Encodings of amino acids and their impact on signal peptide prediction

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Outline

1. Motivation
2. Amino acid properties
   - Size
   - Polarity
   - PI
   - Hydrophobicity
   - α-chain
3. Methods
   - Amino acid groupings
   - Cross-validation
4. Cross-validation
   - AUC
   - H
   - Specificity
   - Mean cleavage site displacement
5. Conclusions and perspectives

To reduce dimensionality of the problem, signalHsmm aggregates amino acids to four physicochemical groups.

Groups
H, K, R
C, F, I, L, M, U, V, W
N, Q, S, T
A, D, E, G, P, Y

Classification of amino acids used by signalHsmm.

Is the default grouping optimal?

How does grouping of amino acids influence detection of signal peptides and cleavage sites?

Assumptions:

1. The optimal number of amino acid groups is 4.
2. Important properties are: size, polarity, charge, hydrophobicity and probability of being in the α-chain.
3. All properties above are equally important and distinguish signal peptides from matures proteins.

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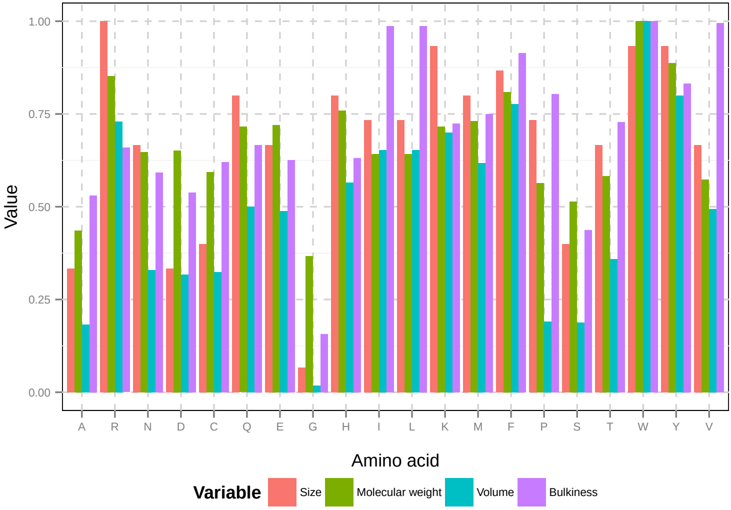
Value
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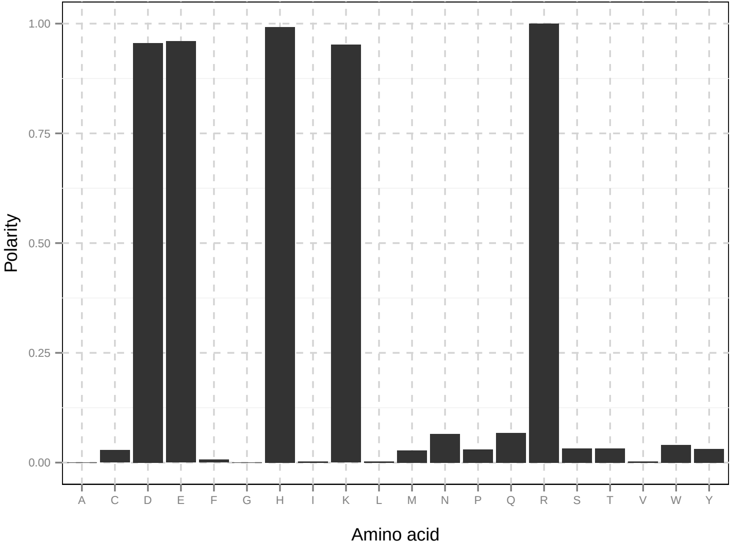
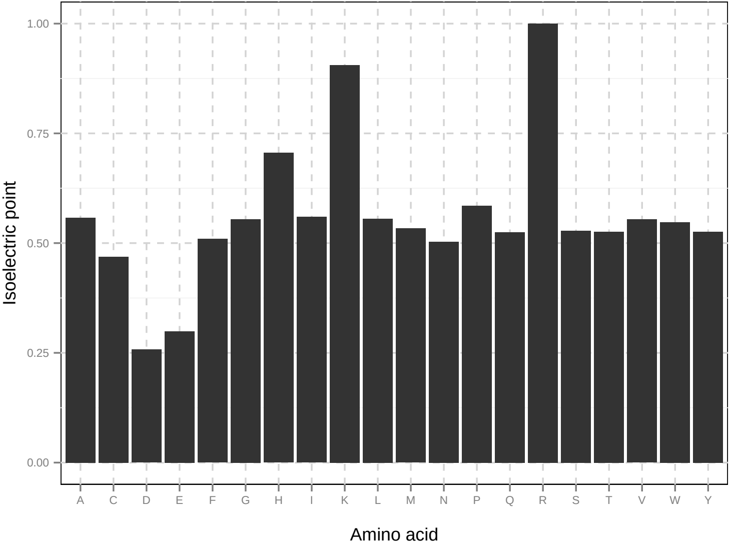
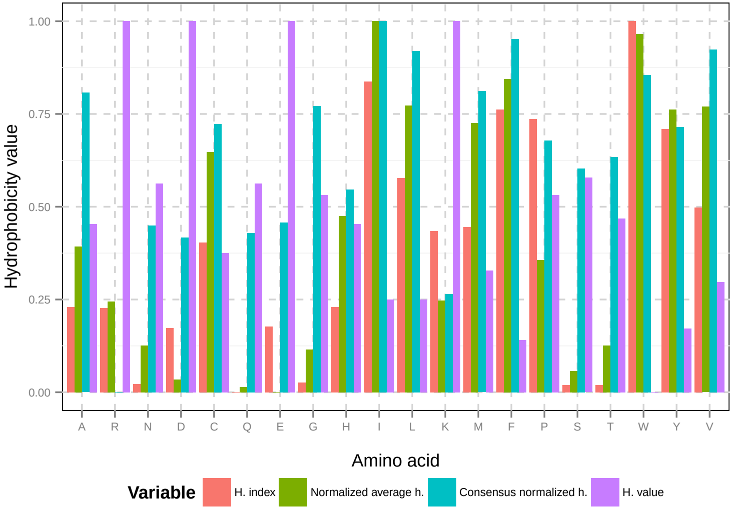
0.75
0.50
0.25
0.00
A
R
N
D
C
Q
E
G
H
I
L
K
M
F
P
S
T
W
Y
V
Amino acid
Variable
Size
Molecular weight
Volume
Bulkiness


1.00
0.75
0.50
0.25
0.00
Polarity
A
C
D
E
F
G
H
I
K
L
M
N
P
Q
R
S
T
V
W
Y
Amino acid


Isoelectric point
1.00
0.75
0.50
0.25
0.00
A
C
D
E
F
G
H
I
K
L
M
N
P
Q
R
S
T
V
W
Y
Amino acid


Hydrophobicity value
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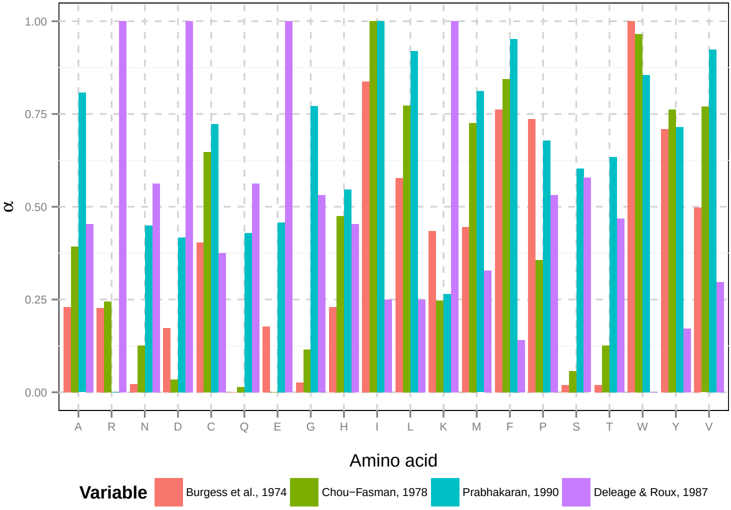
0.75
0.50
0.25
0.00
A
R
N
D
C
Q
E
G
H
I
L
K
M
F
P
S
T
W
Y
V
Amino acid
Variable
H. index
Normalized average h.
Consensus normalized h.
H. value


1.00
0.75
0.50
0.25
0.00
α
A
R
N
D
C
Q
E
G
H
I
L
K
M
F
P
S
T
W
Y
V
Amino acid
Variable
Burgess et al., 1974
Chou−Fasman, 1978
Prabhakaran, 1990
Deleage & Roux, 1987

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For each combination of each variant of all properties:

1. calculate euclidean distance between amino acids;
2. cluster amino acids (complete-linkage clustering);
3. extract four highest clusters of amino acids.

67 amino acid groupings in total (signalHsmm, 2 standard, 65 newly created).

For each grouping:

1. sample 3722 from 134044 negative sequences (to have balanced data set);
2. perform 5-fold cross-validation using all groupings (train an instance of signalHsmm using a single grouping);
3. repeat steps 1:2 15 times.

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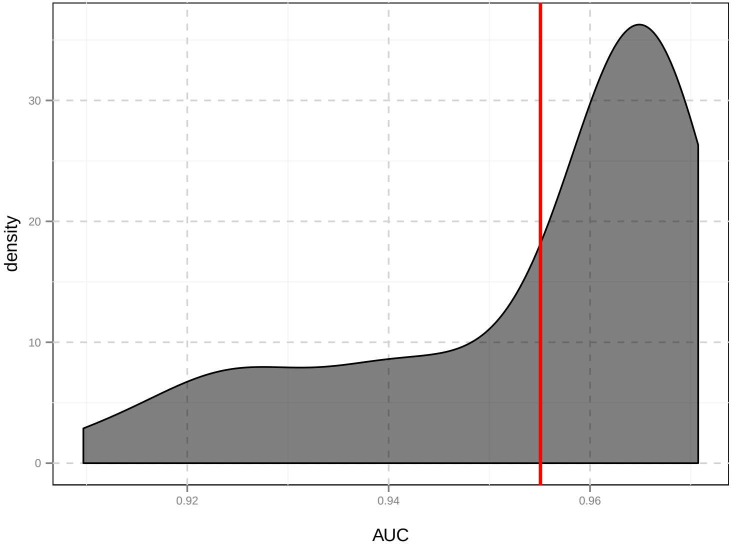
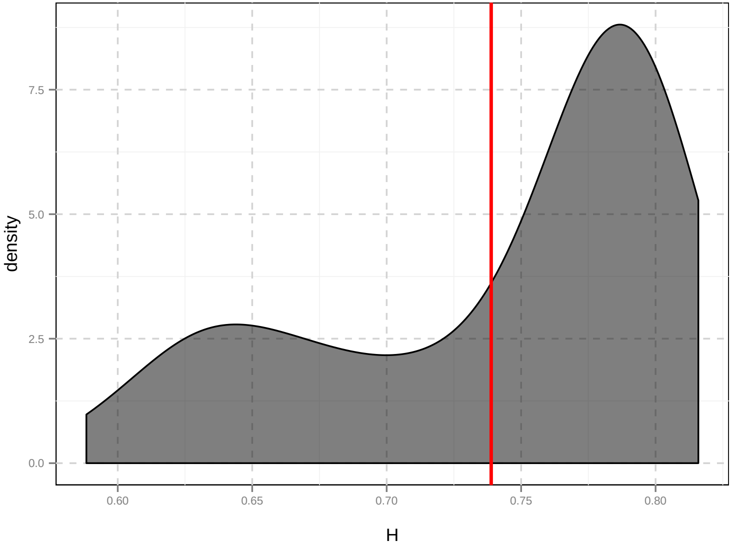

density
30
20
10
0
0.92
0.94
0.96
AUC

Groups
A, F, I, L, M, V, W
K, R
C, G, N, P, Q, S, T, Y
D, E, H

Best grouping of amino acids - AUC.

Groups
A, L, M, N, Q, S, T, V
D, E, H, K, R
C, G
F, I, P, W, Y

Worst grouping of amino acids - AUC.

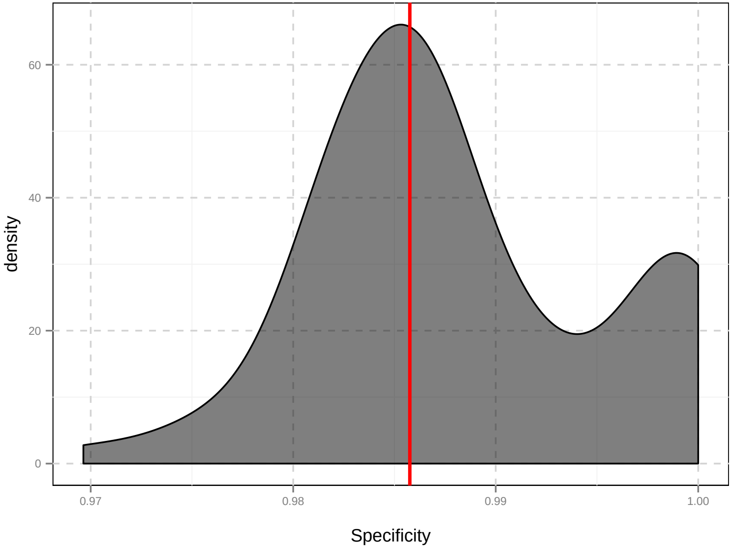

density
7.5
5.0
2.5
0.0
0.60
0.65
0.70
0.75
0.80
H

Groups
A, F, I, L, M, V, W
K, R
C, G, N, P, Q, S, T, Y
D, E, H

Best grouping of amino acids - H.

Groups
A, L, M, N, Q, S, T, V
D, E, H, K, R
C, G
F, I, P, W, Y

Worst grouping of amino acids - H.

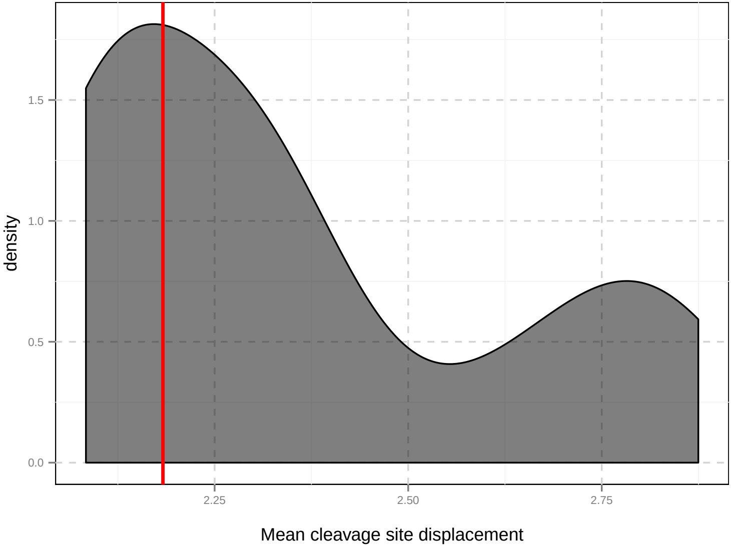

density
60
40
20
0
0.97
0.98
0.99
1.00
Specificity

Groups
A, C, G, S
H, K, R
F, I, L, M, N, P, Q, T, V, W, Y
D, E

Best grouping of amino acids - specificity.

Groups
A, M
D, E, H, K, R
G, N, Q, S, T
C, F, I, L, P, V, W, Y

Worst grouping of amino acids - specificity.

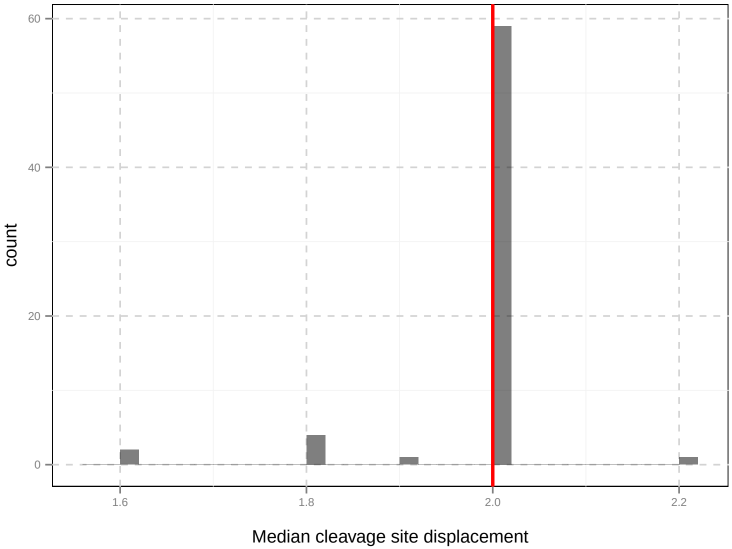

density
1.5
1.0
0.5
0.0
2.25
2.50
2.75
Mean cleavage site displacement

Groups
A, C, G, N, P, Q, S, T
H, K, R
D, E
F, I, L, M, V, W, Y

Best grouping of amino acids - mean cleavage site displacement.

Groups
A, G, I, L, M, P, V
H, K, R
D, E
C, F, N, Q, S, T, W, Y

Worst grouping of amino acids - mean cleavage site displacement.


count
60
40
20
0
1.6
1.8
2.0
2.2
Median cleavage site displacement

Groups
A, C, G, N, P, Q, S, T, V
H, K, R
D, E
F, I, L, M, W, Y

Best (ex aequo) grouping of amino acids - median cleavage site displacement.

Groups
A, C, G, I, N, P, Q, S, T, V
H, K, R
D, E
F, L, M, W, Y

Best (ex aequo) grouping of amino acids - median cleavage site displacement.

Groups
A, G, I, L, M, P, V
H, K, R
D, E
C, F, N, Q, S, T, W, Y

Worst grouping of amino acids - median cleavage site displacement.

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Grouping on amino acids has strong impact on misclassifications.

Detection of signal peptides:

1. charged amino acids should be grouped separately;
2. aromatic amino acids should not be grouped together;

Detection of cleavage sites:

1. hydrophobic amino acids should be grouped together;
2. amino acids typical for cleavage sites (A, G, I, L, P, V) should not be grouped together.