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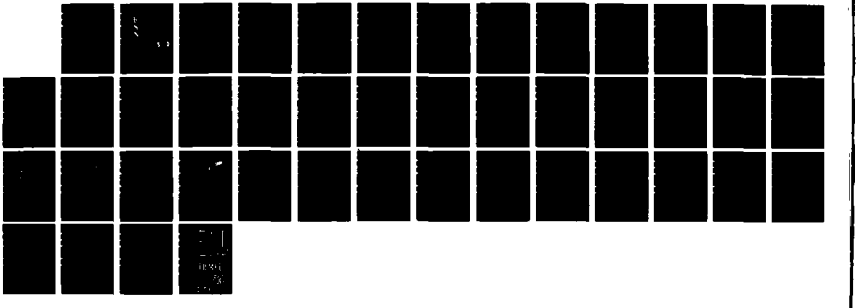

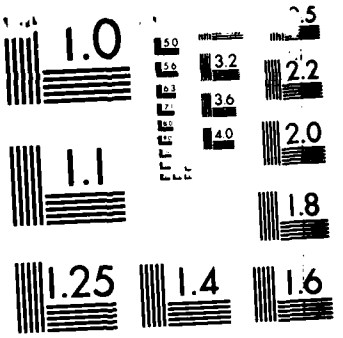

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European Science Notes (~~ESN~~) is a monthly publication with brief articles on recent developments in European scientific research. The publication is not intended to be part of the scientific literature. The value of ESN articles to Americans is to call attention to current developments in European science and technology and to the institutions and people responsible for these efforts. ESN authors are primarily ONRL staff members. Occasionally articles are prepared by or in cooperation with staff members of the USAF European Office of Aerospace Research and Development or the US Army Research, Development and Standardization Group. Qualified US scientists travelling in Europe may also be invited to write an ESN article.

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Biological Sciences

Although this center was founded only 4 years ago, its scientists have been productive in both basic and applied research in biotechnology. This productivity applied across a number of research areas.

This conference, which included a number of plenary lectures in microbial genetics engineering and enzyme technology, gave clear evidence of the increasing interest of biotechnology in existing and potential industrial applications.

The First International Conference on protein engineering was held in London, 21 and 22 November 1985. The presentations emphasized the increasing importance of protein engineering in basic and applied research directed to biotechnology. Recent advances in protein engineering, molecular graphics, nuclear magnetic resonance, and protein crystallography applied to protein structures analysis and the UK Institute in Protein Engineering are discussed.

Material Sciences

Research at the École des Mine de Paris is very closely related to France's industrial needs, but important fundamental, as well as applied, research is being done there--work that US researchers would find beneficial.

Mechanics

The presentations in this conference were devoted to simulation of boundary-layer and free shear flows by both direct and large eddy simulation. Summary comments emphasized the need for moving toward more engineering rather than research-oriented calculations.

This article reviews the work being done in turbulent flow and heat transfer in square- and circular-sectioned U-bends, modeling of fluid dynamics problems, and experiments to characterize the structures of turbulent jets.

Physics

A group of scientists in the Physics Department of the Clarendon Laboratory has made significant achievements in the development of a great variety of gas-discharge and metal-vapor lasers. Latest attempts focus on the construction of efficient VUV lasers.

Theoretical and experimental laser development research at the Physics Department of Milano University and the Center of Quantum Electronics of the Polytechnic of Milan, is described. Selected topics include studies on the novel superradiant-regime free electron lasers; collective variable description of FELs; development of compact, mode-locked, highly efficient CW-pumped solid state lasers, and femtosecond pulse production.

The optical research pursued over the last ten years at Uppsala University, Sweden, has resulted in a group which is involved in various industrial projects where tailored optical properties are required. A new scatter instrument to support the photo electron spectroscopy research, and the optical properties of materials research are described.

News and Notes

* * *

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Biological Sciences

CENTER FOR BIOTECHNOLOGY, TEL-AVIV UNIVERSITY, ISRAEL

by Claire E. Zomzely-Neurath. Dr. Zomzely-Neurath is the Liaison Scientist for Biochemistry, Neurosciences, and Molecular Biology in Europe and the Middle East for the Office of Naval Research's London Branch Office. She is on leave until July 1986 from her position as Director of Research, the Queen's Medical Center, Honolulu, Hawaii, and Professor of Biochemistry, University of Hawaii School of Medicine.

The Center for Biotechnology, Tel-Aviv University, Israel, was started four years ago by Professor Ephraim Katzir-Katchalski, who is also the director. He has a joint appointment as Professor at the Weizmann Institute of Science, Rehovot, Israel, in the Department of Chemical Physics. Professor Katzir-Katchalski, who has an international reputation in biophysics/biochemistry, set up the biotechnology center in Israel in the rapidly expanding area of biotechnology research.

Although the center has been in existence for only a short time, the scientific staff has made important contributions in biotechnology research in several areas such as: (1) immobilization of cells and enzymes; (2) use of cytometry and cell sorting for bacterial identification, tumor immunology, etc.; (3) cellulose degradation; (4) thermophilic methane and ethanol fermentation; and (5) microcariers for culturing mammalian cells. The main fields of interest and some projects of the senior staff of the biotechnology center are presented in the following section.

Katzir-Katchalski and his group are engaged in research on biological macromolecules including enzymes, other proteins, and nucleic acids as well as enzyme-polymer conjugates and immobilization of enzymes and cells. They have recently used a specific monoclonal antibody (Mab) for the preparation of a highly active immobilized carboxypeptidase A (CPA). Previously, this group had reported on the preparation and purification of several mouse Mab's to CPA. Studies of their effect on the enzymic activity of CPA showed that the antibodies obtained could be classified as: (1) antibodies (Abs) inhibiting mainly the peptidase activity of the enzyme; (2) Abs inhibiting the enzyme's activity; (3) Abs affecting both activities, and (4) Abs which bind to the enzyme but have no marked effect on its catalytic properties. In their present study, a monoclonal antibody (Ab 100), which was prepared, purified, and characterized, binds to CPA with a high affinity constant (about $10^9 M^{-1}$). The Mab obtained did not affect either the peptidase or the esterase activities of the enzyme. Covalent binding of the Mab to Eupergit C, or noncovalent binding to Sepharose-Protein A, yielded carriers reacting specifically with CPA to give immobilized enzyme preparations displaying full catalytic activity and improved stability. Katzir-Katchalski et al., noted that the literature data available suggest that for practically all enzymes known, it might be possible to prepare Mabs that bind with high affinity without affecting the enzyme catalytic activity. Therefore, this group believes that their method represents a general procedure for the preparation of highly active immobilized enzymes which are important for biotechnological processes. Katzir-Katchalski and coworkers are also studying monoxygenase activity of rat liver micromoses immobilized by entrapment in a crosslinked pre-polymerized polyacrylamide hydrazide.

Katzir-Katchalski has a patent pending on a reagent for the specific identification of enzymes and isoenzymes in clinical specimens with monoclonal antibodies. A current research and development (R&D) project supported by the Israel Council for R&D is the influence of monoclonal antibodies on the activity, conformation, and stability of an enzyme.

R. Lamed and coworkers are carrying out research on thermophilic methanol and ethanol fermentation, cellulose degradation, and reductive biotransformations as well as on thermostable enzymes and their applications. They have recently used flow cytometry for rapid identification of *Streptococcus pyogenes* and also characterized a cellulose-binding cellulase-containing-complex in *Clostridium thermocellum*. In another study, Lamed et al., found a discrete cell surface organelle of *Clostridium thermocellum* which exhibits separate antigenic, cellulose-binding, and various cellulytic activities; it is termed cellulosome. The major characteristics of the cellulytic system of *Clostridium thermocellum* coincided with those of the purified cellulosome. Lamed and his group are also studying enzyme diffusion and action on soluble and insoluble substrate biopolymers.

Lamed has obtained a patent on the use of co-cultures in the production of ethanol by the fermentation of biomass. Lamed and his group are engaged also in several R&D projects. These are: (1) cellulase-containing structures in cellulytic anaerobic bacteria; (2) synthetic applications of alcohol dehydrogenase from *Thermoanaerobium brockii* (both supported by the Israel National Research Coucil); (3) differential inhibition of methanogenesis from acetate by ionophores and inhibitors present in agricultural waste (supported by Migal Galilee Technological Center); and (4) applications of flow cytometry in bacteriology (supported by Hy Laboratories, Ramot, and the joint fund of Commerce and Industry).

G. Fleminger and colleagues are engaged in studies of the intracellular activity of proteolytic enzymes, the biosynthesis and processing of bioactive peptides and microprotein chemistry. They have carried out sequential hydrolysis of proline-containing peptides with immobilized aminopeptidase. Work on enkephalin-containing peptides has involved processing of these peptides in isolated bovine adrenal chromaffin granules, studies on the synthesis of adrenal peptide E and its biological activities, and changes in rat adrenal catecholamines and proenkephalin metabolism after denervation. They found that denervation of rat adrenal glands markedly increases proenkephalin messenger RNA and that intact proenkephalin is the major enkephalin-containing peptide produced in rat adrenal glands following denervation. Fleminger et al., are also studying soluble and immobilized closteridial aminopeptidase and aminopeptide P which they have found to be metal-requiring enzymes. They have recently developed a method for the sequential hydrolysis of proline-containing peptides with immobilized aminopeptidases.

Current R&D projects being carried out by Fleminger and his group include: (1) the purification and characterization of a lysozomal dipeptidyl carboxypeptidase; and (2) studies of the interaction of lysozymes with anti-lysozyme monoclonal antibodies.

J. Rishpon and her group are carrying out studies in bioelectrochemistry, including modified electrodes, biosensors and computerized electrochemical systems. They have recently finished a study on a combined system for automated ellipsometry and for network analysis based on a microcomputer. A current R&D project is the development of a glucose sensor based on a computerized enzyme electrode.

Y. Shabtai and his group are engaged in studies on the development of computer-controlled fermentation and separation processes, and microbial and cell-culture bioprocesses. These researchers have been carrying out extensive studies on the production in *Acinetobacter* species such as *Acinetobacter Calcoaceticus* of the bioemulsifier Emulsun. They have obtained a patent on the production of α-Emulsuns for industrial use. A current R&D project is the development of a combined fermentation-pervaporation system for the production of ethanol by immobilized yeasts.

A. Freeman and colleagues are carrying out various research projects such as: (1) immobilization of whole cells and enzymes; (2) enzyme and cell stabilization; and (3) controlled-release pesticides. They have developed a method for gel entrapment of enzymes in crosslinked prepolymerized polyacrylamide hydrazide. Freeman et al., are also investigating factors affecting cell attachments, spreading and growth on derivatized microcarriers. Their objective is to develop new microcarriers for culturing mammalian cells. Current R&D projects are: (1) biotransformations with immobilized plant cells (supported by Israel National Council for R&D); (2) controlled-release pesticides (supported by Ramot); and (3) immobilized-whole-cell-reactor coupled with membrane separation unit (supported by the Israel National Council for R&D and the Commission of the European Communities). Freeman has a patent pending on enzyme electrodes.

E. Sakar and his group are engaged in the following projects: (1) flow cytometry and cell sorting; (2) drug uptake in cancer treatment; (3) tumor immunology; (4) early diagnosis of immune disorders; (5) rapid bacterial identification; and (6) mutant selection by flow sorting. Current R&D projects are: (1) rapid bacterial identification by flow cytometry (supported by Hy Laboratories Ltd.); (2) development of a flow cytometric method for strain improvement of microorganisms of industrial interest (supported by Israel National Council for R&D and the joint fund of the Ministry of Commercial Industry and Ramot); (3) the use of flow cytometric techniques in the screening and selection of bacterial overproducers of cell-surface polymers and bioemulsifiers (supported in part by Petroleum Fermentation a.v.); (4) development of a method for the rapid production of monoclonal antibodies of potential use in cancer diagnosis and therapy (supported by the Ashkenzazi Cancer Research Center); (5)

drug targeting of human tumors using monoclonal antibodies; and (6) anthracycline drug uptake by blood and bone marrow cells in human leukemias.

Conclusion

Although the Center for Biotechnology, Tel-Aviv University, Israel, has only been in existence for about 4 years, the scientists at this center have been very productive both in basic and applied research in biotechnology. The applied research receives support from the government (Israel National Council for R&D) as well as industrial firms.

12/3/85

BIOTEC '85 INTERNATIONAL CONFERENCE AND EXHIBITION FOR BIO AND GENE TECHNOLOGY, DUSSELDORF, WEST GERMANY

by Claire E. Zomzely-Neurath.

The Biotec '85 International Conference and Exhibition for Bio and Gene Technology was held from 15 through 17 October 1985 at the Conference and Exhibition Center in Düsseldorf. The program encompassed two main areas of biotechnology research: microbial genetic engineering and enzyme technology. These research topics are currently being emphasized by scientists engaged in biotechnology studies--the potential application for industry and the market for products and eventual sales is very large. The scientific sessions encompassed basic as well as applied biotechnology research with some presentations by scientists from industry. It was evident that research in biotechnology by European scientists is being pursued vigorously and is of high quality.

Although the participants came from 17 different countries, the attendance was relatively small (about 300) with 50 percent of the participants from West Germany and 10 percent from each of the following countries: France, The Netherlands, Switzerland, Belgium, and the US. The program included plenary (symposium) lectures, short communications, poster sessions and exhibitions by a total of 34 companies from Germany, Denmark, Belgium, and Finland. A list of the conference topics is shown in Table 1.

The following sections deal with some of the topics presented in the scientific sessions.

Microbial Genetic Engineering

J. Davis, former President of Biogen SA, Geneva, Switzerland, and now at the Pasteur Institute, Paris, France, discussed the topic of genetic engineering and the transfer of basic information to commercial products. In his lecture, Davis emphasized that with the advent of genetic engineering techniques it has become possible to produce large amounts of proteins, many of which are close to development as human and animal pharmaceuticals. Initially, progress was slow; i.e., production of interferons by recombinant DNA (rDNA) technology was started in 1970 but is only now being produced at an industrial level by companies. However, during the past few years methods for finding and expressing genes as well as new purification methods have evolved, and the protein products of rDNA technology are of higher purity, which is required to meet the stringent standards for human use. Thus, Davis believes that with the present improved methods as well as the continuing improvement of existing technology, the progress from basic findings to production of compounds for the marketplace will be much faster in the future. Davis pointed out that products for the health care market, i.e., new pharmaceuticals, is growing rapidly. He anticipates that by 1995, the chemotherapy market will be $30 billion and immunostimulants, $2 billion. Some of the compounds which are in various stages of development or being produced commercially are:

1. Colony stimulating factors (CSF's) which stimulate host defense systems against invading organisms.
2. Erythropoietin--for differentiation and proliferation of red blood cells.
3. Factor VIII--for hemophilia.
4. Plasminogen activators--for heart disease.
5. Protease inhibitors (e.g., α-antitrypsin for emphysema).
6. Interleukin-2--as an immunnostimulant.
7. Bovine growth hormone--to improve yields of milk and meat.
8. Interferons--for antiviral, antitumor effect.
9. Insulin--for diabetes.
10. Human growth hormone--for growth and wound healing.
11. Vaccine--for hepatitis B, foot and mouth disease, etc.

P. Valenzuela, Chiron Corporation, Emeryville, California, discussed the use of yeast as a host for foreign gene expression and protein secretion. The expression of heterologous genes in recombinant micoorganisms has demonstrated

Table 1

Conference Program of the International Conference and Exhibition for Bio and Gene Technology

Plenary Lectures

Microbial Genetics Engineering, Chairman: C.P. Hollenberg, Institute for Microbiology, University of Düsseldorf, West Germany.

Protein Production by Genetic Engineering: Gene to Market Place, J. Davies, Biogen S.A., Geneva, Switzerland.

Synthesis and Secretion of Pharmaceutical Products from Yeast, P. Valenzuela, Chiron Research Laboratories, Chiron Corporation, Emeryville, California.

New Substitutes for Old Organisms by Gene Technology, C.P. Hollenberg, Düsseldorf, West Germany.

Gene Technology in Brewing and Other Fermentations, R.S. Tubb, Research Laboratories of the Finnish State Alcohol Company, (Alko Ltd.), Helsinki, Finland.

New Approaches to Amino Acid Biosyntehtic Technology, D.M. Andrews, Genex Corporation, Gaithersburg, Maryland.

Progress in the Improvement of Plants by Gene Transfer Methods, J. Schell, Max Planck Institute, Cologne, West Germany.

New Biotechnological Approaches to Environmental Pollution Problems, A.M. Chakrabarty, University of Illinois Medical Center, College of Medicine at Chicago, Department of Microbiology and Immunology, Chicago, Illinois.

Enzyme Technology. Chairman: H. Sahm, Institute for Biotechniology, Jülich, West Germany.

Trends in Enzyme Technology, M.R. Kula, Institute for Biotechnological Research, Braunschweig, West Germany.

The Enzyme Membrane Reactor--a New Chemical Engineering Concept, C. Wandrey, Institute for Biotechnology, Jülich, West Germany.

Enzymatic Synthesis of D- and L-amino Acids from Racemic and Achiral Compounds, K. Soda, Laboratory of Microbial Biochemistry, Institute for Chemical Research, Kyoto University, Japan.

Conversion of Starch to Liquid Sugar and Ethanol, R.F. Finn, School of Chemical Engineering, Cornell University, Ithaca, New York.

Structure Analysis in Protein Engineering, K.M. Ulmer, University of Maryland, Adelphi, Maryland.

Chemical Modification of Enzymes, M.H. Keyes, Enzyme Technology Anatrace, Inc., Toledo, Ohio.

Design and Construction of Biologically Active Peptides and Proteins, E.T. Kaiser, Laboratory of Bioorganic Chemistry and Biochemistry, Rockefeller University, New York.

Food Processing Enzyme, H. Uhlig, Rohm Chemical Company, Darmstadt, West Germany.

Detergent Enzymes, M. Bahn and R.D. Schmid, Biotechnology Research and Development, Henkel Company, Düsseldorf, West Germany.

Why do Enzymes Irreversibly Inactivate at High Temperature? A.M. Klibanov, Department of Applied Biological Sciences, Massachusetts Institute of Technology, Cambridge, Massachusetts.

Short Communications

Cloned Lipase Gene and Its Use as a Secretion Vector System in Staphylococcus carnosus, K.H. Schliefer, Institute for Botany and Microbiology, Technical University of Munich, West Germany.

Isolation and Characterization and Expression in E. coli of the Acinetobacter calcoaceticus Mutarotase Gene, C. Gatz, Institute for Physical Biology, University of Düsseldorf, West Germany.

Cloning and Expression of Synthetic Genes for the Blood Coagulation Inhibitor Hirudine in E. Coli, M. Rieger, Gene Biotech Company, Heidelberg, West Germany.

Immunoregulatory Organogenic Peptides, C. Birr, Organogen, Medical Molecular Biological Institute, Heidelberg, West Germany.

Process Scale High-pressure Liquid Chromatography of Biological Macromolecules, M. Colpan, Diagen Company, Düsseldorf, West Germany.

Immobilization of Enzymes on Microorganisms, W. Hartmeier, Institute for Microbiology, Technical University, Aachen, West Germany.

Method of Enzymatic Peptide Synthesis, F. Widmer, Carlsberg Biotechnology Ltd., Copenhagen, Denmark.

Urokinase and Pro-urikinase from Recombinant Microorganisms, L. Flohe, Grünenthal Company, Stolberg, West Germany.

the applicability for the production of clinically significant proteins. Most of his work has been with *E. coli*. However, Valenzuela stated that because of the favorable economics of its fermentation the yeast *Saccharomyces cerevisae* is becoming increasingly popular as the host. Yeast strains are being engineered for the production of growth factors, enzymes, and viral antigens for therapeutic and diagnostic purposes. The most dramatic example of the use of yeast in the pharmaceuticals industry is the recombinant hepatitis B surface antigen particles similar to those found in chronic human carriers. The particle is highly antigenic and immunogenic in animals and man. A vaccine made from the yeast antigen has been shown to be safe and effective in humans and will probably be the first recombinant vaccine to be approved for human use.

Valenzuela and his research group are also working on human acquired immune deficiency syndrome (AIDS), which leads to collapse of the immune system. They have been able with rDNA techniques to produce recombinant proteins in yeast

which are all recognized by antibodies present in the serum of AIDS patients. These recombinant proteins are presently being used in the development of highly specific blood screening and diagnostic tests of AIDS by the Chiron Company. These recombinant antigens should be of use in the future development of AIDS vaccine.

Since yeast cells secrete few proteins, it is advantageous to secrete the desired heterologous protein into this medium because it facilitates purification and allows for continuous fermentation. Valenzuela et al., have developed yeast strains able to secrete foreign proteins--most notably, human epidermal growth factor (EGF)--by using the secretion signal from the yeast a-factor, a naturally secreted yeast pheronome. Purified biosynthetic human EGF is identical in structure and biological activity to that isolated from human urine. Animal studies using the recombinant EGF have shown that the hormone is effective in corneal and skin wound healing and is now being tested at over 100 burn centers in the US.

Superoxide dismutase (SOD) which is a cytoplasmic enzyme also found in serum, plays important roles in the intracellular defense against damage by superoxide radicals. These radicals are centrally involved in the inflammatory response of phagocytes and in the damage that occurs after ischemia. Valenzuela et al., have used yeast cells to produce high levels of human SOD by fermentation. Structural analysis shows that the enzyme made in yeast is N-terminally acetylated and in all respects identical to the enzyme isolated from human erythrocytes. These researchers are also making the following compounds in their yeast system: insulin-like growth factor; growth hormone releasing factor, and interleukin-2. Another point he made is that protein products must be injected, otherwise they would be degraded in the stomach and intestinal tract. This limits the market; but if it were possible to administer proteins orally, the potential market would be enormous. Thus, one approach is to learn more about protein receptors--how the proteins get into cells, the antagonists, etc.--so that one could synthesize small molecules which could be given orally in place of proteins. Valenzuela believes there will be increasing emphasis on the production of small molecules made by microorganisms, plants, etc. (like amino acids, steroids, hormones, alkaloids, and antibiotics) using recombinant DNA technology.

C.P. Hollenberg, Institute for Microbiology, University of Düsseldorf, West Germany, spoke about the need of developing new substitutes by gene technology for use in biotechnological processes. Plant biomass, the only continuous source of organic material, is at present utilized only to a small extent as a substitute for industrial fermentations. Of the three major groups of organic compounds derived from plants, cellulose, starch, and sugar only the later substance can be directly fermented by yeast commercially. Celluloses and starch first have to be hydrolyzed into simple sugars, but this process is being applied industrially only in the case of starch. Thus, a great potential for the improvement of yeasts by gene technology will be in constructing yeast strains that (1) produce amylase to hydrolyze starch, (2) produce cellulases to hydrolyze celluloses, or (3) are able to ferment xylose. The same applies to bacterial species like *Zymomonas*, suitable for alcohol fermentation. In recent years studies have been undertaken in several laboratories to develop strains to meet these requirements. The genes can then be taken from these organisms and inserted into yeast by gene technology and thereby use cellulose (wood and paper pulp, or crop plant waste) for industrial fermentation. Hollenberg and his group have recently constructed some amylotytic and cellulolytic yeast strains and have introduced the gene for making α-amylase into yeast.

A potential substrate from animal origin is lactose or milk sugar, a disaccharide that cannot be utilized for alcoholic fermentation by *Saccharomyces cerevisiae*. The milk yeast *Kluyveromyces lactis* can utilize lactose, but has no efficient alcohol fermentation. Hollenberg et al., are working on the transfer of the genes for cellular uptake and hydrolysis of lactose to *Saccharomyces cerevisiae* in order to obtain efficient lactose fermentation.

K.H. Schliefer, Technical University of Munich, West Germany, reported on the cloning of the lipase gene using a new host system, a strain of *Staphylococus carnosis*. This strain is nonpathogenic and can secrete exoproteins like lipase. An expression/secretion system was constructed, and two strains secreting lipase were found. The gene was subcloned and sequenced.

C. Gatz, Institute of Physical Biology, University of Düsseldorf, presented her research on the isolation, characterization, and expression in *E. coli* of the *Acinetobacto calcoaceticus* mutarotase gene. Mutarotase is used to determine the concentration of glucose and is produced presently from mammalian tissue. However, production of this

enzyme by gene technology is cheaper because it is then possible to scale up production and make it efficiently in large amounts. Gatz and her coworkers fused promoter *E. coli* with the mutarotase gene from *Acinetobacter calcoceticus* and screened a gene bank with synthetic oligonucleotides synthesized as a mixed probe. The gene fragments that hybridized to the gene probes were eluted and cloned into PBR 27 to enrich the gene fragment content. Two colonies were found that contained mutarotase sequences. Because the product, mutarotase was secreted into the median in the system used by Gatz et al., it was relatively easy to purify the enzyme synthesized.

M. Rieger, Gene Biotech Co., Heidelberg, West Germany, reported on the cloning and expression of synthetic genes for the blood coagulation inhibitor, Hirudin, from *E. coli*. Hirudin is secreted by leeches and prevents blood from clotting. It has been purified and sequenced and found to be a specific inhibitor of α-thrombin which is involved in the blood clotting process. Rieger and his group prepared synthetic oligonucleotide probes based on the known amino acid sequence of Hirudin. Using recombinant DNA (rDNA) techniques they were able to obtain expression of Hirudin in *E. coli*. The Hirudin made by rDNA had the correct amino acid sequence, reacted with antibody to Hirudin and showed the correct biological activity; i.e., inhibited blood clotting. This research makes it possible to prepare Hirudin by gene technology more efficiently and cheaply than its preparation from natural sources like the leech.

L. Flohé Grünethal Company, Stolberg, West Germany, presented his work on the production of urokinase and prourokinase from recombinant microorganisms. Urokinase, also called plasminogen activator can dissolve blood clots and is already being used clinically. The problem is that it is very expensive because it is isolated from urine and is present in only minute amounts. Flohé and his group began their studies to try to prepare urokinase by rDNA technology about 4 years ago. They first purified and sequenced urokinase in order to be able to design oligonucleotide probes. However, they found a lot of homology with many other proteins, which was bad for designing genetic probes because specific sequences are required for this. In addition, urokinase was found to contain a carbohydrate residue that could make it difficult to be placed in the correct location in an *E. coli* or yeast system. Therefore, Flohé et al., decided to try for the production of the pro-form, a protein of high molecular weight and precursor of the active low molecular form, urokinase. They prepared the complimentary DNA (cDNA) to the messenger RNA (mRNA) for prourokinase. Cloning of the cDNA resulted in 2/12,000 positive colonies which contained part of the urokinase gene. Restriction fragments were generated to make more probes. They were finally able to obtain prourokinase from the recombinant microorganisms. The prourokinase was as effective as urokinase but different in selectivity. It is now being scaled up for clinical use for trials next year.

D.M. Anderson, Genex Corporation, Gaithersburg, Maryland, spoke about the application of new technologies to both fermentation and synthetic amino acid production. L-amino acids are important compounds with a wide range of commercial uses. The primary methods for L-amino acid production are fermentation and synthesis (chemical and/or enzymatic). Recently, modern genetic methods and gene cloning have been used to improve microorganisms for L-amino acid production by fermentation, and several improved synthetic processes using enzymatic catalysts have also been developed. Genex has focussed on synthetic methods and has developed improved enzymatic processes for the production of: (1) L-phenylalanine from t-cimannic acid and ammonia using phenylalanine ammonia lyase; (2) L-serine from glycerine and formaldehyde using serine hydroxymethyltransferase (SHMT); (3) L-tryptophan from glycine, formaldehyde, and indole using SHMT and tryptophanase; (4) L-cysteine from L-serine, acetic anhydride, and NaSH using O-acetylserine sulfhydrases; and (5) L-tyrosine from glycine, formaldehyde, and phenol using SHMT and β-tyrosinase.

A.M. Chakrabarty, Department of Microbiology and Immunology, University of Illinois Medical Center, College of Medicine, Chicago, Illinois, reported on new biological approaches to environmental pollution problems. Many synthetic compounds as well as natural hydrocarbons are being released into the environment in massive amounts as herbicides, pesticides, industrial solvents, refrigerants, and motor fuels or inadvertently as oil spills, dioxin contaminated chemicals, etc., which can cause enormous pollution problems because of their persistence in nature. However, natural bacterial strains have been isolated that can degrade single chlorinated compounds such as p-chlorobiphenyl; 3-chlorobenzoic acid; 2,4-dichlorophenoxyacetic acid; or simple hydrocarbons such as octane, naphthalene,

toluene, etc. In most cases, the degradative enzymes appear to be coded by genes borne on transmissible plasmids.

Many degradative genes for hydrocarbons and chlorinated compounds have been cloned and the nature of their regulation has been studied by sequencing the gene clusters and looking for the presence of regulatory signals. The promoter region of the chlorocatechol gene cluster exhibits considerable homology with the putative promoter sequence of *XylABC* and *Rhizobium nif* operons. The plasmid nature of the degradative genes has been exploited in the laboratory to develop a strain of *Pseudomonas cepacia* AC1100, capable of utilizing a persistent compound such as 2,4,5-T as its sole source of carbon and energy. The phenoloxyacetic degradative genes of the 2,4-D degradative plasmid pJP4 demonstrate homology with a plasmid DNA sequence from the 2,4,5-T degrading strain of *Pseudomonas cepacia* AC1100. Transposon mutagenesis, however, demonstrates the occurence of some 2,4,5-T degrading genes on the chromosome of this strain and such genes appear to be bounded by repeated sequences derived from other bacterial genes. Thus, both plasmids and chromosomal genes appear to be involved in the degradation of 2,4,5-T in *Pseudomonas cepacia*.

According to A.M. Chakrabarty, studies that are extremely important for solving future environmental pollution problems include the role of regulatory signals, repeated sequence, and genetic rearrangements in the evolution of genes involved in the degradation of toxic, chlorinated compounds; as well as the effectiveness of genetically manipulated bacteria and their products in the removal of oily wastes and synthetic pollutants.

Enzyme Technology

M.R. Kula, Institute for Biotechnical Research, (GBF) Braunschwerg, West Germany, discussed the new trends in enzyme technology. A similar but more detailed report was given at the Biotechnics '85 Congress held in Hanover, West Germany, 5 through 8 October 1985, and was presented in ONR, London report C-13-85. In summary, the new developments in enzyme technology include:

1. Use of special bioreactors which retain the catalyst in its active form and allow continuous operation and repetitive use of the catalyst. In such bioreactors, either isolated enzymes or whole microorganisms can be used and reaction engineering techniques can be applied to optimize and scale-up enzyme catalyzed processes.

2. Use of enzymes in the presence of organic solvents while maintaining the biological activity for long periods of time.

3. Development of methods for efficient regeneration of expensive coenzymes required for the performance of many enzymes; this will result in a more economic enzyme catalyzed synthesis.

4. Improvement of existing catalysts by protein engineering and site-directed mutogenesis.

K. Soda, Laboratory of Microbial Biochemistry, Institute for Chemical Research, Kyoto University, Japan, reported on methods for the enzymatic synthesis of D- and L- amino acids from racemic and achiral compounds which have been developed by Soda and his group. Stereoselectivity is one of the most salient characteristics of enzymes. They catalyze reactions with only one of an enantiomeric or diastereomeric pair of chiral compounds except racemases and a few others. Soda et al., have developed enzymatic procedures for the synthesis of optically active amino acids on the basis of stereospecificity of enzymes. The procedures are classified into the following three categories from the standpoint of starting materials: (1) racemic starting materials, (2) achiral starting materials, and (3) optically active starting materials. Soda described the synthesis of L- and D-amino acids, which are important as nutrients and starting materials in the pharmaceutical industry, with microbial pyridoxal enzymes and NAD enzymes belonging to categories 1 and 2 above.

Soda spoke about his method for the production of D-methinine and D-aminobutyrate from racemic methionine. He and his group purified to homogenicity and crystallized the pyridoxal enzyme methionine γ-lyase from *Pseudomonas putida*. This enzyme catalyzes the conversion of L-methinine into methanthiol, α-ketobutyrate, and NH_3. When DL-methionine is incubated with the enzyme, D-methionine and α-ketobutyrate are produced and separated easily. In the reaction system containing methimine γ-lyase and D-amino acid aminotransferase of *Bacillus sphaericus*, DL-methinine is converted into equimolar amounts of D-methionine, D-α-aminobutyrate, α-ketobutyrate, and α-keto-γ-methylbutyrate which are separated from each other by ion exchange chematography.

Soda et al., have also produced L-leucine from its keto analogue. They purified and crystallized leucine dehydrogenase from *Bacillus sphaericus*. This enzyme catalyzes the reversible

deamination of leucine and some other branched-chain or straight chain amino acids. An enzymatic method reported recently by C. Wandrey, Biotechnology Institute, Jülich, West Germany, for the production of L-leucine from α-ketoisocaproate and ammonia with a membrane reactor was used by Soda et al. However, they cloned the gene of thermostalile leucine dehydrogenase into *E. coli* cells to produce the enzyme more abundantly and to readily purify it. The stabler enzyme markedly enhanced the productivity of the reactor system.

Soda et al., have produced L-alanine from racemic lactate. The gene of thermostable alanine dehydrogenase of *E. stearothermophilus* was cloned into racemase-less mutant cells of *E. coli* which intracellularly produce both L- and D-lactate dehydrogenases. The three enzyme reactions are coupled in the cells, and L-alanine is produced exclusively from racemic lactate in a high yield. Soda also reported on the production of L-tryptophan, L-cysteine derivatives, and L-selenocysteine derivatives from racemic serine, and production of L-lysine from racemic α-amino-ε-caprolactam.

M.H. Keyes, Enzyme Technology Anatrace Inc., Ohio, reported on a simple chemical method for the generation of enzyme-like activity in protein material. The method consists of the following steps: (1) perturbation of the native conformation, (2) addition of a modifier, and (3) crosslinking of the perturbed protein with a bifunctional reagent. The method has been used successfully in the following conversions:

Starting Material	Induced Activity
Ribonuclease	Esterase
Albumin	Esterase
Alpha-Amylase	Beta-glucosidase
Several Proteins	Glucose Isomerase

Application of this method to ribonuclease has resulted in the formation of two semisynthetic esterases: an "acid-esterase" and a "neutral-esterase" with pH optima at 6.0 and 7.5 respectively. These semisynthetic esterases have been partially purified by means of ammonium sulfate precipatation and gel filtration on Biogel P-30™. While esters containing aromatic groups were the best substrates for these esterases, significant differences existed in their specificity. The application of ion exchange chromatography allowed not only the separation of the neutral- and acid-esterases, but faster separation of the neutral esterase into four components. Application of the method to ribonuclease illustrates that several different semisynthetic esterases possessing unique properties were prepared from a single protein starting material. It is also noteworthy that the semisynthetic enzyme can also be obtained by using various protein starting materials. For instance, several proteins were used to generate activity similar to glucose isomerase. These semisynthetic enzymes differed in their pH optima, metal ion requirements, and other properties. Thus, a versatile method has been developed to generate enzyme-like activity which can be used in a wide variety of applications.

C. Birr, Organogen and Medical Molecular Biology Institute, Heidelberg, West Germany, presented a brief report on immunoregulatory peptides which is a focused research project at Organogen in conjunction with scientists at the Institute. Thymosin α_1, an immunoregulatory peptide, is made by Organogen. Birr et al., are interested in developing other immunoregulatory peptides for the correction of probable immune deficiency effects: (1) acceleration of aging, (2) enhanced probability of cancer, (3) suseptibility to infections, and (4) rejection of skin grafts, etc. They have tested fragments of Thymosin α_1 to see which are active and are presently producing the active fragments in 200 g amounts in the pilot plant at Organogen.

Conclusion

The emphasis on biotechnology research in microbial genetic engineering and on enzyme technology at the Biotechnica '85 Congress in Düsseldorf reflects the dominant focus of biotechnology scientists today. The scientific sessions were of high quality with innovative research presented by European scientists as well as scientists from the US and Japan. In addition to basic research, increasing interest of participants and speakers in existing and potential application to industry was very evident.

12/3/85

FIRST INTERNATIONAL CONFERENCE ON PROTEIN ENGINEERING, LONDON, UK

by Claire E. Zomzely-Neurath.

The First International Conference on Protein Engineering was held from 21 through 22 November 1985 at the Gloucester Hotel in London, UK. This conference was sponsored by Oyez Scientific

and Technical Services, Limited. Protein engineering is a new phase in the area of biotechnology with a great potential for practical application. The topics covered at the conference included recent advances in new areas and techniques for designing proteins such as site directed mutogenesis, and molecular graphics as well as recent advances in protein crystallography and nuclear magnetic resonance (NMR) for analysis of protein structure. In addition, present and future commercial applications of protein engineering were also presented at this small, focused meeting. The format of the meeting is shown in Table 1.

Advances in Protein Engineering

T.M. Kaethner, PA Technology, UK presented some of the current achievements in protein engineering and discussed potential markets for products obtained by this area of biotechnology. I will report in detail the content of his excellent lecture.

Protein engineering has demonstrated how to dissect the structures and modify the function and selectivity of such diverse proteins as a neuroreceptor, peptide hormone, hydrolase, protease, anti-protease, transmembrane "pump", and other enzymes involved in antibiotic resistance and basic metabolism. The biological specificity of proteins, their stability *in vitro*, and catalytic characteristics can be altered. The phenomenal growth in biotechnology and its success to date are largely attributable to advances in obtaining expression of foreign proteins in novel host organisms. Protein engineering now takes this a leap forward by achieving designed alterations in proteins and their expression in the same range of host organisms.

Catalysis and transduction are processes that are fundamental to life. The central role played by proteins in these two processes is falling increasingly under industrial scrutiny, both to harness the catalytic potential of enzymes (proteins) and to exploit the specificity of protein-ligand interactions when designing novel pharmaceutical and agrochemical products. Traditionally, when industry has commercialized processes based on enzyme catalysis, process improvements have involved either the identification of novel sources of enzymes, or mutagenesis/selection programs to generate advantageous enzyme characteristics. Recent developments in biotechnology have the potential to subordinate these indirect non-specific routes. Thus, advances in molecular biology now permit the extensive manipulation of gene templates so that the amino acid sequence of proteins can be altered in a predetermined fashion. This application has been termed protein engineering; i.e., the creation or alteration of the functionality of a protein by rational redesign of its structure.

Numerous properties of enzymes have been discussed in recent years as candidates for manipulation by protein engineering. Often, the modifications envisaged for engineered proteins segregate according to *in vitro* or *in vivo* applications. Thus, stability characteristics such as enhanced thermal stability, activity over a broad pH range, resilience in organic media, prolonged activity after immobilization onto various process substrata, resistance to proteases and broad range solubility characteristics are advantageous in industrial enzymology.

The successes achieved by protein engineering in the rational modification of protein function have been remarkable both from the point of view of the diversity of systems already investigated and the unambiguous specificity of information generated according to Kaethner and G.M. Tonge. In 1984, it was considered virtually impossible to computer model proteins and their hydrogen bonding, electrostructure and hydrophobic interaction made with the substrate nor to predict the effect of altering the active site. Yet this year Fersht et al., (1985) have applied protein engineering of an active site to quantify the role of hydrogen bonding in biological specificity.

Many of the early examples of site-directed mutagenesis for protein engineering have been summarized by Zoller and Smith (1983). Another powerful aspect of the technology, the rational design of fusion proteins to facilitate downstream processing of biotechnology products has been reviewed by Brewer and Sassenfeld (1985).

In vivo beta-lactamase functions in the periplasmic space of bacteria to hydrolyze and to deactivate the beta-lactamose ring of penicillin derivatives. During transport across the inner membrane, the signal peptides of beta-lactamase (comprising 23 amino acids) is cleaved. Critical features of the signal sequence for transport and processing have been probed to reveal that determinants for such activities do not reside in signal sequence alone. The essential nature of an active site serine in β-lactamase has been confirmed and a serine to cysteine substitution not only releases activity towards penicillin but confers susceptibility of residual activity to a sulfhydryl

Table 1

Program of the First International Conference on Protein Engineering

Advances in Site Directed Mutagenesis; G. Winter, Laboratory of Molecular Biology and Biophysics, University of Oxford, UK.
Advances in Protein Engineering; T.M. Kaethner and G.M. Tonge, PA Technology, Melbourn, UK.
The Determination of Protein and Enzyme Three Dimensional Structure; G. Dodson, University of York, UK.
Recent Advances in X-ray Crystallography; L.N. Johnson, Laboratory of Molecular Biology and Biophysics, University of Oxford, UK.
Application of Synchrotron Radiation to Protein Crystallography; J.R. Helliwell, Science and Engineering Research Council (SERC), Daresbury Laboratory and University of York, UK.
Use of Molecular Graphics in Drug Design; D.N.J. White, Chemistry Department, University of Glasgow, UK.
Commercial Applicaiton of Protein Engineering; A. Kossiakoff, Department of Biocatalysts, Genentech Inc., US.
Molecular Graphics as a tool in Protein Engineering; A. Moffrew, IBM Ltd., UK.
NMR and Protein Conformations; K. Wüthrich, Institute of Molecular Biology and Biophysics, Eidgenössiche Technische Hoschschule (ETH), Zurich, Switzerland
The UK Initiative in Protein Engineering; D. Yarrow, Science and Engineering Research Council, UK.

reagent. Similarly, the catalytic activity of dihydrofolate reductase has been analyzed by rational changes to the active site. A single Asp to Asn modification was associated with a 1000-fold decrease in specific activity, supporting the thesis that Asp is involved in stabilizing a protonated transition state. A Gly to Ala mutation in a region of the protein predicted to be sensitive to steric perturbation totally abolished activity.

Analysis of the x-ray crystallographic structure of insulin has suggested that the full length of the native C-peptide (35 amino acids) might not be essential for linking the relevant termini of the insulin A and B chains. An engineered pro-insulin molecule has been designed and synthesized. This molecule has an abbreviated primary sequence for the C-peptide (hexapeptide) which had chromatographic and immunologies properties consistent with the natural pro-insulin.

The molecular action of inhibitory alkylating agents such as N-ethylmaleimide (NEM) on bacterial transport proteins has been studied by several groups. In the lactose permease of *E. coli* (M-protein, lac y gene product) a cysteine to glycine substitution suggested that this active site sulfhydryl was not essential for transport activity, but that its alkylation with NEM inhibits binding of the transport substrate. The molecular basis for the coupling of lactose transport activity with protein gradients has also been investigated. Hydropathy plots and antibody interactions have been used to generate a model for transmembrane folding of the lactose permease and chemical modification of the protein has implicated histidine residues as being associated with proton/lactose symport activity. Site-directed mutagenesis (His to Arg) has revealed that of the four histidine residues present in lactose permease, two (His 35-39) play no essential role in transport. Mutagenesis of His 205 is associated with total loss of transport function whereas mutation of His 322 destroys proton-coupled lactose uptake while leaving the facilitated diffusion of lactose operational.

Stability against thermal inactivation has been engineered into phase T_4 lysozyne (Perry and Wetzel, 1984). On the basis of theoretical calculations and a visual scan of the modeled crystal structure for T_4 lysozyme, a single mutation was introduced (Ile to Cys) to permit the formation of a solitary disulfide bridge via mild oxidation with tetrathionate or glutathione buffer. Residual activity of the mutatant enzyme was about 200-fold greater than the wild-type after 3 hours incubation at 67°C. Improved stability has been engineered with human fibroblast interferon (INF-β) by removal of one of its three cysteine residues (Mark et al., 1984). Antiviral IFN-β forms inactive dimers and oligomers and a Cys 17 to Ser mutation was engineered to reduce the possibilities for potentially damaging inter- and intra-molecular disulfide bridge formations. The resulting mutant protein retains solid-type antiviral activity but displays improved storage characteristics.

Construction of a hybrid repressor protein, differing from its parent by four amino acids in the putative alpha-helix specificity determining region has been used to demonstrate the molecular basis of the DNA sequence-specificity of these DNA-binding proteins. Sequence specificity of the bacteriophage lambda 434 repressor protein switched to that for the cro protein following directed mutagenesis of the former to give a

hybrid bearing putative CRO recognition features.

Extensive studies on the biochemistry, physiology and molecular biology of the acethycholine receptor have provided a detailed understanding of this ligand-gated channel protein. Site-directed mutagensis in the absence of crystallographic data has now enabled a fundamental analysis of those specific regions of the receptor considered to be involved in acetylcholine binding and transmembrane channel formation (M. Shina et al., 1985).

Site-directed mutagenesis has been applied to probe the catalytic activity and role of conformational changes in aspartate transcarbamoylase. Similarly a phylogenetically conserved Phe of cytrochrome C has been found to be non-essential for election transfer reactions but does not participate in determining the cytrochrome C reduction potential (Pielak et al., 1985).

A possible solution to the incidence of emphysema (environmentally-induced and hereditary) arises from studies on the consequence of directed mutagenesis of a Met residue at the elastase binding site of α_1-antitrypsin (Courtney et al., 1985). A Met 358 to Val mutation generated a fully active elastase inhibitor which was resistant to oxiditive inactivation, while a Met 358 to Arg mutation produced an efficient antithrombotic protein. Of a complimentary nature is work on the redesign of the substrate specificity of trypsin (Craik et al., 1985).

The basis of active site binding and catalytic activity is being systematically analyzed in tyrosyl-tRNA synthetase. A range of mutant enzymes has been generated which are active but have altered kinetic parameters. The molecular explanation offered for an engineered 130-fold reduction in Km (ATP) in one mutant was confirmed in a series of experiments in which enzymes bearing double modifications in the active site were constructed. In a momentous step Fersht et al., (1985) have now offered the progenitor for future studies of enzyme active sites. Their quantitation of active site hydrogen bonding as a biological specificity determinant encapsulates the future potential of protein engineering. Thus, according to Kaethner and Longe, we now have not only an analytical tool to dissect the processes of catalysis and transduction but a "rudder with which to steer them".

The application of protein engineering to agricultural problems such as pest control, disease resistance, and metabolic partitioning was also discussed by Kaethner and Lange. However, these topics will not be described as agriculture is out of the scope of this article.

Potential market sectors for engineered proteins were discussed and include industrial enzymes, food technology, pharmaceutical and agricultural industries, and the developing biosensors field. Kaethner and Longe think that over the next 10 to 15 years protein engineering may capture a percentage of these markets and may even dominate select sub-sectors. The world market for industrial enzymes is currently worth some $400 million per year and is attributable to three classes of enzymes: proteases, carbohydrases and lipases. Food technology has need of improved or novel proteins for numerous roles such as sweetening, gelling and viscosity modifications, meat tenderizing and preservation against spoilage. This total market exceeds $80 billion per year and is potentially addressable by protein engineering. Revenues from the pharmaceutical and agrochemicals industries currently exceed $80 billion per year each and both industries are already reliant upon some of the component skills of protein engineering to generate sales (for example, molecular graphics for drug and pesticide design; genetic engineering for the production of improved organisms and therapeutics). Several market leaders in these industrial sections have already initiated in-house programs for protein engineering.

The development of biosensors for a wide range of applications is attracting considerable commercial attention at present. Predictions on the market for biosensors to the year 2000 could exceed the $1 billion mark. Realization of these predictions is heavily dependent upon advances in protein engineering. Initial target features may be the provision of external scaffolding for signal transduction systems and stability (resistance to desiccation, amenability to immobilization, retention of full activity after immobilization etc).

Molecular Graphics as a Tool in Protein Engineering

A.J. Moffrew, IBM Limited, UK presented a lecture on the very new area of molecular graphics applied to protein engineering. Computer graphics, as pointed out by Moffrew offers the researcher a method of interacting with a computer in a way that relies on scientific experience rather than knowledge of computers. It allows interaction with a molecular model directly rather than via a programming language and virtually replaces the need for a physical model.

Moffrew listed several benefits of computer modeling: (1) computer models of proteins do not degrade; (2) programs can quickly inform the researcher about the model's structural properties; (3) removal of physical limitations allows researchers to explore conformations/configurations more easily; (4) using different representations and displaying various molecular properties aid researchers to gain insight into protein structure; (5) different molecular conformations may be composed easily; and (6) some researchers have been shown to be more creative working with computer graphics.

In his lecture, Moffrew discussed computer graphics hardware, software for molecular modeling and some applications of computer graphics for modeling proteins. For detailed information the two reviews by Moffrew (1985 a and b) are recommended. In this report I will only mention briefly some of the uses of computer graphics in protein research which were discussed by Moffrew.

Electron Density Fitting. The use of computer graphics that was primarily responsible for the developments in relative interaction was electron density fitting. When a researcher is carrying out an x-ray crystallographic determination of a macromolecule, there is a slow laborious step when a model is fitted to an electron density map. This step has been greatly speeded up using computer graphics. Electron density is normally contoured in two planes resulting in a mesh representation. Vector representation is used for the protein. Fitting is accomplished by manipulating the protein to sit in the mesh contours.

Enzyme-Substrate Interactions. The study of protein-protein and protein-substrate interactions is of great interest at this time. As an aid to this process, M. Barry and colleagues at Washington University, St. Louis, have contoured the cleft surface using the van der Waals radii plus an extra carbon radius. The resulting restricted volume gave the limits within which all substrate atoms had to lie. Mesh contouring was used for the envelope and stick representation for the substrate model being manipulated. The modeler finds a position where the stick molecule sits without passing through the contoured envelope. This is very similar to the electron density fitting problem. Further chemical considerations are used to refine the substrate orientation.

R. Langridge and colleagues at University of California, San Francisco (UCSF), have developed a dot representation of the molecular surface which could be manipulated in realtime. Refinement of the method has led to faster calculation of the molecular surface approaching the situation where the dot surface alters as protein conformation is changed.

DOCKER is a program for docking polypeptides into protein active sites. The polypeptide is allowed to be flexible and is positioned interactively. Steril hindrance is indicated by blinking bonds and energy refinement of the substrate is used to improve the fit. TOM is a docking program which has been built on top of the election density fitting program. Here the substrate is not restricted to being a polypeptide and energy minimization is performed interactively. The UCSF group is developing a fast interaction energy which is capable of updating the screen in real-time.

Investigating Homologenous Proteins. A recurring problem in protein research is the small number of useful proteins that have been analyzed by x-ray crystallography. To carry out modeling which is of interest, more three-dimensional models of proteins are required. One approach is to look at the protein from different species which has already been solved by x-ray crystallography. If two such proteins are shown to possess a high degree of homology, a researcher may be able to build a model of the unknown protein with some confidence. Graphics is used to investigate the level of structure homology.

Hypothetical Protein Structures. There are proteins of great interest where there is no solved structure from a different species. However, there may be sufficient homology with a class of solved proteins so that it is still possible to carry out molecular modeling. For example, Blundell, Sibanda and Pearl (1984) modeled the aspartyl proteinase mouse renin (and later human renin) using as the starting point a second aspartyl proteinase, pepsin, from the specimen *Endothia parasitica*. Such models are useful but hypothetical and require corroborating data such as x-ray analysis. Other approaches to building a protein model from the sequence are also available. B. Robson and coworkers at Manchester University, UK use an energy minimization procedure which has been producing significant results with small and medium sized polypeptides. M.J.E. Sternberg and colleagues have adopted a different algorithmic approach which defines regions of secondary structure from the amino acid sequence and then folds them in such a way as to bury hydrophobic sidechains. This approach leaves the researcher with a set of possible conformations which can

usually be reduced to one or two candidates on inspection.

Site-directed Mutagenesis. There are many groups both in industry and academia working on site-directed mutagenesis experiments. Rational protein design is developing in biotechnology research groups in the same way that rational drug design has developed in the pharmaceutical industry. The major limitation of this approach is the number of proteins for which accurate atomic coordinates have been determined. However, in those examples where 3-dimensional coordinates do exist, a researcher is able to consider the protein and look for substitutions that could change the proteins properties in a desired way. A graphics system can then be used to model the substitution, perhaps using a molecular mechanics energy minimization. This can indicate how the protein could be disrupted on making the candidate substitution.

Use of Molecular Graphics in Drug Design

D.N.J. White, Chemistry Department, University of Glasgow, UK presented a detailed and informative lecture on protein model building and enzyme/substrate docking in drug design. There are three broad subtechniques of molecular modeling which find wide application in drug design. The first subtechnique seeks to characterize possible new drugs by induction and by using the known structures and biological activities of previously synthesized components. The composite active conformation that is common to the known structures is found by molecular modeling that uses multiple minimum optimization techniques and flexible molecule superposition algorithims. Any proposed new drugs must be able to reach this active conformation from their solution conformations with only a small expenditure of energy, and must possess a similar charge distribution to members of the existing family. When the conformation of the receptor enzyme, or better still, an enzyme/substrate complex, has been determined by x-ray crystallography, then the second subtechnique may be used; a necessary, but not sufficient, requirement for biological activity is that the drug-substrate must fit into the active site of the receptor enzyme without significant steric strain. The most likely candidate for subsequent synthesis is the one that results in the greatest reduction in enthalpy on docking (i.e., fitting into the active site). Molecular modeling is used to provide the investigator with a continuous realtime estimate of the enthalpy of the system as a substrate is manually "piloted" into the active site of the receptor.

If the x-ray structure of the receptor enzyme is unknown, the docking approach can still be used provided that the crystal structure of a protein homologous with the receptor enzyme is known. The third subtechnique, of protein model building, may then be used to construct an accurate three-dimensional structure of the receptor enzyme from the known crystal structure of its homologous protein. If the structure of more than one protein homologous to the receptor enzyme has been determined crystallographically, then the model building process is correspondingly easier. Once the model has been built using molecular graphics it may be used for docking experiments.

The first subtechnique (induction) has only tenuous links with protein engineering whereas the second and third are of key importance in this context.

Protein Model Building. Homologous proteins most frequently, but not always, contain a different number of amino acids so that the first problem faced by the investigator is the optimal alignment of the amino acid sequences of the two, or more, proteins. Sequence alignment may be achieved in two ways; either by means of a computer program which considers only the amino acid sequences and the statistics of their substitution frequencies, or by superposition of the three dimensional structures of the proteins where the highly conserved regions of the proteins will superimpose almost exactly. The two techniques frequently give different answers but not usually completely different. The sequence alignment based on an optimal three-dimensional correspondence of the residues is the most important for model building studies. However, the technique is useless if only two proteins are involved; one of known structure and sequence and the second of known sequence only. In this case sequence alignment programs must be used. An effective procedure for alignment on the basis of amino acid sequences is the dot matrix method.

Substitution, Deletion and Substitution via Molecular Graphics. In order to substitute one amino acid for another, the residue to be altered is first pointed out on the graphics screen using a hand held "mouse" and the new residue selected from a menu of possibilities in the same way. The old side chain is then removed and the new one substituted in a similar conformation to the old one. Hydrogen bonds involving the old side chain are conserved in the new, if possible; and new hydrogen donors or acceptors are paired up with existing acceptors or donors, if possible, by means

of scans around the chi torsion angles. Similarly if the new side chain is longer than the old, the undefined chi's are characterized by energy calculations. This whole process is automatic, instantaneous and incorporates a wide range of checks to prevent inconsistent operations.

A residue displayed on the graphics screen is selected for deletion in the same manner as selection for substitution. The atoms comprising the selected residue are then deleted and the polypeptide chain rejoined with a long bond. A special purpose full relaxation energy minimizer is then used to reoptimize the local structure to accommodate the deleted residue. Tests involving known structures have shown that this procedure produces realistic results. The process is more computationally intensive than the substitute algorithm but still takes only a few seconds to run on a modern workstation or a few minutes on a multi-user micro-computer. Like the substitute operation, it is fully automatic and only requires selection of the residue to be deleted. Insertion is analogous to deletion except that the polypeptide chain must be expanded to accommodate a new residue. The point of insertion and the new residue are selected as before, and a special purpose energy minimizer used to adjust the local geometry to accept the new residue.

Enzyme/Substrate Docking. As with protein model building, there are several approaches to docking, dependent on the amount of experimental data available. The ideal is to start from a crystal structure of the enzyme containing a good inhibitor. The key electrostatic interactions, hydrogen bonds, salt bridges and hydrophobic contacts between enzyme and inhibitor are then defined and serve as a starting point for the design of even better inhibitors. In the absence of a crystal molecular structure, modeling must be used in an attempt to characterize the key enzyme inhibitor interactions.

The molecular modeling system will provide some way of indicating short intermolecular contacts and favorable hydrogen bonding situations. An automatic docking procedure is then used which executes multiple calculations beginning with a rigid inhibitor in random or operator defined orientations in space. The docking program "learns" as it goes along in that initially the inhibitor is allowed to pass through the enzyme model to reach the active site. When the active site is reached an optimization procedure orients the inhibitor in such a manner as to minimize the calculated energy of the enzyme/inhibitor complex. When convergence has been reached with the rigid inhibitor, user designated torsion angles are optimized as well to reduce the energy even further. At this point a number of low energy enzyme/inhibitors are available and then may be manually optimized to climb over local energy barriers that the computer program cannot deal with. White and his group have recently developed a procedure which allows realtime, on-the-fly calculation of the intermolecular potential energy as a function of all of the interactions concerned to optimize the docking method.

NMR and Protein Conformation

K. Wüthrich, Institute for Molecular Biology and Biophysics (ETH), Zurich, Switzerland spoke about the nuclear magnetic resonance (NMR) approach to studies of biological macromolecules. The application of NMR to such studies is of very recent origin. With the use of two-dimensional experiments, NMR has become the first technique applicable for determination of three-dimensional biopolymer structures in solution and other non-crystalline states. Also, NMR can provide detailed information on the molecular dynamics and on intermolecular interactions which cannot be optimized with other presently available methods. For the practicing biologist and biophysicist the results obtained by NMR represent an important compliment and extension of structural data from single crystal x-ray studies.

Present NMR studies of macromolecular structures are based primarily on three recent developments: (1) two-dimensional spectroscopy improves the resolution of highly complex NMR spectra and efficiently delineates networks of scalar coupling and dipole-dipole couplings which may extend over the entire molecule; (2) new strategies for studies of proteins and nucleic acids enables the individual NMR lines to be assigned to distinct nuclear spins in the macromolecules; and (3) new concepts have been developed and implemented for determination of the spatial structures of polymer chains from data on scalar and dipolar couplings between nuclear spins.

Overall, the success of a NMR project depends critically on obtaining numerous resonance assignments for distinct, individual spins. These represent the basis for spatial structure determination, as well as for studies of the molecular dynamics and of intermolecular interactions. The latter may include projects relating to timely topics, such as nucleic acid-drug interactions in e.g., cancer chemotherapy, or

regulation of protein and nucleic acid functions by specific interactions with low molecular weight effectors or with other macromolecules. The use of NMR has already opened new avenues into structure-function correlations with biopolymers.

In addition to its use in basic research, NMR finds technical applications in the evaluation of the action of drugs and for product control in the production of proteins by genetic engineering or by chemical methods. With regard to these practical applications, it is encouraging that NMR is a particularly powerful method for comparative studies of groups of related molecular structures. For example, once the NMR spectra of a particular protein have been analyzed, the investigations may be efficiently extended to homologous proteins. Following the results previously obtained for the parent compounds, sequence-specific resonance assignments and identification of the regular secondary structure may then typically be obtained within a few days. For some pertinent references see Haval and Wüthrich, 1985; Williamson, Havel and Wüthrich, 1985; Kline and Wüthrich 1985; and Wüthrich, 1985 at the end of this article.

Crystallography

The impact of x-ray analysis of protein crystals on biochemistry has been fundamental. The principles of protein and nucleic acid structure have been established and unsuspected evolutionary relationships have been discovered. Enzyme catalysis is being investigated as a structural as well as a chemical event. The structural basis for allosteric or cooperative behavior and electron transport are being studied. With the knowledge of the protein's molecular structure site, specific mutagenesis becomes a directed and intelligent technique. These developments are very important for protein crystallography: it is transformed from a largely descriptive science to one which, when coupled with mutagenic experiments, can investigate and probe protein functions.

G. Dodson, University of York, UK, presented a detailed lecture on the determination of protein and enzyme three-dimensional structure using x-ray crystallography. Dodson also discussed several important developments in protein crystallographic methods which have significantly extended the capacity to determine crystal structure: molecular replacement methods; and the use of high intensity x-ray radiation from synchrotron sources. The molecular replacement method is a technique which allows phase determination via the exploitation of crystallographic symmetry. Three of the most spectacular examples of the use of his method are the study of the structure of haemocyanin whose molecule exhibits 6-fold symmetry and the cold and polio virus analysis with 30-fold local symmetry. However, initial molecular replacement calculations failed to produce a sufficiently accurate set of phase angles for useful structural analysis. With increasing knowledge of protein structures this method has been modified so that it utilizes this knowledge to calculate estimates of the phase angle. For a review of this method see Machen, 1985.

The other recent development is the use of high-intensity x-ray synchrotron sources. This method allows the collection of diffraction data in a fraction of the time spent on conventional x-ray generators. Photographs, which under normal conditions need several hours of exposure can be taken in several minutes. Secondly, synchrotron radiation is emitted as a continuous spectrum. By selecting x-rays of appropriate wavelengths it is possible to explore anamalous dispersion which in principle eliminates the need to analyze more than one heavy atom derivative.

Hajdu et al., Laboratory of Molecular Biophysics, University of Oxford, UK presented studies on catalysis with glycogen phospharylase b using these new advancements in x-ray crystallography while J.R. Helliwell, University of York and SERC Daresbury Laboratory, UK spoke at length about applications of synchrotron radiation (SR) to protein crystallography. Helliwell, one of the developers of SR, pointed out that this method is speeding up structure determination by overcoming technical problems as well as opening up totally new avenues of structural studies.

The intensity of the focused, tunable monochromatic beam on the Daresbury SR's wiggler is in excess of three to four orders of magnitude more than a conventional source and is used to overcome problems of weak scattering and of radiation damage measuring vast quantities of high resolution data and studying large unit cells. Also feasible are tunable methods for the location of metal atoms and phase determination. The focused white beam from the SR's wiggler offers even more intensity and is used in kinetic crystallography studies of enzyme catalysis and diffraction from very small sample volumes. Also, diffuse intensities are easily measurable with tightly collimated SR and may well be of future aid in studies of protein structure dynamics.

The UK Initiative in Protein Engineering

This topic was presented by D. Yarrow, Science and Engineering Council. A meeting was held in London in 1983 at which academic scientists, then active in fields relevant to protein engineering, gave an account of current work and future plans to an audience comprising representatives from a wide range of companies. At this meeting there was general agreement that protein engineering was an emerging area of science of considerable commercial potential, but in which much fundamental research needed to be done to elucidate structure/function relationships. It was believed that this was an area of pre-competitive research in which companies could usefully benefit from collaborating in the development and funding of a core program of protein engineering research at academic institutions.

The intention was that once a company had developed its ideas and thinking, perhaps based on results of the core program, to the stage where it could identify achievable commercial objectives, it would work on target proteins in-house or through one-to-one contacts so to retain confidentiality. In the early part of 1984, the Biotechnology Directorate of the Science and Engineering Research Council (SERC) entered into a discussion with a number of companies to meet the protein engineering needs of industry. However, it was intended that the SERC program should relate closely with the work of other research councils such as the Medical Research Council (MRC). Companies interested in developing the concept of a core program were invited to join with academics nominated by SERC to form a Program Definition Group. This group drew up a project definition for the core program.

A program steering group was appointed as well as a program manager who was responsible for the coordination of the activities of the academic groups and to ensure effective transfer of information to companies. Within the Research Council System, the Program Definition Group has been able to pull together a community of researchers from different disciplines, and to establish a mechanism for the coordination of their activities and the transfer of information to companies. Support for the program launched early in 1985 has come from the SERC and industry.

The projects in UK Universities currently supported under the above program, Phase I are:

- Bribeck College--structure production
- Leeds University--methanol oxidase
- Bristol University--heat stability in enzyme systems
- Oxford University--antibody engineering
- York University--enzymes involved in antibiotic production
- Imperial College--subtilisin, glucose ismerase
- Sheffield University--studies of crystallization

Further projects will be added to the program during the next twelve months.

Conclusion

The First International Congress on Protein Engineering emphasized the increasing importance of this new area of biotechnology both in basic and applied research with a tremendous potential for the latter. Recent advances in techniques applied to protein engineering such as site-directed mutagenesis, molecular graphics, use of NMR for analysis of protein structures and improved x-ray crystallography methods using molecular replacement and high-intensity x-ray synchrotron sources were presented in detail by top researchers in these areas. A member of the Scientific Research Council of the UK presented a program of university/industry collaboration in protein engineering which was organized in 1984 and funded jointly by these two groups.

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1/6/86

Material Sciences

ÉCOLE des MINE de PARIS--FRANCE'S PREMIER ACADEMIC CENTER FOR MATERIALS RESEARCH

by Kenneth D. Challenger. Dr. Challenger is the Liaison Scientist for Materials Science in Europe and the Middle East for the Office of Naval Research's London Branch Office. He is on leave until May 1986 from the Naval Postgraduate School, where he is Associate Professor of Materials Science.

The École des Mine de Paris (EMP) is small, approximately 300 students, but is the premier French educational institution for graduate studies in materials science and related fields (such as mining, chemistry, geology and mechanics). It is by their own estimate one of the three top "Grandes Écoles" in France. A graduate from this institution is assured one of the top jobs in industry, government, or education. The number of applicants per year far exceeds the admission quotas; for example, 64 students were selected out of 4000 applicants in 1980. The normal annual enrollment now is about 100 new students per year.

Research is new to EMP. EMP was founded as a teaching institution over 200 years ago, but only in the last 15 years has research become an important aspect of its activities. Due to space limitations in Paris, some of the new research laboratories have been built outside Paris at Fontainebleau, Evry, and Valbonne.

The administrative structure of EMP was too complex to handle research contracts with industrial firms, so a foundation-like organization, ARMINES, was established for that purpose in 1967. Today ARMINES handles over 1700 research contracts with a total amount of over MF100 (about $13 million). The Ministry of Industry supplies about 55 percent of the operating funds to EMP; the rest comes from ARMINES through the many research contracts.

The research center with the largest portion of ARMINES support (11 percent of the total research budget) is the Centre des Matériaux located inside the SNECMA (France's gas turbine manufacturer) plant in Evry (approximately 15 km south of Paris). Forty-five permanent staff and about 50 students are performing the research in this center.

I visited the Centre de Matériaux (CDM) with the prime objective of reviewing their research on composite materials. However, during the visit I had the opportunity to meet with researchers from some of the other research groups at CDM. This article will review, albeit in a cursory fashion, some of the research activities at CDM that are relevant to the US Navy research activities; a later article will focus on the details of their research activities on composite materials.

The Research Groups at the Centre de Matériaux

Some outstanding research is being performed by the researchers at CDM. The research activity is divided into eight groups: Powder Metallurgy (Yves Bienvenu); High Temperature Deformation (Jean-Loup Strudel); Microstructure-Mechanical Property Correlations (Luc Remy); Mechanical Metallurgy (André Pineau); Numerical Simulation (George Cailletaud); Surface Corrosion (Jean-Paul Henon); Composites (Anthony R. Bunsell); and Ceramics (Daniel Broussaud).

Powder Metallurgy

This research activity involves considerable interaction with the SNECMA engine group located in an adjacent building. Most of the research involves the characterization of nickel-base metal powders to be used in gas turbine high temperature components. The relationships between the powder characteristics and the densification processes used to bond these particles together are studied. Normal sintering mechanisms, liquid phase sintering mechanisms, and the mechanisms of densification during hot-isostatic-pressing (HIP) and hot-unidirectional pressing (UDP) are under investigation. This group does not make their own powders but receives them from the same sources that SNECMA uses for its gas turbine components.

One recent study examined the effects of the powder characteristics on the HIP behavior of low-carbon astrology, a heavily alloyed nickel-base alloy used in the hot sections of gas turbines. The structure of rotating anode and argon atomized powders were characterized and found to include many different morphologies (due to collisions between the particles themselves and with the container walls during solidification). The powders produced by the rotating anode methods densified more slowly. This was attributed to a more uniform particle size, the absence of easily deformed splat zones, and a coarse-grained dendrite structure. Room temperature hardness does not correlate well with the behavior during consolidation since the room temperature hardness is probably closely related to the γ' distribution and γ' is unstable at the consolidation temperature; hence, the grain size probably dominates the deformation characteristics during consolidation.

The chemical analysis of prior particle boundaries has been carefully determined by microchemical analysis techniques. Transmission electron microscopy, scanning transmission electron microscopy with X-ray microanalysis, and auger scanning microscopy have been carried out. Solid state sintering and the final mechanical properties of the consolidated powders depend strongly on the precipitation and segregation at these prior particle boundaries. Bienvenu and his colleagues have found that argon-atomized powders have a greater segregation of C and Ti on their surfaces than do powders produced by the rotating anode method. An intermediate degassing stage at 350°C for 24 hours prior to the first sintering step reduces C, Ti, O, and S on the particle surface, and a heat treatment of 1120°C for 2 hours at a pressure of 1 Pa before HIP was found to further reduce the final concentration of these elements on the prior particle boundaries.

These studies and similar studies on the 7XXX aluminum alloys are in progress. Publication of the results is generally restricted due to Bienvenu's close collaboration with SNECMA. The research is very important and is contributing to the improvement of gas-turbine components by increasing the understanding of the micromechanisms responsible for the mechanical properties of these high performance powder metallurgy materials.

Mechanical Properties

A. Pineau and his colleagues have been important contributors to the development of fracture mechanics as applied to creep, fatigue, static, and dynamic fracture for many years. Most of his work has been associated with the nuclear power industry in France and thus the materials and problems that he has studied are centered on the materials used in electrical generating power plants. This research group is very active and has significant publications in all of the above mentioned fields. Some of the most significant results include: (1) the development of a fracture mechanics approach to creep crack growth that separates the initiation stage from the creep crack growth stage; (2) the development of a fracture criteria,

termed the local ductile fracture criteria, which can also be used to describe fracture in the cleavage and the ductile to brittle transition temperature ranges; and (3) the development of an effective stress intensity factor to describe the crack growth behavior of "short" cracks (*ESN* 39-12, 558, [1985]).

Pineau's largest program at present is the evaluation of methods to describe the arrest of cracks in A508 steel which are propagated by stresses caused by the presence of a thermal gradient. This is a major program and is worthy of continual attention.

Composites

Since this research will be reviewed in detail in a later article I have only listed the current activities without discussion or detail.

The research by A. Bunsell could be classified as fundamental, but it fits the needs of the French industry. About 20 years ago France decided that it was falling behind many other countries in the technology of composite materials. They perhaps started too soon because the initial efforts were spent on developing boron fiber reinforced metals. Then carbon fiber technology was developed and essentially leap-frogged the boron fiber reinforced materials leaving the French with a large investment in an outdated technology. I believe the reason that the French now are increasing their activities in the metal-matrix composite field is because researchers in the US are active and the results are not being released. (So there must be something good in these materials!).

The French rocket engine manufacturers made a strong plea to the government to develop carbon-carbon composites, and these materials are now at a very advanced stage of development in France. (Several companies are capable of weaving very complicated shapes with the carbon fibers).

The present research at CDM focuses on the characterization of the properties of single fibers; carbon, polymer, glass, aramide, SiC and Al_2O_3 fibers are being studied by all standard microscopic and chemical analysis techniques. In addition, Bunsell has a unique mechanical testing facility for creep and fatigue testing of single fibers in a temperature range of -150°C to 1600°C. The relative humidity can be controlled for tests in the RT to 100°C temperature range. The most exciting research is just beginning; SiC bundles (approximately 500 fibers) fabricated into an Al metal matrix as 0.5 mm diameter wire are being characterized (this is a collaborative program with Nippon Carbon).

Bunsell's work and facility for testing single fibers is unique and should be considered for collaboration with the US.

Ceramics

This is a large program at CDM; it is focused on the reinforcement of ceramic matrices with both discontinuous and continuous fibers. Woven continuous SiC fibers in an SiC matrix are under study as are many other combinations of materials. The emphasis of the research is on the fabrication techniques for materials that will be used in gas turbines and automobile engines and on the resulting mechanical properties of those materials. Unfortunately, the people that I planned to visit for details of the ceramics programs were not available during my visit. However, this research may be one of the leading ceramic research programs in Europe, I will attempt to make another visit to CDM specifically to discuss the ceramics program.

Numerical Simulation

George Cailletaud is the head of this group. He does only a small amount of research of his own but is very actively involved in a support role in the research of the other groups. For example, constitutive equations are being developed in collaboration with Pineau and Strudel; models for fiber-matrix interaction in composites are under development with Bunsell; and models of the mechanisms for the densification of metal powders are being developed with Bienvenu. This simulation group is only two years old, but it appears to be respected and used to a large extent by the other groups.

Summary

The research at the CDM seems to be the most important in France for the development of advanced materials. The researchers are performing both fundamental and applied research. The fundamental research is closely linked to the needs of French industries. The center is small, but it attracts the best students and faculty in France. It is a research center where improved communications with US researchers would definitely be mutually beneficial.

12/3/85

Mechanics

EUROMECH 199--EDDY SIMULATION OF TURBULENT FLOWS

by Eugene F. Brown. Dr. Brown is the Liaison Scientist for Fluid Mechanics in Europe and the Middle East for the Office of Naval Research's London Branch Office. He is on leave until September 1987, from the Virginia Polytechnic Institute and State University, where he is a Professor of Mechanical Engineering.

EUROMECH 199--Eddy Simulation of Turbulent Flows was held at the Technical University of Munich, Munich, West Germany, on 30 September through 2 October 1985. Approximately 60 scientists were in attendance with the majority of participants being from West Germany. There were a total of 31 presentations at this meeting. In this article, I have chosen to report on nine papers which seemed to me to be the most significant.

The presentations were devoted to simulating boundary-layer and free shear flows by both direct and large eddy simulation (LES). Both methods involve the solution of the Navier-Stokes equations. They differ in the manner in which these equations are solved. The direct simulation approach uses meshes of extremely fine resolution in an attempt to simulate the turbulence of even the finest scale. In the large eddy simulation approach only the large-scale turbulence structures are calculated by the Navier-Stokes equations. The effect of the small-scale (subgrid scale) turbulence (that is, the presence of eddies smaller than that which can be resolved by these calculations) is modeled by means of empirical correlations. The advantage of the LES technique is a significant reduction in computational time. The disadvantage is that the proper modeling of the subgrid structure is not always clear, particularly for non-isotropic turbulence.

It is widely accepted that near-wall coherent structures play a major role in production and control of turbulence. The nature of these structures, however, is less clear. Three types of turbulence structures have been identified experimentally; these are: (1) hairpin vorticities, (2) elongated sublayer vorticities, and (3) ring vortices. Work presented at the meeting by P. Moin (National Aeronautics and Space Administration [NASA], Ames), based upon an examination of several direct and large-eddy simulation calculations, indicated that the nature of the turbulence structures can be described by the presence of the hairpin vortices alone. This he determined from a detailed numerical analysis of the results of the simulations. These vortices appear in the boundary layer with their heads projecting up into the flow at an angle of about 45 degrees and the legs bent and lying in the plane of the flow, pointing upstream (Figure 1). These hairpins are formed from the roll-up of sheets of span-wise vorticity by random velocity fluctuations and their subsequent stretching by the mean strain rate. The simulations provide a transverse regularity very close to that measured in the experiments. Elongated vortices which are often proposed as the dominant sublayer structure, were, in fact, not observed in the simulations which were examined. It was speculated that the elongated vorticities observed by others might only be the "footprint" of the legs of the hairpin vortices.

By using the eddy decomposition theorem, it was found that 30 percent of the turbulence kinetic energy and 70 percent of the Reynolds shear stress were produced by the coherent structures. In addition, from examining maps of the turbulence structure, it was found that without exception each region of high Reynolds stress was associated with the presence of coherent structures.

Those observations were supported by a direct simulation of a wall-bounded shear flow presented by J. Kim (NASA, Ames). Two million grid points were used in the calculation, which was checked with a four million grid point calculation in order to check grid insensitivity. The grid was stretched in the vertical direction. This produced a mesh that varied from 0.05 to 4.4 wall units (y^+ units) across the boundary-layer. In the stream-wise direction the spacing was 18 wall units; in the transverse directions, 6 wall units. The coarse mesh calculations required approximately 20-30 hours on a CRAY XMP.

The evolution of the large-scale turbulence structures depends on the frequency and phase of any perturbations which are present. R.W. Metcalfe (Flow Research, Kent, Washington) presented his pseudo-spectral calculations which showed the effect of perturbations of different spatial orientation, frequency, and phase on the energy spectra of the turbulence. In some cases it was

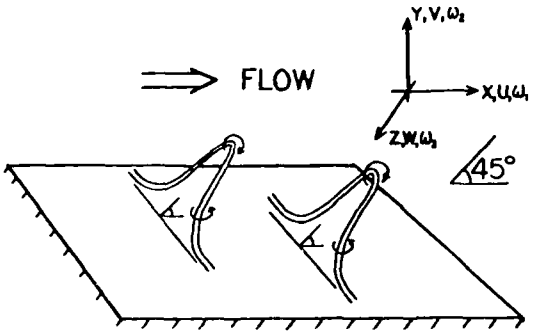


Figure 1. Hairpin vortices.

found that the paring process is stimulated by these disturbances. In some cases the paring process is suppressed. The inhibited paring surpresses vortex breakdown, as well, and results in a decreased growth of the mixing layer. In such cases the initial coherence of the flow is retained for a very long time.

U. Schumann (Deutsche Forshungs- und Versuchsanstalt für Luft- und Raumfahrt [DFVLR], Oberpfaffenhofen) presented the results of his LES calculations which were directed toward examining the effects of buoyancy on turbulence structures. The finite difference method which was used employed second-order, finite-difference approximations in space and time on a staggered grid. A small section, comprising perhaps 20 percent of the boundary layer, was selected for computation. Based on this computational volume, the Reynolds number was approximately 58,000. Reasonable agreement with experiment was obtained. The calculations required approximately 11 hours on a CRAY 1S.

The Smagorinsky model is frequently used for subgrid scale modeling, but this model is by no means universal. An alternative model is the one-equation model. Such a model was described by K. Horiuti (University of Tokyo, Japan). The model is an improvement on a one-equation model first used by Schumann. It was found that similar results were obtained with both the Smagorinsky and the one-equation models; however, significant differences were discovered in the distribution of the two point spanwise correlation. The reason for this difference is currently being explored. The use of the conservative form of the Navier-Stokes equations caused a substantial effect on the calculations; when the nonconservative form was used, considerably different results were obtained. The calculations were carried out on a HITAC S-810 computer at the University of Tokyo. Horiuti's experience was that reasonable results could be obtained from his calculations, even though the mesh was relatively course (32^3).

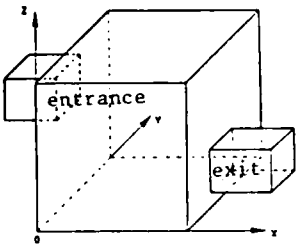
T. Kobayashi (University of Tokyo, Japan) described his calculations of turbulent plane Couette flow using LES. He too used a relatively course mesh. The Reynolds number was 50,000. He found that for the prediction of mean velocity profiles, LES did much better than the conventional k-ε calculations. In addition, he found that his LES results were equivalent to the direct simulation results for the velocity distribution but compared unfavorably with the turbulent intensity. Both conventional Couette flow and a case with rectangular corrugations on the stationary wall were run.

D. Laurence (Electricité de France, Chatou) presented his LES calculations for the flow through a cubical cavity. The geometry is shown in Figure 2a, and the results, in the form of the local velocity vectors, are shown in Figure 2b. This was one of the few calculations to attempt a solution of a complex flow configuration. He used a finite element/split operator approach. In order to enforce the periodic boundary conditions, a staggered mesh employing a translating grid was used. Careful attention was given to the manner in which each of the terms in the governing equations was modeled. I had the impression that this was first-quality work. I will shortly be visiting with Laurence to learn more about his calculations.

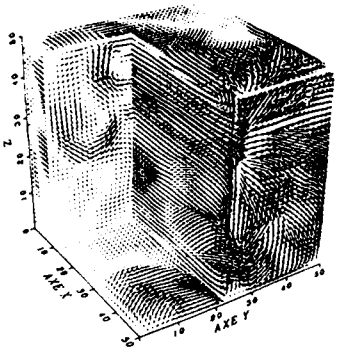
Almost all papers were devoted to fully developed turbulence. T. Herbert's paper (Virginia Polytechnic Institute and State University) entitled *Vortical Mechanisms in Shear-Flow Transition* was an exception. The ultimate goal of his work was to unravel the phenomena of turbulence transition. Herbert's calculations (beautifully demonstrated with a movie) used linear stability theory to:

- Explain and predict three-dimensional routes to turbulence,
- Reveal mechanisms and generic properties of transition,
- Understand feedback loops leading to turbulence, and
- Predict lower limits of transition to turbulence.

L. Klyser (DFVLR Gottingen) was concerned with the nonlinear aspects of



a.



b.

Figure 2. Confined turbulent jet simulation: (a) geometry; (b) computations.

vortex breakdown which are present in the later stages of transition. In particular, he investigated both the classical and subharmonic types of transition mechanisms. In his solution of the three-dimensional, time dependent, Navier-Stokes equations he reversed the spacial and temporal roles by creating a time periodic flow by moving the frame of computational reference with respect to the Tollmien-Schlichting waves. By properly exciting the flow (both in phase and amplitude) it was possible to produce both types of transition as well as suppress the transition mechanism if such control were applied early enough in the transition process.

In his summary comments Schumann emphasized the need for careful treatment of the boundary conditions in all turbulence simulations. Proper treatment of boundary conditions is essential in the accurate simulation of all flows, but in turbulent flows it takes on a special significance because of the well-known exponential growth of small disturbances which occurs there. Use of recent turbulence research to more accurately specify boundary conditions at the walls and inlet will improve the accuracy of turbulence simulations. A point made by both Schumann and, later, by W. Rodi (University of Karlsruhe, West Germany) was that it is time to be moving on toward more engineering rather than research-oriented calculations. Rodi in particular felt that the turbulence simulation community should do more by way of providing information on pressure fluctuations and length scales. These are quantities which turbulence modelers could use to develop affordable computation schemes for calculating flows of engineering importance.

11/29/85

FLUID MECHANICS RESEARCH AT THE UNIVERSITY OF MANCHESTER INSTITUTE OF SCIENCE AND TECHNOLOGY

by Eugene F. Brown.

Last fall, I visited with members of the staff of the Thermodynamics and Fluid Mechanics Division, which is part of the Department of Mechanical Engineering of the University of Manchester Institute of Science and Technology (UMIST). The division is headed by Professor Brian E. Launder who is well known for his work on the numerical modeling of turbulent flows.

The division is fortunate to have access to the University of Manchester's Regional Computer Center for its large-scale computations. Two CDC 7600s and a CYBER 205 supercomputer are located at the Center. These facilities are readily available to the students and staff of the Division. Computing time is made available through funds supplied by the UK's Science and Engineering Research Council (SERC). Additional computer time may be purchased through research contracts which the division has with various industries and government agencies.

Launder has just completed a 5-year ONR research contract which was devoted to experiments and computations on turbulent flow and heat transfer in square- and circular-sectioned U-bends. In addition to providing a comparison with Launder's calculations, this data should prove useful in future studies involving the assessment and development of computer codes for the prediction of complex three-dimensional flows.

An interesting feature of the square-sectioned flow brought to light by the experiments was that the heat transfer coefficient on the concave wall is only about twice that on the convex

wall at the mid-plane position halfway around the bend. A much greater variation had been expected because of the small radius of the bend. This confirms that estimates of the effects of large perturbations on turbulent shear (which occur here) cannot be inferred by linearly extrapolating the effects of small perturbations (which typified previous investigations). For these measurements, a high-accuracy, balance-type heat flux sensor (Figure 1) was constructed which allowed measurements to be made without the disturbing effects produced by the more common temperature gradient or transient methods.

An interesting feature in the circular-sectioned experiments was the breakdown of the classical single cell recirculating flow structure into a kidney-shaped vortex and a weak secondary vortex. In particular, the cross-stream flow undergoes a second reversal in its sense of motion and becomes redirected toward the pipe's inner radius. As a result, a region of negative cross stream flow (directed from the inner to the outer radius) is trapped between the core and the wall.

As far as the computations were concerned, the square-sectioned case was troublesome. Serious disagreement existed between the experiments that were contributed by Professor J.A.C. Humphrey's group at the University of California, Berkeley and Launder's calculations. Despite the fact that the equations look less complicated for the square-sectioned case than for the round-sectioned case, the former is undoubtedly much more complicated, both physically and experimentally. The structures are very different in what superficially appear to be two very similar flows. For the circular-sectioned bend much better agreement was obtained.

A new parabolic sublayer wall treatment was developed for the computations. It allows the use of a finer grid near the wall region without any significant increase in the storage requirements or any additional penalties as far as the convergence rate is concerned.

In attempting to resolve the difficulties experienced with the square-sectioned case, a modification of the source term in the dissipation rate equation was undertaken. Suggestive improvement was observed in the computations at some locations, but overall the computed flow pattern cannot be said to be any better than when the "standard" modeling was employed. However, the computations at least demonstrated that the level of numerical diffusion in the

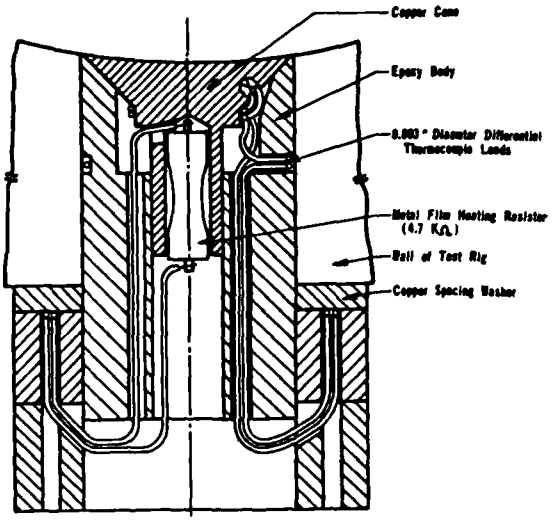


Figure 1. Heat flux sensor.

modeling was sufficiently low that the predicted results showed an undeniable sensitivity to the turbulence model being employed. The results of this work are described in UMIST Report TFD/85/5(R), *Computation of Flow and Heat Transfer in Flow Around a 180° Bend* (October 1985).

Work is now under way to reveal the source of the discrepancies discovered in the square-sectioned calculations. Experiments are also being conducted to measure the effect of thinner entrance boundary layers and to provide data at low Reynolds numbers (less than twenty thousand).

Michael Leschziner, a lecturer in the division, is involved in the modeling of a wide variety of fluid mechanics problems ranging all the way from classical, two-dimensional, parabolic shear flows to three-dimensional, unsteady, recirculating flows. The applications of his work include multi-element airfoils, rocket plume mixing, loss coefficients in engine exhaust systems, and the characterization of fuel/air mixing in diesel engines. For complex geometries he has developed orthogonal, quasi-orthogonal, and matching non-orthogonal grids utilizing a zonal approach to combine regions of different geometrical shape. In order to control the amount of numerical diffusion he uses the QUICK variation of the traditional TEACH algorithm and has employed both algebraic stress and algebraic-flux turbulence models.

Finite element calculations are being carried out by Philip L. Betts,

who is a senior lecturer in the division. Originally he adopted the finite element method because of its facility for treating surface wave phenomena. The turbulence models contained in Betts' code include both an anisotropy-corrected k-ε model and a simplified algebraic stress model. This contrasts with many other finite element codes which are relatively crude with respect to the sophistication of their turbulence modeling. His code makes use of the Balancing Tensor Diffusivity correction technique in order to overcome the severe time-step stability restrictions of the forward Euler method in regions of high advection. Betts has developed finite element solutions for a number of fluid mechanics problems including turbulent natural convection in tall cavities, the backward-facing step problem, and the simulation of buoyancy effects in the atmospheric surface layer.

Andrew J. Yule joined the division in 1981. Dr. Yule, under SERC funding is characterizing the large eddy structures in the far downstream region (greater than twenty diameters) associated with both free and confined jet mixing. For these measurements he is using an array of crossed hot-wire probes. An important component of these experiments is the careful measurement of the inlet boundary conditions. Such data is especially valuable to computational fluid dynamicists who are often frustrated in their attempts to simulate such flows because of a lack of this information. The jet velocity used in these tests ranged from 25 to 50 m/s. Current descriptions of the mixing phenomena regard it as being a combination of gradient diffusion and intermittent bulk convective effects. The information gathered in these tests should be useful in developing two-scale mixing models.

Summary

The work being conducted at UMIST represents a very satisfactory balance between fundamental and applied research. It is clear that Launder's division is capable of both computational and experimental research of the highest quality. The high caliber of his faculty and the availability of the University's enviable computational resources and technical support staff will assure for UMIST a leading role in fluid mechanics research in the years to come.

11/25/85

Physics

ADVANCED LASER DEVELOPMENT AT THE CLARENDON LABORATORY

by Paul Roman. Dr. Roman is the Liaison Scientist for Physics in Europe and the Middle East for the Office of Naval Research's London Branch Office. He is on assignment until September 1987.

In the last decade the Physics Department at Oxford University's world renowned Clarendon Laboratory has built up a medium-sized, high quality, enthusiastic, and enterprising laser development group. Specialties of this group, led by Professor C.E.W. Webb and his equally experienced assistant, Dr. T. Andrews, are the development and improvement of gas- and metal-vapor lasers. As is now increasingly more frequent in England with basic research that has a high probability of rapidly developing into devices with considerable industrial potential, the university research group is closely linked with a medium sized company, called Oxford Lasers. This company, which has foreign representations and now employs over 20 engineers and scientists, was founded by Webb and three other physicists in 1977. At that time he realized that the years' work he did on developing efficient N_2-lasers was without avail to his and his colleagues' future research potential. Because of the lack of an R&D oriented backing company, he simply had to give away the basic system for free to any other university research group which wished to use it. Moreover, once he helped a research group to build one of his N_2-lasers, they kept calling on his department to assist them with maintenance. So, running projects "the old way" became impractical; hence the foundation of Oxford Lasers.

Excimer Lasers

The first notable success of the Clarendon--Oxford Lasers cooperation was the development in 1978 of highly efficient, compact, wall-plug operable KrF (and other rare gas-halide) lasers. Apparently, these were among the first in the world that, instead of electron-beam excitation, used simple gas discharge pumping. This product line has been greatly enlarged now and the latest result is a single multigas excimer laser system that, using different gases (from F_2 through ArF to N_2^+ and atomic F, or

even CO_2) can operate between 157 nm and 10.6 μm on eleven main wave- lengths. The device uses a unique transverse discharge system where pre-ionization is supplied by the spark-connection of the high-tension feed to the capacitors. Since, upon request, I can supply detailed technical specifications of this system, I will not go into details; instead I will describe in the next section the current focus of activities centering on metal vapor lasers.

Metal Vapor Lasers

It is quite instructive to follow the history of how Webb's group developed frontline elemental copper vapor lasers.

Initial efforts aimed at producing the copper vapor from the dissociation of some copper compound (such as a Cu-halide): a double-pulse transverse discharge pumping was needed, the first pulse doing the dissociation, the second pumping the copper atoms. The 500°C evaporation temperature proved impractical; using $CuNO_3$ reduced this to 200°C, and using various Cu-organic molecules indeed did not require any external heating at all. However, to achieve high repetition rates, the pumping had to be pushed to such high levels that again the device operated at a much too high temperature. This gave the researchers the obvious "great" idea: since high temperatures cannot be avoided, one might just as well work with elemental copper to start with, even though the evaporation temperature is high and, to achieve good efficiency, the operating temperature must be kept at about 1500°C. The copper powder is just "spoonfed" into the tube in little heaps. The buffer gas, neon-plus-helium, maintains an axial dc discharge. The Ne^+/He ratio can be used to regulate the green/yellow spectral intensity ratio of the laser beam.

Of course, working at such high temperatures required the solution of grave technical problems, including appropriate sealing and the upholding of a very hot region in a substantial section of the tube. The details of the system are not within the scope of this article, but I think it is worthwhile to reproduce here the laser tube configuration (see Figure 1).

Now the unusual features of this laser are described. The average power output is 70W, for a repetition rate between 7 and 8 kHz. If a higher, 25 kHz repetition rate is required, the power still stays up at the 20W level. One gets about 10 mJ energy delivered per pulse. The duration of a pulse can be adjusted to fall between 70 and 10 ns.

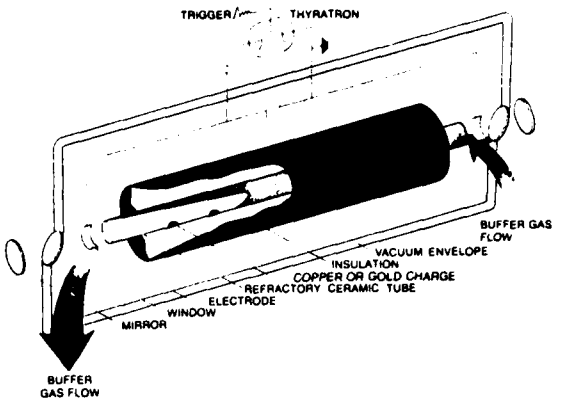


Figure 1. Metal vapor laser tube configuration.

Thus, the laser has a peak power of several hundred kilowatts. Only regular 220 V mains power-connection is needed, and the plug-to-laser light efficiency is 1.5 percent. This high efficiency and the high power output make the copper laser eminently suitable for dye laser pumping and subsequent tunable frequency doubling. Of course, the Cu laser output may be also used directly for frequency doubling experiments. (Since the two Cu laser frequencies are 510 and 578 nm, in this way efficient ultraviolet laser light can be obtained.) Combination of high power and high repetition rate make other advanced applications feasible: such as high speed photography (with frame cameras or streak cameras), and high brightness, large screen TV displays. For many of our readers, another application will seem even more attractive: the use for significantly improved laser ranging. In this application, apart from the high power and very high repetition rate, the controlled presence of two (yellow and green) wavelengths is an additional bonus.

The next step of metal vapor laser development concerned itself with the use of other metals. First, the scientists developed an elemental gold vapor laser, using the very same plasma tube as for the Cu laser. The optimal active zone operation-temperature is not much higher: it is around 1600°C. With this device, a recent world record was achieved, namely, an output power of over 15W, still at over 10 kHz repetition rate. In this case, the output is not so evenly distributed between the two laser lines: the 628 nm red line carries perhaps 8 or 9 times as much power as the 312 nm ultraviolet line.

A brochure, entitled "Copper and Gold Lasers" is available from Oxford Lasers (60/62 Magdalen Road, Oxford, OX4 1RD); it describes many additional details of the Cu and Au laser systems. It also mentions that the system may be used with Mn, Pb, and Ba. But presently, the Webb group is directing much of their effort to developing a strontium vapor laser (main line in the blue region). In addition, they are expanding additional effort on achieving not only higher powers for the Cu and Au lasers, but also a better beam quality--so far a somewhat neglected aspect.

Yet another currently studied innovative topic with metal vapor lasers is the development of laser tubes that can operate on a simultaneous filling with different metal vapors and thus produce a multispectral output. So far good results have been achieved by a system that contains both gold and copper vapors (and thus, produces, essentially, a yellow, a green, and a red laser radiation). The new discharge tube has provisions for keeping the two metals in separate zones along its length. By careful choice of the conductivity of the thermal insulator surrounding each of these zones, their temperature can be adjusted separately, so as to achieve optimum vapor pressure for each metal. Mixing of the two metals is prevented by providing a low-temperature buffer zone between the two active regions. The relative output powers of the Cu and Au transitions can be regulated by adjusting the relative length of each of the two zones. With this, still experimental device, the scientists achieved a remarkable power over 1W on each of the three lines simultaneously. Earlier attempts with combined Cu-Au lasers managed only a total output of 17 mW of which only 0.04 mW was on the red gold transition.

The 3-color laser will be particularly useful for applications in multicolor displays and, more importantly, in sophisticated lidar applications. Actually, plans for also including strontium into the vapor combination are underway. If successful, this will lead to a red-yellow-green-blue multilaser.

Novel Vacuum Ultraviolet Lasers

I want to conclude this review of the Clarendon Laboratory Physics Department's laser development work by reporting, very briefly, on an exciting attempt to produce a reasonably high power VUV laser output by some direct method (as opposed to the more conventional approaches that use either frequency upconversion or difficult pumping of, say, hydrogen, right out from its groundstate into some Rydberg state). The project, focus of much excitement and discussed with some proprietary reticence, is based on using the phenomenon of laser induced fluorescence. The basic idea is to use discharge-pumping on some "diatomic molecule" (I suspect, they mean HCl) to get it into a metastable state; then they excite *this* state by pumping with an excimer laser. They already demonstrated efficient production of this laser induced fluorescence; and utilizing several vibrational sublevels, demonstrated the generation of a series of coherent ultraviolet lines from, I believe, 70 to 300 nm. They told me that this process can be scaled up. Soon the researchers also plan to construct a two-pass laser cavity arrangement. The mirrors will be MgF_2-coated Al; but of course, on the exit-mirror a hole must be used for outcoupling.

Conclusion

Webb's group has an interesting history. Its self-supporting industrial arrangement proved a fine source not only for problem-less research-expansion (often enabling the employment of visiting scientists), but also for the attraction of a good number of gifted postgraduate students. The successes and the dynamism of the group bodes well for a fine future.

11/1/85

FREE ELECTRON LASER THEORY AND NOVEL SOLID STATE LASER DEVELOPMENT AT MILAN'S ACADEMIA

by Paul Roman.

Milan, the industrial capital of modern Italy, has a long tradition of both theoretical and experimental university research in the natural sciences. The spirit of Leonardo da Vinci is alive today. There are two major academic centers: the Università and the Politecnico di Milano. In November 1985 I visited the Physics Department at the former and the Center for Quantum Electronics at the latter. Collective variable description of free electron lasers (FELs), quantum theory of high-gain FELs, unusual operational regimes of FELs, and related studies keep Professor R. Bonifacio, the Head of the University Physics Department's quantum-electronics group and his colleagues (about six faculty members, two postdoctorals, and six doctoral students) excited and busy. A few blocks away, Professor O. Svelto's Center of Quantum

Electronics, a Consiglio Nazionale delle Richerche (CNR) supported independent research institute of the Polytechnic University (which is associated with the Institute of Physics and directly employs about 20 researchers, five technicians, and a varying number (about 10) of graduate students) focuses on new concepts in solid state laser development and the general theory and development of CW-pumped solid-state lasers, CW-mode-locking, and femtosecond systems. Electronic instrumentation, development of avalanche photodiodes, single-photon counters with less that 60 ps time resolution, and biomedical-biochemical applications (using argon-laser pumped conventional dye lasers) are also vigorous research areas.

In the following I have selected some activities which personally I found either unusual and front-line research or which, I believe, have special importance for the Navy.

FEL Theory at the University

Ever since the first successful operation of a FEL in the mid-seventies, these devices have been the object of very keen theoretical interest and amazing experimental development. A review of FEL-principles and performance potentials has been given in previous *ESN* articles (see *ESN* 39-9:430 and *ESN* 38-4:206-211).

One of the most exciting aspects of FEL research is to extend efficient operation into the far-ultraviolet and soft X-ray region. In this case (because of high mirror losses) high gain is absolutely necessary to achieve oscillation. Such high gain operation at these short wavelengths appears possible for FELs operating in the Compton mode, even in a single-pass configuration. This, already experimentally verified result, is based on the cooperative instability of the travelling-wave-tube-type, for a FEL process developing from noise. These studies refer to the amplified spontaneous emission regime (ASE). About a year ago Bonifacio and F. Casagrande, using the same idea of instability for a single-pass device, developed the basic concepts concerning FEL operation in a quite different regime, which they call "superradiant" (SR). (Bonifacio told me that he would prefer the word "superfluorescent", a phenomenon discovered by him earlier and which differs from the classical superradiance in that it does not presume the previous preparation of an ensemble where all atoms contribute coherently to a single giant dipole moment.)

The SR regime is defined by Bonifacio in the following way. It can be shown that in the ASE regime the electrons exhibit a strong self-bunching, and the radiated power from N bunched charges is proportional to $N^{4/3}$. On the other hand, according to the interpretation of the FEL process as a many-electron, stimulated compton scattering, one is led to expect that under suitable conditions the peak power should scale as N^2. This is superradiant emission.

Bonifacio and Casagrande, in a contribution to the International Workshop on Coherent and Collective Properties in the Interaction of Relativistic Electrons and Electromagnetic Radiation at Como, in late 1984, demonstrated that the condition for SR operation requires the presence of dissipative effects; these are dominant in a certain short-bunch limit. The physical condition for achieving SR operation implies a high gain over the wiggler length. In addition, the electron bunches must be shorter than a certain, well defined "cooperation length".

Apart from the already mentioned characteristic feature of the SR regime, namely that the radiated power is proportional to N^2, the scientists also showed that the power is also proportional to γ^2, the square of the relativistic factor.

Since the theory of the SR regime FEL is an example of a cooperative phenomenon (where N relativistic electrons, interacting with a radiation field and a strong magnetic pump field self-bunch and radiate proportional to $N^2\gamma^2$), Bonifacio and Casagrande recently turned their interest to a more general study of a collective variable description of a FEL. Apart from this obvious motivation, they also noted that a long-time (i.e., long undulator) analysis of FEL equations in the high-energy regime shows well behaved, nearly periodic undamped oscillations of the radiated intensity, despite the underlying chaotic behavior of the particles. This has further stimulated the scientists to develop a description of the FEL by means of a few relevant collective variables. They want this description to be applicable for the whole dynamical range, i.e., both in the linear and nonlinear range of high-gain FEL amplifiers. Such a description will be analogous to that of conventional lasers which is usually given in terms of a few relevant macroscopic variables. The analogy is, of course, not perfect because, in contrast to "material" lasers which are open systems with a dissipative dynamics, FELs are governed by a basically Hamiltonian dynamics.

In a recently prepared manuscript Bonifacio and Casagrande, in cooperation

with Visiting Scientist L. de Salvo Souza, formulated a collective variable description of FEL. This theory reproduces, for example, the same cubic characteristic equation which rules the instability and the high-gain behavior of the microscopic description. The authors also showed that the collective description determines the build-up time of the radiated intensity (i.e., the time at which the first peak is emitted), as well as the height of the first peak, within a few percent compared to the values obtained from the full set of microscopic equations.

The SR regime investigation of FELs motivated Bonifacio and Casagrande to perform yet another study: the complete quantum treatment of high-gain FELs. A quantum analysis is important because of the relevant role played by fluctuations: large initial intensity fluctuations may lead to large fluctuations of the peak times. The authors, in a yet unpublished manuscript, developed a full quantum treatment which includes the initial stage of the ASE regime, so that it becomes possible to describe the onset of the process, evaluate the effect of the fluctuations on the build-up time, and calculate the power level of the radiation. The photon statistics can also be determined. I think that the essential point in the calculations is the following. Assuming each electron to be initially in a minimum uncertainty wave packet and assuming that the system operates on resonance, the authors succeeded to obtain expressions of the mean photon number and of other quantities that show the onset of the process due to quantum fluctuations of the electron positions and momentum. In case of initially well localized electrons (within a radiation wavelength), the threshold condition for ASE starting from quantum fluctuations turns out to be more severe than the corresponding classical condition. Another outcome of the study is that, in a properly defined limit, the classical results can be recovered in which the source of fluctuations is the electron shot-noise.

Further studies will complete these calculations for the subtleties of the SR regime operation.

Solid-State Laser Research at the Center for Quantum Electronics

The laser research in the Center for Quantum Electronics (which is historically the leading laser group in Italy, operating since the early 60s) has two focal areas: (1) generation of femtosecond pulses, and (2) development of single-mode solid state lasers.

My first comment on the short-pulse generation effort is that, rather innovatively, this is also largely a solid state laser development effort. By this I mean that Svelto's research group emphasized strongly the need for more efficient pumping of the dye laser system that is conventionally used for short-pulse generation. To this end, they found it necessary to develop a high repetition rate, short-pulse, mode-locked Nd:YAG laser. They succeeded recently in constructing a rod-configuration laser which is pumped by a Kr lamp in a CW-mode, so that it has an astounding repetition rate of 100 MHz. Mode-locking is achieved by acousto-optic modulation. The pulse length is only 80 ps. Because of the high repetition rate, the peak power is relatively low: around 1kW. Now, this is an advantage for the envisaged use in pumping a dye laser with the second harmonic, since it allows the use of a KTP-crystal frequency doubler which, compared with other customary crystals, has a very high conversion efficiency but a relatively low damage threshold.

At this point I briefly describe the actual short-pulse generation equipment. This has at its heart the usual, synchronously pumped Rodamine-6 dye laser (pumped by the powerful and high rep. rate output of the frequency doubled Nd:YAG system), but there is also introduced a second jetstream of another dye that acts as a saturable absorber. The resonating cavity is coupled to an antiresonant ring which actually contains the saturable absorber jet. This arrangement leads to additional pulse shortening.

I now return to the development-story of the efficient driving solid state laser. The construction of this was preceded by a very general and thorough study of optical pump-efficiency of solid state lasers, in a unified manner, for such diverse active materials as ruby, Nd:YAG, Nd:glass, alexandrite, Nd:Cr:GSGG (gallium-scandium-gadolinium-garnet). This study, published in August 1985 by Svelto and his associates P. Laporta and V. Magni (*Journal of Quantum Electronics*, Vol QE-21, No. 8), considers the pump efficiency of the laser as a product of four factors: the lamp radiative efficiency; the transfer efficiency of the pump cavity; the absorption efficiency of the rod; and the power quantum efficiency of the active material. The comprehensive analysis of the optical pumping of solid-state lasers achieved in this investigation furnishes a method to branch out into current investigations which aim at future improvement of

pumping efficiency in a large class of devices.

Another related research line, the results of which will be published soon in *Applied Optics*, is the work of Svelto, F. Docchio, and L. Pallaro. These scientists carried out a comparative study of pump cavities for compact pulsed Nd:YAG lasers, which obviously have industrial, medical, and military applications. They have studied two different kinds of elliptical cavities (of different dimensions and eccentricity), one close-coupled diffusive cavity, and one close-coupled reflecting cavity. They investigated the role of the type and geometry of the pumping cavity. They found that high efficiency is obtained with the two elliptical cavities, while a more uniform beam distribution can be obtained with the two close-coupled cavities. Furthermore, the scientists found that the close-coupled reflective cavity gives an efficiency comparable to the diffusive type, but it has a superior beam quality.

Finally, I will make a few remarks on the second major research area, the innovative development of optimized single-mode solid state lasers. Laporta's and co-workers' major insight in this area is the following. The thermal lensing effect is usually considered as a nuisance and attempts are made to eliminate it. However, Laporta's group showed that, when combined with suitably arranged external mirrors, the thermal lensing effect can lead to an "internal beam expansion". In this way one can arrange that the TEM_{∞} mode occupies a bigger region inside the rod: in fact, the TEM_{∞} mode can be made to completely fill up the cross section. Clearly, efficient mode-locking is the outcome. The problem currently studied is one of optimization: rod and mirror length and positioning are some of the parameters that must be so arranged as to obtain maximal mode utilization, at maximal pumping power, and with maximal stability against mechanical perturbations.

A typical step in this direction is the current research of Laporta, V. Magni, and S. De Silvestri, in which they study the role of the rod position in single-mode solid state resonators, especially in regard to the optimization of a CW mode-locked Nd:YAG laser. The general theoretical analysis was confirmed by experiments performed on a CW mode-locked Nd:YAG laser with a standard convex-concave resonator, and the experimental arrangement allowed for the optimization of the output power by simply a proper positioning of the rod. Using a commercial laser oscillator, a remarkable mode-locking average power of 8W, with a pulse duration of 75 ps has been obtained, without the presence of apertures in the resonating cavity. This is a significant improvement of the results that arise without rod-positioning techniques.

Concluding Remarks

I did not attempt to see all of the laser work that is being done at Milan's universities, but even this limited coverage should indicate that the universities have strong, front-line academic centers, suitable both for basic research and for early R&D activities. Industrial research laboratories in Milan carry further the development phase--subsequent *ESN* articles will review some of these efforts.

I want to make clear that the selection of topics described in the present article is by no means a judgment on the importance done by other university and polytechnic scientists. In particular, I should note that, because it is outside of my current area of coverage, I did not review the outstanding work of Dr. L. Lugiato (Department of Physics, University of Milano), who contributed significantly, with solid work, to our understanding of optical bistability and chaos in lasers.

11/21/85

OPTICAL RESEARCH AT UPPSALA UNIVERSITY

by Paul A. Temple. After completing a one year sabbatical at the University of Technology, Loughborough, England, Dr. Paul A. Temple, a research physicist, returned in January 1986 to the Naval Weapons Center, China Lake, California.

Scattered Light Measurements

Background. When a beam of light is incident on an optical surface most of the light is reflected. However, some of the light is absorbed, some is transmitted through the optic and some of the light is reflected into nonspecular directions. This latter "scattered" light can limit the usefulness of optical systems. For example, the ability to discern a dim object near a bright source can be limited by scattering. A good example is the difficulty of driving a car toward the setting sun when the windshield is dirty or pitted. Other examples are the scatter-imposed limitation in rotational sensitivity of laser gyros, the angular resolution in astronomical instruments, and the spectral

resolution of wavelength resolving instruments. The US Navy's interest in both the technical consequences and the theoretical understanding of scattered light is evidenced by the optical evaluation facility at the Naval Weapons Center, China Lake, California, where activity in optical scatter spans nearly three decades.

Scatter measurements are made for two basic reasons: to characterize a specific optical component for use in a system, and to gain a better understanding of the fundamental optical processes leading to scatter. Most of the scattering measurements reported in the optical literature have been made in the infrared (λ (wavelength) = 20 to 0.8 μm) and visible (λ = 0.8 to 0.4 μm). This is because of the availability of laser light sources to make these measurements and, more importantly, the applications for the optical surfaces which were in the infrared and visible regions of the spectrum.

In the last few years, interest and applications in the ultraviolet (UV) (λ = 0.4 to 0.2 μm), vacuum ultraviolet (VUV), and x-ray wavelengths (λ less than 0.2 μm) has seen rapid growth. The new light sources which have become available are various dye, frequency-multiplied, and excimer lasers and the continuously tunable storage ring sources. These last devices made use of the large nuclear physics machines where charged particles are stored in a circular racetrack. When the particle beam bends, it emits synchrotron radiation which extends from the visible into the x-ray region. New applications range from newspaper printing to satellite-based UV and x-ray telescopes for astronomical observation. All of these devices use optical surfaces where scatter characteristics affect performance.

A New Instrument. This report describes a new scatter instrument which has been developed by Dr. Lars Mattsson at Uppsala University, Uppsala, Sweden. This instrument has been constructed to support the photoelectron spectroscopy group at Uppsala University. The scatterometer is designed to be used in the 0.6 to 0.03 μm wavelength range. Since air absorbs radiation shorter than about 0.19 μm, this instrument is built into a vacuum chamber. This limits sample size to 50 mm by 50 mm, and 25 mm in thickness. The entire instrument, including vacuum pumps, is portable and may be moved to a synchrotron light source, if desired. However, at this time, the light sources used will be a selection of discharge lamps in conjunction with a monochromator.

The instrument is designed to make angle-resolved scatter measurements rather than the somewhat simpler "total integrated scatter" measurements where all of the light scattered away from the specular is measured after it is collected by a hemispherical mirror. Angle-resolved measurements give information on both the intensity and direction of the scattered light. They are useful in a practical sense since knowing the angular distribution of scattered light makes it possible to optimize the instrument or the optic itself. The theoretical understanding of scatter is also aided by the more complete description given by angle-resolved measurements.

By configuring the sample and detector so the specular beam is detected, the reflectance of the sample may be measured. This allows reflectance measurements to be made at a variety of angles of incidence. Again, such measurements are very helpful in both a practical and theoretical sense.

The primary goal for the instrument is to provide a testing facility for optical components, such as the focussing VUV-polariser and holographically produced diffraction gratings, manufactured at Uppsala. However, UV and VUV scattering is an almost unexplored field and the instrument will be used by university staff and graduate students for fundamental studies. Areas of research interest are surface-plasma radiation found in the UV-region, scatter from ion-beam etched holographic gratings for the VUV, and the influence of reflective coatings on the scattering properties of the surface.

Research on the Optical Properties of Materials

The "energy crisis" of the 70s stimulated research into alternative energy sources and into energy saving schemes. In the Solid State Physics Department, Uppsala University, the optical properties of materials research is typical of the efforts spawned by that crisis. The group, which consists of seven members, was originally concerned with the development of solar absorber materials. That work has now expanded into the areas of dwelling window coatings, mineral wool optical properties, and associated industrial projects. Solar absorber work now represents less than half of the groups effort.

The most straightforward technique for solar energy utilization is by solar thermal conversion, where the sun's radiation is used to heat directly some working fluid. A selective surface used as a solar absorber should ideally

absorb all the incoming solar energy between 0.3 and 3 μm wavelength and have low emittance for longer wavelength black body radiation for the working temperature of the absorber. For example, a black body at 100°C has its emission peak at 7-μm, with essentially no emission for wavelengths shorter than 3-μm.

The simplest approach to selective surfaces is to use a single material whose intrinsic optical reflectance spectrum matches the required spectral profile of the ideal absorber. There are only a few materials which show promising intrinsic optical properties. Several nitrides in thin film form have been investigated at Uppsala (Karlsson, 1981) and in cooperation with the Optical Sciences Center, University of Arizona (Karlsson et al., 1983, and Kallsson et al., 1984). These include thin films of TiC_xN_y, HfN, ZrN, and TiN. The latter has optical properties much like gold and is used on cosmetic surfaces to simulate that material. While the materials do not have ideal optical properties, they are mechanically much tougher than the noble metals which they simulate.

The next simplest solar absorber is based on a tandem effect between an absorbing surface layer and a reflecting metallic base. The performance can be improved by choosing a surface layer thickness which causes it to be anti-reflecting (in the visible) for the metal base. Several papers have been published by the Uppsala group in this area. These include the preparation of various oxides on stainless steel (Karlsson et al., 1982; Valkonen et al., 1982; Karlsson et al., 1984) and on copper (Ribbing, 1984). The thermal and environmental stability of these materials has also been investigated at Uppsala. The bulk of the support for this work has come from the Swedish Board for Technical Development.

A second aspect of the energy crisis resulted in increased interest in energy conservation. Those living in northern latitudes are familiar with double or triple glazing of windows to reduce heat loss. It is possible to augment multiple glazing with appropriate thin film coatings on individual glass window panes. These so-called heat-mirror coatings for insulation and passive solar heating should have the highest possible transmittance for incoming solar radiation and highest possible reflectance in the outgoing infrared part of the spectrum. Other important aspects of the coating are durability and color.

The Uppsala group has published work on the use of thin films of Cu, Ag, Au, Cr, Fe, Co, Ni, and Al for spectrally selective coatings on window glass (Valkonen, 1984). When thin metal films are applied, a coating of around 10 nm or less thickness is necessary to preserve visible transmittance. There is a tendency for such films to undergo cluster formation. The discontinuous nature of such films strongly reduces the performance in the infrared. The Uppsala group has recently demonstrated a substantial reduction in island formation in thin silver films by using rf-assisted dc magnetron sputter deposition (Valkonen, 1984).

Their most recent efforts have been in the design and fabrication of metal/dielectric multi-layer coatings and doped semi-conductor coatings, particularly SnO_2. Through computer modeling, it has been found that thin metal coatings, such as the familiar copper coated windows seen on some modern buildings, are effective in reducing heat loss to the outside by reflecting infrared radiation back into the building. On the other hand, heavily-doped, semi-conductor coatings, which are also good heat reflectors, are more transparent to the solar spectrum and allow heat flow into the building (Karlsson, 1985). Much of this work is supported by the Swedish Council for Building Research.

The work pursued over the last ten years at Uppsala has resulted in a group which is now involved in various industrial projects where tailored optical properties are needed to assure proper product performance.

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News and Notes

BIOTECHNOLOGY RESEARCH AND DEVELOPMENT (R&D) IN SWEDEN

In Sweden, R&D in the field of biotechnology is financed by different foundations and by industry itself.

Only a few large companies like Pharmacia and the Swedish Sugar Company are active in basic research. Most basic research work is carried out at universities. The Swedish National Board for Technical Development is funding research projects in areas like molecular biology, fermentation and enzyme research as well as down-stream processing. The annual budget is about $2.9 million. Other funders of basic research more or less related to biotechnology are the Medical Research Council, The Cancer Fund, and the Swedish National Science Research Council.

Applied research in biotechnology is mainly financed by the companies active in this field. The Swedish National Board for Technical Development is funding risk projects with companies at a 50:50 basis totalling about $1.5 million per year.

Thus far, the different funding agencies have operated very independently but now a National Committee for Biotechnology is being established. Members of this committee will be representatives from funding agencies and from industry. Its purpose is to coordinate the support of R&D and to work out a national policy.

Claire E. Zomzely-Neurath
12/20/85

UK GOVERNMENTAL BIOTECHNOLOGY SUPPORT

Governmental sponsorship of biotechnological innovation in industry is still in the build-up phase. From roughly $14.5 million spent annually by the Department of Trade and Industry in direct support of research and development in and for industry only $3 million per year is allocated to biotechnology. A Biotechnology Unit has been established for the management of this sponsorship at the Laboratory of the Government Chemist, London, UK.

The Biotechnology Unit has identified four key areas of biotechnology of strategic importance and is devoting an increasing proportion of its resources and efforts to them. The four areas are: (1) enzymes, production and use; (2) diagnostics including biosensors; (3) agricultural biotechnology; and (4) process plant and instrumentation.

Basic research in the UK is funded in universities by the University Grants Commission and the Research Councils and in public sector research institutes by government departments and Research Councils. The Research Councils alone had a commitment of basic research in the biosciences of about $3.3 million in 1983-1984.

Only in the Science and Engineering Research Council (SERC) has a dedicated Biotechnology Directorate been formed. This Directorate seeks industrial advice in the award of research grants to universities, advocates joint funding of projects with industry, and aims in consultation between academics and industrialists to direct support into strategically important areas. These areas include: (1) immobilized cells and

enzymes; (2) plant genetics and biochemistry; (3) a large-scale growth of mammalian and plant cells; (4) fermentation technology; (5) microbial physiology; (6) new reactor design; (7) new concepts in downstream processing; and (8) sensors and bioelectronics.

Claire E. Zomzely-Neurath
12/20/85

WEST GERMAN GOVERNMENTAL PROGRAM IN APPLIED BIOLOGY AND BIOTECHNOLOGY

The West German Federal Government has recently published its governmental program for applied biology and biotechnology as a framework program for the support of research activities in biology and biotechnology.

The objectives laid down in the program are: (1) encouragement of scientific and technical peak performances; (2) improvement of innovation conditions; (3) R&D support in sectors of public interest; (4) technology assessment; (5) improvement of conditions for young scientists; and (6) support of international cooperation.

The program at first defines the opportunities and status of biology and biotechnology. Then governmental measures are applied to the different sectors as shown below in figures of budgetary planning for 1986.

Institutional Support

Research Centers	Millions US Dollars
Institute for Biotechnological Research, (GBF); European Molecular Biology Center	23.7
Genetic centers and key projects	10.0
Support of company start ups	1.2
Cooperative Research Support	
Genetic technology, microorganisms	5.6
Cell culture techniques	6.4
Bioprocess technology, enzyme technology	7.3
New sectors	0.8
Plant building, renewable materials	2.0
Replacements for animal biological safety tests million	7.5

In total, the Federal Government plans to spend about 70 million US dollars in 1986 for applied biology and biotechnological research. This figure is planned to increase to 110 million by 1989 in accordance with the objectives of the new program.

Besides the Federal Government, other public sources are financing biotechnology in West Germany. At the end of 1984, a total of 682 research projects in genetic engineering were underway in 61 institutions funded at about 25 million US dollars.

Claire E. Zomzely-Neurath
12/20/85

EUROPEAN COMPUTING CENTER FOR TURBULENCE AND COMBUSTION

Informal discussions involving representatives from a number of European countries including the UK, Italy, Spain, France, and Germany have taken place over the past few months with the aim of proposing establishment of a European computing center for turbulence and combustion. Each member nation would contribute its share to the support of the center, which would be governed by a board of directors representing both industrial and research organizations. The proposed facility would comprise a computing capability equivalent to four CRAY XMP's. Its location has not yet been decided.

The improved understanding of combustion and turbulence which will result from the calculations made at this center will lead to improvements in the products of a number of high-tech European industries including the aerospace, nuclear, and automobile industries. It is argued that in order for its products to remain competitive with those from the US and Japan, a computational capability similar to that which exists in those two nations must be established in Europe.

In a preliminary working document describing the proposed center, the need for it was defended by comparing the computational resources available for calculations of turbulence and combustion in the US and Europe. As of 1984 the US, had perhaps, 24 CRAY and five CYBER 205 supercomputers available for such calculations at such places as NASA Ames, NASA Langley, Los Alamos Scientific Laboratory, Lawrence Livermore Laboratory, and the four university supercomputer centers set up by the National Science Foundation. This compares with seven CRAYs and three CYBERs which were available for such calculations in Europe.

The objective is to be capable of 10^{15} operations in a reasonable length of time. At the present time 10^{13} operations require approximately 100 hours

on a CRAY XMP-4; therefore, a computational capability corresponding to the power of several CRAY XMP's would be required. Additional equipment would consist of peripheral memory (more than 10^{10} words) and image processing equipment to facilitate comparison between the calculations and experiments. The goal is to establish a center in which all members would share in accordance with their needs and to which free access would be provided not only to the computational resources but also to the results of the computations.

It is proposed that the center would consist of a nucleus of permanent professional staff supplemented by visiting scientists, who would be in residence for various lengths of time. (This is an arrangement similar to that of the Institute for Computer Applications in Science and Engineering [ICASE], at National Aeronautics and Space Administration [NASA] Langley.) One estimate of the cost of the European center is $40 million per year.

A multidisciplinary organization is planned to allow communications between experimentalists, theoreticians, reactive and non-reactive fluid mechanicians, and specialists in numerical analysis, computer science, and expert systems. This exchange is expected to involve many different European research centers, universities, and industries. An organizational feature contributing to exchange of information is that the calculations would be carried out in a decentralized fashion from terminals located throughout Europe. This decentralization would facilitate comparisons between the calculations made in various countries and, in addition, facilitate comparisons with experimental results which would be assembled systematically in a data bank and made available to all users. Finally, the composition of the board of directors, representing both the research and industrial communities, would assure that the results of the research carried out at the center would be useful not only in improving the products of European industries but also would be conducted in such a way that the specialists having access to the center would be able to organize their research according to their own interests.

Representatives from many European countries met in Brussels on 19 November 1985 to discuss their interests in proposing such a center and how it could be established. Working committees were set up with the intent of producing by March 1986 a consensus document describing the philosophy, organization, structure, and financial support options for the center. The coordinator for the center is Professor Charles Hirsch of the Free University of Brussels.

Eugene F. Brown
11/22/85

ONE-DAY MEETING ON REFINED TURBULENCE MODELING

A one-day meeting on Refined Turbulence Modeling was held at Hydraulic Research Limited in Wallingford, England on 28 November 1985. The purpose of the meeting was to define the state of the art of turbulence modeling in mechanical and civil engineering and, by bringing engineers in both fields together, to encourage a useful interchange of ideas.

In the field of mechanical engineering, refined turbulence models have been used for many years. Civil engineers involved in the hydraulics of coastal flows, however, have typically used relatively simple turbulence models. With recent increases in computer power and the development of more sophisticated turbulence models, it should now be possible not only to improve the solution of existing problems but also to increase the scope of civil engineering problems which can be studied.

The program consisted of invited lectures by Professor W. Rodi (University of Karlsruhe), Dr. A. Hauguel (Electricité de France), Professor B. Launder (University of Manchester Institute of Science and Technology), Professor D.C. Leslie (Queen Mary College), and Professor D.B. Spalding (Imperial College).

After surveying the history of turbulence modeling, Rodi presented a number of applications, including bouyant jets and open channel flows. Hauguel reviewed his laboratory's work on coastal hydraulic calculations and atmospheric plume dispersal. Lauder discussed his group's calculations of separated flows, high-accelerated flows, flows in rotating ducts, impinging jets, and flow in 180° bends (see *ESN* 40-3:98-100). Finally, Leslie presented his work on large eddy simulation including some projected studies on free surface waves, and Spalding talked about an intuitive approach to turbulence employing a two-fluid model.

It was concluded that there is no single turbulence model (no matter how refined) which is suitable for all purposes. The best turbulence model depends upon the problem you want to solve, the nature of the flow variables

you wish to calculate, and the accuracy with which you want them to be predicted.

Approximately 60 people attended the meeting, with attendees almost evenly split between the mechanical engineering and the civil engineering (hydraulics and oceanographic) communities. Most of the participants were from England.

Eugene F. Brown
11/29/85

DIFFRACTION LIMITED LASER BEAM EXPERIMENTS IN MILAN

The achievement of high power laser beams which are such that their spatial spread is not more than the theoretically obtainable minimum defined by diffraction, is of great importance not only for laboratory studies, but also for industrial and military applications (including directed energy weapons). There are two research groups in Milano, Italy which are engaged in work aimed at such a goal.

Two major approaches to achieve diffraction limited performance are generally known. One uses a stable resonator configuration and employs a small internal aperture. The disadvantage is a considerable reduction of active lasing volume, hence reduced efficiency. The other approach is the adoption of an unstable resonator configuration; this, however, leads to unfavorable beam profiles. Both Milano groups combine ideas from the two basic approaches to achieve their goal.

In the Center for Quantum Electronics (an institute affiliated with the Politecnico, see *ESN* 40-3:104-107), researchers under the leadership of Professor O. Svelto noted that there is a third, less known configuration, which they call an "unconfined resonator". Here both mirrors are convex, but the one from which the escaping (unconfined) radiation is emanating, is given a Gaussian reflectivity contour. Apparently, other research groups achieved with this arrangement a large mode volume and good beam limitation. However, the fabrication of Gaussian reflectivity profiles, especially if large beam cross-sections are required, is rather difficult. Svelto, instead, had the novel idea of replacing the Gaussian reflectivity profile mirror by a Fabry-Perot etalon where one of the endplates is given a shape that leads to a Gaussian distribution in the reflected intensity (see Figure 1).

Experiments with an unconfined resonator using this etalon at one end of the cavity fed by a Nd:YAG laser are in an early stage at this time.

In contrast, the work on diffraction limited YAG and TEA-CO_2 lasers, conducted at the CISE Research Institute by Dr. P.G. Gobbi and coworkers, is in a rather advanced stage. Gobbi reported his results at a recent conference on lasers and electrooptics and a patent is pending. The device is called a "self filtering unstable resonator" (SFUR). As already noted above, unstable resonators in the positive branch realization have become increasingly popular for high power oscillators. But the beam of such a device (independently of how the energy is coupled out) evolves from a truncated near field pattern which, when it propagates, develops fringes that become unstable and can even cause damage in the optical elements. Also, when their beam is focused, the energy spreads over larger spots. Gobbi's idea was to use a negative branch realization of an unstable resonator, eliminating the well known difficulty with unstable resonator systems (the presence of a focal point inside the cavity, shared by the mirrors). The difficulty is actually circumvented by an appropriate positioning and correct choice for the size of a field-limiting aperture. This arrangement leads also to a very smooth field profile with excellent propagation characteristics. More specifically, Gobbi chooses the radius of the pinhole aperture (PH), set at the focal plane (see Figure 2), so that the first zero

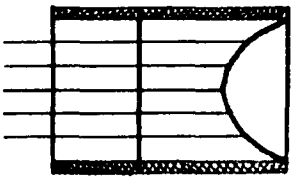

Figure 1. Gaussian Fabry-Perot.

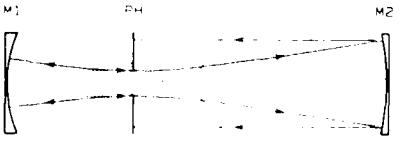

Figure 2. Schematic of the SFUR's operating principle.

of the Airy pattern, formed after a reflection on the mirror M1, exactly matches with it. In this way, only the central disk is propagated further; it is magnified, Fourier transformed, and collimated by the mirror M2. It is then presented at the aperture plane ready to start another similar cycle.

Both the calculations and the verifying experiments indicated that the SFUR always operates in single transverse mode, the lowest order mode eigenvalve being more than two orders of magnitude greater than that of the next lowest order mode. The resonator output is highly focusable (almost diffraction limited), and sensitivity to mirror misalignment is low.

An interesting laboratory application of the YAG-SFUR was to use 200 mJ unfocused output to generate the second harmonic in KD*P with a remarkable efficiency of 40 percent. Early industrial versions (marketed by Quanta Systems SRL, Modena, Italy) have been used for drilling in the free-running version, and for a variety of scientific applications in the Q-switched versions.

Paul Roman
11/22/85

AN ONRL SPONSORED GYROTRON WORKSHOP

King's College, London, hosted on 25 and 26 November an international, high-level, specialist-oriented workshop on the latest results in, and problems of gyrotron research. The meeting was sponsored in full by ONR London.

Gyrotrons are essentially sophisticated microwave vacuum tube devices, capable of achieving extremely high frequencies and powers (currently up to about 300 GHz and a few hundred kilowatts, respectively). (For a review, see *ESN* 39-5:217.)

There were 19 invited participants and two British observers. Six speakers came from Great Britain, eight from continental Europe and the Middle East, and five from the US. There were overviews, special achievement reports, technical contributions, and discussions of the industry's experience.

The highlight was probably a long round-table discussion on open questions regarding the theoretical formations of gyrotron operation and problems addressed to gyrotron designers. The meetings were conducted in an open and unusually interactive manner.

For more details, see ONR, London, report C-14-85, which you can order by filling out the return mailer inside the back cover of this issue. In addition, a forthcoming special gyrotron issue of the International Journal of Electronics (to appear toward the middle of 1986) will publish the full texts of the formal talks.

Paul Roman
11/27/85

ONRL COSPONSORED CONFERENCES

ONR, London, can nominate two registration-free participants in the conferences it supports. Readers who are interested in attending a conference should write to the Scientific Director, ONRL, Box 39, FPO New York 09510.

Growth Factors in the Nervous System, Kent, UK, 24-26 March 1986.

The Interaction of Molten Salts and Metals: Current Understanding of Hot Corrosion and New Approaches to Practical Problems, University of York, York, UK, 2-4 July 1986.

International Optical Computing Conference, Jerusalem, Israel, 7-11 July 1986.

Sixth International Symposium on Gas Flow and Chemical Lasers, Jerusalem, Israel, 8-12 September 1986.

Naval Applications and Environmental Chemistry of Organotins, Padua, Italy, 11 September 1986.

SCIENCE NEWSBRIEFS FOR DECEMBER

The following issues of *Science Newsbrief* were published by the ONR, London, Scientific Liaison Division during December. *Science Newsbrief* provides concise accounts of scientific developments or science policy in Europe and the Middle East. Please request copies, by number, from ONR, London.

Science Newsbrief Number	Title
3-57	Space Physics Climatology and Observations--Courses, by LDCR Rich Kelley, USN.
3-58	Electro-Optics News from Marconi, by Paul Roman.
3-59	Instant Powder Metallurgy by Spray Deposition, by Kenneth D. Challenger.

DECEMBER MAS BULLETINS

The following *Military Applications Summary (MAS) Bulletins* were published by the ONR, London, Military Applications Division during December. The *MAS Bulletin* is an account of naval developments in European research, development, test, and evaluation. Its distribution is limited to offices with the US Department of Defense. DoD organizations should request copies of the *Bulletins*, by number, from ONR, London.

MASB Number	Title
133-85	Environmental Remote Sensing Applications Center (ERSAC) Livingston, Scotland
134-85	Minature Microflex Rate Gyro Developed in UK
135-85	Fiber-Optic Perimeter Security Systems
136-85	Oceanographic Remote Sensing at Technical University of Denmark
137-85	Program for International Polar Oceans Research (PIPOR)
138-85	The First International Conference on Materials in Aerospace London, UK, 2-4 April 1986
139-85	Automatic Missile Detection Radar
140-85	DRFM Developments at Thorn EMI in the UK
141-85	International Morse Code Equipment
142-85	European Space Update
143-85	New French Space Oceanography Organization
144-85	Limpet Mine Disposal Equipment
145-85	Fourth Quarterly Index 1985
146-85	Annual Subject Index 1985

ONRL REPORTS

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C-12-85 *Seventh European Immunology Congress, Jerusalem, Israel*, by Claire E. Zomzely-Neurath. The Seventh European Immunology Congress was held in Jerusalem from 8 through 13 September 1985. This report focuses on presentations dealing with interferons and interleukines; immunoregulation; immune, endocrine, and neural systems correlations and interactions; immunodeficiency; as well as immunomodulation and immunopharmacology.

C-13-85 *Biotechnica'85: 1st International Congress for Biotechnology, Hannover, West Germany*, by Claire E. Zomzely-Neurath. This report provides a review in some detail of the presentations in the three general areas of the topics: measurement of process control and development of models; biocatalyst preparation, utilization, and improvement; and animal and plant cell cultures. The report concludes that the excellent presentations showed that biotechnology research in Europe and the UK is of high caliber and represents a greatly increased emphasis on basic as well as applied research in biotechnology.

C-14-85 *State-of-the-Art Survey of Gyrotron Research: ONRLWS*, by Paul Roman. The workshop/survey held at King's College, London, UK, on 25 through 26 November 1985 included presentations from the US, the UK, Continental Europe, and the Middle East. This report gives brief coverage of all the presentations, and focusses, in particular, on areas of controversy in both theory and method.

C-15-85 *The Damage Tolerance of Carbon Fiber Reinforced Composites--A Workshop Summary*, by Kenneth D. Challenger. The workshop in Glasgow, Scotland held on 12 September 1985 included participants from the US, the UK, Australia, and France. This report discusses six critical problem areas associated with damage tolerance of carbon-fiber reinforced composite materials: damage tolerant materials, testing methods, structural life prediction, damage tolerant design concepts, repair methods, and nondestructive testing.

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