An Optimized Neural Network for Contact Prediction

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Using Contact Predictions

- 3D structure prediction is hard.
- Local structure predictions like secondary structure predictions are good.
- Tools for searching fold space are good but challenged by complexity.

With contact predictions we would use a small but accurate number of contact predictions as constraints in Undertaker, Rosetta.

But contact prediction is hard.

Residue-Residue Contact Definitions

Contact between residues is not actual contact (i.e. van der Waals distance).

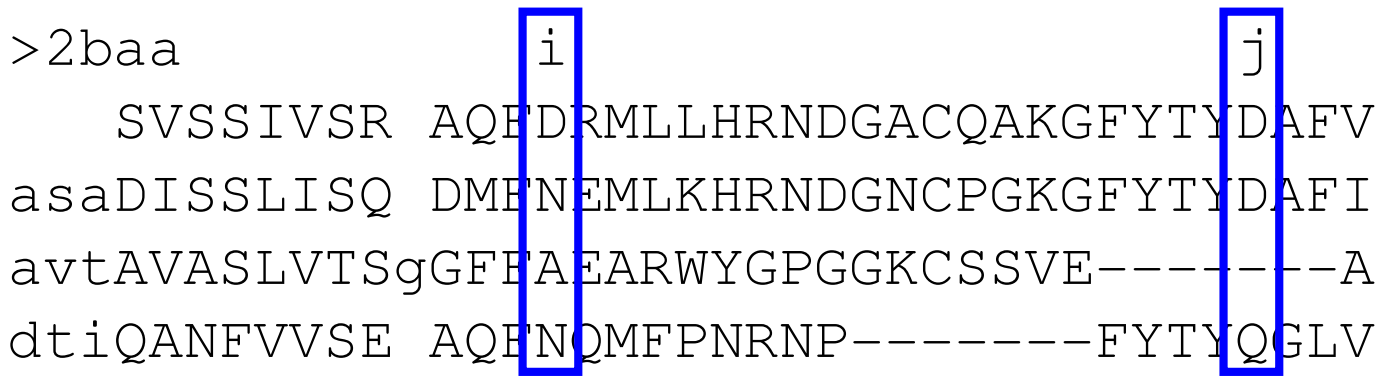
- CASP: Contact between two residues i, j is when the distance between their respective C_β atoms is less than 8 Å.
- We define *separation* as $|i - j|$

Method: Neural Network

- Upside: can provide excellent classification.
- Downside: black box - gives little or no information about feature relationships.
- Software based on `fann`, fast artificial neural network.
- Used Improved Resilient Back-propagation.
- CASP6 approach: used all inputs we could.
- CASP7 goal: use good inputs while eliminating weak or redundant inputs.

Multiple Sequence Alignment

We use multiple sequence alignments from SAM-t04 as a source of evolutionary data:



We have features for single columns, i and j, and for paired columns, (i, j).

Thinning the Sequence Alignment

If the sequences are too similar, we tend to see false correlations.

We use *thinning* to reduce the sample bias.

To thin a MSA to 50%, we remove sequences from the set until no pair of sequences has more than 50% percent identity.

- 80% thinning and sequence weighting for single column features.
- 50% thinning and NO weighting for paired features.

Single-column Features

- Distribution of residues in the column.
  - Regularized by using mixtures of Dirichlet distributions.
- Entropy over distribution.
- Predicted local features.
  - A secondary structure alphabet (str2)—13 classes.
  - A burial alphabet—11 classes

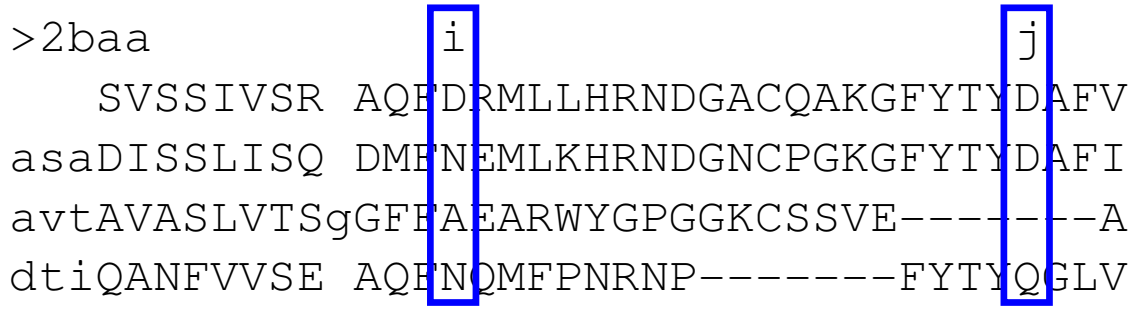
Inputs: Using Windows

For single columns we input values from features for
$i-2, i-1, i, i+1, i+2$,
$j-2, j-1, j, j+1, j+2$.
Tests indicated this window width was the best.

Exception is entropy with no window.

$(20+13+11)*5*2+2=442$ inputs—so far!

Paired-columns Features



Yields pairs: `DD, ND, NQ`. No pairing with gaps.
For features:

- Contact propensity
- E-values from mutual information
- Joint entropy
- Number of pairs between the two columns
- Log(|i-j|)

Contact Propensity

The log likelihood two amino acids (A, L) are in contact.

- Contact propensity is log(prob(contact(x, y))/prob(x)prob(y)).
- Contact propensity is largely due to the hydrophobicity (M. Cline et al. '02).
- Some very small part is due to other signals.
- We average the propensity over all sequences.
- Results show a significant increase in the signal.

Correlated Mutations

When a residue in a protein structure mutates, there is a possibility that a nearby residue will also mutate in compensation.

- beta bridges
- sidechain-sidechain interactions
- functional regions

We can detect these correlated mutations with correlation statistics.

Mutual Information

$$\mathrm{MI}_{i,j} = \sum_{k=1}^{T} p(r_{i,k}, r_{j.k}) \log \frac{p(r_{i,k}, r_{j,k})}{p(r_{i,k}) p(r_{j,k})}$$

where $r_{i,k}$ is the residue in column i, pair k.

- Mutual information is a very weak predictor by itself.
- We can improve by calculating an E-value over possible MI values.

Mutual Information E-value

- Shuffle residues in one column and calculate the mutual information value.
- Repeat 500 times recording the MI values.
- Determine parameters for Gamma distribution by using moment matching.
- Use that distribution and original MI value to derive a p-value.
- Derive E-value from p-value.

Joint Entropy

$$\mathrm{Ent}_{i,j} = \sum_{x \in R} \sum_{y \in R} \frac{C_{x,y}^{i,j}}{T} \log \left(\frac{C_{x,y}^{i,j}}{T} \right)$$

- i and j represent the indices of the pair of columns,
- R is the set of twenty residues and T is the number of valid residue pairs,
- $C_{x,y}^{i,j}$ is the count of amino acid pairs, x, y, for columns, i, j.

There are a LOT of Pairs

- We track only the top (10*length) values for each statistic.
- We sort each list according to value to get a rank.
- We calculate the Z-values using means and s.d. over all pairs ($i + \text{separation} <= j$).
- We form a final set over the intersection of the lists.

We keep data on value, Z-value, and rank.

Use Rank and/or Value for Inputs?

We experimented with using the rank, values, and Z-values of the pair values.

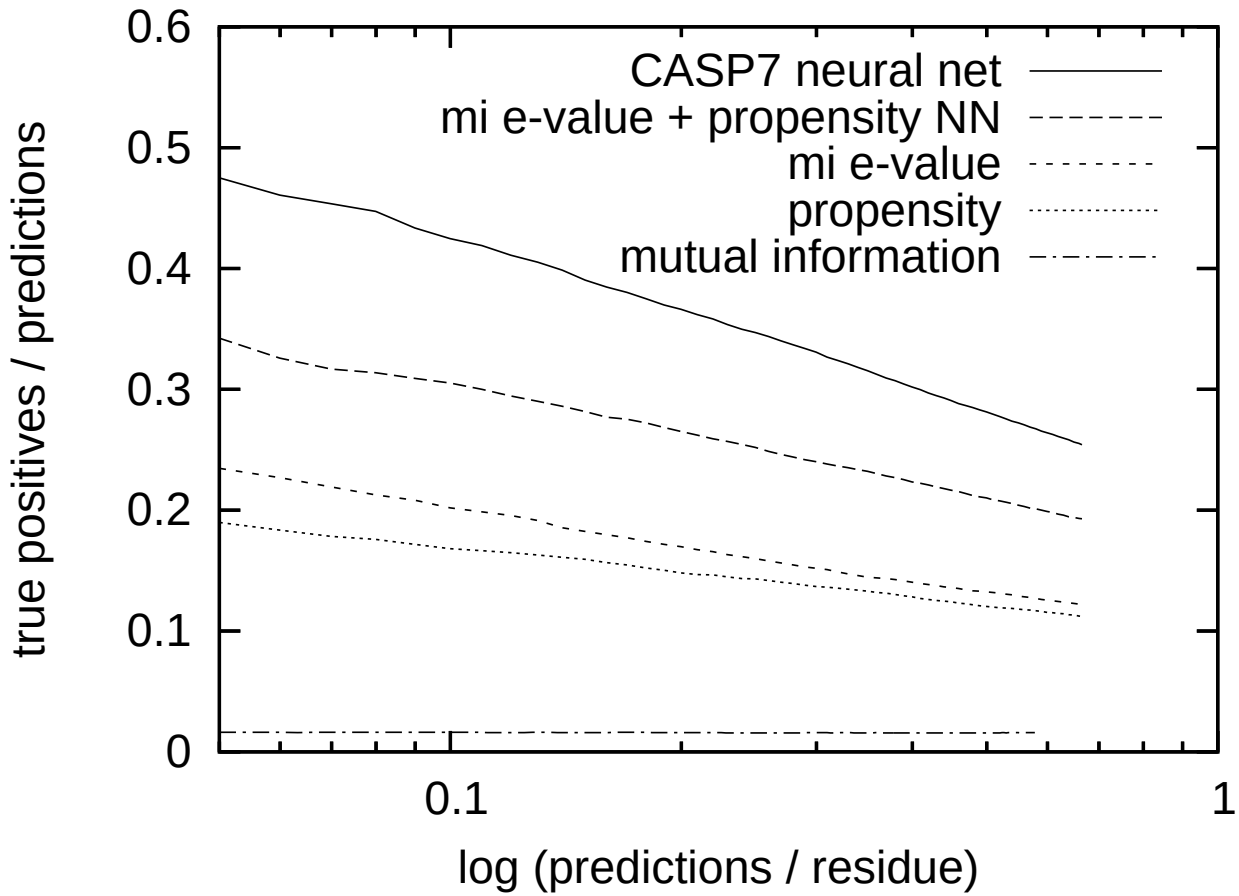
- For contact propensity we use -log(rank).
- For MI E-values we use -log(rank) and Z-value.
- For joint entropy we use -log(rank).

Misc. Input

for input number 449:

- Log of sequence length.

Evaluation: Comparing Predictors



Results for separation $>= 9$.

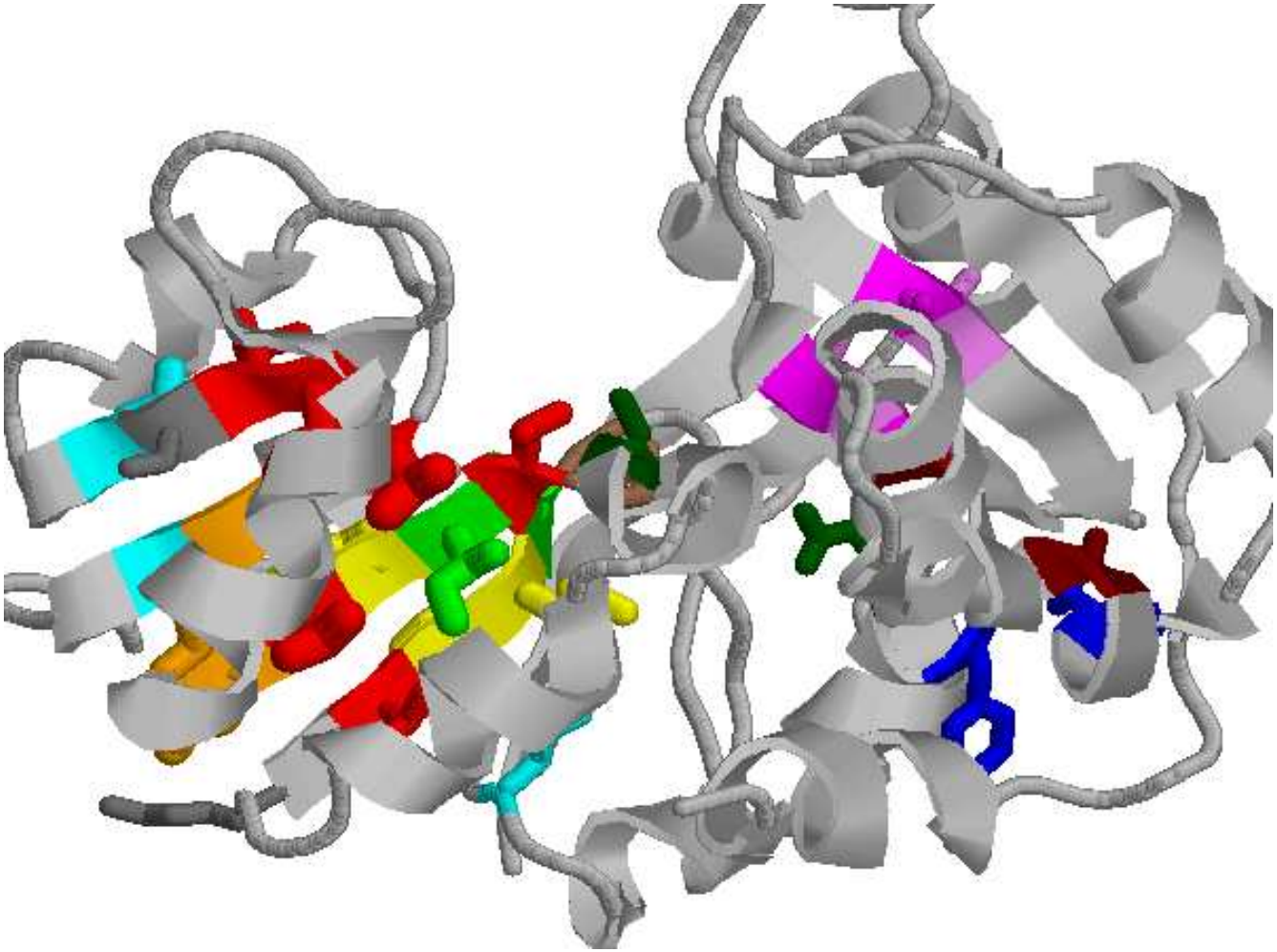
CASP7 Results

For 0.1 predictions/residue and separation $>= 12$.

- We show two good results: T0321 and T0350.
- We show a bad result: T0307.
- We compare accuracy to difficulty of target
  - using BLAST E-values.
  - using Zhang Server GDT.
- We compare accuracy to number of sequences in MSA.
- We examine how confident can we be in the neural net output scores.

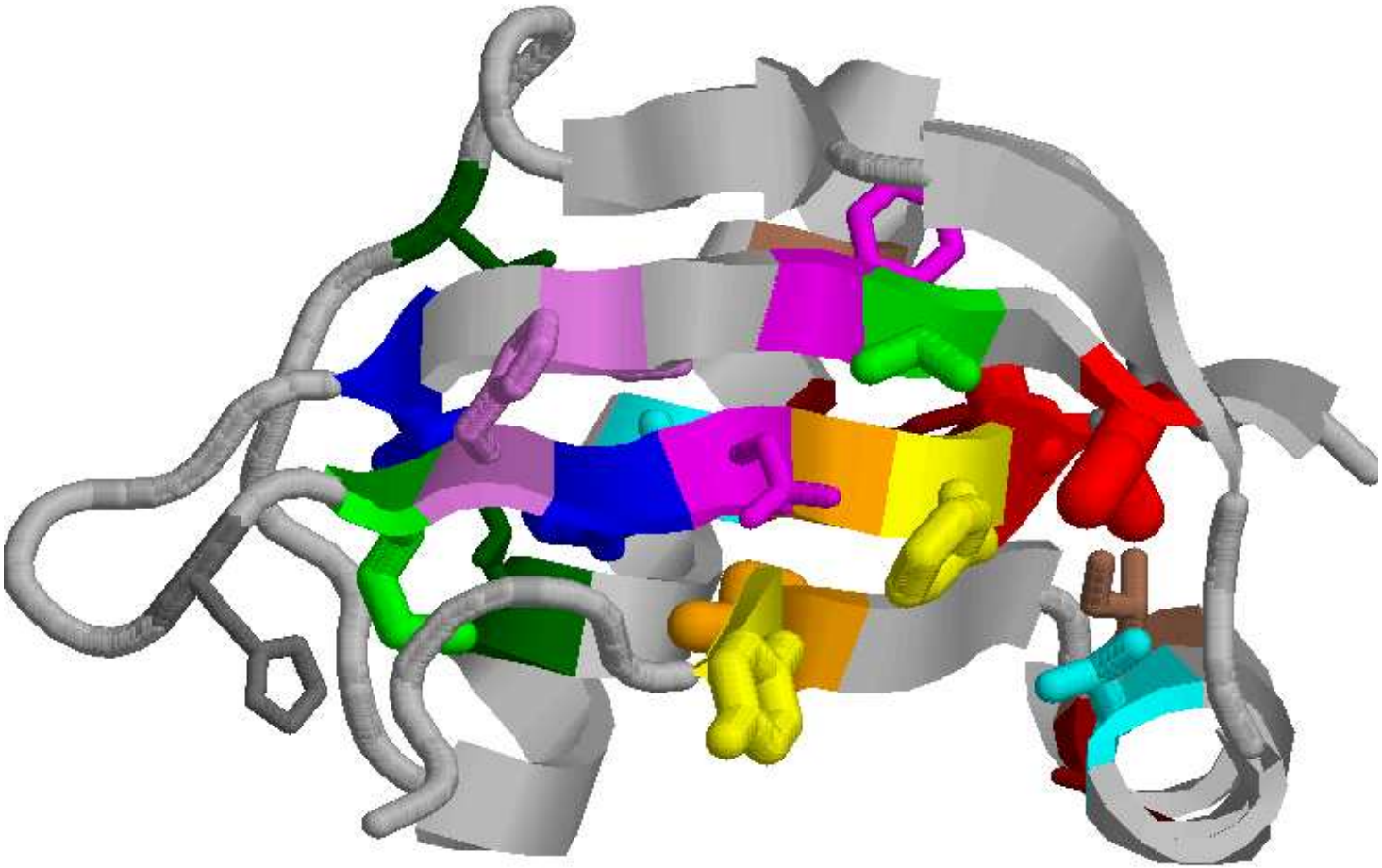
The Good: T0321

Thickness of side-chains represents neural net output.

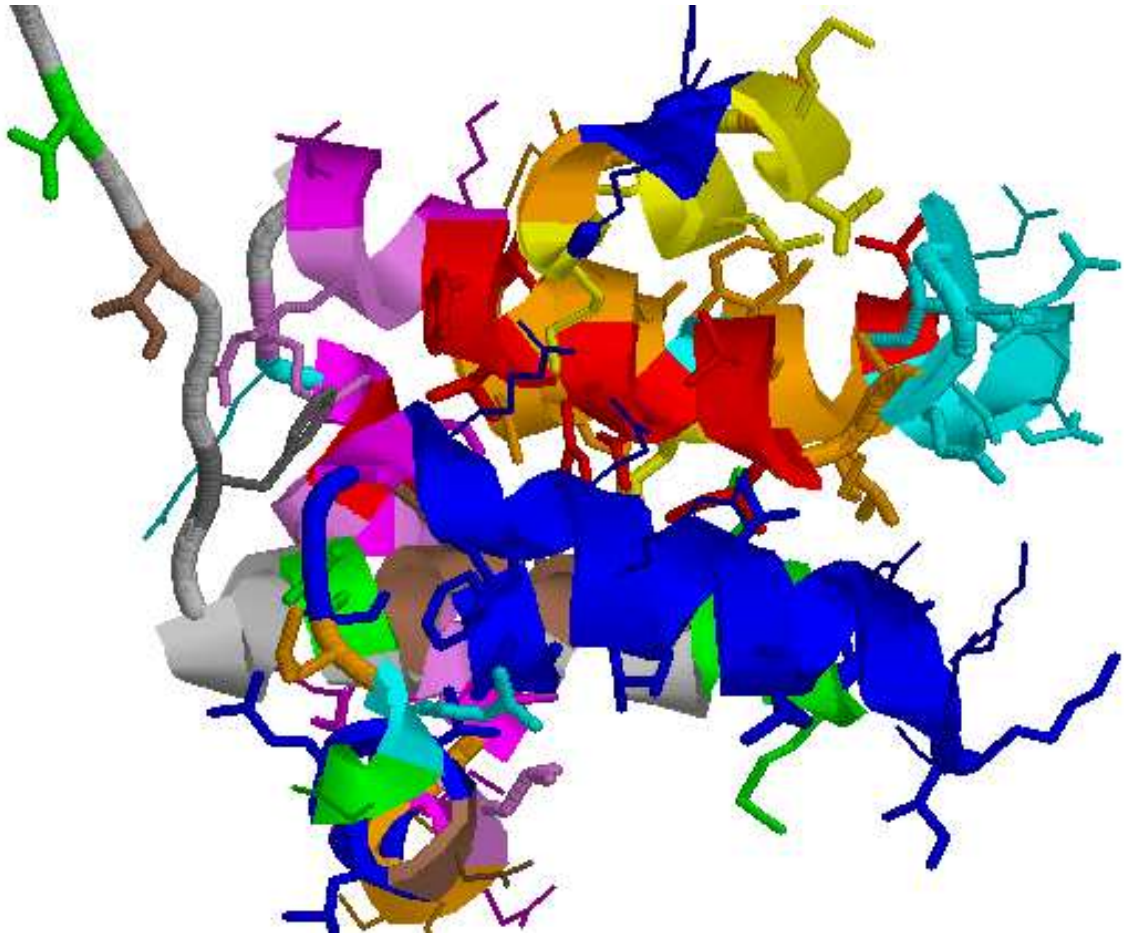


The Good and Difficult: T0353

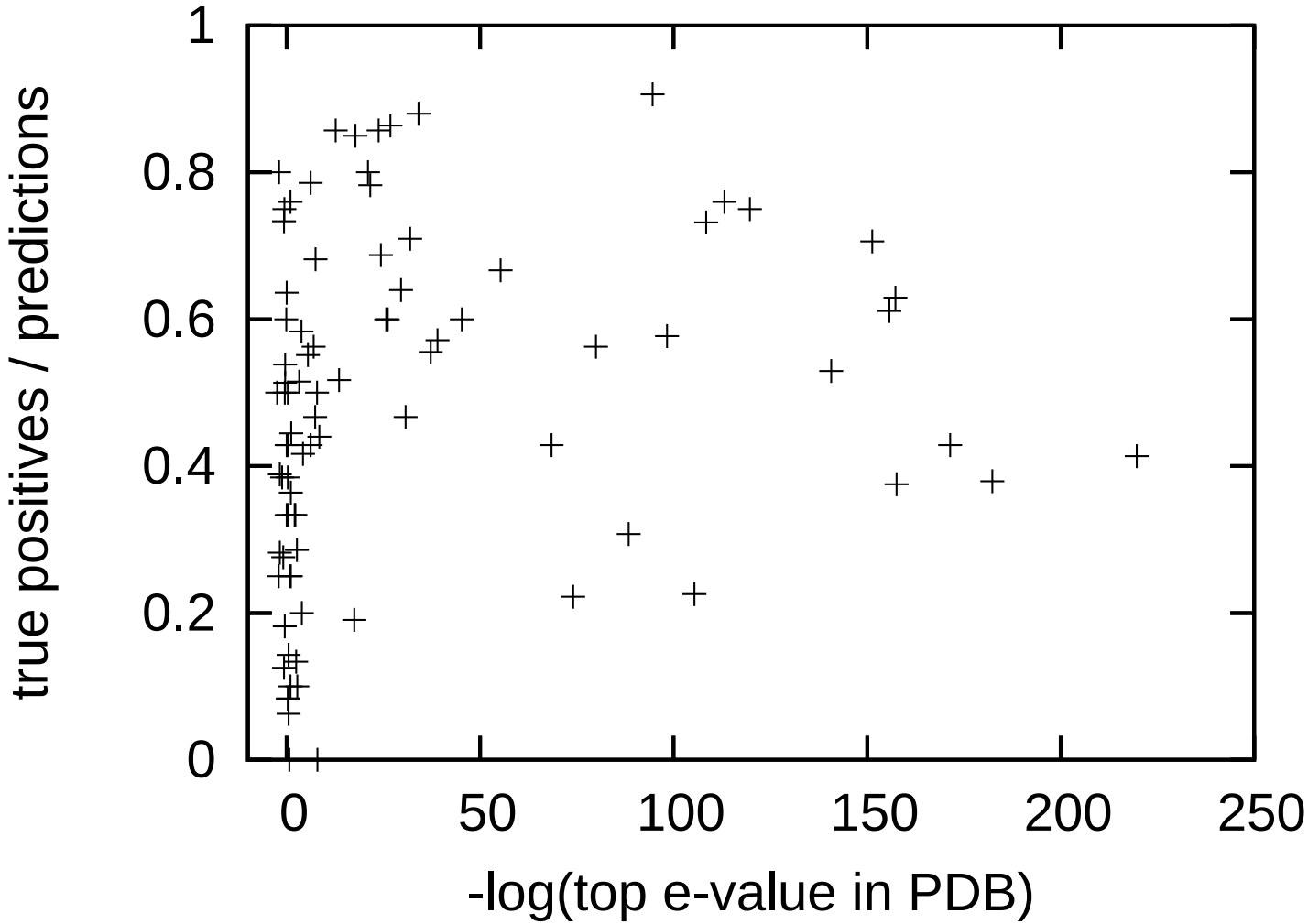
T0353 is from the free modeling class.



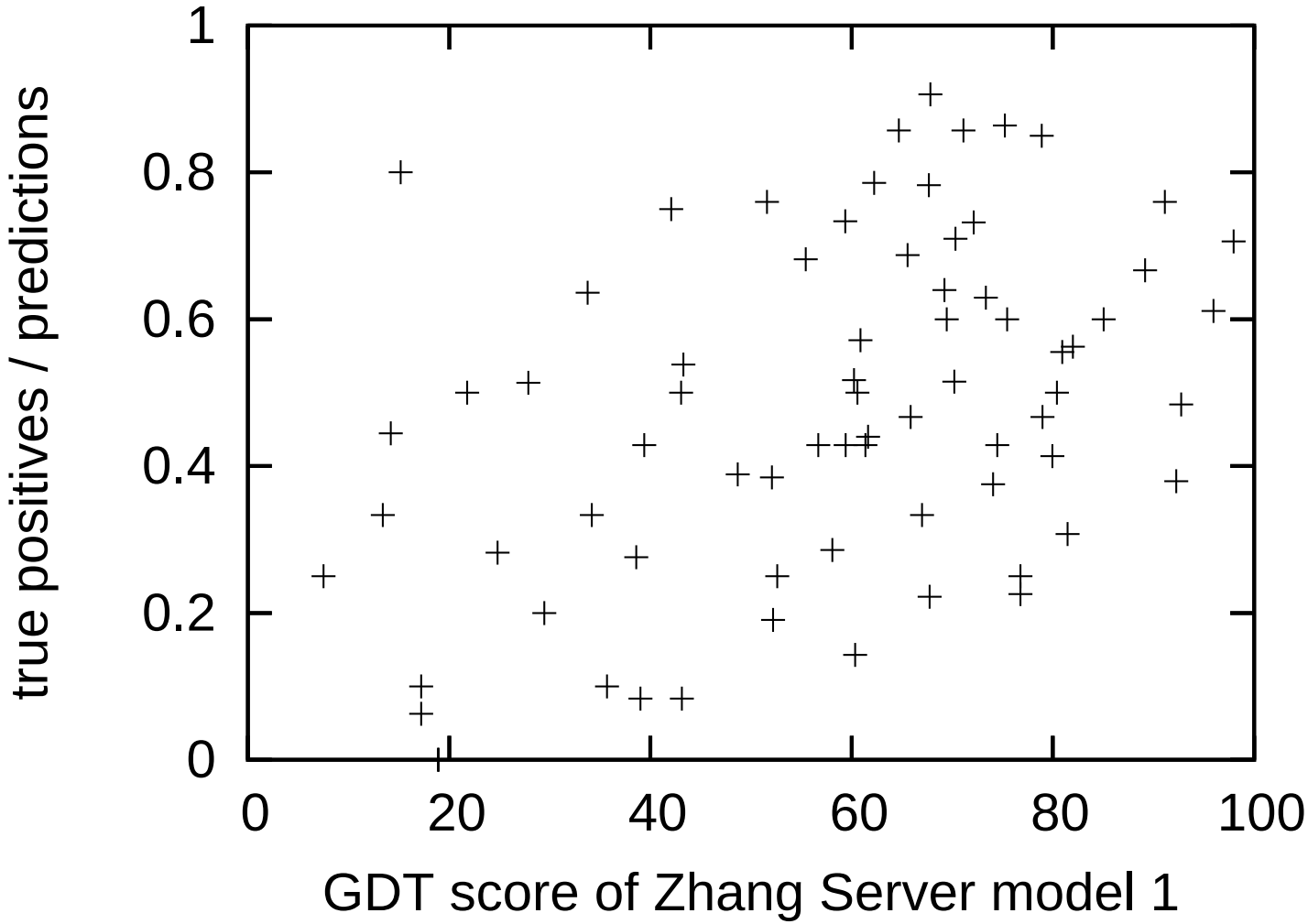
The Bad: T0307



Accuracy vs. Log BLAST E-value

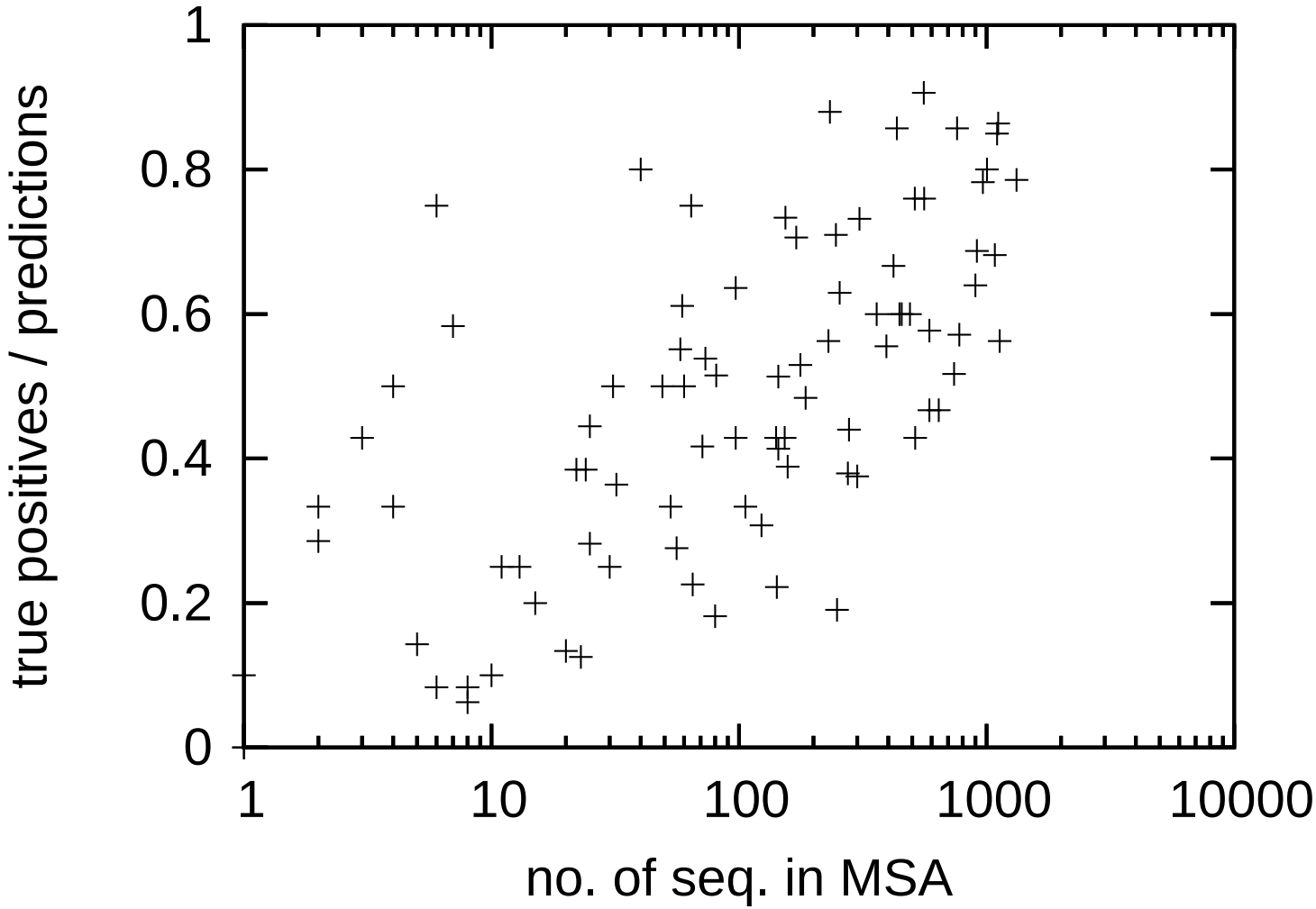


Accuracy vs. Zhang Server GDT

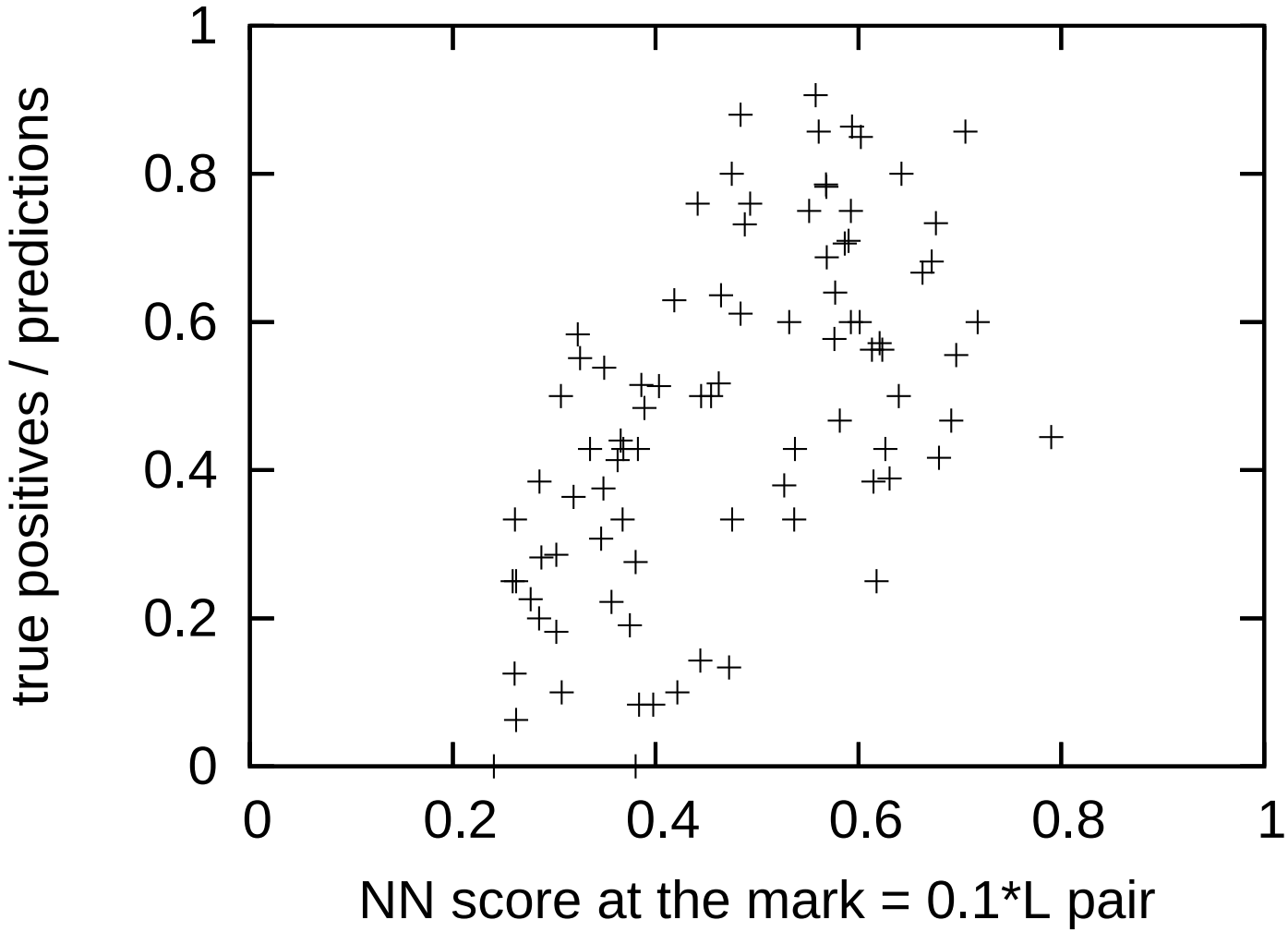


Pearson's r: 0.45

Accuracy vs. # Seq. in MSA



Accuracy vs. Neural Net Score



Pearson's r: 0.58

Conclusion and Future Work

Conclusions:

- Contact predictions go from very poor to very good.
- Contact predictions may sometimes be useful.
- Poor correlation between neural net score and accuracy.

Future work:

- Improve calibration of neural network score.
- Investigate separate predictor(s) for small alignments.
- Demonstrate usefulness of contact predictions.

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