

---

# Contents

<b>1</b>	<b>The Aqueous Interface of a Soluble Protein or the Birth of Epistuctural Biology</b>	<b>1</b>
1.1	The Aqueous Interface as Determined by the Structure of a Soluble Protein	2
1.2	Protein Dehydrons Generate Interfacial Tension: Breakdown of the Conventional Dielectric Theory at Nanoscales	6
1.3	The Aqueous Interface from a Structure-Centric Perspective: Many-Body Problem for the Drug Designer	10
1.4	Dehydrons Promote Protein Associations: A Structural Perspective	13
1.5	Dehydron Stickiness: Epistuctural View of Biomolecular Interfaces	16
1.6	Biomolecular Interfaces and Drug-Target Associations: A Glimpse at New Possibilities for Molecular Engineering	19
1.7	Biomolecular Interfaces Constrain the Architecture of Soluble Proteins	21
	Problems	30
	References	31
<b>2</b>	<b>Electrostatic Exploration of Biomolecular Interfaces: The Chemical Function of Interfacial Water</b>	<b>35</b>
2.1	Interfacial Tension and Non-Debye Polarization of Interfacial Water	35
2.2	Non-Debye Polarization of the Aqueous Interface of a Soluble Protein	39
2.3	Chemical Functionality of the Aqueous Interface: A Consequence of the Breakdown of Debye's Dielectric Picture	42
2.4	A New Twist on Enzyme Catalysis: Nanoscale Packing Defects as Catalytic Stimulators	48
	Problems	50
	References	51

<b>3</b>	<b>Semiempirical Solution to the Protein Folding Problem Through a Combination of Structural and Epiststructural Approaches. . . . .</b>	<b>53</b>
3.1	Structure-Centric Approach to Protein Folding: Cooperativity and Wrapping Delineate a Many-Body Problem. . . . .	54
3.2	Hydrogen-Bond Wrapping Requires Cooperative Folding . . . . .	56
3.3	Generating Cooperative Folding Trajectories . . . . .	58
3.4	Wrapping Patterns Along Folding Pathways . . . . .	62
3.5	Nanoscale Dielectric Theory of Folding Cooperativity: The Conventional “Effective Permittivity” Approach . . . . .	67
3.6	The Dehydronic Field Commits the Chain to Fold . . . . .	71
3.7	The Biomolecular Interface in Protein Folding: The Principle of Minimal Epiststructural Distortion . . . . .	72
3.8	What Did It Take to Solve the Protein Folding Problem?. . . . .	78
	Problems. . . . .	79
	References. . . . .	81
<b>4</b>	<b>Packing Defects and Protein Hydration: Dynamics of the Aqueous Interface . . . . .</b>	<b>83</b>
4.1	Dynamic Singularities of Biomolecular Interfaces . . . . .	83
4.2	Impact of Protein Packing Defects on Interfacial Dynamics. . . . .	84
4.3	Dehydrons Loosen up the Aqueous Interface . . . . .	86
4.4	Displacing Loose Hydrating Molecules: A Blueprint for the Drug Designer . . . . .	90
4.5	How Do Dehydrons Steer Interfacial Water? . . . . .	92
	Problems. . . . .	93
	References. . . . .	95
<b>5</b>	<b>Proteins in the Order–Disorder Twilight: Unstable Interfaces Promote Protein Aggregation. . . . .</b>	<b>97</b>
5.1	Dehydron Clusters and Disordered Regions . . . . .	97
5.2	Semiclassical View of Discrete Dielectrics Around Dehydrons . . . . .	99
5.3	Semiclassical Treatment of Dielectric Modulation of Interfacial Water Around Dehydrons . . . . .	102
5.4	Dielectric Quenching in the p53 DNA-Binding Domain: A Study Case. . . . .	106
5.5	Proteins with Dehydron Clusters: Structural View of the Order–Disorder Twilight . . . . .	108

5.6	Inferring Dehydrons from Protein Sequence: Water-Exposed Backbone and Disorder Propensity . . . . .	111
5.7	Misfolding and Aggregation: Massive Violation of Architectural Constraints for Protein Structure . . . . .	115
	Problems. . . . .	120
	References. . . . .	124
<b>6</b>	<b>Evolution of Protein Structure Degradation and Lessons for the Drug Designer . . . . .</b>	<b>127</b>
6.1	An Evolutionary Context for the Drug Designer . . . . .	127
6.2	Comparing Protein Wrapping Across Species: Hallmarks of Nonadaptive Traits. . . . .	129
6.3	Wrapping and Natural Selection . . . . .	129
6.4	How Do Humans Cope with Inefficient Selection? . . . . .	132
6.4.1	Regulatory Patterns Segregating Paralog Proteins . . . . .	133
6.4.2	Wrapping Deficiency Causes Dosage Imbalance Causes Regulation Dissimilarity . . . . .	136
6.5	Human Capacitance to Cope with Dosage Imbalances in Under-Wrapped Proteins . . . . .	142
6.6	Fitness Catastrophes for the Human Species Arising from Nature's "Evolutionary Gambit" to Promote Interactome Complexity. . . . .	143
6.7	Why Should the Drug Designer Be Mindful of Molecular Evolution? . . . . .	145
6.8	Some Consequences for Evolutionary Technology. . . . .	147
	Problem . . . . .	148
	References. . . . .	148
<b>7</b>	<b>Chemical Functionality of the Aqueous Interface in Soluble Proteins . . . . .</b>	<b>151</b>
7.1	Dehydrons Induce Chemical Basicity in the Aqueous Interface . . . . .	151
7.2	Exploring the Chemical Functionality of Dehydrons in Specific Proteins . . . . .	156
7.3	The Dehydron as a Two-Step Catalytic Engine. . . . .	161
7.4	Quantum Mechanical Exploration of Chemical Events Involving Dehydrons. . . . .	161
7.5	Methodology for Quantum Mechanical Assessment of the Chemical Role of Dehydrons . . . . .	163
7.6	Capturing Chemical Events Involving Dehydrons . . . . .	165
	Problem . . . . .	172
	References. . . . .	172

<b>8</b>	<b>The Biomolecular Interface as a Selectivity Filter for Drug-Based Targeted Therapy . . . . .</b>	<b>175</b>
8.1	The Control of Drug Specificity: An Imperative for Drug Design . . . . .	176
8.2	Epiststructural Drug Design: Ligands Wrap Protein Packing Defects upon Binding to the Target Protein . . . . .	180
8.3	Poor Dehydron Wrappers Make Poor Drugs Even at High Affinity: The <i>Staurosporine</i> Lesson . . . . .	182
8.4	The Biomolecular Interface as a Selectivity Filter . . . . .	183
8.5	Epiststructure-Based Drug Design . . . . .	184
8.6	Wrapping-Based Selectivity . . . . .	187
8.7	Targeting Dehydrons is an Effective Strategy for Selectively Blocking Protein Functions . . . . .	189
8.8	Advantages and Shortcomings in Targeting Activation-Loop Dehydrons . . . . .	190
	Problem . . . . .	190
	References. . . . .	191
<b>9</b>	<b>Wrapping-Based Re-engineering of an Anticancer Drug to Make it Safer . . . . .</b>	<b>193</b>
9.1	Building a Safer <i>Imatinib</i> . . . . .	193
9.2	Unique Dynamic Singularities in the Aqueous Interface of the Target Protein Provide the Blueprint for Imatinib Redesign . . . . .	194
9.3	<i>In Silico</i> Assays of the Efficacy of a Wrapping Drug to Displace Labile Interfacial Water. . . . .	197
9.4	High-Throughput Screening: Test Tube Validation of the Engineered Specificity . . . . .	197
9.5	In Vitro Assays: Selectively Modulating the Impact of Imatinib. . . . .	202
9.6	In Vitro Assay of the Selective Anticancer Activity of the Wrapping Design. . . . .	206
9.7	Enhanced Safety of the Wrapping-Based Imatinib Redesign in Animal Models of Gastrointestinal Stromal Tumor. . . . .	209
9.8	Controlled Specificity Through Rational Design . . . . .	212
	Problems. . . . .	212
	References. . . . .	214
<b>10</b>	<b>Biomolecular Interfaces Provide Universal Markers for Drug Specificity and Personalized Medicine . . . . .</b>	<b>217</b>
10.1	Universal Selectivity Filter for Rationally Designed Kinase Inhibitors: An Imperative for Drug Safety and Personalized Medicine . . . . .	218

10.2	A Computational Tool Box for Comparative Analysis of Biomolecular Interfaces Across the Human Kinome . . . . .	219
10.2.1	Dehydron Inference for Proteins with Unreported Structure . . . . .	219
10.2.2	Alignment of Targetable Regions in the Biomolecular Interface Across the Human Kinome . . . . .	220
10.3	Is the Biomolecular Interface Pharmacologically Relevant? . . . . .	221
10.4	Wrapping-Based Target Library for the Human Kinome: Broadening the Technological Base of Drug Discovery . . . . .	226
10.5	Annotations in a Library of Specificity-Promoting Target Features . . . . .	228
10.6	Kinome-Wide Dehydron Library as a Biotechnological Resource . . . . .	233
10.7	Wrapping Specificity for Personalized Molecular Medicine . . . . .	233
	Problem . . . . .	239
	References . . . . .	240
<b>11</b>	<b>Controlling Induced Folding Through Wrapping Drug Design . . . . .</b>	<b>243</b>
11.1	Induced Folding: The <i>Bête Noire</i> of Drug Design . . . . .	244
11.2	Wrapping the Floppy Target: A Tractable Case of Induced Folding . . . . .	244
11.3	Crating Floppy Regions in Drug Targets . . . . .	247
11.4	Steering Induced Folding: A Dynamic Selectivity Filter . . . . .	251
11.5	WBZ_4: First JNK Inhibitor Designed Using Dynamic Information . . . . .	252
11.6	Induced Disruption of Preformed Dehydrons: A Design Strategy Based on Boosting Entropy? . . . . .	253
	Problems . . . . .	254
	References . . . . .	257
<b>12</b>	<b>Wrapping Drug Combinations for Therapeutic Editing of Side Effects: Systems Biology Meets Wrapping Technology . . . . .</b>	<b>259</b>
12.1	The Editor Concept in Multicomponent Drug Therapy . . . . .	259
12.2	Editing Out Pernicious Side Effects Through Combination Drug Therapy . . . . .	260
12.3	Designing a Therapeutic Editor Using the Wrapping Selectivity Filter . . . . .	265
12.4	Therapeutic Editing: Toward a Proof of Principle . . . . .	267
12.5	Future Perspectives for the Editing Therapy . . . . .	270
	Problem . . . . .	271
	References . . . . .	283

<b>13</b>	<b>Multitarget Control of Drug Impact: A Therapeutic Imperative in Cancer Systems Biology</b>	285
13.1	Is Systems Biology Truly Advocating for Promiscuous Drugs in Anticancer Therapy?	285
13.2	Cleaning Dirty Drugs with the Dehydron Filter: Rationale	288
13.3	Cleaning Dirty Drugs with Dehydron Filters: The Proof of Concept	290
13.4	Taming <i>Staurosporine</i> Promiscuity Through the Dehydron Filter	294
13.5	Systems Biology Inspires Wrapping Designs of Multitarget Drugs	297
13.6	Taming Sunitinib Promiscuity to Enhance Safety and Therapeutic Efficacy	303
13.7	Controlled Promiscuity: A Paradigm Shift?	304
	Problem	307
	References	308
<b>14</b>	<b>Engineering Therapeutic Alignments Between Immune Response and Molecularly Targeted Cancer Treatment</b>	311
14.1	Removal of Drug-Induced Immunosuppressive Effects in Anticancer Drug Therapy: An Imperative for the Pharmaceutical Industry	311
14.2	Therapeutic Shortcomings of Anticancer Drugs that Suppress the Adaptive Immune Response	312
14.2.1	Undesired Cross-Reactivity Modulating the Immune Response	312
14.2.2	Predictably Immunosuppressive Anticancer Drugs	315
14.3	Strategies to Redesign Anticancer Drugs and Turn Them Immunosynergic	315
14.4	Evaluation of Immunosynergic Drug Prototypes	319
14.5	Building Immunosynergies in the Context of HIV-1 Induced Immunosuppression	320
	Problem	321
	References	321
<b>15</b>	<b>High-Level Quantum Chemistry Empowers the Wrapping Technology for Drug Design</b>	325
15.1	Incorporating Quantum Mechanical Effects into Drug Design	325
15.2	Halogen Bond Synergizing with a Wrapping Interaction: A Novel Motif for Drug Design	326
	Problems	328
	References	329

---

<b>Epilogue: New Frontiers</b> . . . . .	331
<b>Appendix 1: Code for Dehydron Identification</b> . . . . .	335
<b>Appendix 2: Answers to Problems</b> . . . . .	343
<b>Index</b> . . . . .	367

Biomolecular Interfaces

Interactions, Functions and Drug Design

Fernandez Stigliano, A.

2015, XIX, 372 p. 145 illus., 59 illus. in color., Hardcover

ISBN: 978-3-319-16849-4