**Crystal Molecular Dynamics**

**by**

**Paweł A. Janowski**

**A dissertation submitted to the**

**Graduate School of New Brunswick**

**Rutgers, the State University of New Jersey**

**in partial fulfillment of the requirements**

**for the degree of**

**Doctor of Philosophy**

**Graduate Program in Chemistry and Chemical Biology**

**and**

**Graduate Program in Computational Biology and Molecular Biophysics**

**Written under the direction of**

**Prof. David A. Case**

**and**

**Prof. Darrin M. York**

**and approved by**

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**New Brunswick, New Jersey**

**August, 2015**

# 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.

I thank all my colleagues, my lab mates, my teachers, all the wonderful scientists I have had the pleasure to work with. Thank you for showing me how exciting science is!

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.

Finally, and in a special way, I thank my advisors, Prof. David Case and Prof. Darrin York. You have challenged and inspired me constantly and at the same time been caring guides along the path. I have learned so much from you, not just about science but about what it means to be good human beings. I will remain forever grateful.

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

Contents

[Abstract of the dissertation ii](#_Toc423532554)

[Acknowledgements iv](#_Toc423532555)

[Contents vi](#_Toc423532556)

[Abbreviations used vii](#_Toc423532557)

[Chapter 1. Introduction 1](#_Toc423532558)

[1.1. Biomolecular Crystallography 2](#_Toc423532559)

[1.2. Molecular Dynamics 2](#_Toc423532560)

[1.3. Goals and overview 2](#_Toc423532561)

[Chapter 2. Developing molecular dynamics of crystals. 3](#_Toc423532562)

[2.1. Fav8 1 3](#_Toc423532563)

[2.2. Fav8 2 3](#_Toc423532564)

[2.3. 4lzt 3](#_Toc423532565)

[2.4. DNA/RNA 3](#_Toc423532566)

[Chapter 3. Applications of molecular dynamics of crystals 3](#_Toc423532567)

[3.1. Hairpin 3](#_Toc423532568)

[3.2. RnaseA 3](#_Toc423532569)

[Chapter 4. Improved crystallographic methods through crystal molecular dynamics 3](#_Toc423532570)

[4.1. AFITT 3](#_Toc423532571)

[4.2. Phenix-Amber 4](#_Toc423532572)

# Abbreviations used

MD – Molecular dynamics;

BX – Biomolecular crystallography;

# Introduction

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.

## Biomolecular Crystallography

### What is crystallography

Blah blah

### Theory

Blah blah

### Refinement

Blah blah

## ***Molecular Dynamics***

### What is Molcular Dynamics?

Blah blah

### Theory

Blah blah

### Molecular Dynamics of Crystals

Blah blah

## Goals and overview

Blah blah

# 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