MAD Becoming Sane?*

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Multiwavelength anomalous diffraction (MAD) is a highly successful new phasing method in macromolecular crystallography. MAD exploits physical changes to a sample crystal during the data collection experiment to derive phase information. The anomalous scattering factors of selected atoms in the crystal change with the incident x-ray energy in the vicinity of an atomic resonant frequency. The attractiveness of MAD is due to the possibility of deriving accurate phase estimates from data measured from one sample crystal in one experiment. The advent of cryogenic sample protection and specialized beamlines has resulted in an explosion of successful MAD experiments. MAD phasing depends critically on determination of the partial structure of anomalous scatterers. In cases where their number is small or the crystal symmetry is simple, Patterson methods are sufficient for establishing the partial structure of anomalous scatterers. However, this is often not the case. Much of the success of MAD is due to the Se label in selenomethionine (SeMet) because of its biological incorporation in place of the amino acid methionine. Thus, for SeMet problems, the complexity of the anomalous-scatterer partial structure is proportional to the size of the protein, on average one SeMet for every 50-60 amino acids. A bottleneck in solving large Se partial structures has been eliminated recently by application of statistical direct methods to structures having up to 80 Se sites in the crystallographic asymmetric unit. Despite the additional challenge of MAD problems, there is no indication that the upper limit has been reached in size of protein or anomalous-scatterer partial structure to which direct methods can be applied successfully. MAD is rapidly becoming the method of choice for solving new protein crystal structures, limited only by availability of beam time.

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