Molecular Motion, Structure and Surface of Proteins, Membranes and Polymers - Simulation by Dynamic Finite Volume Models (FVM)

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Molecular Modelling – volume and surface data

Molecular modelling is the common method for **interpretation of structural data** of macromolecular systems. While this is done at an atomic level for crystallizable proteins (< 0.1 nm resolution), the modelling of non-crystallizable macro-molecular systems is usual with lower resolving models of typically 0.3 - 1 nm resolution.

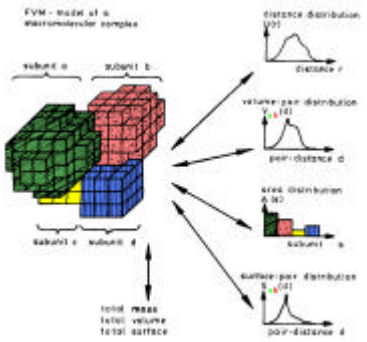
Low resolution modelling is required for a variety of **macromolecular systems** in biology and chemistry: membranes, polymers, DNA-protein complexes, large protein complexes and proteins showing extended molecular motion, e.g. molecular motors.

One oportunity for low resolution molecular modelling is the construction of models consisting of spheres, e.g. by the "**multibody method**" of Glatter [1]. Those multibody models describe the mass distribution inside macromolecules well, if constructed by an assembly of several 100 spheres / 100,000 mass. Thus this is the most common modelling method for the interpretation of X-ray and neutron scattering of solutions (SAXS, SANS). Unfortunately the surface description is strongly restricted, which excludes the interpretation of surface related structure research methods by multibody models.

The **Finite Volume Method FVM** was designed for interpretation and combination of structural data from solution scattering (SAXS, SANS, PCS) with electron microscopy, surface labeling, crosslinking and surface distance estimation by fluorescence coupling (Förster coupling) [2,3]. With the current improvements, it is suitable for modelling of **molecular motion, volume and surface pair relations, and deuterium - hydrogen exchange**.

Molecular complexes (multi-subunit) and surface

a) subunits in a complex



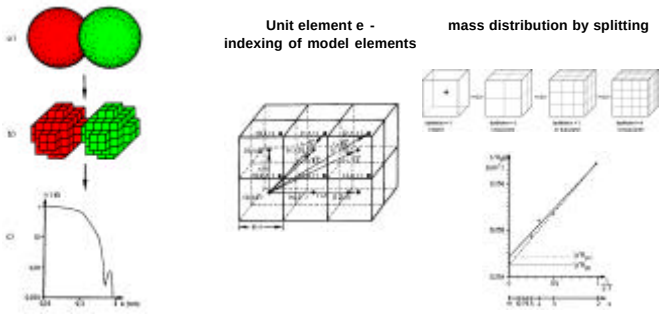
b) mass pair distribution

c) surface pair distribution

a) The FVM model of a macromolecular complex (multi-subunit) describes each subunit or domain within by a separate element type. As a result the method can give, in addition to the conventional distance distribution P(r), subunit-domain and pair related functions, i.e the area distribution by subunits, **b)** the subunit-pair volume (mass) distribution V_{ab}, **c)** and the subunit-pair surface distance distribution S_{ab}, which is experimentally estimated by labeling, crosslinking and Förster-coupling (fluorescence energy transfer estimation after double dye labeling).

Finite Volume Method FVM - cube models

a) **b)** **c)**



The Finite Volume Model of a macromolecular complex **(a)** consists of an assembly of **cubes of equal size** in an orthogonal raster (matrix). The **position** of a model element inside the FVM-model **(b)** is defined by the unit vector e (element size = resolution) and a triple of **finite indices** (ix, iy, iz).

The **mass distribution inside the model elements (c)** is in the improved FVM procedure described by a set of points, defined by the "splitting factor" s. The number of the mass points is the third power of the split factor s. As shown in the diagram ($1/R_g$ vs. $1/(s-1)$), a split factor of s = 3 isenough for most applications (convergent R_g).

Hydrogen-deuterium exchange, surface estimation

a) **b)**

In Neutron-, NMR and IR experiments the solvent **protons H** may be replaced by **deuterium D** by an extent of ? (relative deuteration). The deuteration dependent scattering density of the solvent is:

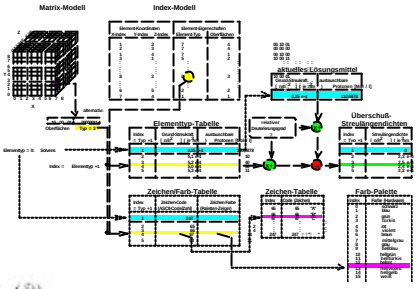
$$\rho(\delta) = \rho_0 + \rho e(\delta)$$

In a macromolecule matter type i (protein, polymer, lipid) only a part of the protons can be solvent-exchanged (in proteins 1/3):

$$\rho i(\delta) = \rho_{o,i} + [(1-\delta)\rho H + \delta\rho D]ci,H$$

Thus the H/D-exchange related scattering power of the molecular complex with respect to the partially deuterated solvent yields the distance distribution function P(r) = U(r, ?, ?):

$$U(r,\delta,\rho_{solv}(\delta)) = d^3 \sum_{i=1}^{n} \sum_{j=1}^{n} (\rho_i(\delta) - \rho_{solv}(\delta)) \times (\rho_j(\delta) - \rho_{solv}(\delta)) \left| r_{ij} \right|$$



The H/D-exchange (a), which is done in several Neutron-, NMR and IR-experiments, has to be calculated separately for solvent and the different subunits (types) of the macromolecular model. In the current FVM-program FINIX, this is done by lookup-tables for each type of matter (model) and solvent (b). By further index-pointer linked reference tables, the specific model surface and representation is estimated and evaluated.

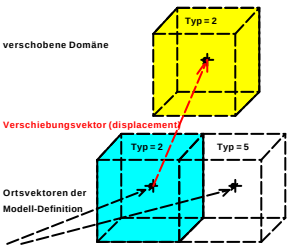
Molecular motion (dynamics) Modelling

a) Size and mass of elements

The mass of the modell elements decreases rapidly with the resolution e. The number of amino acid residues (M ≅ 110 g/Mol) inside a model element is given for typical proteins.

Element size e [nm]	Element mass [g/Mol]	Amino acids / model element
1,6	3334	30,3
1,4	2233	20,3
1,2	1406	12,8
1	814	7,4
0,94	678	6,1
0,8	**417**	**3,8**
0,7	280	2,5
0,515	**110**	**1,0**

b) Molecular motion by displacement vector

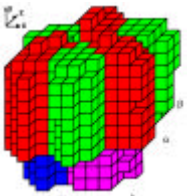


a) The mass of the model elements decreases with their size. For typical proteins (v' = 0.74 cm^3/g) an element size of e = 0.515 nm corresponds to 1 amino acid residue / cube. Bio-membranes are well modelled by e = 0.8 nm, i.e. the lipid bilayer corrresponds to 6 cubes (headgroup – 4 x hydrophobic core – headgroup).

b) Molecular motions are described by the addition of a displacement vector to the resting position definition of all elements of the appropriate type. This vector is defined separately for each element type (subunit) and is organized as an array of time. This allows the calculation of a structural film of a molecular motion of a molecular complex.

Test : Application : F_1ATPase

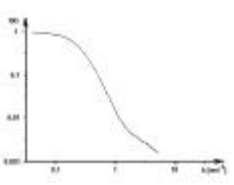
The test-model "micro-bear" consists of 1540 model elements. At 0.8 nm resolution the mass is 641 759.



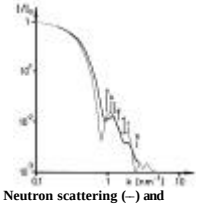
FVM model of F_1ATPase from 606 elements of 0.94 nm size

Conclusions :

- - FVM models are suitable for **data interpretation and combinatation** of solution scattering, labeling, crosslinking
- - **molecular motion - dynamics** are modelled using a displacment vector-film
- - **subunits , domains** are distinguished
- H/D-exchange **is estimated**



Model neutron scattering in H_2O: 1% subunit motion is detectable.



Neutron scattering (–) and modelling (…) of F_1ATPase from *Micrococcus luteus* [4].

References

[1] Glatter, O. et al. a) Acta Phys. Austriaca **(1980)**52, 243-256, b) Meisenberger, O. et al., FEBS Lett **(1980)** 112, 39-41, [2] Nawroth, T., Physica B **(1989)** 156, 493-495 [3]; Nawroth, T., Habilitation thesis, Mainz **1995**, [4] a) Neidhardt, A., Nawroth T., Hütsch , M.; Dose, K.; FEBS Lett. **(1991),** 280, 179-182; b) Nawroth, T., Neidhardt, A., Dose, K., Conrad, H., Munk, B., Physica B **(1989)** 156, 485-488 c) Gruber, G., Godovac-Zimmermann, J., Nawroth, T., BBA **(1994)**186, 43-51 ; d) Nawroth, T., Gebhardt, R., Zwicker, K., Grillo, I., May, R.P. **(2003)** Physica B, in press