

Contents

1	Introduction	7
1.1	Protein crystallography	7
1.2	The phase problem	8
1.3	Experimental phasing	9
1.4	Ab initio phasing	10
1.4.1	Direct methods	10
1.4.2	Molecular replacement	10
1.4.3	Low-resolution phasing	10
1.5	Phase improvement	11
1.5.1	Density modification	11
1.5.2	Model building	12
1.5.3	Refinement	12
1.6	Conditional Optimization	14
1.7	Scope and outline of this thesis	15
2	Conditional Optimization: a new formalism for protein structure refinement	17
2.1	Introduction	18
2.2	Conditional Formalism	19
2.3	Experimental	23
2.3.1	Implementation	23
2.3.2	Test case	24
2.3.3	Refinement protocols	24
2.4	Results	29
2.4.1	Refinement of scrambled models	29
2.4.2	Refinement of random atom distributions	32
2.5	Discussion	34
3	Development of a force field for conditional optimization of protein structures	35
3.1	Introduction	36
3.2	Mean-force potential for protein structures	36
3.2.1	Brief review of the conditional formalism	36
3.2.2	The general parameter set	38
3.2.3	Protein-specific force fields	40

3.3	Experimental	41
3.4	Results & discussion	44
3.4.1	Stability of correct structures	44
3.4.2	Searching behaviour in optimization	45
3.5	Conclusions	50
4	The potentials of conditional optimization in automated model building	53
4.1	Introduction	54
4.2	Experimental	55
4.3	Results	59
4.4	Discussion & conclusions	64
5	Testing conditional optimization for application to <i>ab initio</i> phasing of protein structures	67
5.1	Introduction	68
5.2	Experimental	69
5.2.1	Test case	69
5.2.2	Optimization protocol	70
5.2.3	Phase probability estimation	72
5.3	Results	72
5.3.1	Condensation and the influence of low-resolution data	72
5.3.2	Quality of the phase probability estimates	73
5.3.3	Convergence behaviour	77
5.4	Discussion	79
5.4.1	The Alpha-1 test case	79
5.4.2	Implications for further development	82
5.5	Conclusions	84
6	Summary & general discussion	85
	Bibliography	87
	Samenvatting & algemene discussie	91
	Curriculum Vitae	93
	Dankwoord	94