**Crystal Molecular Dynamics**

**by**

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# Abstract of the dissertation

**Improved Molecular Dynamics and Macromolecular Crystallography through Simulations of Biomolecular Crystals**

**By Paweł A. Janowski**

**Dissertation Directors**

**David A. Case Ph.D and Darrin M. York Ph.D**

We present a broad effort at the development of crystal simulation methodology and its application to benefit both macromolecular crystallography and molecular dynamics methods. Crystallography is the current method of choice for structural determination of biomolecules, but it is hampered by the inherently time and space averaged nature of the experiment as well as methodological limitations that do not sufficiently account for the heterogeneous and dynamic nature of crystals. Molecular dynamics has proven itself as a method capable of probing the physics and chemistry of biomolecules on an atomic scale, but requires continued development of the underlying force field parameters to more accurately reproduce observables. Our effort has focused on developing the framework for molecular dynamics simulations of biomolecular crystals. We first present our methodology for performing crystal simulations and show how it is applied first to simple peptide crystals and then to increasingly complex biomolecular systems. Next we demonstrate the utility of crystal simulations for validation of molecular dynamics methods through two case studies of the biophysics of enzyme reactions. Finally we demonstrate the improvement to crystallographic methods that can be gained by incorporating molecular dynamics methods. Our work is of great benefit to both the molecular dynamics and macromolecular crystallography communities and proposes specific approaches to integrate the two fields for the benefit of both.

# Acknowledgements

I thank the Lord for the beautiful gift of His Creation, for the flowers, the mountains, the creatures and the fascinating molecular mechanisms of life that testify to His love. Thank you for the gift of reason, free will and desire of the Good, the True and the Beautiful that drives us in all our pursuits. May we one day attain the fullness of Love.

I thank Maria my wife who accompanied me throughout this path in person and in spirit. Thank you for your care, your patience, your inspiration. We have truly walked the past five years together in friendship. May we walk many more!

I thank my parents, Jolanta and Andrew, for their love in raising me to be the person I am. Thank you for teaching me what is important in life and what is not. I am forever indebted in the bond of filial love.

I thank my family and my friends for all your kindess, your love, all the good times spent together that will forever form part of the treasure of my memories. Without those wonderful times shared together, I would have been hard pressed to keep my sanity along the way.

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I thank all of the good people I have met. Each encounter with each one of you enriches both of us. Only in relationship with others does man become truly man. Never stop being who you are. I love you all.

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To the loving memory of my Father who would have wanted to be here but is even closer than we can imagine.

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# Abbreviations used

MD – Molecular dynamics;

BX – Biomolecular crystallography;

FT – Fourier transform;

Å – Ångstrom;

PDB – Protein Data Bank;

# Introduction

## Introduction and background

When, during my initial visit to Rutgers, Prof. David Case first mentioned the idea of improving crystallography through molecular dynamics of crystals, I felt a tinge of excitement. I had studied crystallography for two semesters during my undergraduate coursework at Jagiellonian University in Krakow. Lectures were eloquently delivered by one of the best teachers I’ve ever had, Prof. Krzysztof Lewiński. However, despite all my effort I could not grasp the essence of how a seemingly random pattern of dots on a sheet of paper could be turned into a three dimensional model of a biomolecule. I liked crystallography, but I also respected it and I feared it because I felt like there was something powerfully beautiful and mysterious about it. So when Dr. Case floated this idea of molecular dynamics of crystals I was excited: here was a chance to make up for my previous failing, to finally come to understand crystallography or to die trying. And to do that by using the molecular dynamics that I wanted to focus my Ph.D. studies on… it was the perfect project.

Thus I have happily spent the last five years focused on our effort to simulate biomolecular crystals with molecular dynamics. The original question we asked ourselves was simple: what can we learn from molecular dynamics of crystals? And this was quickly reformulated into the following four overarching questions that form the focus of this work:

1. What is the best way to carry out molecular dynamics of biomolecular crystals?
2. How can we use crystal simulations to improve molecular dynamics methods?
3. How can we use crystal simulations to improve crystallography methods?
4. What can we learn about real crystals from our simulations of crystals?

What follows is a brief introduction to the methods of crystallography and molecular dynamics, with special emphasis on aspects that relate directly to our work. We then discuss the goals and specific aims of this research and present the general organization of the dissertation before moving on to a presentation of the work in subsequent chapters.

### Crystallography background

Crystallography is a biophysical technique used to probe the three-dimensional distribution of atoms in molecules by analyzing the diffraction pattern of electromagnetic radiation on a crystal. As the name implies, crystallography requires that billions of copies of the molecule of study arrange themselves in a regular repeating array which is, by definition, a crystal. When used to study the structure of biomolecules, the method is referred to as macromolecular crystallography (MX). The fact that protein molecules can form crystals has been known for almost 150 years. In general, crystal formation of biomolecules is promoted by slowly removing solvent from a solution of the protein of study. If the solvent is removed too quickly or if the solution is not of the required purity, the protein molecules will precipitate out of the solution and form an amorphous powder. However if the solution becomes supersaturated slowly the molecules may pack themselves in a regularly repeating array held together by non-covalent chemical interactions in a way that minimizes the overall energy of the solute. Finding the exact conditions under which a given biomolecule crystallizes can be very challenging and in many cases constitutes the crux of the crystallographic method.

Once crystallized, the regularly repeating array of the crystal acts as a diffraction grating when light is shined upon it. Diffraction refers in general to the physical behavior of waves as they impact objects or slits. Etimologically, the term was coined by Francesco Maria Grimialdi in 1660 and comes from the Latin diffringere meaning “to break up into pieces”. In particular a regularly spaced array of slits or objects will cause the waves scattered off each object to interfere with each other. Wave crests lining up leads to constructive interference resulting in waves of higher amplitude, whereas when crests and troughs mix, destructive interference results in low amplitudes. Because of the dual nature of electromagnetic radiation, when light shines on diffraction grating it behaves like a wave and interference leads to the formation of bands (in the case of a one-dimensional diffraction grating) or spots (in the case of a two-dimensional diffraction grating). James Gregory’s observation of the diffraction pattern of light shining through a bird feather in the late 17th century constituted the discovery of the first diffraction grating.

A crystal is a repeating array of objects and thus can naturally act as a diffraction grating. However, because the wavelength of visible light is much larger than the typical spacing between array planes in molecular crystals, the diffraction of light on molecular crystals is not observed. The breakthrough moment for crystallography came in 1912 during a conversation between Paul Peter Ewald and Max van Laue, when van Laue suggested that x-rays (discovered in 1895 by Wilhelm Roentgen) might have a shorter wavelength that would allow their diffraction on crystals to be observed. In 1912 van Laue recorded the first ever x-ray diffraction pattern on a copper sulfate crystal. Shortly thereafter the father-son pair of William Lawrence Bragg and William Henry Bragg formulated the law that describes the diffraction of x-rays on a crystal. The first diffraction pattern from a protein crystal was obtained by John Desmond Bernal and Dorothy Hodgkin using pepsin, and the first three-dimensional structure of a protein molecule solved using x-ray crystallography was myoglobin in 1958 by John Kendrew. Van Laue, the Braggs and Kendrew all received Nobel Prizes for their work. In all thirteen Nobel Prizes have been award for work on or using crystallography.

The raw experimental data obtained in a crystallography experiment is a diffraction pattern (fig 1). This pattern is obtained as a beam of x-rays is focused on a crystal and the x-ray photos scatter (diffract) off the electron clouds of the atoms that make up the crystal. For the work presented here it is crucial to understand that the diffraction pattern is not obtained in a single instant from single x-rays scattering off the crystal. Rather it is obtained over a significant period of time usually ranging from a few up to about 30 minutes. The diffraction spots themselves require the constructive interference of a enormous number of x-rays to be observed. Furthermore the xrays themselves diffract off the billions plus molecules that make up the crystal. Thus one can say that crystallography is truly a time and space averaged experimient.

The diffraction patterned obtained in the crystallography experiment contains to essential pieces of information. The first of these is the location and spacing of the diffraction spots. The spots appear on the vertices of an array called the reciprocal space lattice which is a mathematical construct directly related to the parameters of the real space lattice. The real space lattice is the lattice of the crystal being studied. The appearance of diffraction spots can be described via the equation that is know as Bragg’s Law (named for the younger of the two Braggs mentioned above). Essentially, diffraction spots can only form in locations where the x-rays arrive in phase (in more simple language, where the crests and troughs of the arriving x-ray waves are lined up with each other). The condition for this to happen is that the distances of the paths that all the arriving x-rays travelled must all differ by an integral number of wavelengths (wavelength is the distance from one crest of the wave to the next) of the x-rays. This is presented schematically in Figure xx. The resulting description of the formation of diffraction spots is Bragg’s Law:

|  |  |  |
| --- | --- | --- |
|  |  | (Eq. ) |
|  |  |  |

where d is the spacing between a given set of planes in the array, θ is the angle at which the x-rays impact the set of planes, *n* is a positive integer and λ is the wavelength of the x-rays. The lattice (spacing between planes) and wavelength are constant under normal experimental conditions. Thus they uniquely specify the angle at which the scattered x-rays interact constructively and form a diffraction spot. Each spot thus corresponds uniquely to a specific set of planes in the array. Furthermore the angle is inversely proportional to the spacing. In other words smaller diffraction angles correspond to larger plane spacing in the lattice. Diffraction spots closer to the center of the diffraction pattern carry information about larger-scale features of the crystal. This is the basis for the concept of resolution: usually the diffraction pattern is only measured up to a certain radius: beyond that the angle of diffraction is too large and the spots too weak to be reliably recorded. Most importantly, by accurately measuring the location and spacing of the diffraction spots, one can deduce the spacing of the crystal’s array and thus obtain the parameters of the crystal unit cell (the three box dimensions *a*, *b*, *c* and three box angles α,β,γ.

The other essential information in the diffraction pattern are the intensities of the diffraction spots. Where the location of the spots reveals the unit cell parameters of the crystal array, the intensities of the spots tell us about the actual distribution of scattering objects, i.e. atoms, within each unit cell. The intensity of wave is equal to the square of it’s amplitude:

|  |  |  |
| --- | --- | --- |
|  |  | (Eq. ) |
|  |  |  |

We know from the previous discussion and Bragg’s Law that an identical scattering object located at each lattice plane of a certain spacing *d* would produce an ideal constructive interference between x-rays and consequently a diffraction spot at angle θ. But what happens if there are additional scattering objects located between the planes (Fig 1). The x-rays scattering off these objects will arrive at the diffraction location with a phase different from that of the rays scattering from the primary object. The resulting amplitude of the x-ray wave arriving at the diffraction spot location is obtained by summing the waves diffracted of each object within the crystal unit cell. Because the objects do not all lie integral distances of the scattering plane away from each other, the resulting waves that are summed are not all perfectly in phase. This results in an attenuation of the amplitude of the resulting wave and in extreme cases (Fig…) can results in a complete disappearance of the spot. If we treat the scattering electron density in the unit cell as continuous and divide it into infinitesimal sections *dx* along the scattering vector, the amplitude of the resulting diffraction spot can be obtained by integrating the partial x-ray wave scattered by each section *dx* of electron density:

|  |  |  |
| --- | --- | --- |
|  |  | (Eq. ) |
|  |  |  |

(Eq. 3) is presented for the one dimensional case but the generalization to three dimensions is straightforward. Each partial wave has an amplitude proportional to the electron density at *x* but with a phase relative to *x=0* of *2πhx*. The integration is performed over the unit cell vector *h* and the position *x* are described in fractional coordinates. ρ(x) is the electron density at position *x.* ***Fh*** is called the structure factor and is a wave described by an amplitude  and a phase . The intensity of the diffraction spot is related to the structure factor amplitude via (Eq. 2) As it turns out, this equation is equal to the mathematical transformation known as the Fourier Transform (FT). If the electron density is presented discontinuously as a set of scattering points(atoms) we obtain the discreet form of the structure factor equations:

|  |  |  |
| --- | --- | --- |
|  |  | (Eq. ) |
|  |  |  |

which we have now presented in three dimensions. *f* is the scattering contribution of atom *i* in the scattering direction corresponding to reflection ***h***. Conversely if we sum over each one of the diffracted waves (at each diffraction spot), we obtained the scattering electron density:

|  |  |  |
| --- | --- | --- |
|  |  | (Eq. ) |
|  |  |  |

Here again we present the one-dimensional form for pedagogical purposes. The summation is over all the diffraction spots of order *h*. This equation corresponds to the form of the inverse Fourier Transform and is the mathematical inverse of the (Eq. 3). Thus we arrive at one of the fundamental concepts of x-ray crystallography: the electron density of the crystal unit cell is the inverse FT of the diffraction pattern.

Now let us examine what is needed to calculate the electron density. (Eq. 5) states that we need to perform a summation over each diffraction spot. For each spot we need the amplitude and phase of its corresponding structure factor. The amplitude is readily obtained as the square root of the intensity measured in the experiment, but unfortunately there is no information about the phase. This is known as a phase problem. Many ingenious (and difficult to implement) methods exist to tackle the phase problem. Here let it suffice to say that if a sufficiently good estimate of the phases is obtained from which a sufficiently good estimate of the electron density can be calculated, then one can move on to the next part of the process, refinement, that is of much greater concern to us in the present work. In practice, the great majority of biomolecular structures are solved today by a technique called molecular replacement where a sufficiently good initial estimate of the electron density and phases is obtained by comparison to another similar molecule whose structure is already known.

Supposing that a fairly good estimate of the structure of the molecule has been obtained, one can move on to the next stage in the crystallography process which is called refinement (structural refinement, crystallographic refinement). Let us summarize what information we have at this stage. From the experiment we have the amplitudes of all the structure factors. If we also had the phases we could be able to calculate the electron density by (Eq. 5), but we usually don’t have the phases. One the other hand we have an estimated structure of the molecule. This is referred to as a model and usually consists of a position relative to the crystal unit cell for each atom that we know makes up the molecule we are studying. From these atomic positions we can calculate the overall all electron density of the model (the electron density is modelled by some mathematical function of the atom type. The functions most commonly used today are the Cromer-Mann Gaussian functions. ) Then from the electron density of the model we can calculate amplitudes and phases via (Eq. 3). We now have a set of experimentally measured structure factor amplitudes which are commonly referred to as Fobs, and we have a set of structure factor amplitudes calculated from the current best estimate model of the molecule, which are commonly referred to as *Fcalc*­. We can now quantify how well the proposed model accounts for the experimental data (or alternatively, how well the experimental data describes the proposed model) by comparing *Fcalc* to *Fobs*. This is usually done by a statistic known as the R-factor:

|  |  |  |
| --- | --- | --- |
|  |  | (Eq. ) |
|  |  |  |

where and are the amplitudes of the *F­­obs* and *Fcalc* set of structure factors respectively. We can envision the following process: given a starting model we calculate the R-factor. We know uses the phases obtained from the model via (Eq. 3) together with the experimental amplitudes *Fobs* to calculate an electron density via (Eq. 5). Next we adjust the atomic positions of our model to better fit the electron density calculated from *Fobs.* From there we calculate a new set of *Fcalc*and a new R-factor. If the R-factor is better (lower) than the previous one, than the new model is better than the previous model. This iterative process of calculating the electron density using phases from the model and adjusting atomic positions of the model to fit the resulting density is called refinement.

Refinement is a complex process and one could carry out the process just described by hand for a very long time and not obtain any significant improvement. Fortunately refinement can be formulated mathematically as a non-linear optimization problem and solved via one of many known mathematical algorithms. In the most basic formulation a least squares residual between the observed and calculated structure factor amplitudes is minimized:

|  |  |  |
| --- | --- | --- |
|  |  | (Eq. ) |
|  |  |  |

However, in practice this problem is often not well-defined because of the low ratio between the observed data (the set of structure factor amplitudes) and the parameters to be estimated via the optimization (the set of x,y,z coordinates of all the atoms in the asymmetric unit of the crystal) combined with the various sources of noise and error inherent in the x-ray diffraction experiment. Therefore several approaches exist to increase the data to parameter ratio. For example one can decrease the number of parameters to be refined by ignoring some set of atomic coordinates such as the hydrogens. Alternatively, one can increase the set of “observed” data by incorporating previous knowledge about the structure of molecules into the equation. For example, we know that an sp3 carbon-carbon bond should have a length of 1.54Å. This knowledge imposes a set of restraints on the final solution set of atomic positions in the molecule. Thus the residual to be minimized becomes:

|  |  |  |
| --- | --- | --- |
|  |  | (Eq. ) |
|  |  |  |

Here the x-ray term correspond to the same residual as in (Eq. 7). The chemistry (also sometimes called stereochemistry or geometry term) corresponds to the summed residual over all the restraints where r0 is the target value of the restraint and rcalc is the value of the restraint in the proposed model. *w* is a relative scaling weight that is adjusted in the refinement procedure to adjust the relative weight between the x-ray and the restraint term. The restraints used can be obtained from a variety of previously known information about the chemical structure of molecules but most commonly include knowledge of bond lengths, angles and torsions. The most popular crystal refinement programs in use today apply a set known as the Engh & Huber restraints which were derive from survey of accurate small molecule crystal structures from the Cambridge Crystallographic Database.

In practice several additional levels of complexity are present in modern refinement programs. First, the least squares formulation of the residual to be minimized is most often replaced with a maximum likelihood formulation. This allows for a statistical treatment of observation and restraint probabilities. The chemistry restraints can be incorporated as *a priori* knowledge in a Bayesian formulation. Statistical probability estimates can then be obtained on the resulting parameters. Furthermore, by incorporating this statistical knowledge a large degree of the model bias present in the calculated electron density maps due to the use of phases obtained from the model can be removed. Second, sophisticated mathematical algorithms such as the Limited memory Broyden–Fletcher–Goldfarb–Shanno (L-BFGS) algorithm are implemented to optimize the residual based on gradients of its component terms. Third the equation for calculating the structure factors from the model is often more complex than the integral shown in (Eq. 3) as it includes contributions from overall anisotropy and fluctuations and from the contribution of the unmodelled bulk solvent atoms that don’t show up distinctly in the experimental electron density. Lastly, crystallographic refinement usually proceeds in stages where the refinement of the x,y,z positions of the atoms in the asymmetric unit is just one stage. Other parameters that affect the calculated structure factors are refined in the other stages. Arguably the most important of these are the B-factors. Where the x,y,z coordinates describe the mean positions of the atom in the structure, B-factors describe how that atom’s instantaneous position fluctuates around that mean. A significant portion of that oscillation can be ascribed to thermal fluctuations. Thus B-factors are often also referred to as temperature factors. B-factors can be isotropic (describing a spherical isotropic fluctuation around the mean position and leading to a single additional parameter to be refined per atom) or anisotropic (describing a three dimensional elliptical oscillation, requiring a symmetric 3x3 tensor and thus 6 additional parameters to be refined per atom). In real space B-factors act like a convolution of a Gaussian function with the electron cloud around the mean position of an atom, effectively smearing out that atom’s electron density. The equation for the FT of the electron density thus becomes:

|  |  |  |
| --- | --- | --- |
|  |  | (Eq. ) |
|  |  |  |

Importantly the isotropic B-factor is related to the physical mean displacement of the atom around its mean position by the following equation:

|  |  |  |
| --- | --- | --- |
|  |  | (Eq. ) |
|  |  |  |

Other stages within the refinement process include refinement of bulk solvent contribution, overall anisotropic scaling parameters, atomic occupancies and alternate conformations, rigid body motion and translation-libration-screw (TLS) parameters. A full completion of each of the stages of refinement is usually referred to as a macrocycle. A complete solution of a crystallographic structure usually requires many macro-cycles of refinement interspersed with stages of manual adjustment of the structure to better fit the electron density.

The end result of refinement and of the crystallography experiment in general is a complete three dimensional structure of the atoms in the molecule as it is found in the crystal of study. As of July 4th, 2015, there were 110071 biomolecular structures in the Protein Data Bank (PDB) of which 98000 had been solved by x-ray crystallography. This represents 89% of all solved biomolecular atomic structures making x-ray crystallography by far the most important contributor of data to structural biology.

### Molecular Dynamics Background

Molecular dynamics is... F=ma, U=… etc. Standard force field used in Amber… Each term means…

Additional stuff, such as thermostat, shake, etc.

Standard simulation is done in solvated box, not crystal. Usually insert, remove, equilibrate…

MD has shown itself to be remarkably useful and successful. In the core just a simplified model. So much not modelled, but … examples….

### Goals and overview

Both methods exteremely valuable but also suffer from limiations. These limitations can be overcome at least in part through MD of crystals. Let’s look at each one.

Crystallography: First sources of error and noise. Sometimes so high (low res) that indeterminate. Simulations if reliable could tell us more to help resolve. Second, time and space average… End up with single static view. Myopic because one best rep view of the average. In fact crystals move (dynamic) and heterogenous. Recent efforts by several group aimed at resolving this. Ensemble refinement. Networks stuff from Fraser. Diffuse scattering from … Move and insights about functions. Also insights about crytals. By simulating over multiple copies (space) and ns (time) we can undo the averaging and get time-space resolved glimpse. A more comprehensive view of the crystal. Also, information about crystals: solvent distribution, etc lead to better refinement techniques. Finally, in itself a better set of priors.

MD is good but usually run as solvated box. Good sense but drawback that not comparing against experimental… Validation from crystals. Look directly at experimentals such as structure, fluctuations, electron density and amplitudes… Can check how well it’s doing and modify ff…

Organization: Part II developing methodology for simulating crystals. Apply to larger and conclusions about MD… Part III crystal syms applied to scientific investigation : two cases where used to validate Part III md of crysals applied to improve cyrstallograpjhy methods… Copyrights…

# Developing molecular dynamics of crystals.

## Fav8 1

Blah blah

## Fav8 2

Blah blah

## 4lzt

Blah blah

## DNA/RNA

Blah blah

# Applications of molecular dynamics of crystals

## Hairpin

Blah blah

## RnaseA

Blah blah

# Improved crystallographic methods through crystal molecular dynamics

## AFITT

Blah blah

## Phenix-Amber

Blah blah