Multivariate methods for macromolecular structure solution from experimental phases

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Traditionally, the process of macromolecular structure solution consists of separate experimental phasing, density modification and model building with refinement (Fig. 1a). First, experimental phasing provides initial estimates of the phases using a probability distribution P_{ph} of several structure factors with a known relation. The initial map constructed using the initial phases is then repeatedly modified in order to introduce expected protein electron map features into the it. Since this process also introduces errors into the map, the resulting map is usually recombined with the initial map using a reciprocal space probability distribution P_{DM}, followed by another density modification iteration of the recombined map. After several iterations, the recombined map is used for iterative tracing of the model with its reciprocal space refinement using probability distribution P_{ref}.

Typically, only the experimental phasing target P_{ph} is regarded a function of several related structure factors which inherit the information about phases. The probability distributions P_{DM} and P_{ref} are considered univariate functions of a single structure factor, ignoring the experimental phase information. While this approach is often sufficient, the use of the extra information may be essential at lower resolutions as it increases the low observations-to-parameters ratio or in the case of weak initial phases as it enables to retain and further improve the quality of the phase estimates.

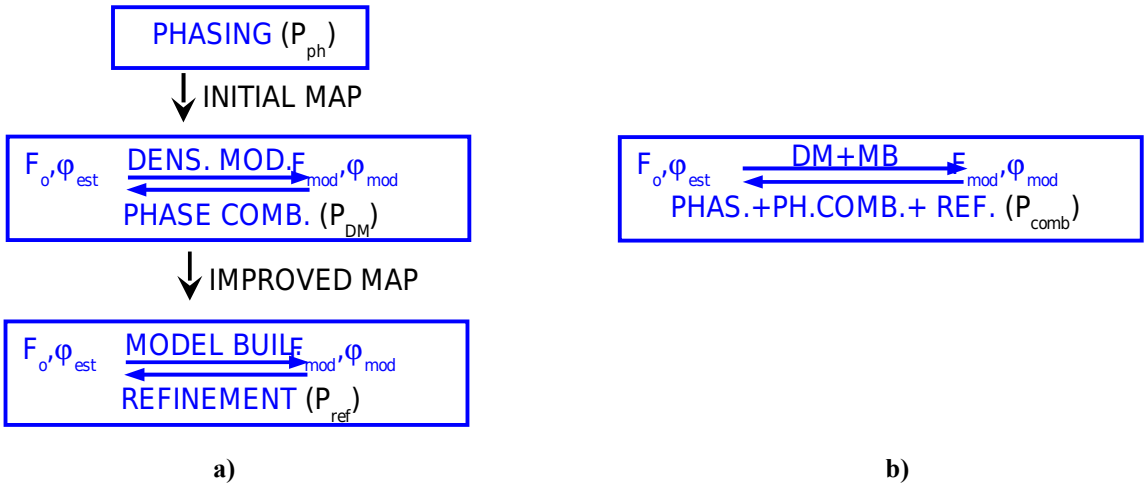

Figure 1. Process of structure solution from experimental phases.

a) The traditional process of structure solution. The steps are separated and a different function (P) is used in phasing, density modification phase combination and model refinement.
b) The new structure solution in which a single multivariate function incorporates phase information and density modification information in the current model refinement.

The phase information can be indirectly incorporated into the univariate targets P_{DM} and P_{ref}, using the phase distribution obtained from phasing [1]. However, this method suffers by several theoretical and practical shortcomings. Indeed, we have shown that direct incorporation of the experimental phase information by a multivariate function for model refinement, modeling the related structure factors and the correlations between them, removes unjustified assumptions and provides higher quality models than the refinement function with indirect

phase information incorporation [2]. Similarly, we have shown that a multivariate function for combination of the density modified maps and experimental maps can lead to significant improvements in quality of the electron density maps [3].

Recently, we have derived a novel multivariate likelihood target function for refinement of a (partial) model which incorporates both the phase information and the density modification information directly in the refinement function. The function enables to consider the traditionally separate steps of macromolecular X-ray structure determination from experimental phases as one unified process (Fig 1b) that can lead to combined and significant improvements.

The new function has been implemented in the refinement program Refmac5 [4] and combined with density modification and model building in the CRANK suite [5]. Tests performed show the new approach allows for many structures to be built automatically that eluded current methods, especially for data at lower resolutions or with weak experimental phase information.

References

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