Seminar Bioinformatics:
Modulation of Protein-Protein-Interactions

PERLA
Computer-aided design of proteins

- Oliver Mueller -

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Roadmap

- Introduction to computer-aided design of proteins
  - What?
  - Why?
  - Methods (classical vs. computer-aided)
  - The PDZ domain as an example
- PERLA (Functionality)
- Computer-aided design of a PDZ domain via PERLA
- Results
  - Binding affinity and specificity of designed PDZ domains
  - Validation of PERLA
- Conclusions
  - Pros and Cons
  - Future
- References & discussion
Introduction
What is computer-aided design of proteins?

- entails the use of computational methods to develop novel proteins

Source:
- image of the left PDZ domain taken from http://bcz102.ust.hk/Protein_Structure_Gallery.html
- images of the right PDZ domains taken from http://www.fmp-berlin.de/nmr/pdz/pdz_index.html
Introduction
What is computer-aided design of proteins?

- mostly protein cores have been re-designed
- but automatic design of an entire protein also is possible (e.g. re-design of *Betanova* [2])

Figure 10. Superposition of the NMR and PERLA-modelled structure of peptide LLM. The backbone is shown in grey and side-chains from residues 3, 5, 12, 15 and 17 are in blue (NMR) and in red (PERLA).

Source:
- image taken from reference [2]
Introduction

Why do we do computer-aided design of proteins?

- helps to understand protein folding and structure
- allows to randomize the interaction surface of one or more protein-binding domains and thus speeds up the screening process (protein identification and purification)
- important role in modern molecular and cell biology research
- pushes on drug design
Introduction
Classical methods in protein identification

- raising primary antibodies
- affinity chromatography
- pull down experiments
- western blotting

(Source: image taken from http://www.vu-wien.ac.at/i123/allvir/WesternB.html)

⇒ very time consuming lengthy procedures
Introduction
Computer-aided methods in protein identification

- rational design at an early stage to reduce the number of possible solutions (drug discovery)

- disadvantage: these computational methods require precise 3D information of the molecules (binding domain & ligand) ⇒ limitation
Introduction

Computer-aided methods in protein identification

- use nonstructured stretches in the target protein (the protein to be bound) sequence that adopt a particular conformation upon interaction with the binding domain

- condition frequently met by C-termini (nonstructured and solvent accessible in most proteins)

- C-termini in several organisms have complex sequences, so that the last 4 amino acid residues are sufficient to uniquely specify ~74-97% of the proteins
Introduction
Computer-aided methods in protein identification

- explore the possibility to use C-termini as target for antibody binding

- **PERLA**

⇒ safes time and money + other advantages

Source:
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Introduction

PDZ domains

- PDZ domains are small globular domains of 80-90 residues that fold into a structure with a $\beta$-sandwich of 5-6 $\beta$-strands and two $\alpha$-helices.

Source: image taken from http://www.mshri.on.ca/pawson/images/domains/pdz/PDZ.jpg
Introduction
PDZ domains

- peptide ligand binding:

The peptide ligand binds in a hydrophobic cleft composed of a β-strand (βB), an α-helix and a loop that binds the peptide carboxylate group. It binds in an anti-parallel fashion to the βB strand, with the C-terminal residue occupying a hydrophobic pocket.

Source: image taken from http://www.mshri.on.ca/pawson/images/domains/pdz/PDZ.jpg
Introduction

PDZ domains

- **domain binding and function (I):**
  PDZ heterodimers form a linear head-to-tail arrangement that involves recognition of an internal residue on one of the partner proteins.

PDZ domains bind to the C-terminal 4-7 residues of their target proteins, frequently transmembrane receptors or ion channels.

ribbon model of the nNOS (green) syntrophin A (gold) PDZ heterodimer

*Source: image taken from http://www.xrayce.com/bioinfo/pdz.html*
Introduction

PDZ domains

- *domain binding and function (II):*
  PDZ domains can also heterodimerize with PDZ domains of different proteins, potentially regulating intracellular signalling.

Specificity of PDZ-ligand recognition due to side-chain side-chain interaction and positioning of an $\alpha$-helix involved in ligand binding.
Introduction
PDZ domains

- an example for PDZ/PDZ interaction:
  - PDZ domain protein:
    Post-Synaptic Density protein 95 (PSD-95)
  - binding partner:
    neural Nitric Oxide Synthase (nNOS) via PDZ2
  - binding site:
    PDZ/PDZ interaction

- understanding of binding behaviour allows better design of artificial binding partners for chemotherapy
Roadmap

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  - Why?
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  - The PDZ domain as an example

- PERLA (Functionality)
PERLA
Overview (I)

- PERLA:
  Protein Engineering Rotamer Library Algorithm
- developed 1999 by Emmanuel Lacroix
- structure energy-based computer program
- builds selected amino acids in a polypeptide template
- enables identification and sorting of amino acid sequences with optimal stability for a desired 3D structure
- allows the generation of single and multiple residue mutants of a protein
PERLA
Overview (II)

- uses a scoring function which uses an all-atom molecular mechanics force field (ECEPP/2)* to calculate the interaction energies

- performs strict inverse folding:
  - a fixed backbone structure is decorated with amino acid side-chains from a Rotamer Library (thus the name PERLA)

- dead-end elimination:
  - reduces sequence space to increase the performance of the algorithm

* Empirical Conformational Energy Program for Peptides
PERLA
Design process (I)

- selection of residues of the PDZ domain that could establish specific interactions with the ligand
- identification of side chains that contact the positions to be mutagenized
- placement of the natural amino acids at each position selected for mutagenesis
- elimination of those side chain conformations and amino acids that are not compatible with the rest of the structure
finally, all possible pairwise interactions are explored to eliminate combinations that are less favourable

output consists of sequences and PDB coordinates ranked in terms of free energy

if obtained number of AA combinations is too high select the best 10-20 sequences and carry out a second round to reduce the number of combinations
side-chain rotamer library constructed from the analysis of the protein database (all-atom configurations are given therein)

occupancy distribution of every side-chain rotamer determined by using a temperature-simulated annealing (mean-field approximation)

optimizes van der Waals, hydrogen bonding and electrostatic interaction energies taking into account the side-chain flexibility by sampling subrotamer-configurations (5°, 10° and/or 15° rotations around the side-chain dihedral angles)
PERLA
Scoring function

- side-chain interaction energy

\[ \Delta G_{\text{SC}}^{\text{Perla}} = (E_{\text{Hel}}^{\text{Perla}})_{XY} - (E_{\text{RC}}^{\text{Perla}})_{XY} + (E_{\text{Hel}}^{\text{Perla}})_{AA} - (E_{\text{RC}}^{\text{Perla}})_{AA} \\
- (E_{\text{Hel}}^{\text{Perla}})_{XA} + (E_{\text{RC}}^{\text{Perla}})_{XA} + (E_{\text{Hel}}^{\text{Perla}})_{AY} + (E_{\text{RC}}^{\text{Perla}})_{AY} \]

Hel: helical conformation
RC: extended conformation

- includes entropy (considered separately for the main chain and the side-chains) and solvation

- most terms are balanced with respect to a reference state to simulate the denatured protein
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Design of a PDZ domain

Selection of the PDZ domain

- class I: recognizes Thr / Ser residue at p(-2)
- class II: recognizes aliphatic residue at p(-2)
  \[ \Rightarrow \text{good structural homology} \]

Source: image taken from reference [1]
Design of a PDZ domain

Selection of the PDZ domain

- structural differences mainly due to the displacement of the $\alpha$-helix involved in peptide binding w.r.t. the $\beta$-sheet

*Fig. 1* Superposition of the ribbon diagrams of the third PDZ domain of PSD-95 (PDB entry 1BE9; red), CASK/LimmZ (1KWA; blue) and the PDZ of nNOS (188Q; green).

*Source:* image taken from reference [1]
Design of a PDZ domain
Selection of the PDZ domain

- displacement related to changes in specificity (e.g. an aromatic amino acid leads to displacement of the $\alpha$-helix to accommodate bulky side-chains)

Source: image taken from reference [1]

Fig. 1 Superposition of the ribbon diagrams of the third PDZ domain of PSD-95 (PDB entry 1BE9; red), CASK/Lm2 (1KWA; blue) and the PDZ of nNOS (1BBQ; green).
Design of a PDZ domain

Selection of the PDZ domain

- PDZ/3: mutation of p(-1) (Ser, Arg) of the ligands to Asp abolishes binding to the PDZ-domain
- \textit{nNOS}: Tyr77 at the N-terminus of the \(\alpha\)-helix forms an H-bond to the side-chain of Asp p(-2) \(\rightarrow\) displacement
- PDZ/3: His at equivalent position: steric clash
- \textit{CASK/Lin} recognizes aromatic residues: displacement to accommodate bulky side-chains
Design of a PDZ domain

Selection of the PDZ domain

Source: table taken from Bioinformatics II lecture, Thomas Lengauer
Design of a PDZ domain

Selection of the PDZ domain

- class I: recognizes Thr / Ser residue at p(-2)
- class II: recognizes aliphatic residue at p(-2)

⇒ good structural homology

- selection of PDZ/3 of the PSD-95 protein (class I domain that could also be class II compatible)

<table>
<thead>
<tr>
<th></th>
<th>P-4</th>
<th>P-3</th>
<th>P-2</th>
<th>P-1</th>
<th>P0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>X</td>
<td>X</td>
<td>-T/S-</td>
<td>X</td>
<td>-Φ</td>
</tr>
<tr>
<td>Class II</td>
<td>X</td>
<td>X</td>
<td>-Φ</td>
<td>X</td>
<td>-Φ</td>
</tr>
<tr>
<td>Eg5</td>
<td>T</td>
<td>S</td>
<td>I</td>
<td>N</td>
<td>L</td>
</tr>
<tr>
<td>Hyd</td>
<td>K</td>
<td>I</td>
<td>T</td>
<td>W</td>
<td>V</td>
</tr>
<tr>
<td>Pol</td>
<td>K</td>
<td>R</td>
<td>T</td>
<td>E</td>
<td>V</td>
</tr>
<tr>
<td>Cript (wt)</td>
<td>K</td>
<td>Q</td>
<td>T</td>
<td>S</td>
<td>V</td>
</tr>
<tr>
<td>NL</td>
<td>S</td>
<td>T</td>
<td>T</td>
<td>R</td>
<td>V</td>
</tr>
</tbody>
</table>

Source: table taken from reference [1]
Design of a PDZ domain

Selection of the PDZ domain

Summary Information

Title: The Third Pdz Domain From The Synaptic Protein Psd-95 In Complex With A C-Terminal Peptide Derived From Cript.

Compound: Mol_Id: 1; Molecule: Psd-95; Chain: A; Fragment: The Third Pdz Domain Of Psd-95
Engineered: Yes
Mol_Id: 2; Molecule: Cript; Chain: B; Fragment: C-Terminal Peptide

Authors: D. A. Doyle, A. Lee, J. Lewis, E. Kim, M. Sheng, R. Mackinnon

Exp. Method: X-ray Diffraction
Classification: Peptide Recognition
Source: Rattus norvegicus

Primary Citation: Doyle, D. A., Lee, A., Lewis, J., Kim, E., Sheng, M., Mackinnon, R.: Crystal structures of a complexed and peptide-free membrane protein-binding domain: molecular basis of peptide recognition by PDZ. Cell 85 pp. 1067 (1996)

Deposition Date: 20-May-1998
Release Date: 21-Oct-1998

Resolution [Å]: 1.82
Space Group: P 41 3 2

Unit Cell: a 89.34  b 89.34  c 89.34
Angles [°]: alpha 90.00  beta 90.00  gamma 90.00

Source: table taken from http://www.rcsb.org/pdb/cgi/explore.cgi?pid=1766117218326&pdbId=1BE9
Design of a PDZ domain

Selection of the PDZ domain

- high resolution structure available (X-ray)
- PDB entry 1BE9
- wt domain recognizes two class I ligands:
  - *Cript* (wt ligand)
  - *NL*

<table>
<thead>
<tr>
<th>Class</th>
<th>P-4</th>
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<td>-Φ</td>
<td>X</td>
<td>-Φ</td>
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<td>T</td>
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<td>I</td>
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<td>L</td>
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<td>T</td>
<td>W</td>
<td>V</td>
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<td>Pol</td>
<td>K</td>
<td>R</td>
<td>T</td>
<td>E</td>
<td>V</td>
</tr>
<tr>
<td><em>Cript</em> (wt)</td>
<td>K</td>
<td>Q</td>
<td>T</td>
<td>S</td>
<td>V</td>
</tr>
<tr>
<td><em>NL</em></td>
<td>S</td>
<td>T</td>
<td>T</td>
<td>R</td>
<td>V</td>
</tr>
</tbody>
</table>

*Source:* table taken from reference [1]
Design of a PDZ domain

Selection of the target

- two different design exercises:
  - change specificity of PDZ/3-wt to recognize a class II and then a new class I target peptide
  - create new PDZ domains that could specifically recognize the amino acids located at p(-1) and p(-3)

<table>
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<td>X</td>
<td>-Φ</td>
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<td>S</td>
<td>T</td>
<td>T</td>
<td>R</td>
<td>V</td>
</tr>
</tbody>
</table>

Source: Table taken from reference [1]
Design of a PDZ domain

Computer-based engineering

- binding interface of PDZ/3 wild type (defined by visual inspection):

Source: image taken from reference [1]
# Design of a PDZ domain

Table 1 Mutations considered and selected by Perla

<table>
<thead>
<tr>
<th>Residue</th>
<th>Mutations considered</th>
<th>Best fit (1st round)</th>
<th>Best fit (2nd round)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leu 323</td>
<td>A,V,I,L,F</td>
<td>F,L</td>
<td>F,L</td>
</tr>
<tr>
<td>Phe 325</td>
<td>A,V,I,L,F</td>
<td>F,L</td>
<td>F,L</td>
</tr>
<tr>
<td>Asn 326</td>
<td>S,T,N,Q,D,E,K,R</td>
<td>K,T</td>
<td>K,T</td>
</tr>
<tr>
<td>Ile 327</td>
<td>A,V,I,L,F</td>
<td>I,L</td>
<td>I,F</td>
</tr>
<tr>
<td>Ile 328</td>
<td>S,T,N,Q,D,E,K,R</td>
<td>K,T</td>
<td>T,K</td>
</tr>
<tr>
<td>Glu 331</td>
<td>D,E</td>
<td>E</td>
<td>E</td>
</tr>
<tr>
<td>Leu 342</td>
<td>S,T,N,Q,D,E,K,R</td>
<td>K,R</td>
<td>K,R</td>
</tr>
<tr>
<td>His 372</td>
<td>A,V,I,L,F</td>
<td>A,L</td>
<td>A,L</td>
</tr>
<tr>
<td>Glu 373</td>
<td>N,Q,D,E,A,V,I,L,F</td>
<td>E,I</td>
<td>E,I</td>
</tr>
<tr>
<td>Ala 376</td>
<td>A,V,I,L,F</td>
<td>A,V</td>
<td>A,V</td>
</tr>
<tr>
<td>Lys 380</td>
<td>N,Q,D,E,K,R</td>
<td>K,R</td>
<td>K,R</td>
</tr>
</tbody>
</table>

# sequences:
- PDZ-Eg5: $2.3 \times 10^9$
- PDZ-hyd: $3.9 \times 10^{22}$
- PDZ-pol: $1.4 \times 10^4$

hyd (KITWV)
- Asn 326 A,C,D,E,F,H,I,K,L,M,N,Q,R,S,T,V,W,Y A A
- Leu 342 A,C,D,E,F,H,I,K,L,M,N,Q,R,S,T,V,W,Y A A
- Tyr 397 A,C,D,E,F,H,I,K,L,M,N,Q,R,S,T,V,W,Y I,F F

pol (KRTEV)
- Asn 326 K,N,R,Q,S,T,E E
- Ile 328 K,N,R,Q,S,T,E T
- Ser 339 K,N,R,Q,S,T,E,A,V V
- Phe 340 K,Q,R,N,D,E R
- Leu 342 K,Q,R,E, R,E
- Tyr 397 F F

Source: table taken from reference [1]
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Results

Binding affinity and specificity

- fluorescence polarisation assays to determine binding affinity $K_d$ of the complexes

Source: graph taken from reference [1]
Results

Binding affinity and specificity

- binding of the four PDZ domains is specific

Table 2 Affinity and specificity of the binding between the PDZ domains and their target peptides

<table>
<thead>
<tr>
<th>PDZ</th>
<th>$K_d$ (µM)</th>
<th>Specificity ($K_i$ wt / $K_i$ target)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pol</td>
<td>$26 \pm 3.20$</td>
<td>wt 14 Eg5 N.D. N.D. 1</td>
</tr>
<tr>
<td>hyd</td>
<td>$1 \pm 0.008$</td>
<td>90 N.D. 1 N.D.</td>
</tr>
<tr>
<td>Eg5</td>
<td>$96 \pm 11.6$</td>
<td>9 1 N.D. N.D.</td>
</tr>
<tr>
<td>wt</td>
<td>$20 \pm 1.5$</td>
<td>1 &gt;100 5 9</td>
</tr>
</tbody>
</table>

Source: table taken from reference [1]

1Binding of each of the other PDZ domains to their ligands was competed with the ligand itself (as a control) and the wt peptide. The best competitors are at least an order of magnitude less efficient than the corresponding peptide, suggesting that binding between the four PDZs presented in this work and their corresponding ligands is specific.
Results
Validation of PERLA

- **in vitro** studies
- **in vivo** studies

### Table 3 Two-hybrid interactions between the PDZ domains and their target ligands. A full matrix of all four PDZs and ligands plus controls is shown.

<table>
<thead>
<tr>
<th></th>
<th>pGBK(^1)</th>
<th>GFP</th>
<th>GFP-wt</th>
<th>GFP-Eg5</th>
<th>GFP-pol</th>
<th>GFP-hyd</th>
</tr>
</thead>
<tbody>
<tr>
<td>pGAD(^1)</td>
<td>-(^2)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PDZ-wt</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PDZ-Eg5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PDZ-pol</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>PDZ-hyd</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+++</td>
</tr>
</tbody>
</table>

\(^1\)pGBK and pGAD are plasmids carrying the Gal4 binding and activation domains on their own.

\(^2\)Negative interaction are shown as minus (−). Positive interactions are shown as plus (+). For details on quantitation see Methods.

Source: table taken from reference [1]
Results

Validation of PERLA

- *in vitro* studies
- *in vivo* studies
  - series of two-hybrid analyses
  - overlay assays
  - affinity purification assays
  - pull-down assays

⇒ the designed PDZ domains efficiently recognize their intended peptide (high affinity + stable)
Results
Validation of PERLA

- *hyd*-ligand can bind to PDZ2/MAGI-3
  Observation: in PDZ-hyd, PERLA introduces some of the PDZ2/MAGI-3 residues

⇒ PERLA can identify *in silico* sequences that are similar to those observed by screening methods
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Conclusions
pros ... (I)

- PERLA can be used to
  - generate both, single and multiple residue mutants of a protein
  - change the ligand specificity of a PDZ domain
  - provide precise interaction energies for amino acid pairwise interactions [3]
Conclusions

pros … (II)

- PERLA is well tested and all studies (re-design of PDZ domain \[^1\], \(\beta\)-sheet peptide Betanova \[^2\], \(\alpha\)-helices \[^3\], spectrin SH3 residue clusters \[^4\]) reveal, that some of the designed proteins have significantly higher stabilities than the wild-type protein. This establishes the quality of the structure-based computational approach to protein design.

- the engineered PDZ-domains could be used to purify the target protein from complex cell extracts (specificity)
Conclusions

... and cons (I)

- limitation due to the presence of a certain degree of degeneracy which can make single PDZ domains bind more than a single target sequence
- predicted sequences have to be selected by the operator, because although PERLA in some cases calculated good energy of the complex, no binding of the target occurred
- operator must identify most relevant positions to keep down number of residues to be checked to optimize efficiency
Conclusions

... and cons (II)

- imprecision and overestimation of the interaction because of systematic errors of the scoring function, conformational rearrangements of the peptide structure and insufficient consideration of energy changes occurring in the protein unfolded state

⇒ the scoring function is sensible but requires refinements to better determine hydrogen bonding \[3\]

⇒ all studies claim, that experimental work will always be required until PERLA experiences significant improvements
Conclusions

Future

- this computer-based method can also be applied for designing structured peptides, which might be very helpful to design scaffolds in drug discovery, for example

- engineered PDZ-domains can be used as recognition tools to replace antibodies in western blotting, pull-down experiments, …

- combination of experimental and *in silico* approaches to accelerate discovery of new interacting partners may become standard in the near future
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  - Validation of PERLA
- Conclusions
  - Pros and Cons
  - Future
- References & discussion
References

Computer-aided design of a PDZ domain to recognize new target sequences

Computer-aided design of beta-sheet peptides

[3] SAMO FISINGER, LUIS SERRANO, AND EMMANUEL LACROIX  
Computational estimation of specific side chain interaction energies in α helices

[4] Isabelle Angrand, Luis Serrano, Emmanuel Lacroix  
Computer-assisted re-design of spectrin SH3 residue clusters
Discussion

Thank you for your attention! ;-)

Molecule of the Month:
Self-splicing RNA

http://pdbbeta.rcsb.org/