Models for dielectrics at the molecular and continuum scale

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Competing effects: why this is so hard

Protein sidechains have large electrostatic gradients

Water is a strong dielectric

Hydrophobic groups modify the water structure

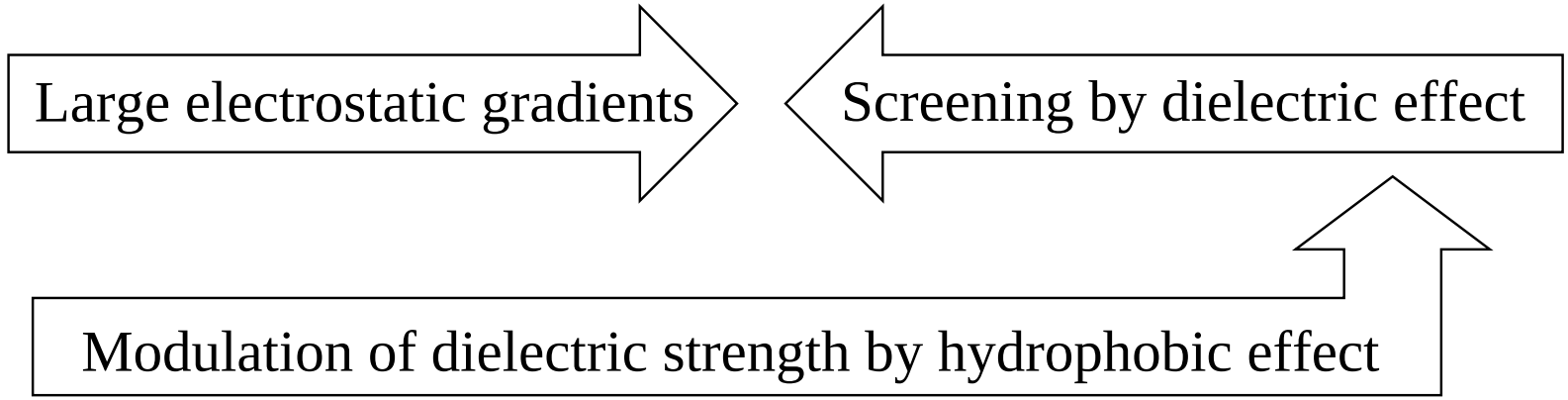


Figure 1: Three competing effects that determine protein behavior. These conspire to weaken interactive forces, making biological relationships more tenuous and amenable to mutation.

Charges in a dielectric are like lights in a fog.

Dielectric model

Consider two charge distributions ρ (fixed charges) and γ (polar groups free to rotate). Resulting electric potential ϕ satisfies

$$\Delta\phi = \rho + \gamma, \tag{0.1}$$

where the dielectric constant of free space is set to one.

Write $\phi = \phi_\rho + \phi_\gamma$, where $\Delta\phi_\gamma = \gamma$ and $\Delta\phi_\rho = \rho$.

Ansatz of Debye [17]: the electric field $\mathbf{e}_\gamma = \nabla\phi_\gamma$ is parallel to (opposing) the resulting electric field $\mathbf{e} = \nabla\phi$:

$$\nabla\phi_\gamma = (1 - \varepsilon)\nabla\phi. \tag{0.2}$$

Thus $\nabla\phi_\rho = \nabla\phi - \nabla\phi_\gamma = \varepsilon\nabla\phi$ and

$$\nabla \cdot (\varepsilon\nabla\phi) = \rho. \tag{0.3}$$

Polarization field and Debeye's Ansatz as projection

Define $\mathbf{p} = \nabla\phi_\gamma$: called the polarization field. Recall $\mathbf{e} = \nabla\phi$.

Write $\mathbf{p} = (\epsilon - \epsilon_0)\mathbf{e} + \zeta\mathbf{e}^\perp$, so that

$$\epsilon = \epsilon_0 + \frac{\mathbf{p}\cdot\mathbf{e}}{\mathbf{e}\cdot\mathbf{e}},$$

with the appropriate optimism that $\mathbf{p} = 0$ when $\mathbf{e} = 0$.

That is, $\epsilon - \epsilon_0$ reflects the correlation between $\mathbf{p}$ and $\mathbf{e}$.

As defined, ϵ is a function of $\mathbf{r}$ and t, and potentially singular.

However, Debye postulated that a suitable average $\widetilde{\epsilon}$ should be well behaved:

$$\widetilde{\epsilon} = \epsilon_0 + \left\langle \frac{\mathbf{p}\cdot\mathbf{e}}{\mathbf{e}\cdot\mathbf{e}} \right\rangle .$$

Interpretation of ε

Manipulations leading to (0.3) valid when ε is an operator, even nonlinear.

In bulk water ε is a (temperature-dependent) constant:

$$\varepsilon \approx 87.74 - 40.00\,\tau + 9.398\,\tau^2 - 1.410\,\tau^3, \quad \tau \in [0,1], \tag{0.4}$$

where $\tau = T/100$ and T is temperature in Centigrade (for $T > 0$) [25].

$\varepsilon >> 1$: opposing field strength $E_\gamma = \nabla\phi_\gamma$ much greater than inducing field.

ε increases with decreasing temperature; when water freezes, it increases further: for ice at zero degrees Centigrade, $\varepsilon \approx 92$.

But model fails when the spatial frequencies of the electric field $\nabla\phi$ are commensurate with the size of a water molecule, since the water molecules cannot orient appropriately to align with the field.

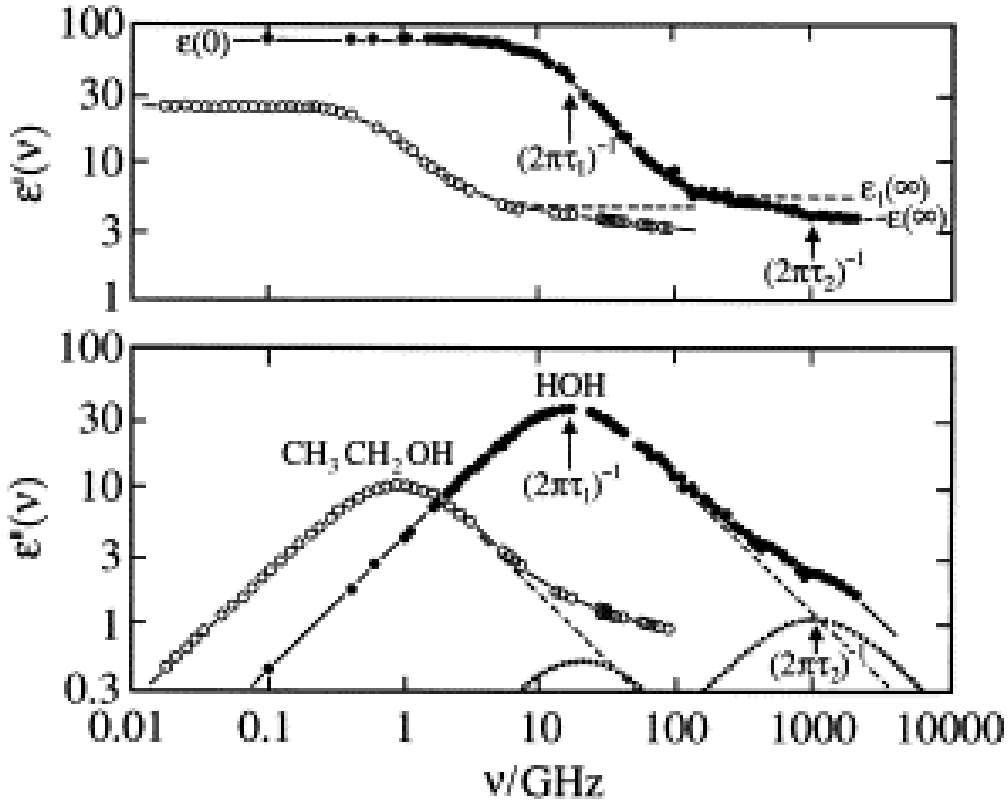
Thus frequency-dependent versions of ε have been proposed, and these are often called 'nonlocal' models since the operator ε must be represented either as a Fourier integral (in frequency space), or as an integral in physical space with a nonlocal kernel [13, 36].

Frequency dependence of dielectric constant

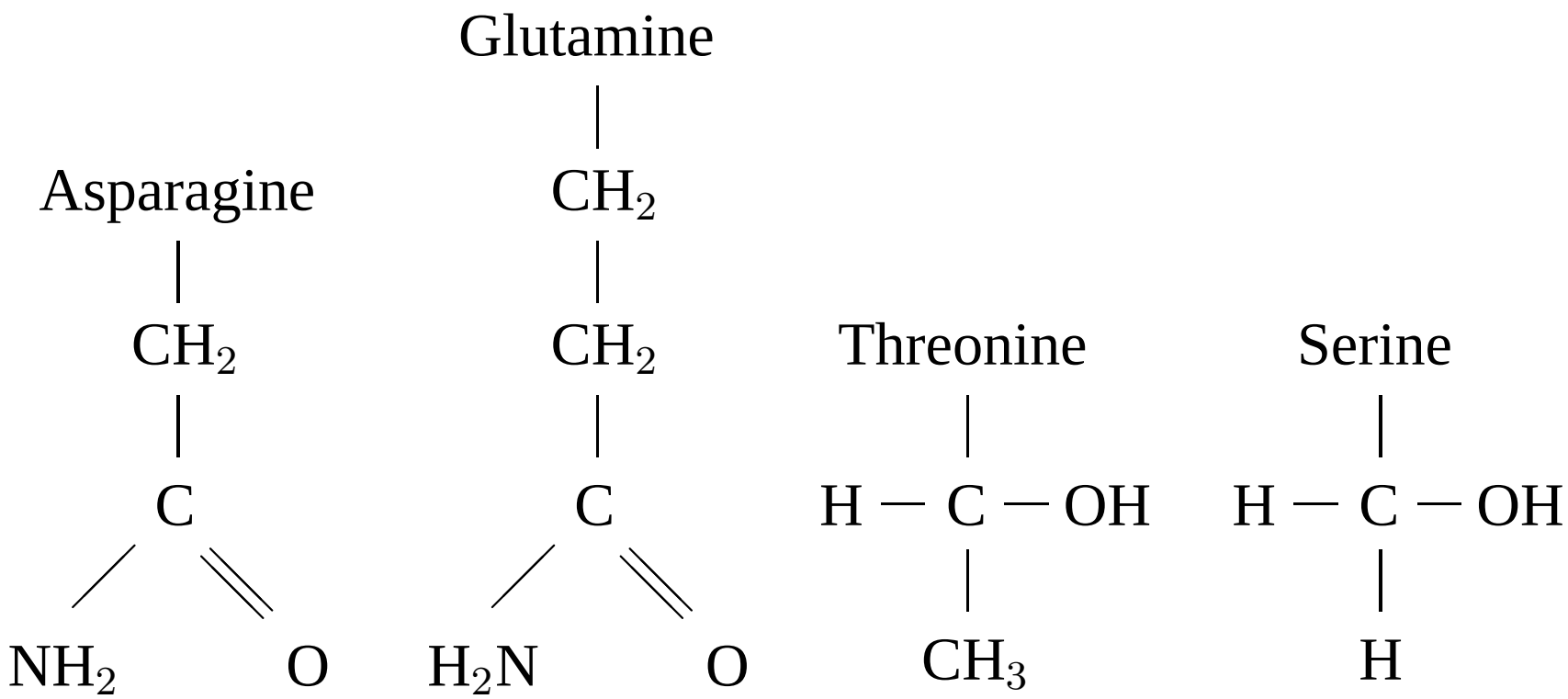
Debye observed that the effective permittivity is frequency dependent:

$$\epsilon(\nu) = \epsilon_0 + \frac{\epsilon_1 - \epsilon_0}{1 + \tau_D^2 \nu^2} \tag{0.5}$$

where τ_D is a characteristic time associated with the dielectric material and ν is the temporal wave number. Many experiments have verified this [28]:

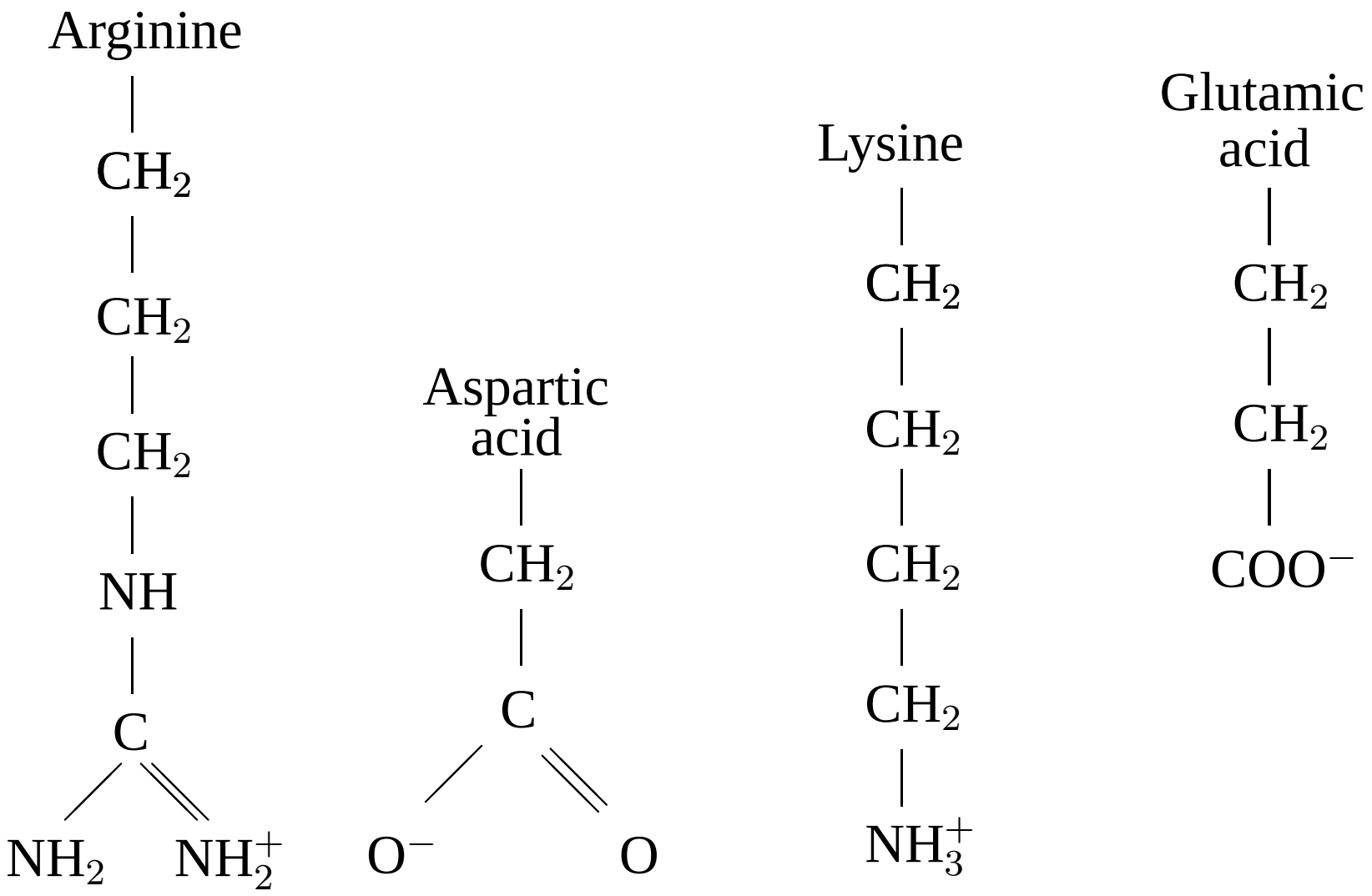


Polar residues cause spatial high frequencies



Some polar sidechains

Charged sidechains form salt bridge networks



Nonlocal dielectric models

The nonlocal dielectric approach for estimating electrostatics was introduced by Dogonadze and Kornyshev [10, 32] about fifteen years ago.

Since then, many studies have been done in the fields of chemistry, physics, and biology (see [9, 10, 11, 13, 31, 32, 36] for example). A good review on these studies is given in [12].

Progress in the development of fast numerical algorithms was made by Hildebrandt *et al.* when they reformulated one commonly-used nonlocal electrostatic continuum model, called the Fourier-Lorentzian nonlocal model, as a system of coupled PDEs [26].

However, the Hildebrandt approach utilizes a complex splitting and certain jump terms, which we have been able to avoid.

A key step is to write the nonlocal dielectric model as an integro-differential equation in which the integral term involves only a convolution of the solution.

This new formulation leads to a fast finite element solver.

The convolution of the solution can be regarded as a unknown function, $u(\mathbf{r})$.

To calculate $u(\mathbf{r})$ we construct an "artificial" partial differential equation such that this equation has u as a solution and is coupled with the original equation of the nonlocal dielectric model.

In this way, the nonlocal dielectric model is reformulated into a system of two partial differential equations.

This approach can be naturally carried out in the framework of the Ritz-Galerkin variational formulation without involving any Helmholtz decomposition of the dielectric displacement field.

Hence, it is quite different from Hildebrandt *et al.*'s approach.

Remarkably, we prove that there is a simple splitting of the system.

The electrostatic potential function $\Phi(\mathbf{r}))$ can be split as a sum of two functions, with the property that these two functions can be found independently as the solutions of one Poisson equation and one Poisson-like equation each suitable for solution by a fast linear solver such as the multigrid method.

Using this solution splitting formula, we develop a finite element algorithm within the FEniCS framework.

Moreover, its computing cost is only double that of solving a classic Poisson dielectric model.

1 Fourier-Lorentzian nonlocal model of water

Let $\Phi(\mathbf{r})$ denote the electrostatic potential function, and $\rho(\mathbf{r})$ be a given fixed charge density function. One commonly-used nonlocal dielectric model, called the Fourier-Lorentzian nonlocal model, is defined by the integro-differential equation

$$\begin{cases} -\epsilon_0 \left[\epsilon_\infty \Delta\Phi(\mathbf{r}) + \frac{\epsilon_s - \epsilon_\infty}{\lambda^2} \nabla \cdot \int_{\mathbb{R}^3} H(\mathbf{r}-\mathbf{r}') \nabla\Phi(\mathbf{r}')\, \mathrm{d}\mathbf{r}'\right] = \rho(\mathbf{r}), & \mathbf{r} \in \mathbb{R}^3, \\ \Phi(\mathbf{r}) \to 0 & \text{as } |\mathbf{r}| \to \infty, \end{cases} \tag{1.6}$$

where ϵ_0 is the permittivity constant of the vacuum, ϵ_s is the permittivity factor for bulk water, ϵ_∞ is the permittivity factor for water in the limit of high frequency [38], λ is a positive parameter used to characterize the polarization correlations of water molecules, and $H(\mathbf{r})$ is the kernel function defined by

$$H(\mathbf{r}) = \frac{1}{4\pi|\mathbf{r}|} e^{-\frac{|\mathbf{r}|}{\lambda}}. \tag{1.7}$$

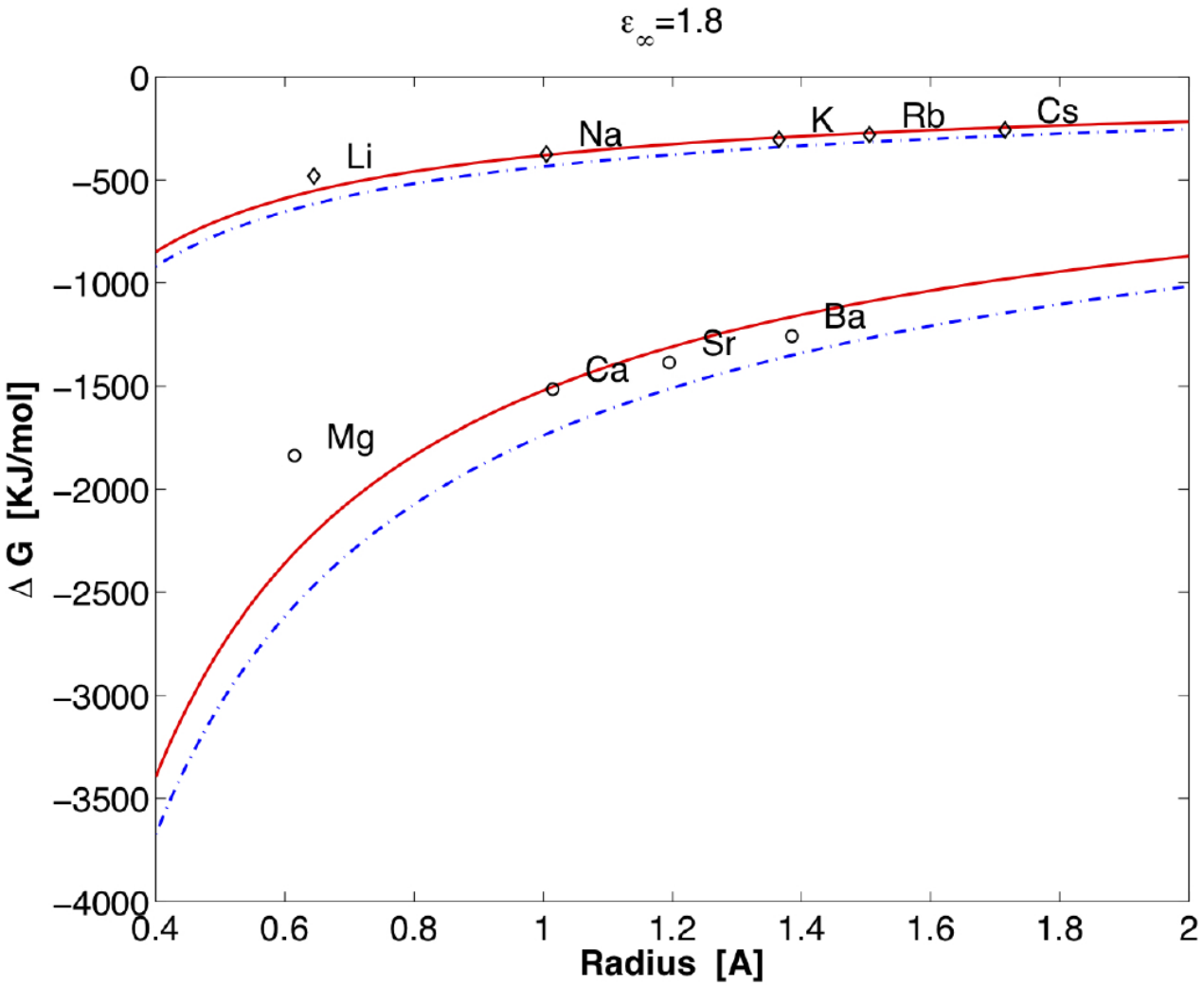


Figure 2: Comparisons of analytical free energy differences calculated from the nonlocal dielectric model with two values of λ ($\lambda = 15$Å and $\lambda = 30$Å) and the values from chemical experiments.

Caveats about the model

The nonlocal model is a much better predictor of important physical phenomena, such as the solvation free energy of ions (Figure 2).

Moreover, it is relatively insenstive to the choice of λ.

Shown in Figure 2 are results for the Born ion approximation for two values of λ that bracket the value $\lambda = 23$Å used in Hildebrandt's thesis [27].

The predicted results are remarkably accurate for most ions, espcially given the uncertainty in the ion radius.

However, they are very sensitive to the choice of ϵ_∞.

We are only accounting for the polar contribution to the free energy difference, and there is a nonpolar part that must also be estimated.

The main difficulty in solving the nonlocal model (1.6) comes from the integral term in which the integration and derivative are mixed together.

Note that $H(\mathbf{r})$ satisfies the following equation

$$-\Delta H + \frac{1}{\lambda^2} H = \delta, \tag{1.8}$$

where δ is the Dirac-delta distribution defined by $\delta(f) = f(0)$ for any f in a test function space. Hence, applying the convolution on the both sides of (1.8) gives

$$(\Phi * \Delta H)(\mathbf{r}) = \frac{1}{\lambda^2}(\Phi * H)(\mathbf{r}) - \Phi(\mathbf{r}), \quad \mathbf{r} \in \mathbb{R}^3. \tag{1.9}$$

As a result, the integral term in (1.6) is simplified as

$$\nabla \cdot \int_{\mathbb{R}^3} H(\mathbf{r} - \mathbf{r}') \nabla \Phi(\mathbf{r}') \, \mathrm{d}\mathbf{r}' = \frac{1}{\lambda^2}(\Phi * H)(\mathbf{r}) - \Phi(\mathbf{r}), \quad \mathbf{r} \in \mathbb{R}^3,$$

so that the nonlocal model (1.6) can be reformulated into the new expression:

$$-\epsilon_\infty \Delta \Phi(\mathbf{r}) + \frac{\epsilon_s - \epsilon_\infty}{\lambda^2} \Phi(\mathbf{r}) - \frac{\epsilon_s - \epsilon_\infty}{\lambda^4}(\Phi * H)(\mathbf{r}) = \frac{1}{\epsilon_0} \rho(\mathbf{r}), \quad \mathbf{r} \in \mathbb{R}^n. \tag{1.10}$$

2 New solution splitting formula

Let Φ be the solution of the nonlocal model (1.6). Then it can be expressed as

$$\Phi(\mathbf{r}) = \frac{1}{\lambda^2 \epsilon_s}[(\epsilon_s - \epsilon_\infty) w(\mathbf{r}) + \epsilon_\infty v(\mathbf{r})], \quad \mathbf{r} \in \mathbb{R}^3, \tag{2.11}$$

where $w(\mathbf{r})$ and $v(\mathbf{r})$ are the functions satisfying the two Poisson-like equations:

$$\begin{cases} -\Delta w(\mathbf{r}) + \dfrac{\epsilon_s}{\lambda^2 \epsilon_\infty} w(\mathbf{r}) = \dfrac{\lambda^2}{\epsilon_0 \epsilon_\infty} \rho(\mathbf{r}), \quad \mathbf{r} \in \mathbb{R}^3, \\ w(\mathbf{r}) \to 0 \qquad \text{as } |\mathbf{r}| \to \infty, \end{cases} \tag{2.12}$$

and

$$\begin{cases} -\Delta v(\mathbf{r}) = \dfrac{\lambda^2}{\epsilon_0 \epsilon_\infty} \rho(\mathbf{r}), \quad \mathbf{r} \in \mathbb{R}^3, \\ v(\mathbf{r}) \to 0 \qquad \text{as } |\mathbf{r}| \to \infty. \end{cases} \tag{2.13}$$

Table 1: Physics parameter values used for computing free energy differences

Constant	Definition	Value
$\mathcal{N}_a$	Avogadro constant	6.022×10^{23}
ϵ_s	Permittivity ratio of bulk water	80 [25]
ϵ_∞	Permittivity ratio of confined water	1.8 [27], 2.34 [40]
ϵ_0	Permittivity of vacuum	8.854×10^{-12} [F/m]
$1e$	One electron charge	1.6×10^{-19} Coulomb

Table 2: Free energy differences produced from chemical experiments for selected ions, together with the atomic radii and their uncertainties from Hildebrandt's thesis [27].

Ion	Radius of Born ball [Å]	Charge [e]	Free energy [KJ/mol]
Na^+	1.005 ± 0.04	1	-375
K^+	1.365 ± 0.05	1	-304
Ca^{2+}	1.015 ± 0.02	2	-1515
Sr^{2+}	1.195	2	-1386

Nonlinear models

Polarization field $\nabla\phi_\gamma$ saturates for large fixed fields:

$$\lim_{|\nabla\phi|\to\infty}(1-\varepsilon)\nabla\phi = \lim_{|\nabla\phi|\to\infty}\nabla\phi_\gamma = C, \tag{2.14}$$

One simple model that satisfies (2.14) is

$$\varepsilon(x) = \varepsilon_0 + \frac{\varepsilon_1}{1+\lambda|\nabla\phi(x)|} \tag{2.15}$$

for some constants ε_0, ε_1, and λ.

Both the nonlocal and nonlinear models of the dielectric response have the effect of representing frequency dependence of the dielectric effect.

$|\nabla\phi(x)|$ provides a proxy for frequency content, although it will not reflect accurately high-frequency, low-power electric fields.

Combination of nonlocal and nonlinear dielectric models may be needed.

Local model for dielectric effect?

Wrapping modifies dielectric effect Hydrophobic (CH_n) groups remove water locally.

This causes a reduction in ε locally.

(Resulting increase in ϕ makes dehydrons sticky.)

This can be quantified and used to predict binding sites.

The placement of hydrophobic groups near an electrostatic bond is called wrapping.

Like putting insulation on an electrical wire.

We can see this effect on a single hydrogen bond.

Unit of hydrophobicity

A single carbonaceous group CH_n can enhance the strength and stability of a hydrogen bond.

Consider the effect of such a group in

- methyl alchohol versus ethyl alchohol
- ethylene glycol versus propylene glycol
- (deadly versus drinkable)

Can we see a molecular-level effect analogous to the change in dielectric permittivity?

What can a simple model of dielectric modulation predict?

3 Wrapping electrostatic bonds

By 1959, the role of hydrophbicity in protein chemistry was firmly established [29].

Soon afterward [22, 30], the role of hydrophobicity in enhancing the stability and strength of hydrogen bonds in proteins was demonstrated.

However, the story developed slowly, and a careful interpretation is required.

The paper [30] studied a model molecule, N-methylacetamiden, that is similar to the peptide backbone in structure and forms the same kind of amide-carbonyl (NH–OC) hydrogen bond formed by the backbone of proteins.

Infrared absorbtion measurements were performed to assess the strength and stability of the hydrogen bonds formed by N-methylacetamiden in various solvents (including water) with different degrees of polarity.

The paper's main conclusion might be misinterpreted as saying that hydrogen bonds are not significant for proteins in water [30]: "It seems unlikely, therefore, that interpeptide hydrogen bonds contribute significantly to the stabilization of macromolecular configuration in aqueous solution."

However, the authors did confirm the oppositve view in less polar solvents, so we would now say that their study indicated the value of hydrophobic protection of hydrogen bonds in proteins.

The subsequent paper [22] also studied model molecules, including N-methylacetamiden, in solvents based on varying ratios of trans-dichloroethylene and cis-dichloroethylene, via infrared spectroscopy.

They established that “the free energy and enthalpy of association of the amides can be expressed as a function of the reciprocal of the dielectric constant.”

Although the variation in dielectric constants achieved with these solvents only reached a level of one-tenth that of water, this paper quantified the effect of dielectric modulation on the strength and stability of hydrogen bonds in systems similar to proteins.

Thus it remained only to connect the variation in the dielectric constant to quantifiable variations in protein composition.

Although the energetic role of peptide hydrogen bonds remains a subject of significant interest [7, 8], it now seems clear that the variation in hydrophobicity in proteins has a significant and quantifyable effect on the behavior of proteins [18].

According to [39], “The prevailing view holds that the hydrophobic effect has a dominant role in stabilizing protein structures.”

The quantitative use of hydrophobicity as a marker for ‘hot spots’ in proteins has had significant success among diverse groups [15, 19].

Attempts to quantify hydrophobicity in sidechains has a long history [33].

The concept we call wrapping here is very similar to what has been termed **blocking** [5] and **shielding** [24, 34].

We prefer the term wrapping sinces it evokes the image of providing a protective layer around a charged environment.

The term ‘shielding’ has a related meaning in electronics, but it is also easy to confuse with ‘screening’ which for us is what the water dielectric performs. The material used for shielding in a coaxial cable is a type of cylindrical screen, and it is a conductor, not an insulator.

In an experimental study [5] of hydrogen exchange [6], the authors stated that (hydrophobic)

"amino acid side chains can enhance peptide group hydrogen bond strength in protein structures by obstructing the competing hydrogen bond to solvent in the unfolded state. Available data indicate that the steric blocking effect contributes an average of 0.5 kJ per residue to protein hydrogen bond strength and accounts for the intrinsic beta-sheet propensities of the amino acids."

Although this result is clearly quantitative, it should be understood that the experimental technique is indirect.

Hydrogen exchange [6] refers to the exchange of

hydrogen for deuterium in a highly deuterated environment, and it most directly measures the lack of hydrogen bonds.

Numerical simulations of peptides also contributed to the growth in understanding of the quantitative effect of hydrophobic groups on hydrogen bonds.

Based on computational simulations [37], the authors stated that their results provided “a sound basis with which to discuss the nature of the interactions, such as hydrophobicity, charge-charge interaction, and solvent polarization effects, that stabilize right-handed alpha-helical conformations.”

One might ask what minimal quantum of wrapping might be identifiable as affecting the strength or stability of a hydrogen bond.

The work on hydrogen exchange [5, 6] shows differences in the effect on hydrogen bonds for various hydrophobic sidechains (Ala, Val, Leu, Ile) which differ only in the number of carbonaceous groups.

More recent experiments [34] have looked directly at the propensity to form alpha-helical structures of polypeptides (13 residues) which consisted of X=Gly, Ala, Val, Leu, or Ile flanked on either side by four alanine residues with additional terminal residues (Ac-KAAAAXAAAAKGY-NH2).

These experiments directly measured the strength and stability of hydrogen bonds in these small proteins.

The experimental evidence [34] again shows differences between the different sidechains X in terms of their ability to increase helix propensity, and hence their effect on the hydrogen bonds supporting helix formation.

This observation was further developed in a series of papers [1, 2, 3, 4].

More recent, and more complex, experiments [23] confirm that hydrogen bond strength is enhanced by a nonpolar environment.

Based on the accumulated evidence, we take a *single carbonaceous group to be an identifiable unit of hydrophobicity.*

There is perhaps a smaller, or another, unit of interest, but at least this gives us a basis for quantification of the modulation of the dielectric effect.

It is perhaps surprising that such a small unit could have a measurable effect on hydrophocity, but we already remarked on comparable effects of a single carbonaceous group regarding toxicity of alchohols and antifreezes.

It is possible that removal of water can be promoted by components of sidechains other than purely carbonaceous ones.

For example, we noted that the arginine residue does not solvate well [35], in addition to the fact that it contains significant carbonaceous groups.

A computational study [24] of a 21-residue peptide including a triple (tandem) repeat of the sidechains AAARA concluded that

"the Arg side chain partially shields the carbonyl oxygen of the fourth amino acid upstream from the Arg. The favorable positively charged guanidinium ion interaction with the carbonyl oxygen atom also stabilizes the shielded conformation."

Note that the second sentence indicates a possible sidechain-mainchain hydrogen bond.

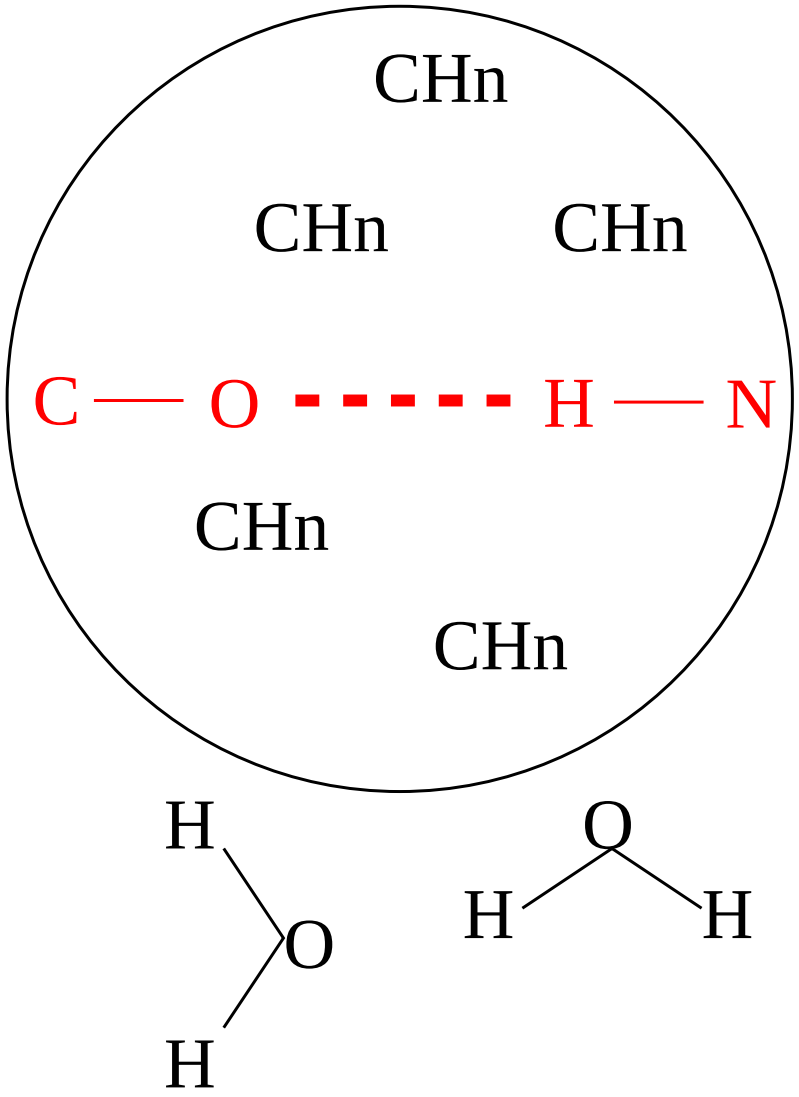
Since wrapping is of interest because of its implications for hydrophobicity, one could attempt to model hydrophobicity directly as a scalar quantity.

Such an approach using a sidechain-based evaluation has been taken [14, 15] based on estimates of hydrophobicity provided earlier [33].

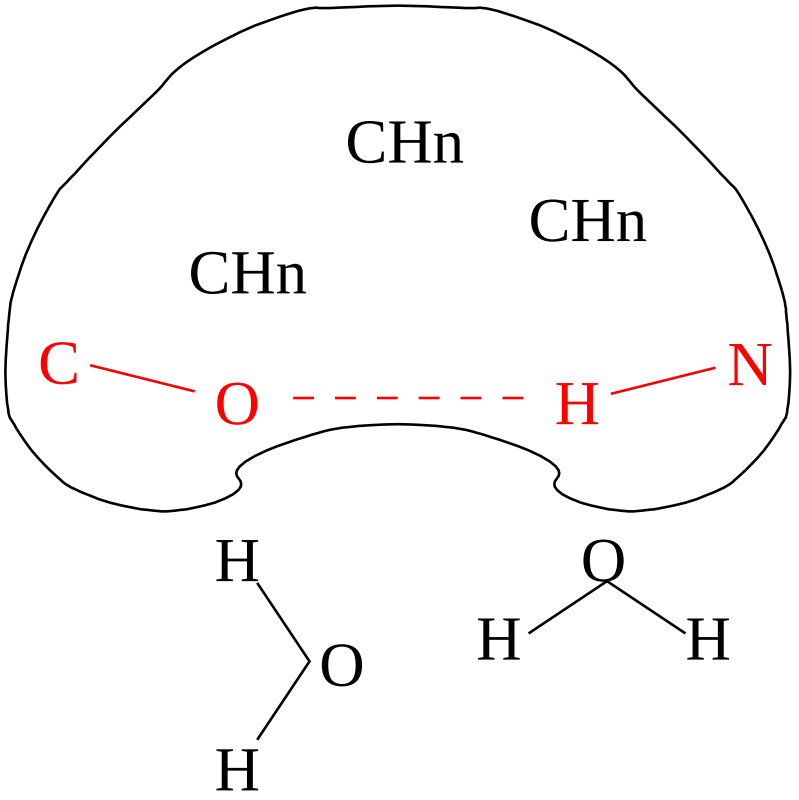
We have defined wrapping as an integer quantity defined for each bond, but this could (by interpolation) be extended as a function defined everywhere, and the use of a cut-off function [14, 15, 33] essentially does that.

But the scalar quantity of real interest with regard to electrostatic bonds is the dielectric.

Wrapping protects hydrogen bond from water



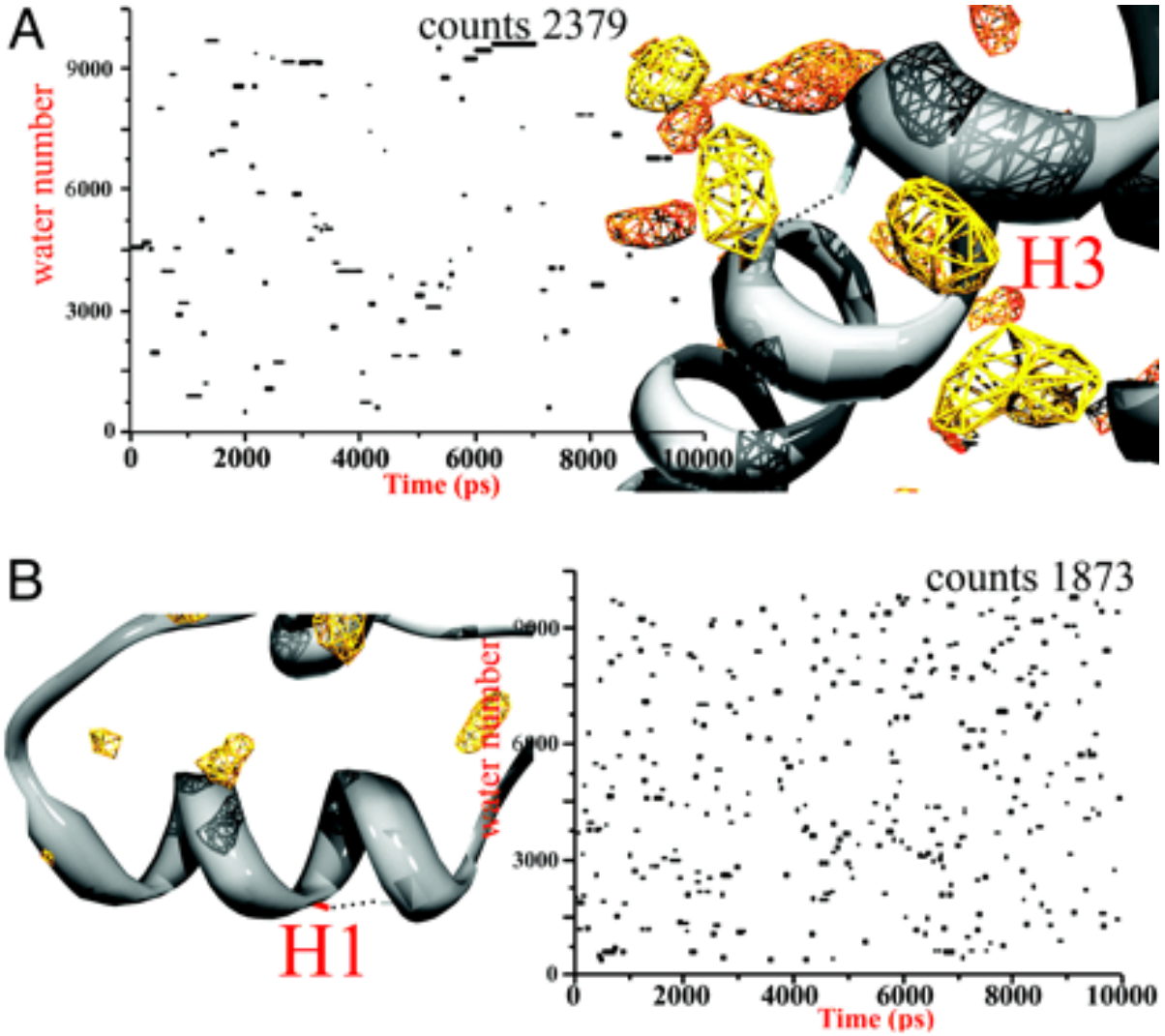
Well wrapped hydrogen bond



Underwrapped hydrogen bond

Extent of wrapping changes nature of hydrogen bond

Hydrogen bonds (B) that are not protected from water do not persist.



From De Simone, et al., PNAS 102 no 21 7535-7540 (2005)

Dynamics of hydrogen bonds and wrapping

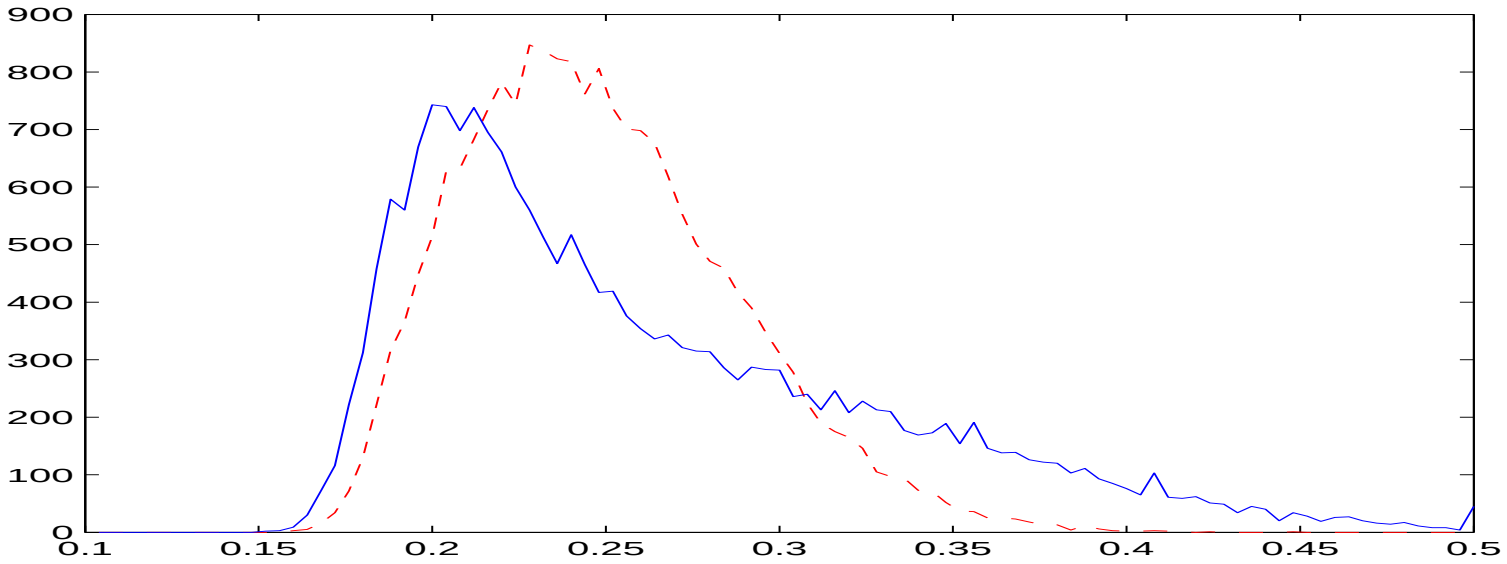
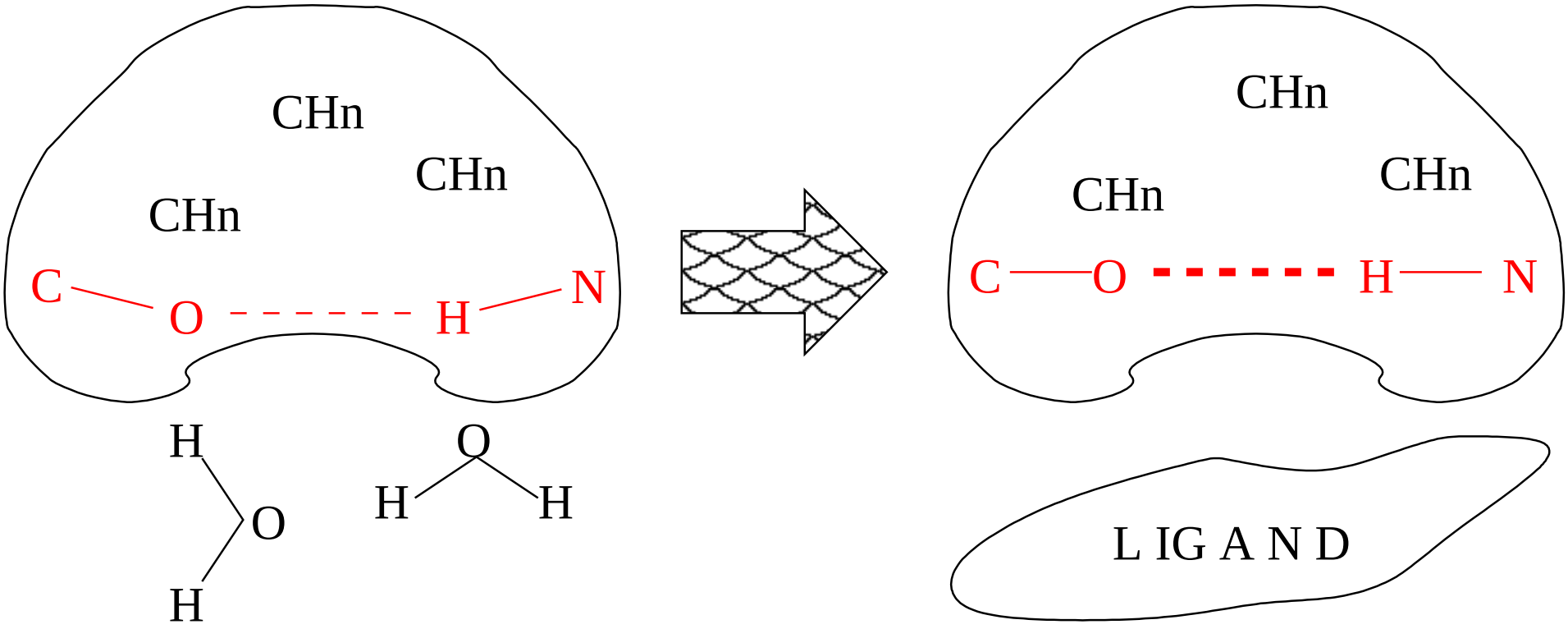


Figure 3: Distribution of bond lengths for two hydrogen bonds formed in a structure of the sheep prion [16]. Horizontal axis measured in nanometers, vertical axis represents numbers of occurrences taken from a simulation with $20,000$ data points with bin widths of 0.1 Ångstrom. Distribution for the well-wrapped hydrogen bond (H3) has smaller mean value but a longer (exponential) tail, whereas distribution for the underwrapped hydrogen bond (H1) has larger mean but Gaussian tail.

Ligand binding removes water



Binding of ligand changes underprotected hydrogen bond (high dielectric) to strong bond (low dielectric)

No intermolecular bonds needed!

Intermolecular bonds are like the power cord on my computer.

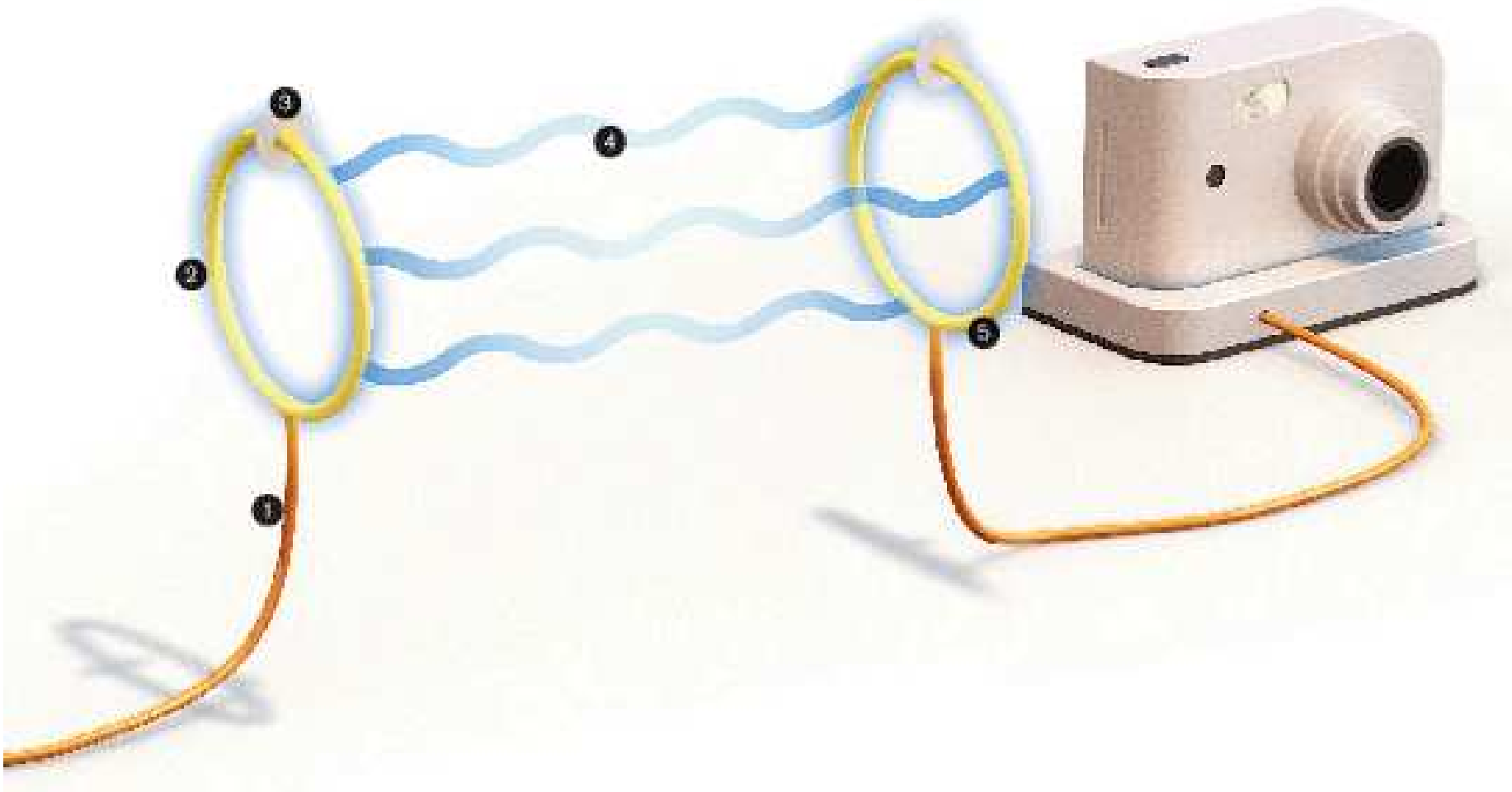
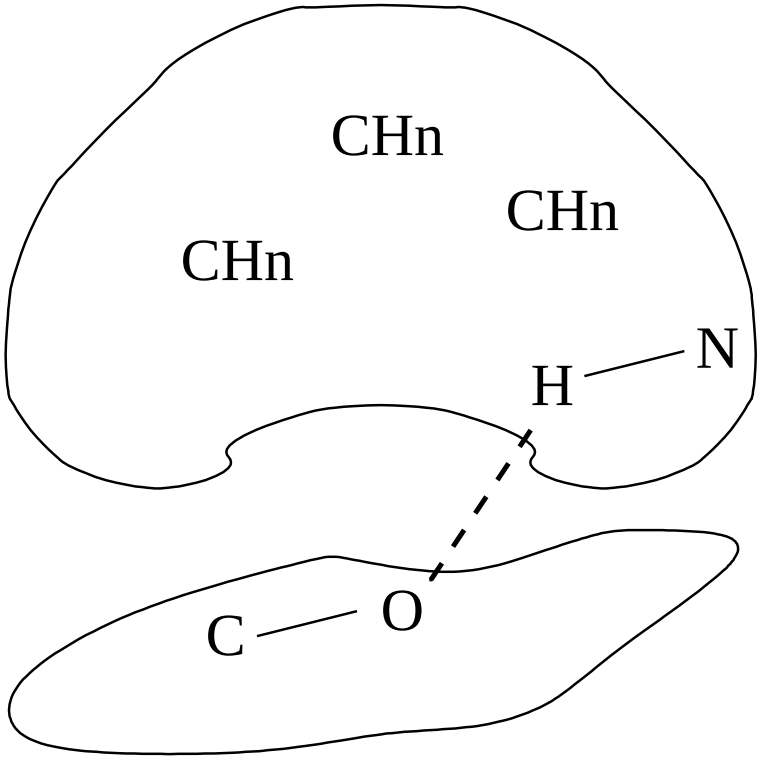
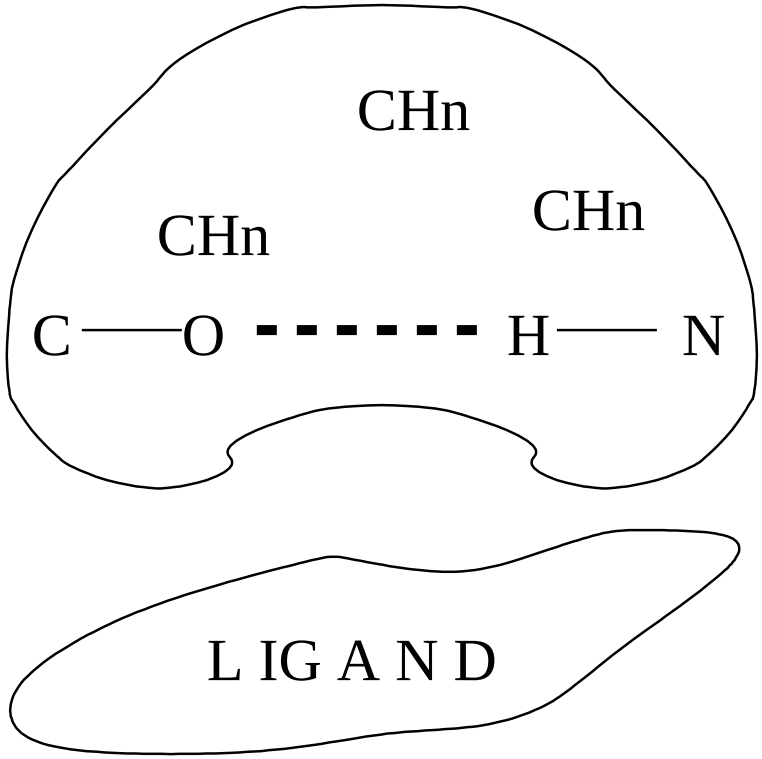


Figure 4: Wireless Charging (from Technology Review).

Intramolecular bonds are like the charger on electric toothbrush.

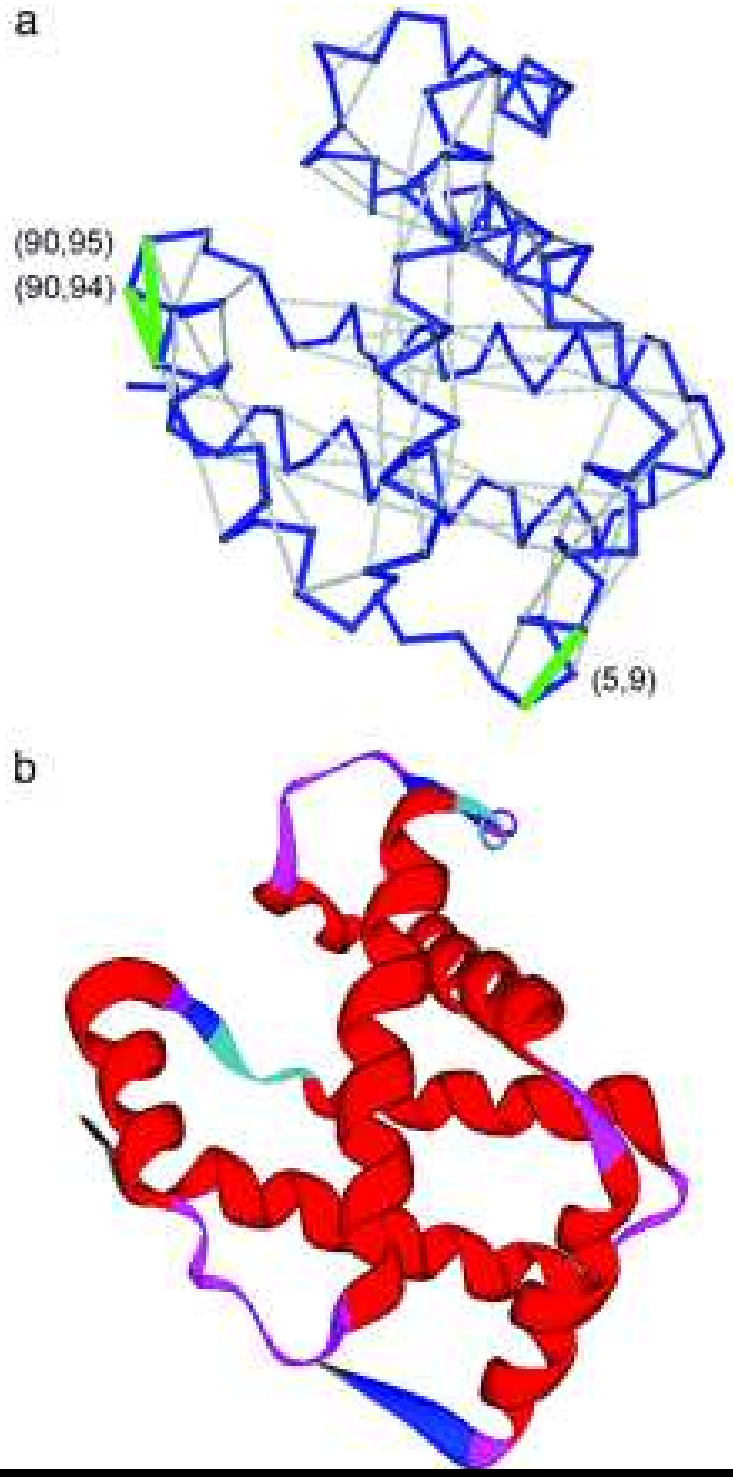
Intermolecular versus intramolecular H bonds





Energetic contribution to binding comparable

but can be better for intramolecular.



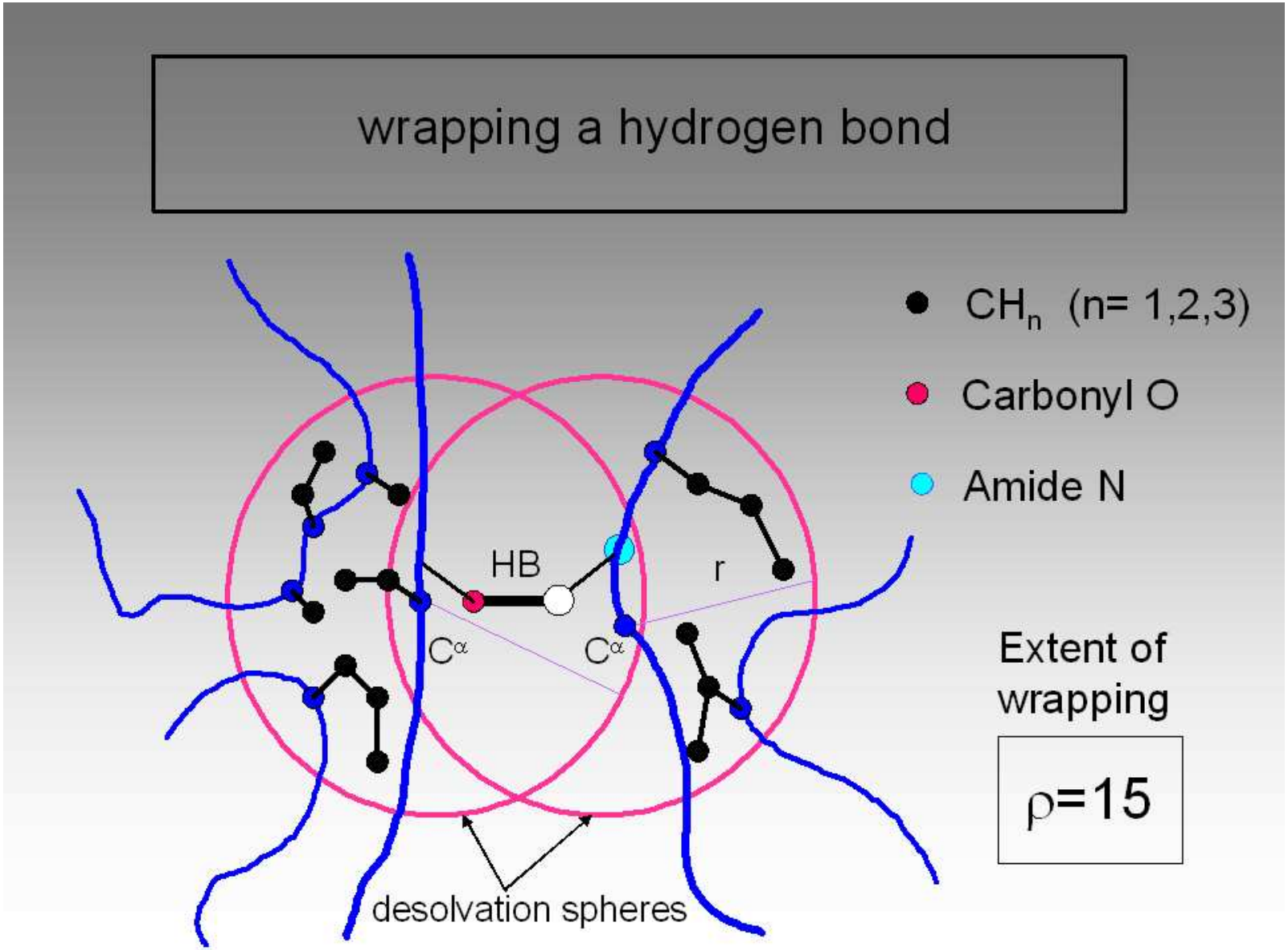
Dehydrons

in human hemoglobin, From PNAS 100: 6446-6451 (2003) Ariel Fernandez, Jozsef Kardos, L. Ridgway Scott, Yuji Goto, and R. Stephen Berry. Structural defects and the diagnosis of amyloidogenic propensity.

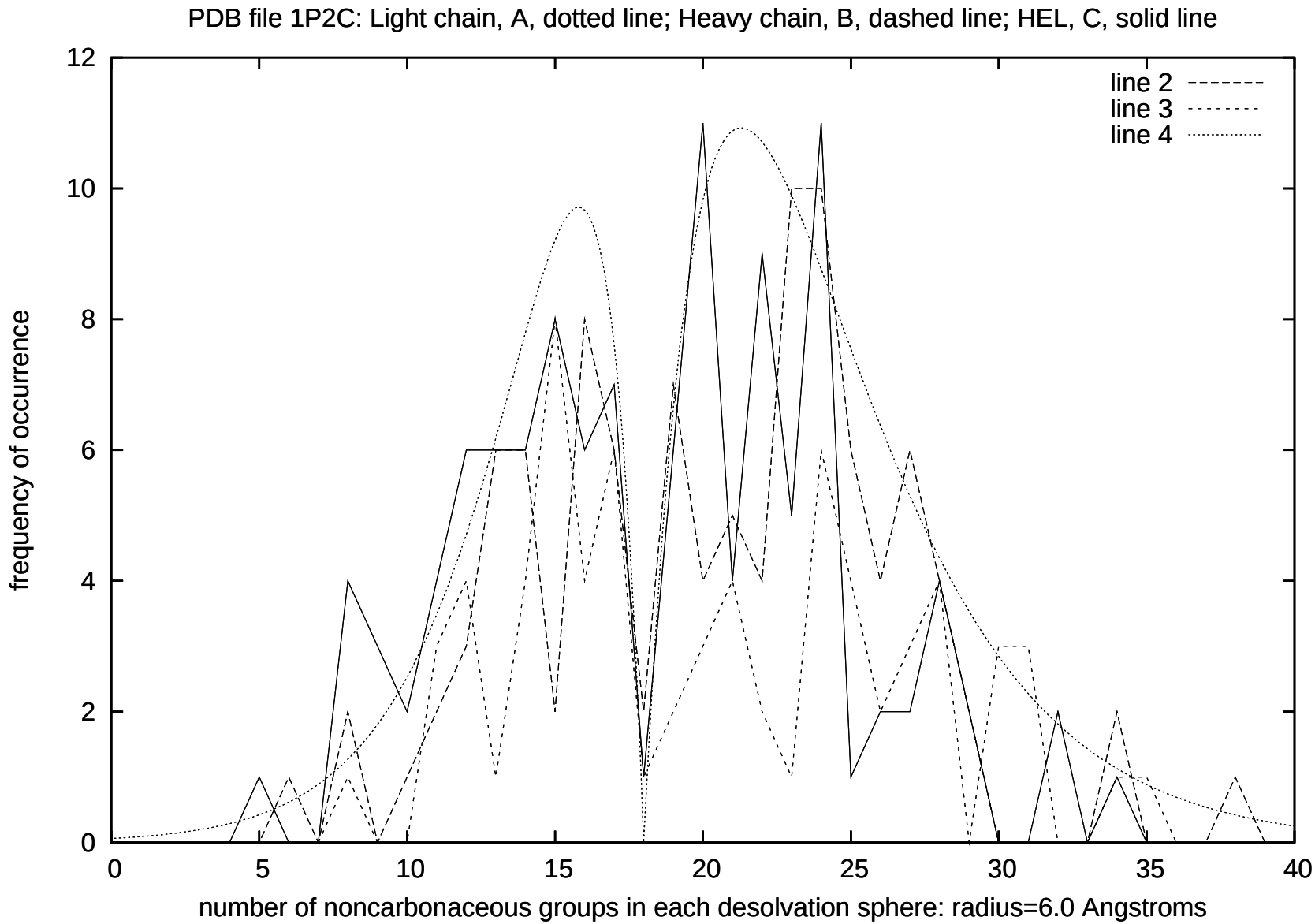
Well-wrapped hydrogen bonds are grey, and dehydrons are green.

The standard ribbon model of “structure” lacks indicators of electronic environment.

Wrapping made quantitative by counting carbonaceous groups in the neighborhood of a hydrogen bond.



Distribution of wrapping for an antibody complex.



Stickiness of dehydrons

Attractive force of dehydrons predicted and measured in

Ariel Fernandez and L. Ridgway Scott. Adherence of packing defects in soluble proteins. Phys. Rev. Lett. 2003 91:18102(4)

by considering rates of adhesion to phospholipid (DLPC) bilayer.

Deformation of phospholipid bilayer by dehydrons measured in

Ariel Fernandez and L. Ridgway Scott. Under-wrapped soluble proteins as signals triggering membrane morphology. Journal of Chemical Physics 119(13), 6911-6915 (2003).

Single molecule measurement of dehydronic force in

Ariel Fernandez. Direct nanoscale dehydration of hydrogen bonds. Journal of Physics D: Applied Physics 38, 2928-2932, 2005.

Fine print: careful definition of dehydron requires assessing modification of dielectric enviroment by test hydrophobe. That is, geometry of carbon groups matters, although counting gets it right $\approx$ 90% of the time [20].

Charge-force relationship

Here's the math....

Charges ρ induce an electric field $\mathbf{e} = \nabla\phi$ given by

$$\nabla\cdot(\varepsilon\nabla\phi) = \nabla\cdot(\varepsilon\mathbf{e}) = \rho, \tag{3.16}$$

where ε is the permittivity of the medium. Energy $= \int \rho\phi\, dx$.

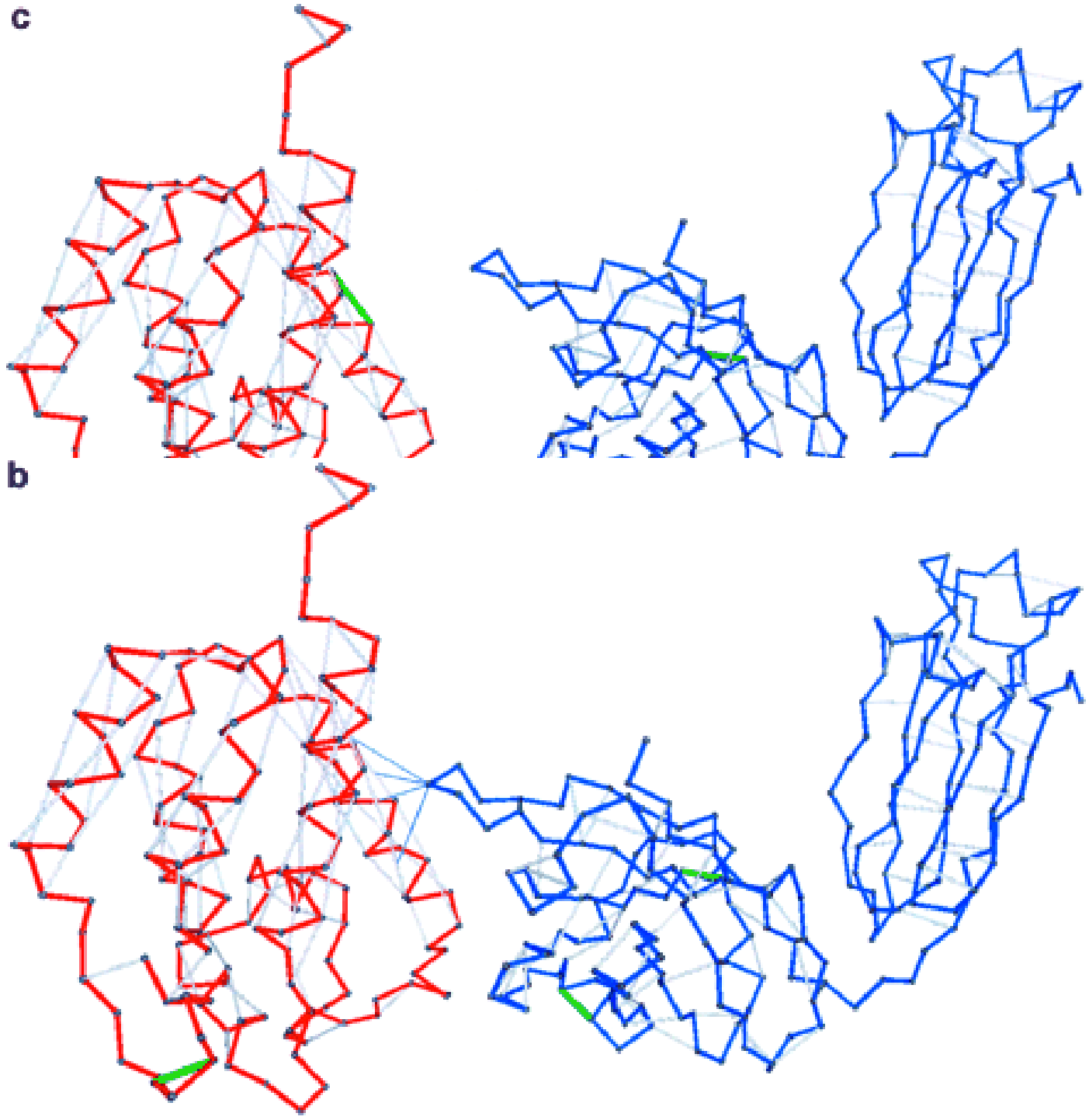
When the medium is a vacuum, ε is the permittivity of free space, ε_0.

In other media (e.g., water) the value of ε is much larger.

The quantity ε measures the strength of the dielectric enviroment.

Water removal decreases the coefficient ε in (3.16), and increases ϕ.

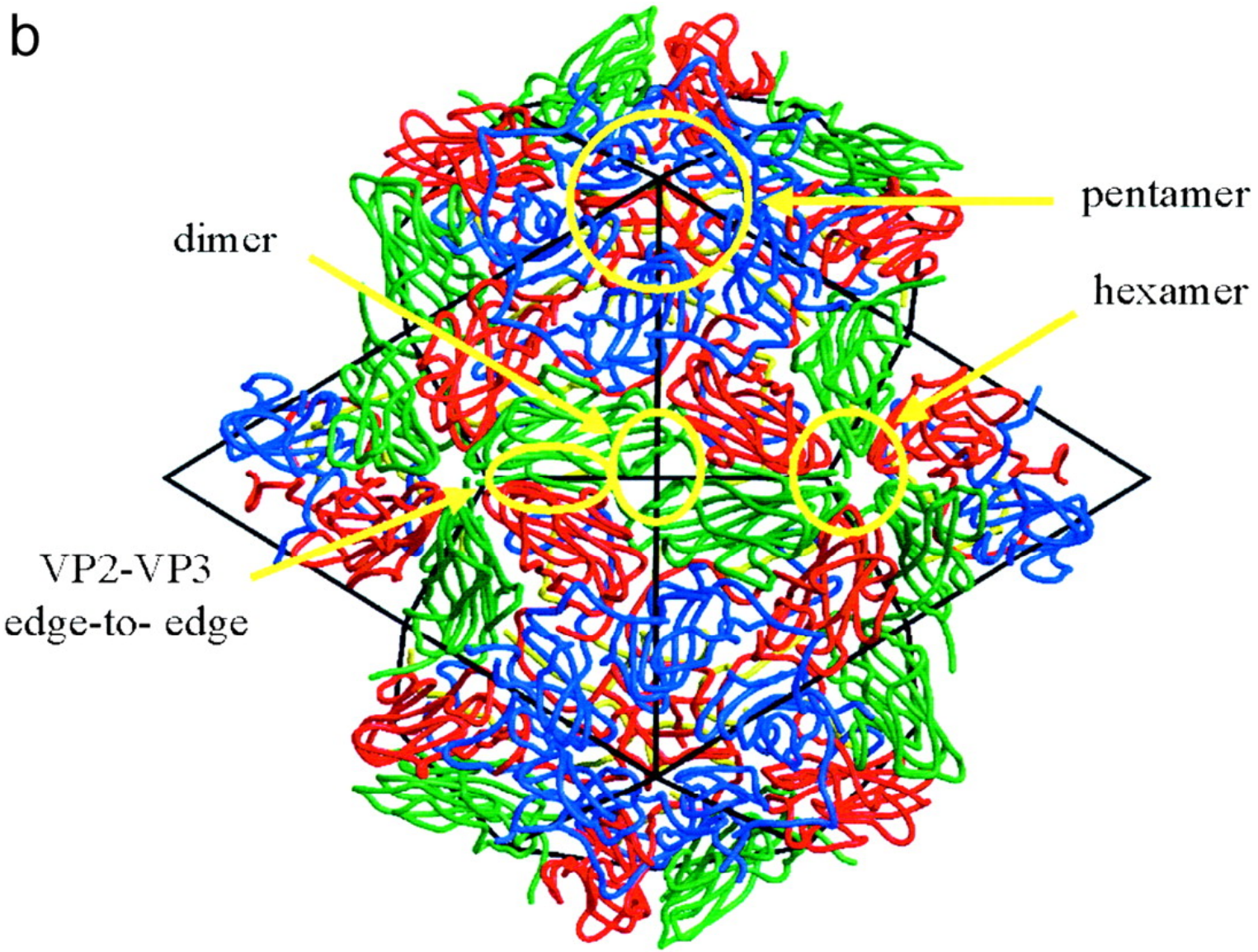
Hydrophilic groups contribute to the right-hand side ρ in (3.16).



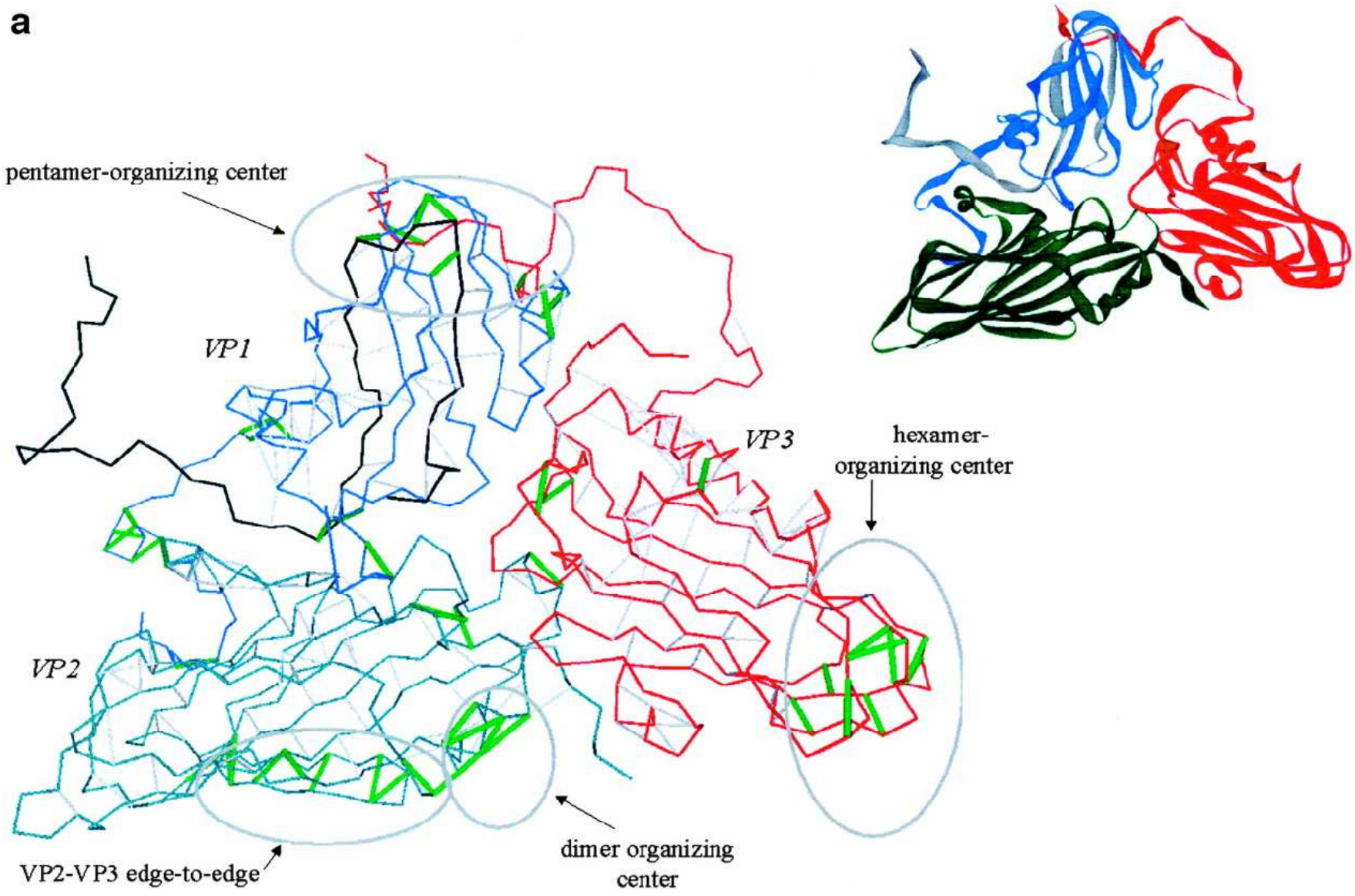
The HIV protease has a dehydron at an antibody binding site.

When the antibody binds at the dehydron, it wraps it with hydrophobic groups.

A model for protein-protein interaction



Foot-and-mouth disease virus assembly from small proteins.



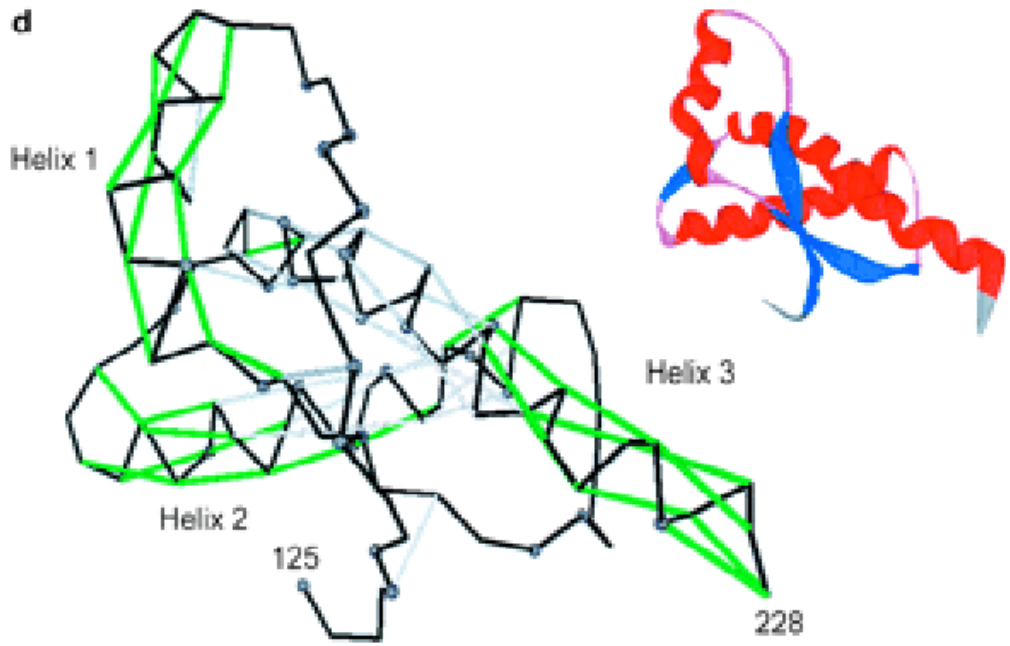
Dehydrons guide binding of component proteins VP1, VP2 and VP3 of foot-and-mouth disease virus.

4 Extreme interaction: amyloid formation

Standard application of bioinformatics: look at distribution tails.

If some is good, more may be better, but too many may be bad.

Too many dehydrons signals trouble: the human prion.



From PNAS 100: 6446-6451 (2003) Ariel Fernandez, Jozsef Kardos, L. Ridgway Scott, Yuji Goto, and R. Stephen Berry. Structural defects and the diagnosis of amyloidogenic propensity.

5 Dehydrons as indicators of protein interactivity

If dehydrons provide mechanism for proteins to interact, then more interactive proteins should have more dehydrons, and vice versa.

We only expect a correlation since there are (presumably) other ways for proteins to interact.

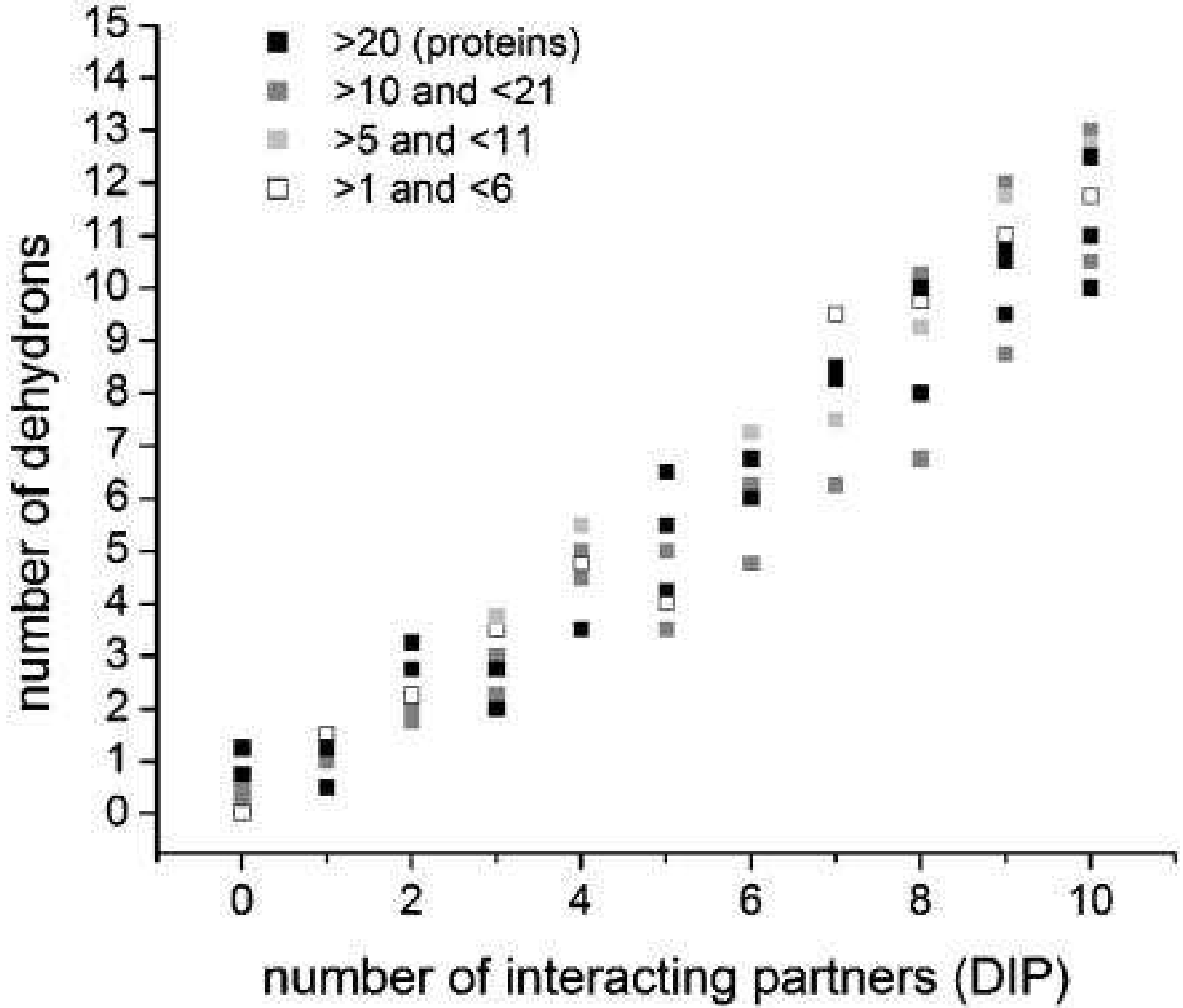
The DIP database collects information about protein interactions, based on individual protein domains: can measure interactivity of different regions of a given protein.

Result: Interactivity of proteins correlates strongly with number of dehydrons.

PNAS 101(9):2823-7 (2004)

The nonconserved wrapping of conserved protein folds reveals a trend toward increasing connectivity in proteomic networks.

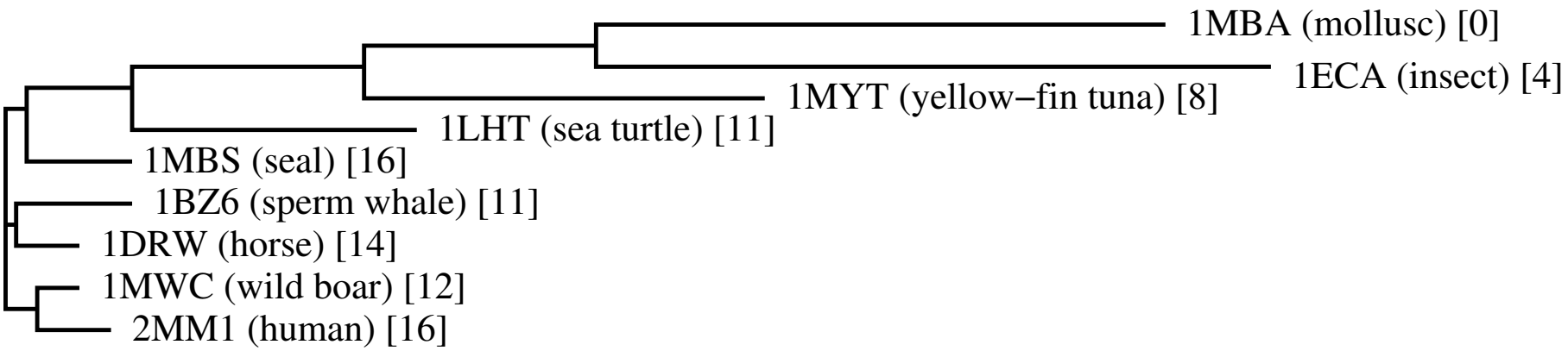
Ariel Fernández, L. R. Scott and R. Steve Berry

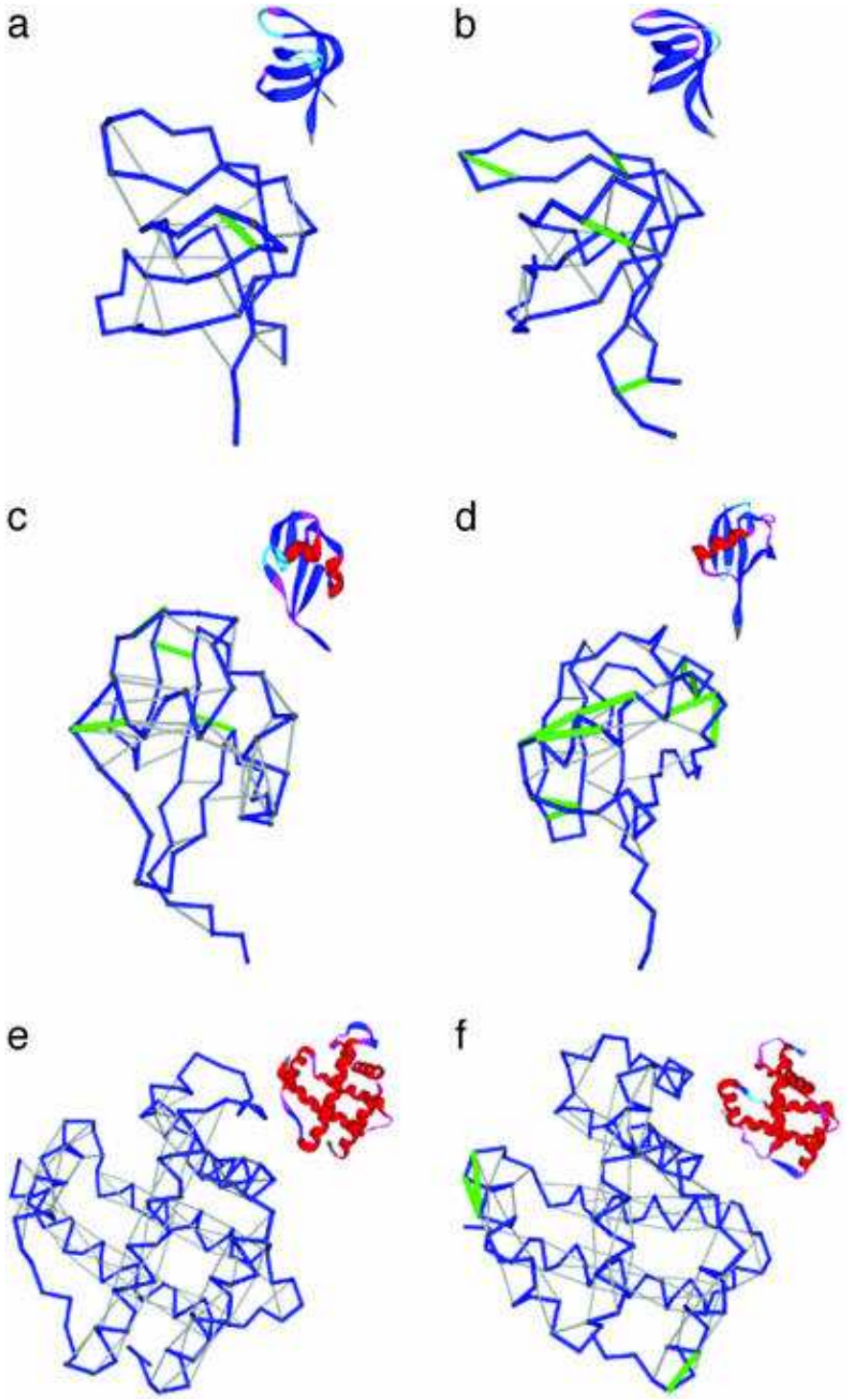

>20 (proteins)
>10 and <21
>5 and <11
>1 and <6
number of dehydrons
number of interacting partners (DIP)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
0
2
4
6
8
10

6 Dehydron variation over different species

Species (common name)	peptides	H bonds	dehydrons
Aplysia limacina (mollusc)	146	106	0
Chironomus thummi thummi (insect)	136	101	3
Thunnus albacares (tuna)	146	110	8
Caretta caretta (sea turtle)	153	110	11
Physeter catodon (whale)	153	113	11
Sus scrofa (pig)	153	113	12
Equus caballus (horse)	152	112	14
Elephas maximus (Asian elephant)	153	115	15
Phoca vitulina (seal)	153	109	16
H. sapiens (human)	146	102	16

Number of dehydrons in Myoglobin of different species





Anecdotal evidence:

the basic
structure is similar, just the
number of dehydrons increases.

SH3 domains are from

nematode C. elegans (a)

H. sapiens (b);

ubiquitin is from
E. coli (c) and H. sapiens (d);

hemoglobin
is from Paramecium
(e). and H. sapiens-subunit (f).

Genetic code

Genetic code minimizes changes of polarity due to single-letter codon mutations, but it facilitates changes in wrapping due to single-letter codon mutations.

First Position	Second Position: u	Second Position: c	Second Position: a	Second Position: g	Third Position
u	uuu, uuc: Phe 7 ||	ucu, ucc, uca, ucg: Ser 0 +−	uau, uac: Tyr 6 +−	ugu, ugc: Cys 0 +−	u, c
	uua, uug: Leu 4 ||		uaa: stop; uag: stop	uga: stop; ugg: Trp 7 +−	a, g
c	cuu, cuc, cua, cug: Leu 4 ||	ccu, ccc, cca, ccg: Pro 2 ||	cau, cac: His 1 +−	cgu, cgc, cga, cgg: Arg 2 ++	u, c, a, g
			caa, cag: Gln 2 +−		
a	auu, auc, aua: Ile 4 ||	acu, acc, aca, acg: Thr 1 +−	aau, aac: Asn 1 +−	agu, agc: Ser 0 +−	u, c
	aug: Met 1 +−		aaa, aag: Lys 3 ++	aga, agg: Arg 2 ++	a, g
g	guu, guc, gua, gug: Val 3 ||	gcu, gcc, gca, gcg: Ala 1 ||	gau, gac: Asp 1 −−	ggu, ggc, gga, ggg: Gly 0 +−	u, c, a, g
			gaa, gag: Glu 2 −−		

First digit after residue name is amount of wrapping. Second indicator is polarity; $||$: nonpolar, $+-$: polar, $--$: negatively charged, $++$: positively charged.

7 Wrapping technology in drug design

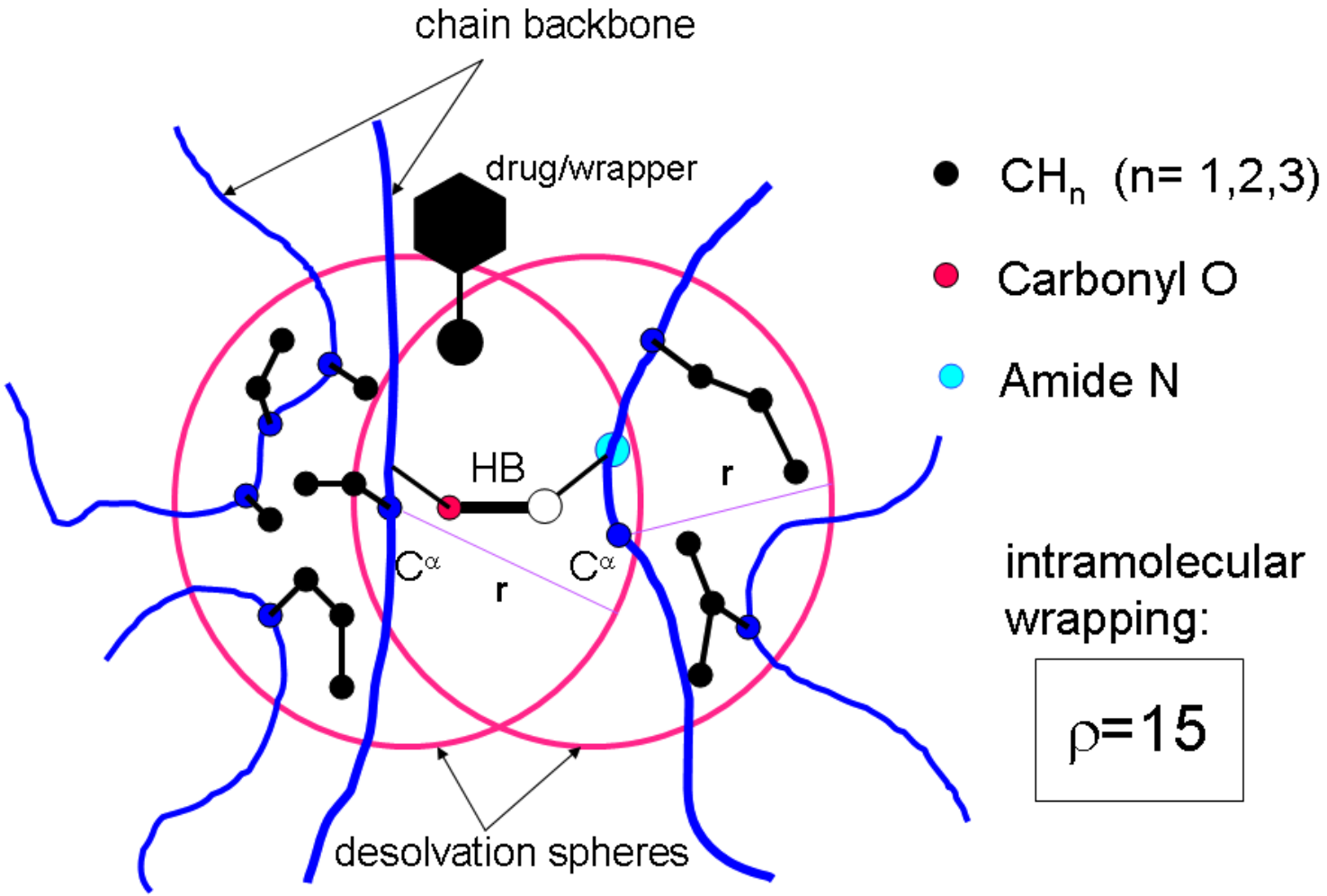
Synopsis of “Modulating drug impact by wrapping target proteins” by Ariel Fernández and L. Ridgway Scott, *Expert Opinion on Drug Discovery* 2007.

Drug ligands often bind to proteins near dehydrons, enhancing their wrapping upon attachment.

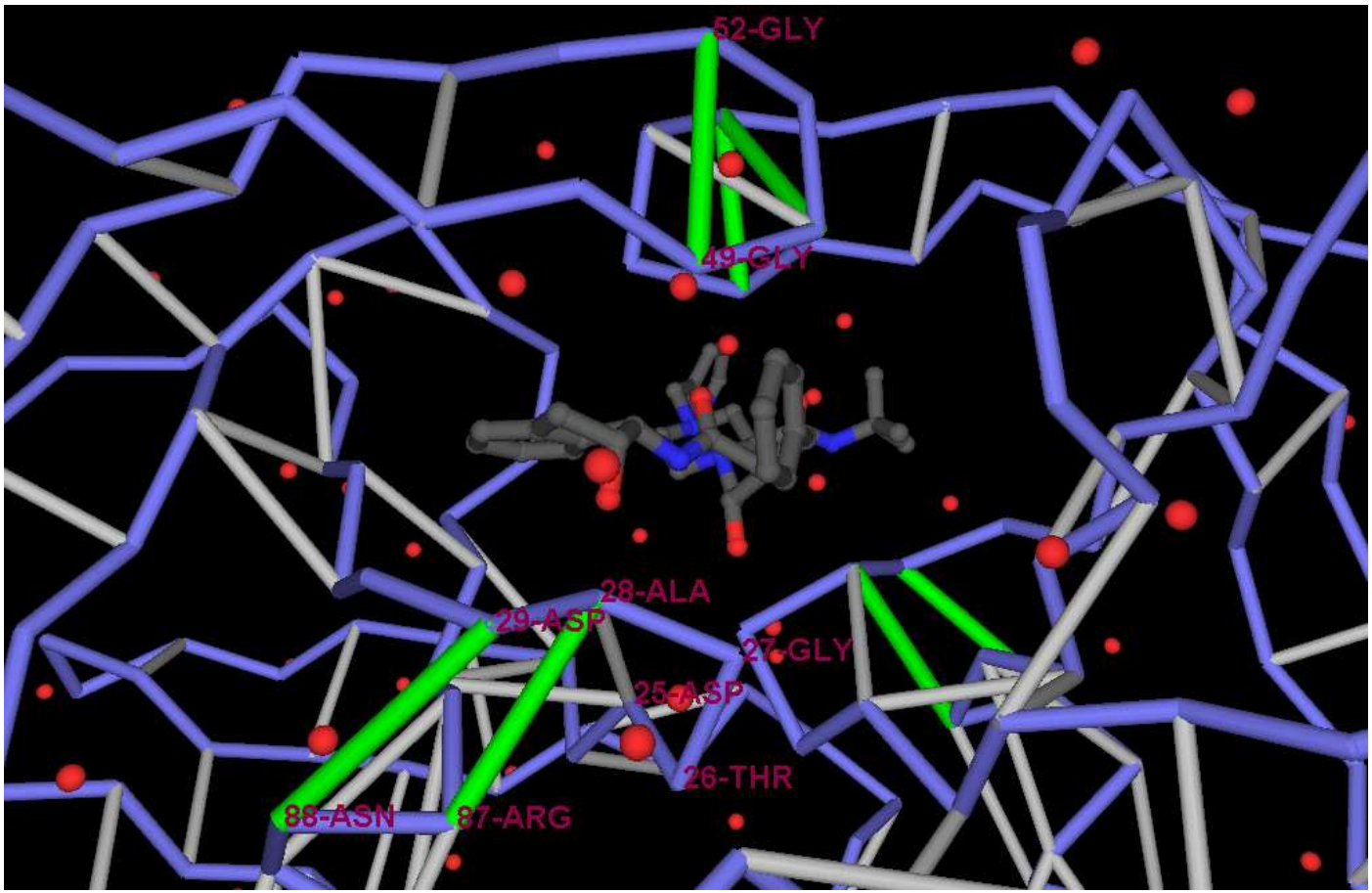
Drug side effects often caused by binding to proteins with structure similar to target.

We can exploit the differences in dehydron patterns in homologous proteins to make drugs more specific.

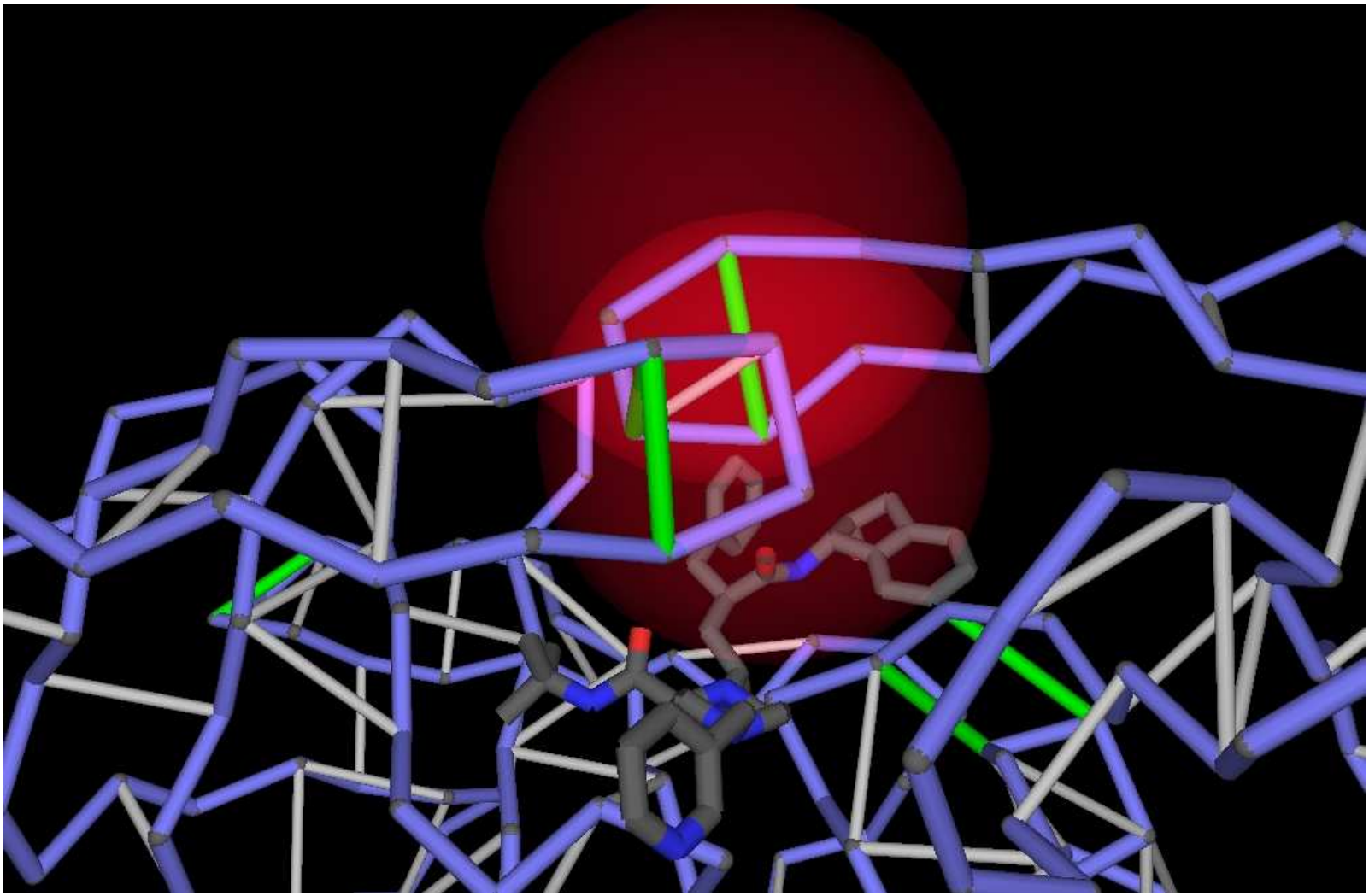
Drug ligand provides additional non-polar carbonaceous group(s) in the desolvation domain, enhancing the wrapping of a hydrogen bond.



HIV-1 protease with ‘dehydron wrapper’ inhibitor



Detail of the protease cavity, pattern of packing defects, and inhibitor positioned as dehydron wrapper.



Desolvation spheres for flap Gly-49–Gly-52 dehydron containing nonpolar groups of the wrapping inhibitor.

Drug specificity

Tyrosine kinases: a family of proteins with very similar structure.

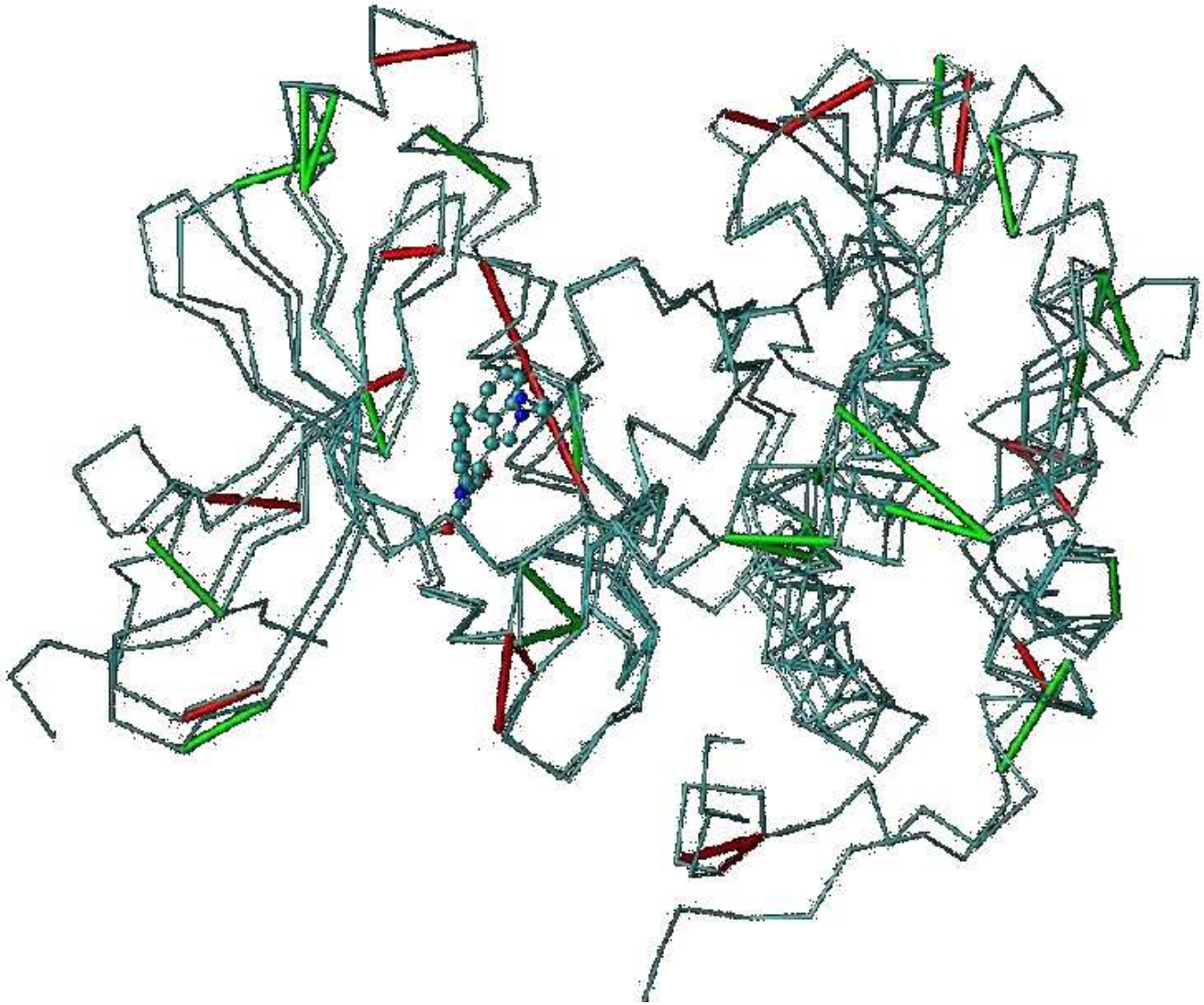
- They are called paralogous because they are similar proteins within a given species.
- These are presumed to have evolved from a common source.
- They are a crucial target of cancer drug therapy.

Gleevec targets particular tyrosine kinases and has been one of the most successful cancer drugs.

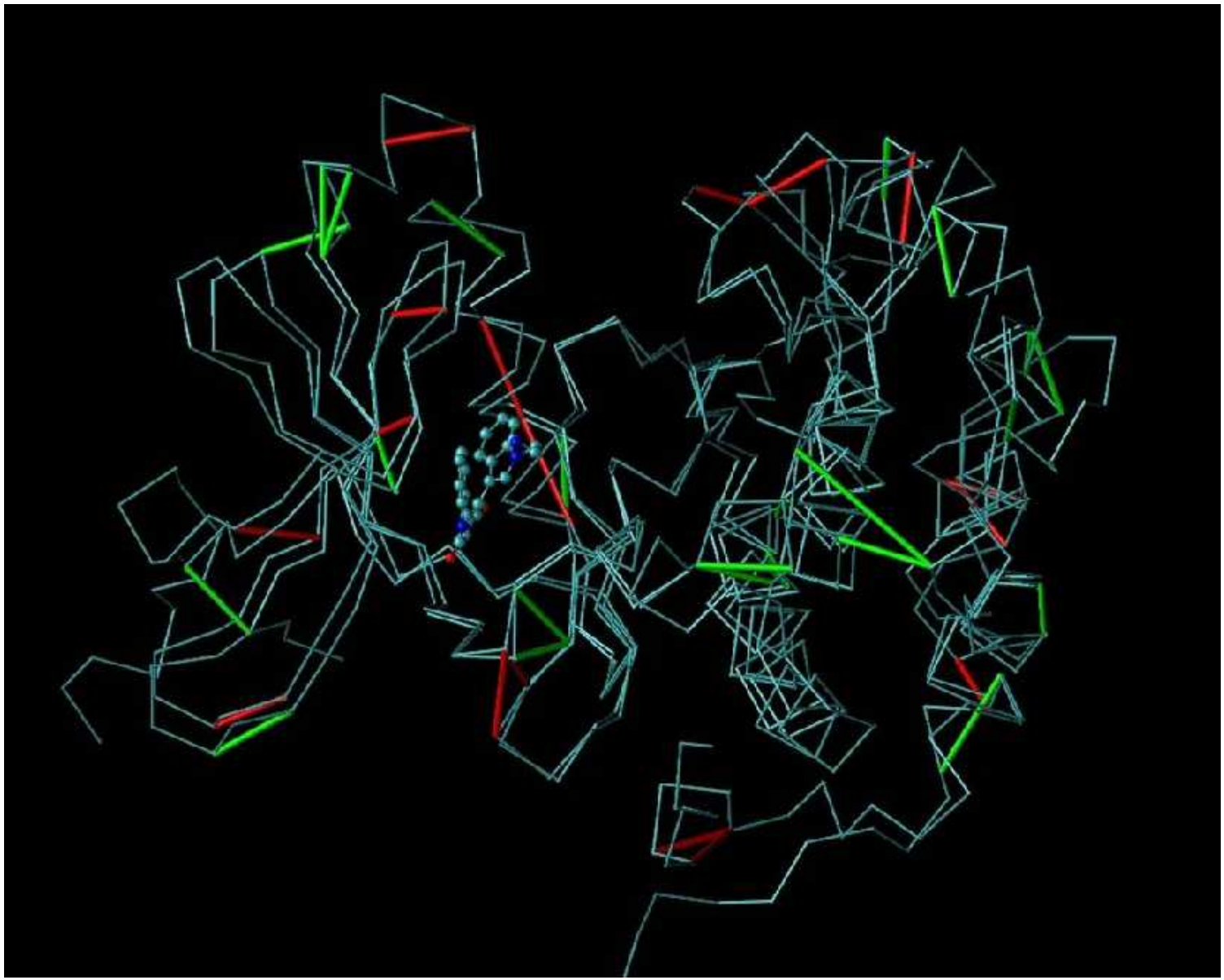
However, it also targets similar proteins and can cause unwanted side effects (it is cardiotoxic).

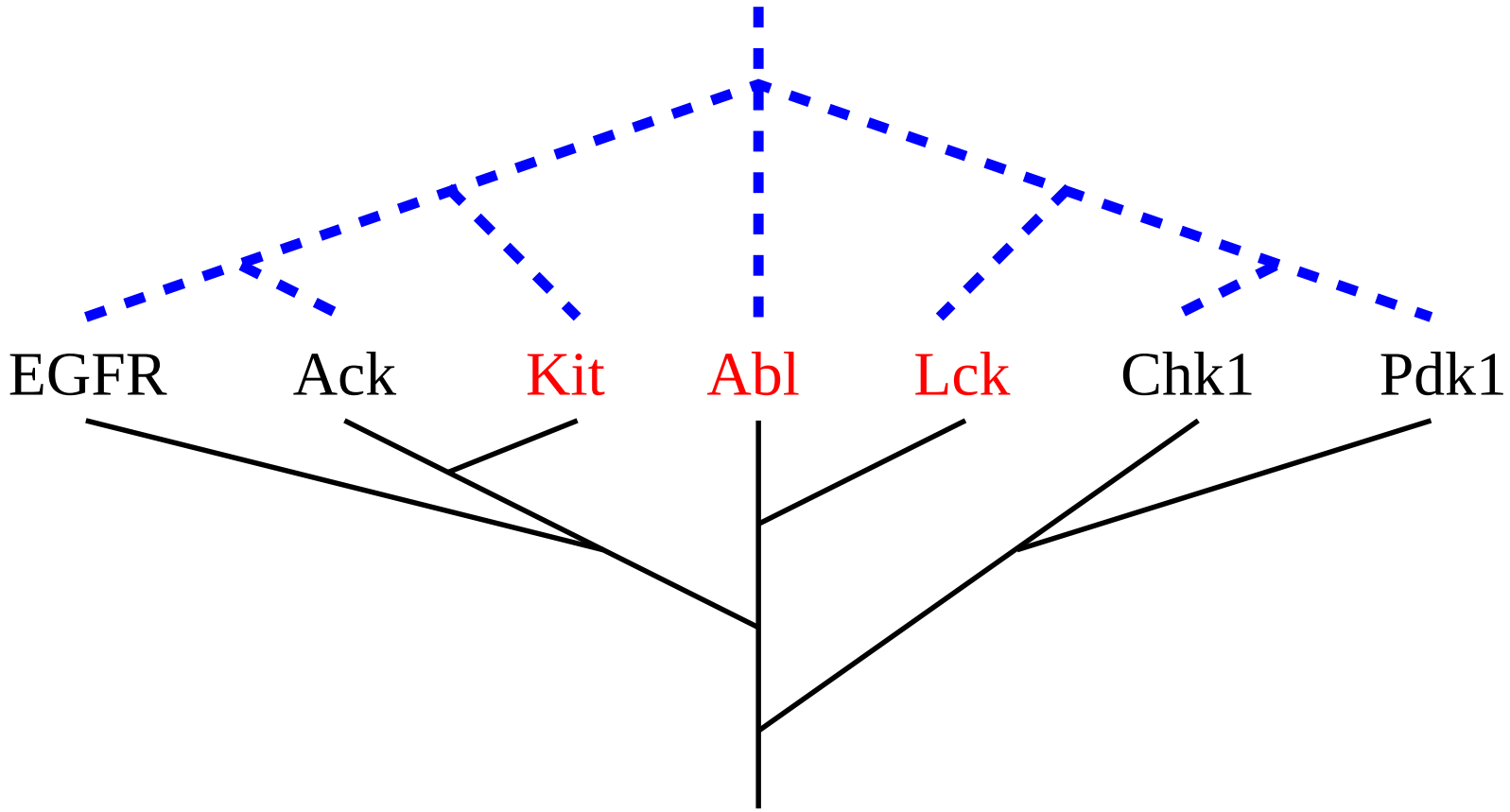
Differences between the dehydron patters in similar proteins can be used to differentiate them and guide the re-design of drug ligands.

Aligned backbones for two paralog kinases; dehydrons for Chk1 are marked in green and those for Pdk1 are in red.

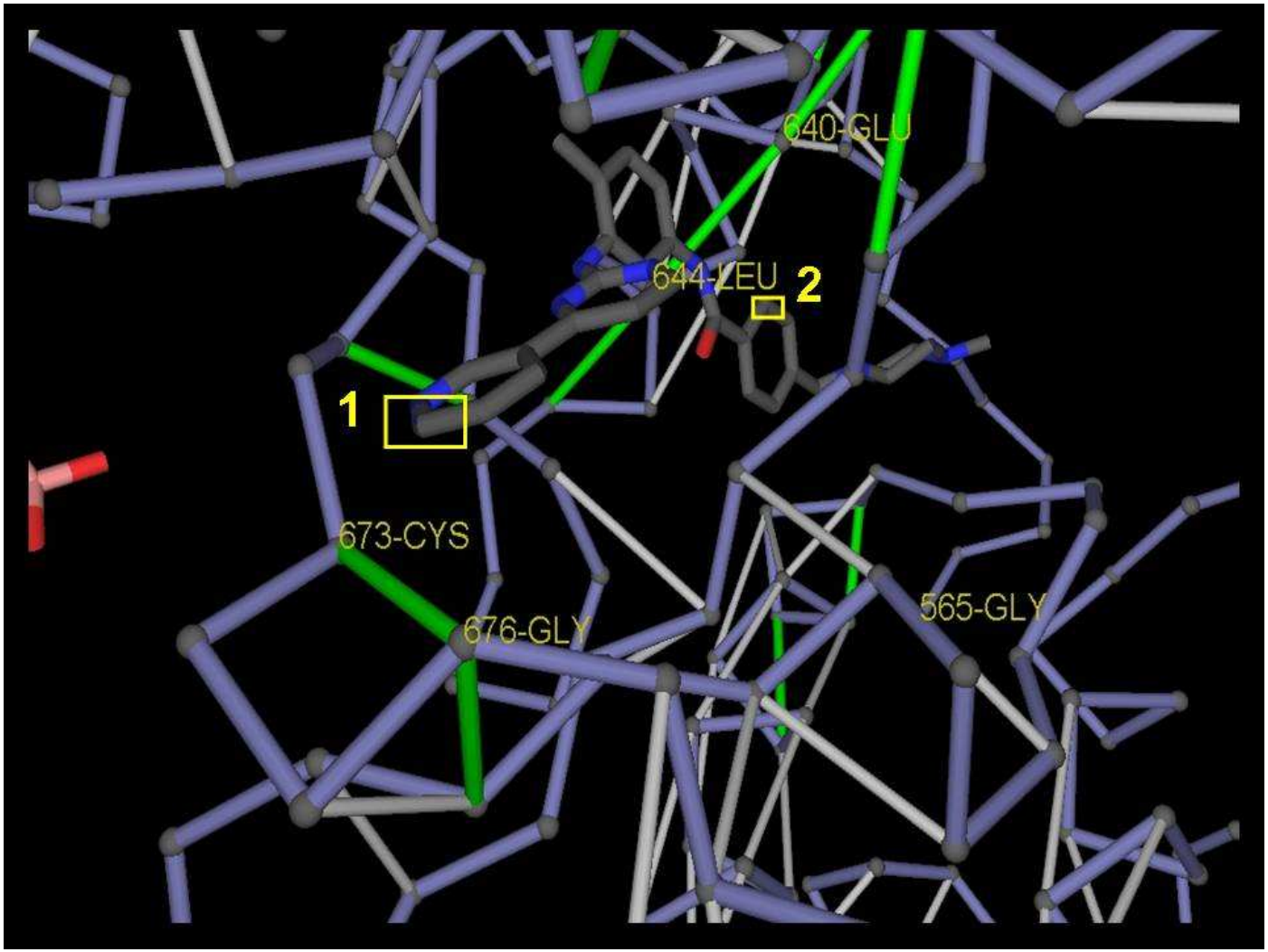


Aligned backbones for two paralog kinases; dehydrons for Chk1 are marked in green and those for Pdk1 are in red.

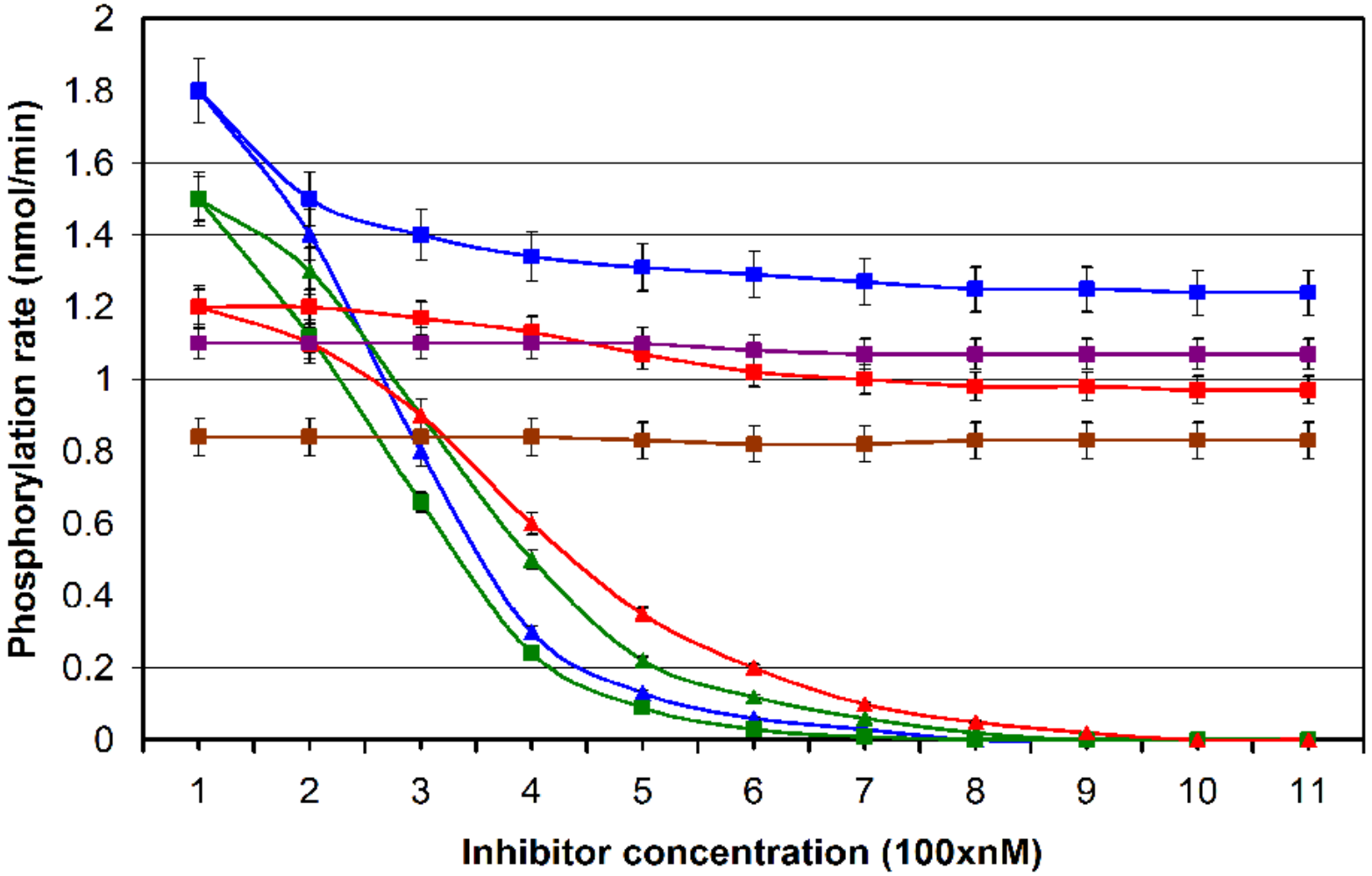




Packing similarity tree (PST, bottom in black) for the seven structurally aligned paralogs of Bcr-Abl. The PST restricted to the alignments of the Gleevec wrapped region in Bcr-Abl is shown (top) with blue dashed lines. The paralogs in red have the most similar packing in the region that aligns with the Gleevec wrapped region in Bcr-Abl and are also primary targets of this inhibitor.

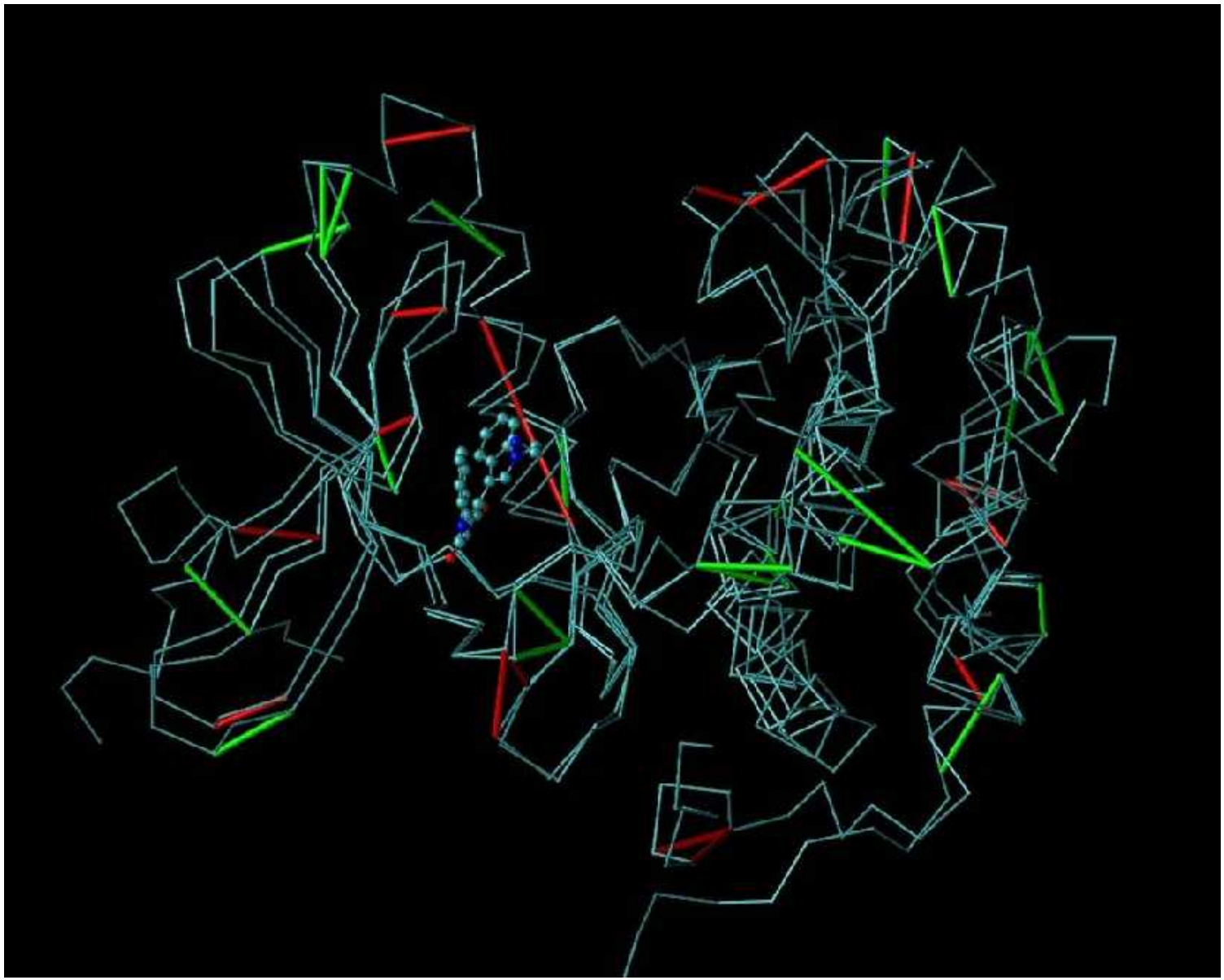


Dehydron Cys673-Gly676 in C-Kit is not conserved in its paralogs Bcr-Abl, Lck, Chk1 and Pdk1. By methylating Gleevec at the para position (1), the inhibitor becomes a selective wrapper of the packing defect in C-Kit.



Phosphorylation rates from spectrophotometric assay on the five kinases Bcr-Abl (blue), C-Kit (green), Lck (red), Chk1 (purple), and Pdk1 (brown) with Gleevec (triangles) and modified Gleevec methylated at positions (1) and (2) (squares). Notice the selective and enhanced inhibition of C-Kit.

Aligned backbones for two paralog kinases; dehydrons for Chk1 are marked in green and those for Pdk1 are in red [21].



8 Remaining challenges

Modeling hydrogen placement

- Hydrogens not resolved by imaging techniques, e.g., in Histidine sidechain

Role of ionic solvents

- How do ions affect local dielectric behavior?

Increasing entropy versus decreasing enthalpy

$$\Delta G = \Delta H - T\Delta S \tag{8.17}$$

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