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**DEVELOPMENT AND APPLICATION OF PHOTSENSITIVE DEVICE
SYSTEMS TO STUDIES OF BIOLOGICAL AND ORGANIC MATERIALS**

Progress Report

For the Period January 1, 1993 - December 31, 1993

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I) INTRODUCTION & SUMMARY

This progress report summarizes results, as of August, 1993, for DoE grant DE-FG-02-76ER60522 during the fiscal period 1/1/93 to 12/31/93, which is the first year of a 3-year grant cycle. The overall goals of the grant are to develop advanced x-ray detector technologies, especially as applicable for biological and materials research at the national laboratories, and to train graduate and post-doctoral students on the use of these technologies via the performance of original biological and materials research. As summarized below, there has been good progress toward achieving the research goals of the original 3-year proposal; in consequence, the research plan and the total budget for the rest of 1993 and beyond is still well described by the original proposal.

Work under this grant is guided by the philosophy that useful instrumentation and technique development proceeds best when it is coupled to the performance of basic biological and materials research. To insure this coupling, the Princeton Biophysics group has avoided division into "instrumentation" and "applications" specialists; rather, each group member is simultaneously involved in both the development of instrumentation and the application of the instrumentation developed to basic research problems being worked on by that individual.

Accomplishments since the last progress report include:

- A) A 1k x 1k fiber optically coupled CCD detector was assembled, tested at CHESS and is slated for extended user trials this Fall. A 2k x 2k CCD detector is being assembled for permanent installation at CHESS.
- B) X-ray detector phosphors, calibration techniques, and system software have been developed.
- C) The design of a Pixel Array Detector, a collaborative project with the Advanced Photon Source, has been initiated.
- D) The properties of biomembrane lipids under extremes of pressure have been investigated. High pressure instrumentation and techniques have been developed.
- E) The physics of mesophase formation in biomembrane lipid, surfactant, and polymeric systems have been studied. This includes study of the interaction of membrane proteins with elastically strained lipid bilayers.
- G) Work has been initiated on the use of thermal diffuse scatter from proteins as a probe of protein dynamics.
- H) Studies on luminescent phenomena have been reported.

Since the last progress report (dated 15 May, 1992), this work has been resulted in 10 published papers, 7 abstracts, 1 Ph.D. thesis and 1 technical report. In addition, eight research papers are in various stages of preparation. Copies of publications not previously submitted with earlier progress reports are attached. Capsule summaries of the major research accomplishments and work in progress are given, below. The publications refer to the list at the end of this report.

II) RESEARCH ACCOMPLISHMENTS

A) CCD Detectors

Ref: Tate et. al., (1993a & b).

Most of the effort of the group during the last year has been focussed on the development of large format CCD detectors for macromolecular crystallography. Three detectors are involved. Each utilizes a thin phosphor screen to convert x-rays to light, which is then conveyed via fiber optics to a low-noise CCD.

The first detector is a 512x512 pixel (hereafter referred to as the "512 detector") consisting of a 75mm 1-stage proximity focussed diode intensifier fiber optically coupled to a 5:1 reducing fiber optic taper, which is in turn coupled to a 512² pixel Thomson CCD. The 512 detector was fabricated in 1992 and transported to the Cornell High Energy Synchrotron Radiation Source (CHESS) in Sept., 1992 for testing on the "old" A-1 line, which was a fixed wavelength, 3-pole wiggler beam line. The purpose of this experiment was to compare the performance of the detector against the image plate system in use at CHESS and to gather information on detector design which would be needed for a dedicated device at the storage ring. The detector was used to collect a number of full rotation sets on lysozyme test crystals. Several of the data sets were interleaved with image plate exposures so that a direct comparison of the CCD detector and image plate data could be performed for identical crystals under identical diffraction conditions. A final purpose of the experiment was to refine detector calibration procedures suitable for use at storage ring sources.

The data sets, when analyzed and compared against the image plate data, demonstrated that the CCD detector data was at least as good in quality as the image plate data. Just as importantly, the ease and flexibility of data collection was vastly improved with the CCD detector. This is especially important at storage ring sources because overhead associated with the acquisition and readout of image plate data is the main factor affecting the efficiency of data collection with these devices. The CCD detector was also used to obtain thermal diffuse scatter from protein crystals. This is a demanding application which requires both the capabilities of the CCD detector and the x-ray intensity of the storage ring. The results showed that the thermal diffuse scatter rotates with the crystal, suggesting that it results from motions of segments of the protein which are incoherent from unit cell to unit cell yet spatially locked to the crystal lattice. More will be said about this, below.

Information gathered during operation of the 512 detector was used to complete the design, fabrication and assembly of a second CCD detector. This consists of a 75 mm 3:1 fiber-optic taper coupled directly to a Thomson 1024² pixel CCD (the "1k detector"). Improvements in the design of the phosphor screen, the low noise of the CCD and electronics, and the relatively small 3:1 taper ratio eliminated the need for an image intensifier while still allowing quantum limited performance. The elimination of the image intensifier vastly simplified the design of the detector and removed a difficult to obtain, expensive, failure-prone part. It also removed the major source of signal induced background in the detectors (due to light and electron scatter in the image tube) and, since there was now no image tube photocathode to be cooled, allowed the front phosphor to be kept at room temperature. A thermoelectrically cooled cryostat was designed and constructed to take advantage of these changes. Experience with the 512 detector also was important in setting the specifications for a new CCD detector computer operating system, the first version of which was written for the 1k detector.

The 1k detector was transported to CHESS and tested with a variety of virus and protein crystals in March, 1993 at the F-1 beamline, which is currently the most powerful beamline in use for macromolecular crystallography. The data collected from these crystals met our highest expectations and have given us great confidence in the 1k detector design. The test crystals were provided by prominent crystallographic laboratories (e.g., Steve Harrison's lab at Harvard and Michael Rossmann's lab at Purdue), each of whom sent personnel to be involved in the data collection. The obvious quality of the data, coupled with the ease of data collection, have resulted in a great deal of encouragement from the crystallographic community to quickly install CCD detectors for dedicated macromolecular use.

The success with the 1k detector design was also used to complete the design of a similar detector based on a larger (115 mm) fiber optic taper and a 2048^2 pixel CCD ("2k detector"). This detector, as described in the 3-year proposal for this grant, is intended for eventual permanent installation at CHESS and is a product of a collaboration between our group, Eric Eikenberry (R.W. Johnson Med. School), Princeton Scientific Instruments Co., Eddie Arnold (Rutgers University) and CHESS. The detector differs from the 1k design primarily by the use of a different, larger CCD, and a fiber optic taper with a larger input area. As opposed to the 1k detector, the CCD and readout electronics consists of four parallel channels, thereby decreasing the time required to read out the detector and providing some novel modes of data collection (software selectable).

Although almost all of the 2k detector has been ready for quite some time, completion of the device has been stalled by the failure of EG&G Reticon to deliver a CCD which meets specifications. The strategy, therefore, that has been adopted is to take the 1k detector back to CHESS and leave it there as a dedicated detector until such a time as the 2k detector is ready. The plan is to install the detector as the main data collection instrument on the A-line at CHESS, which has been completely rebuilt with a multi-pole permanent magnet wiggler and which is expected to exceed even the F-1 line in intensity. The A-line should be fully commissioned this Fall. Barring unforeseen problems, we expect to install the detector beginning in September of this year. The plan for the 2k detector, should EG&G Reticon continue to fail to provide a suitable CCD, is to retrofit to either of two other 2k CCDs (Fairchild and Thomson) which have recently become available. Fortunately, these CCDs are a bit larger than the Reticon chip, so the existing fiber optic taper (an expensive part which would take the better part of a year to obtain) could be remachined to fit at modest cost.

It should be noted that, whereas the 2k CCD parts have been mostly provided by the collaborators, the 1k detector was assembled entirely with Princeton-owned parts. It was intended for permanent installation at a rotating anode source at Princeton where it is needed to replace an aging vidicon-based detector which is showing signs of photocathode failure. This rotating anode beamline is essential for the thesis work of several of our graduate students. Our hope is that the vidicon detector will last until we can complete the 2k detector and bring the 1k detector back to Princeton.

We proposed to proceed to develop mosaic arrays of CCDs after the construction of the 2k detector. This work is now entering the design stage. As noted in the original 3-year proposal to

this grant, we hope to use resources from this grant to develop prototype CCD modules. However, a complete mosaic array, which would involve either nine or sixteen modules, would require capital funds and assembly personnel which are outside the bounds of this grant; hence, the intention always was to have the sources themselves provide funds for the mosaic detectors they would acquire. We are pleased to report that MacCHESS has written the needed capital items into its NIH Resource Renewal proposal. The proposal was favorably reviewed, and, although the funds have been scaled back, there does appear to be enough for one large-scale mosaic array. Although the exact amounts have yet to be determined, we are optimistic that the MacCHESS grant will also include sufficient funds for a subcontract to Princeton University for a person to assist in the fabrication of the array.

B) Phosphors & Software

Gruner et al., 1993; Barna et al., 1993.

The input phosphor limits detector capabilities in several ways: The luminous efficiency of the phosphor limits the reduction ratio of the fiber-optic taper, i.e., if more optical photons were produced by each x-ray then one could tolerate larger losses in the taper and, therefore, use a larger taper ratio. Large ratio tapers allow the use of smaller, faster, more readily available CCDs. The temporal decay of light from the phosphor limits the time resolution of the detector. And finally, the stopping power and light scattering properties of the phosphor limit the spatial resolution of the detector.

Phosphor screens are readily made by settling powders of ceramic phosphor onto a suitable substrate. This is rather old technology involving considerable "black art" to optimize the specific settling conditions. We have spent considerable effort in optimizing the conditions for settled screens suitable for x-ray diffraction work; therefore, we were very interested in quantitatively measuring and understanding the limits of settled screens. Our measurements over the last year have yielded some surprising results: It is possible to settle screens with efficiency and resolution which is much better than one might expect from measured properties of monocrystals of phosphor and the usual assumptions of light propagation in settled powders. We demonstrated that the high performance of the screens ultimately stems from the rather complicated diffusion of light through high index phosphor powders and the physics of light acceptance and propagation into a fiber optic faceplate. This work has shown assumptions normally taken in the literature on settled phosphor screens to be largely incorrect. It has had the practical consequence of helping us to considerably improve the performance of the phosphors used on the CCD detectors.

Our phosphor development in the future will be considerably strengthened by the recent arrival of Dr. John Shepherd as a Post-doc in the group. Dr. Shepherd is an Engineering Physicist whose areas of expertise include phosphor screen fabrication and the electro-optics of x-ray detection. We have also benefited by conversations with Dr. Mel Tacotsky. Dr. Tacotsky is an inorganic chemist who developed the rare earth oxysulfide phosphors which now dominate x-ray detection. He is a rich source of information on rare earth chemistry and photophysics. With his advice, we hope to synthesize and characterize rare earth phosphors which are not commercially

available but which appear to be more efficient than the rare earth oxysulfides. Line items in the requested budget are for equipment which would be needed for the synthesis.

Software development for the CCD detectors has, not surprisingly, proven to be more time consuming than hardware development. The operating system for the new generation of CCD detectors, which now totals more than 100,000 lines of code, has evolved from the highly successful operating system used on our earlier devices. The software not only provides needed calibration, data display and manipulation capabilities, but integrates the detector flexibly into complicated experimental data acquisition protocols. We have taken pains in designing the new operating system to provide for expansion to arbitrary formats and have coded most of it in C for portability. Although software development is a never ending task, we think that the new operating system will serve us as a flexible kernel for at least the next few years.

Considerable effort has also been expended on developing detector calibrations. The unprecedented precision and accuracy potentially available with CCDs, as well as the variable x-ray wavelength capability of synchrotrons, tax the precision of all prior calibration procedures. Detailed measurements showed, for example, an unexpected dependence of efficiency which varies systematically with the angle of incidence of x-rays into the phosphor screen and the x-ray wavelength. Almost all of our prior x-ray work has been in the small angle scattering regime at a single wavelength (Cu K-alpha), in which case this effect is negligible. We initiated the measurements because the requirements of high resolution crystallography would involve wide angle diffraction over a range of wavelengths. It is disturbing that other groups who have been using phosphor screens for wide-angle crystallography have not noted the correct angle-dependent effect, suggesting that the calibrations now in use with, for example, the Enraf-Nonius Fast system, will not perform well at storage rings. A similar systematic effect may also present with the polycrystalline screens used for image plates. We are presently conducting measurements to test this possibility.

C) Pixel Array Detectors

Pixel Array Detectors (PADs) are custom fabricated solid state devices in which each pixel has its own data handling and storage electronics. We have proposed a novel PAD for MHz imaging at the APS in collaboration with Dr. Brian Rodricks of the Advanced Photon Source Instruments Division. This detector is intended to meet the need for a very fast, high performance device for time-resolved Laue macromolecular crystallography. In combination with the APS as a source and a suitable triggerable protein system, PADs offer the possibility of performing time resolved diffraction of proteins on the 10 microsecond time scale with single protein crystals.

PAD development will be very expensive because it requires many cycles of custom integrated circuit development at a silicon foundry. Originally, we proposed to have the APS contract such development directly to a suitable foundry, with our group at Princeton performing the chip design and detector testing and Dr. Rodricks taking care of the rather extensive off-detector electronics. Although the collaboration was approved by the APS, contracts have not been let because of cutbacks in funding available to the APS. In consequence, we have sought a slower, but lower initial cost route for PAD development.

We are fortunate in that the Princeton Physics department recently hired a highly experienced low-noise analog circuit chip designer for work on the Superconducting Super Collider.

Given the circumstances of the SSC, this engineer could be available to us for quarter time now and possibly for larger time fractions in succeeding years. Largely at the urging of this engineer (Bob Wixted), Orbit, one of the more popular silicon foundry houses, has instituted a CCD process ideally suited to our PAD needs. Orbit allows test integrated circuits to be fabricated on spare sections of wafers at relatively modest cost. Our present plan is to request funds from the APS for some fraction of Bob Wixted's time and for the relatively modest test circuits which would be needed to develop the PAD electronics. In conjunction with the x-ray detector expertise already within the group, we feel that a positive start on PAD development could thus be made at low cost. Discussions with Wixted have already led to substantial changes in the original basic design.

D) Pressure Effects on Biomembrane Lipids

So, 1992; So et al., 1992; 1993; Osterberg et al., 1993; Erramilli et al., 1993; Gleeson et al., 1993.

We have continued a highly fruitful line of studies on biomembrane lipids under extreme pressure. There are many motivations for high pressure studies of membrane and protein systems: The pressure sensitivity of biological systems is poorly understood; the pressure-temperature phase diagrams of biomembrane lipids are incredibly rich; pressure is an ideal trigger for time resolved x-ray studies; and the thermodynamics of macromolecules under pressure is a fertile area for basic research. The studies which have most recently been performed build on the rather extensive expertise within the group on the development of instrumentation and methods for x-ray studies in the 0 to 3 kbar range.

So (1992) and So et al. (1992; 1993) report the results of static high pressure investigations of the phase diagram of biomembrane lipids, most notably, unsaturated phosphatidylethanolamines. These reports also describe the instrumentation which was developed in order to perform this work, including a high pressure dilatometer, various novel high pressure x-ray cells, light scattering apparatus, and equipment for rapidly exploring the P-T phase diagram. The phase diagrams are full of surprises, such as the appearance of unexpected, new phases and exhibit rich dynamics. These results establish beyond question that changes in the properties of lipid bilayers composed of curvature-elastically strained monolayers, as is the case for many living systems, are non-negligible at pressures (hundreds of bar) which are readily tolerated by cells. The key finding is that the coupling to pressure is via change in the membrane spontaneous curvature, which is, in turn, coupled to the differential anisotropic bilayer compressibility, not the bulk compressibility. We believe this may answer the long standing puzzle as to why cells exhibit pressure sensitivity even though they are practically incompressible.

Osterberg et al. (1993) and Erramilli et al. (1993) will report on a time-resolved study at the NSLS of the behavior of lipid dispersions after a pressure jump. This involved the fabrication of an x-ray pressure apparatus which could perform pressure steps of up to 3 kbar in a few msec and the use of CCD detectors in line-shift mode to record x-ray data as rapidly as every 7 msec. The emphasis was on the pressure induced bilayer to nonbilayer phase transition. The most surprising result was that all the data could be rescaled onto a single curve spanning five decades of time, suggesting that the phase transition proceeds by a single mechanism. We also examined the time

dependence in the change of lattice spacing, due to water uptake, when the pressure is jumped without inducing a phase transition. These findings pertain to flow in porous media in which the geometry varies with the degree of water imbibed. These results have been reported, in part, at both the American Physical Society and Biophysical Society meetings. Many of the results are not yet understood.

Gleeson et al. (1993) reports on the effect of negative pressure on lipid-water dispersions. Negative pressure is a metastable state which is obtained by placing liquids under tension; the systems eventually relaxes via cavitation. Negative pressures of several hundred bar were obtained.

E) Amphiphilic Mesophases

Mannock et al. 1992; Turner et al., 1992; Boni et al., 1993; Keller et al., 1993; Hajduk et al., 1993.

We have continued to study the physical and chemical properties of amphiphilic materials, including novel, synthetic lipids, lipid-protein mixtures and block co-polymers. Detailed information may be found in the reprints. Of particular note is Keller et al. (1993), in which the conductivity of black lipid films are used to show that the spontaneous curvature modulates the ion-channel activity of the small protein, alamethicin. This is a highly significant result since it unequivocally demonstrates that the elastic strain field of the bilayer affects the functional organization of a protein. As such, it provides a rationale for the lipid composition of biomembranes. Hajduk et al. (1993) is a study of the dynamics of block copolymer phase transitions and which has elicited considerable interest from the polymer materials science community. We are especially proud of this study because the motivation for studying these polymers was the high degree of structural parallelism between copolymer and lipid phase morphology. It is a good example of the value of cross-disciplinary science.

F) Thermal Diffuse Scatter from Proteins

The very wide dynamic range of the CCD detectors allowed the collection of bright crystallographic reflections without loss of the very weak diffuse scatter which exists between the reflections. We were very surprised upon examining the data obtained at CHESS to observe that this diffuse scatter is highly structured and that the scatter pattern is clearly incoherent but rotates with the crystal and has the symmetry of the crystal lattice. Our interpretation of this scatter is that it arises from protein fluctuations which represent movement relative to axes fixed within the protein. As such it would be unit cell to unit cell uncorrelated but, none the less, locked to the crystal lattice.

Study of this scatter has evolved into a collaboration with Dr. Steve Ealick, Director of MacCHESS, and now forms the basis of the Ph.D. theses of Mike Wall and Sandor Barna. Our long term goal is to combine observations of the diffuse scatter with pressure studies to examine the dogma that thermally driven protein fluctuations are important for protein function. The strategy is as follows: Proteins unfold under high pressure, presumably because the folded state encapsulates low density, water-excluded pockets. Hence, one expects that just below the unfolding pressure, the magnitude of protein fluctuations should increase. If so, this should be apparent in the diffuse x-ray scatter. Further, if fluctuations are needed for activity, one expects large

changes in chemical activity of the protein just below the unfolding pressure. We wish to see if changes in the chemical activity correlate with changes in the diffuse scatter. If not, then it is hard to justify the role of thermally driven fluctuations.

This line of inquiry is attractive for a variety of reasons: There are very few direct structural probes of protein fluctuations; crystallography at high pressures is a largely open field (and one which we are well positioned to exploit); and the mechanism of pressure-induced protein unfolding is not well understood. This line of inquiry also plays well to our strengths: Synchrotron radiation, high pressure diffraction apparatus and advanced x-ray detection are all needed to do this work; the study deals with very fundamental questions of protein function; and the science is highly multidisciplinary.

G) Luminescent Studies

Reynolds, 1992.

Study of luminescent phenomena has long been performed under this grant, mostly by Dr. George Reynolds at the Marine Biological Laboratory in Woods Hole, MA. Dr. Reynolds has continued this line of work, with recent attention focussed on lyoluminescence, the light emitted when certain crystalline substances are solvated. Although lyoluminescence has been known for more a very long time, the mechanism is still very much a mystery. Dr. Reynolds has also been very active in assisting the Navy in consideration of subsurface luminescent sources in the sea.

III) PUBLICATIONS SINCE THE LAST PROGRESS REPORT

A) Published

1. J.A. Barry, H. Lamparski, E. Shyamsunder, F. Osterberg, J. Cerne, M.F. Brown and D.F. O'Brien (1992). ^{31}P NMR and x-ray diffraction study of the effect of photopolymerization on lipid polymorphism. *Biochem. J.* 10114-10120.
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10. D.A. Mannock, R.N.A.H. Lewis, R.N. McElhaney, M. Akiyama, H. Yamada, D.C. Turner and S.M. Gruner (1992). The effect of the chirality of the glycerol backbone on the bilayer and nonbilayer phase transitions in the diastereomers of di-dodecyl- β -D-glucopyranosyl glycerol. *Biophys. J.* **63**: 1355-1368.
11. F. Osterberg, S.M. Gruner, M. Kriechbaum, A.D. Polcyn, E. Shyamsunder, V. Skita, P.T.C. So and M.W. Tate (1993). Time-resolved x-ray diffraction of pressure-jump induced relaxations in membranes. *Bull. Amer. Phys. Soc.* **38**: 599 (abstract).
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13. G.T. Reynolds (1992). Lyoluminescence. *J. Luminescence* **54**: 43-69.
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B) In Preparation or Submitted

1. S.L. Barna, M.E. Wall, M.W. Tate, E.F. Eikenberry, and S.M. Gruner (1993). Calibration procedures for x-ray detectors utilizing phosphor screens. (In preparation).
2. S. Erramilli, F. Osterberg, M. Kriechbaum, A. Polcyn, V. Skita, M.W. Tate, P.T.C. So and S.M. Gruner (1993). Pressure-jump induced mesomorphic phase transitions in lipids: A time-resolved synchrotron radiation study. (In preparation).
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6. F. Osterberg, A. Wieslander, L. Rilfors, G. Lindblom, S.M. Gruner (1993). Measurement of spontaneous curvature stability in lipid extracts from *Acholeplasma laidlawii* grown on different fatty acids. (In preparation)
7. M.W. Tate, E.F. Eikenberry and S.M. Gruner (1993a). Coupling format variations in Charge Coupled Device-based x-ray detectors. (In preparation).
8. M.W. Tate, E.F. Eikenberry, S. Barna, M. Wall and S.M. Gruner (1993b). A megapixel CCD x-ray detector for macromolecular crystallography (in preparation).

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