Nanopore automata

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Contents

1   Abstract

State machine algorithms for aligning Nanopore reads.

2   Specification

Initial goal (Preliminary Results) is simple reusable code for aligning a segmented nanopore read (with segment currents summarized) to a reference sequence.

Longer-term goals (Specific Aims) include

- quasi-hierarchical series of models for processed→raw data (raw, FAST5, FASTQ, FASTA)

- transducer intersection-style models for read-pair alignment

- systematic strategies for approximation/optimization algorithms, climbing the hierarchy (starting with k-mer or FM-index approaches)

- transducer intersection models for aligning reads from different sequencing technologies

2.1   Parameterization algorithm

Given the following inputs

- Reference genome (FASTA)

- Segment-called reads (FAST5/HDF5)

Perform the following steps

- Perform Baum-Welch to fit a rich model

Rich model incorporates segment statistics.

2.2 Reference search algorithm

Given the following inputs

- Reference genome

- Segment-called reads (FAST5/HDF5)

- Parameterized rich model

Perform the following steps

- Perform Viterbi alignment

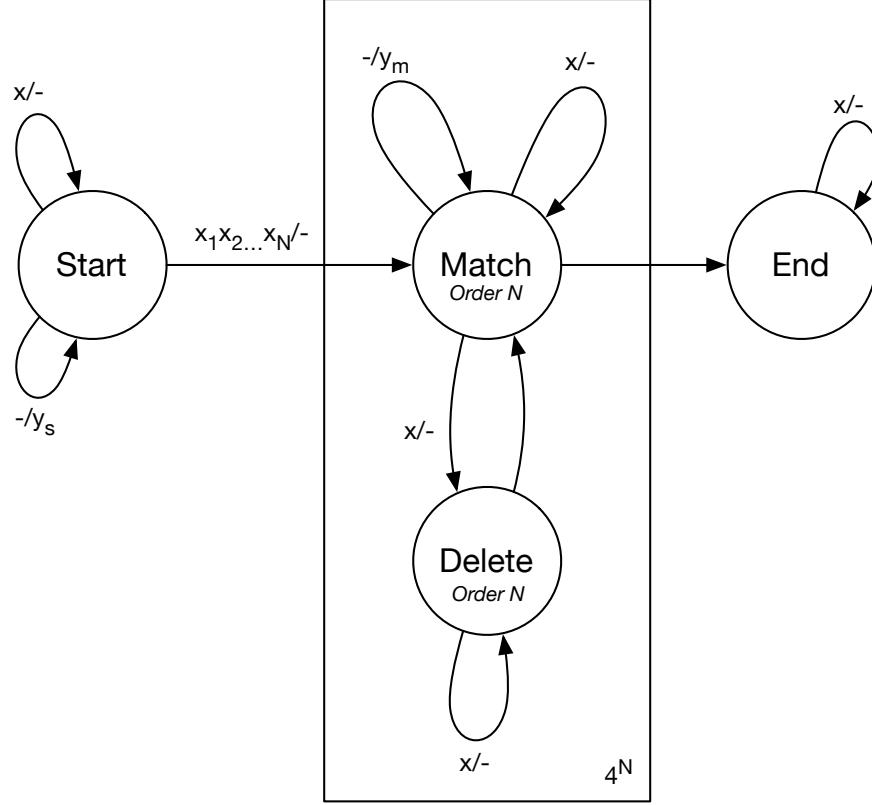## 2.3 Implementation

Libraries etc.

HDF5...

2.4 Evaluation

Strategy...

Data sets...

3 Methods

Model & inference algorithms.

3.1   Model

- Order-N Mealy transducer.

- Input alphabet: $\Omega = \{A, C, G, T\}$ (nucleotides)

- Output alphabet: $\Re$ (real numbers signifying current levels)

- States: Start, End, { Match$_{x_1 \ldots x_N}$, Delete$_{x_1 \ldots x_N}$: $x_1 \ldots x_N \in \Omega^N$}

- Parameters: $p^{\mathrm{StartEmit}}, p^{\mathrm{BeginDelete}}, p^{\mathrm{ExtendDelete}}, \mu^{\mathrm{Start}}, \tau^{\mathrm{Start}},$

  $\{p^{\mathrm{MatchEmit}}_{x_1 \ldots x_N}, \mu^{\mathrm{Match}}_{x_1 \ldots x_N}, \tau^{\mathrm{Match}}_{x_1 \ldots x_N} : x_1 \ldots x_N \in \Omega^N\}$

Transitions:

Source	Destination	Weight	Absorbs	Emits
Start	Start	$p^{\text{StartEmit}}$ $\times P(y_s \mid \mu^{\text{Start}}, \tau^{\text{Start}})$		$y_s \sim \text{Normal}(\mu^{\text{Start}}, \tau^{\text{Start}})$
Start	Start	1	$x \in \Omega$	
Start	$\text{Match}_{x_1 \ldots x_N}$	$1 - p^{\text{StartEmit}}$	$x_1 \ldots x_N \in \Omega^N$	
$\text{Match}_{x_1 \ldots x_N}$	$\text{Match}_{x_1 \ldots x_N}$	$p^{\text{MatchEmit}}_{x_1 \ldots x_N}$ $\times P(y_m \mid \mu^{\text{Match}}_{x_1 \ldots x_N}, \tau^{\text{Match}}_{x_1 \ldots x_N})$		$y_m \sim \text{Normal}(\mu^{\text{Match}}_{x_1 \ldots x_N}, \tau^{\text{Match}}_{x_1 \ldots x_N})$
$\text{Match}_{x_1 \ldots x_N}$	$\text{Match}_{x_2 \ldots x_{N+1}}$	$(1 - p^{\text{MatchEmit}}_{x_1 \ldots x_N})$ $\times (1 - p^{\text{BeginDelete}})$	$x_{N+1} \in \Omega$	
$\text{Match}_{x_1 \ldots x_N}$	$\text{Delete}_{x_2 \ldots x_{N+1}}$	$(1 - p^{\text{MatchEmit}}_{x_1 \ldots x_N})$ $\times p^{\text{BeginDelete}}$	$x_{N+1} \in \Omega$	
$\text{Match}_{x_1 \ldots x_N}$	End	$1 - p^{\text{MatchEmit}}_{x_1 \ldots x_N}$		
$\text{Delete}_{x_1 \ldots x_N}$	$\text{Delete}_{x_2 \ldots x_{N+1}}$	$p^{\text{ExtendDelete}}$	$x_{N+1} \in \Omega$	
$\text{Delete}_{x_1 \ldots x_N}$	$\text{Match}_{x_1 \ldots x_N}$	$1 - p^{\text{ExtendDelete}}$		
End	End	1	$x \in \Omega$	

3.2 Baum-Welch algorithm

As usual.

3.3 Viterbi algorithm

As usual.

4 Results

5 Discussion

6 Acknowledgments

7 Figure Legends

8 Appendix

8.1 Exponential distribution

$$
\begin{aligned}
x &\sim \text{Exponential}(\kappa) \\
P(x|\kappa) &= \kappa \exp(-\kappa x) \\
\text{E}[x] &= \kappa^{-1} \\
\text{Var}[x] &= \kappa^{-2}
\end{aligned}
$$

Rate parameter κ.

8.2 Gamma distribution

$$
\begin{aligned}
x &\sim \text{Gamma}(\alpha, \beta) \\
P(x|\alpha, \beta) &= \frac{x^{\alpha-1}\beta^{\alpha}\exp(-x\beta)}{\Gamma(\alpha)} \\
\text{E}[x] &= \alpha/\beta \\
\text{Var}[x] &= \alpha/\beta^2
\end{aligned}
$$

Shape parameter α, rate parameter β. $\Gamma()$ is the gamma function

$$
\Gamma(\alpha) = \int_0^\infty z^{\alpha-1}\exp(-z)dz
$$

Note $\Gamma(n) = (n-1)!$ for positive integer n.

8.3 Normal distribution

$$
x \sim \text{Normal}(\mu, \tau)
$$

Mean μ, precision τ (precision is reciprocal of variance).

$$P(x|\mu, \tau) = \sqrt{\frac{\tau}{2\pi}} \exp\left(-\frac{\tau}{2}(x - \mu)^2\right)$$