Geometric-based and physics-based simulations of RNA folding

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Computer Science and Genome Center
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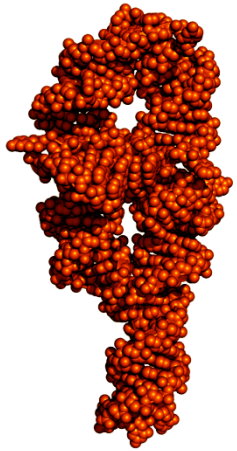
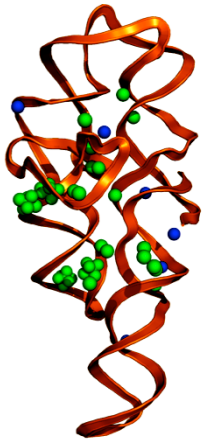
1) Geometry:
(solvation + ligand binding)



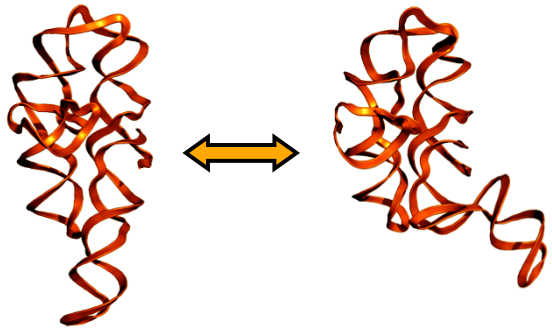
folding

2) Physics:
(hydration+ion binding)



4) Computational design:
(Sequence from structure)

3) Dynamics:
(folding pathways)



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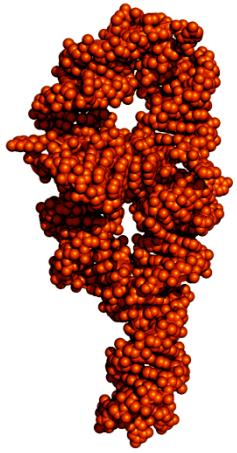
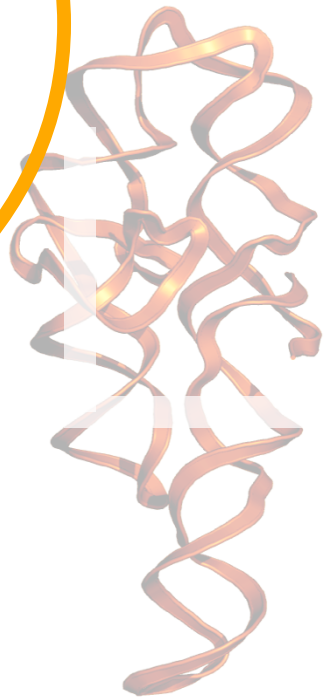


folding



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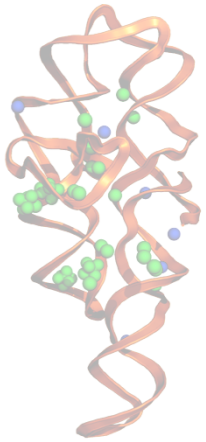

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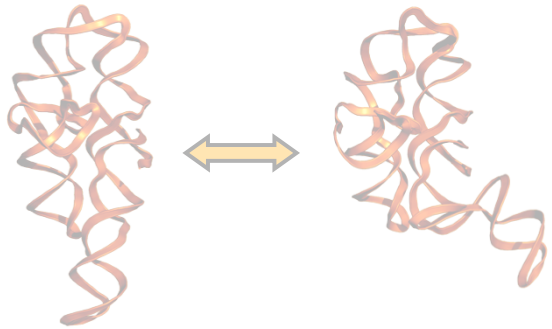
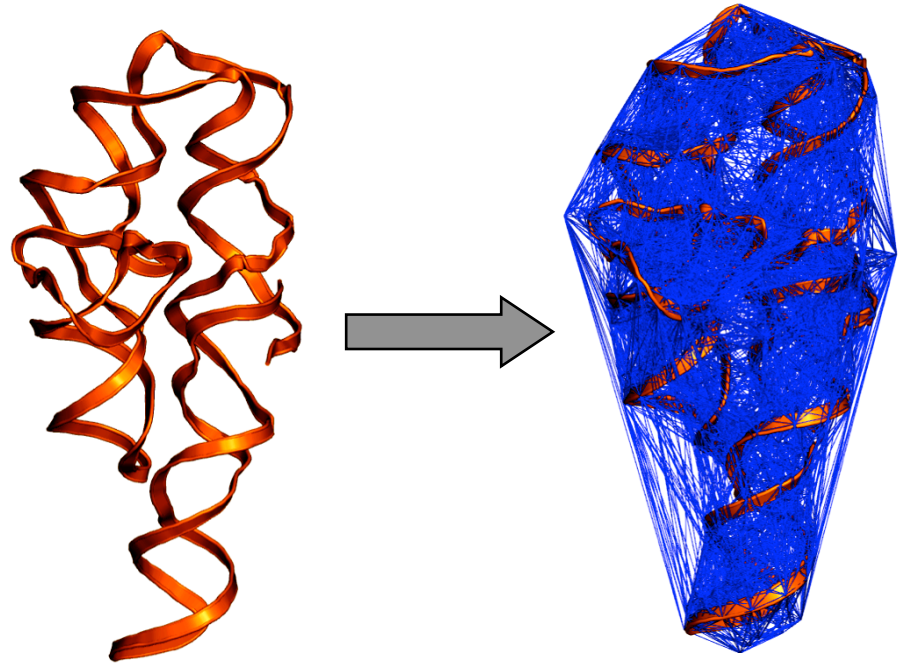


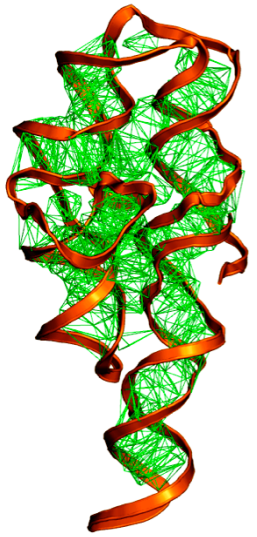
Computing the Surface Area and Volume of RNA



P4-P6 domain
Group I intron

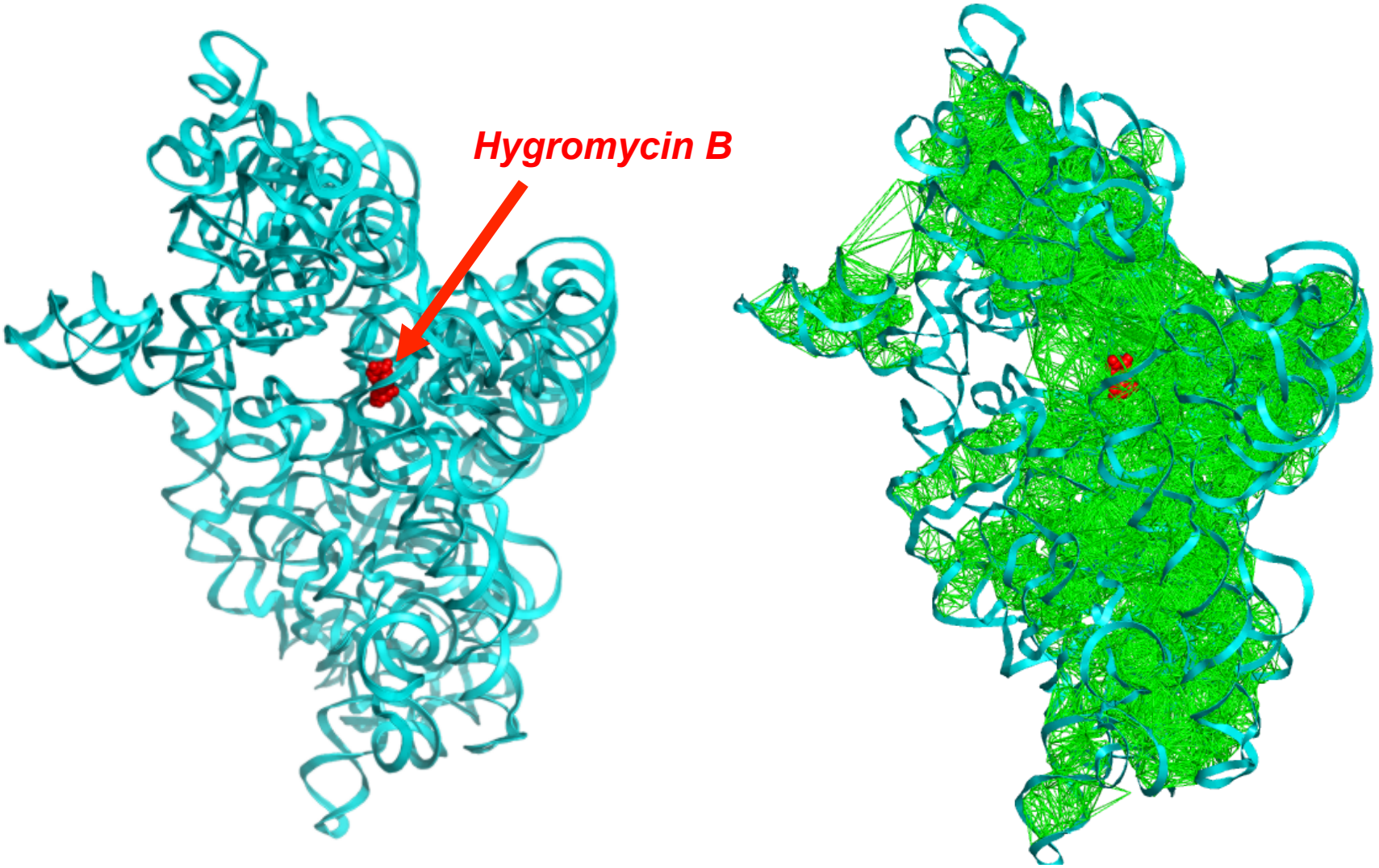
Delaunay Complex

K complex



Pocket

BINDING POCKETS IN 16S RIBOSOMAL RNA



PDB structure: 1HZN

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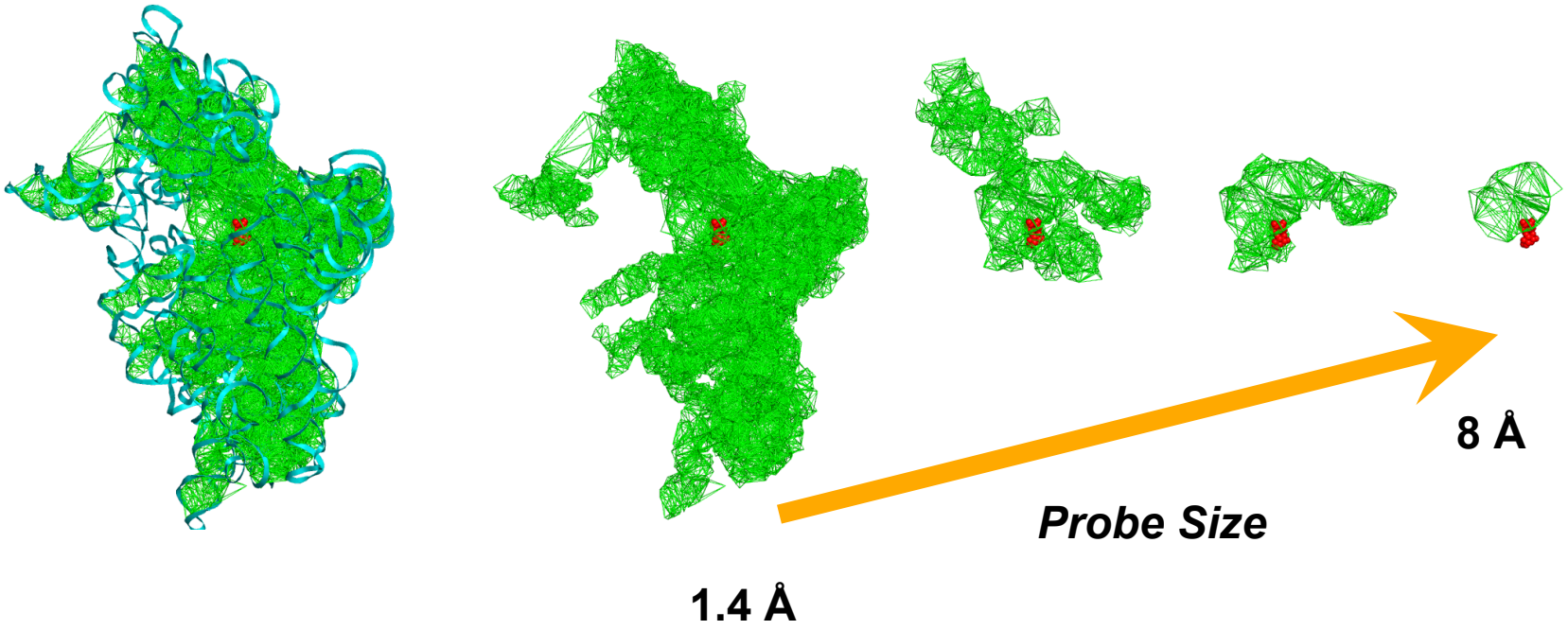

ProGeom: Performances

Protein/ RNA	# of atoms	Delaunay	Dual Complex	Volume	Find Pockets	Pocket Volume
1TIM	2288	0.02	0.01	0.01	0.02	0.00
Intron	5013	0.05	0.01	0.03	0.09	0.00
GroEL	66136	1.76	0.35	0.80	22.72	0.44
1ihm *(Norwalk virus)*	677,040	78.27	9.39	5.87	2695.0	115.0
2dum *(Human adenovirus)*	5,214,540	8577.0	99.0	59.3	Still running…	Still running…

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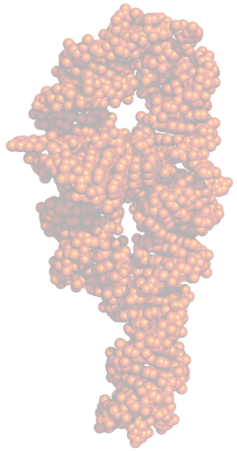
1TIM	2288	0.02	0.01	0.01	0.02	0.00
		0.02	**0.01**	**0.01**	**0.02**	**0.00**
Intron	5013	0.05	0.01	0.03	0.09	0.00
		0.05	**0.01**	**0.03**	**0.01**	**0.00**
GroEL	66136	1.76	0.35	0.80	22.72	0.44
		0.79	**0.17**	**0.54**	**0.16**	**0.00**
1ihm *(Norwalk virus)*	677,040	78.27	9.39	5.87	2695.0	115.0
		8.76	**2.60**	**2.31**	**2.7**	**0.01**
2dum *(Human adenovirus)*	5,214,540	8577.0	99.0	59.3	Still running…	Still running…
		53.6	**26.2**	**18.94**	**23.0**	**0.11**

1) *Geometry:*
(solvation + ligand binding)



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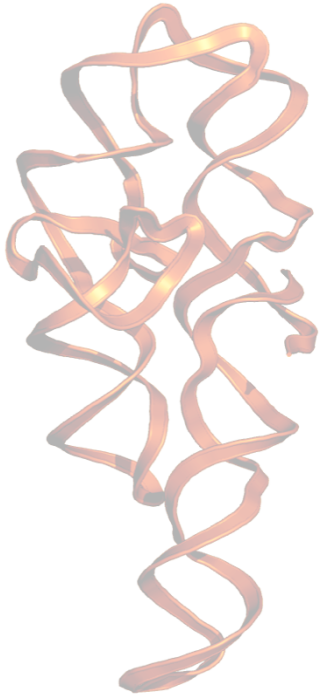

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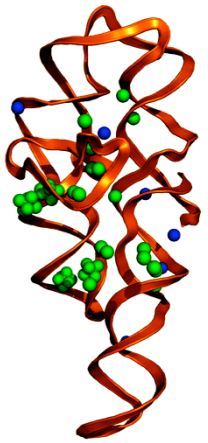

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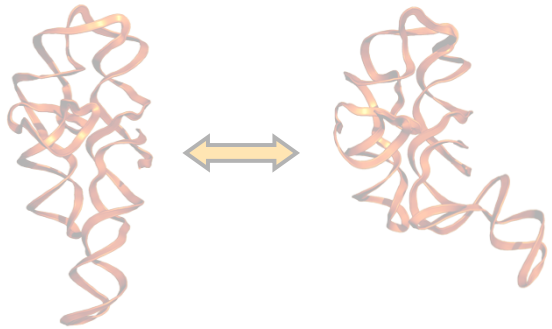
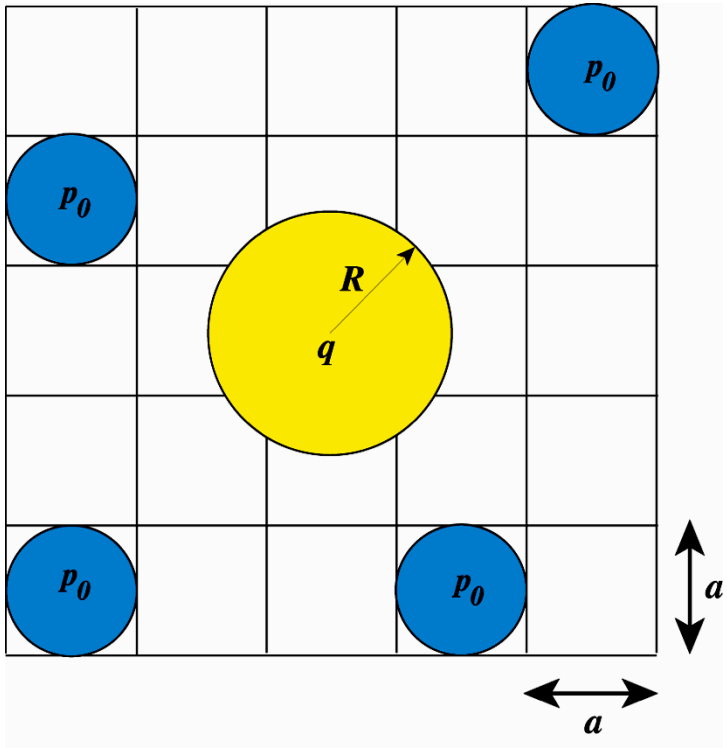


Problems with Poisson Boltzmann

- Dimensionless ions
- Uniform solvent concentration
- No water-water interactions, no interactions between solvent and ions and between ions and ions

A Dipolar Poisson-Langevin approach



Partition function:

$$Z = 1 + e^{\beta(\mu_{dip})} \left\langle e^{\beta\, \vec{p}_0 \cdot \vec{E}} \right\rangle_{orientation}$$

$$Z = 1 + e^{\beta(\mu_{dip})} \frac{\sinh(\beta p_0 E)}{\beta p_0 E}$$

As $N_{dip} = N_A c_{dip} a^3 = \dfrac{\partial \log(Z)}{\partial \beta \mu_{dip}}$ we get $e^{\beta \mu_{dip}} = \dfrac{N_A c_{dip} a^3}{1 - N_A c_{dip} a^3}$

Hence:

$$Z = 1 + \frac{N_A c_{dip} a^3}{1 - N_A c_{dip} a^3} \frac{\sinh(\beta p_0 E)}{\beta p_0 E} = 1 + \lambda_{dip} \frac{\sinh(\beta p_0 E)}{\beta p_0 E}$$

A Dipolar Poisson-Langevin approach

The contribution of the dipoles to the total free energy of the system is:

$$\beta F_{dip} = -\ln(Z)$$

and the total free energy is:

$$\beta F = -\frac{\beta}{2}\int \varepsilon \left|\vec{\nabla}\phi(\vec{r})\right|^2 d\vec{r} + \beta \int \rho_{solute}(\vec{r})\phi(\vec{r})d\vec{r}$$
$$-\frac{1}{a^3}\int \ln\left(1+\lambda_{dip}\frac{\sinh\left(\beta p_0\left|\vec{\nabla}\phi(\vec{r})\right|\right)}{\beta p_0\left|\vec{\nabla}\phi(\vec{r})\right|}\right)d\vec{r}$$

A Dipolar Poisson-Langevin approach

The system is at a minimum when $\dfrac{\partial F}{\partial \phi} = 0$

This leads to a modified Poisson equation:

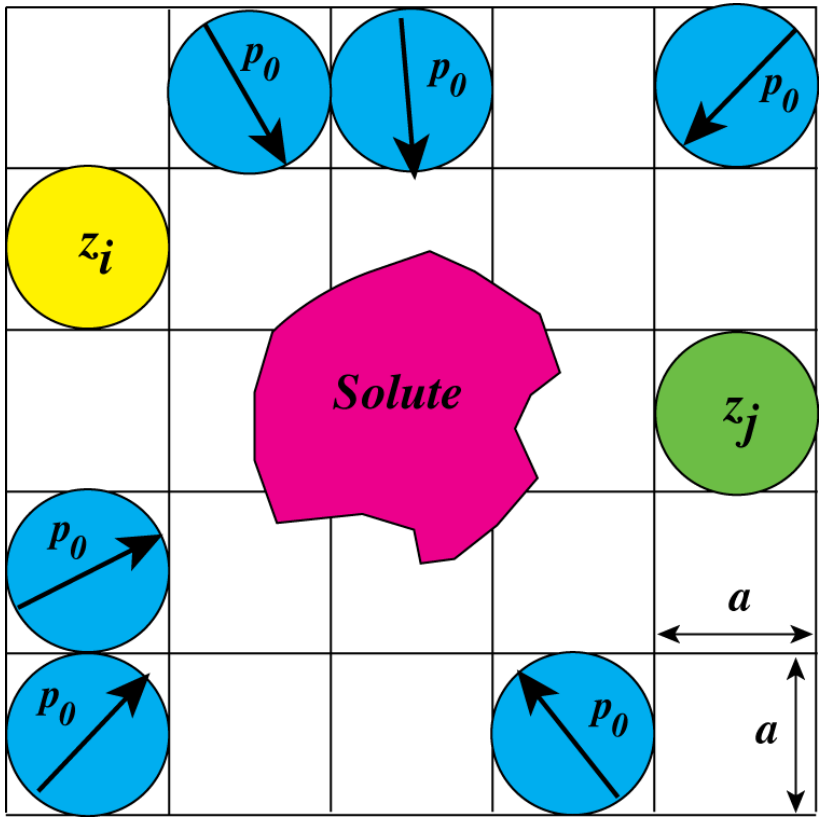
$$\nabla \bullet \left(\varepsilon_0 \vec{E}(\vec{r}) + \beta p_0^2 \frac{\lambda_{dip} F_1\left(\beta p_0 \left|\vec{E}(\vec{r})\right|\right)}{a^3 Z} \vec{E}(\vec{r}) \right) = -\rho(\vec{r})$$

with

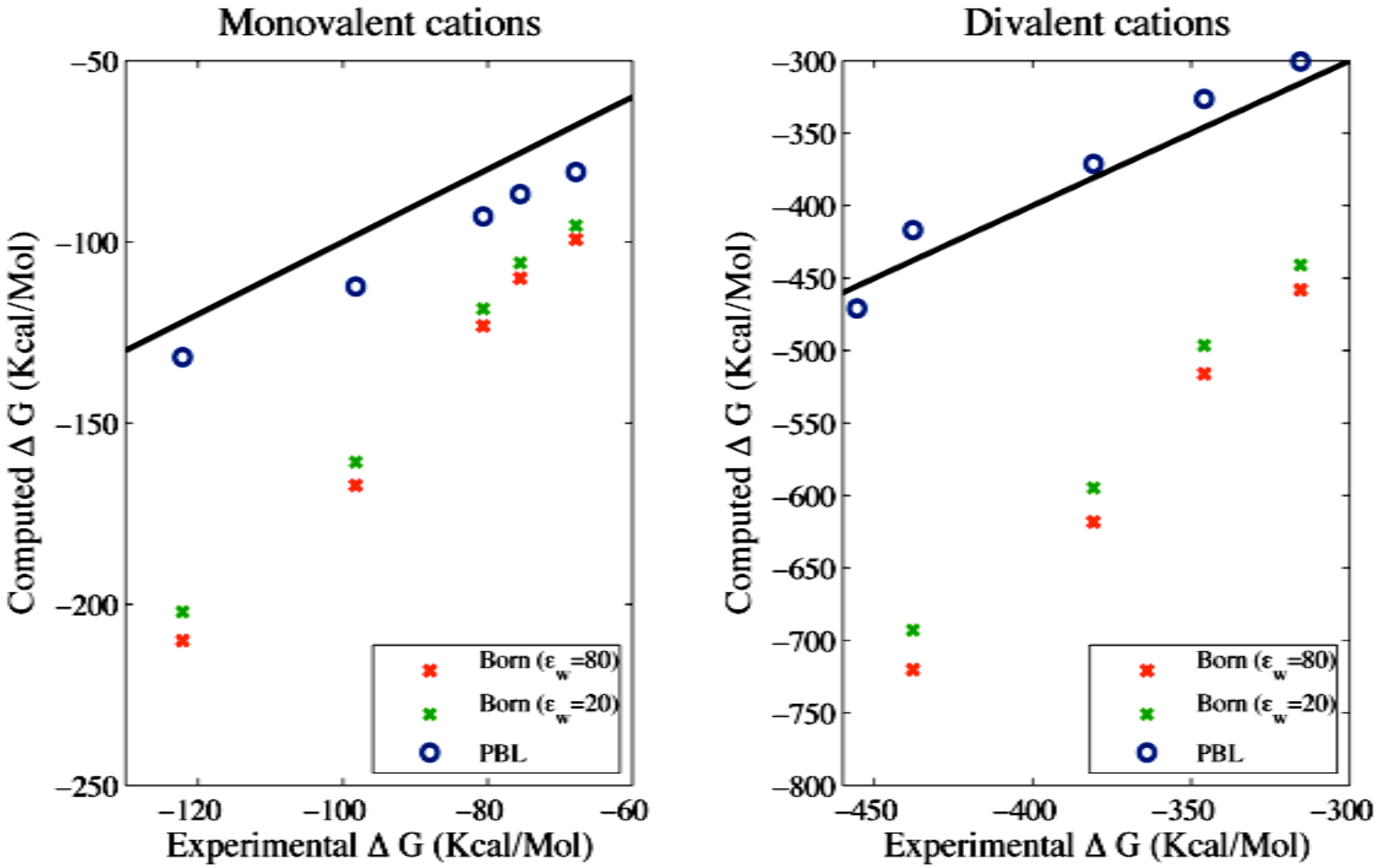
$$F_1(x) = \frac{\sinh(x)}{x^2} L(x) = \frac{\sinh(x)}{x^2}\left(\frac{1}{\tanh(x)} - \frac{1}{x}\right)$$

Dipolar Poisson-Boltzmann Langevin Equation

$$\nabla \bullet \left(\varepsilon_0 \vec{E}(\vec{r}) + \beta p_0^2 \frac{\lambda_{dip} F_1\left(\beta p_0 \left|\vec{E}(\vec{r})\right|\right)}{a^3 D(\phi(\vec{r}))} \vec{E}(\vec{r}) \right) = -\rho(\vec{r}) - \frac{2zec_{bulk} \sinh(z\beta e\phi(\vec{r}))}{a^3 D(\phi(\vec{r}))}$$

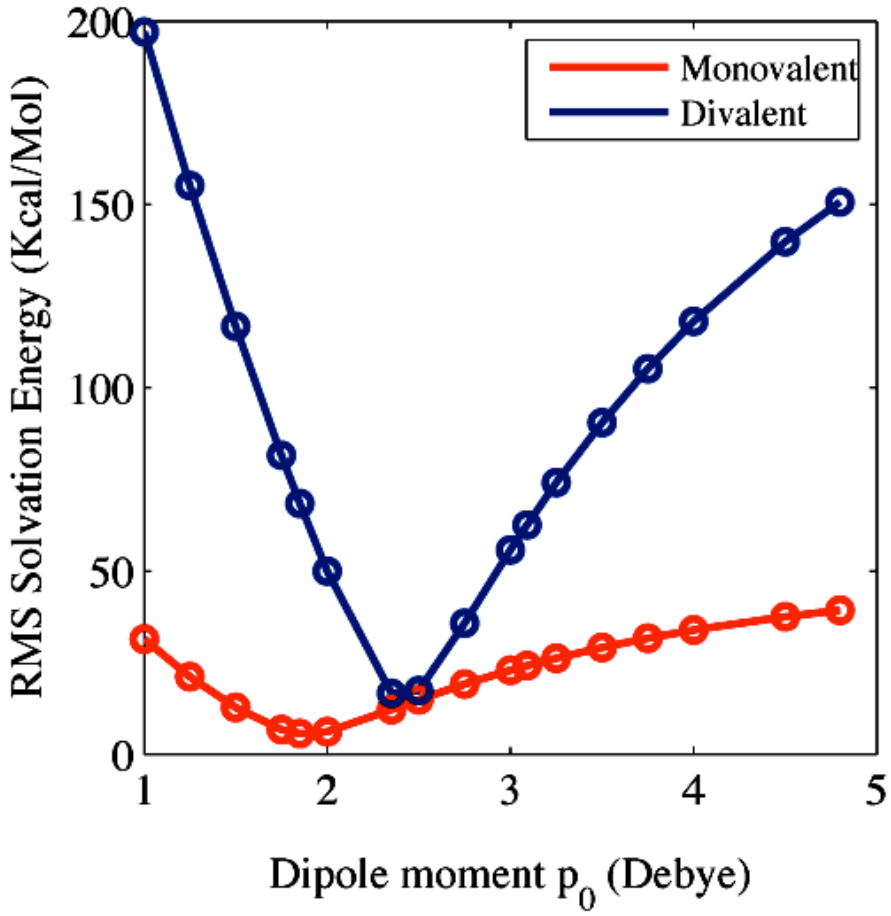


Comparison with experiments

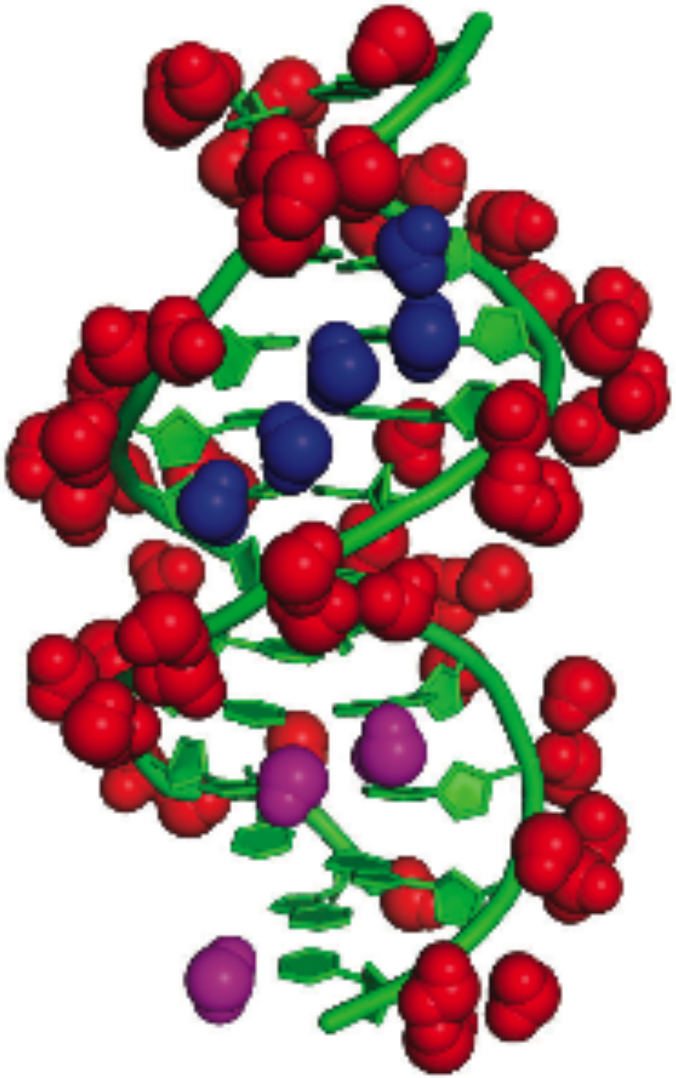


p_0=2.35D, a=3Å

Properties of Water around ions



DNA solvation



Higher densities of water around DNA:

-around phosphates (red)

-Loose, in major groove (magenta)

- ordered, in minor groove (blue)
(spine of hydration)

In agreement with the X-ray data
on the dodecamer of Dickerson!