A Constraint-Based Approach to the Phase Problem in X-Ray Crystallography

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Abstract. X-ray crystallography is one of the main methods to establish the three-dimensional structure of biological macromolecules. In an X-ray experiment, one can measure only the magnitudes of the complex Fourier coefficients of the electron density distribution under study, but not their phases. The problem of recovering the lost phases is called the phase problem. Building on earlier work by Lunin/Urzhumtsev/Bockmayr we describe a constraint-based approach to the phase problem. We introduce the mathematical foundations, derive a basic integer programming formulation, and discuss possible refinements by including additional constraints.

1 Introduction

Knowledge about the three-dimensional structure of biological macromolecules is an essential foundation of structural biology and biotechnology. In X-ray crystallography the arrangement of atoms within a crystal is determined from a three-dimensional representation of the electron density. From X-ray experiments one gets *diffraction data* depending on the molecular structure, i.e., the intensities of reflections of X-rays diffracted by the crystal. X-rays are scattered exclusively by the electrons in the atoms, so one is searching for a relation between the measured intensities of the beams diffracted at the object in question and the crystal structure, which can be described by the electron density distribution. Electron density represents probabilistically where electrons can be found in the molecule. The first step on the way to estimate a crystal's electron density is the collection of crystallographic data. This is done with the help of a *diffractometer* or a synchrotron: an X-ray beam is diffracted by the crystal in a discrete set of directions and the reflection intensities are measured. With the help of this diffraction data and the usage of mathematical as well as experimental methods, an electron density map can be derived. *Direct methods* use mathematical techniques to compute an electron density map from the diffraction data without any further experiments. The main problem here is the *phase problem*: experiments provide only the intensities of the X-rays diffracted in different directions and so the electron density magnitudes can be calculated, whereas the information about the phase shift is lost.

Lunin, Urzhumtsev and Bockmayr [2] proposed a 0-1 integer programming approach to direct phasing. As a research contribution to a crystallographic journal, this article is not easily accessible. In the present paper, we introduce this work to the constraint programming community. We describe the mathematical foundations, derive step by step the basic integer programming formulation, and discuss possible refinements by including additional constraints.

2 Basic terminology

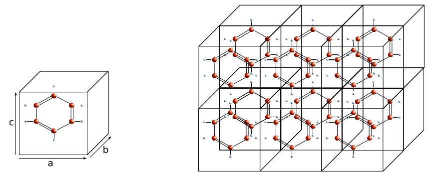
Vectors, matrices as well as higher-dimensional arrays will be noted with bold letters, $\mathbf{x} \cdot \mathbf{y}$ denotes the scalar product of two vectors $\mathbf{x}$ and $\mathbf{y}$.

Every crystal consists of identical molecules, resp. complexes of molecules strictly ordered in all three dimensions. This means that we can find a parallelepiped containing such a complex of molecules which builds up the whole crystal if it is repeatedly stacked together in all three dimensions. This parallelepiped, in general, is not unique. It is defined by the length of its edges as well as the angles between them and is called *unit cell*. These base units, translated in three dimensions, build up a *crystal lattice*.

We will denote the unit cell's volume with V_{cell}. Let $\mathbf{b}_1, \mathbf{b}_2, \mathbf{b}_3 \in \mathbb{R}^3$ span the unit cell. Then we can write every vector $\mathbf{r} \in \mathbb{R}^3$ in this basis, i.e., $\mathbf{r} = x_1\mathbf{b}_1 + x_2\mathbf{b}_2 + x_3\mathbf{b}_3$, where $\mathbf{x} = (x_1, x_2, x_3)^T \in \mathbb{R}^3$ is the vector of coordinates of $\mathbf{r}$ with respect to the basis $\{\mathbf{b}_1, \mathbf{b}_2, \mathbf{b}_3\}$.

The real function $\rho(\mathbf{r}),\ \mathbf{r} \in \mathbb{R}^3$, describing the electron density distribution in the crystal, has three linearly independent periods corresponding to the length of the unit cell's edges, i.e., $\rho(\mathbf{r}) = \rho(\mathbf{r} + k_1 \cdot \mathbf{b}_1 + k_2 \cdot \mathbf{b}_2 + k_3 \cdot \mathbf{b}_3)$, $k_1, k_2, k_3 \in \mathbb{Z}$. This means, if we know the electron density distribution's values in the unit cell, we know its values in the whole crystal, due to periodicity.

For the vector of coordinates $\mathbf{x} = (x_1, x_2, x_3)$ the electron density function has integer periods in all three directions, i.e. $\rho(\mathbf{x}) = \rho(\mathbf{x}+\mathbf{k}), \forall \mathbf{x} \in V, \forall \mathbf{k} \in \mathbb{Z}^3$. A vector $\mathbf{r} \in \mathbb{R}^3$ is inside the unit cell iff $\mathbf{x} \in V = [0, 1)^3$.



(a) Unit cell (b) Crystal

Fig. 1: Unit cells building a crystal: a) a unit cell, b) crystal built of unit cells

3 The phase problem

We are searching for the electron density distribution $\rho(\mathbf{x})$ over the crystal. Due to the crystal structure, ρ is a periodic function and therefore can be developed into a *Fourier series* [1,4]

$$\rho(\mathbf{x}) = \frac{1}{V_{cell}} \sum_{\mathbf{h} \in \mathbb{Z}^3} \mathbf{F}(\mathbf{h}) \exp(-2\pi i(\mathbf{h} \cdot \mathbf{x})),\ \mathbf{x} \in V. \tag{1}$$

The Fourier coefficients $\mathbf{F}(\mathbf{h}), \mathbf{h} \in \mathbb{Z}^3$, which are called *structure factors* in crystallography, are given by the formula

$$\mathbf{F}(\mathbf{h}) = \int\limits_V \rho(\mathbf{x}) \exp(2\pi i(\mathbf{h} \cdot \mathbf{x}))d\mathbf{x}. \tag{2}$$

Since the structure factors are complex numbers, they can be written as

$$\mathbf{F}(\mathbf{h}) = F(\mathbf{h}) \exp(i\varphi(\mathbf{h})), \tag{3}$$

where $F(\mathbf{h}) = |\mathbf{F}(\mathbf{h})|$ is the *magnitude* and $\varphi(\mathbf{h}) \in [0, 2\pi[$ the *phase*.
The only experimental data we get in X-ray-crystallography are the reflection intensities. The intensity $I(\mathbf{h})$ of a reflection is proportional to the magnitude of the squared structure factors, with a known constant of proportionality, i.e., $C \cdot I(\mathbf{h}) = |\mathbf{F}(\mathbf{h})|^2, C \in \mathbb{R}$. Thus, all we can calculate from our experimental data are the structure factor magnitudes. The phase information is lost and must be restored by other means. This is called the *phase problem*.

4 The electron density distribution on a grid

4.1 Grid electron density

Instead of calculating the electron density distribution in the whole unit cell, we will work on a grid. Using discrete Fourier transforms we will then calculate electron densities at the grid points. The chosen division numbers along the unit-cell axes represent the resolution of the electron density map we are searching for.
Consider a grid $\mathit{\Pi} = [0, M_1 - 1] \times [0, M_2 - 1] \times [0, M_3 - 1] \subseteq \mathbb{Z}^3$, where $M = M_1 M_2 M_3$ is the total number of grid points. Let $\mathbf{M}$ be the diagonal matrix $\mathbf{M} = \mathrm{diag}(M_1, M_2, M_3)$, $M_1, M_2, M_3 \in \mathbb{N}$. Given the values $\mathbf{y_j}$ of a periodic function f on the grid points $\mathbf{j}$, i.e.,

$$\mathbf{y_j} = f(\frac{j_1}{M_1}, \frac{j_2}{M_2}, \frac{j_3}{M_3}), \quad \mathbf{j} = (j_1, j_2, j_3) \in \mathit{\Pi} \tag{4}$$

the *three dimensional discrete Fourier transform* $\mathcal{F}$ calculates the Fourier coefficients of a trigonometric polynomial interpolating f in these grid points [6]:

$$\mathcal{F}(\mathbf{h}) = \frac{1}{M} \sum_{\mathbf{j} \in \mathit{\Pi}} \mathbf{y_j} \exp(2\pi i(\mathbf{h} \cdot \mathbf{M}^{-1}\mathbf{j})), \ \forall \mathbf{h} \in \mathit{\Pi}. \tag{5}$$

The values $\mathbf{y_j}, \mathbf{j} \in \mathit{\Pi}$, can be recovered from the Fourier coefficients $\mathcal{F}(\mathbf{h}), \mathbf{h} \in \mathit{\Pi}$, by the *inverse discrete Fourier transform*:

$$\mathbf{y_j} = \sum_{\mathbf{h} \in \mathit{\Pi}} \mathcal{F}(\mathbf{h}) \exp(-2\pi i(\mathbf{h} \cdot \mathbf{M}^{-1}\mathbf{j})), \ \forall \mathbf{j} \in \mathit{\Pi}. \tag{6}$$

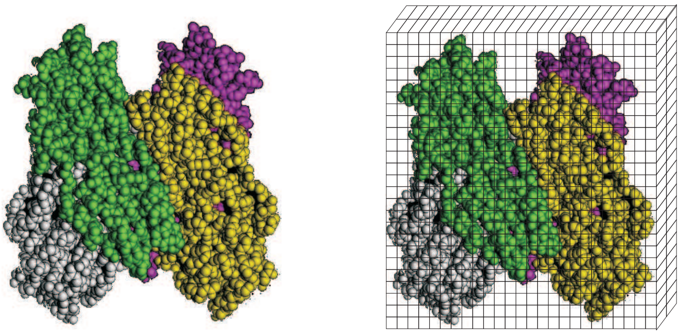

(a) Protein (b) Discretisation

Fig. 2: Discretisation of a protein: a) Protein, b) Protein discretisation

The values of the electron density function $\rho(\mathbf{x}),\ \mathbf{x} \in V$ at the grid points are described by the *grid electron density function* $\rho_g(\mathbf{j}) = \rho(\mathbf{M}^{-1}\mathbf{j})$. We define the *grid structure factor* $\mathbf{F}_g(\mathbf{h})$ by the discrete Fourier transform

$$\mathbf{F}_g(\mathbf{h}) = \frac{1}{M}\sum_{\mathbf{j}\in\Pi} \rho_g(\mathbf{j}) \exp(2\pi i(\mathbf{h}\cdot\mathbf{M}^{-1}\mathbf{j})),\ \forall \mathbf{h} \in \Pi. \tag{7}$$

If we know the grid structure factors, we can restore the grid electron densities

$$\rho_g(\mathbf{j}) = \sum_{\mathbf{h}\in\Pi} \mathbf{F}_g(\mathbf{h}) \exp(-2\pi i(\mathbf{h}\cdot\mathbf{M}^{-1}\mathbf{j})),\ \forall \mathbf{j} \in \Pi, \tag{8}$$

using the inverse discrete Fourier transform.

4.2 Structure factors vs. grid structure factors

In order to clarify the relation between the structure factors and the grid structure factors, we start with equation (7) and use (1), see also [5]:

$$\begin{aligned} V_{cell}\mathbf{F}_g(\mathbf{h}) &= \frac{V_{cell}}{M}\sum_{\mathbf{j}\in\Pi} \rho(\mathbf{M}^{-1}\mathbf{j}) \exp(2\pi i(\mathbf{h}\cdot\mathbf{M}^{-1}\mathbf{j})) \\ &= \frac{1}{M}\sum_{\mathbf{j}\in\Pi}(\sum_{\mathbf{p}\in\mathbb{Z}^3} \mathbf{F}(\mathbf{p}) \exp(-2\pi i(\mathbf{p}\cdot(\mathbf{M}^{-1}\mathbf{j})))) \cdot \exp(2\pi i(\mathbf{h}\cdot\mathbf{M}^{-1}\mathbf{j})) \\ &= \frac{1}{M}\sum_{\mathbf{p}\in\mathbb{Z}^3} \mathbf{F}(\mathbf{p}) \sum_{\mathbf{j}\in\Pi} \exp(2\pi i((\mathbf{h}-\mathbf{p})\cdot\mathbf{M}^{-1}\mathbf{j})) = \sum_{\mathbf{k}\in\mathbb{Z}^3} \mathbf{F}(\mathbf{h}+\mathbf{M}\mathbf{k}). \end{aligned}$$

The last equation holds due to

$$\sum_{\mathbf{j}\in\Pi} \exp\left(2\pi i\left((\mathbf{h}-\mathbf{p})\cdot\mathbf{M}^{-1}\mathbf{j}\right)\right) = \begin{cases} \mathbf{M}, & \text{if } \mathbf{h}-\mathbf{p} = \mathbf{M}\mathbf{k},\ \text{for } \mathbf{k} \in \mathbb{Z}^3 \\ 0, & \text{otherwise.} \end{cases}$$

Introducing $R(\mathbf{h}) = \dfrac{M}{V_{cell}} \sum_{\mathbf{k} \in \mathbb{Z}^3 \setminus \{0\}} \mathbf{F}(\mathbf{h} + \mathbf{M}\mathbf{k})$ we can write

$$\mathbf{F}_g(\mathbf{h}) = \frac{\mathbf{F}(\mathbf{h})}{V_{cell}} + \frac{R(\mathbf{h})}{M}. \tag{9}$$

The value of $R(\mathbf{h})$ depends on the magnitudes and phases of all structure factors and is generally unknown. But, it may be negligibly small if the grid is fine enough and if the indexes $\mathbf{h}$ are relatively small in comparison with the grid dimensions. Still, it may be significant if one of the indices is close to $\dfrac{M_1}{2}$, $\dfrac{M_2}{2}$ or $\dfrac{M_3}{2}$, cf. [2].

4.3 Inequalities for the grid electron density values

Using (7) we can obtain grid density values $\rho_g(\mathbf{j})$ from the grid structure factors $\mathbf{F}_g(\mathbf{h})$ by solving the system of equations

$$\mathbf{F}_g(\mathbf{h}) = \frac{1}{M} \sum_{\mathbf{j} \in \mathit{\Pi}} \rho_g(\mathbf{j}) \, \exp(2\pi i(\mathbf{h} \cdot \mathbf{M}^{-1}\mathbf{j})), \ \forall \mathbf{h} \in \mathit{\Pi}. \tag{10}$$

This equation system would be linear in $\rho_g(\mathbf{j})$ if the grid structure factors were known. Next we use (9) to relate the unknown grid structure factors $\mathbf{F}_g(\mathbf{h})$ to the true structure factors $\mathbf{F}(\mathbf{h})$, whose magnitude can be observed in the X-ray experiment. Given an upper bound $|R(\mathbf{h})| \le \varepsilon_1(\mathbf{h}), \ \forall \mathbf{h} \in \mathit{\Pi}$, we get the following system of inequalities for the grid density function:

$$\Big| \sum_{\mathbf{j} \in \mathit{\Pi}} \rho_g(\mathbf{j}) \exp(2\pi i(\mathbf{h} \cdot \mathbf{M}^{-1}\mathbf{j})) - \frac{M}{V_{cell}} \mathbf{F}(\mathbf{h}) \Big| \le \varepsilon_1(\mathbf{h}), \ \forall \mathbf{h} \in \mathit{\Pi} \tag{11}$$

5 Recovering the phases

We will now deduce further constraints restricting the possible phases of the structure factors $\mathbf{F}(\mathbf{h})$. Here, we have to distinguish between centric and acentric reflections.

5.1 Symmetries

We say that the density distribution $\rho(\mathbf{x})$ displays the symmetries of a space group $\mathit{\Gamma} = \{(\mathbf{R}_\nu, \mathbf{t}_\nu)\}_{\nu=1}^{n_{sym}}$, $n_{sym} \in \mathbb{N}$, with $\mathbf{R}_\nu$ being a rotation matrix and $\mathbf{t}_\nu$ a translation vector if the following holds [9]:

$$\rho(\mathbf{R}_\nu \mathbf{x} + \mathbf{t}_\nu) = \rho(\mathbf{x}), \forall \mathbf{x} \in \mathbb{R}^3, \forall \nu \in \{1, \ldots, n_{sym}\}. \tag{12}$$

From (12) and (2) we can derive the following symmetries for the structure factors [8]:

$$\mathbf{F}(\mathbf{h}) = \exp(2\pi i(\mathbf{h} \cdot \mathbf{t}_\nu)) \, \mathbf{F}(\mathbf{R}_\nu^T \mathbf{h}), \ \forall \mathbf{h} \in \mathit{\Pi}, \forall \nu \in \{1, \ldots, n_{sym}\}. \tag{13}$$

If $\mathbf{R}_\nu^T \mathbf{h} = -\mathbf{h}$ for some ν, $\mathbf{h}$ is called *centric reflection*, otherwise it is called *acentric*.

5.2 Centric reflections

Using (13) and the Hermitian symmetry $\mathbf{F}(-\mathbf{h}) = \overline{\mathbf{F}(\mathbf{h})}$ of the structure factors, we obtain the following phase restrictions for centric reflections:

$$\text{if } \mathbf{R}_\nu^T \mathbf{h} = -\mathbf{h} \text{ then } \varphi(\mathbf{h}) = \psi(\mathbf{h}) \text{ or } \varphi(\mathbf{h}) = \psi(\mathbf{h}) + \pi \text{ with } \psi(\mathbf{h}) = \pi(\mathbf{h} \cdot \mathbf{t}_\nu). \quad (14)$$

So, if the reflection is centric, only two values of the phase, $\psi(\mathbf{h})$ or $\psi(\mathbf{h}) + \pi$, with $\psi(\mathbf{h})$ being known, are possible. Thus, we can introduce a new variable $\alpha(\mathbf{h}) \in \{0, 1\}$, representing the phase ambiguity. In our inequality system (11), we can replace $\mathbf{F}(\mathbf{h})$:

$$\mathbf{F}(\mathbf{h}) = F(\mathbf{h}) \exp(i\varphi(\mathbf{h})) = F(\mathbf{h})(2\alpha(\mathbf{h}) - 1) \exp(i\psi(\mathbf{h})). \quad (15)$$

Taking real and imaginary parts, this results in the following inequalities for centric reflections $h \in \Pi$:

$$\Big| \sum_{\mathbf{j} \in \Pi} \cos(2\pi(\mathbf{h} \cdot \mathbf{M}^{-1}\mathbf{j}))\rho_g(\mathbf{j}) - (2\alpha(\mathbf{h}) - 1)\frac{M}{V_{cell}} F(\mathbf{h}) \cos\psi(\mathbf{h}) \Big| \le \varepsilon_1(\mathbf{h}), \quad (16)$$

$$\Big| \sum_{\mathbf{j} \in \Pi} \sin(2\pi(\mathbf{h} \cdot \mathbf{M}^{-1}\mathbf{j}))\rho_g(\mathbf{j}) - (2\alpha(\mathbf{h}) - 1)\frac{M}{V_{cell}} F(\mathbf{h}) \sin\psi(\mathbf{h}) \Big| \le \varepsilon_1(\mathbf{h}). \quad (17)$$

Thus the inequalities become linear in $\rho_g(\mathbf{j})$ and $\alpha(\mathbf{h})$ if the structure factor magnitudes $F(\mathbf{h})$ are known.

5.3 Acentric reflections

For the acentric reflections, the phase can take any value from 0 to 2π. [2] suggests for this case to restrict the phase of the structure factor to one of four possible values $\pm\frac{\pi}{4}$, $\pm\frac{3\pi}{4}$. Introducing two new variables $\alpha(\mathbf{h}), \beta(\mathbf{h}) \in \{0, 1\}$ and taking the real and imaginary part leads to the following inequalities for acentric reflections $\mathbf{h} \in \Pi$:

$$\Big| \sum_{\mathbf{j} \in \Pi} \cos(2\pi(\mathbf{h} \cdot \mathbf{M}^{-1}\mathbf{j}))\rho_g(\mathbf{j}) - (2\alpha(\mathbf{h}) - 1)\frac{M}{V_{cell}} F(\mathbf{h}) \frac{1}{\sqrt{2}} \Big| \le \varepsilon(\mathbf{h}), \quad (18)$$

$$\Big| \sum_{\mathbf{j} \in \Pi} \sin(2\pi(\mathbf{h} \cdot \mathbf{M}^{-1}\mathbf{j}))\rho_g(\mathbf{j}) - (2\beta(\mathbf{h}) - 1)\frac{M}{V_{cell}} F(\mathbf{h}) \frac{1}{\sqrt{2}} \Big| \le \varepsilon(\mathbf{h}). \quad (19)$$

The error $\varepsilon(\mathbf{h})$ is given by $\varepsilon(\mathbf{h}) = \varepsilon_1(\mathbf{h}) + \varepsilon_2(\mathbf{h})$. Here $\varepsilon_2(\mathbf{h})$, introduced by the sampling of the phase value can be estimated by $\varepsilon_2(\mathbf{h}) \le \frac{1}{\sqrt{2}} \frac{M}{V_{cell}} F(h)$.

6 Constraint-based modeling of the phase problem

6.1 Constraint system

In the context of direct phasing, it may be sufficient to find a binary *envelope* of the regarded molecules, i.e., a binary function representing areas where the electron density is above a certain level [2]. Using this idea, we may replace the unknowns $\rho_g(\mathbf{j})$ by binary variables $z_\mathbf{j} \in \{0,1\}$, for each grid point $\mathbf{j} \in \mathit{\Pi}$. The value of $z_\mathbf{j}$ should be 1 if the electron density $\rho_g(\mathbf{j})$ is above a certain level and 0 otherwise, so the solution of the problem provides a binary envelope of the regarded molecules.

We end up with a system of linear inequalities in 0-1 variables for representing the electron density values at grid points. We use the following notations (the superscripts R and I stand for the real and imaginary part resp.)

$$a^R_\mathbf{j}(\mathbf{h}) = \cos(2\pi(\mathbf{h}\cdot\mathbf{M}^{-1}\mathbf{j})),\ a^I_\mathbf{j}(\mathbf{h}) = \sin(2\pi(\mathbf{h}\cdot\mathbf{M}^{-1}\mathbf{j})), \tag{20}$$

For centric reflections, we set

$$y^R_\mathbf{h} = y^I_\mathbf{h} = \alpha(\mathbf{h}), \tag{21}$$
$$b^R_\mathbf{h} = 2\kappa F(\mathbf{h})\cos\psi(\mathbf{h}),\ \ b^I_\mathbf{h} = 2\kappa F(\mathbf{h})\sin\psi(\mathbf{h}), \tag{22}$$
$$c^R_\mathbf{h} = \kappa F(\mathbf{h})\cos\psi(\mathbf{h}),\ \ c^I_\mathbf{h} = \kappa F(\mathbf{h})\sin\psi(\mathbf{h}), \tag{23}$$

and for acentric reflections

$$y^R_\mathbf{h} = \alpha(\mathbf{h}),\ \ y^I_\mathbf{h} = \beta(\mathbf{h}), \tag{24}$$
$$b^R_\mathbf{h} = 2\kappa F(\mathbf{h})2^{-1/2},\ \ b^I_\mathbf{h} = 2\kappa F(\mathbf{h})2^{-1/2}, \tag{25}$$
$$c^R_\mathbf{h} = \kappa F(\mathbf{h})2^{-1/2},\ \ c^I_\mathbf{h} = \kappa F(\mathbf{h})2^{-1/2}. \tag{26}$$

Here $\kappa \geq 0$ is a scaling factor reflecting that the magnitudes $F^{obs}(\mathbf{h})$ we get from the analysis of the diffraction pattern correspond to a real electron density distribution, and not to a binary one [2].

To further simplify, we will write

$$A^R(\mathbf{h},\mathbf{z},\mathbf{y}(\mathbf{h})) = \sum_{\mathbf{j}\in\mathit{\Pi}} a^R_\mathbf{j}(\mathbf{h})z_\mathbf{j} - \left(b^R_\mathbf{h} y^R_\mathbf{h} - c^R_\mathbf{h}\right), \tag{27}$$
$$A^I(\mathbf{h},\mathbf{z},\mathbf{y}(\mathbf{h})) = \sum_{\mathbf{j}\in\mathit{\Pi}} a^I_\mathbf{j}(\mathbf{h})z_\mathbf{j} - \left(b^I_\mathbf{h} y^I_\mathbf{h} - c^I_\mathbf{h}\right). \tag{28}$$

Then our binary variables $z_\mathbf{j}, y^R_\mathbf{h},\ y^I_\mathbf{h}$, with $\mathbf{j},\mathbf{h} \in \mathit{\Pi}$ have to satisfy

$$|A^R(\mathbf{h},\mathbf{z},\mathbf{y}(\mathbf{h}))| \leq \varepsilon_\mathbf{h} \text{ and } |A^I(\mathbf{h},\mathbf{z},\mathbf{y}(\mathbf{h}))| \leq \varepsilon_\mathbf{h},\ \forall \mathbf{h} \in \mathit{\Pi}, \tag{29}$$

where $\varepsilon_\mathbf{h} = \varepsilon_1(\mathbf{h})$ for centric and $\varepsilon_\mathbf{h} = \varepsilon(\mathbf{h})$ for acentric reflections.

6.2 Objective function

One possibility to work with the inequality system (29) is to apply a penalty method. Whenever $|A^R(\mathbf{h},\mathbf{z},\mathbf{y}(\mathbf{h}))| > \varepsilon_\mathbf{h}$, we include $|A^R(\mathbf{h},\mathbf{z},\mathbf{y}(\mathbf{h}))|$ as a penalty term, similarly for $|A^I(\mathbf{h},\mathbf{z},\mathbf{y}(\mathbf{h}))|$. This can be modelled as a mixed-integer optimisation problem with the help of additional variables $r^R_\mathbf{h}, r^I_\mathbf{h}, \mathbf{h} \in \mathit{\Pi}$ representing the penalties:

$$\begin{aligned} \min \quad & \sum_{\mathbf{h}\in \mathit{\Pi}} (r^R_{\mathbf{h}} + r^I_{\mathbf{h}}) && (30) \\ \text{subject to} \quad & 0 \le r^R_{\mathbf{h}},\ \ 0 \le r^I_{\mathbf{h}}, \quad \forall \mathbf{h} \in \mathit{\Pi} && (31) \\ & -\varepsilon_{\mathbf{h}} - r^R_{\mathbf{h}} \le A^R(\mathbf{h}, \mathbf{z}, \mathbf{y}(\mathbf{h})) \le \varepsilon_{\mathbf{h}} + r^R_{\mathbf{h}}, \quad \forall \mathbf{h} \in \mathit{\Pi}, && (32) \\ & -\varepsilon_{\mathbf{h}} - r^I_{\mathbf{h}} \le A^I(\mathbf{h}, \mathbf{z}, \mathbf{y}(\mathbf{h})) \le \varepsilon_{\mathbf{h}} + r^I_{\mathbf{h}}, \quad \forall \mathbf{h} \in \mathit{\Pi} && (33) \\ & z_{\mathbf{j}}, y^R_{\mathbf{h}},\ y^I_{\mathbf{h}} \in \{0,1\}, \quad \forall \mathbf{h}, \mathbf{j} \in \mathit{\Pi} && (34) \end{aligned}$$

7 Ongoing and further work

In this paper, we have described for a constraint programming audience the basics of our constraint-based approach to the phase problem in X-ray crystallography. Preliminary computational experiments and a crystallographic discussion of the results can be found in [2]. In this earlier work, we used the local search pseudo-Boolean solver WSATOIP [7], which was efficient only for a very small grid size ($6\times6\times6$ or $8\times8\times8$). To increase performance, we are currently experimenting with state-of-the-art integer programming and pseudo-Boolean solvers that have been developed in recent years.

Another line of research consists in modeling different geometric properties of crystals. This results in new constraints which can be added to the model, in order to increase the quality of the solutions. One such constraint is the connectivity constraint stating that the number of connected components in the binary envelope has to be less or equal to the number of molecules in the unit cell [3]. A corresponding integer programming formulation has been developed and is currently being tested.

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