From Sequences to Structures: A Computational Probability Approach Based on Percolation Theory

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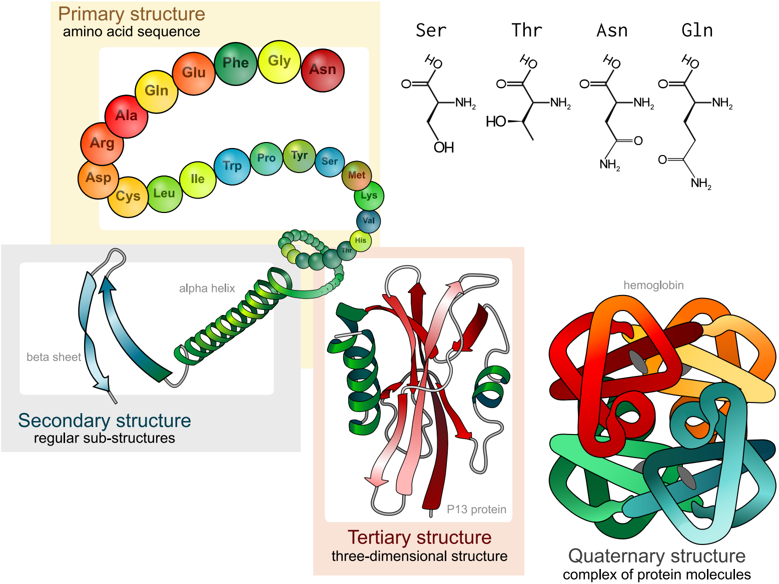
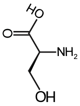
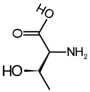
Protein Structure



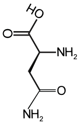
Ser



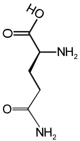
Thr



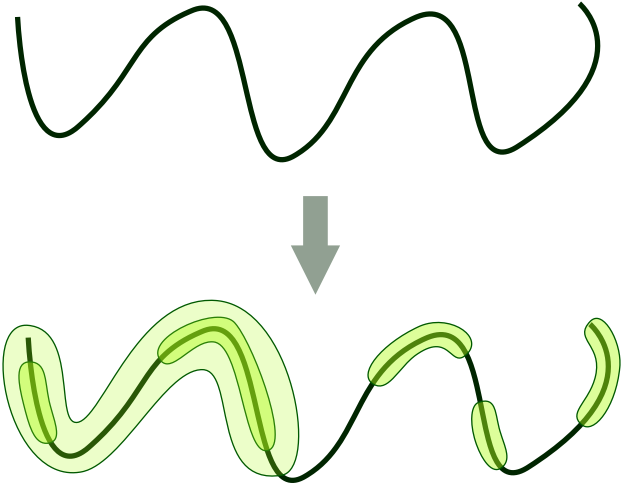
Asn



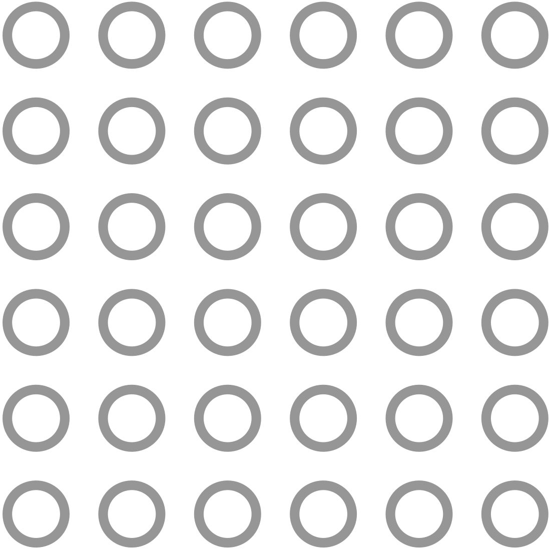
Gln



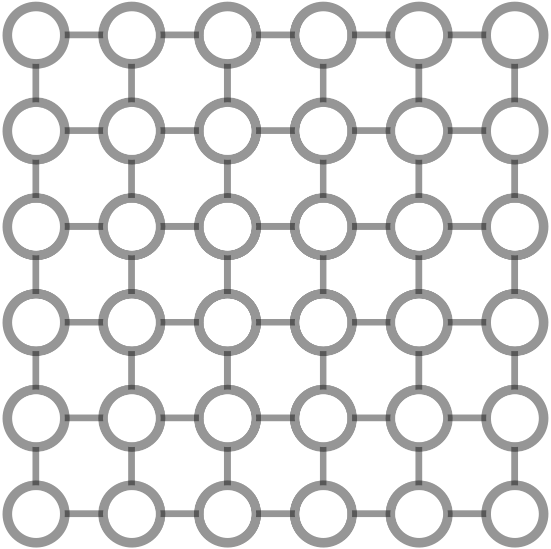
Can we find probably structurally important segments in a sequence?



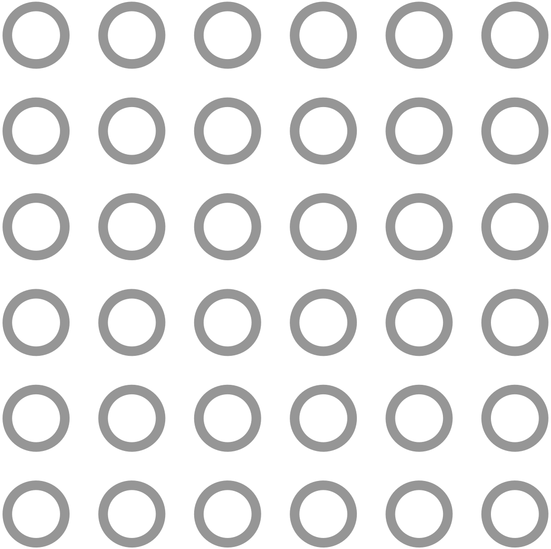
Percolation Example



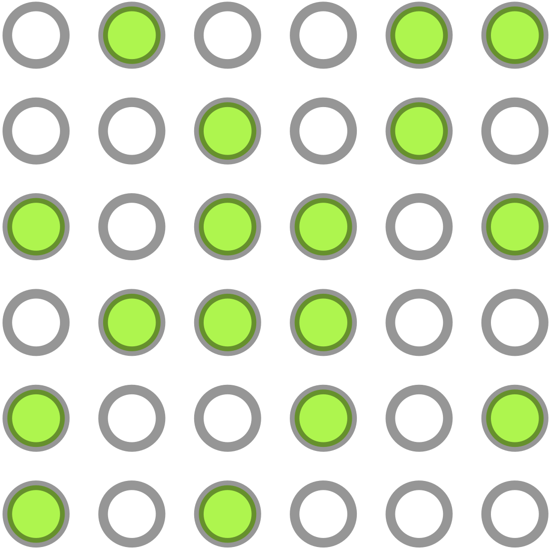
Percolation Example



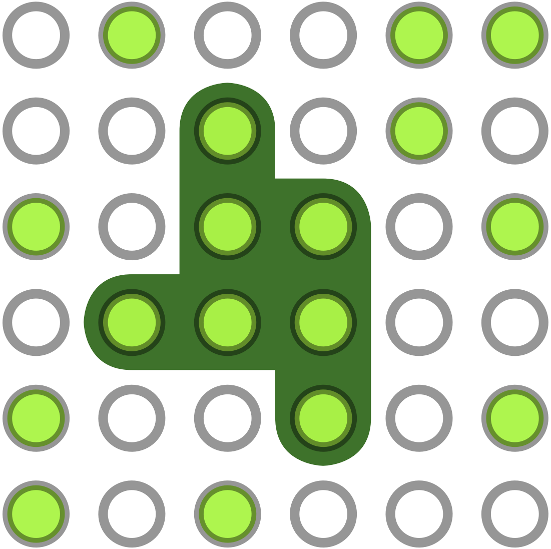
Percolation Example



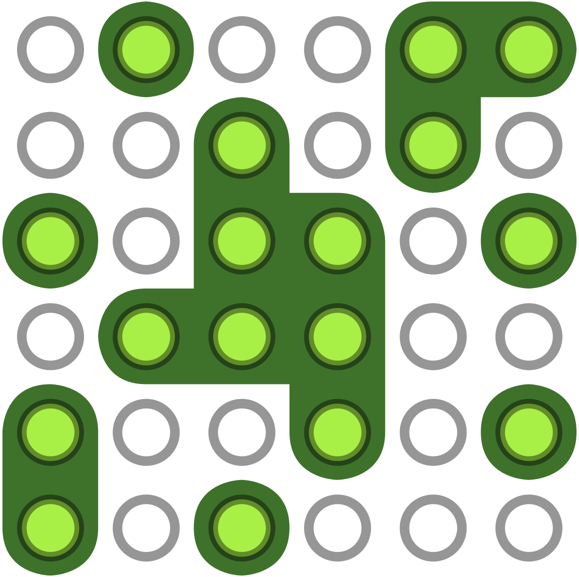
Percolation Example



Percolation Example



Percolation Example



Clusters in a sequence of nodes

We would like to develop a mathematical model that can identify structurally important clusters in sequences of nodes.

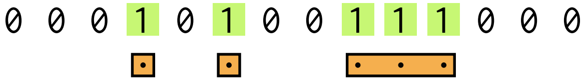
Clusters in a sequence of nodes

Assuming that some of the nodes in the sequence promote cluster formation, consider the following system:

There is a sequence of *1*s and *0*s.

```
0 0 0 1 0 1 0 0 1 1 1 0 0 0
```

*1*s form clusters, while *0*s do nothing.



```
0 0 0 1 0 1 0 0 1 1 1 0 0 0
```

Clusters in a sequence of nodes

Intro
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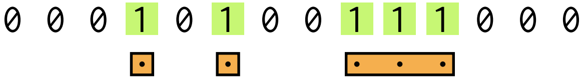
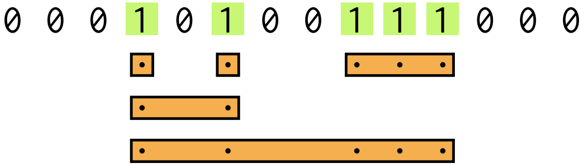
Connect only immediate neighbors.



0 0 0 1 0 1 0 0 1 1 1 0 0 0

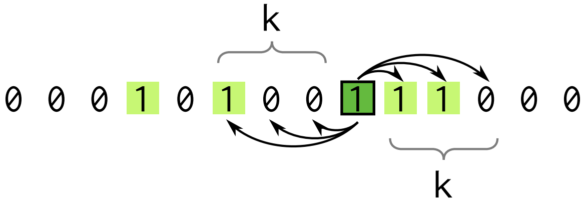
Is it good enough? Not really. We would like to capture clusters separated by *0*s.



0 0 0 1 0 1 0 0 1 1 1 0 0 0

Clusters in a sequence of nodes

Generalize: Each node is connected to k many nodes to the right, and k many to the left. $k \geq 0$.



The resulting clusers *may have gaps* of at most $k - 1$ consecutive *0*s.

Clusters for different k

0 0 0 1 0 1 0 0 1 1 1 0 0 0

k=0

k=1

k=2

k=3

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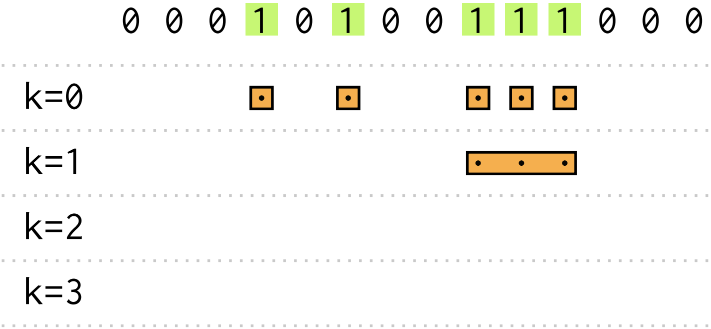
Clusters for different k

	0	0	0	1	0	1	0	0	1	1	1	0	0	0
k=0				⊡		⊡			⊡	⊡	⊡			
k=1														
k=2														
k=3														

Clusters for different k



Clusters for different k

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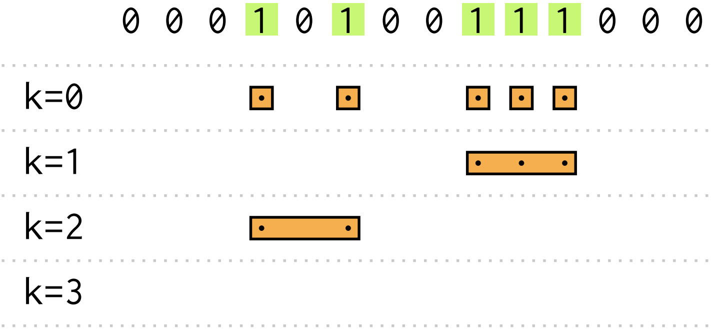


0 0 0 1 0 1 0 0 1 1 1 0 0 0

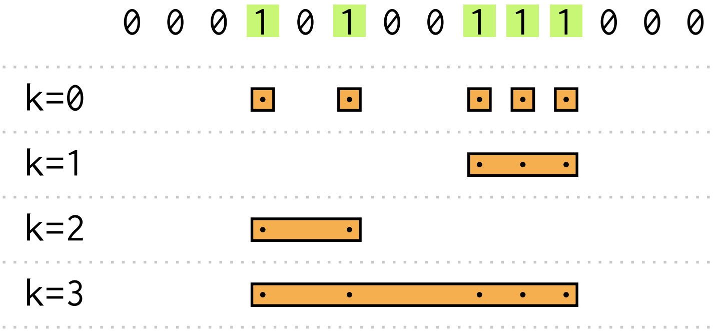
k=0

k=1

k=2

k=3

Clusters for different k



0 0 0 1 0 1 0 0 1 1 1 0 0 0

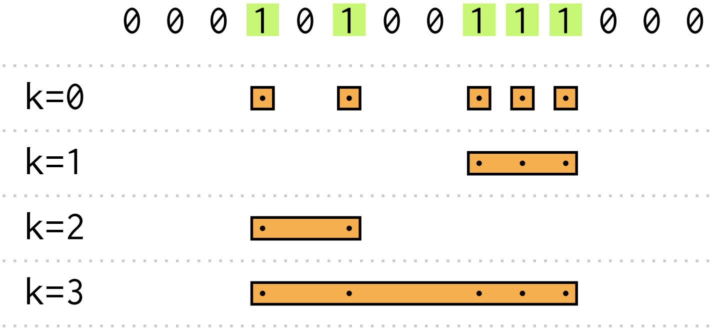
k=0

k=1

k=2

k=3

Clusters for different k



0 0 0 1 0 1 0 0 1 1 1 0 0 0

k=0

k=1

k=2

k=3

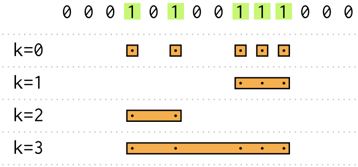
Too many clusters! Which are really important?

Probabilistic model

If it is observed that *1*s and *0*s are found in sequences with certain probabilities:

- p is the probability of *1*s, and
- $q = 1 - p$ is the probability of *0*s,

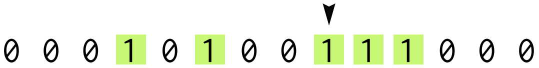
we can compute, how probable each of the clusters is.



Probabilistic model

Def. *Size of a cluster is the number of 1s in it.*

Def. *Given a 1, let $w_{k,s}$ be the probability to find that 1 in a cluster of size s at level k.*


0 0 0 1 0 1 0 0 1 1 1 0 0 0

$$w_{k,s} = (\beta_{k,s} - \beta_{k-1,s}) \cdot q^{2k},$$

$$\text{where } \beta_{k,s} = s(p\alpha_k)^{s-1}, \text{ and } \alpha_k = \frac{1-q^k}{1-q}.$$

Choosing the best cluster

Ok, if we found a cluster, how rare is it?

Def. Weight *of a cluster with size s at level k is*

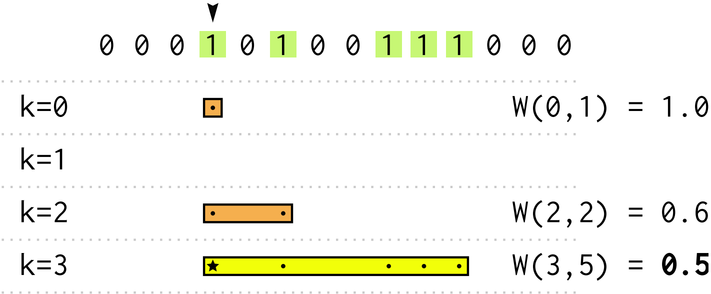
$$W(k,s) = \frac{1}{\zeta_k} \min\left(\sum_{t=1}^{s} w_{k,t}, \sum_{t=s}^{\infty} w_{k,t} \right)$$

The normalizing constant $\zeta_k = \sum_{s=1}^{\infty} w_{k,s}$.

If a cluster has very small weight, it is not very likely to occure at random. Thus we can expect that it is important.

If a given *1* belongs to several clusters, we choose the one with the *least* weight.

Choosing the best cluster



0 0 0 1 0 1 0 0 1 1 1 0 0 0

k=0 W(0,1) = 1.0

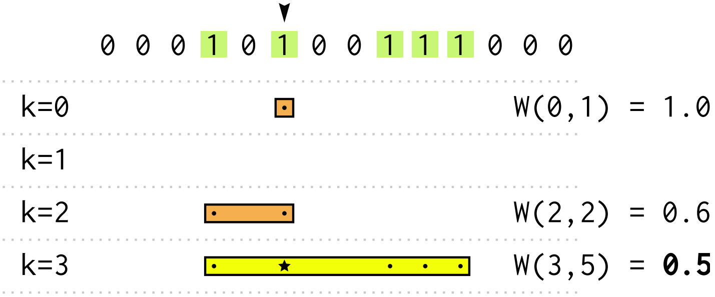
k=1

k=2 W(2,2) = 0.6

k=3 W(3,5) = **0.5**

If a given *1* belongs to several clusters, we choose the one with the *least* weight.

Choosing the best cluster



0 0 0 1 0 1 0 0 1 1 1 0 0 0

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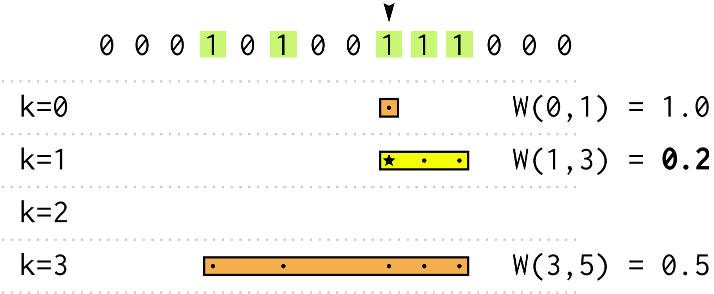
Choosing the best cluster



0 0 0 1 0 1 0 0 1 1 1 0 0 0

k=0 W(0,1) = 1.0

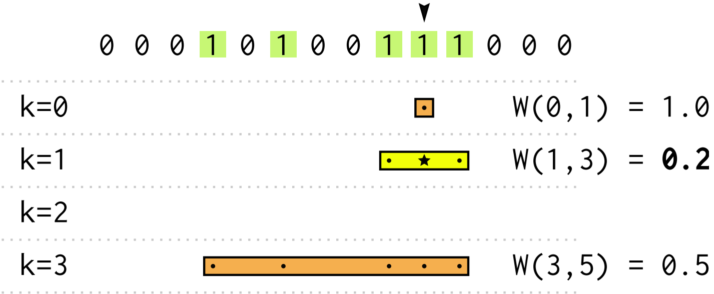
k=1 W(1,3) = **0.2**

k=2

k=3 W(3,5) = 0.5

If a given *1* belongs to several clusters, we choose the one with the *least* weight.

Choosing the best cluster



0 0 0 1 0 1 0 0 1 1 1 0 0 0

k=0 W(0,1) = 1.0

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k=2

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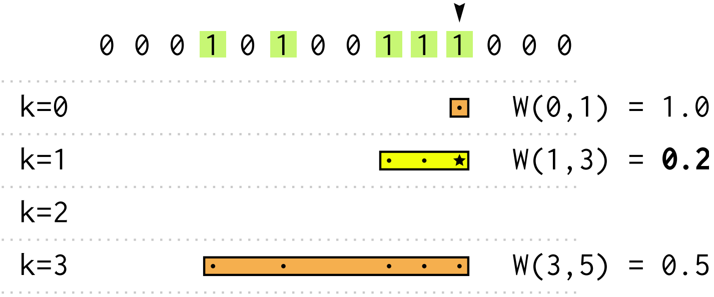
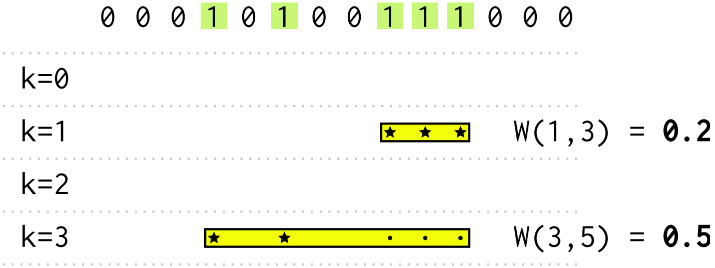
If a given *1* belongs to several clusters, we choose the one with the *least* weight.

Choosing the best cluster



If a given *1* belongs to several clusters, we choose the one with the *least* weight.

Chosen best clusters can be nested



0 0 0 1 0 1 0 0 1 1 1 0 0 0

k=0

k=1 ★ ★ ★ W(1,3) = **0.2**

k=2

k=3 ★ ★ • • • W(3,5) = **0.5**

If a given *1* belongs to several clusters, we choose the one with the *least* weight.

Choosing the best cluster

It can be nice to know the distribution of the best clusters. At what level k they are usually found?

Let $P(k)$ be the probability that, for a given 1, the best cluster is at the level k.

Theorem. $P(k) = 0$ *for all* k.

That is, for any cluster, you can always find a better one, if the sequence is long enough.

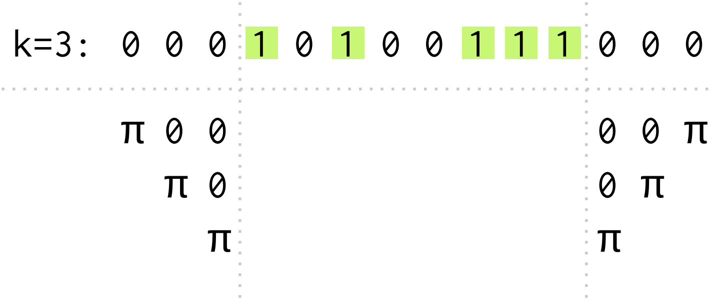
We have to stop clusters growing infinitely large!

Need for breakers

Some nodes that were previously zeroes now become *breakers*. Once reached, they stop cluster growth completely. Call them π in our single-character notation.

Let π also denote the probability of breakers.

$$p + q + \pi = 1$$



```
k=3:  0 0 0 | 1 0 1 0 0 1 1 1 | 0 0 0
      ------+-----------------+------
      π 0 0 |                 | 0 0 π
        π 0 |                 | 0 π
          π |                 | π
```

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Probability $w_{k,s}$ for the breakers case

With the introduction of breakers, we actually can get three types of clusters:

Open on both sides:

$$w_{k,s}^{(0\pi)} = (\beta_{k,s} - \beta_{k-1,s}) \cdot q^{2k}$$

With a breaker on one side:

$$w_{k,s}^{(1\pi)} = (\beta_{k,s} - \beta_{k-1,s}) \cdot 2q^{k} \alpha_k \pi$$

With breakers on both sides:

$$w_{k,s}^{(2\pi)} = (\beta_{k,s} - \beta_{k-1,s}) \cdot (\alpha_k \pi)^2$$

Weight $W(k,s)$ for the breakers case

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With the introduction of breakers, we actually can get three types of clusters:

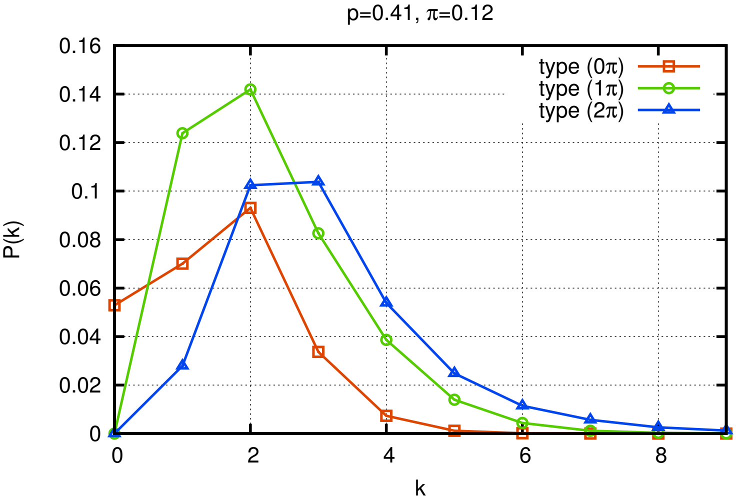
$$W^{(X\pi)}(k,s) = \frac{\min\left(\sum_{t=1}^{s} w_{k,t}^{(X\pi)},\ \sum_{t=s}^{\infty} w_{k,t}^{(X\pi)}\right)}{\sum_{t=1}^{\infty}\left(w_{k,t}^{(0\pi)} + w_{k,t}^{(1\pi)} + w_{k,t}^{(2\pi)}\right)}$$

where $X \in \{0,\ 1,\ 2\}$.

$$\sum_{t=1}^{\infty} w_{k,t}^{(X\pi)} = \sum_{t=1}^{\infty} (\beta_{k,t} - \beta_{k-1,t}) \cdot C_k^{(X\pi)} = (B_k - B_{k-1}) \cdot C^{(X\pi)},$$

where $B_k = \dfrac{1}{(p\alpha_k - 1)^2}$, $C_k^{(0\pi)} = q^2$, $C^{(1\pi)} = 2q^k\alpha_k\pi$, and $C_k^{(2\pi)} = (\alpha_k\pi)^2$. Also, $\alpha_k = (1-q^k)/(1-q)$ (the same as before).

$P(k)$. The probability to choose a cluster at level k.



Experiments with pretein databases

Can we make our method find secondary structures (helices and strands)?

How amino acids map to $\{1,\ 0,\ \pi\}$? Use genetic algorithm.

We simply say that if a residue is covered by any of our clusters, we predict that it belongs to a helix or a strand. Then, check, how good the prediction is.

$$\text{Fitness} = \frac{\text{number of correctly predicted residues}}{\text{total number of residues}}$$

Experiments with pretein databases

We get with fitness 67%:

$$\begin{aligned} \{V,\ I,\ L,\ F,\ M,\ Y,\ W,\ A\} &\longrightarrow 1 \\ \{P,\ G\} &\longrightarrow \pi \\ \text{others} &\longrightarrow 0 \end{aligned}$$

Hydrophobic amino acids are responsible for cluster formation.

Can we really predict secondary structures?

Secondary structure prediction?

There are “Helix”, “Strand”, and “Coil” regions.

1) Drop clusters that have size $s = 1$.

2) We predict that residues in clusters formed at levels $k = 1$ and $k = 2$ are *Strands*.

3) We predict that the remaining residues in other clusters are *Helices*.

4) The rest residues are *Coils*.

$$\text{Q3} = \frac{\text{number of correctly predicted residues}}{\text{total number of residues}}$$

Secondary structure prediction?

Genetic algorithm on randomly selected records from DSSP produced the following map:

$$\begin{aligned} \{V,\ I,\ L,\ F,\ M,\ Y\} &\rightarrow 1 \\ \{P,\ G\} &\rightarrow \pi \\ \text{others} &\rightarrow 0 \end{aligned}$$

With this map, on a standard protein dataset CB-513, we get

$$Q3 = 55\%.$$

This is not 70-80%, but still it is better than, e.g. Chou-Fasman method that has $Q3 = 46 - 48\%$.

Future work

1. To go beyond secondary structures:
   - How to make breakers weaker?
   - Probabilistic assignment of the map residue $\longrightarrow \{1, 0, \pi\}$.
   - Get rid of breakers, and insert strings of zeroes instead, e.g. $P \longmapsto 00000$, and $G \longmapsto 00$.
2. How far can we get in predicting sec. structures?
   - Map pairs or triples of residues to $\{1, 0, \pi\}$.
   - Search for helices and strands separately.
3. Use clusters to guide protein folding simulation.