EMDataBank Model Challenge Face-to-Face meeting

Monday May 29, 2017 / Hyatt Regency New Orleans 4th floor Imperial 11 9:30 AM to 3 PM

Attendees

In person:	Remote via GoToMeeting:
• Helen Berman • Paul Adams • Tom Terwilliger • Jane Richardson • Wah Chiu • Cathy Lawson • Andriy Kryshtafovych • Amber Eakin • Alex Wlodawer	• Paula Flicker • Randy Read • Jaime Fraser* • Arjen Jakobi* • Yana Gofman* *attended for part of meeting

Agenda/Presentations

time	topic	Presentation link	who
9:30	Welcome/Introductions/ Model Challenge Overview	overview ppt	Wah Chiu/Paul Adams Cathy Lawson
10:00	Assessor Presentation	emringer-pdf	Jaime Fraser
10:30	Coffee break		
10:45	Model Comparison Overview	em-vs-casp-ppt	Andriy Kryshtafovych
11:15	Assessor Presentation	density-analysis-ppt	Jane Richardson
12:45	Assessor Presentation	ab-initio-models-ppt	Tom Terwilliger
1:30	Recommendations		Paul Adams
2:30	Timeline for Challenge Completion		Wah Chiu

Notes

Paul Adams/Short-term Goals

1. Review progress in Model Challenge evaluation
2. Identify any barriers to evaluation
3. Establish timeline for completion
4. Face to face meeting among challengers, assessors and committee members
5. Develop a plan for publication of challenge results
6. Discuss future Challenge activities

Cathy Lawson/Overview

1. Timeline to this point:
    a. February – September 2015 Development Phase Committee meetings

   b. June 2015 Face-to-face meeting to define targets, goals parameters
   c. October 2015 – June 2016 Challenge Phase 16 participants submitted 106 models
   d. June 2016 – April 2017 ”Blind” Assessment Phase: rank models by quality Model Assessment pages created 6 participating review groups
   e. May 2017 – face-to-face meeting to discuss assessment progress
2. Goals for today:
   a. Define major issues with model assessment for cryoEM-derived structures
   b. Hear from our Assessors:
      i. Overview of method(s) investigated
      ii. Targets/models looked at Issues encountered
      iii. What did you find out?
3. Discussion points:
   a. Most of the models were submitted within 48 hours of the deadline which could potentially have had an impact on model quality
   b. Since reported effort for creating the ab initio models was low, not clear why some submitters did not cover all of the targets.

Jaime Fraser/EMRinger

1. Working with Ben Barad, Andriy K, and Paul Adams, looked at EMRinger scores as generated on Andriy’s model-compare website. EMRinger compares dihedral ***X***1 angle C-gamma position vs. map density. It is a way to measure the quality of backbone placement.
2. A server is available that can be used to generate EMRinger score for any map + model http://emringer.com/
3. Looked at challenge models for which correlation coefficients were also available (Phenix and TEMPy). Correlation coefficients by these two methods are well correlated with each other, but EMRinger scores are not correlated. (Tom noted: correlation coefficients could be artificially low if comparing 1 copy model vs whole complex map, e.g. for viruses).
4. EMringer scores for the model challenge models follow the same trend score vs. reported resolution trend as deposited structures.
5. Challenges/future plans: modify tool to include nucleic acids, carbohydrates.
6. Question from Jane : Does it make a difference whether the model was created ab initio vs. using a template? Jaime: EMRinger could be used in principle for ab initio / c-alpha only models as opposed to other tools that require sequence.
7. Question: what is best possible score that can be reached? Answer: at ~4 A should be possible to get score of ~2, higher resolution structures could exceed 5.
8. Comment from Alex: for X-ray, this method would only be applicable to strictly experimental maps (MAD/SAD), owing to model bias of typical maps.
9. Further analysis: Will create plot of EMRinger score vs. resolution for all of the models (current plot includes only structures with correlation coefficient scores).
10. Comment from Tom: Some ribosome structures with poor sequence match have high EMRinger scores. Jaime: polyalanine or polyglycine regions are excluded from the scoring. The score is weighted by the # of residues that can be scored.

Andriy Kryshtafovych/Model Comparison Site

1. Background: Andriy has organized CASP project for 15 of its 23 years.
2. The EM model challenge evaluation required completely different set of tools and levels of organization.
3. GDT_TS score (from Adam Zemla) — great for predicted models, Jane suggests we could come up with something similar for EM. (improvement on RMSD score).
4. Going forward need to do something about issues such as 2char chain ids/mmcif.
5. Jane/Tom: For 3D graphics views it would be good to be able to click on residue and get the # from 3d popups
6. Tom: Uniform process for superposing reference structures onto maps. one reference structure for each map. Show same scores for the reference models.
7. Tool needed to look at model superimposed on the map.
8. Discussion: At the beginning we have "taken what we can get" next time we will want to impose stricter requirements so that it will be easier to do the analyses/comparisons.

Jane Richardson/Map-Model comparisons

1. Used in-house graphics software "King" to look at map/model pairs.
2. Noticed that negative density seems to be quite strong for EM maps, different from situation with X-ray maps. Following some discussion: a convention is needed for scaling EM map density.
3. Phosphate in RNA has lower density for EM vs X-ray because of charge: correlation coefficient calculations need to take this into account.
4. Molprobity analyses sugar pucker (P-perp test) and common nucleic acid backbone rotamers (suites). Looking at RNA in the submitted ribosome structures, found that some are better and some are worse than the original model. Modellers are not using rotamer frequency as prior probability.
5. Proteins: looked at rotamers and also occurrence of non-proline *cis* peptide bonds (cis-nonPro, which for some reason is more abundant in carb processing proteins). PDB entry 5a1a has 9 cis-nonPro, but only 3 are correct.
6. Tracing through side-chains, register issues were seen in some *ab initio* models. It will be important to separate out optimized models vs *ab initio* models in order to give appropriate feedback on how to improve.
7. Conclusions: ab initio and optimized models need to be evaluated separately; map treatment matters a lot (sharpening, corrections); what feedback can best help improve the modeling?
8. Discussion: what map should be deposited to EMDB? Important to have the map that is referred to in the paper, but sometimes this is multiple maps. Create a "combined map" depending on regions? Also, half-maps used to determine FSC should likely be required.

Tom Terwilliger/ ab initio Models

1. disclaimer —he was one of the modellers, made sure that tools would work at least on his models.

2. Goals for ab initio modelling: (a) Fraction of model built correctly (b) Accuracy of model (c) Accuracy of sequence assignment
3. Challenges for ab initio modelling: (a) Chain may be broken (b) Chain direction may be backwards (c) Chain may have insertions/deletions (d) Depositors may have masked region for model-building (also, likely that many of the modellers went to PDB and found model that was used to "cut out" map).
4. Approaches in ab initio model evaluation: (a) Count C-alpha or P within 3 A of a target (b) Separately evaluate chains matching in forward/reverse directions (c) Identify insertions and deletions (d) Work with unique region built. Tool: phenix.chain_comparison

Opportunities/Recommendations

1. Define global and local validation criteria for EM-based models
2. Develop tailored validation approaches for ab initio models and re-refined (template-based) models
3. Propose improvements to current validation tools to accommodate EM-based models (e.g. reading mmCIF format)
4. Clarify the maps and associated metadata that should be deposited to EMDB
5. Better methods/standards for defining EM map analysis parameters (e.g. contour levels)
6. Develop plans for future competitions, including improved model submission guidelines

Timeline for Completion

Step 0	Oral Report from the other evaluators	June 15, 2017
Step 1	collect written summary report outcomes of analysis from evaluators	July 1, 2017
Step 2	provide the evaluators the description of the workflow from the challengers	July 10 2017
Step 3	distribute the reports to the challengers	July 21 2017
Step 4	Feedbacks from challengers	August 15 2017
Step 5	refine the evaluators reports	Sept 1 2017
Step 6	Face to face meeting	Oct 5-8 2017