Learning Advisors for Multiple Sequence Alignment

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Parameter advising

Aligners often use one default parameter choice for all inputs.

• The default attempts to have good average accuracy across benchmarks.

• An optimal default choice can be found by inverse alignment [Kececioglu and Kim 2007].

• The default may be a poor choice for specific inputs.

Can we boost aligner accuracy by an input-dependent choice of parameter values?
An advisor has two ingredients:

1. the advisor set of parameter choices used to generate candidate alignments, and
2. an advisor estimator that ranks alignments by estimated accuracy.
Our accuracy estimator **Facet** (Feature-based Accuracy Estimator) is

- a linear combination
- of real-valued feature functions
Parameter advising is selecting a parameter choice $p$ from a set $P$ to maximize the accuracy of an aligner $\mathcal{T}$.

- Given estimator $E_c$, an advisor finds a parameter choice $\tilde{p}$ for input sequences $S$.

$$\tilde{p} := \arg\max_{p \in P} E_c\left(\mathcal{T}_p(S)\right)$$

- The oracle is a perfect advisor that uses true accuracy.
Problems

Finding a parameter advisor involves solving two problems:

• learning advisor coefficients, and
• finding a advisor set of parameter choices.
Problems

There is an issue with defining the accuracy of an advisor when there are ties in estimator value:

• In practice the advisor selects among the alignments that have maximum estimator value.

• When learning an advisor we want to maximize the expected accuracy.
We learn the estimator using examples consisting of

- an alignment $A_{ij}$ produced by aligning benchmark $i$ using parameter choice $j$,
- the associated feature vector $F_{ij} = F(A_{ij})$,
- the true accuracy $a_{ij}$ of $A_{ij}$.

To correct for bias in easy benchmarks we assign a weight $w_i$ to each.
A parameter choice $i$ consists of an assignment of the values of the alignment parameters.

• For Opal a parameter choice is a 5-tuple

$$(\sigma, \gamma_I, \gamma_E, \lambda_I, \lambda_E)$$

• The universe $\mathcal{U}$ is a collection of these parameter choices.
Problems

• The potential output set of parameter choices for the advisor on benchmark $i$ with parameter set $P$ is

$$O_i(P) := \left\{ j \in P : E_c(A_{ij}) \geq e_i^* - \epsilon \right\}$$

where

$$e_i^* := \max \left\{ E_c(A_{i\tilde{j}}) : \tilde{j} \in P \right\}$$

• The expected accuracy of the advisor is the average accuracy over these parameter choices

$$A_i(P) := \frac{1}{|O_i(P)|} \sum_{j \in O_i(P)} a_{ij}$$
Advisor Sets

The input to the Advisor Set problem is

- **cardinality bound** $k$,
- **benchmark weights** $w_i$, where $\sum_i w_i = 1$, $0 \leq w_i \leq 1$
- **accuracies** $a_{ij}$, where $0 \leq a_{ij} \leq 1$
- **feature vectors** $F_{ij} = (f_{ij1}, f_{ij2}, \cdots, f_{ijt})$, where $0 \leq f_{ijh} \leq 1$
- **error tolerance** $\varepsilon \geq 0$
- **estimator coefficients** $c = (c_1, \ldots, c_t)$, where each $c_i \geq 0$ and $\sum_i c_i = 1$, and
- **universe of parameters choices** $U$. 
Advisor Sets

The output is

- a set $P \subseteq U$ of parameter choices, where $|P| \leq k$ that maximizes the objective function

$$
\sum_{i} w_i A_i(P)
$$

The Advisor Set problem is \textbf{NP}-complete.
Finding advisor sets

Advisor Set can be modeled as an integer linear program.

• ILP cannot be solved to optimality in a reasonable amount of time.

• Optimal sets for small cardinalities $k$ can be found by exhaustive search.

We have an approximation algorithm that

• finds an $\frac{l}{k}$-approximation of the optimal advisor set, 
• for any constant $l \leq k$.

The approximation ratio is tight for tolerance $\varepsilon = 0$. 
Advisor Estimator

The input to the Advisor Estimator problem is

• weights $w_i$ on the benchmarks,
• accuracies $a_{ij}$ of the alternate alignments,
• feature vectors $F_{ij}$ for the alternate alignments,
• error tolerance $\varepsilon$, and
• advisor set $P$ of parameter choices.
The output is

- estimator coefficient vector \( c = (c_1, \ldots, c_t) \), where each \( c_i \geq 0 \) and \( \sum_i c_i = 1 \) that maximizes the objective function

\[
\sum_i w_i A_i(P)
\]

The Advisor Estimator problem is \textbf{NP-complete}. 
Learning the estimator

To learn the estimator we find optimal coefficients that fit

- accuracy values of the examples, or
- accuracy differences on pairs of examples.

![Diagram showing alignment accuracy (F) vs. estimator value (E)]
Experimental results: Advisor estimator

Best features trend well with accuracy.

Facet estimator has better spread than its features.
Known estimators display very different trends. For parameter advising, an estimator needs to have good slope and spread.
Experimental results: Advisor estimator

Advising accuracy of various accuracy estimators

As the cardinality of $P$ increases, Facet accuracy increases.
Experimental results: Advisor sets

Advising accuracy on oracle, exact and greedy parameter sets

The greedy set is essentially as good as the optimal exact set.
Experimental results: Advisor sets

Advising accuracy on oracle, exact and greedy parameter sets

Finding advisor sets improves accuracy of other estimators.
Summary

Our current work has made the following contributions:

• **New estimator Facet** that is significantly more accurate for parameter advising

• **Problem formulations** for learning an advisor that are NP-complete

• **Difference-fitting** technique for estimator coefficients that is close to optimal

• **Approximation algorithm** for advisor sets that is close to optimal
Further research

• Develop a core column predictor for feature functions

• Extend the estimator from protein to DNA alignments

• Expand the definition of a parameter choice to include the aligner.
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Come see my poster
Today: 31
Sunday: N25

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Feature functions

There are three types of protein secondary structure

• α-helix,
• β-strand,
• coil.
Secondary structure blockiness

A block $B$ in alignment $A$ is

- an interval of at least $l$ columns,
- a subset of at least $k$ rows,
- with the same secondary structure for all positions in $B$. 
Secondary structure blockiness

A packing $P$ for alignment $A$ is

- a set of blocks from $A$,
- whose columns are disjoint.

The value of $P$ is the number of substitutions it contains.
Secondary structure blockiness

The blockiness score of an alignment is

- the maximum value of any packing $P$ of an alignment $A$
- normalized by the total number of substitutions in the alignment
**Theorem** (Evaluating Blockiness)

Blockiness can be computed in \( O(mn) \) time, for an alignment with \( m \) rows and \( n \) columns.

**Algorithm**

- Graph construction takes \( O(mn) \) time.
- Graph has \( O(n) \) nodes, \( O(ln) \) edges.
- Longest path takes \( O(n) \) time.
Results

Accuracy of advisors by default parameter bin

In all bins, Facet outperforms all estimators.
Alignment accuracy is measured with respect to a reference alignment.

- accuracy is the fraction of substitutions of the reference that are in the computed alignment,
- measured on the core columns of the reference.

```
reference alignment
... a D E h s ...
... d S R – d ...
... a N H l t ...
```

```
computed alignment
... a D E h – s ...
... d S R – – d ...
... a N – H l t ...
```

66.7% accuracy
Contributions

Our approach **Facet** (“Feature-based ACcuracy EsTimator”)  
- estimates accuracy by a polynomial on the features,  
- efficiently learns the polynomial coefficients from examples,  
- uses novel features that are fast to evaluate,  
- utilizes an optimal feature subset.

Applied to **parameter advising**, Facet:  
- finds an optimal parameter set of a given cardinality,  
- outperforms other estimators in accuracy across the full range of benchmarks,  
- boosts aligner accuracy on hard benchmarks by 20% over the best default parameter choice.
Optimal Advisor

The input is

- **cardinality** bound \( k \),
- **weights** \( w_i \) on the benchmarks,
- **accuracies** \( a_{ij} \) of the alternate alignments,
- **feature vectors** \( F_{ij} \) for the alternate alignments, and
- an **error tolerance** \( \varepsilon \),

Output

- set \( P \subseteq \{1, \ldots, m\} \) of **parameter choices** where \( |P| \leq k \), and
- estimator **coefficients** \( c = (c_1, \ldots, c_l) \in Q \)
Learning the estimator

**Difference-fitting** tries to find a monotonic estimator that matches positive differences in true accuracy.

\[
c^* := \arg\min_{c \in \mathcal{R}^t} \sum_{(A, B) \in \mathcal{P}} w_{AB} \left( \max \left\{ \left( F(B) - F(A) \right) - \left( E_c(B) - E_c(A) \right), 0 \right\} \right)
\]

- all possible coefficients
- all important pairs of examples
- true accuracy difference
- estimated difference
- only penalize underestimating differences
- controls influence of large errors