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Clustering of Multidimensional Random Variables to Improve HMM Sequence Alignment Accuracy

Project proposal

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1 Introduction

1.1 Clustering

Given $X = \{x_i | x_i \in \mathbb{R}^d, i \in (1 \dots n)\}$ and $m \in \mathbb{N}$, where n is the number of points, m - number of clusters.
Clustering algorithm takes X and m and outputs $C = \{c_i | c_i \in (1 \dots m), i \in (1 \dots n)\}$.

Figure 1: Example of clustering for $d = 2$, $m = 2$, color represents class.

1.2 Strings

Definition 1.1. String of length l over alphabet $A = \{1 \dots m\}$ is a map $s : \{1 \dots l\} \to A$. Usually elements of A are denoted as characters for convenience.

Definition 1.2. Alignment of strings s_1 and s_2 of lengths l_1 and l_2 respectively, over alphabet A is a pair of strings $\hat{s}_1$ and $\hat{s}_2$ of length l over alphabet $A \sqcup \{-\}$, such that there exists increasing functions $f_i : \{1 \dots l_i\} \to \{1 \dots l\}$ such that $\hat{s}_i|_{\hat{s}_i^{-1}(A)} \circ f_i = s_i$.

Remark. $\mathrm{Im}(f_i) = \hat{s}_i^{-1}(A)$

Example 1.1. Alignment of strings $s_1 = CABCAABA$ and $s_2 = ABADBBAD$ over alphabet $\{A, B, C, D\}$.

$$\left\| \begin{array}{c|cccccccc} s_1 & \mathrm{C} & \mathrm{A} & \mathrm{B} & \mathrm{C} & \mathrm{A} & \mathrm{A} & \mathrm{B} & \mathrm{A} \\ s_2 & \mathrm{A} & \mathrm{B} & \mathrm{A} & \mathrm{D} & \mathrm{B} & \mathrm{B} & \mathrm{A} & \\ \hat{s}_1 & \mathrm{C} & \mathrm{A} & \mathrm{B} & \mathrm{C} & - & \mathrm{A} & \mathrm{A} & \mathrm{B} & \mathrm{A} \\ \hat{s}_2 & - & \mathrm{A} & \mathrm{B} & - & \mathrm{A} & \mathrm{D} & \mathrm{B} & \mathrm{B} & \mathrm{A} \end{array} \right\|$$

Definition 1.3. For given matrix $G \in \mathbb{R}^{|A| \times |A|}$ and $p \in \mathbb{R}$ score of alignment $\hat{s}_1, \hat{s}_2$ is

$$S(\hat{s}_1, \hat{s}_2) = \sum_{i=1}^{l} \delta_i, \text{ where } \delta_i = \begin{cases} g_{\hat{s}_1(i)\hat{s}_2(i)}, & \hat{s}_1(i) \neq - \text{ and } \hat{s}_2(i) \neq - \\ p, \end{cases}$$

Theorem 1. If G is symmetric and $g_{ij} = \begin{cases} 0, & i = j \\ > 0, \end{cases}$ and $p > 0$, then we can define metric for strings over alphabet A as

$$d(s_1, s_2) = \min\{S(\hat{s}_1, \hat{s}_2)\}$$

Proof. □

Definition 1.4. For a string s of length l, sub-string s_s is a string of length l_s, such that there exists an function

$$f : \{1 \dots l_s\} \to \{1 \dots l\}$$
$$f(i) = i + d$$
$$s \circ f = s_s$$

Definition 1.5. For a string s_1 and s_2 of lengths l_1, l_2 correspondingly, define string-sub-string score as

$$S_s(s_1, s_2) = \min\{S(s_s, s_2) | s_s \text{ is a sub-string of } s\}$$

and corresponding alignment $\hat{s}_1, \hat{s}_2$ are pair of strings of lengths l over alphabet $A \sqcup \{-\}$ such that there exists increasing functions $f_1 : \{1 \dots l_1\} \to \{1 \dots l\}$

Definition 1.6. For a string s of length l and set of strings $R = \{s_1 \dots s_n\}$ of lengths $\{l_1 \dots l_n\}$ correspondingly, multiple alignment is tuple $\hat{s}, \hat{s}_1 \dots \hat{s}_n$, of strings of length l over alphabet $A \sqcup \{-\}$, such that $\sum_{i=1}^{n} S(\hat{s}, \hat{s}_i)$ is minimal.

Definition 1.7. Set of reads R for string s of length l and rate r is

$$R = \{s_s | \text{length of } s_s > l, S_s(s, s_s) < r\}$$

2 Task

Given reference string s_r and reads R for an unknown target string s_t, we know that $S(s_r, s_t) < D$ and whant to find s_t.

Plan:

1. Make multiple alignment of R over s_r.
2. Estimate most likely difference between s_r and s_t.

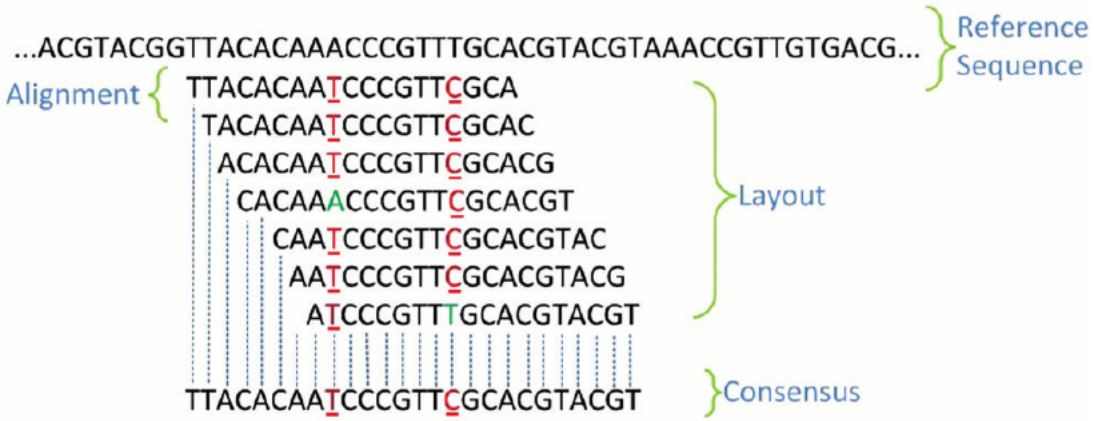

Figure 2: Example of reference string, target string and reads.