# Structural (and sequence-based) analysis of transcriptional regulation

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# Credits and acknowledgements

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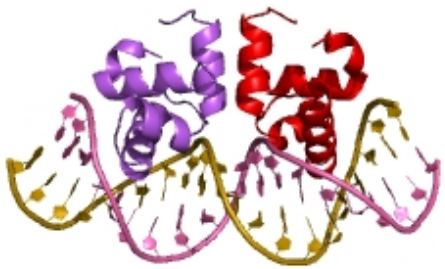
# Purpose of this work

- **Motivation:** characterization of regulatory sequences by exploiting protein-DNA complexes at the Protein Data Bank



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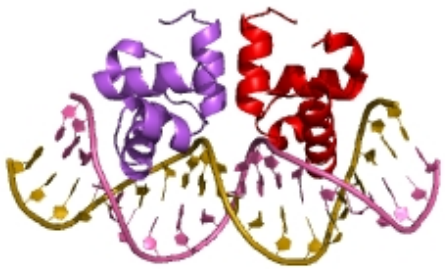
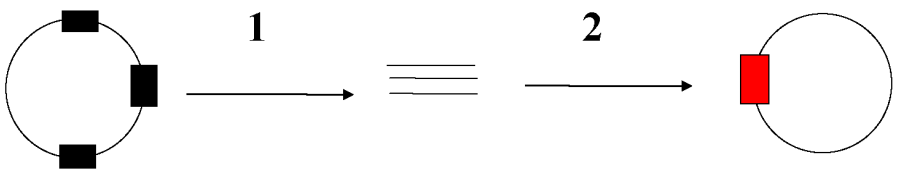


- **Value:** adding 3D information to sequence-based protocols



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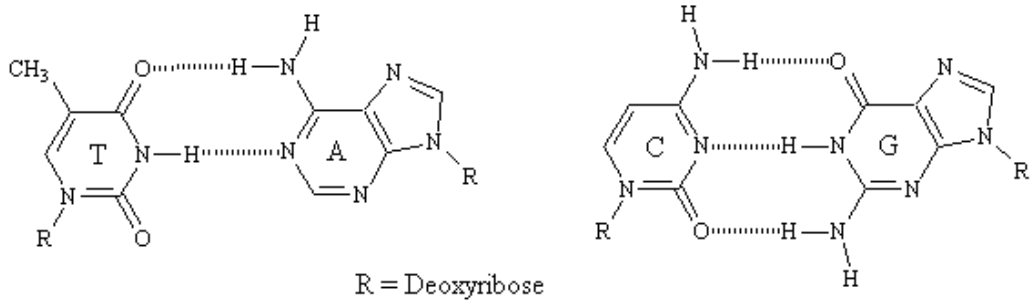

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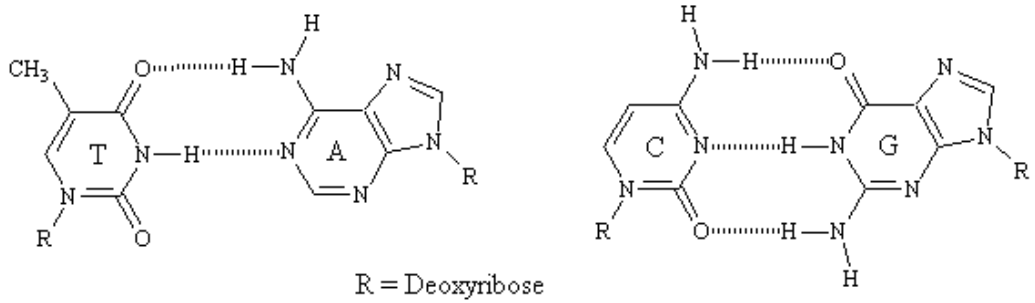


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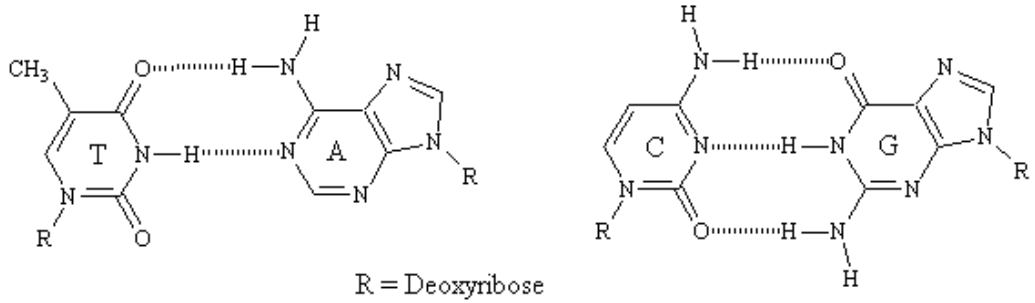


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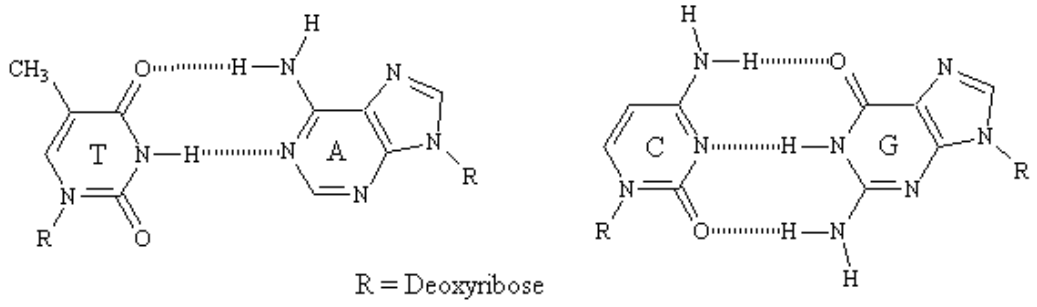


- Indirect readout:
  - sequence-specific deformation of DNA base steps (Olson)
- Stabilizing interactions, not sequence-specific

# Example of interface: E.coli NarL (1je8)

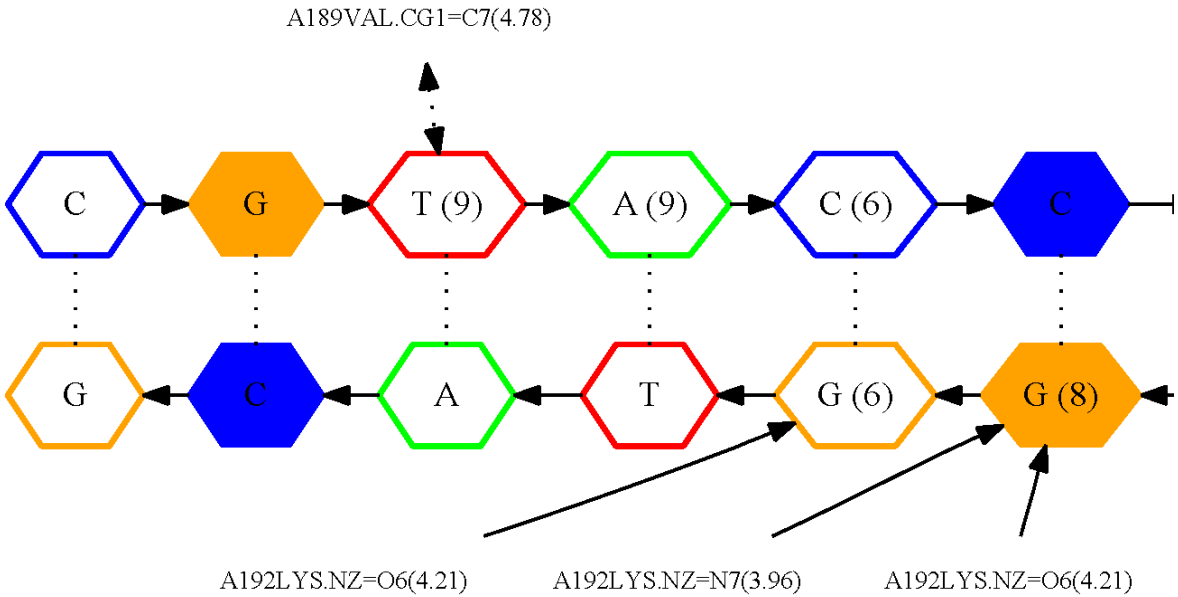


Figure: atomic interface dissected with modified version of HBPLUS (numbers in bases are total 4.5Åcontacts, Mirny)

# Derivation of weight matrices for direct readout

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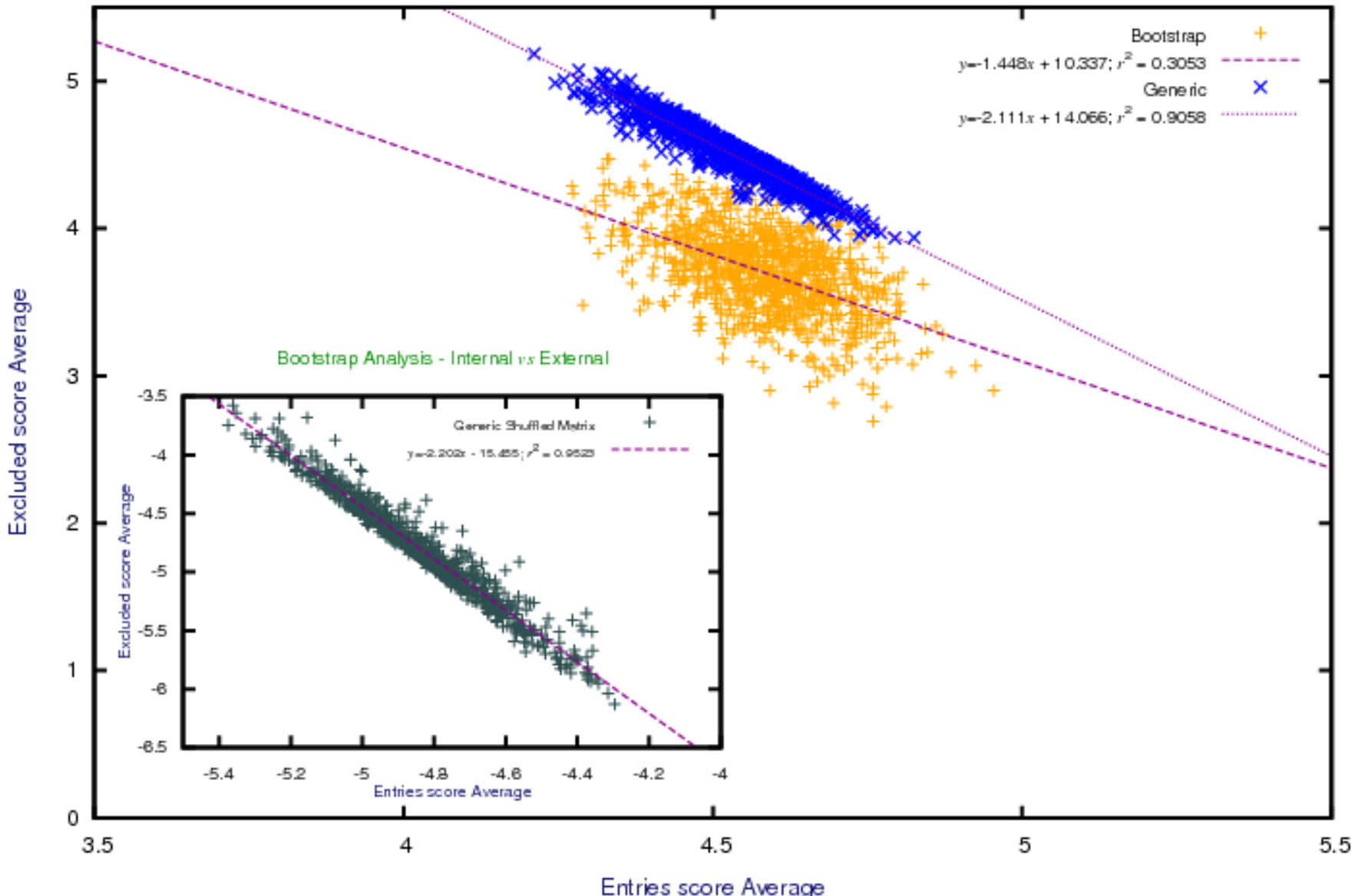
- weights calculated as $w_{pn} = ln(\frac{(n_{pn}+exp_{pn})/(N_p+1)}{exp_{pn}})$

---------- H BONDS----------

THYMINE

| | | N1 | O2 | N3 | O4 |
|---|---|---|---|---|---|
| R | | | | | |
| | NE | -6.497 | 1.645(5) | -6.497 | 1.135(3) |
| | NH1 | -6.497 | 3.127(22) | -6.497 | 1.135(3) |
| | NH2 | -6.497 | 2.926(18) | -6.497 | 2.338(10) |
| K | | | | | |
| | NZ | -5.591 | 2.489(16) | -5.591 | 2.019(10) |
| S | | | | | |
| | OG | -4.625 | 2.545(5) | -4.625 | 1.629(2) |
| T | | | | | |
| | OG1 | -4.382 | 2.408(3) | 1.311(1) | 2.695(4) |
| N | | | | | |
| | OD1 | -5.509 | -5.509 | 1.097(1) | -5.509 |
| | ND2 | -5.509 | 3.293(9) | -5.509 | 3.987(18) |

# Bootstraps of atomic interface matrices



# Biological relevance of contact-based binding scores

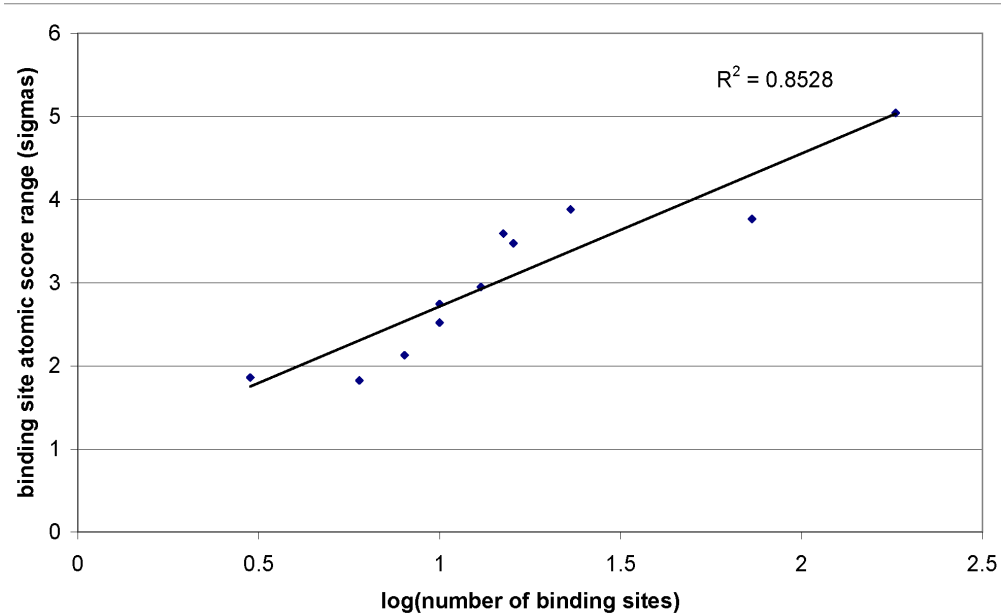



Figure: Atomic interface matrices yield scores that correlate with approximate measures of binding specificity for 11 E.coli TFs

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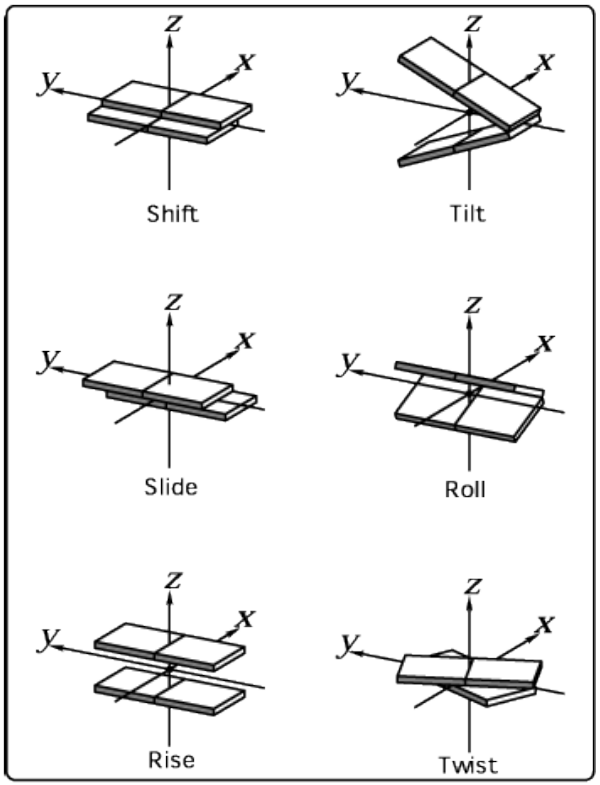

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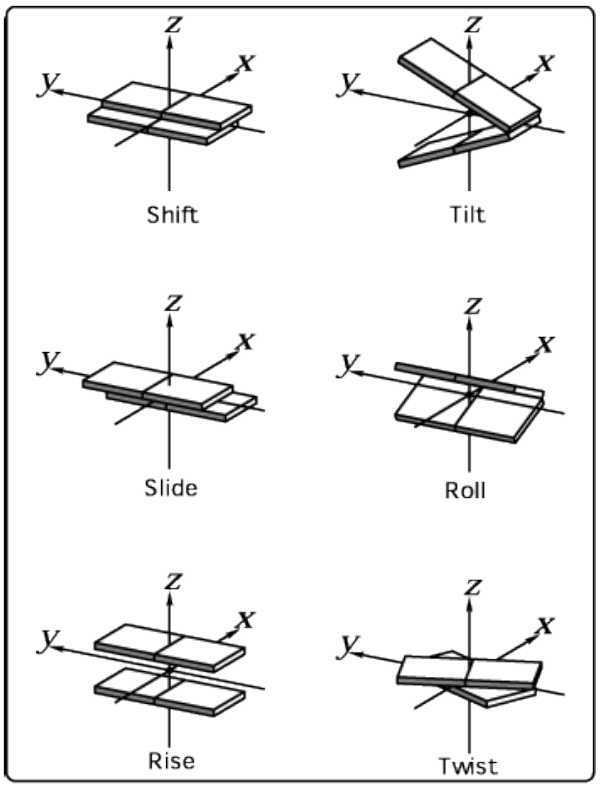


- $deformation = \sum_{st=0}^{n} \sum_{i=0}^{6} \sum_{j=0}^{6} spring_{ij} \Delta\theta_{i,st} \Delta\theta_{j,st}$ (Olson)

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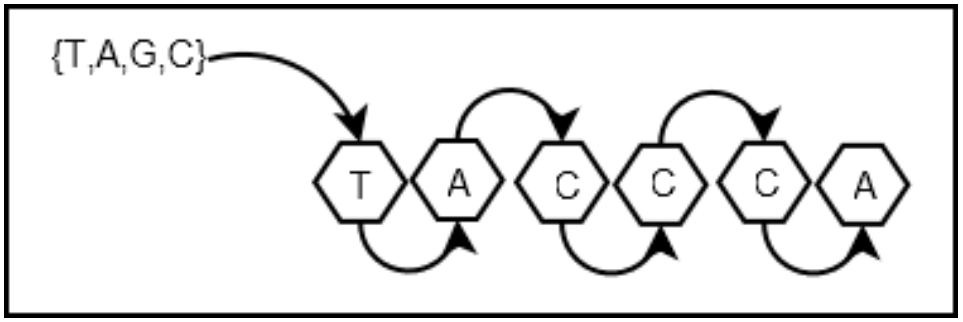

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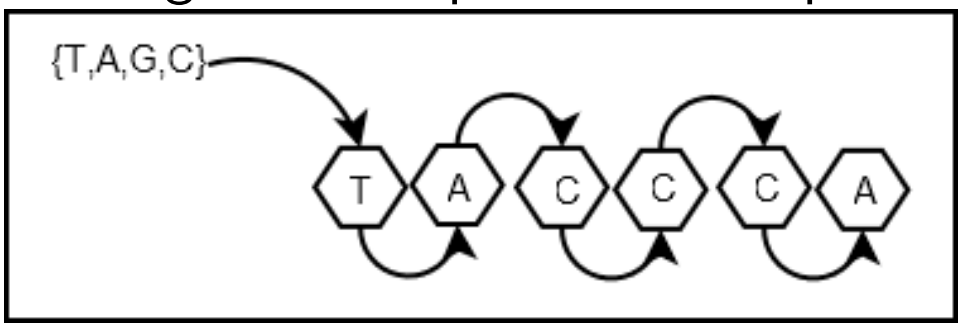


- score threaded mutations as
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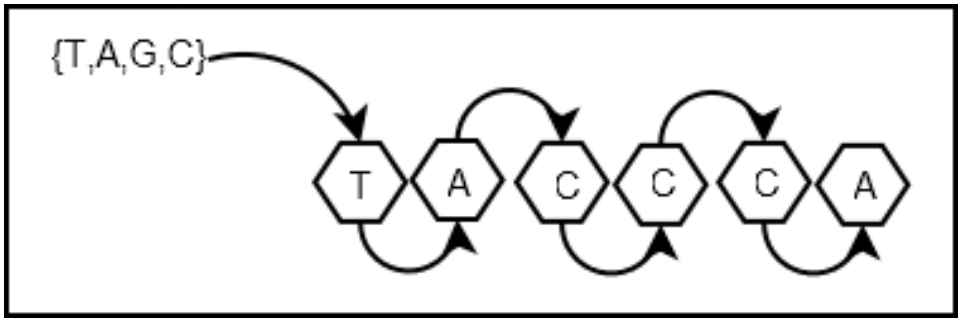
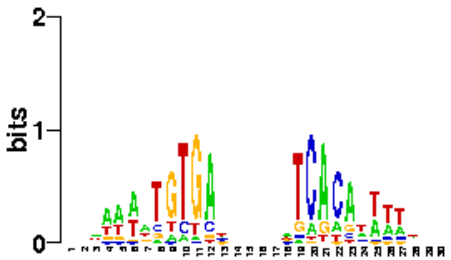



- score threaded mutations as
  $w(n) = e^{(-((1-D)*direct(n)+D*indirect(n)))}$ **(check D!)**
- derive structure-based position weight matrix (PWM)

```
A | -1.38  0.36 -0.68 -2.23 -0.13  0.58
C | -0.95  0.09  1.07  1.28  0.12 -0.25
G | -1.10 -1.60 -0.91 -2.02 -0.08 -0.33
T |  1.11  0.25 -1.79 -1.90  0.06 -0.34
```

# Structure-based PWM for CRP (1cgp)

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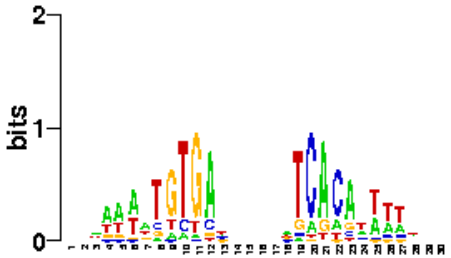


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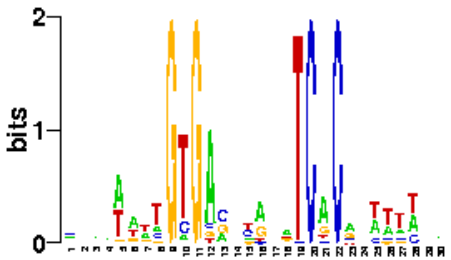
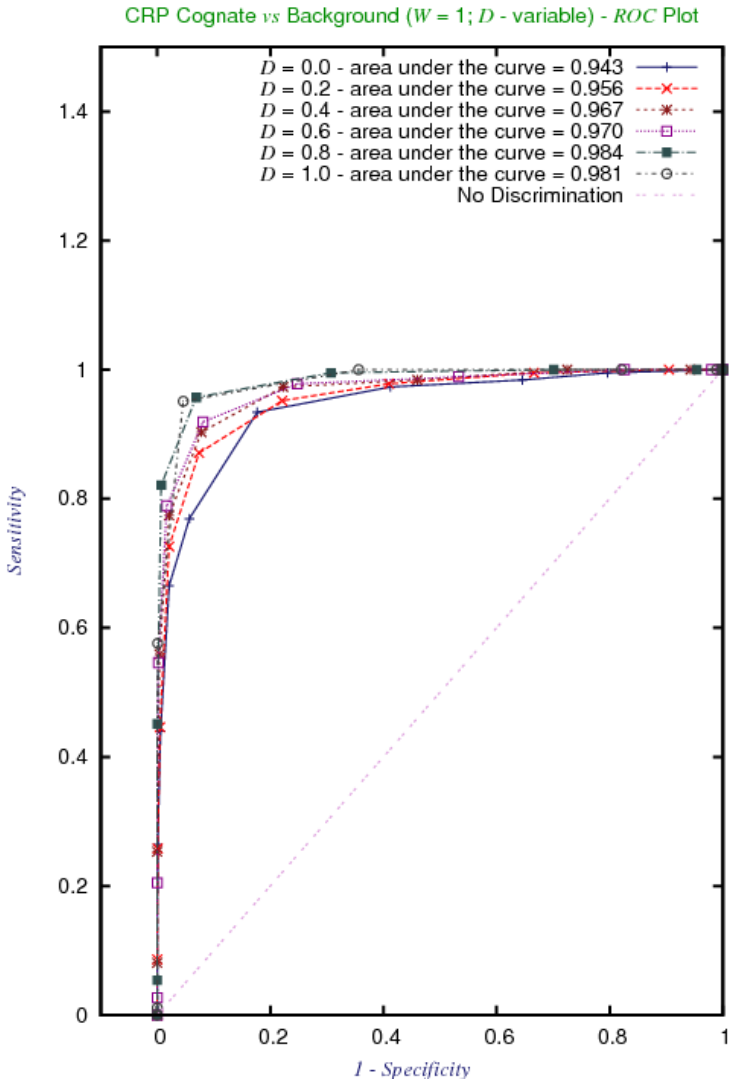



Figure: structure-based logo

# Benchmark of DNAPROT with genomic-sized sequences




ROC curve of the structure-based PWM for CRP after scanning $10^6$ random sequences (with similar %GC), mixed with 186 cognate sites extracted from RegulonDB 5.0

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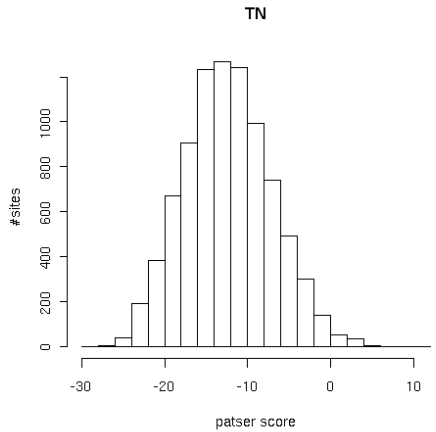
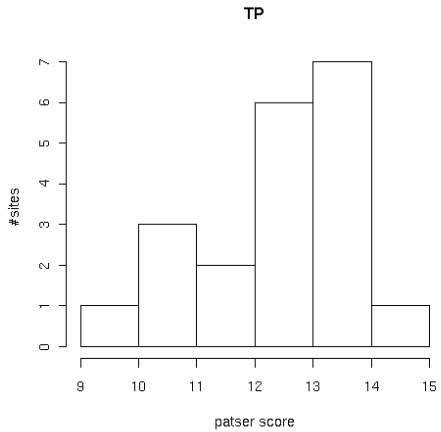
  - structure-based PWMs (DNAPROT + PDB complexes)

# Comparison to PATSER predictions for PurR (20 TPs)



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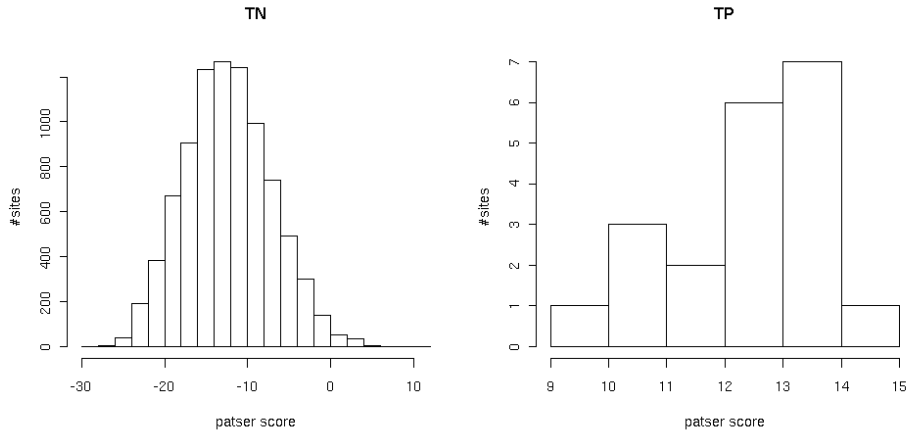


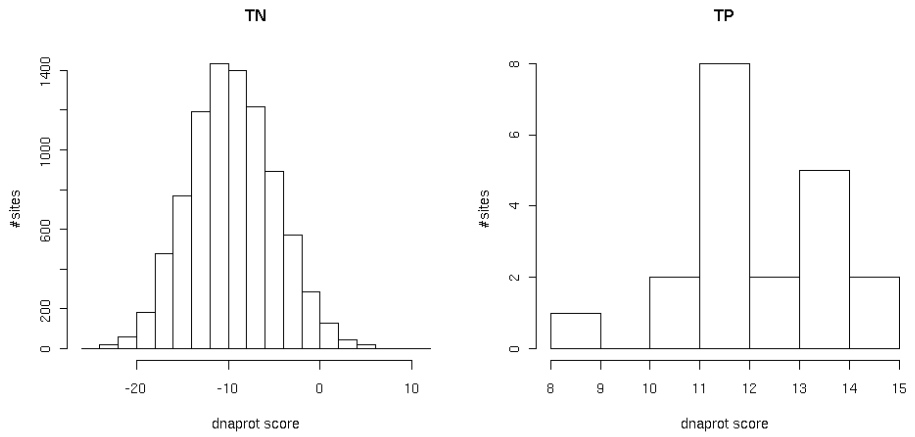

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| TF | resol(A) | R(obs) | contacts | sites/genome | dnaprot50Z | ROC50Z | patserZ | corr |
|---|---|---|---|---|---|---|---|---|
| PurR(2puo) | 2.9 | 0.16 | 6/6 | 20 / 8719 | 4.58 | 4.46 | 4.69 | 0.80 |
| MetJ(1cma) | 2.8 | 0.22 | 2/5 | 30 / 10631 | 2.05 | 2.17 | 2.9 | 0.35 |
| NarL(1je8) | 2.12 | 0.23 | 8/9 | 54 / 23327 | 2.42 | 1.42 | 2.79 | 0.42 |
| CRP(1cgp) | 3.0 | 0.24 | 6/8 | 613 / 202137 | 2.59 | 3.39 | 3.52 | 0.65 |
| PhoB(1gxp) | 2.5 | 0.25 | 4/4 | 17 / 6789 | 1.01 | 1.27 | 2.75 | 0.06 |
| FadR(1h9t) | 3.25 | 0.27 | 6/11 | 5 / 2169 | 1.99 | 1.66 | 4.73 | -0.96 |

Table: Performance of DNAPROT compared to PATSER in terms of median Z-scores of true positive sites

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- **Challenge:** can we use comparative models?