Approaches to docking

Density-based docking

- Does not need one-to-one correspondence of map and model
- Can potentially handle modular docking
- Little human intervention
- Density data fully explored
- Independent of contour level
- Relative expensive calculation, can be slow

Approaches to docking

Surface-based docking

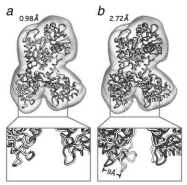
- Can potentially handle modular docking if modules have distinct surface features
- Little dependency on internal features
- Density data not fully explored
- Corresponds to high-pass filtering, therefore potentially error prone
- Expensive calculation, can be slow

Approaches to docking

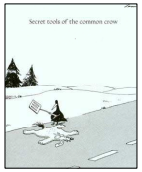
Local refinement, flexible docking

- Can potentially account for local variations
- Can use additional information (stereo chemistry, normal modes)
- Reduces observable to parameter ratio
- Serious danger of over-fitting

MODULAR VERSUS FLEXIBLE



Wriggers & Birmanns, JSB 2001
Vollmann & Hanein, Meth Enzym, 2004



We need proper tools to do proper docking

Part I: Sticking in the model

Approaches to docking

Manual docking

- Immediate visual feedback
- Heavy human intervention
- High level of subjectivity
- Prone to biasing
- Dependent on contour level

Approaches to docking

Landmark-based docking

- Reduced representation, therefore fast
- Moderate human intervention
- Loss of data
- Error of docking position hard to assess
- Needs one-to-one correspondence of map and model

Scripps Cryo Course, November 2005

COMBINING ELECTRON MICROSCOPY WITH ATOMIC MODELS

Niels Volkmann
The Burnham Institute for Medical Research
10901 North Torrey Pines Road
La Jolla, California, USA
niels@burnham.org

Electron Microscopy can give structural information on many complex systems but is most often limited to non-atomic resolution (usually between 10-30Å)

Techniques for determination of atomic structures are limited by size or crystallinity requirements

We can gain atomic-level information on large complexes by docking atomic models of components into lower-resolution reconstructions from electron microscopy

All we need to do is to stick an atomic model into the EM density, wiggle and deform it to fit the density better and then we have atomic resolution information, right?

No, wrong!

We try to find the correct positions of highly localized atoms within a relatively featureless density (Atoms into Blobs).

Finding a "perfect fit" is the easy part, figuring out if the fit is meaningful, that is the hard part.

Part III:
Finding confidence intervals

Numerical Recipes

To be genuinely useful a docking procedure should provide:

(i) accurate, globally best parameters
(ii) error estimates on these parameters
(iii) a statistical measure for goodness-of-fit

"Unfortunately many practitioners of parameter estimation never proceed beyond item (i)! They deem a fit acceptable if a graph of data and model 'looks good'. This approach is known as chi-by-eye."

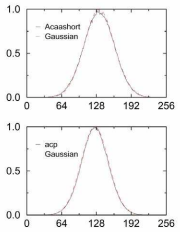
Numerical recipes in C, Press et al, page 518

Correlation Coefficient

$$CC = \frac{\sum_i (a_i - \bar{a})(e_i - \bar{e})}{\sqrt{\sum_i (a_i - \bar{a})^2 \sum_i (e_i - \bar{e})^2}}$$

CC is a Maximum Likelihood measure if noise is uniform Gaussian and *a* and *e* are independent, related by an affine relationship (i.e. $e = ca + d$)

Cross-correlation is not a maximum likelihood measure; requires an identity relationship between *a* and *e* (i.e. $e = a$)



Approaches to docking

Use of other filters

- *Masking* can enhance performance for relatively noise-free maps
- Corresponds somewhat to high-pass filtering and is thus susceptible to high frequency noise
- Core *weighting* can improve performance for multimers with certain shape characteristics
- Filters usually slow down calculation

Approaches to docking

Compare atomic positions directly with density

Convert atomic model to density, then compare

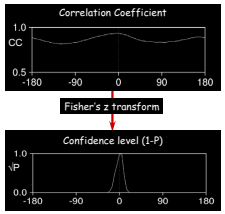
Convert atomic model and density to something else, then compare

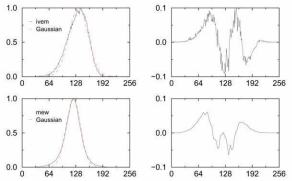
Addressing (ii) and (iii):

Solution Sets

Define confidence level at which solutions are still equivalent to the fit with the globally highest score of the similarity measure.

Statistically, all the solutions within this set satisfy the data equally well and have equal probability, at the chosen confidence level, to be the 'true' solution.





Once we decided on a particular docking approach and a particular similarity measure, how do we proceed?

Part II:
Evaluating the quality of the fit

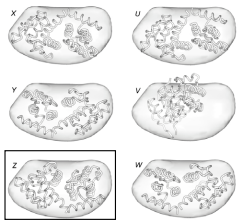
Similarity Measures

Measure the fit between atomic model and reconstruction

Maximum Likelihood gives the best possible unbiased estimate (Neyman and Pearson)

Many of the more common similarity measures are some approximation to maximum likelihood

DENSITY CORRELATION VERSUS LAPLACIAN FILTER



Application Example

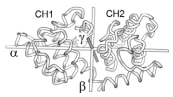
Helical reconstruction of actin-bound smooth muscle myosin

- Step 1: isolate myosin contribution from reconstruction
- Step 2: define modules
- Step 3: dock largest module
- Step 4: subtract contribution of docked module

Solution Sets

Degeneracies can be easily detected by analyzing solution sets

DETECTION OF DEGENERACIES: LOW-RESOLUTION PSEUDO SYMMETRY



Fimbrin

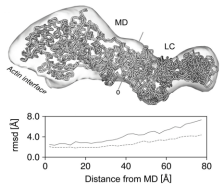
Hanein et al., NSB 1998

Solution Sets

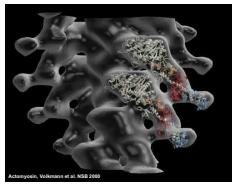
The sets can be used to calculate parameters of interest as a property of the set, for example the

Coordinate error can be estimated by the rmsd value of the atom position within the whole set

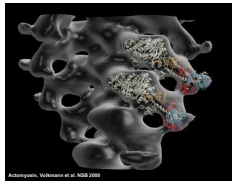
CONFORMATIONAL VARIATION



Volkmann et al., NSB 2000

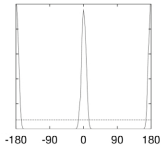


Actomyosin, Volkmann et al. NSB 2000

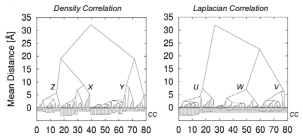


Actomyosin, Volkmann et al. NSB 2000

DETECTION OF DEGENERACIES: LOW-RESOLUTION PSEUDO SYMMETRY



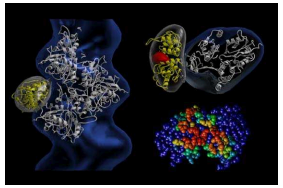
DETECTION OF DEGENERACIES, CLUSTER ANALYSIS



Volkmann & Hanein, Meth Enzym, 2003

Solution Sets

Interaction probabilities, the probability that certain residues take part in interactions, can be estimated by integrating over the solution sets



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