Announcements

- Videos: SciVee
  www.rostlab.org

THANKS:
  Tim Karl -
  Manfred - Dominik

- LAST lecture: Feb 2
- Examen: Feb 9, 10:30 (likely Multimedia room)
  • Makeup: May 6
EVAlation
V.

SNAP: Screening for Non-Acceptable Polymorphisms
V.1. SNAP Intro
Predict protein function
Big changes may not matter!

Sequence identity implies structural similarity!

C Sander & R Schneider 1991 Proteins 9:56-68
B Rost 1999 Prot Engin 12:85-94
SNPs are changes of one single nucleotide / letter

SNPs are changes of one single nucleotide / letter

Wikipedia
Discover diversity and movement

“Bushmen ... more different from each other than ... European and Asian”

“migration from Siberia into New World ... 5,500 years ago, independent of ... Native Americans and Inuit”
Yana Bromberg, Rutgers University
non-synonymous SNP = nsSNP

Mutation

SNP – single nucleotide polymorphism
Coding region SNP
nsSNP – non-synonymous SNP

DNA
ACGGACGGACTCTCATATATACTACTCCTTGATGGGCTCCGAAATATG

Non-coding region
Coding region

Protein: MGSEIC
non-synonymous SNP = nsSNP

Mutation

SNP – single nucleotide polymorphism
Coding region SNP
nsSNP – non-synonymous SNP

DNA
ACGGACCGAACCTCTCATATATACACTACTCCTTGATGGGCTCCGAAATATG

Non-coding region
Coding region

Protein: MGSEI0
SNP risk classification

Non-sense
Splicing regulation
**Mis-sense/non-synonymous (nsSNPs)**
Regulatory region
Post-transcriptional regulation
Untranslated / up- or downstream

V.2. Other methods
Test Set: 3 proteins, ~6500 mutants
PolyPhen

Test Set: 1551 SWISS-PROT & 440 cross-species variants

SNPs3D

Train/Test Set: 3768 HGMD variants and 2309 cross-species variants

nsSNP effects: some in silico methods

- **SIFT**
P C Ng & S Henikoff (2003) NAR 31:3812-14

  > Sequence
  VHLTP EKSA VTALWGKVNV
  DEVGGEALGR LLVVYPWTQR
  FFESFGDLST PDAVMGNPKV
  KAHGKKVLGA
  Mutant: E6V

- **PolyPhen**

  > Sequence
  VHLTP EKSA VTALWGKVNV
  DEVGGEALGR LLVVYPWTQR
  FFESFGDLST PDAVMGNPKV
  KAHGKKVLGA
  Mutant: E6V

- **SNPs3D**
P Yue, Z Li & J Moult (2005) JMB 353:459-63
## Prediction Performance Comparison

**SDM, Crescendo, (PICCOLO, CREDO and BIPA), SIFT, MUpro, MAPP and I-Mutant2.0**

<table>
<thead>
<tr>
<th>Method</th>
<th>TP</th>
<th>FP</th>
<th>TN</th>
<th>FN</th>
<th>Sum</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDM</td>
<td>535</td>
<td>274</td>
<td>4594</td>
<td>3025</td>
<td>8428</td>
<td>15.03</td>
<td>94.37</td>
<td>60.86</td>
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<tr>
<td>Crescendo</td>
<td>186</td>
<td>126</td>
<td>4482</td>
<td>3695</td>
<td>8489</td>
<td>4.79</td>
<td>97.27</td>
<td>54.99</td>
</tr>
<tr>
<td>PICCOLO</td>
<td>220</td>
<td>257</td>
<td>4920</td>
<td>3746</td>
<td>9143</td>
<td>5.55</td>
<td>95.04</td>
<td>56.22</td>
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<tr>
<td>CREDO</td>
<td>380</td>
<td>413</td>
<td>4764</td>
<td>3586</td>
<td>9143</td>
<td>9.58</td>
<td>92.02</td>
<td>56.26</td>
</tr>
<tr>
<td>BIPA</td>
<td>80</td>
<td>20</td>
<td>5157</td>
<td>3886</td>
<td>9143</td>
<td>2.02</td>
<td>99.61</td>
<td>57.28</td>
</tr>
<tr>
<td>COMBINED</td>
<td>1252</td>
<td>984</td>
<td>4193</td>
<td>2714</td>
<td>9143</td>
<td>31.57</td>
<td>80.99</td>
<td>59.55</td>
</tr>
<tr>
<td>SIFT</td>
<td>2709</td>
<td>2071</td>
<td>3011</td>
<td>1092</td>
<td>8883</td>
<td>71.27</td>
<td>59.25</td>
<td>64.39</td>
</tr>
<tr>
<td>MAPP</td>
<td>2659</td>
<td>1642</td>
<td>2395</td>
<td>1065</td>
<td>7761</td>
<td>71.40</td>
<td>59.33</td>
<td>65.12</td>
</tr>
<tr>
<td>I-Mutant2.0</td>
<td>1485</td>
<td>1677</td>
<td>2189</td>
<td>1061</td>
<td>6412</td>
<td>58.33</td>
<td>56.62</td>
<td>57.30</td>
</tr>
<tr>
<td>MUpro</td>
<td>175</td>
<td>146</td>
<td>5031</td>
<td>3791</td>
<td>9143</td>
<td>4.41</td>
<td>97.18</td>
<td>56.94</td>
</tr>
</tbody>
</table>

Table 1. TP= True Positives, FP= False Positives, TN= True Negatives. TP/FP/TN/FN are numbers of unique mutations. The Sum column shows the number of times the method succeeded and an observation was possible and therefore reflects the robustness of the method. Sensitivity, Specificity and Accuracy defined in text.
V.3. SNAP data
Misfunction/neutral
ENTRY A000006 - Variant 2616650
CROSS-REFERENCE MC4R_HUMAN
PROTEIN Melanocortin 4 receptor (MC4R);
CHANGE-POINT Asn 62 Ser (homozygous)
DISEASE In obesity
FUNCTION Responsiveness to alpha-MSH [-]

Non-neutral: 40,641
Neutral: 14,334

SNAP data: neutral

EC# = general_class . acts_on_class . further_class_spec . spec_by_substrate_class
3.1.3.48 → hydrolase . on ester bonds . phosphoric monoester cmpnds . PTP-phosphotase

Same EC# = Same Function

Query: 61

YYQLFEMLNKVGAFOHLRLKEHTHTVFNKGGRTGALDFRFTGAPFNLKAFHTTSQLSL 120
YY LF LM KVGA +LRLKEHTHTFVN+GGR G LDFRF TGAPFNGLKAFFTTSQL

Sbjct: 61

YYNLFNLMENVKGAKQNLRLKEHTHTFVNQGGRIGELDFRFTGAPFNGLKAFFTTSQDLT 120

Neutral: 26,840

Availability of data for nsSNP limiting

<table>
<thead>
<tr>
<th></th>
<th>Non-neutral</th>
<th>Neutral</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMD</td>
<td>40,641</td>
<td>14,334</td>
</tr>
<tr>
<td>EC</td>
<td>26,840</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>40,641</td>
<td>41,174</td>
</tr>
</tbody>
</table>

81,815 mutants
6,821 proteins
# SNAP data: by accessibility

<table>
<thead>
<tr>
<th></th>
<th>Proteins</th>
<th>Effect</th>
<th>Neutral</th>
<th>Total</th>
<th>Ratio neutral to non-neutral</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>6413</td>
<td>39987</td>
<td>40830</td>
<td>80817</td>
<td>1.02</td>
</tr>
<tr>
<td><strong>Buried</strong></td>
<td>5144</td>
<td>19741</td>
<td>14800</td>
<td>34541</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td>4841</td>
<td>12285</td>
<td>13073</td>
<td>25358</td>
<td>1.06</td>
</tr>
<tr>
<td><strong>Exposed</strong></td>
<td>4150</td>
<td>7961</td>
<td>12957</td>
<td>20918</td>
<td>1.62</td>
</tr>
</tbody>
</table>
SNAP: results
SNAP: input features

SNAP
- Biochemical characteristics
- Alignment profiles
- Probability of residue triplets
- Pfam domains
- Solvent accessibility
- Secondary structure
- Residue flexibility

SNAPannotated
- SWISS-PROT annotations
- SIFT predictions
SNAP: neural network

Prob. (TNR) > ? Prob. (TLR)
SNAP: neural network

<table>
<thead>
<tr>
<th>SNP effect</th>
<th>Node score</th>
</tr>
</thead>
<tbody>
<tr>
<td>neutral</td>
<td>min</td>
</tr>
<tr>
<td>non-neut</td>
<td>max</td>
</tr>
</tbody>
</table>

SNP effect | Node score |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>neutral</td>
<td>max</td>
</tr>
<tr>
<td>non-neut</td>
<td>min</td>
</tr>
</tbody>
</table>
SNAP: neural network

<table>
<thead>
<tr>
<th>SNP effect</th>
<th>Node score</th>
</tr>
</thead>
<tbody>
<tr>
<td>neutral</td>
<td>min</td>
</tr>
<tr>
<td>non-neut</td>
<td>max</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<th>Node score</th>
</tr>
</thead>
<tbody>
<tr>
<td>neutral</td>
<td>max</td>
</tr>
<tr>
<td>non-neut</td>
<td>min</td>
</tr>
</tbody>
</table>

Score: $-100 \leq S \leq 100$
SNAP clearly best for subtle cases

<table>
<thead>
<tr>
<th>PMD/EC data</th>
<th>Unknown</th>
<th>Accuracy Non-Neutral</th>
<th>Coverage Non-Neutral</th>
<th>Accuracy Neutral</th>
<th>Coverage Neutral</th>
<th>Overall two-state accuracy (Q2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIFT</td>
<td>2374 (3%)</td>
<td>79.8+/-0.6</td>
<td>63.4+/-1.2</td>
<td>70.1+/-2.7</td>
<td>84.3+/-1.2</td>
<td>74.0+/-1.4</td>
</tr>
<tr>
<td>PolyPhen</td>
<td>1647 (2%)</td>
<td>79.1+/-0.7</td>
<td>66.9+/-1.4</td>
<td>71.8+/-2.7</td>
<td>82.7+/-1.1</td>
<td>74.9+/-1.3</td>
</tr>
<tr>
<td>SNAP</td>
<td>0</td>
<td>76.3+/-0.8</td>
<td>83.3+/-1.0</td>
<td>82.0+/-2.4</td>
<td>74.7+/-2.2</td>
<td><strong>78.9+/-1.3</strong></td>
</tr>
</tbody>
</table>

Accuracy = \(100 \times \frac{\text{# correct predictions}}{\text{total # of predictions}}\)

Coverage = \(100 \times \frac{\text{# correct predictions}}{\text{total # of observations}}\)

Y Bromberg & B Rost 2007 NAR 35:3823-35
SNAP clearly best for subtle cases

<table>
<thead>
<tr>
<th>PMD/EC data</th>
<th>Unknown</th>
<th>Accuracy</th>
<th>Coverage</th>
<th>Accuracy</th>
<th>Coverage</th>
<th>Overall two-state accuracy (Q2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td></td>
</tr>
<tr>
<td>SIFT</td>
<td>2374 (3%)</td>
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<td>0</td>
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<td>74.7 +/- 2.2</td>
<td>78.9 +/- 1.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>“Hard” PMD/EC data</th>
<th>Correct classification</th>
<th>Incorrect classification</th>
<th>Overall two-state accuracy (Q2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIFT</td>
<td>7,566</td>
<td>8,675</td>
<td>46.6%</td>
</tr>
<tr>
<td>PolyPhen</td>
<td>7,966</td>
<td>8,275</td>
<td>49.1%</td>
</tr>
<tr>
<td>SNAP</td>
<td>10,124</td>
<td>6,117</td>
<td>62.3%</td>
</tr>
</tbody>
</table>

Accuracy = \(100 \times \frac{\text{# correct predictions}}{\text{total # of predictions}}\)

Coverage = \(100 \times \frac{\text{# correct predictions}}{\text{total # of observations}}\)
SNAP in Pictures

80,000 mutants w/known effects on function

Accuracy = 100 * \(\frac{\text{# correct predictions}}{\text{total # of predictions}}\)

Coverage = 100 * \(\frac{\text{# correct predictions}}{\text{total # of observations}}\)

© Yana Bromberg, 2010 Columbia University

Y Bromberg & B Rost 2007 NAR 35:3823-35

© Burkhard Rost (TU Munich)
SNAP performance by exposure
SNAP reliability index

Predictions

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.8</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td>0.49</td>
<td></td>
</tr>
</tbody>
</table>
SNAP reliability index

Cumulative accuracy vs. cumulative percentage predicted with $RI \geq n$ for non-neutral (red) and neutral (green) cases.
SNAP RI ~ severity of change

Normalized percentage of predictions

Neutral
Intermediate
Severe

Difference between two SNAP output units

© Burkhard Rost (TU Munich)
## SNAP: examples

<table>
<thead>
<tr>
<th>Gene</th>
<th>nsSNP</th>
<th>Disease</th>
<th>Function</th>
<th>Prediction (RI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HXK4</td>
<td>S131P</td>
<td>Diabetes Mellitus</td>
<td>Significant increase in affinity for ATP</td>
<td>Non-neutral (2)</td>
</tr>
<tr>
<td>PAX6</td>
<td>G64V</td>
<td>Cataract</td>
<td>Reduction of DNA binding activity</td>
<td>Non-neutral (5)</td>
</tr>
<tr>
<td>MC4R</td>
<td>I301T</td>
<td>Obesity</td>
<td>Severe change of basal activity &amp; EC50</td>
<td>Non-neutral (3)</td>
</tr>
<tr>
<td>HXK4</td>
<td>M107T</td>
<td>Polymorphism</td>
<td>Not conclusive</td>
<td>Neutral (0)</td>
</tr>
<tr>
<td>CFTR</td>
<td>P1013L</td>
<td>Cystic Fibrosis</td>
<td>Not conclusive</td>
<td>Non-neutral (5)</td>
</tr>
<tr>
<td>NKX25</td>
<td>A127G</td>
<td>Secundum atrial septal defect</td>
<td>Not conclusive</td>
<td>Neutral (6)</td>
</tr>
<tr>
<td>HBB</td>
<td>R104T</td>
<td>Polymorphism</td>
<td>Not conclusive</td>
<td>Non-neutral (3)</td>
</tr>
<tr>
<td>P53</td>
<td>R337H</td>
<td>Adrenocortical carcinoma</td>
<td>Does not affect transactivation capacity</td>
<td>Non-neutral (3)</td>
</tr>
</tbody>
</table>
SNAP input detail
Annotations help

![Bar chart showing percentage of SNPs predicted correctly and number of SNPs predicted correctly for annotation, alignment, and all combined.]
Crucial sites identified in insulin

http://www.rostlab.org/servers/SNAP/

Y Bromberg & B Rost
2007 NAR 35:3823-35

Y Bromberg G
Yachdav & B Rost
2008 Bioinformatics 15:2397-8

model: SWISS-MODEL
SNAP: results
New directions

- in silico alanine scan
- comprehensive in silico mutagenesis
- prediction of binding hot spots

Y Bromberg & B Rost (2008) Bioinformatics 24: i207-212
Targeted Mutagenesis

Ala, Cys, Gly,…

Residue Scan

Ala
In silico mutagenesis

Targeted Mutagenesis

Residue Scan

comprehensive all against 19 non-native
Prediction and mutagenesis

>MC4R_HUMAN
MVNSTH|RMGMTSLHLWNRSSYRLHSASESSLGKGYSDG
GCEYQVFVSPEVFVTGVSLLLLENLVIAIAKNKNLHSPMY
FFICSLAVADMLVSNSGSETIVITLNLNSTDTDAQSFTVNI
NVIDSVICSSLLASICSLLSIAVDRYFTIFYALQYHNIIMTVKR
VGIINISCIWAACTVGILFIYSDSSAVIICLITMFFTMLALMAS
LYVHMFLLARLHIIKRIAVLPGTGAIROQANMKGAFTLTILIG
VFVVCWAPFLLHLIFYISCQNPYCVCFSVHFNLVLYLILIMCN
SIIDPLIYALRSQELRKTKEIICCYPLGGLCDLSSRY

<table>
<thead>
<tr>
<th>nsSNP</th>
<th>Prediction</th>
<th>Reliability</th>
<th>Exp Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>R7H Neutral</td>
<td>5</td>
<td>89%</td>
<td></td>
</tr>
<tr>
<td>S30F Non</td>
<td>4</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>E100A Non</td>
<td>3</td>
<td>78%</td>
<td></td>
</tr>
</tbody>
</table>

R7H, S30F, E100A

Y Bromberg & B Rost 2008 Bioinformatics 24: i207-212

slide: © Yana Bromberg
MC4R_HUMAN
MVNSTHRGMHTSLHLWNRSSYRLHSNASESLGKGYSDG
GCYEQLFVSPEVFVTGVISSLLENILVIVAIAKKNKLHSPMY
FFICSLAVADMLVSVNSGETIVITLLNSTDTDNASFTVNI
NVIDSVICSSALLASICSLLSSIAVDRYFTIFYALQYHNI
MTVKRVGIIISCIWAATVSGILFIYSDDSAVIICLITMFFMLAL
MASYLVHMFMLARLHIKRIAULPGTAGAINMKGAITLTILIG
VFVVCWAPFFLHLIFYISCPQNYVCFSMNLYLILIMCN
SIIDPLIALRSEQELRKTFKIEICCYPGLCDLSSRY

R7H, S30F, E100A

ALL MUTANTS
(19 substitutions per position)

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</tr>
</tbody>
</table>

Y Bromberg & B Rost 2008 Bioinformatics 24: i207-212

slide: © Yana Bromberg

© Burkhard Rost (TU Munich)
Prediction and mutagenesis

>MC4R_HUMAN
MVNSTHRGMHTSLHLWNRSSYRLHSNASESLGKGYSDG
GCYEQLFVSPEVFVTGVLGILLENILVIVAIAKKNKLNHPMY
FFICSLAVADMLVSVSNGETIVITLLNSTDTDAQSFTVNI
NVIDSVICSSLICSSLISIAVDRYFTIFYALQYHNMTVKR
VGIIIACWAATVSGIYIPSDSSAVIICLTMFFMLAMAS
LYVHMLMARLIKRIAVLPGTAIRQGANMKGAIITLILIG
VFVVCWAPFFLHFLFYSCPQNYCVCFSNFNYLILIMCN
S11DDPLIYALRSQELRKTKEIICCYPLGGLCDLSSRY

<table>
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<td>3</td>
<td>78%</td>
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</table>

R7H, S30F, E100A

ALL MUTANTS (19 substitutions per position)

ALL PREDICTIONS (19 substitutions per position)

Y Bromberg & B Rost 2008 Bioinformatics 24: i207-212

slide: © Yana Bromberg

© Burkhard Rost (TU Munich)
In silico “alanine” scan

Correlation of average over 19 possible SNAP predictions per location to single residue scores

Y Bromberg & B Rost 2008 *Bioinformatics* 24: i207-212
Mutation effects reveal functional units
Protein-protein hot spot binding
Protein-protein hot spot binding

![Graph showing the number of samples in given ddG range for non-neutral and neutral cases.]

![Graph showing the absolute value of ddG against reliability index with prediction direction.]

Friday January 28, 2011
Predict binding hotspots

Varying SNAP cutoff for hot spot classification
(DeltaG cutoff >= 1kCal/mol)

Accuracy vs. Coverage

Y Bromberg & B Rost (2008) Bioinformatics 24: i207-212
Important residues in binding sites

Y Bromberg & B Rost 2007 NAR 35:3823-35
Y Bromberg G Yachdav & B Rost 2008 Bioinformatics 15:2397-8
Functional residues

Mean over non-native  Conservation  Other scoring
In silico mutagenesis

Experimental

Lacl repressor from E. coli
4011 mutants (12-13 substitutions/residue)
SNAP prediction accuracy: ~73%

Experimental: P Markiewicz et al. 1994 JMB 240:421-33
Y Bromberg & B Rost unpublished
In silico mutagenesis

Experimental

Predicted (SNAP)

LacI repressor from E. coli
4011 mutants (12-13 substitutions/residue)
SNAP prediction accuracy: ~73%

Experimental: P Markiewicz et al. 1994 JMB 240:421-33
Y Bromberg & B Rost unpublished

© Yana Bromberg, 2010 Columbia University
Melanocortin receptor (MC4R)

Y Bromberg et al. 2009 FASEB 9:3059-69

© Burkhard Rost (TU Munich)
Differential view on 2 similar receptors

Y Bromberg et al. 2009 FASEB 9:3059-69
Honorary Co-Chairs

Peter Schuster
Univ. Vienna, Austria

Kurt Zatloukal
Genome-Austria Tissue Bank Graz, Austria

ISCB Conferences Director

Steven Leard
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# Key Submission Deadlines

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<tr>
<th>Event</th>
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<tr>
<td>Special Interest Groups</td>
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<td>Tutorials</td>
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**Note:**
- Visit the ISMB/ECBB 2011 website for more details.
- Use the Google search query “ismbeccb 2011” for additional information.