



## UvA-DARE (Digital Academic Repository)

### Hydration layer dynamics and association mechanisms of food and antifreeze proteins

*A Molecular Dynamics and Transition Path Sampling study*

Brotzakis, Z.F.

**Publication date**

2017

**Document Version**

Other version

**License**

Other

[Link to publication](#)

**Citation for published version (APA):**

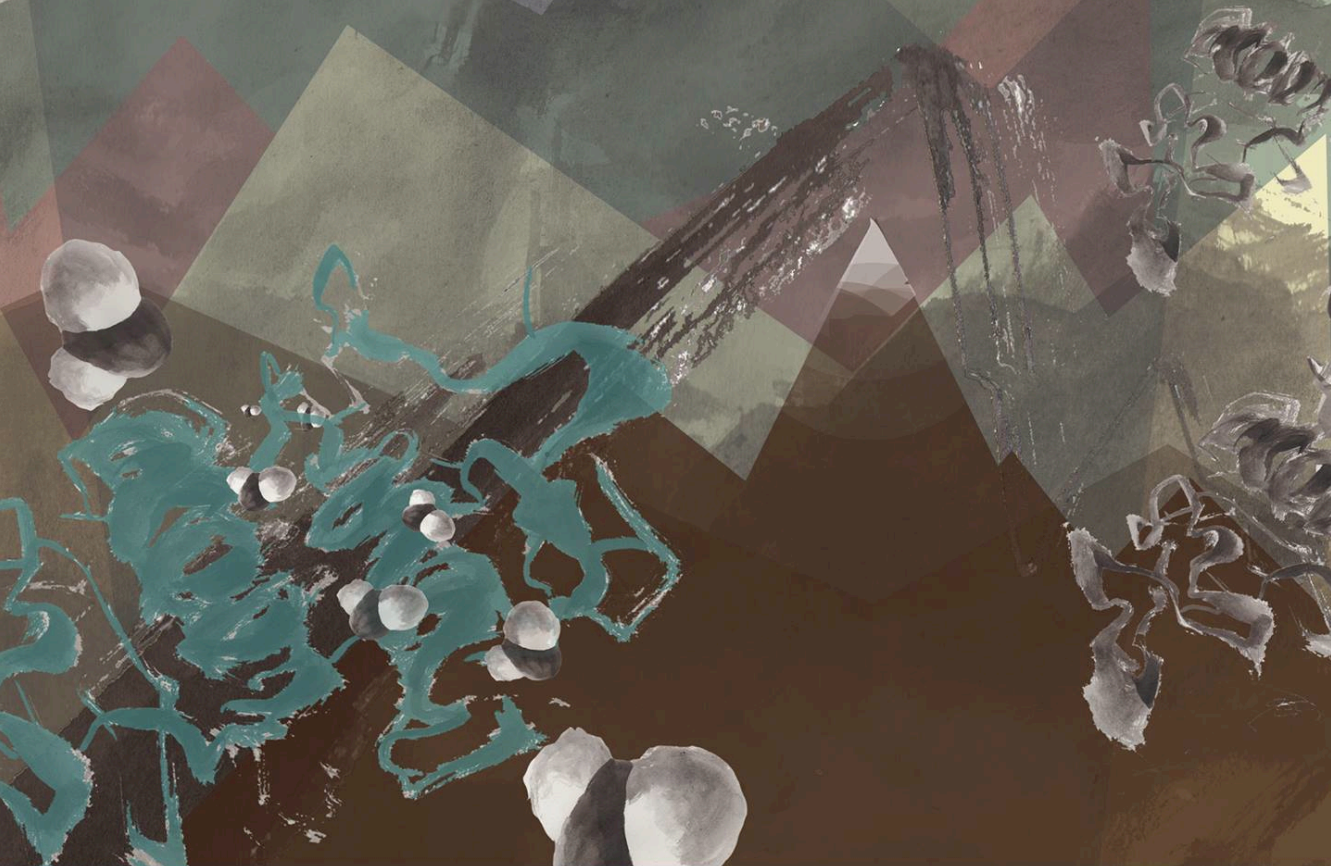
Brotzakis, Z. F. (2017). *Hydration layer dynamics and association mechanisms of food and antifreeze proteins: A Molecular Dynamics and Transition Path Sampling study*. [Thesis, fully internal, Universiteit van Amsterdam].

**General rights**

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

**Disclaimer/Complaints regulations**

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, P.O. Box 19185, 1000 GD Amsterdam, The Netherlands. You will be contacted as soon as possible.



# Hydration layer dynamics and association mechanisms of food and antifreeze proteins

A Molecular Dynamics and Transition Path Sampling study

Zacharias Faidon Brotzakis



# Hydration layer dynamics and association mechanisms of food and antifreeze proteins

A Molecular Dynamics and Transition Path Sampling study

## ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor  
aan de Universiteit van Amsterdam,  
op gezag van de Rector Magnificus  
prof. dr. ir. K. I. J. Maex  
ten overstaan van een door het College voor Promoties ingestelde  
commissie, in het openbaar te verdedigen in de Agnietenkapel

op dinsdag 7 maart 2017, te 10.00 uur

door

**Zacharias Faidon Brotzakis**  
geboren te Athene, Griekenland

Promotiecommissie

Promotor:

- prof. dr. P. G. Bolhuis (HIMS, Universiteit van Amsterdam)

Overige leden:

- prof. dr. H. J. Bakker (FOM institute AMOLF)
- prof. dr. D. Laage (École Normale Supérieure Paris)
- prof. dr. E. J. Meijer (HIMS, Universiteit van Amsterdam)
- prof. dr. L. Visscher (Vrije Universiteit Amsterdam)
- dr. I. K. Voets (Technische Universiteit Eindhoven)
- dr. J. Vreede (HIMS, Universiteit van Amsterdam)

Faculteit der Natuurwetenschappen, Wiskunde en Informatica

ISBN: 978-94-028-0537-6

The research reported in this thesis was carried out at the Van 't Hoff Institute for Molecular Sciences, Faculty of Science, University of Amsterdam (Science Park 904, 1098 XH, Amsterdam, The Netherlands) with financial support by NanoNextNL, a micro and nanotechnology consortium of the Government of The Netherlands and 130 partners.).

# Contents

<b>1</b>	<b>Introduction</b>	<b>7</b>
1.1	Proteins in nature and technology . . . . .	7
1.1.1	Protein function . . . . .	7
1.1.2	Food Proteins . . . . .	8
1.1.3	Ice binding and anti-freeze proteins . . . . .	8
1.2	Protein structure and interactions . . . . .	9
1.2.1	Structure of proteins . . . . .	9
1.2.2	Protein-protein interactions . . . . .	10
1.3	The role of solvent (water) and co-solutes (e.g. salts) on protein stability . . . . .	13
1.4	Protein association . . . . .	16
1.5	Molecular simulations . . . . .	20
1.6	Aim of the thesis . . . . .	21
1.7	Outline of the thesis . . . . .	22
<b>2</b>	<b>Methods</b>	<b>25</b>
2.1	Molecular Dynamics . . . . .	26
2.1.1	Molecular Dynamics of solvated proteins . . . . .	29
2.2	Rare Event methods . . . . .	32
2.3	Transition Path Sampling . . . . .	32
2.3.1	Monte Carlo of trajectories . . . . .	34
2.3.2	Shooting move . . . . .	35
<b>3</b>	<b>Dynamics of hydration water around native and misfolded <math>\alpha</math>-lactalbumin</b>	<b>41</b>
3.1	Introduction . . . . .	42
3.2	Methods . . . . .	43
3.2.1	Simulation setup . . . . .	43

3.2.2	Analysis . . . . .	44
3.2.3	Polarisation-resolved femtosecond infrared spectroscopy . . . . .	46
3.3	Results and Discussion . . . . .	47
3.3.1	Hydrogen bond dynamics . . . . .	47
3.3.2	Reorientation dynamics . . . . .	50
3.4	Conclusions . . . . .	60
<b>Appendices</b>		<b>62</b>
Appendix 3.A	Water HB and reorientation dynamics analysis. . . . .	62
<b>4</b>	<b>Correlation between water structure and dynamics in the hydration layer of a type III ocean pout anti-freeze protein</b>	<b>75</b>
4.1	Introduction . . . . .	75
4.2	Methods . . . . .	77
4.2.1	Simulation setup . . . . .	77
4.2.2	Analysis . . . . .	78
4.3	Results and Discussion . . . . .	81
4.3.1	Water reorientation dynamics slows down at surface . . . . .	81
4.3.2	Water reorientation dynamics differs locally . . . . .	82
4.3.3	Hydration water structure . . . . .	83
4.3.4	Structure - reorientation time correlation . . . . .	84
4.3.5	Effect of dehydration . . . . .	87
4.4	Conclusions . . . . .	89
<b>Appendices</b>		<b>91</b>
Appendix 4.A	Water structure and dynamics for different temperatures and forcefields. . . . .	91
<b>5</b>	<b>Stability and growth mechanism of self-assembling anti-freeze cyclic peptides</b>	<b>99</b>
5.1	Introduction . . . . .	100
5.2	Methods . . . . .	101
5.2.1	System setup . . . . .	101
5.2.2	Molecular dynamics . . . . .	102
5.2.3	Transition Path Sampling . . . . .	103
5.3	Results and Discussion . . . . .	105
5.3.1	Nanotube equilibrium properties . . . . .	105
5.3.2	Mechanism of self-assembly by Transition Path Sampling . . . . .	108
5.3.3	Analysis of the path ensemble . . . . .	111

5.3.4	Comparison of the association time scales . . . . .	115
5.4	Conclusion . . . . .	117
<b>Appendices</b>		<b>119</b>
	Appendix 5.A Brute force MD and sequences of different nanotubes . . . . .	119
<b>6</b>	<b>Spring shooting, a novel efficient transition path sampling move</b>	<b>123</b>
6.1	Introduction . . . . .	123
6.2	Methods . . . . .	126
	6.2.1 Derivation of the spring shooting algorithm . . . . .	126
	6.2.2 Simulation details . . . . .	130
6.3	Results and Discussion . . . . .	133
	6.3.1 2D Langevin model . . . . .	133
	6.3.2 FF dimer association . . . . .	139
	6.3.3 Dissociation of $\beta$ -lactoglobulin dimer . . . . .	144
6.4	Conclusion . . . . .	145
<b>Appendices</b>		<b>146</b>
	Appendix 6.A Initialization of the $\beta$ -lactoglobulin dimer paths . . . . .	146
<b>7</b>	<b>Elucidating the mechanism and role of solvent for <math>\beta</math>-lactoglobulin dimerization using Transition Path Sampling</b>	<b>151</b>
7.1	Introduction . . . . .	151
7.2	Methods . . . . .	153
	7.2.1 Molecular Dynamics . . . . .	153
	7.2.2 Transition path sampling . . . . .	154
	7.2.3 Analysis of the water dynamics . . . . .	158
7.3	Results-Discussion . . . . .	162
	7.3.1 Transition Path Sampling . . . . .	162
	7.3.2 Hydration states of water . . . . .	169
7.4	Conclusions . . . . .	173
<b>Appendices</b>		<b>174</b>
	Appendix 7.A Initialization of paths /Analysis . . . . .	174