Neutrons Will Play an Increasingly Important Role in Direct Methods of Phase Determination

1. It's easier to solve the phase problem with neutrons than with x-rays.
2. Hydrogen/deuterium replacement makes readily available diffraction data for a structurally isomorphous pair.
3. Since neutrons do not cause radiation damage, both neutron and x-ray diffraction data can be collected from one and the same crystal specimen.

Summary

The probabilistic theory of the structure invariants, when neutron diffraction data alone are available, yields, as in the X-ray case, the formulation of the phase problem as a problem in constrained global minimization (the minimal principle). The latter, in turn, leads (again as in the X-ray case) to a modified *Shake-and-Bake* algorithm (*Neutron Shake-and-Bake*) that explicitly exploits the property of the neutron density function, which, owing to the presence of hydrogen atoms ($_1H^1$), takes on negative as well as positive values.

Normalized Structure Factor E_H and Neutron Density Function $\rho(r)$

For each fixed reciprocal lattice vector, **H**, the normalized structure factor E_H is defined by

$$E_H = |E_H| \exp(i\varphi_H) = \frac{1}{\sigma_2^{1/2}} \sum_{j=1}^{N} f_j \exp(2\pi i H \bullet r_j)$$

where

$$\sigma_n = \sum_{j=1}^{N} f_j^n,$$

F_j is the neutron scattering factor of the atom labeled j, and N is the total number of atoms in the unit cell. The corresponding neutron density function is

$$\rho(r) \approx 0 \text{ if } r \neq r_j$$

$$\rho(r) \approx \frac{1}{\sigma_2^{1/2}} f_j \text{ if } r = r_j$$

$$\rho(r) \gtrless 0$$

According as *r* is the position vector of a hydrogen atom or (usually) of a non-hydrogen atom, respectively. Let $N=N_p$)positive) + N_n (negative) atoms.

The Phase Problem is a Problem in Constrained Global Minimization

In analogy with the X-ray diffraction case, one defines the minimal function m(Φ) for neutrons, a function of the phases, by means of

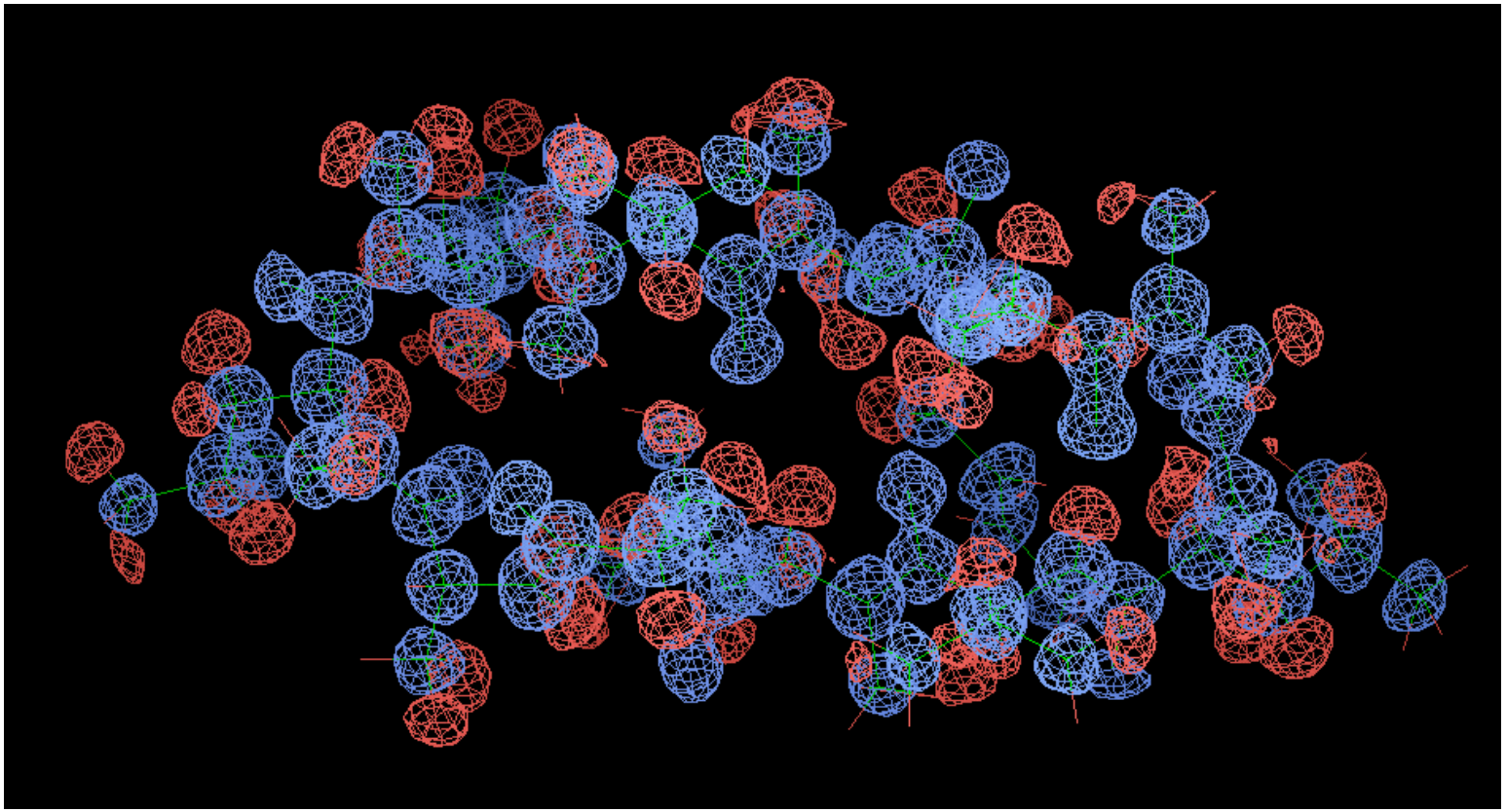
$$m\left(\Phi\right) = \sum_{H,K} A_{HK} \left\{ \cos\Phi_{HK} - \frac{I_1\left(A_{HK}\right)}{I_0\left(A_{HK}\right)} \right\}^2 \Bigg/ \sum_{H,K} A_{HK}$$

And formulates the minimal principle: The constrained global minimum of m(Φ) yields the true values of the phases for any choice of origin and enantiomorph.

It is important to stress the role of the constraints which consist of the identities that the phases must of necessity satisfy. The unconstrained global minimum of m(Φ), in contrast, does not yield the answer we seek.

Solving the Phase Problem with Neutron Data alone Using Neutron *Shake-and-Bake*, NSnB.

The straightforward solution of the crystal structure of cyclosporin ($C_{62}H_{111}N_{11}O_{12}\bullet H_2O$) by a modified *Shake-and-Bake* procedure, using experimental neutron diffraction data alone, shows that the positivity of the density function is not a necessary prerequisite for solving the phase problem. The initial applications strongly suggest that positivity is actually a hindrance.



F map produced by extending the phases from the 900 |*E*| values by peaklist optimization. This map is contoured at ±3σ(ρ); the phase error of the 4121 terms is ~15°. Although all 113 H atoms reside in negative density, still about 20% of these sites fail to display in negative density at less than the -3σ(ρ) contour that is shown.

It's Easier to solve the Phase Problem when the Density Takes on Both Positive and Negative Values

Cyclosporin	Success Rate	‹|δφ|›	# atoms
NSnB			
(H-structure)	6%	30º	199
(D-structure	0.3%	50º	199
X-RAY			
(SnB)	1.1%	13º	86
(RANTAN)	0.1%	25º	86

Structural Isomorphism

$$\varphi_{HK} = \varphi_H + \varphi_K + \varphi_{-H-K}$$

$$P\left(\Phi\right) = \frac{1}{2\pi I_0\left(A_{HK}\right)} \exp\left(A_{HK}\cos\Phi\right)$$

A_{HK} is a function of 6 magnitudes

$|E_H|$, $|E_K|$, $|E_{H+K}|$; $|G_H|$, $|G_K|$, $|G_{H+K}|$

$$A_{HK} \gtrless 0$$

$|A_{HK}|$ may take on very large values even at reduced resolution

Hydrogen/Deuterium Replacement Makes Neutron Diffraction Data Readily Available for a Structurally Isomorphous Pair

Cyclosporin Pair

$$S = C_{62}D_{111}N_{11}O_{12}\bullet D_2O$$

$$T = C_{62}D_{106}H_5N_{11}O_{12}\bullet H_2O$$

The Cyclosporin Map at 2.27Å Resolution