Laboratory of Computational Biophysical Chemistry

UNIVERSIDADE DE SÃO PAULO — SCIENTIA VINCES

Electrostatic interactions *in* and *between* biomolecules:

From fundamentals concepts to applications

Part 1

BIOINFORMÁTICA USP

STAMiNA Global Network

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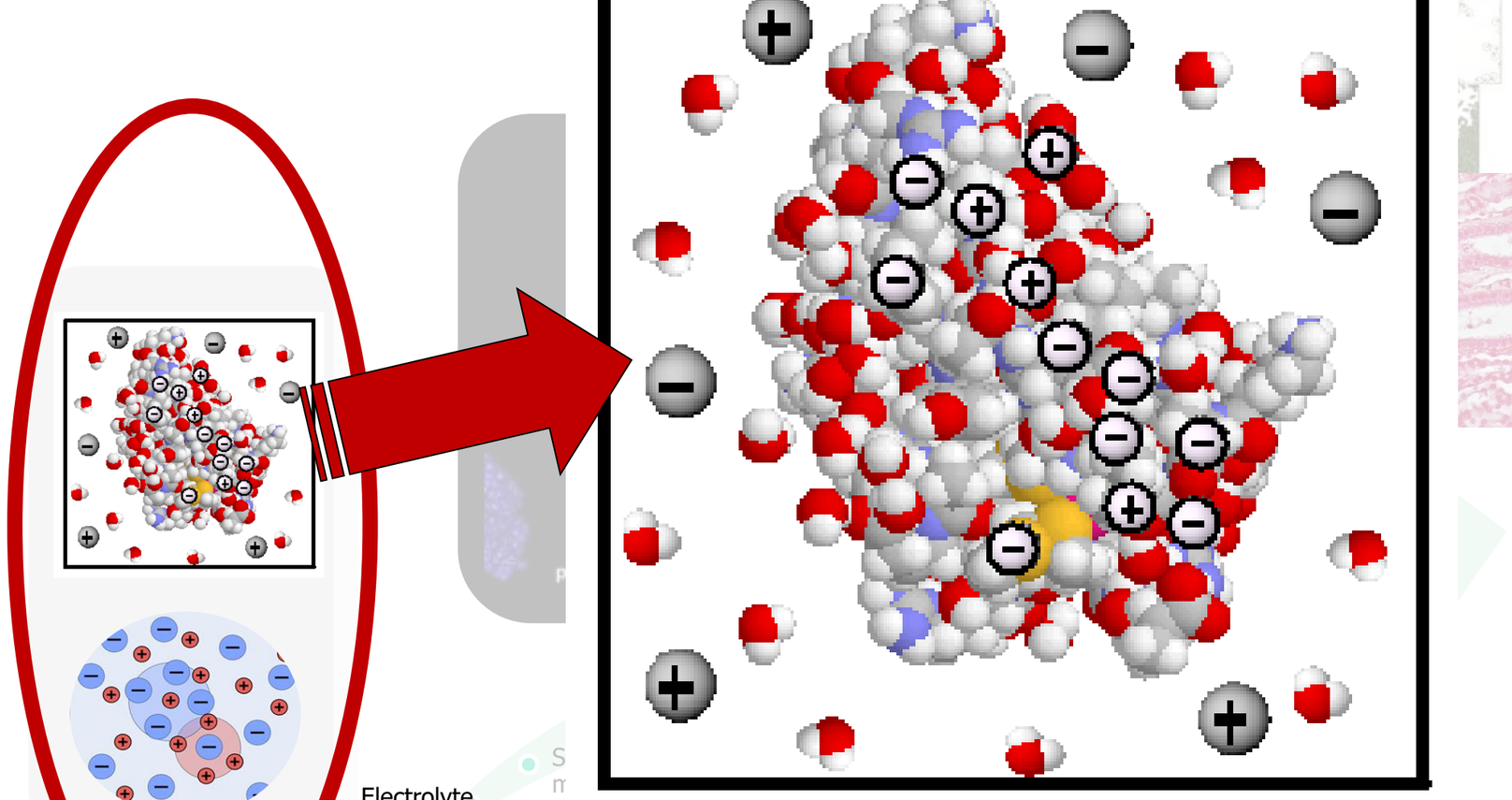
flbarroso@usp.br

March 10, 2020

1

From Molecular to Macroscopic Scale (Bio2020)

Experiments, **theory** and computer simulation



2

Bibliography

- **Electrostatic**:
  - Basic Physics: Hallyday & Resnick, Ritz & Milford, etc...
  - More specific/advanced: C. J. F. Böttcher, "*Theory of Electric Polarization*", Elsevier, Amsterdam, 1973.

- **Physical Chemistry**:
  P. W. Atikins, "*Physical Chemistry*", Oxford University Press,
  Silbey, Alberty & Bawendi, "*Physical Chemistry*". John Wiley & Sons, 2004

- **Mathematical Methods**:
  G. Arfken, "*Mathematical Methods for Physicists*",
  Academic Press, London, 1970.

- **Molecular Modelling:**
  A. R. Leach, *"Molecular Modelling - Principles and Applications"*, Longman, Singapore, 1996.

+ specific scientific papers

Syllabus (set of 3 lectures)

- ✓**Motivation**
- ✓ **Basic physical chemistry**
- ✓ **Measuring electrostatic properties**
- ✓ **The TK model**
- ✓ **Basic ideas of the PB**
- ✓ **Constant-pH computational methods**
- ✓ **Peculiar phenomena**
- ✓ **Other examples**

Syllabus

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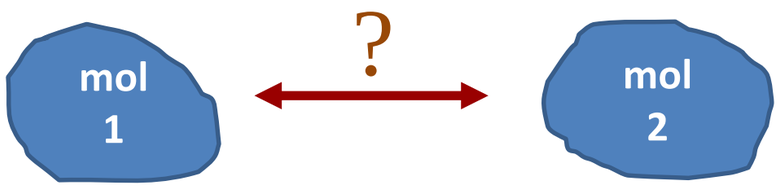
Motivation

Electrostatic interactions

Why???

Intermolecular interactions



$V_{12} =$ electronic repulsion +

+ charge transfer +

+ **multipole-multipole** electrical interaction +

+ **induced multipole-multipole** electrical interaction +

+ dispersion

All these terms depend on the molecular properties derived from the Schrödinger equation

INTERMOLECULAR AND SURFACE FORCES

SECOND EDITION

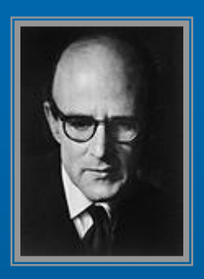
JACOB N. ISRAELACHVILI

Department of Chemical & Nuclear Engineering and Materials Department
University of California, Santa Barbara
California, USA

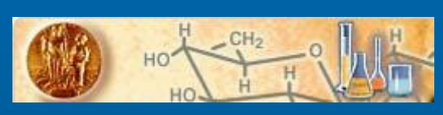
ACADEMIC PRESS
Harcourt Brace & Company, Publishers
London San Diego New York Boston
Sydney Tokyo Toronto

Protein electrostatics

- Structure/Folding
- Hydration
- Catalysis
- Binding/Ionization



Perutz

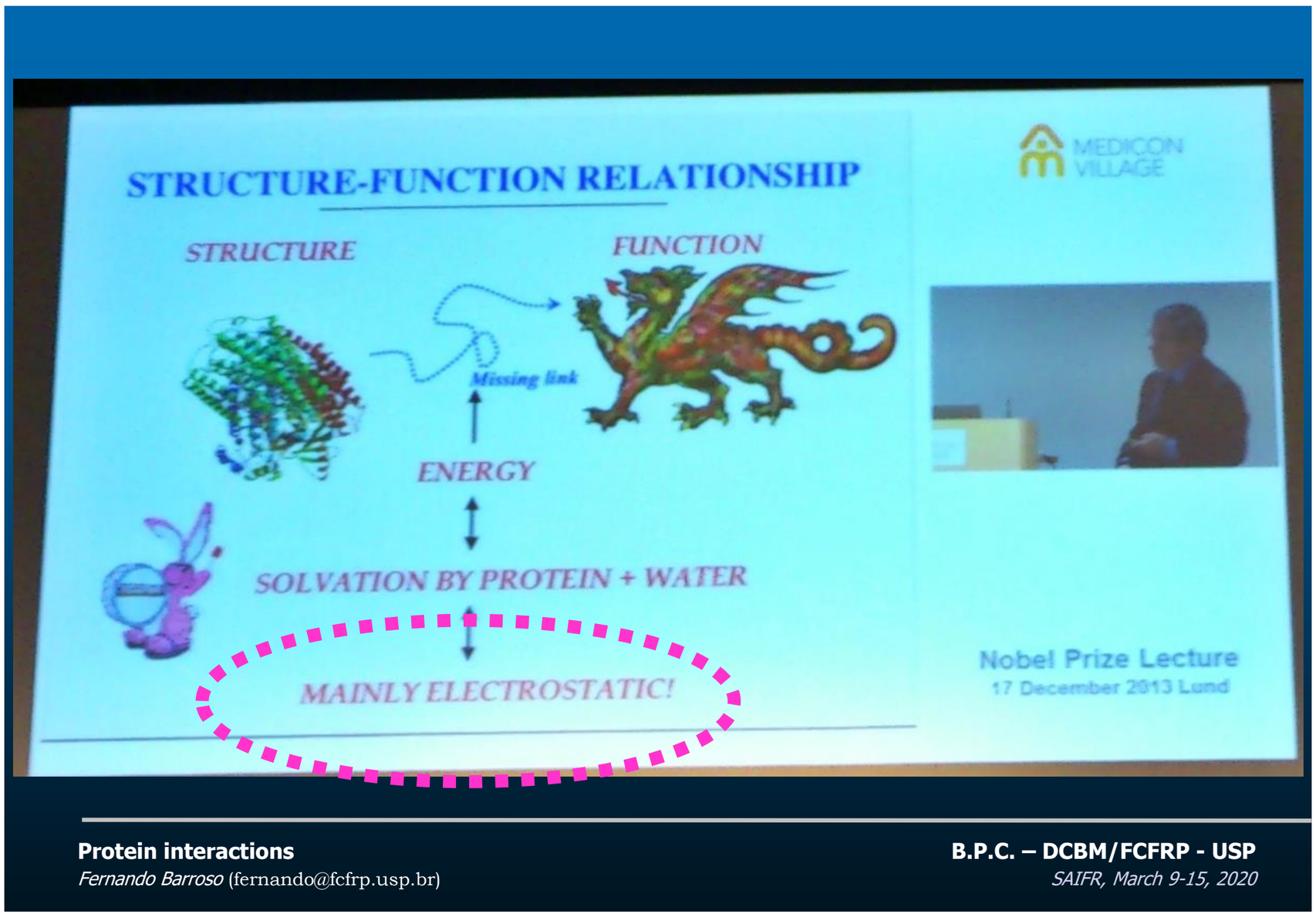


Science. 1978 Sep 29;201(4362):1187-91.

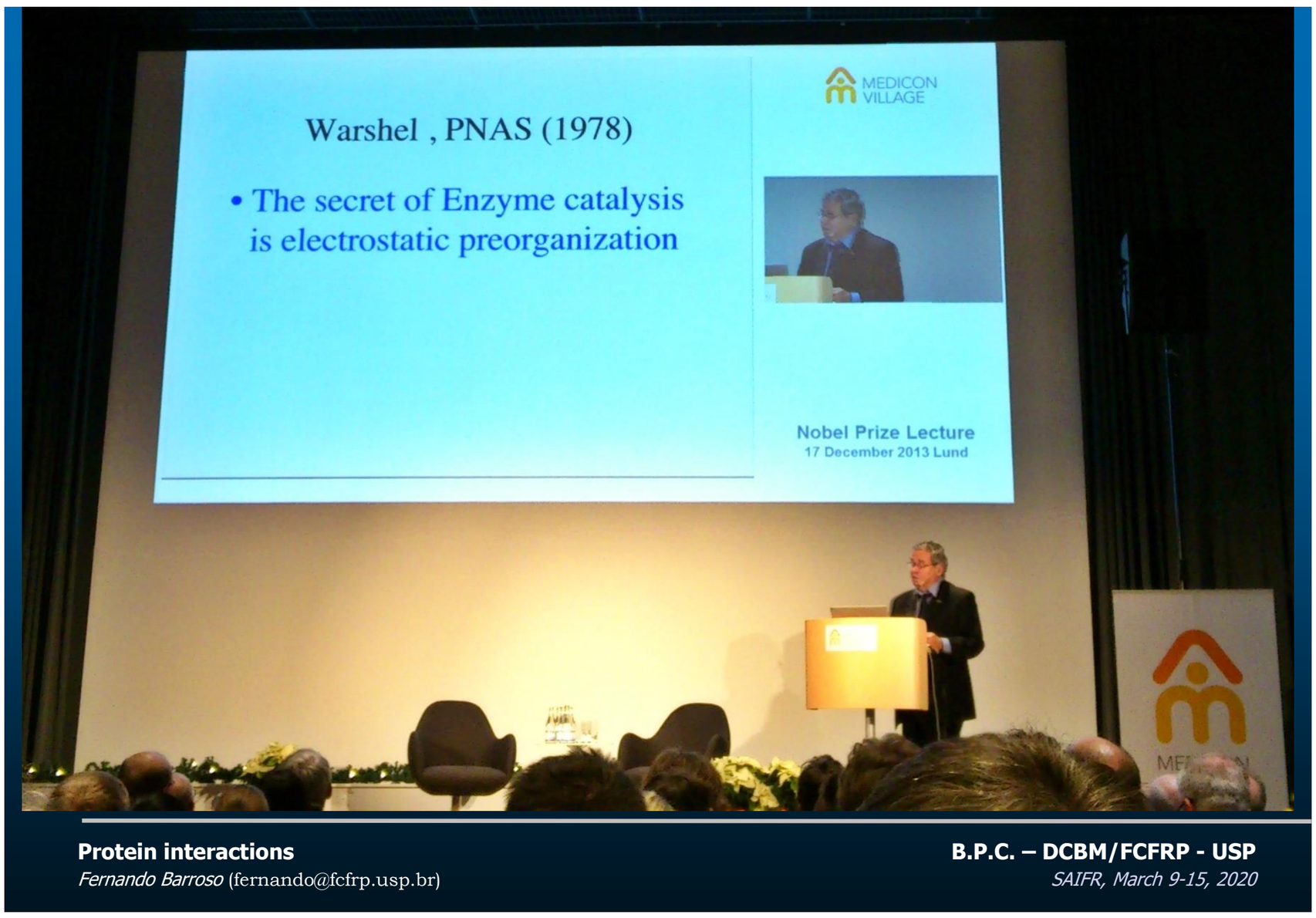
Electrostatic effects in proteins.

Perutz MF.

Electrostatic effects dominate many aspects of protein behavior. When polypeptide chains fold up, most polar side chains seek the exterior, where they can be solvated. Water bound in the interior has been found between the domains of enzymes of the chymotrypsin family, and between the subunits of hemoglobin and tobacco mosaic virus protein. Assembly of this protein from disk to virus is triggered by electrostatic interactions between neighboring subunits. Lysozyme stabilizes the constellation of charges involved in the transition state of its substrate by both permanent and induced dipoles. All factors that lower the oxygen affinity of hemoglobin act by strengthening the salt bridges that constrain its quaternary deoxy (T) structure. Enzymes of thermophile bacteria owe their extra stability mostly to additional salt bridges. The rate of denaturation of hemoglobins by alkali is determined by the ionization of internal side chains with pK's of about 12.


STRUCTURE-FUNCTION RELATIONSHIP
STRUCTURE
FUNCTION
Missing link
ENERGY
SOLVATION BY PROTEIN + WATER
MAINLY ELECTROSTATIC!
MEDICON VILLAGE
Nobel Prize Lecture
17 December 2013 Lund
Protein interactions
Fernando Barroso (fernando@fcfrp.usp.br)
B.P.C. – DCBM/FCFRP - USP
SAIFR, March 9-15, 2020

13


Warshel , PNAS (1978)
• The secret of Enzyme catalysis is electrostatic preorganization
MEDICON VILLAGE
Nobel Prize Lecture
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Protein interactions
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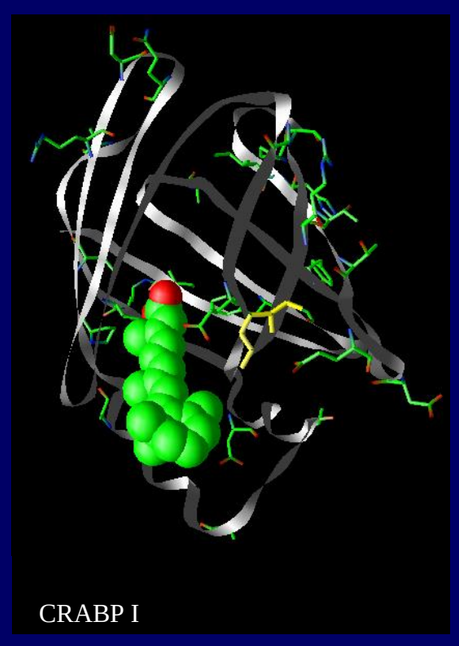
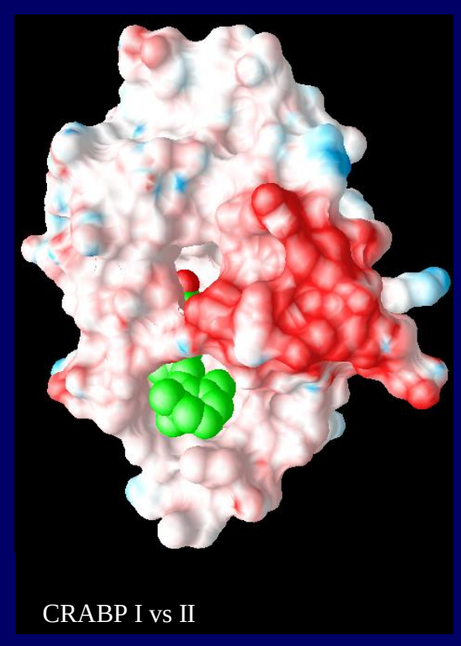
CRABP I e II: biological function *vs* electrostatic interactions



Electrostatic potential



Biocomputing Molecular Biophysics
Physical Chemistry
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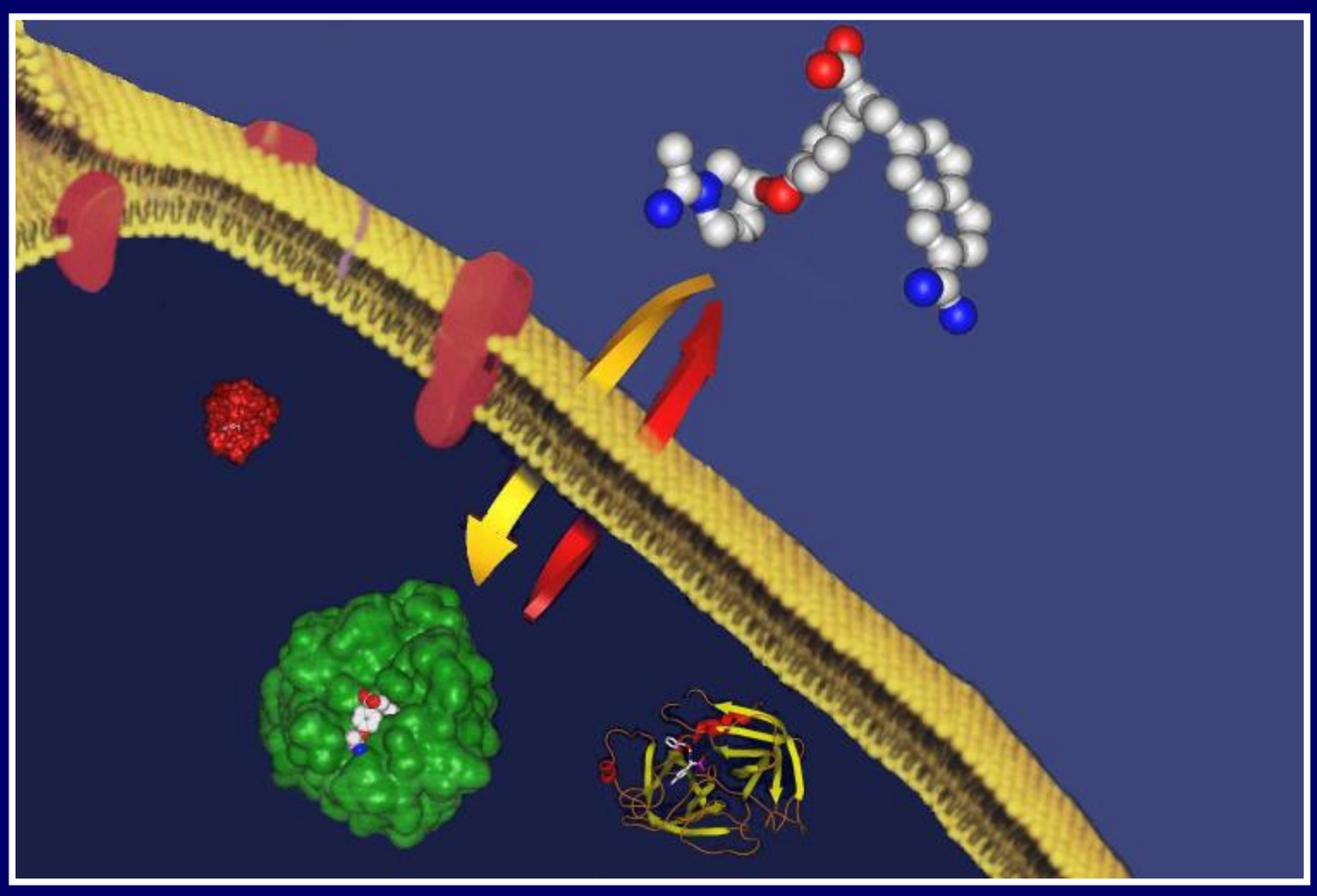

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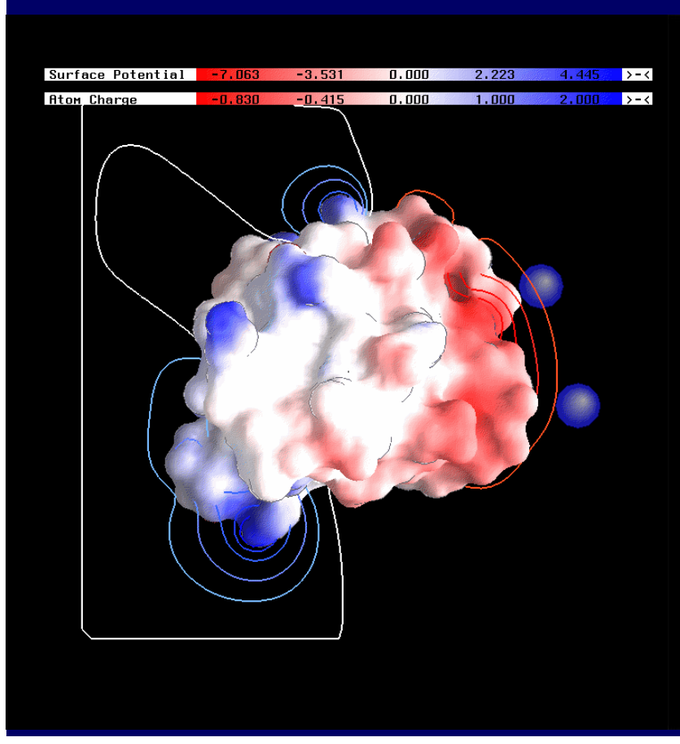
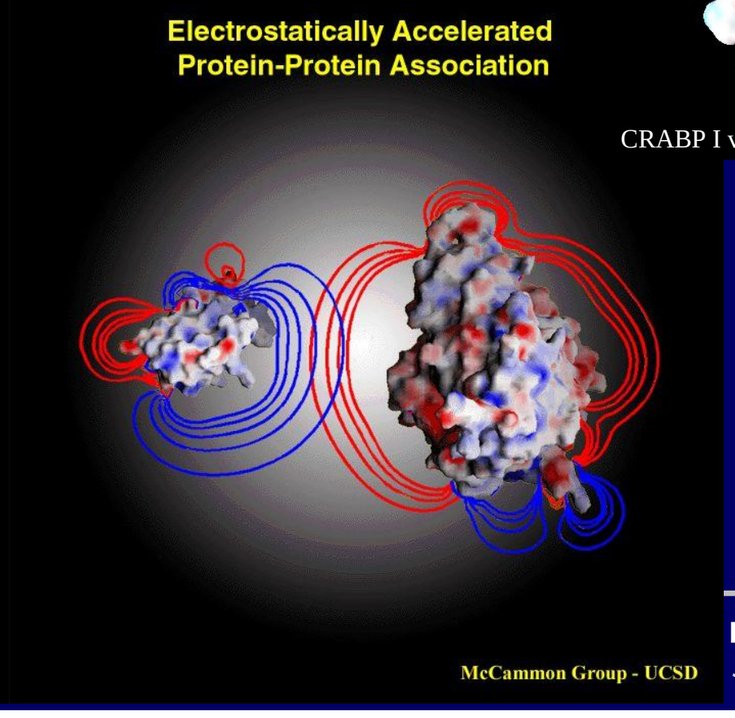
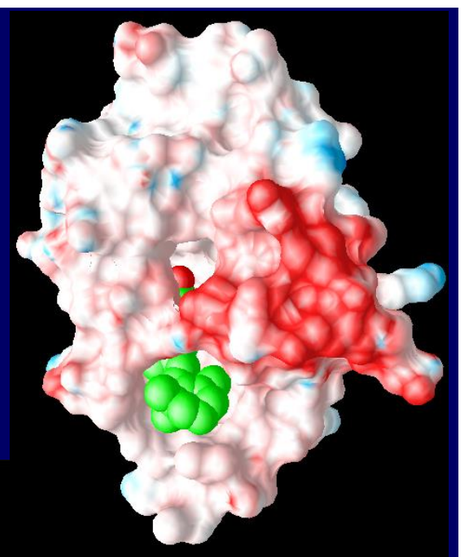
Electrostatic calculations are useful….

- ❑ Electrostatic potential comparisons
- ❑ Inspection of ligand binding sites
- ❑ Interactions with other charged objects

  (visual + thermodynamics)







CRABP I vs II

DCBM/FCFRP - USP

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Laboratory of Computational Biophysical Chemistry

Basic physical chemistry

Fernando Barroso, FCFRP/USP

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18

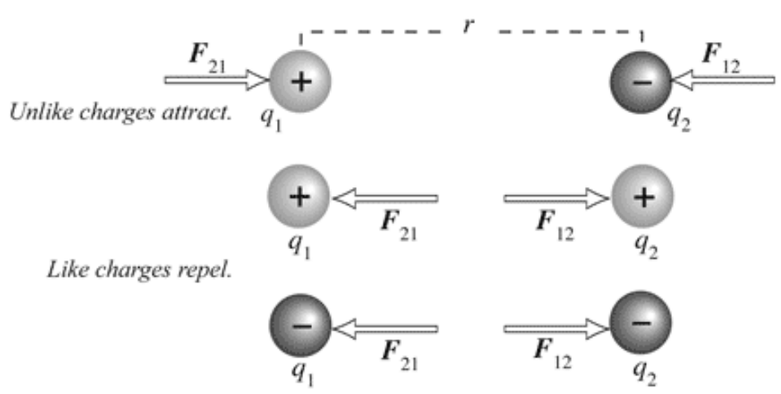
Coulombic law?!

Electrostatic interactions in proteins?

Electrostatic Force - Coulomb's Law

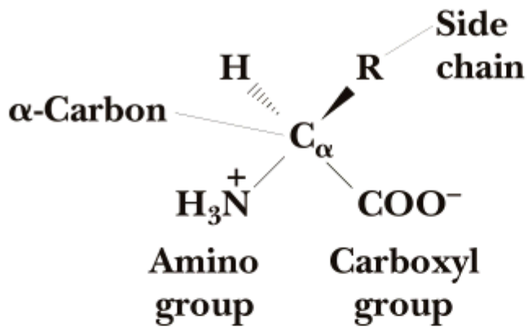
$$F = k\frac{q_1 q_2}{r^2}$$

F = electrostatic force
q = electric charge
r = distance between charge centers
k = Coulomb constant
$9.0 \times 10^9\ N \cdot m^2/C^2$



Amino Acids

Building Blocks of Proteins



[Biochemistry 2/e - Garrett & Grisham]

protonated deprotonated

$$RNH_3^+ \Leftrightarrow H^+ + RNH_2$$ Charge varies from **+1** to **0**

$$RCOOH \Leftrightarrow H^+ + RCOO^-$$ Charge varies from **0** to **-1**

Acid-base equilibrium

Dissociation of a weak acid (HA)

$$HA_{(aq)} \Leftrightarrow H^+_{(aq)} + A^-_{(aq)}$$

$$K_a = \frac{a_{H^+} a_{A^-}}{a_{HA}}$$

activities

thermodynamic equilibrium constant

$$a = \gamma c$$

For an *ideal* system,

$$K_s = \frac{c_{H^+} c_{A^-}}{c_{HA}}$$

concentrations

stoichiometric equilibrium constant

Acid-base equilibrium

$$HA_{(aq)} \Leftrightarrow H^+_{(aq)} + A^-_{(aq)}$$

$$pK_a = -\log K_a$$

$$\uparrow pK_a \Rightarrow \downarrow K_a$$

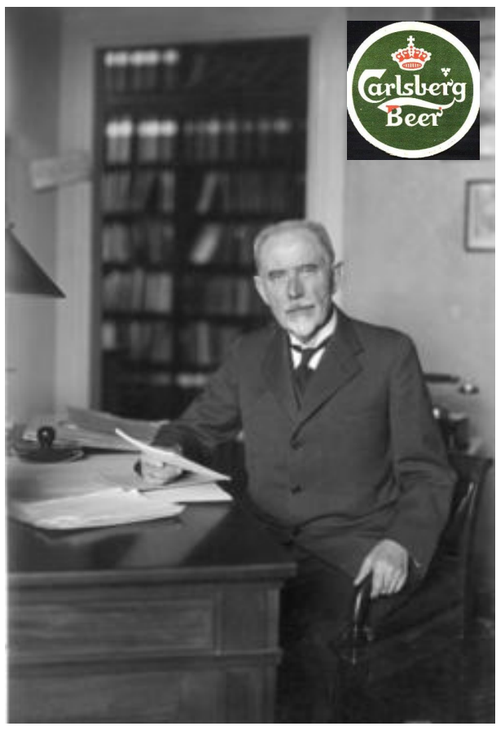
$pK_a = -\log K_a$

$$\Delta G^0 = -RT \ln K_a = -RT(2.3 \log K_a)$$

$$\therefore \Delta G^0 = +(2.3RT)\, pK_a$$

- **pK_a** is a measure of the tendency for a group to give up a proton

The Sorensen definition of pH as Hydrogen ion concentration



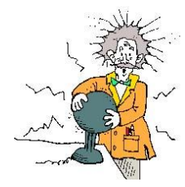
‘**the power of hydrogen**’
the scale provides a simple and universal measurement of the amount of hydrogen ions in a solution, which affects its acidity and how it reacts chemically.

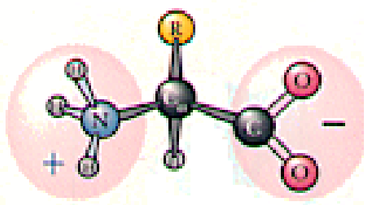
$$pH = -\log c_{H^+}$$

Notional definition

$$pH = -\log a_{H^+}$$

Aminoacids can have electrical charge!





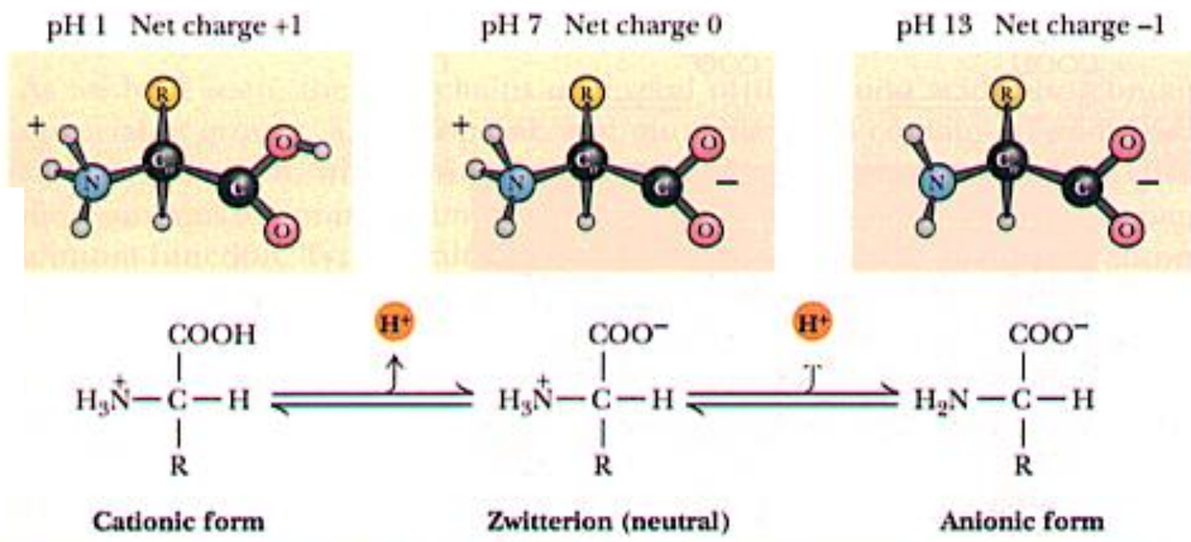
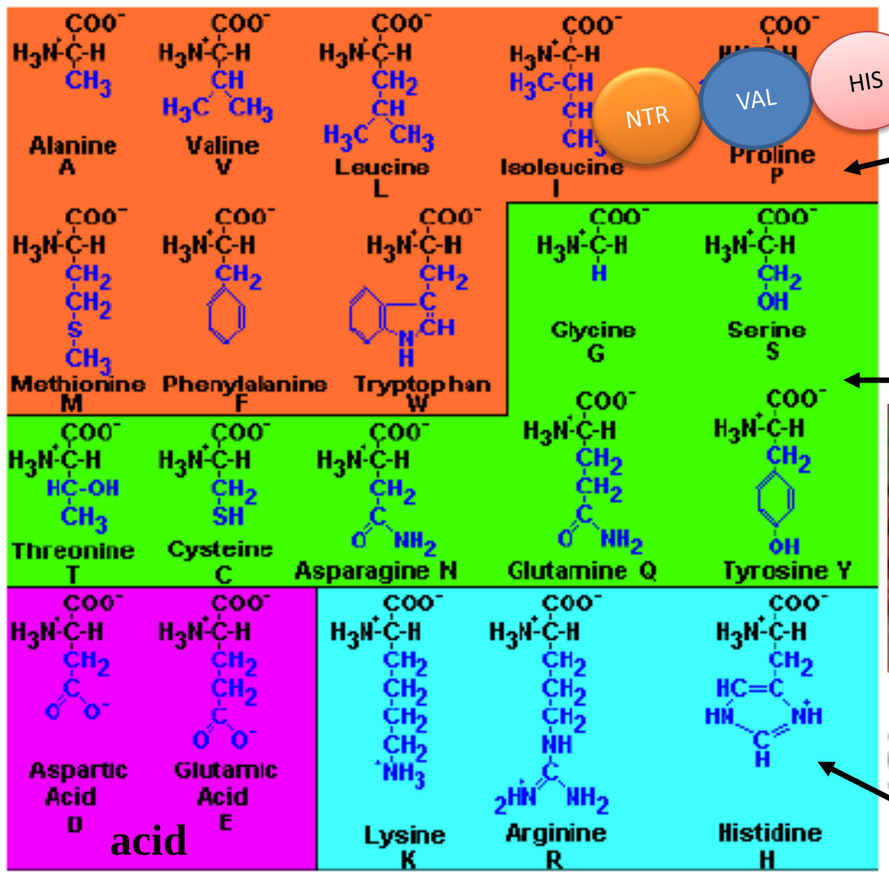


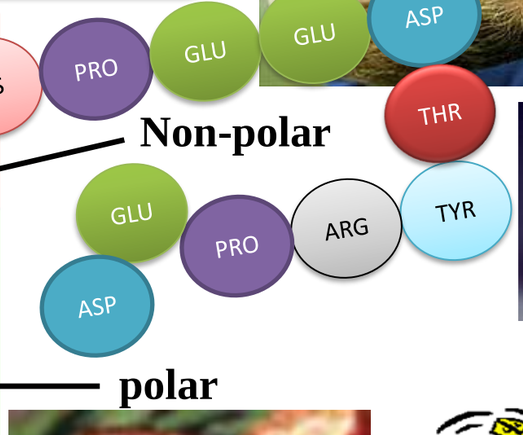
Figure **3.6** The ionic forms of the amino acids, shown without consideration of any ionizations on the side chain. The cationic form is the low pH form, and the titration of the cationic species with base will yield the zwitterion and finally the anionic form.
(Figure courtesy of Irving Geis.)

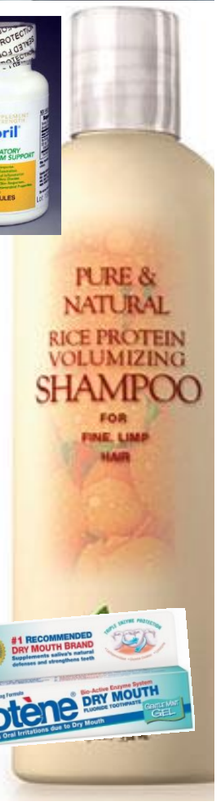
[Biochemistry 2/e - Garrett & Grisham]

$$pH = -\log c_{H^+}$$

Proteins are involved in virtually every segment of human activity: scientific, industrial, service and commercial

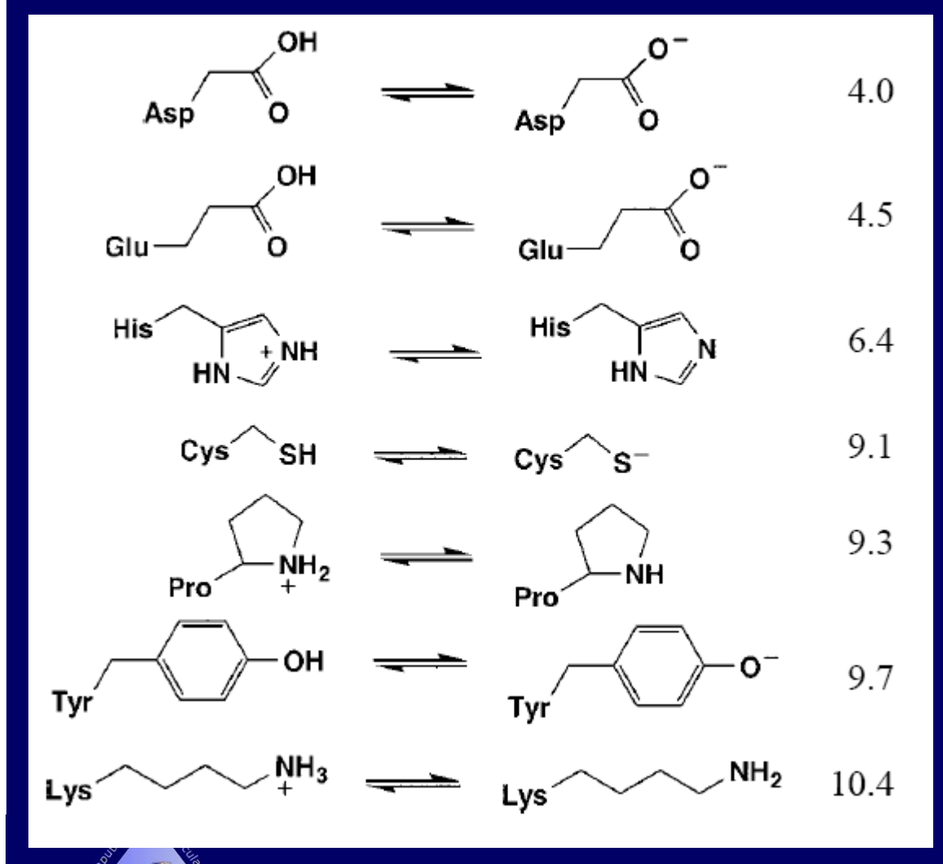




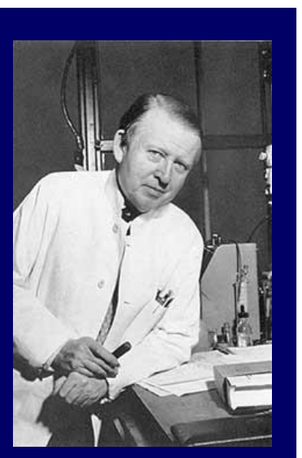


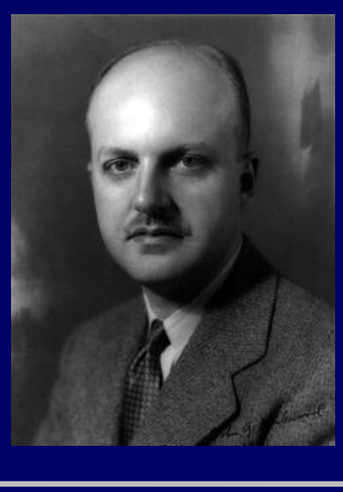
25

Protein electrostatics

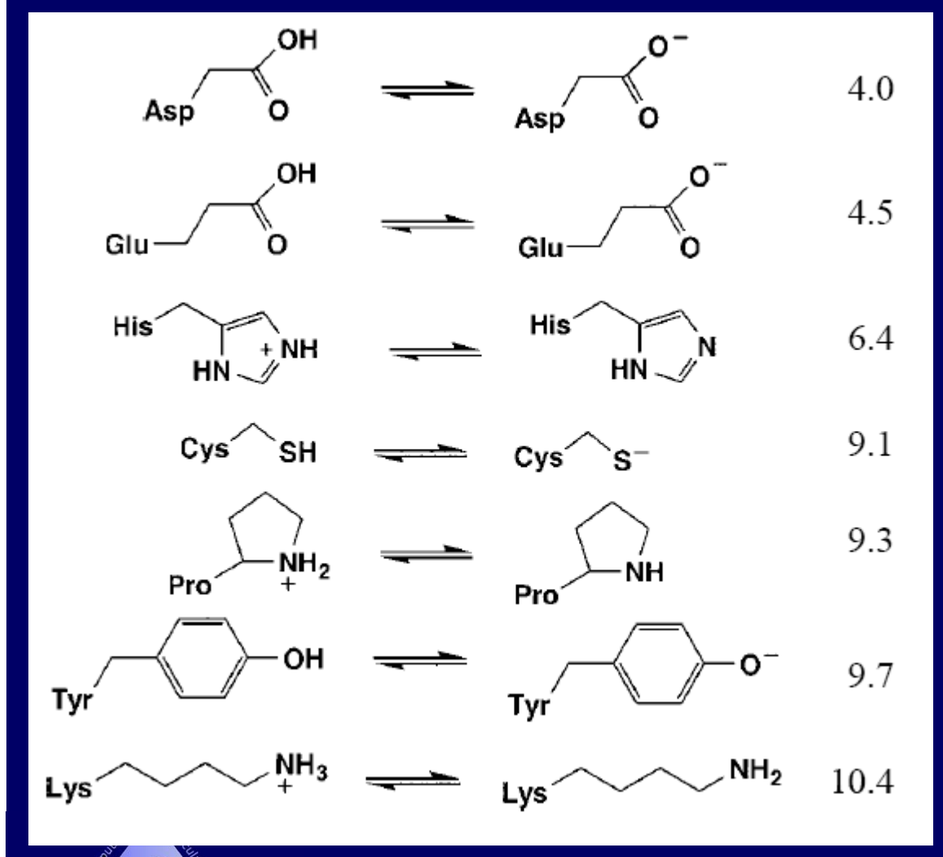


Lindstrøm-Lang

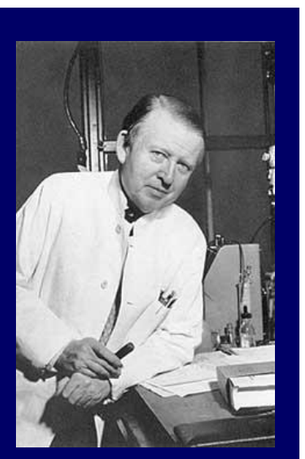


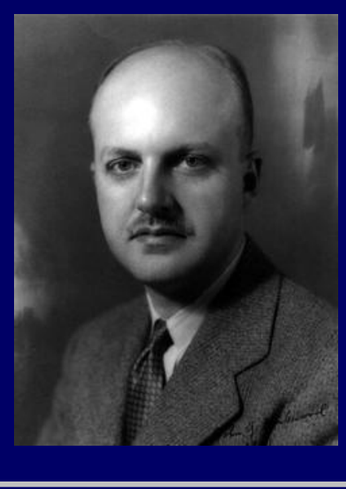


Protein electrostatics



Lindstrøm-Lang



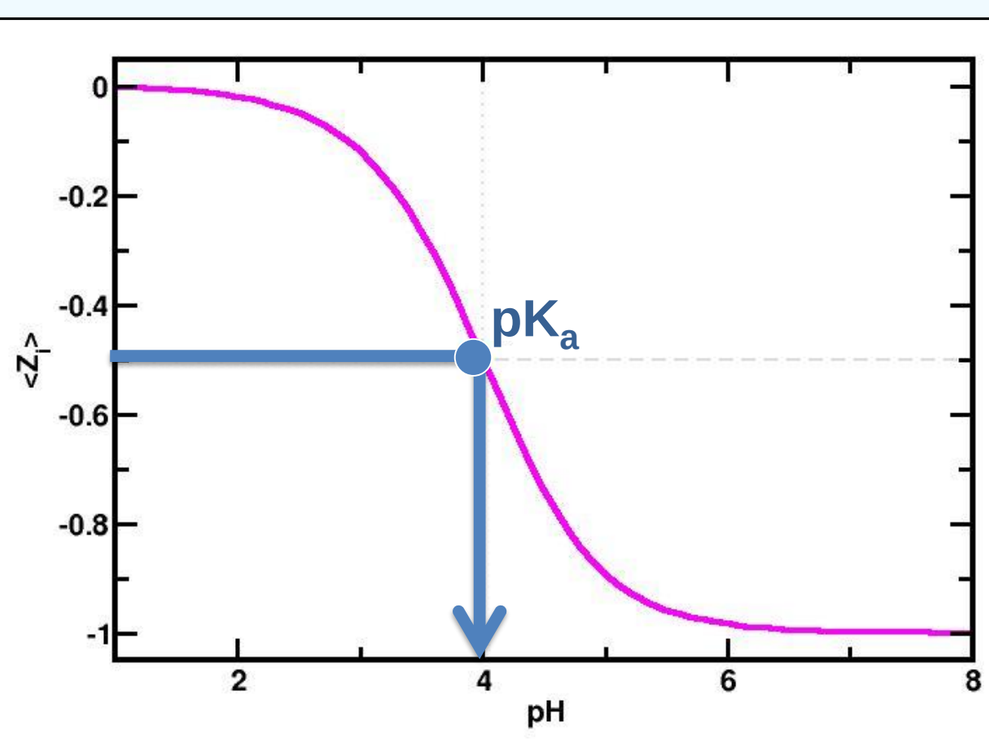


Degree of ionization

$RNH_3^+ \Leftrightarrow H^+ + RNH_2$ Charge varies from **+1** to **0**

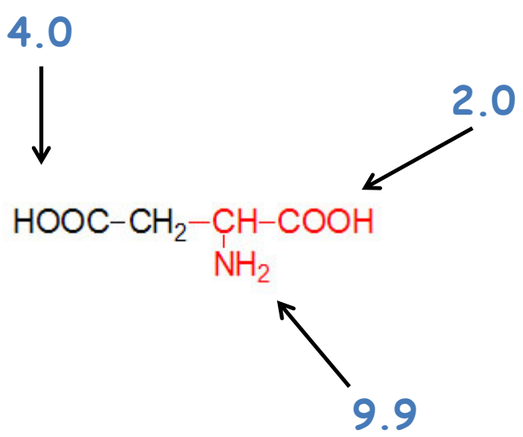
$RCOOH \Leftrightarrow H^+ + RCOO^-$ Charge varies from **0** to **-1**

$$\alpha_i = \frac{10^{pH-pK_i}}{1+10^{pH-pK_i}} \Rightarrow \begin{cases} Z_i = \alpha_i \text{, for basic aa.} \\ Z_i = -(1-\alpha_i) \text{, for acidic aa.} \end{cases}$$

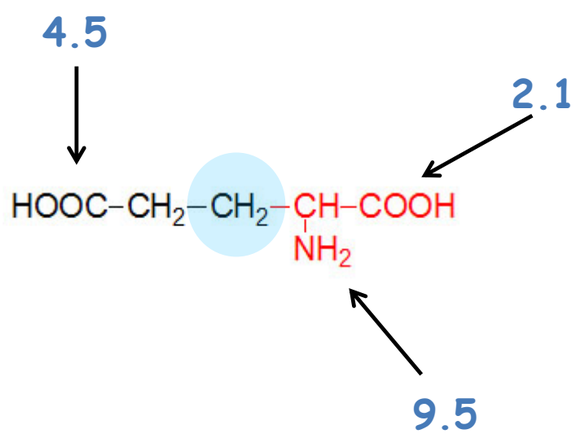


But, in real systems...

Aspartic Acid



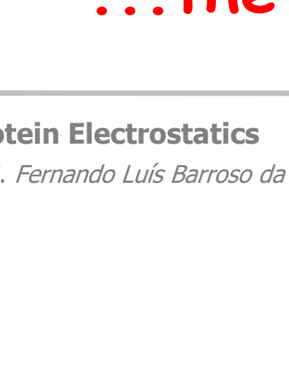
Glutamic Acid

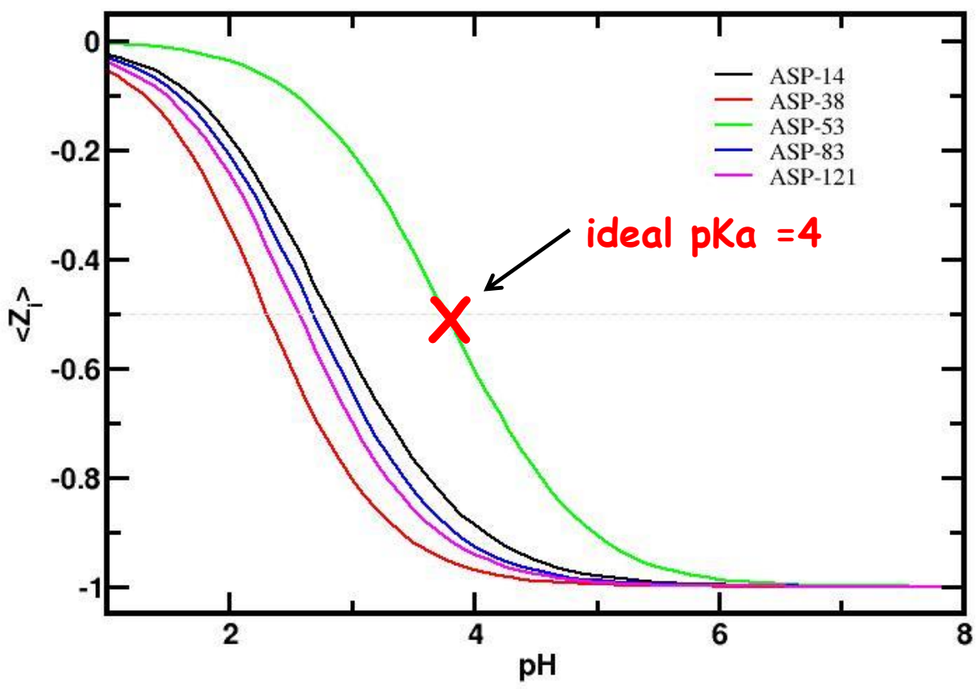


...the neighbourhood can affect the pKa!

pH controls aminoacids charges

Ribonuclease





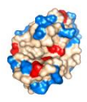
[FLBDS & DMK, JCTC 2017]

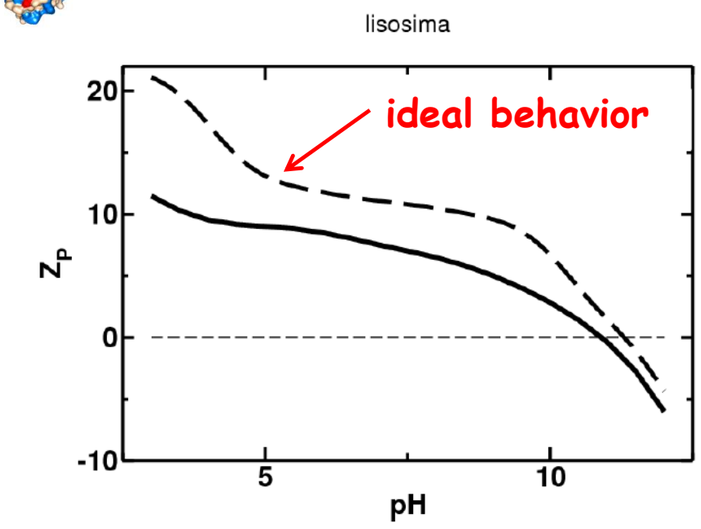
Ideal titration behavior

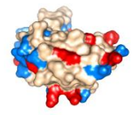
$$Z_{total} = \sum_{i=1}^{N_P} N_{aa_i} Z_i$$

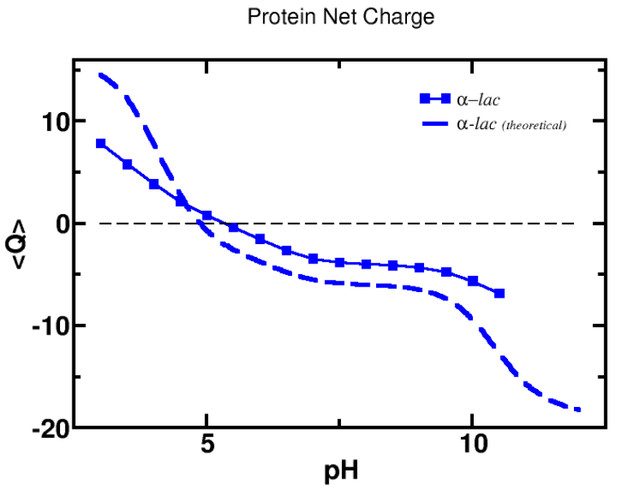
$Z_i = \alpha_i$, **for basic aa.**

$Z_i = -(1-\alpha_i)$, **for acidic aa.**









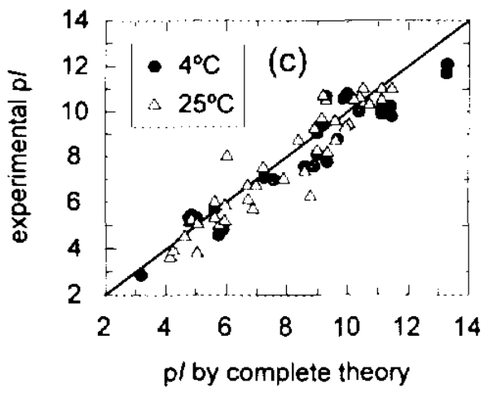
ANALYTICAL BIOCHEMISTRY **231,** 82–91 (1995)

Polypeptide Amino Acid Composition and Isoelectric Point

II. Comparison between Experiment and Theory

Costas S. Patrickios*,[1] and Edna N. Yamasaki†

*School of Chemistry and Molecular Sciences, University of Sussex, Falmer, Brighton, East Sussex BN1 9QJ, United Kingdom; and †Laboratorio de Neurobiologia da Retina, Programa de Neurobiologia, Instituto de Biofisica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, Ilha do Fundao, Rio de Janeiro 21949-900, Brazil

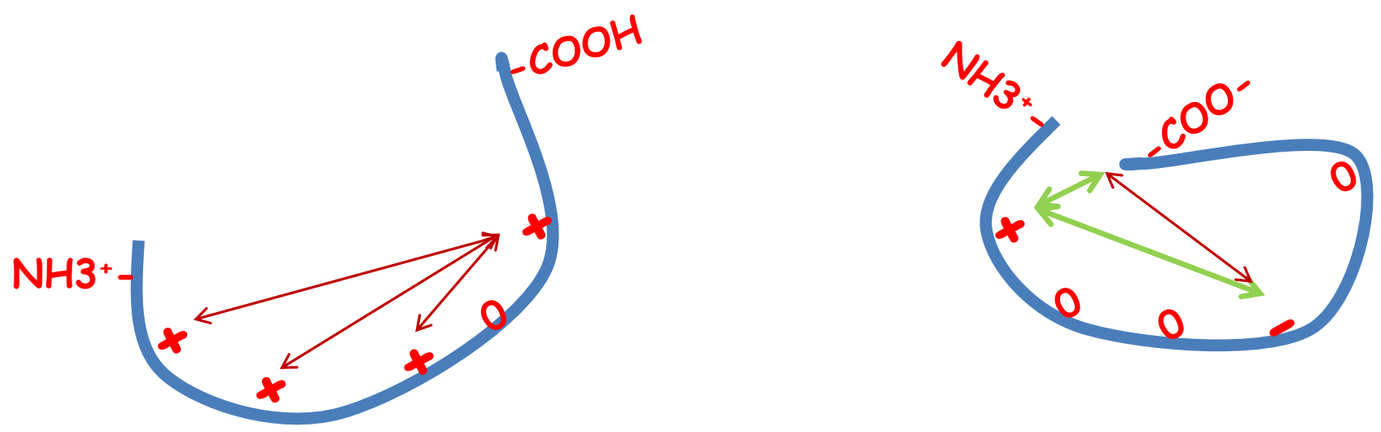


(Calixto & Barroso Da Silva, 2010)

	Propriedades de proteínas isoladas		
Proteína	***pI* (ideal)**[28]	***pI* (PB)**[29]	***pI* experimental**
Lisozima (2LZT)	10,6	11,1	11,1 [13]
Calbindina (3ICB)	4,5	4,5	4,5 [14]
BPTI (4PTI)	10,0	10,4	10,6 [168]
Ribonuclease A (3RN3)	9,4	9,9	9,6 [168]
RMSD	**0,81**	**0,36**	–

Laboratory of Computational Biophysical Chemistry

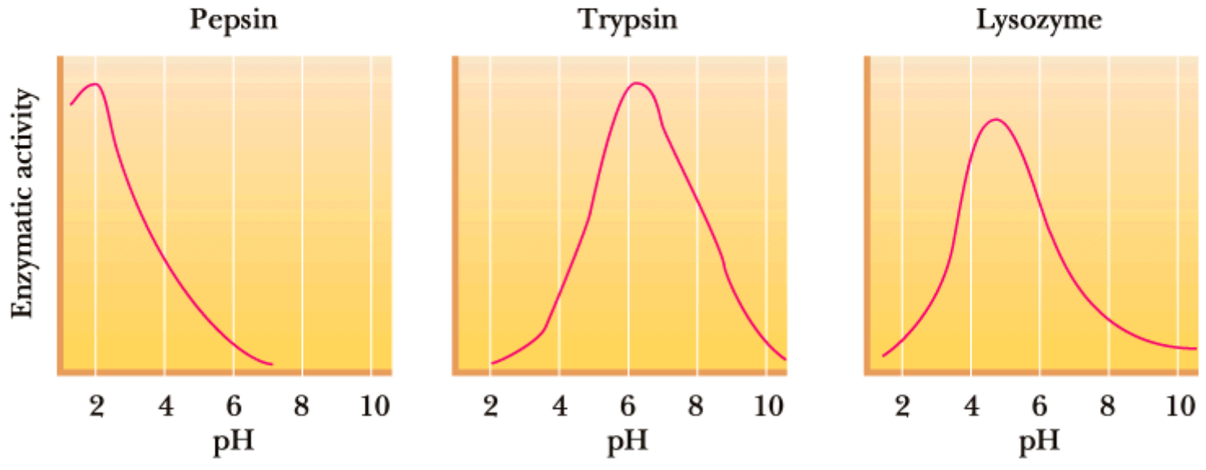
pH controls conformation!



pH

pH controls function!

Garrett & Grisham: Biochemistry, 2/e
Figure 12.16

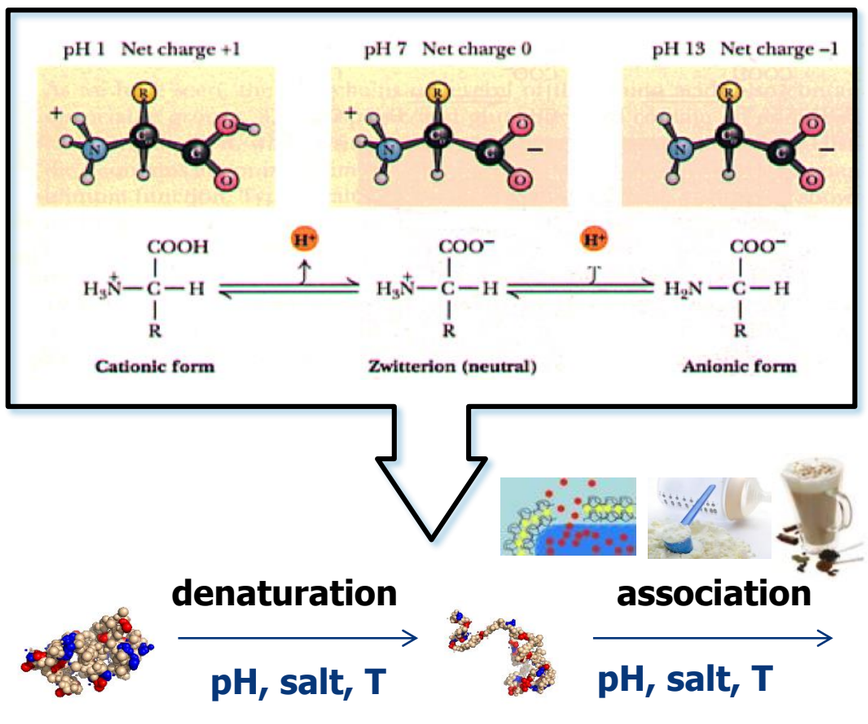


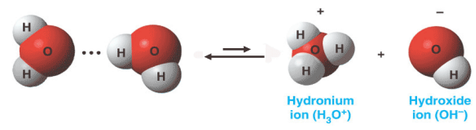
Saunders College Publishing

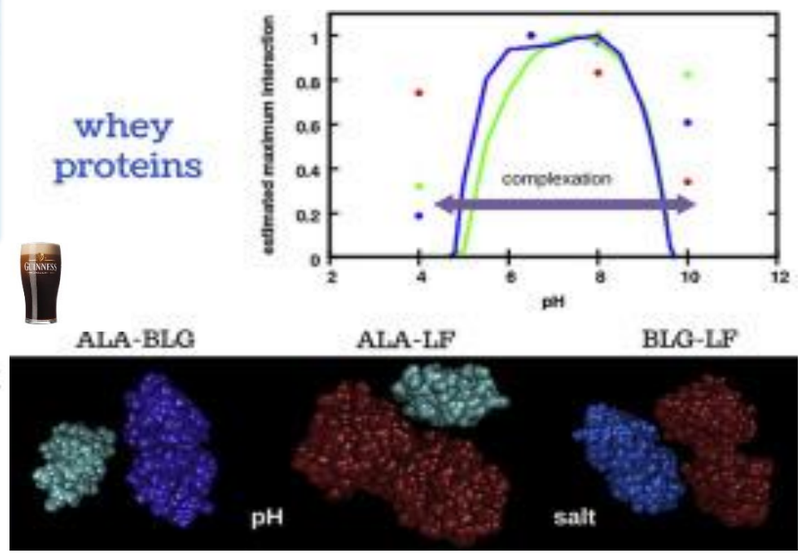
pH in biochemistry, food and pharmaceuticals

$$q(pH) = \frac{1}{1 + e^{-\ln 10 (pK_a - pH)}}$$

- **pH** is the decimal logarithm of the reciprocal of the hydrogen ion activity. (charge, conformation and function)
- **pK_a** is a measure of the tendency for a group to give up a proton.



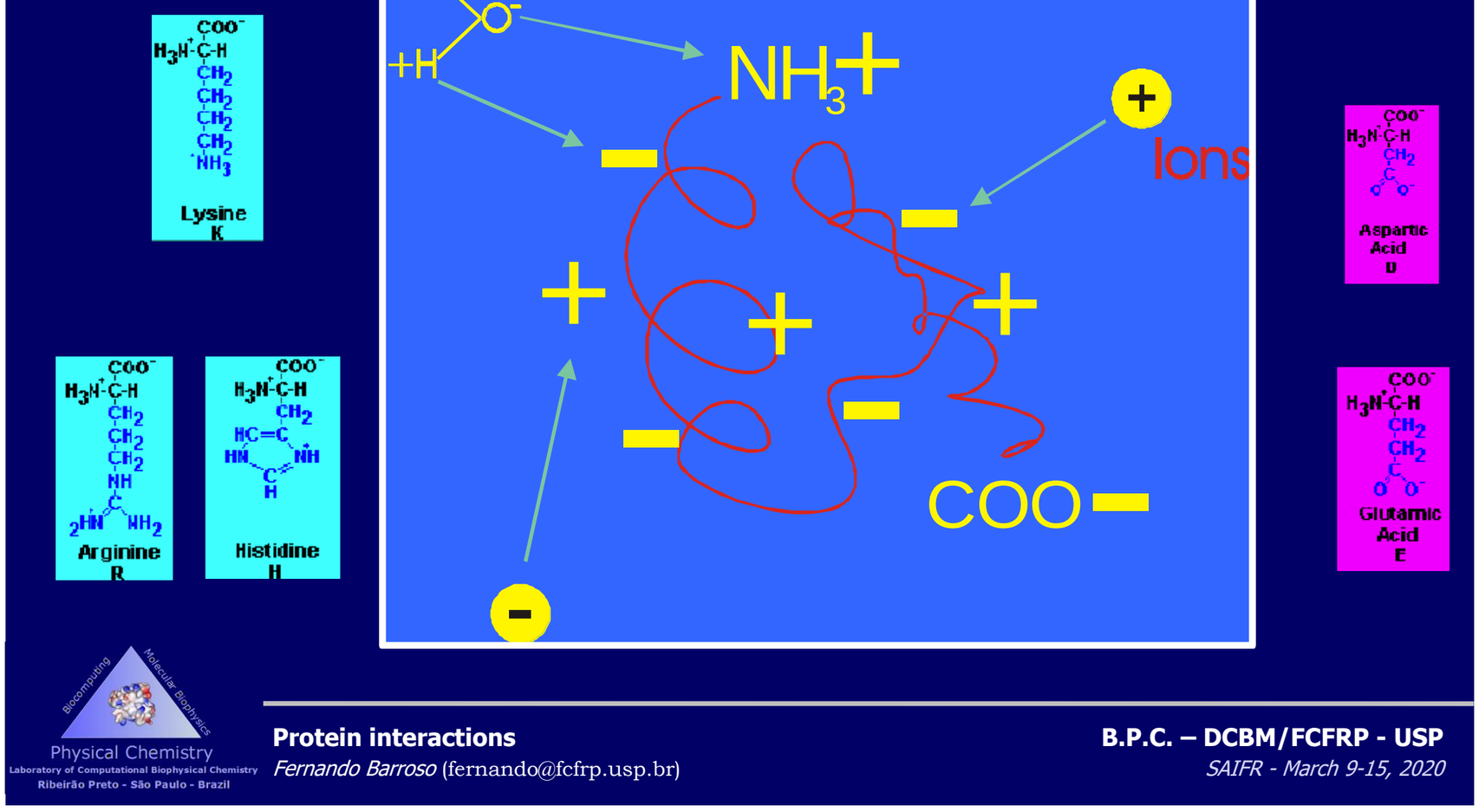




[LD & FLBDS, *Food Hydrocolloids*, 2016]

35

Electrostatic interactions



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Protein interactions
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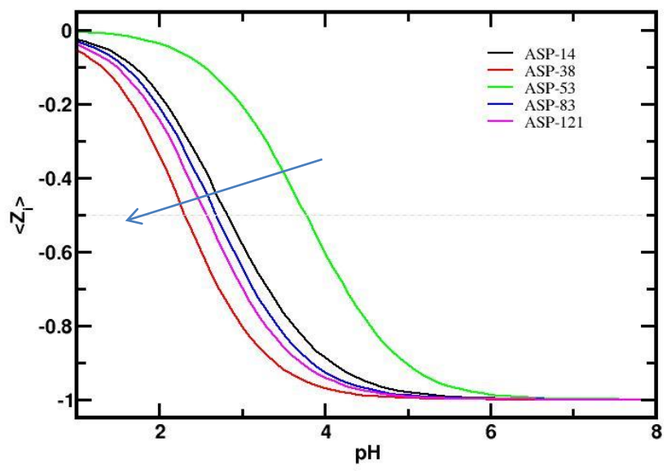
B.P.C. – DCBM/FCFRP - USP
SAIFR - March 9-15, 2020

36

"Model" pKas for aminoacids

Laboratory of Computational Biophysical Chemistry

$$\alpha_i = \frac{10^{pH - pK_i}}{1 + 10^{pH - pK_i}}$$



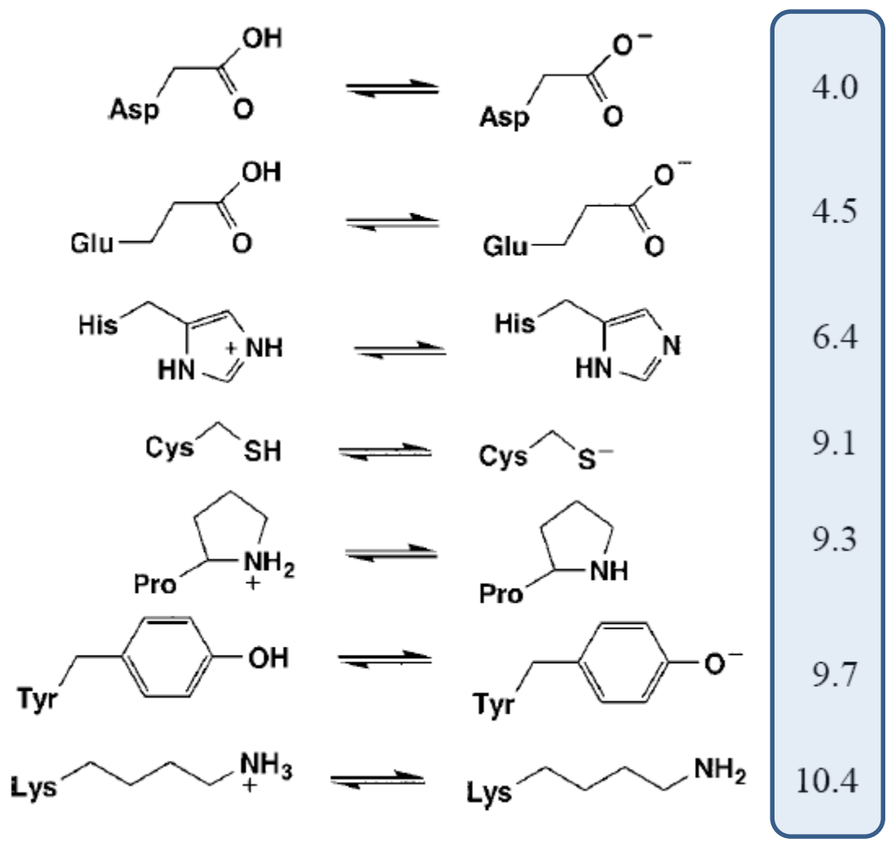


TABLE III
INTRINSIC pK'S OF TITRATABLE GROUPS AT 25°

Type of group	Model compounds[a]	Proteins[b] Dilute salt solution	Proteins[b] GuCl 6 M
α-Carboxyl	3.8	3.6	3.1
Aspartyl carboxyl	4.0	(4.6)[c]	3.9
Glutamyl carboxyl	4.4	(4.6)[c]	4.35
Imidazole	6.3	6.6	6.4
α-Amino	7.5	[d]	7.4
Thiol	9.5	[d]	9.5
Phenolic	9.6	9.8	9.95
ϵ-Amino	10.4	10.0	10.3
Guanidyl	12	12	12

[a] Obtained from pK values of small model compounds (see reference, footnote a, Table I). Corrections for electrostatic and other effects have been made to yield pK values representative of the unperturbed group.

Gly-Gly-**X**-Gly-Gly

Gly-Gly-**X**-Ala

Protein Science (2006), 15:1214–1218

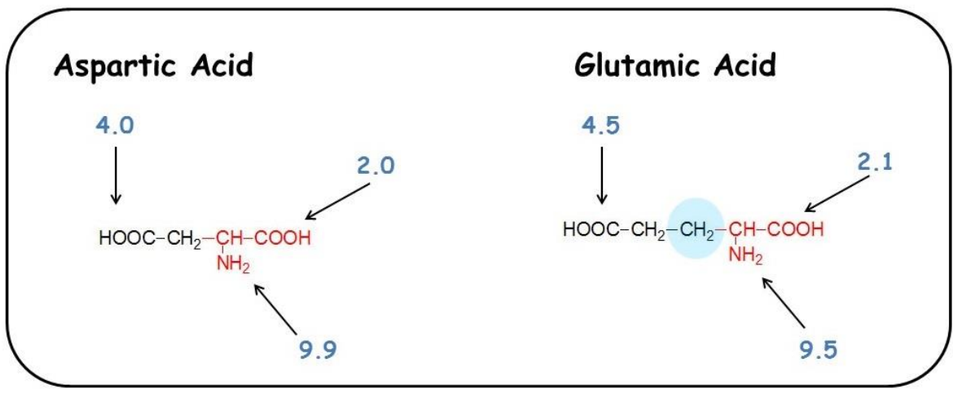


Table 1. *pK values for the ionizable groups in proteins from the literature*

Group	Cohn and Edsall[a]	Nozaki and Tanford[b]	Gurd Lab[c]	Wuthrich Lab[d]	Creighton[e]
α-Carboxyl	3.0–3.2	3.8	3.3	—	3.5–4.3
Asp	3.0–4.7	4.0	3.9	3.9	3.9–4.0
Glu	4.4	4.4	4.2	4.2	4.3–4.5
His	5.6–7.0	6.3	6.8	6.9	6.0–7.0
α-Amino	7.6–8.4	7.5	8.1	—	6.8–8.0
Cys	9.1–10.8	9.5	—	—	9.0–9.5
Tyr	9.8–10.4	9.6	10.0	10.2	10.0–10.3
Lys	9.4–10.6	10.4	10.5	11.0	10.4–11.1
Arg	11.6–12.6	12.0	—	—	12.0

These pK values were measured at various temperatures, as noted below. Typically, the error in the measurements is ± 0.1–0.2. In some studies no salt was present, and in some the ionic strength was not given. We have not corrected any of the values given in the original articles. Usually the errors in measuring the pK values are greater than these corrections (Tanford 1962).
[a]Determined using various model compounds at 25°C, as described in Table 1 in Chapter 20 of Cohn and Edsall (1943).
[b]Determined using various model compounds at 25°C, as described in Table 3 of Nozaki and Tanford (1967).
[c]Determined with Gly-Gly-X-Gly-Gly pentapeptides by ^{13}C NMR at 26°C, except for Tyr, which was determined at 33°C (see Gurd et al. 1972; Keim et al. 1973). Both termini of the peptides were not blocked.
[d]Determined in Gly-Gly-X-Ala tetrapeptides by ^{13}C NMR at 35°C (see Richarz and Wuthrich 1978). Both termini of the peptides were not blocked.
[e]From Creighton's textbook on protein biochemistry that references some of the values from the previous columns (Creighton 1993).

39

Protein Science (2006), 15:1214–1218

Table 2. *Measured pK values based on the alanine pentapeptides compared to the pK_{int} values of Nozaki and Tanford*

Group	pK_{int}[a] (N&T)	pK[b] (this work)
α-Carboxyl	3.8	3.67 ± 0.03
Asp	4.0	3.67 ± 0.04
Glu	4.4	4.25 ± 0.05
His	6.3	6.54 ± 0.04
α-Amino	7.5	8.00 ± 0.03
Cys	9.5	8.55 ± 0.03
Tyr	9.6	9.84 ± 0.11
Lys	10.4	10.40 ± 0.08

[a]From the model compound data in Table 3 of Nozaki and Tanford (1967).
[b]The pK values of the ionizable groups in the alanine pentapeptides used in this work measured in 0.1 M NaCl at 25°C. The errors are the standard deviations from the average of three independent experiments for the α-carboxyl, Glu, α-amino, and Tyr; and two independent experiments for Asp, His, Cys, and Lys. For all of the titrations, the error in the pK value from fitting the experimental data to Equations 1 or 2 was <0.03.

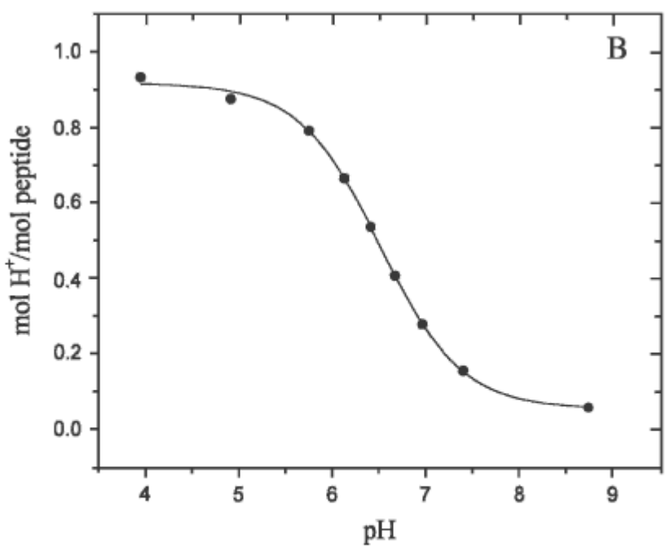


Figure 1. Potentiometric titration curves of the side chain Glu carboxyl group in Ac-AA**E**AA-NH2 (*A*), and of the side chain His imidazole group in Ac-AA**H**AA-NH2 (*B*). The peptides were dissolved in 0.1 M KCl and titrated with HCl at 25°C. The lines are the best fit of the data to Equation 2.

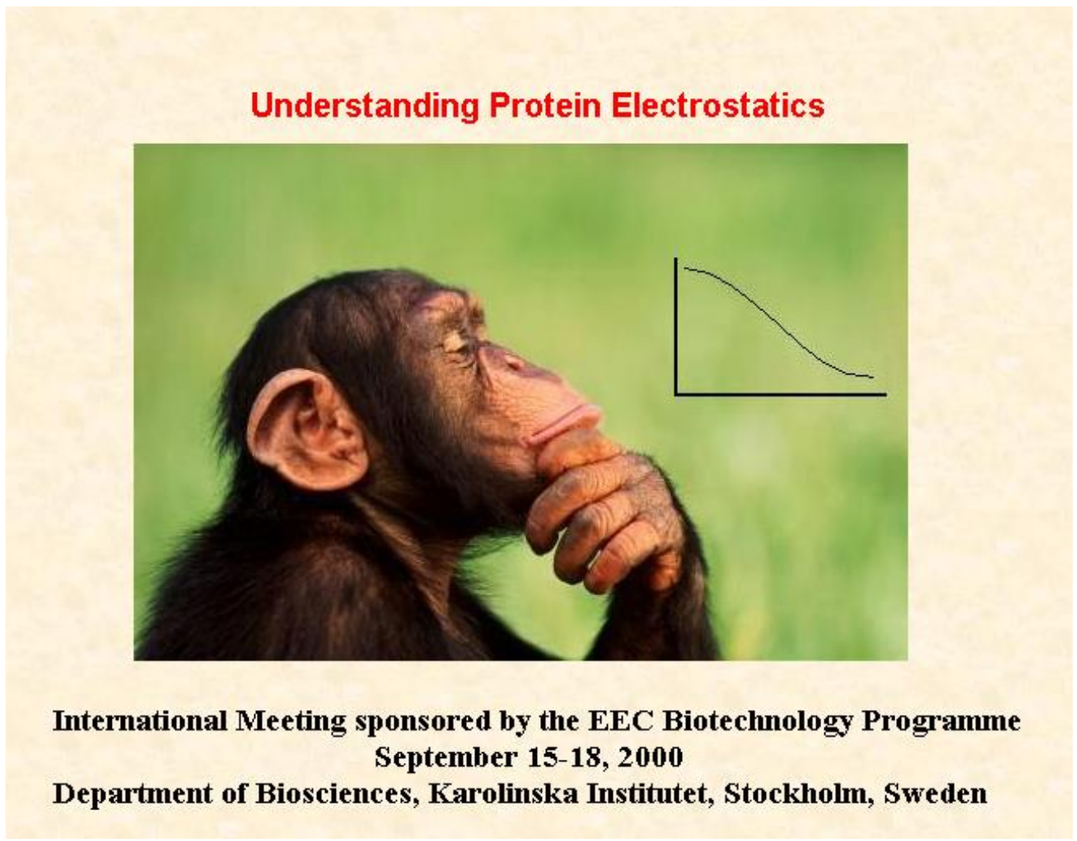
Laboratory of Computational Biophysical Chemistry

Measuring electrostatic properties

Fernando Barroso, FCFRP/USP
SAIFR - March 9-15, 2020

41

Main ideas about what we know...



42

Experiments (Borkovec, Jönsson and Koper, 2000)

- **Potentiometric titration**
- **NMR** (the most powerful technique)
- **Ultraviolet/visible spectroscopy**
- **Infrared spectroscopy**
- **fluorescence spectroscopy**

43

OM PROTEINSTOFFERNES IONISATION

AF

K. LINDERSTRØM-LANG.

Det er en kendt Sag, at Adsorptionsteorien, som har bidraget saa meget til at uddybe og udvide vort Kendskab til Stoffernes indbyrdes Vekselvirkning og til de Forhold, som betinger Fasernes Koeksistens, efterhaanden er taget i Brug ved Behandlingen af saa forskelligartede Problemer, at det ikke har kunnet undgaas, at den har draget Spørgsmaal ind under sig, som burde være taget op paa bredere Basis, — jeg sigter her til Proteinstoffernes Forhold.

Overalt, hvor Adsorptionsteorien bringes i Anvendelse, benyttes Formlen: »Koncentrationsændringer i Grænseoverfladen« til Beskrivelse af de Associationsfænomener, der optræder, naar man suspenderer Partikler af et Medium i et andet, men man kan ikke se bort fra, at en saadan Betragtningsmaade rummer en Ensidighed, der, saa vidt jeg kan se, stammer fra det empirisk-termodynamiske Udspring, Adsorptionsteorien har. Nogen fysisk Mening har denne Synsmaade først, naar Partiklerne er saa store, at de hver for sig staar i Faseligevægt med Dispersionsmidlet og har en Overflade i egentlig Forstand. Dette er imidlertid næppe Tilfældet ved Proteinstofferne; sættes nemlig efter S. P. L. Sørensen[1]) Ægalbuminpartiklernes Molekulstørrelse lig 35000, kommer hver Partikel til at indeholde ca. 3000 Atomer, og den formentlige Overflade kun ca. 1000, hvilket for det første udgør

44

Some theoretical landmarks

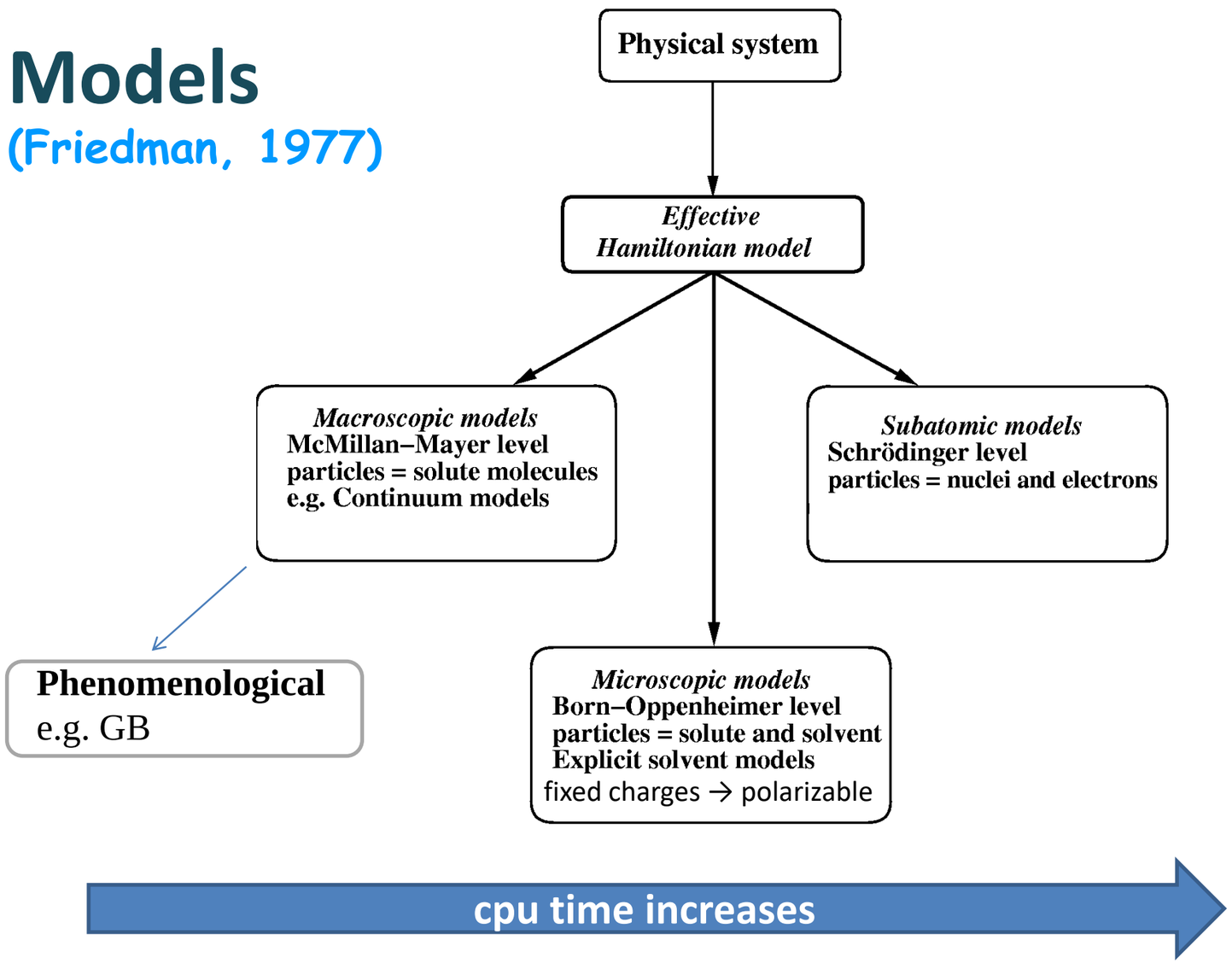
- **Linderstrøm-Lang (1924)**
- **Kirkwood (1937)**
- **Tanford-Kirkwood (1957)**
- **Warwiker & Watson (1982)**
- **Jönsson & Svensson (1990)**
- **Baptista, Marte & Petersen (1997)**
- **Jensen & co-authors (2011)**

Continuum

Empirical & fast

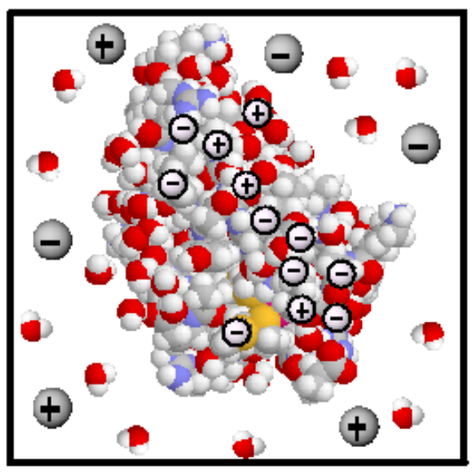
Models

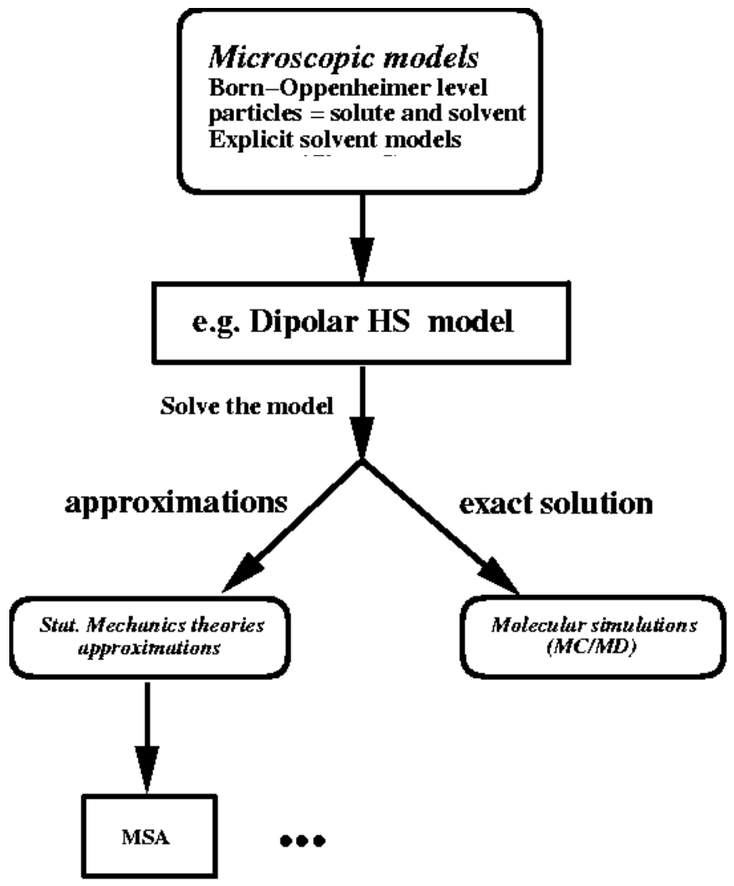
(Friedman, 1977)



[FLBDS, 2000]

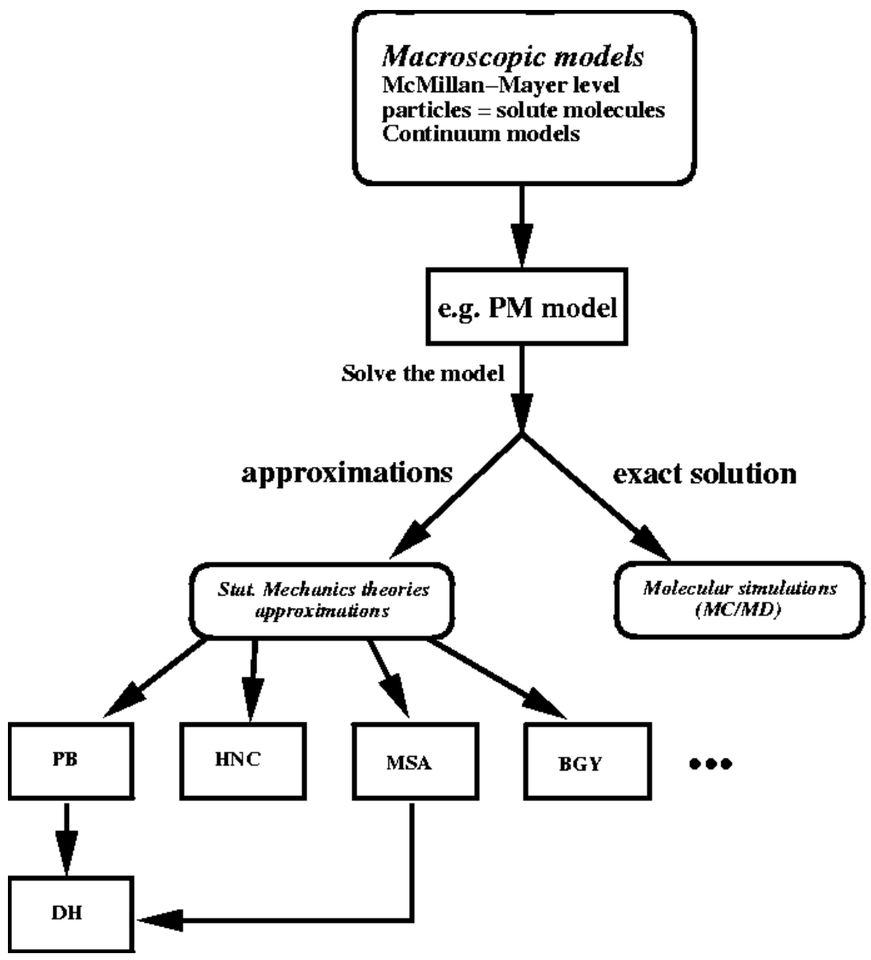
Microscopic models





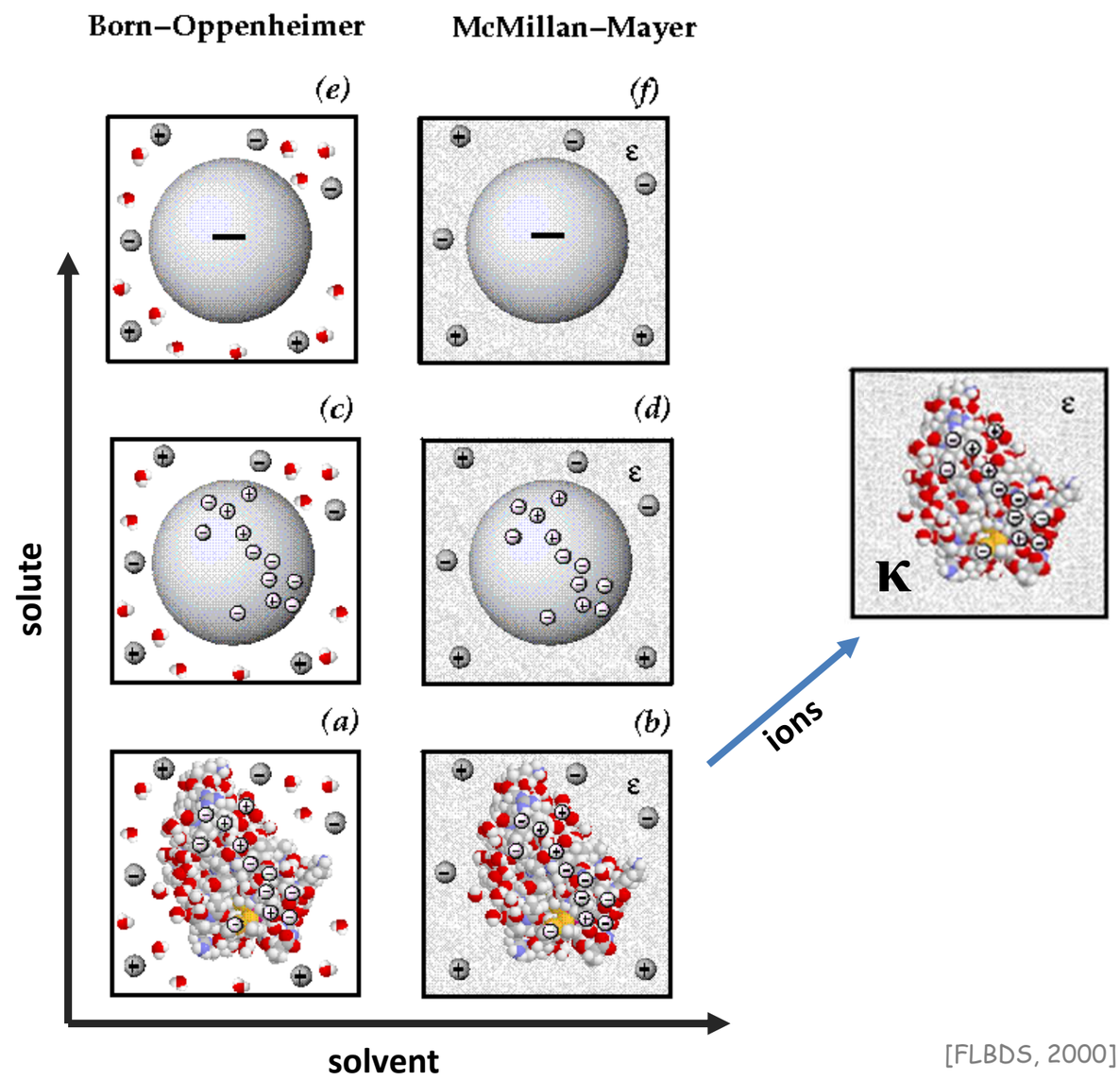
[FLBDS, 2000]

Macroscopic models



[FLBDS, 2000]

Models



[FLBDS, 2000]

Take care!

"Simulations are fiction aspiring to emulate reality. Pretty pictures and even a few good numbers do not guarantee good science"

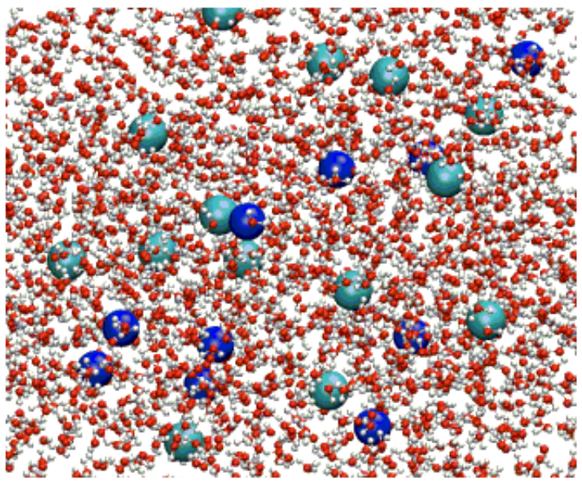
(Peter Steinbach, Center of Molecular Modeling, NIH, USA)

From Nathan Baker:

Explicit solvent simulations

- Sample the configuration space of the system: ions, atomically-detailed water, solute
- Sample with respect to a particular ensemble: NpT, NVT, NVE, etc.
- Molecular dynamics or Monte Carlo
- Advantages:
  - High levels of detail
  - Additional degrees of freedom readily included
  - All interactions are explicit
- Disadvantages
  - Slow and uncertain convergence
  - Boundary effects
  - Poor scaling
  - Some effects still not considered in may force fields...

13



[Baker, 2012]

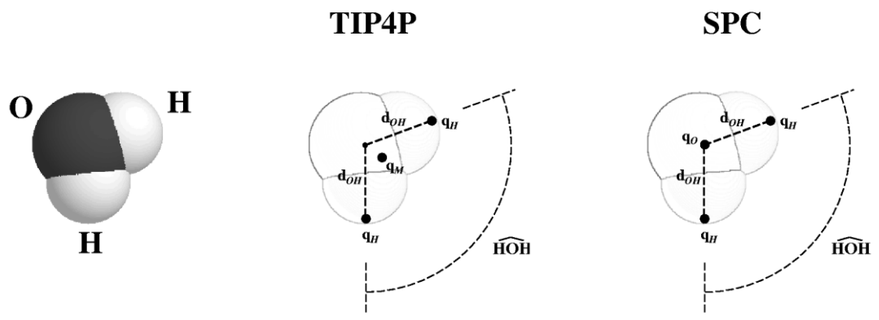
51

It is difficult to reproduce water dielectric properties by atomistic models...

TABLE 2: Water Model Properties at 298 K, 1 atm[a]

	r_c (nm)	LRC	μ (D)	ϵ_r	ρ (kg m^{-3})	α_P (10^{-4} K^{-1})	$\partial\alpha_P/\partial T$ (10^{-6} K^{-2})	κ_T (GPa^{-1})	$k_BT^2\alpha_P$ (kJ mol^{-1})
SPC	1.40	no	2.27	66	973.8	7.4	6.2	0.53	0.55
SPC/E	1.40	no	2.35	71	995.5	5.0	7.5	0.47	0.37
SPC/E	0.85	yes	2.35	71	998.9	5.0	6.8	0.46	0.37
TIP3P	0.85	yes	2.35	98	986.0	8.9	5.3	0.57	0.66
TIP4P	0.85	yes	2.18	52	994.1	5.6	8.9	0.51	0.41
TIP4P-Ew	0.85	yes	2.32	65	995.7	3.2	10.5	0.47	0.23
experiment				78	997.2	2.56	9.7	0.468	0.19

[a] The dipole moment μ, dielectric constant ϵ_r, density ρ, thermal expansion coefficient α_P and its temperature derivative, isothermal compressibility κ_T, and the liberation correction in the hydration enthalpy are given. r_c is the LJ cutoff radius. LRC is the long-range dispersion correction. All quantities, except for κ_T, were determined from 800 ns *NPT* Simulations: ϵ_r from dipole fluctuations,[49] temperature derivatives at 298 K from finite differences using the temperatures 278, 298, and 323 K. κ_T was determined from a finite difference using 10 ns simulations with ±1% density differences. The experimental data were taken from Wagner et al.[47]



Model	q_O e	q_M e	q_H e	d_{OH} Å	$\widehat{HOH}$ deg	C_6(O,O) $(kJ\text{mol}^{-1}\text{nm}^6)$	C_{12}(O,O) $(kJ\text{mol}^{-1}\text{nm}^{12})$
TIP3P	-0.834		0.417	0.9572	104.52	2.4889×10^{-3}	2.4352×10^{-6}
TIP4P		-1.04*	0.52	0.9572	104.52	2.5543×10^{-3}	2.5145×10^{-6}
SPC	-0.82		0.41	1.0	109.47	2.6171×10^{-3}	2.6331×10^{-6}
SPC/E	-0.8476		0.4238	1.0	109.47	2.6171×10^{-3}	2.6331×10^{-6}

ε=66
ε=71

Table 5.1: Popular water model parameters.
* This single negative charge is located along the $\widehat{HOH}$ bisector with $d_{OM} = 0.15$ Å.

[FLBDS, 2000]

Simple liquid models with corrected dielectric constants

Christopher J. Fennell, Libo Li, and Ken A. Dill

J Phys Chem B. 2012 June 14; 116(23): 6936–6944.

Model parameters for SPC/DC and H_2O-DC

Model	Atom-type	Constraint	d (Å)	q (e^-)	σ (Å)	ε (kJ/mol)
SPC/DC	O			−0.87362	3.15767	0.822882
	H			0.43681	0.00000	0.000000
		O–H	1.00000			
		H–H	1.63299			
H_2O-DC	O			−0.90990	3.18400	0.593000
	H			0.45495	0.00000	0.000000
		O–H	0.95800			
		H–H	1.56441			

Simple liquid models with corrected dielectric constants

Christopher J. Fennell, Libo Li, and Ken A. Dill

PMC full text: J Phys Chem B. Author manuscript; available in PMC 2013 Jul 31.
Published in final edited form as:
J Phys Chem B. 2012 Jun 14; 116(23): 6936–6944.
Published online 2012 Mar 21. doi: 10.1021/jp3002383

Table 5

Liquid properties for water calculated at 298.15 K and 1 atm with standard error of the last digit in parentheses

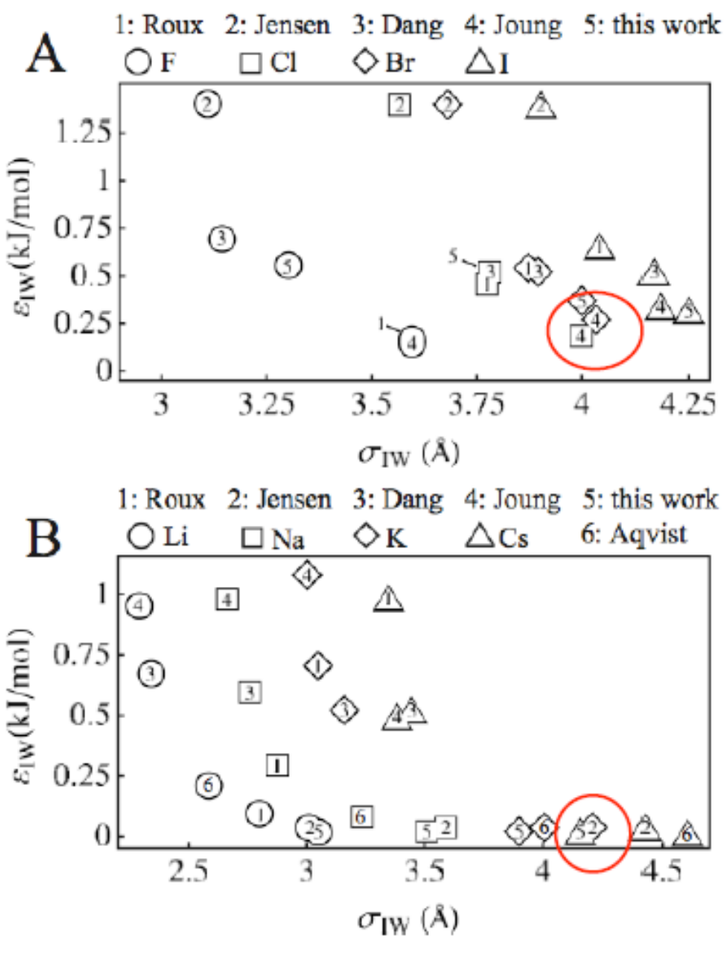
Model	ρ (kg/m^3)	DH_{vap} (kJ/mol)	$\varepsilon(0)$	C_p (J/mol·K)	κ_T (10^5 atm^{-1})	α_p (10^6 K^{-1})	D (10^{-9} m^2/s)	μ (D)
SPC	978.41 (3)	36.820 (1)	65.6 (2)	82.9 (3)	53.7 (5)	71.5 (7)	3.99 (1)	2.27
SPC/E	999.53 (2)	41.905 (1)	71.1 (1)	86.3 (2)	46.1 (2)	49.1 (4)	2.46 (1)	2.35
SPC/DC	998.69 (2)	43.993 (1)	78.3 (6)	83.2 (3)	43.7 (3)	48.8 (9)	2.48 (1)	2.42
H_2O-DC	997.55 (2)	43.366 (1)	78.7 (6)	87.8 (2)	45.0 (2)	44.8 (4)	2.17 (1)	2.42
Expt	997.5[a]	43.99[a]	78.36[a]	75.3[a]	45.84[a]	25.6[a]	2.299[b]	

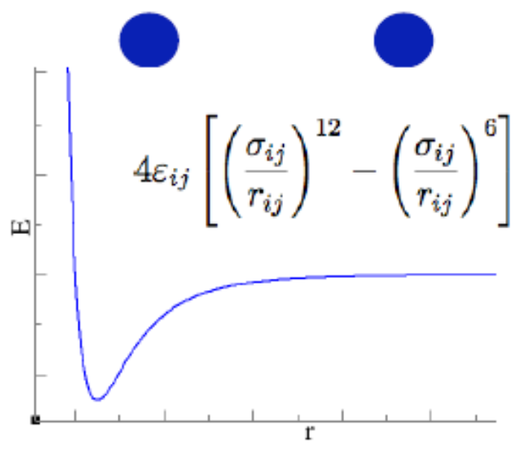
[a]Reference 22
[b]Reference 43

55

simulation ion parameters widely scatter !

Horinek, Mamatqulov, Netz, JCP 130, 124507 (2009)





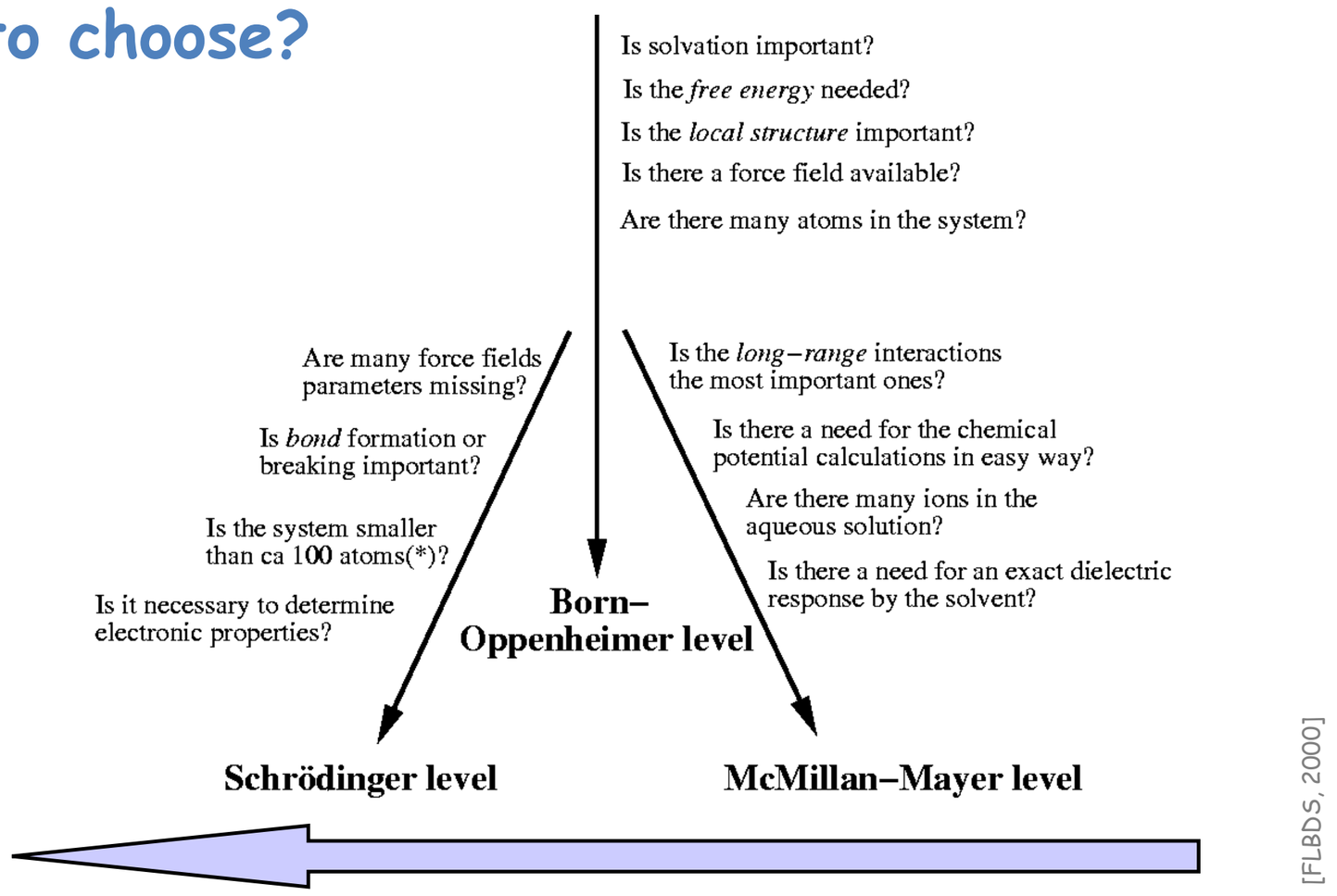
Observation: drastic variations in ionic force fields

Question: rationally designed ?
Honest Answer in most cases: No !

[Netz, 2014]

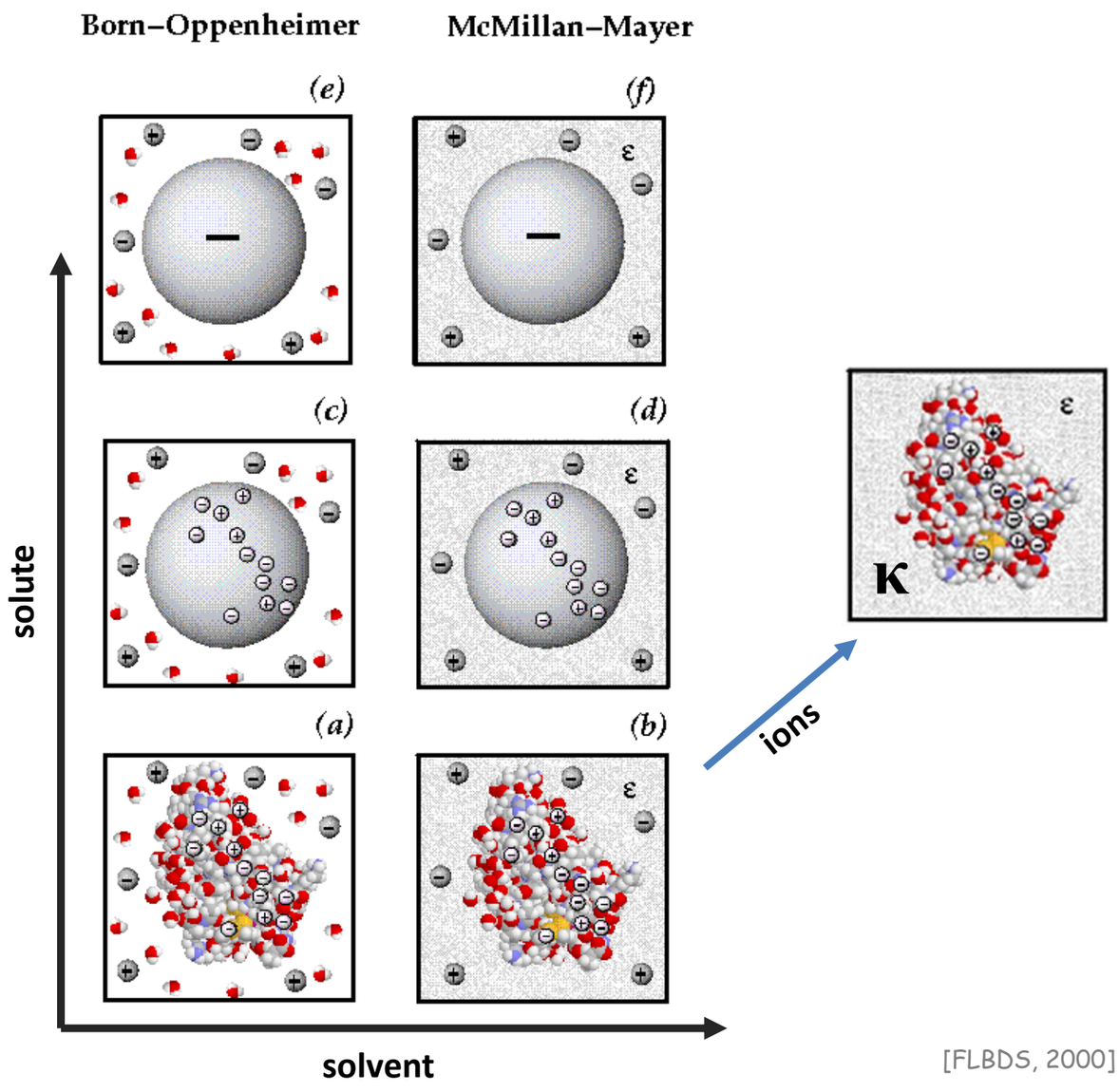
56

How to choose?



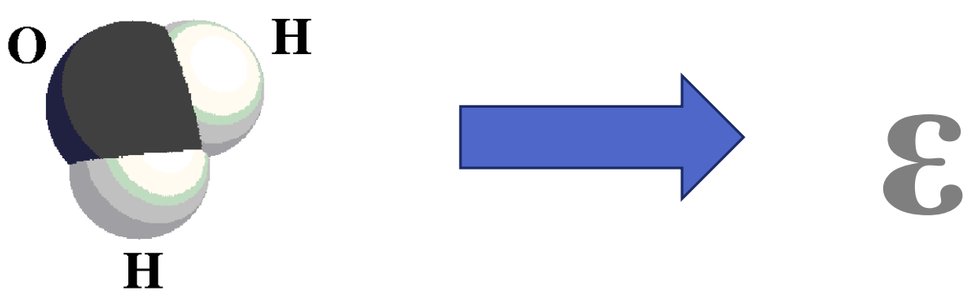
[FLBDS, 2000]

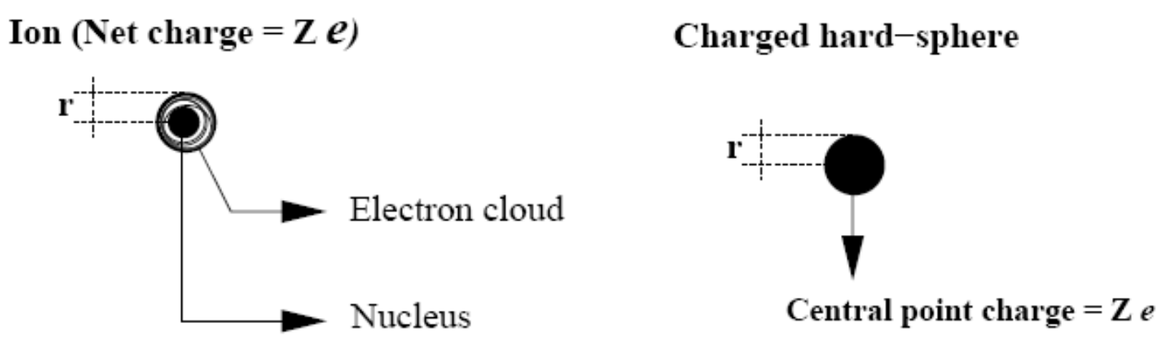
Models

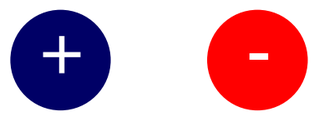


[FLBDS, 2000]

Continuum framework



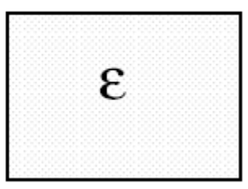




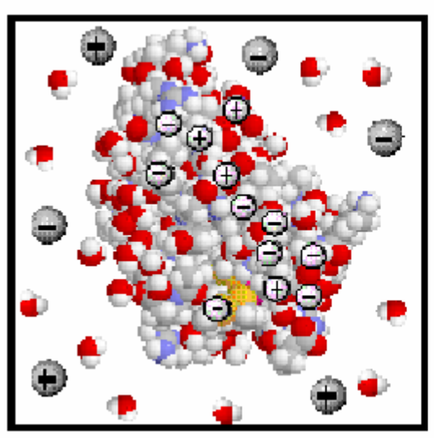
Aproximations...1) charges

Solvent

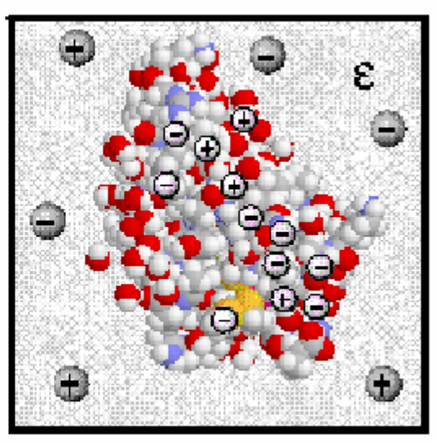
Structure−less continuum medium



Molecular water (explici)



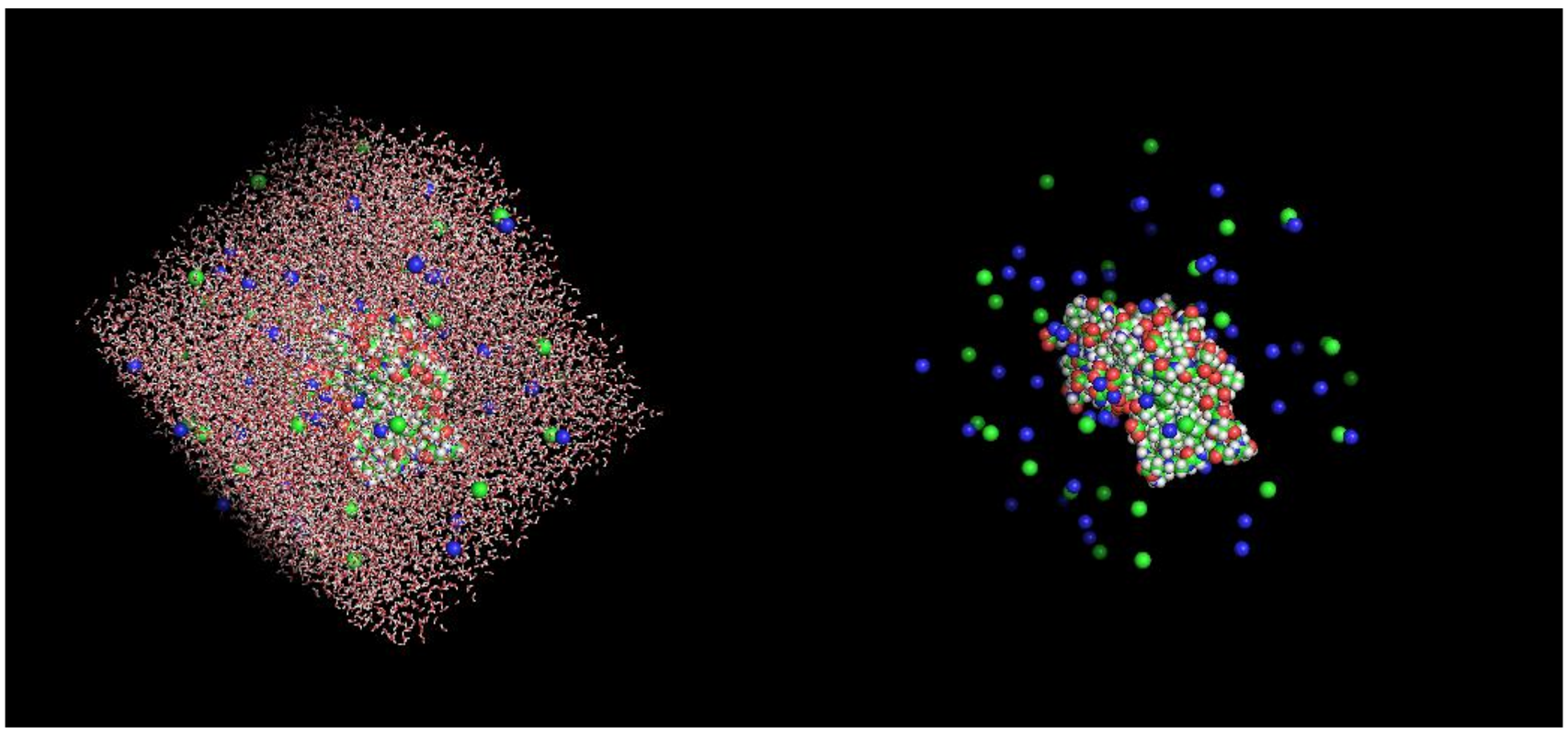
Water as a medium



Aproximations...2) Solvent

61

Big reduction in number of particles



62