

---

# Contents

---

<b>1.</b>	<b>Basis Sets for <i>Ab Initio</i> Molecular Orbital Calculations and Intermolecular Interactions</b>	<b>1</b>
	<i>David Feller and Ernest R. Davidson</i>	
	Introduction	1
	Some Terminology	4
	Gaussian Compared to Exponential Functions	4
	Contracted Gaussians	4
	Polarization Functions	7
	Complete Sets	8
	The Basis Set Superposition Error	9
	Choosing a Basis Set	10
	Molecular Geometries	11
	Energy Differences	15
	One-Electron Properties	20
	In-Depth Discussion	20
	Sources of Gaussian Primitives and Contraction	
	Coefficients	20
	Even-Tempered Gaussians	21
	Well-Tempered Gaussians	22
	MINI- <i>i</i> , MIDI- <i>i</i> and MAXI- <i>i</i> etc.	26
	Still Others	27
	Atomic Natural Orbitals	27
	Functions for Augmenting Basis Sets	29
	Weak Interactions	34
	Conclusion	36
	References	37
<b>2.</b>	<b>Semiempirical Molecular Orbital Methods</b>	<b>45</b>
	<i>James J. P. Stewart</i>	
	Introduction	45
	History of Semiempirical Methods	46
	Complete Neglect of Differential Overlap	47

Complete Neglect of Differential Overlap Version 2	50
Intermediate Neglect of Differential Overlap	51
Neglect of Diatomic Differential Overlap (NDDO)	52
Modified Neglect of Diatomic Overlap	55
Austin Model 1	57
Parametric Method Number 3	58
Self-Consistent Field Convergors	58
Strong and Weak Points of NDDO Semiempirical Methods	61
MINDO/3	62
MNDO, AM1, and PM3	62
Theoretical Experiments	73
Stationary Points	74
General Procedure for Characterizing a Reaction	74
Reaction Path	75
Time-Dependent Phenomena	76
Future of Semiempirical Methods	77
Summary	78
References	78
 3. Properties of Molecules by Direct Calculation	 83
<i>Clifford E. Dykstra, Joseph D. Augspurger, Bernard Kirtman,</i> <i>and David J. Malik</i>	
Introduction	83
Overview of Quantum Mechanical Properties	84
Correspondence between Energy Derivatives and Properties	84
Differentiation of the Schrödinger Equation	85
The Development of Methods for Property Determinations	87
Semiempirical Approaches	87
<i>Ab Initio</i> Methods	89
Detailed View of <i>Ab Initio</i> Methods	92
Hamiltonians and Operators	92
Computational Organization of the Differentiation Process	95
Derivatives of Electronic Wavefunctions	97
Local Space Concepts for Extended Systems	99
Vibrations and Rotations	100
Direct Property Calculations	103
Electrical Properties	103
Magnetic Properties	107
Force Constants	109
Transition Probabilities and Optical Properties	110

---

Summary	111
References	112
 4. The Application of Quantitative Design Strategies in Pesticide Discovery	 119
Ernest L. Plummer	
Introduction	119
The Selection of a Strategy	122
The Well-Designed Substituent Set	126
The Ideal Substituent Set Should Cover All Factors That Control Activity	127
The Ideal Substituent Set Should Cover the Selected Factor Space as Completely as Possible	128
The Ideal Substituent Set Should Span Orthogonal Dimensions of Parameter Space	129
The Ideal Set Should Contain the Minimum Number of Substituents Necessary to Avoid Chance Correlations and Still Meet the Desired Goal	130
Target Compounds Should Be Chosen to Preserve Synthetic Resources But Should Not Be Chosen Just Because They Are Easy to Synthesize	131
The Derivatives Must Be Stable under the Conditions of Bioevaluation	131
Analysis Strategies	132
The Topliss Tree	132
Free-Wilson Analysis	135
A Strategy for Lead Optimization Using Multiple Linear Regression Analysis	138
Choose the Optimal Pattern for Substitution	139
Choose the Factors (Parameters) That Are Likely to Be Important	142
Select a Substituent Set	143
Synthesize and Submit for Biological Evaluation	152
Plot Each Parameter versus Activity	154
Generate Squared Terms if Justified by the Single Parameter Plots	157
Run All Combinations of the Chosen Parameters through Linear Regression Analysis to the Limits of Statistical Significance	158
Repeat the Process Until the QSAR Is Stable	160
Sequential Simplex Optimization (SSO)	161
Conclusion	164
References	165

<b>5. Chemometrics and Multivariate Analysis in Analytical Chemistry</b>	<b>169</b>
<i>Peter C. Jurs</i>	
Introduction	169
Response Surfaces, Sampling, and Optimization	170
Signal Processing	173
Principal Components Analysis and Factor Analysis	175
Calibration and Mixture Analysis	178
Classification and Clustering	182
Classification	183
Clustering	184
Library Searching	186
Molecular Structure-Property Relationships	188
Gas Chromatographic Retention Indices for Diverse Drug Compounds	192
Simulation of Carbon-13 Nuclear Magnetic Resonance Spectra of Methyl-Substituted Norbornan-2-ols	198
Summary and Conclusions	207
References	208
<b>6. Searching Databases of Three-Dimensional Structures</b>	<b>213</b>
<i>Yvonne C. Martin, Mark G. Bures, and Peter Willet</i>	
Why Are Such Methods Needed?	213
Tools for Searching Two-Dimensional Chemical Structures of Small Molecules	217
Computer Representation of Two-Dimensional Chemical Structures	218
Searching Files of Two-Dimensional Chemical Structures	220
Languages for Chemical Programming	222
System Design for Chemical Information Systems	224
Similarity of Small Molecules Based on Two-Dimensional Structure	225
Substituent Effects on Molecular Properties	225
Two-Dimensional Topological Descriptors of Molecular Shape	226
Similarity of Small Molecules Based on Three-Dimensional Structure	226
Three-Dimensional Similarity Based on Geometric Properties	227
Three-Dimensional Similarity Based on Steric Properties	231
Databases of Three-Dimensional Structures of Molecules	234

---

Searching Files of Three-Dimensional Structures of Small Molecules	236
Programs from the Cambridge Crystallographic Data Centre	236
Searching Based Principally on Shape Properties	237
Strategies Based on Screen Searching	238
Strategies Based on a Substructure Specification Language	243
Databases and Searching of Multiple Three-Dimensional Pharmacophoric Patterns	248
Searching Files of Three-Dimensional Protein Structures	249
The Protein Data Bank	249
Identification of Patterns of Atoms	249
Identification of Secondary Structure Motifs	252
Conclusions	253
Appendix: Sources of Databases and Programs	255
References	256
<b>7. Molecular Surfaces</b>	<b>265</b>
<i>Paul G. Mezey</i>	
Introduction	265
Molecular Body and Molecular Surface	266
Classical Models for Molecular Surfaces: Hard Spheres and van der Waals Surfaces (VDWSs)	267
Electron Density Contour Surfaces	269
The Density Domain Approach to Chemical Bonding (DDA)	271
Molecular Electrostatic Potential	274
Molecular Orbitals	276
Solvent Accessible Surfaces	278
Union Surfaces	279
Interpenetration of Molecular Contour Surfaces	281
Shape Analysis of Molecular Surfaces	282
Conclusions	288
References	289
<b>8. Computer Simulation of Biomolecular Systems Using Molecular Dynamics and Free Energy Perturbation Methods</b>	<b>295</b>
<i>Terry P. Lybrand</i>	
Introduction	295
Models	296

Methods	297
Energy Minimization	298
Normal Mode Analysis	298
Monte Carlo	299
Molecular Dynamics	300
Free Energy Perturbation Methods	308
Summary	314
References	315
<b>9. Aspects of Molecular Modeling</b>	<b>321</b>
<i>Donald B. Boyd</i>	
Introduction	321
Quantum Mechanics	323
Why Use Quantum Mechanics?	323
Theory	325
Approximations	326
Comparison of <i>Ab Initio</i> and Semiempirical MO	
Methods	328
Input	329
Output	331
Basis Sets for <i>Ab Initio</i> Calculations	332
Caveats on Basis Sets	334
Post-Hartree-Fock Treatments	334
Selection of an MO Method	336
Numerical Sensitivity of Geometry Optimization	
Procedures	337
Quality of Results from Quantum Mechanical Methods	339
Information from X-Ray Databases for Molecular Modeling	341
Standard Geometries	345
Distance Geometry	345
Summary	348
References	351
<b>10. Successes of Computer-Assisted Molecular Design</b>	<b>355</b>
<i>Donald B. Boyd</i>	
Levels of Success	355
Norfloxacin	359
Metamitron	360
Bromobutide	361
Myclobutanil	362
Conclusion	364
References	365

---

11.	<b>Perspectives on <i>Ab Initio</i> Calculations</b>	373
	<i>Ernest R. Davidson</i>	
	Atomic Orbitals Do Not Work	375
	The Error in $\Psi$ Is Largest Where $\Psi$ Is Largest	376
	The Number of Electron Pairs Is $N(N - 1)/2$	377
	The Computer Cost, at Fixed Accuracy, Grows Like $N!$	378
	Computers Do Not Solve Problems, People Do	379
	<b>Appendix: Compendium of Software for Molecular Modeling</b>	383
	<i>Donald B. Boyd</i>	
	Personal Computers	384
	Minicomputers-Superminicomputers-Workstations	387
	Supercomputers	392
	<b>Subject Index</b>	393