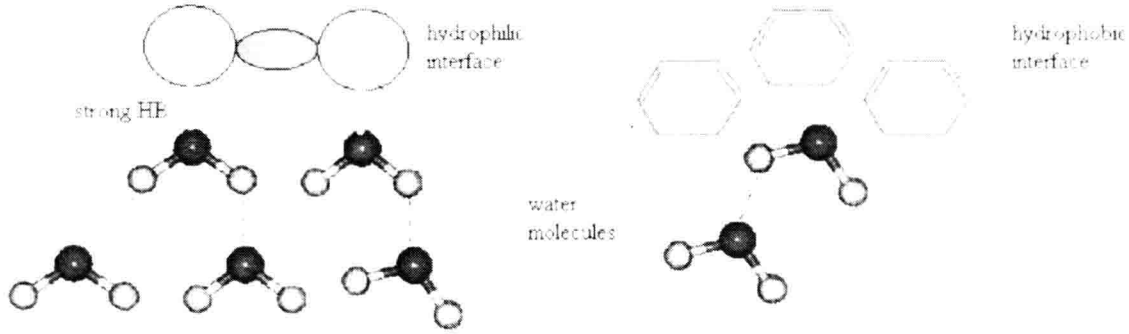

FIGURE 3. The dynamics of water at interfaces. The perturbation of the HB exchange between water molecules at these interfaces lead to a correlation in pairs of this water.

with a macromolecule, the free rotation of a water molecular dipole ($\vec{d}$) is likely to be obstructed by local geometric constraints, strong interactions with surface electric charges, or by a hydrophobic effect (FIG. 3).

This reduces the number of possibilities of hydrogen bond (HB) exchange of this water molecule with other water molecules from its vicinity. The depletion (f) of the HB exchange (say, from m possibilities for a molecule in bulk water, to $m-f$ possibilities at the interface) lowers the entropy of the water molecule and leads to extended lag times for the reorientation of $\vec{d}$. This enhances the probability that one water dipole (i) joins the slowly-fluctuating dipole of a neighbor (j) and creates a relatively long-lived dipole pair (ij). The interspace r_{ij} between dipoles in a pair and, therefore, the spatial ordering of water molecules, ranges between the typical interdistance of bulk water molecules a_0 [$a_0 = (3/4\pi n)^{1/3}$; n is the density of bulk water] and a critical distance (r_c ($r_c > a_0$). The formation of water dipole pairs with the largest interspace (r_c) is favored by the large decrease in entropy, while pairs separated by short distances ($\sim a_0$) correspond to small changes of the entropy. r_{ij} is random within its range ($a_0 \leq r_{ij} \leq r_c$). Consequently, the vector dipole field $\vec{E}$ at each site in the correlated region is also a random variable, and so is the thermodynamic average $\langle \vec{d} \rangle$ of the water molecular dipole moment. The magnitude and distribution of $\vec{E}$ determine the departure of the properties of structured water from those corresponding to bulk water. The probability distribution of $\vec{E}$, $P(\vec{E})$, as well as the maximum most probable value of $\vec{E}$, E_s, were derived based on basic molecular principles.[2] The main assumption of the model, which is physically intuitive, consists in the fact that the librational dynamics favors the formation of structures of water molecules correlated in pairs (FIG. 3). Thus, the approach yields a quantitative description of the librational dynamics of water under the constrains of the vicinal macromolecules.

POLARIZATION EFFECTS AND DIELECTRIC SUSCEPTIBILITY OF CONFINED WATER MOLECULES

The structuring effects lower the dielectric susceptibility of water molecules and induce a "red shift" of their relaxation frequency.[2] The librational dynamics of water is also a source of polarization fields, which contribute to the effective interactions between macromolecules.[4] For the particular case of hydrated hydrophobic molecules, the polarization field in the region of correlated water molecules can induce attractions between hydrophobes (FIG. 4). The hydrophobic interaction—the apparent attraction between hydrophobic species in water—is considered a key factor in maintaining the correct folded conformation of a protein molecule and also the main cause of protein aggregation. This attraction is thought to result, in a way that is still imperfectly understood, from changes in the arrangement of hydrogen bonds between water molecules surrounding a hydrophobe.[2] This gives rise to a local polarization of the interfacial water which is shown to be strong enough to induce long-range attraction between hydrophobic molecules. The polarization fields give rise also to induction effects which make water molecules and hydrophobes actually attract each other,[4,5] but not nearly as strongly as water attracts itself! These recent results[2,4] increased our understanding about the way proteins enhance their intramolecular interactions as they fold or associate. Furthermore, the approach presented

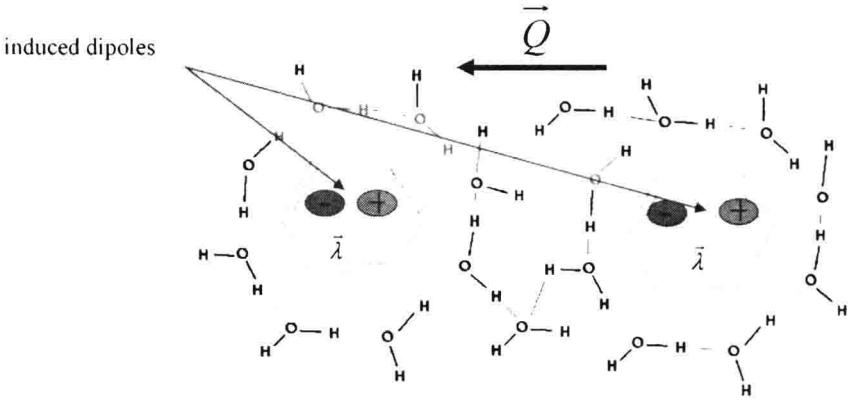

FIGURE 4. Polarization field ($\vec{Q}$) of water structured around hydrophobes. $\vec{\lambda}$ is the induced dipole by the polarization field.

above gives additional support to the idea that water confined in nanoscale hydrophobic environments has quite different solvent properties from those of the bulk liquid.[6]

Water's high dielectric constant is the reason why it is a good solvent for ions: it screens their electrical charges and so prevents them from aggregating. But in the vicinity of hydrophobic residues in a protein chain, the reduction in dielectric constant means that charged residues will interact much more strongly,[2] potentially helping to fix the protein's folds in place. Some details are given below.

Structural changes of water in the vicinity of macromolecules lead to modifications in the dielectric properties of their hydration shells. It was shown[2] that molecules experiencing high constraints ($f/m \rightarrow 1$) are characterized by a low susceptibility to follow an external electric field. From these results one can infer that, in the particular case of hydrophobic interfaces, where water molecules are constrained by the lack of HB exchange, there is a drop in the dielectric permittivity of the surrounding water. The trend of the electric susceptibility is to decrease from that of bulk water ($f < 1$) towards its value at the hydrophobic interface ($f \rightarrow m$). In return, Coulombic interactions between charged groups will systematically be enhanced in the direction of a neighboring hydrophobe. Therefore, hydrophobic residues play an active role in mediating intramolecular interactions between the polar side-chain residues of a protein.[2]

In FIGURE 5 we can see the thermodynamic effects of confinement upon the hindered rotation motion of molecular dipoles in biological water. We display the average dielectric susceptibility of biological water[2] against $\beta E_L d$, $\beta = 1/k_B T$, where $k_B \equiv 1.38 \times 10^{-23}\ JK^{-1}$stands for the Boltzmann constant, T is the temperature and $E_L d$ is the Lorentz energy. An increase of the temperature ($\beta E_L d \rightarrow 0$) lowers the susceptibility of the biological water. Actually, the model of biological water described above correctly predicts that the very-low-temperature susceptibility, which is not relevant to biology, is low (not shown in FIGURE 5), and then increases because of

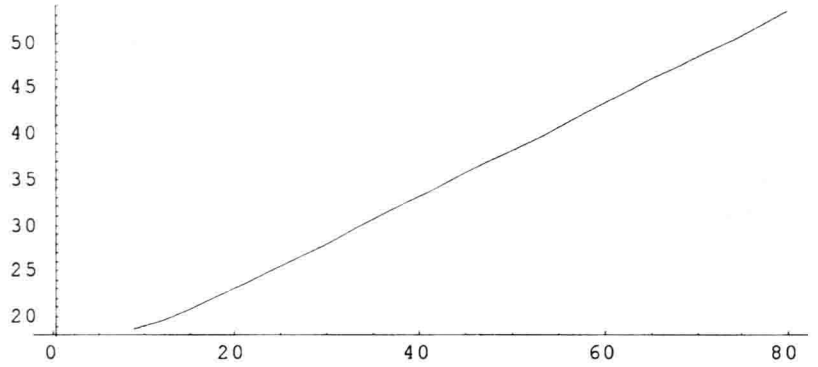

FIGURE 5. Average dielectric susceptibility χ of the hydration layer as a function of temperature ($\beta E_L d = E_L d/k_B T$) for $f/m = 0.5$.

the formal decrease of the polarization field with T, and only decreases again at relatively high temperatures.

In the above context, it is relevant to recall that the solid form of water (ice) has a higher dielectric constant than liquid water, at temperature well above $0K$. For example, the values of the static dielectric constant of ice range from 91.5 at –0.1°C to 133 at –65.8°C.[8] These high values of the dielectric constant are a direct consequence of the ordering of ice, which reduces random fluctuations of internal fields. Nevertheless, the current view is that the degree of ordering in ice is higher than the degree of water ordering around proteins.[9,10] Therefore, in order to recover the ice-like dielectric characteristics within the present theory we need to take into account higher-order correlations between the water dipoles. It is worth mentioning here the recent progress in simulating freezing of water to a known ice structure.[11] The key result of the simulation performed by Matsumoto *et al.*[11] is that ice nucleation occurs once a sufficient number of relatively long-lived hydrogen bonds develop spontaneously at the same location, forming a highly correlated, compact nucleus.

THE ANISOTROPY OF THE HYDRATION WATER OF PROTEINS

It is interesting to compare the water structure at a hydrophobic site, which is, basically, a distribution of dipole pairs, with that corresponding to a hydrophilic site. A hydrophilic group, characterized by a permanent dipole of moment $\vec{\lambda}_0$, aligns neighboring water dipoles along $\vec{\lambda}_0$ in a region of space determined by the interplay between the pair-wise solvent–solute interaction and the entropy change.

The dissimilar behavior of water molecules at these two sites promotes the anisotropy of the hydration shell of a protein.[7] The anisotropy of the hydration shell is essential for the enzyme function and is part of the recognition process by other molecules or proteins. In this context we can say that a polar group is fully expressed on a protein surface when $\lambda_0 / \overline{\langle \vec{\mu} \rangle} \gg 1$.

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