title: Secondary structure prediction - gory details
short title: pp1_SecStrPred_2

lecture: Protein Prediction 1 - Protein structure for Computational Biologist - TUM Summer 2015
Videos:  YouTube / www.rostlab.org

THANKS:
Tim Karl + Carlo Di Domenico

Special lectures:
• 06/18 Thomas Hopf (contacts)

No lecture:
• 05/12 Student assembly (SVV)
• 05/14 Ascension day
• 05/26 Whitsun holiday
• 06/04 Corpus Christi

LAST lecture:  July 7
Examen:  July 9
• Makeup:  Oct 13, 2015 - morning/noon

CONTACT: Inga Weise assistant@rostlab.org

Let it go. Let it out. Let it all unravel. Let it free and it can be.
A path on which to travel.
carlo.de-domenico@tum.de

Announcements

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• Makeup:  Oct 13, 2015 - morning/noon
Today: Secondary structure prediction 1

☐ LAST WEEKs
  • 3D->1D: secondary structure assignment/Prediction

☐ THIS WEEK
  • Secondary structure prediction methods - details

☐ NEXT WEEK
  • Transmembrane prediction
1D prediction: gory details
PHDsec: the un-g(l)ory details

76% is average over distribution: \( \approx 10\% \)
Prediction accuracy varies!

\[ \langle Q_3 \rangle = 72.3\% \; ; \; \sigma = 10.5\% \]
PHDsec: the un-g(l)ory details

- 76% is average over distribution: $\approx 10\%$
- stronger predictions more accurate
Stronger predictions more accurate!

$Q_3$ per protein

fit: $Q_3$ fit = 21 + 8.7 * $Q_3$

H = 0.5  H = 0.8
E = 0.4  E = 0.1
L = 0.1  L = 0.1

$<Q_3>$ = 72.3% ; sigma = 10.5%

Per-residue accuracy ($Q_3$)

Number of protein chains

Reliability index averaged over protein
76% is average over distribution: $\approx 10\%$

- stronger predictions more accurate
- WARNING: reliability index almost factor 2 too large for single sequences
**Details PHDsec: Multiple alignment**

- single sequences => accuracy clearly lower

<table>
<thead>
<tr>
<th>id</th>
<th>nali</th>
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FAQ of secondary structure prediction

- What is the best alignment?
- Limit of prediction accuracy reached?
- Comparative modeling or de novo?
- Ultimate rôle in structure prediction (1D-3D)?
- Will secondary structure and 3D prediction merge completely?
FAQ of secondary structure prediction

What is the best alignment?
Evolution has it!

Sequence identity implies structural similarity!

Don't know region
Different alignment strategies

<table>
<thead>
<tr>
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*significant difference > 0.44*
## Different alignment strategies

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*significant difference* > 0.44  > 0.44
Small vs. big

A: BLAST-E cut-off < 1

B: BLAST-E cut-off < 10^{-20}

C:
# Different alignment strategies 3

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<td>&gt; 0.44</td>
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# Accuracy vs. E-value BLAST

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<th>E-value $^b$</th>
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<td>9.5</td>
<td>5.0</td>
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<tr>
<td>1</td>
<td>9.7</td>
<td>5.2</td>
</tr>
<tr>
<td>$10^{-1}$</td>
<td>9.5</td>
<td>5.3</td>
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<td>$10^{-2}$</td>
<td>9.2</td>
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<td>4.5</td>
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*significant difference* $>0.44$ $>0.39$
# Accuracy vs. E-value PSI-BLAST

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significant difference $>0.44$ $>0.3$
# Accuracy vs. pollution

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<th>h 10&lt;sup&gt;-10&lt;/sup&gt;&lt;sup&gt;c&lt;/sup&gt;</th>
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<tr>
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<td>filtered&lt;sup&gt;d&lt;/sup&gt;</td>
<td>non-filtered&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>1</td>
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<tr>
<td>2</td>
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<td>9.8</td>
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<td>6</td>
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<tr>
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<td>8.1</td>
<td>7.4</td>
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*significant difference*  

>0.44 >0.44 >0.44 >0.44
PSI-BLAST not always best

Prediction accuracy using pairwise BLAST

Prediction accuracy using iterated PSI-BLAST
More = better?
Data deluge not enough for greedy bioinformaticians
FAQ of secondary structure prediction

What is the best alignment?
FAQ of secondary structure prediction

What is the best alignment? ✝️...

... that depends
FAQ of secondary structure prediction

- What is the best alignment? that depends
- Limit of prediction accuracy reached?
- Comparative modeling or de novo?
- Ultimate rôle in structure prediction (1D-3D)?
- Will secondary structure and 3D prediction merge completely?
1D secondary structure prediction: Quo vadis?
How to assess secondary structure prediction methods?
How to assess performance?
Art 2 Assess: Truth from where

☐ Standard of truth:
  PDB -> DSSP -> string HEL
Art 2 Assess: data set size

many many many many?
Art 2 Assess: data set size

many many many many?
Art 2 Assess: data set size

\[
\langle Q_3 \rangle = 72.3\% \text{ ; } \sigma = 10.5\%
\]

Number of protein chains

Per-residue accuracy \((Q_3)\)
Some 500+ proteins appear to work

ANY 500+ do?
Art 2 Assess: data set size

☐ ANY 500+ do?
   NO
   we need to sample the “true distribution”

☐ (redundancy reduction/bias reduction)
Art 2 Assess: standard error

- standard deviation ~ 10% (in Q3)
- assume 2500 “effective” proteins in data set
Art 2 Assess: standard error

- standard deviation ~ 10% (in Q3)
- assume 2500 “effective” proteins in data set

- method 1: Q3=76.521%
- method 2: Q3=76.301%

Do they differ?
Art 2 Assess: standard error

- $\sigma \sim 10\%$ (in Q3) / nprot=2500

- method 1: Q3=76.521%
- method 2: Q3=76.301%

- Rule of thumb: $\text{StdError} = \frac{\sigma}{\sqrt{nprot}}$ -> 0.2%

- YES, the difference is statistically significant (although borderline)
Art 2 Assess: standard error

- $\sigma \sim 10\% \text{ (in Q3)} / n_{prot}=2500$

- method 1: Q3=76.521%
- method 2: Q3=76.301%

Rule of thumb: StdError = $\sigma / \sqrt{n}_{prot}$

- $\rightarrow 0.2\%$

- YES, the difference is statistically significant (although borderline)
Art 2 Assess: standard error

- $\sigma \sim 10\% \text{ (in Q3)} / n_{prot}=2500$

- method 1: Q3=76.521%
- method 2: Q3=76.301%

- Rule of thumb: $\text{StdError} = \frac{\sigma}{\sqrt{n_{prot}}}$
  -> 0.2%

- YES, the difference is statistically significant (although borderline)
Art 2 Assess: data set size

☑ ANY 500+ do?
    NO
    we need to sample the “true distribution”

☑ (redundancy reduction/bias reduction)

☑ is that ENOUGH?
Art 2 Assess: data set

anything else to consider in choosing the data set?
Art 2 Assess: data set

set of sequence-unique/unbiased proteins that are ideally also sequence-unique/unbiased with respect to anything used to develop the methods to assess

-> NEW proteins
Art 2 Assess: standard error

- $\sigma \sim 10\%$ (in Q3) / nprot=100

- method 1: Q3=76.521%
- method 2: Q3=76.301%

Rule of thumb: StdError $= \frac{\sigma}{\sqrt{nprot}}$

$\Rightarrow$ 1%

- YES, the difference is statistically significant (although borderline)
Art 2 Assess: anything else?

Anything else to consider?
Evaluation alternatives

- Method 1 predicts proteins
  P1, P2, P3, P4, P5, P6, P7, P8, P9, P10, P11

- Method 2 predicts
  P2, P4, P6, P8, P10, P11

- Method 3:
  P1, P3, P5, P7, P9, P10, P11

- Method 4:
  P0, P10, P11
Ranking not stable!

29 different worse than 11 identical

Compare methods on identical data sets!!

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
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<tr>
<td>D</td>
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EVA: automatic continuous EVALuation of structure prediction

Satellites/Mirrors

CUBIC Columbia
Rockefeller
CNB Madrid

secondary structure, fold recognition
comparative modelling, fold recognition
inter-residue contacts / distances

Get PDB
Analyse: pairwise BLAST
EVA-DB
Send sequences

META-PP
Collect
Send

Compile results at
EVA - SATELLITES
summary
week
one protein
PDB vs prediction

Results
static
pages

EVA - Mirrors

User
- browse
- query
- ftp

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# EVA: secondary structure

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<tr>
<th>Method</th>
<th>$Q_3^C$</th>
<th>$Q_3^D$ Claim</th>
<th>SOV $^E$</th>
<th>Info $^F$</th>
<th>CorrH $^G$</th>
<th>CorrE $^H$</th>
<th>CorrL $^I$</th>
<th>Class $^K$</th>
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76%
Secondary structure predictions differ
Accuracy varies for proteins!

![Graph showing the accuracy of various protein prediction tools.](image)

- PSIPRED
- SSpro
- PROF
- PHDpsi
- PHD
- JPred2
- PHD

Percentage of all 150 proteins

Percentage correctly predicted residues per protein

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Some proteins predicted better
Averaging over many methods not always good!

Per-protein prediction accuracy averaged over 6 methods
Reliability correlates with accuracy!
Secondary structure prediction 2005

- **history**
  - 1st generation 50-55%
  - 2nd generation 55-62%
  - 3rd generation 1992 70-72%
    - 2000 > 76%
    - 2010 > 78%
# Secondary structure prediction 2005

## History

<table>
<thead>
<tr>
<th>Generation</th>
<th>Year</th>
<th>Accuracy (%)</th>
<th>Value</th>
<th>Improvement</th>
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<td>2nd generation</td>
<td>1980s</td>
<td>55-62%</td>
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<td>7</td>
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<td>3rd generation</td>
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<td>70-72%</td>
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<td>2000</td>
<td>&gt; 76%</td>
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<td>2011</td>
<td>&gt; 78%</td>
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## Secondary structure prediction 2005

### History

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<td>2011</td>
<td>&gt; 78%</td>
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<td>+ 2</td>
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</table>

### What improves (2002)?

- Database growth: +3
- PSI-BLAST: +0.5
- New training: +1
- ‘Clever method’: +1
Quo vadis?

- 1980: 55% simple
- 1990: 60% less simple
- 1993: 70% evolution
- 2000: 76% more evolution
- 2011: 78% even more evolution

what is the limit?
Quo vadis?

- 1980: 55% simple
- 1990: 60% less simple
- 1993: 70% evolution
- 2000: 76% more evolution
- 2011: 78% even more evolution

What is the limit?

- 88% for proteins of similar structure
- 80% for 1/5th of proteins with families > 100
Quo vadis?

- 1980: 55% simple
- 1990: 60% less simple
- 1993: 70% evolution
- 2000: 76% more evolution
- 2011: 78% even more evolution

What is the limit?
- 88% for proteins of similar structure
- 80% for 1/5th of proteins with families > 100
- Missing:
  - Better definition of secondary structure
    - Including long-range interactions
  - Structural switches
  - Chameleon / folding
Conclusion: secondary structure prediction

- big gain through using evolutionary information
- are we going to reach above 80%? How high?
- continuous secondary structure
- better methods
- other features
- use secondary structure: ASP

FAQ of secondary structure prediction

☐ What is the best alignment? that depends
☐ Limit of prediction accuracy reached? no
☐ Comparative modeling or de novo? specialist is best
☐ Ultimate rôle in structure prediction (1D-3D)?
☐ Will secondary structure and 3D prediction merge completely?
Lecture plan (PP1 structure)

01: 04/14 Tue: no lecture
02: 04/16 Thu: no lecture
03: 04/21 Tue: Organization of lecture: intro into cells & biology
04: 04/23 Thu: Intro I - acids/structure
05: 04/28 Tue: Intro 2 - domains
06: 04/30 Thu: Intro 3 - 3D comparisons
07: 05/05 Tue: Alignment 1
08: 05/07 Thu: Alignment 1 contd.
09: 05/12 Tue: SKIP: student assembly (SVV)
10: 05/14 Thu: SKIP: Ascension Day
11: 05/19 Tue: Open questions
12: 05/21 Thu: Alignment 2
13: 05/26 Tue: SKIP: Whitsun holiday (05/23-26)
14: 05/28 Thu: Alignment 3 / Comparative modeling 1
15: 06/02 Tue: Experimental structure determination / 3D -> 1D: Secondary structure assignment
16: 06/04 Thu: SKIP: Corpus Christi
17: 06/09 Tue: 1D: Secondary structure prediction 1
18: 06/11 Thu: 1D: Secondary structure prediction 2
19: 06/16 Tue: 1D: Transmembrane structure prediction 1
20: 06/18 Thu: 1D: Solvent accessibility prediction
21: 06/23 Tue: 1D: Disorder prediction
22: 06/25 Thu: 2D prediction
23: 06/30 Tue: 3D prediction 1
24: 07/02 Thu: Nobel prize symposium
25: 07/07 Tue: wrap up
26: 07/09 Thu: examen, no lecture
27: 07/14 Tue: examen alternative, no lecture
28: 07/16 Thu: