**AB INITIO PHASING STARTING FROM LOW RESOLUTION**

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**Abstract:** Low-resolution phasing is important in the study of large macromolecular complexes and in the case of crystals of limited diffraction power. It allows defining molecular positions in the unit cell, molecular envelopes, and, in favorable cases, secondary structure elements. A multifiltering phasing method is discussed that is designed for the use of different weak low-resolution criteria of a phase set quality.

**Keywords:** phase problem; *ab initio* phasing; direct phasing; low resolution; connectivity; likelihood; Fourier syntheses; histograms; glob models; macromolecules.

1. **Introduction**

1.1. **AB INITIO (DIRECT) PHASING**

Phase determination is a necessary step to transform a set of diffraction magnitudes into images of the electron density distribution. Conventional ways to solve this problem in macromolecular crystallography involve either additional diffraction experiments (using modified wavelengths or crystal content) or knowledge of the model of a homologous object. There exist also methods capable to solve the structure using a single set of structure factor magnitudes and some general properties of electron density distribution (the “atomicity” as a rule). In this paper, we call these phasing methods *ab initio* or “direct” although sometimes these terms are reserved for a more broad
meaning. Such methods are routine in “small molecules” crystallography and last decade they came into macromolecular field (for a possible review see [21]), however, their application requires a high-resolution data set (about 1 Å, usually) that is not always possible in up-to-date macromolecular crystallography. In this paper, we consider an opposite case, namely low-resolution phasing, when the low-resolution edge reflections only are measured [6, 14, 15, 17]. The phasing of such reflections cannot provide one with a fine structure of the studied object, but nevertheless the information obtained may play a significant role for a further success in the structure determination.

We suppose below that the input of the phasing procedure is the structure factor magnitudes \( \{ F_{\text{obs}}(s) \}, s \in S \) for a set \( S \) of reciprocal-space vectors and some additional “general type” information on the object under study. The goal of the phasing is to find structure factors phases \( \{ \phi(s) \}, s \in S \) that allow the Fourier synthesis of the electron density be calculated

\[
\rho(\mathbf{r}) = \frac{1}{V_{\text{cell}}} \sum_{s \in S} F_{\text{obs}}(s) \exp[i\phi(s)] \exp[-2\pi i(s, \mathbf{r})].
\]

1.2. LOW-RESOLUTION PHASING

In this paper, we use the term “low resolution” to note several dozens (or a few hundreds) reflection of the lowest resolution for the given crystal. Depending on the size of the unit cell a Fourier synthesis calculated with these structure factors may present different information on the object studied. If this restricts the resolution approximately by \( d_{\text{min}} > 16 \) Å, the information that can be extracted from Fourier syntheses concerns mostly the macromolecular position in the unit cell and its envelope (Figures 1 and 2). This information can simplify the translation and eventually rotation search in the molecular replacement and facilitates the use of complementary sources of information like electron microscopy reconstructed images. If the resolution exceeds approximately 8 Å, Fourier syntheses may show \( \alpha \)-helixes (Figure 3) and at the resolution of about 4 Å \( \beta \)-sheets become visible. Syntheses of an intermediate resolution \( 16 \) Å \( > d_{\text{min}} > 8 \) Å are the most difficult for interpretation and overcoming this resolution interval presents the largest difficulties in \textit{ab initio} phasing.

The low-resolution reflections are often ignored in the process of structure solution mainly by the following reasons:

- Experimental difficulties when collecting low-resolution diffraction data, especially for crystals with very large unit cells
- Strong influence of the bulk solvent on low-resolution structure factors that makes it difficult to use the corresponding magnitudes in conventional phasing methods