Biophysics Lecture Thursday, March 21st, 2019

Presenter: Emre Brookes

Topic: Calculation of Hydrodynamic Parameters from Structure

Copy of Lecture at:

https://demeler.uleth.ca/biophysics/archive/Brookes

Outline

- Hydrodynamic and Experimental Parameters
- Stokes' law
- Rigid body hydrodynamics
- PDB → models
- Hydration revisited
- Solution isn't rigid

Parameter	Name	Typical Units	Notes*
f_t	Translational frictional coefficient	g/s	comp.
$f_r(x,y,z)$	Rotational frictional coefficient	g cm² / s	comp.
$\varphi = f/f0$ $R_{H} = R_{S}$ R_{G}	frictional ratio Hydrodynamic or Stokes Radius Radius of Gyration	dimensionless nm, Angstrom nm, Angstrom	comp. obs. obs.
D_t	Translational diffusion	cm²/s	obs.
$D_r(x,y,z)$	Rotational diffusion	1/s	obs. (convoluted)
$ \begin{bmatrix} \eta \end{bmatrix} \\ s \\ \tau \\ \overline{v} \\ M $	Intrinsic viscosity Sedimentation coefficient Relaxation time partial specific volume Mass	cm ³ / g S ns cm ³ / g Da	obs. obs. obs. obs. obs.
η_0	Solvent viscosity	cP	obs.
ρ	Solvent density	g / cm³	obs.

*

comp. = computable from structure obs. = observable



 $F_d = 6\pi\eta r v$



Credit: Kraaiennest, Based on: G.K. Batchelor (1967) An introduction to fluid dynamics, Cambridge University Press. Pages 230–235

 $v = \frac{2}{9} \frac{(\rho_p - \rho_f)}{\eta} gr^2$ HOPPLER* KF 3.2

Stokes, G. G. (1851). "On the effect of internal friction of fluids on the motion of pendulums". Transactions of the Cambridge Philosophical Society. 9, part ii: 8–106



Translation and rotational dynamics of a rigid body of arbitrary shape can be described by a 6x6 resistance matrix, \mathbf{R}_0 , which, under low Reynolds number conditions, directly relates the three forces and torques acting upon the the particle to its linear and angular velocities:

$$\mathcal{F} = \mathbf{R}_0 \cdot \mathbf{v}$$

Recall Stokes' law:

$$F_d = 6\pi\eta r v$$

Happel, J., Brenner, H (1973) Low Reynolds Number Hydrodynamics, ch 5. Nordhoff, Leyden.

$$\mathcal{F} = \mathbf{R}_0 \cdot \mathbf{v}$$

This equation can be reformulated as:

$$\begin{pmatrix} \mathbf{F} \\ \mathbf{T}_0 \end{pmatrix} = \begin{pmatrix} \Xi_t & \Xi_{0,c}^T \\ \Xi_{0,c} & \Xi_{0,r} \end{pmatrix} \begin{pmatrix} \mathbf{u}_0 \\ \boldsymbol{\omega} \end{pmatrix}$$

Spotorno, B. et. al. (1996) BEAMS (BEAds Modelling System): a set of computer programs for the generation, the visualization and the computation of the hydrodynamic and conformational properties of bead models of bead models of proteins. Eur Biophys J 25:373-84

$$\mathcal{F} = \mathbf{R}_0 \cdot \mathbf{v}$$

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Force & Torque = Resistance-matrix * linear and angular velocities

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Subscripts: t – translational; r – rotational; θ ,c – roto-translational coupling

Center of reaction : the point in space where the roto-translational coupling tensors are symmetric

Spotorno, B. et. al. (1996) BEAMS (BEAds Modelling System): a set of computer programs for the generation, the visualization and the computation of the hydrodynamic and conformational properties of bead models of bead models of proteins. Eur Biophys J 25:373-84

Tensor

A tensor is a geometric object that maps in a multi-linear manner geometric vectors, scalars and other tensors to a resulting tensor.

Matrices, vectors & scalars whose multi-linear mapping is independent of the coordinate system can be considered tensors.

$$\mathcal{F} = \mathbf{R}_0 \cdot \mathbf{v} \qquad \begin{pmatrix} \mathbf{F} \\ \mathbf{T}_0 \end{pmatrix} = \begin{pmatrix} \Xi_t & \Xi_{0,c}^T \\ \Xi_{0,c} & \Xi_{0,r} \end{pmatrix} \begin{pmatrix} \mathbf{u}_0 \\ \boldsymbol{\omega} \end{pmatrix}$$

An analogous equation can be written for the diffusion.

The relationship between the diffusion matrix and the resistance matrix is given by the generalized Stokes-Einstein equation:

$$\mathbf{D}_0 = k_B T \mathbf{R}_0^{-1}$$

A center of diffusion exists where the roto-translational (coupling) diffusion tensor is symmetric.

Brenner, H (1967) Coupling between the translational and rotational Brownian motions of rigid particles of arbitrary shape. J Colloid Interface Sci 23:407-436

For an ensemble of N beads, it is possible to calculate from Stokes' law the frictional force exerted on the solvent by each bead. However, the motion of each bead creates an internal velocity field in the solvent that must be added to the external one. This "hydrodynamic interaction" tensor can be described by:

$$\mathbf{F}_i (6\pi\eta_0 \,\sigma_i)^{-1} + \sum_{j=1, j\neq i}^N \mathbf{T}_{ij} \cdot \mathbf{F}_j = (\mathbf{u}_i - \mathbf{v}_0)$$

$$\mathbf{T}_{ij} = (8\pi\eta_0 R_{ij})^{-1} \left[\mathbf{I} + \frac{\mathbf{R}_{ij} \mathbf{R}_{ij}}{R_{ij}^2} + \frac{\sigma_i^2 + \sigma_j^2}{R_{ij}^2} \left(\frac{\mathbf{I}}{3} - \frac{\mathbf{R}_{ij} \mathbf{R}_{ij}}{R_{ij}^2} \right) \right]$$

Rotne, J. Prager, S. (1969) Variational treatment of hydrodynamic interaction on polymers. J Chem Phys 50:4831-48 Yamakawa, H. (1970) Transport properties of polymer chains in dilute solutions. J Chem Phys 53:436-43 García de la Torre, J., Bloomfield, V.A. (1977) Hydrodynamic properties of macromolecular complexes. Biopolymers 16:1747-63

$$\mathbf{F}_i (6\pi\eta_0\sigma_i)^{-1} + \sum_{j=1,\,j\neq i}^N \mathbf{T}_{ij} \cdot \mathbf{F}_j = (\mathbf{u}_i - \mathbf{v}_i^0)$$

This N bead hydrodynamic tensor equation can be rewritten as:

$$\sum_{j=1}^{N} \mathbf{B}_{ij} \cdot \mathbf{F}_{j} = (\mathbf{u}_{i} - \mathbf{v}_{i}^{0})$$
$$\mathbf{B}_{ij} = \delta_{ij} \frac{\mathbf{I}}{6\pi\eta_{0}\sigma_{i}} + (1 - \delta_{ij})\mathbf{T}_{ij}$$

García de la Torre, J. (1989) Hydrodynamic properties of macromolecular assemblies. In: Harding S.E., Rowe, A.J. (eds) Dynamic properties of biomolecular assemblies. The Royal Society of Chemistry Special Publication No 74, Cambridge, UK, pp 3-31.

$$\sum_{j=1}^{N} \mathbf{B}_{ij} \cdot \mathbf{F}_{j} = (\mathbf{u}_{i} - \mathbf{v}_{i}^{0})$$
$$\mathbf{B}_{ij} = \delta_{ij} \frac{\mathbf{I}}{6\pi\eta_{0}\sigma_{i}} + (1 - \delta_{ij})\mathbf{T}_{ij}$$

Assemble the 3Nx3N "supermatrix" composed of $\mathbf{B}_{i i}$ and invert:

 $\mathcal{C} = \mathcal{B}^{-1}$

Computationally expensive: $\Omega(N^2 \log N)$

García de la Torre, J. (1989) Hydrodynamic properties of macromolecular assemblies. In: Harding S.E., Rowe, A.J. (eds) Dynamic properties of biomolecular assemblies. The Royal Society of Chemistry Special Publication No 74, Cambridge, UK, pp 3-31.

$$\mathcal{C} = \mathcal{B}^{-1}$$

And now we can compute:

$$\begin{split} &\Xi_t = \sum_i \sum_j \mathbf{C}_{ij} \\ &\Xi_{0,c} = \sum_i \sum_j \mathbf{U}_i \cdot \mathbf{C}_{ij} \\ &\Xi_{0,r} = -\sum_i \sum_j \mathbf{U}_i \cdot \mathbf{C}_{ij} \cdot \mathbf{U}_j + 6\eta_0 \mathbf{V} \mathbf{I} \end{split}$$

Giving us the tensors of the resistance matrix:

$$\mathcal{F} = \mathbf{R}_0 \cdot \mathbf{v}$$

García de la Torre, J. (1989) Hydrodynamic properties of macromolecular assemblies. In: Harding S.E., Rowe, A.J. (eds) Dynamic properties of biomolecular assemblies. The Royal Society of Chemistry Special Publication No 74, Cambridge, UK, pp 3-31.

$$\begin{pmatrix} \mathbf{F} \\ \mathbf{T}_0 \end{pmatrix} = \begin{pmatrix} \Xi_t & \Xi_{0,c}^T \\ \Xi_{0,c} & \Xi_{0,r} \end{pmatrix} \begin{pmatrix} \mathbf{u}_0 \\ \boldsymbol{\omega} \end{pmatrix}$$

And now we can compute:

$$f_t^{(\eta_0)} = \frac{3}{\operatorname{tr}(\Xi_t^{-1})}$$
$$D_t^{(T,\eta_0)} = \frac{k_B T}{f_t^{(\eta_0)}}$$
$$R_s^t = \frac{f_t^{(\eta_0)}}{6\pi m_s}$$

García de la Torre, J. (1989) Hydrodynamic properties of macromolecular assemblies. In: Harding S.E., Rowe, A.J. (eds) Dynamic properties of biomolecular assemblies. The Royal Society of Chemistry Special Publication No 74, Cambridge, UK, pp 3-31.

 $6\pi\eta_0$

$$\begin{pmatrix} \mathbf{F} \\ \mathbf{T}_0 \end{pmatrix} = \begin{pmatrix} \Xi_t & \Xi_{0,c}^T \\ \Xi_{0,c} & \Xi_{0,r} \end{pmatrix} \begin{pmatrix} \mathbf{u}_0 \\ \boldsymbol{\omega} \end{pmatrix}$$

Rotational properties can also be obtained:

$$\begin{split} \Xi_{R,r} &= \Xi_{0,r} - \boldsymbol{r}_{\mathrm{OR}} \times \Xi_t \times \boldsymbol{r}_{\mathrm{OR}} + \Xi_{0,c} \times \boldsymbol{r}_{\mathrm{OR}} - \boldsymbol{r}_{\mathrm{OR}} \times \Xi_{0,c}^{\mathrm{T}} \\ D_r^{k(T,\eta_0)} &= \frac{k_B T}{\Xi_{R,r}^{\mathrm{kk}}} \\ R_S^{r,k} &= \left[\frac{\Xi_{R,r}^{\mathrm{kk}}}{8\pi\eta_0}\right]^{\frac{1}{3}} \end{split}$$

Relaxation times are computed from the three rotational diffusion coefficients.

Intrinsic viscosity can also be computed (more complex)

García Bernal, J.M., García de la Torre, J. (1980) Transport properties and hydrodynamic centers of rigid macromolecules with arbitrary shapes. Biopolymers 10:751-66

$\mathcal{F} = \mathbf{R}_0 \cdot \mathbf{v}$

 \rightarrow Given a collection of non-overlapping spheres with their coordinates, we can solve for the resistance matrix using a hydrodynamic interaction tensor and doing "supermatrix inversion"

 \rightarrow We can also solve for the resistance matrix in another way...

$\mathcal{F} = \mathbf{R}_0 \cdot \mathbf{v}$

- A boundary element method for solving the Stokes flow equations
- Does not depend on hydrodynamic interaction tensors
- Requires tessellation of the arbitrary shape
- Computationally intensive
- Must be repeated multiple times to generate a trajectory



Sergio Aragon and Dina Flamik, Precise computation of transport properties of cylinders by the boundary element method, Macromolecules, 2009, 42 (16), 6290:6299

Must be repeated multiple times to generate a trajectory



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Hitting path



 $\beta = \frac{\# \text{hits}}{\# \text{attempts}}$

$$R_s = \beta R$$

$$f_t^{(\eta_0)} = 6\pi\eta_0 R_s$$

ZENO computes:

- self-capacity
- intrinsic conductivity
- Intrinsic viscosity
- hydrodynamic radius
- translational diffusion coefficient
- electric Polarizability Tensor,
- translational friction coefficient
- radius of gyration
- structure factor...
- of arbitrarily shaped objects

Escaping path

Douglas & Zhou & Hubbard, PRE, Vol 49, Page 5319, (1994). Mansfield & Douglas, PRE, Vol 81, 021803 (2010)



 Starting with a PDB structure, represent each atom with a sphere of fixed diameter. Then cover this primary model with spheres of smaller and smaller size, for each cover, compute SMI and extrapolate (HYDROPRO)





FIGURE 2 (A) A bead-per-atom (BPA) model of lysozyme, which we take as the primary hydrodynamic particle (PHP) that represents this protein. The atomic element radius (AER) is a = 3 Å. (B) A shell model (SHE), derived from the PHP, used for hydrodynamic calculations. The radius of the small beads in this case is $\sigma = 0.8$ Å.

García de la Torre, Huertas & Carrasco Bioph. J. 78, 719–730, 2000 Convert a structure directly (UltraScan SOMO)



AtoB method

Rocco, M.; Brookes, E. H. (2014) Dynamical Aspects of Biomacromolecular Multi-resolution Modelling Using the UltraScan Solution Modeler (US-SOMO) Suite, The Future of Dynamic Structural Science, 189-199, 2014, Springer

UltraScan-SOMO (using MSRoll)



Sergio Aragon and Dina Flamik, Precise computation of transport properties of cylinders by the boundary element method, Macromolecules, 2009, 42 (16), 6290:6299 • UltraScan-SOMO



Brookes, E., Rocco, M., (2016), Calculation of Hydrodynamic Parameters: US-SOMO, in "Analytical Ultracentrifugation: Instrumentation, Software, and Applications", Susumu et al, eds., p 169-193, Springer Japan. doi:10.1007/978-4-431-55985-6_10

- Many PDBs are incomplete (missing side chains etc)
 - If interior, not an issue regarding the computation of friction
 - If exterior, they will effect the computation of friction
 - Mass will be missing
- Sedimentation coefficient is computed from the translational friction, psv and mass, so errors in these will effect s.

$$s = \frac{M(1 - \bar{v}\rho)}{f_t^{(\eta_0)} N_A}$$

• Hydration is critical for proper hydrodynamic parameter computations!







- HYDROPRO, BEST use uniform hydration
- UltraScan SOMO uses a residue correspondence model to hydrate locally for SoMo, AtoB and ZENO methods.

I. D. KUNTZ, JR. AND W. KAUZMANN

HYDRATION OF PROTEINS AND POLYPEPTIDES

TABLE XXIII

Prediction of Protein Hydration from Composition and Polypeptide Results^a

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TABLE XXII

Amino acid residues ^b	Hydration
Ionic	13/2004
Asp ⁻	6
Glu-	7
Tyr-	7
Arg ⁺	3
His ⁺	4 ^d
Lys^+	4
Polar	
Asn	2
Gln	- 2*
Pro	3
Ser, Thr	2.
Trp	2*
Asp	2
Glu	2
Tyr	(3)
Arg	3
Lys	4
Nonpolar	
Ala	en la mile 1 / L
Gly	1
Phe	(0)
Val	1
Ile Leu Met	10

Proposed Amino Acid Hydrations Based on Nuclear Magnetic Resonance Studies of Polypeptides^a

^a After Kuntz (1971a).

^b Standard three-letter code.

" Moles of water per mole of amino acid.

d As Lys+.

· Assumed values based on one water molecule per amide plus one water molecule per side-chain polar group.

Kuntz, ID and Kauzmann.	W	(1974)	Hydration	of Proteins	and Polynentides	Adv in Prot	Chem	28.239-345
\mathbf{M}	<i>''</i> .	(1) 7)	ilyaranon	0/110101113	unu i orypeptides.	<i>Iuv. m ivoi</i> .	Chem.	20.257 545

	Hydration (g H ₂ O/g protein)			
Protein, native	Calculated ^b	Observed ^e		
Lysozyme	0.36	0.34		
Myoglobin	0.45	0.42		
Chymotrypsinogen	0.39	0.34		
Chymotrypsin	0.36	0.33		
Ovalbumin	0.37	0.33		
Bovine serum albumin (BSA)	0.45	0.40		
Hemoglobin (denatured)	0.42	0.42		
BSA + urea	0.45	0.44		
BSA, pH 3	0.32d	0.30		

^a After Kuntz (1971a); see Table XXII.

^b Calculation assumes that all residues are fully hydrated. This is perhaps reasonable for the denatured proteins but leads to a small positive error unless allowance is made for "buried" groups. This correction was done for lysozyme, yielding a calculated value of 0.335.

^o NMR freezing experiments.

^d Calculation assumes that all carboxyl groups are uncharged at pH 3.

Biomolecular hydration: From water dynamics to hydrodynamics

Bertil Halle* and Monika Davidovic

Department of Biophysical Chemistry, Lund University, Box 124, SE-22100 Lund, Sweden

1-The static picture of biomolecular hydration is fundamentally inconsistent with magnetic relaxation dispersion experiments and molecular dynamics simulations, which both reveal a highly dynamic interface where rotation and exchange of nearly all water molecules are several orders of magnitude faster than biomolecular diffusion.

2-Waters near the biomolecular surface have a different density, and alter the local viscosity. It turns out that considering a number of "tightly bound", static water molecules compensate well for this local viscosity effect, otherwise very hard to be directly taken into account.

Methods testing

#	Monomeric proteins	MW	# Multimeric proteins		MW
1	Cytochrome c (1HRC)	12357.5	14 Superoxide dismutase (2SO		31442.2
2	Ribonuclease A (8RAT)	13683.8	15	β-Lactoglobulin (1BEB)	35224.7
3	α-Lactalbumin (1A4V+carb)	15784.7	16	α-Chymotrypsin (4CHA)	50473.5
4	Lysozyme (1AKI)	14306.7	17	Triosephosph. Isom. (1YPI)	52971.4
5	Myoglobin horse CO (1DWR)	17568.3	18	Hemoglobin CO (1HCO)	64559.7
6	Soybean Trypsin Inh. (1AVU)	19962.8	19	Citrate Synthase (1CTS)	97845.5
7	β-Trypsin (1TPO)	23335.9	20	Inorganic Pyrophosph. (1FAJ)	117339.0
8	Trypsinogen (1TGN)	23182.7	21	G3PD apo (2GD1)	143787.8
9	α-Chymotrypsin (4CHA)	25236.5	22	G3PD holo (1GD1)	146437.7
10	Chymotrypsinogen A (2CGA)	25659.0	23	LDH pig H + NAD (5LDH)	148942.6
11	Carbonic Anhydr. B (2CAB)	28820.5	24	LDH pig M + NAD (9LDH)	149063.5
12	Pepsin (4PEP)	34588.6	25	Aldolase (1ADO)	157136.0
13	H. Serum Albumin (1AO6)	66428.6	26	Catalase (4BLC)	235782.0
			27	β-Galactosidase (1BGL)	465557.0

Rocco M., and Byron O. (2015). "Computing translational diffusion and sedimentation coefficients: an evaluation of experimental data and programs". Eur. Biophys. J., 44, 417–431 (DOI:10.1007/s00249-015-1042-9_____

Methods testing – Overall performance



Rocco M., and Byron O. (2015). "Computing translational diffusion and sedimentation coefficients: an evaluation of experimental data and programs". Eur. Biophys. J., 44, 417–431 (DOI:10.1007/s00249-015-1042-9

Methods testing – 21 test proteins – Dt



Rocco M., and Byron O. (2015). "Computing translational diffusion and sedimentation coefficients: an evaluation of experimental data and programs". Eur. Biophys. J., 44, 417–431 (DOI:10.1007/s00249-015-1042-9

Methods testing – overall performance – s



Rocco M., and Byron O. (2015). "Computing translational diffusion and sedimentation coefficients: an evaluation of experimental data and programs". Eur. Biophys. J., 44, 417–431 (DOI:10.1007/s00249-015-1042-9

- D_t is always better matched than *s*. This is likely due to poor psv knowledge/estimation.
- HYDROPRO and BEST both underestimate D_t and s. This is likely due to an excessive expansion of the surface in an attempt to account for hydration.
- SoMo with overlap removal overestimates D_t and s. This is likely due to an excessive shrinkage of the hydrated beads notwithstanding the outward translation.
- AtoB with a 5 Å grid appears to produce reasonable hydrated surfaces leading to very good D_t matching.
- The combination of SoMo models without overlap removal and Zeno computations produces the best Dt matching.

Rocco M., and Byron O. (2015). "Computing translational diffusion and sedimentation coefficients: an evaluation of experimental data and programs". Eur. Biophys. J., 44, 417–431 (DOI:10.1007/s00249-015-1042-9

- Ideally, with sufficient computational resources and sufficiently good simulation software (force fields,etc), one could compute full MD trajectories and calculate the diffusion directly, from which the hydrodynamic radius could be computed.
- Given a trajectory, one can compute rigid body hydrodynamics over each frame and produce statistics.

1. List at least one experimental technique that can provide each observable listed in the Table on slide 3. Comment on their accuracy.

2a. Show the steps to go from

t

$$\mathbf{F}_{i}(6\pi\eta_{0}\sigma_{i})^{-1} + \sum_{j=1,\,j\neq i}^{N} \mathbf{T}_{ij} \cdot \mathbf{F}_{j} = (\mathbf{u}_{i} - \mathbf{v}_{i}^{0})$$

$$\sum_{j=1}^{N} \mathbf{B}_{ij} \cdot \mathbf{F}_{j} = (\mathbf{u}_{i} - \mathbf{v}_{i}^{0})$$
$$\mathbf{B}_{ij} = \delta_{ij} \frac{\mathbf{I}}{6\pi\eta_{0}\sigma_{i}} + (1 - \delta_{ij})\mathbf{T}_{ij}$$

2b. Compute T_{12} for N=2 with spheres of radius 1 and 2 with standard x,y,z coordinates (-1,0,0) and (2,0,0) respectively with a solvent viscosity of 1.

Do one of 2a or 2b, both for extra credit.