**Main Lectures**

**ML-03.03** CRYSTALLOGRAPHY OF RIBOSOMES

A. Yavorski

Department of Structural Biology, Weizmann Institute, Rehovot, Israel, and Max-Planck Research Lab, for Ribosomal Structure, Hamburg, FRG.

Ribosomes are the universal cell organelles responsible for the translation of the genetic code into proteins. A typical bacterial ribosome contains more than a quarter of a million atoms and is of a molecular weight of 2.3 million daltons. It sediments with a coefficient of 70S and is composed of 3 classes of RNA, a total of about 70 proteins, and about 100 ribosomyl transfer factors. These are arranged in two independent subunits of unequal size (1.45 and 0.85 million daltons) which associate upon initiation of protein biosynthesis.

Intensive systematic exploration of crystallization conditions combined with individual tedium led to reproducible formation of crystals of ribosomes, their complexes with components of protein biogenesis, and natural, mutated and chemically modified (with an unclustered guanine) subunits. In all cases the crystallization conditions are chosen to be as close as possible to the natural environment of the ribosomes, and the crystalline ribosomal particles retain their integrity and biological activity for long periods in spite of the natural tendency of ribosomes to disintegrate and in contrast to the short life time of isolated ribosomes in solution. The most suitable crystals are of ribosomal particles from extreme halophilic and thermophilic bacteria. The highest resolution obtained so far is 2.9 Å.

The large unit cell dimensions, the extremely weak diffraction power, the relatively large mosaicity and the shape of the crystals (very thin plates or needles) dictates the performance of all these in X-ray crystallographic analysis with intense and highly collimated synchrotron radiation. At ambient temperature, all ribosomal crystals decay upon the first instance of X-irradiation. To overcome the severe sensitivity of these crystals to the X-ray beam, we developed cryo data collection techniques. These involve the determination of appropriate freezing conditions for each crystal form, shock cooling in liquid propane at liquid nitrogen temperatures and data collection from crystals at about 90 K. Under these conditions the crystals can be irradiaed and stored for periods long enough for the collection of more than one data set.

The strategy of data collection and evaluation, the specific problem of these experiments and the quality of the results are addresses separately (Agronin et al., this volume). In general, the crystallographic data of these crystals is of a reasonable quality with X mesq = 2.9 Å and adequate completeness.

**ML-04.01** CRYSTALLOGRAPHIC ENVIRONMENT AS AN APPROACH TO MOLECULAR RECOGNITION AND DRUG-DESIGN. By Claude Pascard I.C.S.N.-C.N.R.S. Gif-sur-Yvette, France

The molecular recognition process involved in drug design has been extensively studied over the last ten years. Thus, the structural information contained in large libraries such as the Cambridge Structural Database has been crucial in the process of finding new "lead" molecules. When the receptor site is known (by the X-ray structure determination of an inhibitor-enzyme complex), the aim is to find a new ligand complementary with the binding site. With an unknown receptor, the strategy is to identify the pharmacophore, to use its stereo and physicochemical features for mapping the receptor site, and a search is then made for other ligands using recently developed 3D-search programs, in conjunction with crystallographic data banks. Examples of these strategies which have accelerated the research for more potent drugs will be presented.

However, crystallographic results must not be reduced to a source of three-dimensional coordinates. The solid state medium is as rich in structural informations as both the solution state and ab initio calculations. Very valuable informations on desirable active conformation can be retrieved from various crystal structures of a given family of active compounds, wherein the different interactions molecule-solvent, and/or molecule-ion can be compared. These points will be discussed.