Nanopore automata

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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, suitable for long-read assemblers
- 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, for improved assembly
- transducer-based versions of Rahman & Pachter's CGAL

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

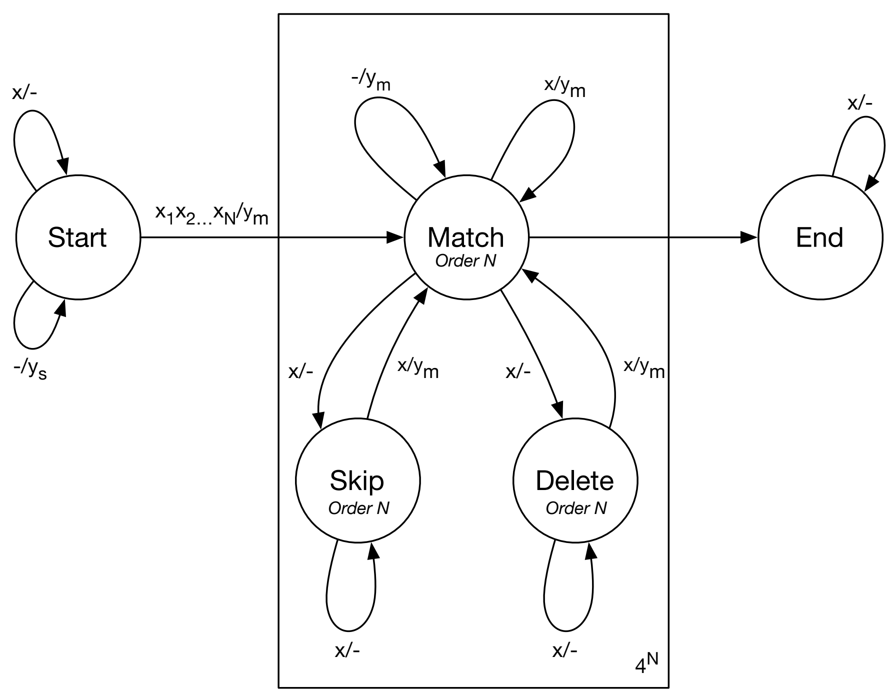
Model & inference algorithms.

3.1 Null model

- Output alphabet: $\Re$ (real numbers signifying current readings)
- K current samples (*ticks*). Sequence is $y_1 \dots y_K$
  - partitioned into a sequence of L *events*: $E_1 \dots E_L$
- Parameters: $p^{\text{NullEvent}}, p^{\text{NullTick}}, \mu^{\text{Null}}, \tau^{\text{Null}}$
- Gaussian emissions: $y_n \sim \text{Normal}(\mu^{\text{Null}}, \tau^{\text{Null}})$
- Probability is

$$
\begin{aligned}
& P(E_1 \dots E_L, y_1 \dots y_K) dy_1 \dots dy_K \\
&= (1 - p^{\text{NullEvent}}) \prod_{\text{events}:E_l} p^{\text{NullEvent}} (1 - p^{\text{NullTick}}) \prod_{\text{ticks}:y_k \in E_l} p^{\text{NullTick}} P(y_k | \mu^{\text{Null}}, \tau^{\text{Null}}) dy_k
\end{aligned}
$$

3.2 Homology model



- Order-N Mealy transducer.
- Input alphabet: $\Omega = \{A, C, G, T\}$ (nucleotides)
- Output alphabet: real numbers partitioned into events, as with null model
- States: Start, End, $\{$ $\text{Match}_{x_1 \ldots x_N}$, $\text{Delete}_{x_1 \ldots x_N}$: $x_1 \ldots x_N \in \Omega^N\}$
- Parameters: $p^{\text{StartEvent}}, p^{\text{BeginDelete}}, p^{\text{ExtendDelete}},$
  $\{p^{\text{Skip}}_{x_1 \ldots x_N}, p^{\text{MatchEvent}}_{x_1 \ldots x_N}, p^{\text{MatchTick}}_{x_1 \ldots x_N}, \mu^{\text{Match}}_{x_1 \ldots x_N}, \tau^{\text{Match}}_{x_1 \ldots x_N} : x_1 \ldots x_N \in \Omega^N\}$

Transducer can *skip* an individual base (no event emissions for that base), or can *delete* a run of bases (no event emissions during the run).

Transitions:

Source	Destination	Weight	Absorbs	Emits
Start	Start	$p^{\text{StartEvent}}$ $\times(p^{\text{NullTick}})^{K_s}(1-p^{\text{NullTick}})$ $\times\prod_{k=1}^{K_s} P(y_s^{(k)}\|\mu^{\text{Start}},\tau^{\text{Start}})dy_s^{(k)}$		$\{y_s^{(k)} : 1 \leq k \leq K$ $K_s \sim$ Geometric($y_s^{(k)} \sim$ Normal(μ^{N}
Start	Start	1	$x \in \Omega$	
Start	$\text{Match}_{x_1 \ldots x_N}$	$(1-p^{\text{StartEvent}})$ $\times(p^{\text{MatchTick}}_{x_1\ldots x_N})^{K_m}(1-p^{\text{MatchTick}}_{x_1\ldots x_N})$ $\times\prod_{k=1}^{K_m} P(y_m^{(k)}\|\mu^{\text{Match}}_{x_1\ldots x_N},\tau^{\text{Match}}_{x_1\ldots x_N})dy_m^{(k)}$	$x_1 \ldots x_N \in \Omega^N$	$\{y_m^{(k)} : 1 \leq k \leq K$ $K_m \sim$ Geometric $y_m^{(k)} \sim$ Normal(μ
$\text{Match}_{x_1 \ldots x_N}$	$\text{Match}_{x_1 \ldots x_N}$	$p^{\text{MatchEvent}}_{x_1\ldots x_N}$ $\times(p^{\text{MatchTick}}_{x_1\ldots x_N})^{K_m}(1-p^{\text{MatchTick}}_{x_1\ldots x_N})$ $\times\prod_{k=1}^{K_m} P(y_m^{(k)}\|\mu^{\text{Match}}_{x_1\ldots x_N},\tau^{\text{Match}}_{x_1\ldots x_N})dy_m^{(k)}$		$\{y_m^{(k)} : 1 \leq k \leq K$ $K_m \sim$ Geometric $y_m^{(k)} \sim$ Normal(μ
$\text{Match}_{x_1 \ldots x_N}$	$\text{Skip}_{x_2 \ldots x_{N+1}}$	$(1-p^{\text{MatchEvent}}_{x_1\ldots x_N})$ $\times(1-p^{\text{BeginDelete}})p^{\text{Skip}}_{x_2\ldots x_{N+1}}$	$x_{N+1} \in \Omega$	
$\text{Match}_{x_1 \ldots x_N}$	$\text{Match}_{x_2 \ldots x_{N+1}}$	$(1-p^{\text{MatchEvent}}_{x_1\ldots x_N})$ $\times(1-p^{\text{BeginDelete}})(1-p^{\text{Skip}}_{x_2\ldots x_{N+1}})$ $\times(p^{\text{MatchTick}}_{x_2\ldots x_{N+1}})^{K_m}(1-p^{\text{MatchTick}}_{x_2\ldots x_{N+1}})$ $\times\prod_{k=1}^{K_m} P(y_m^{(k)}\|\mu^{\text{Match}}_{x_2\ldots x_{N+1}},\tau^{\text{Match}}_{x_2\ldots x_{N+1}})dy_m^{(k)}$	$x_{N+1} \in \Omega$	$\{y_m^{(k)} : 1 \leq k \leq K$ $K_m \sim$ Geometric $y_m^{(k)} \sim$ Normal(μ
$\text{Match}_{x_1 \ldots x_N}$	$\text{Delete}_{x_2 \ldots x_{N+1}}$	$(1-p^{\text{MatchEvent}}_{x_1\ldots x_N})$ $\times p^{\text{BeginDelete}}$	$x_{N+1} \in \Omega$	
$\text{Match}_{x_1 \ldots x_N}$	End	$1-p^{\text{MatchEvent}}_{x_1\ldots x_N}$		
$\text{Skip}_{x_1 \ldots x_N}$	$\text{Skip}_{x_2 \ldots x_{N+1}}$	$p^{\text{Skip}}_{x_2\ldots x_{N+1}}$	$x_{N+1} \in \Omega$	
$\text{Skip}_{x_1 \ldots x_N}$	$\text{Match}_{x_2 \ldots x_{N+1}}$	$(1-p^{\text{Skip}}_{x_2\ldots x_{N+1}})$ $\times(p^{\text{MatchTick}}_{x_2\ldots x_{N+1}})^{K_m}(1-p^{\text{MatchTick}}_{x_2\ldots x_{N+1}})$ $\times\prod_{k=1}^{K_m} P(y_m^{(k)}\|\mu^{\text{Match}}_{x_2\ldots x_{N+1}},\tau^{\text{Match}}_{x_2\ldots x_{N+1}})dy_m^{(k)}$	$x_{N+1} \in \Omega$	$\{y_m^{(k)} : 1 \leq k \leq K$ $K_m \sim$ Geometric $y_m^{(k)} \sim$ Normal(μ
$\text{Delete}_{x_1 \ldots x_N}$	$\text{Delete}_{x_2 \ldots x_{N+1}}$	$p^{\text{ExtendDelete}}$	$x_{N+1} \in \Omega$	
$\text{Delete}_{x_1 \ldots x_N}$	$\text{Match}_{x_2 \ldots x_{N+1}}$	$(1-p^{\text{ExtendDelete}})$ $\times(p^{\text{MatchTick}}_{x_2\ldots x_{N+1}})^{K_m}(1-p^{\text{MatchTick}}_{x_2\ldots x_{N+1}})$ $\times\prod_{k=1}^{K_m} P(y_m^{(k)}\|\mu^{\text{Match}}_{x_2\ldots x_{N+1}},\tau^{\text{Match}}_{x_2\ldots x_{N+1}})dy_m^{(k)}$	$x_{N+1} \in \Omega$	$\{y_m^{(k)} : 1 \leq k \leq K$ $K_m \sim$ Geometric $y_m^{(k)} \sim$ Normal(μ
End	End	1	$x \in \Omega$	

3.3 Baum-Welch algorithm

As usual.

3.4 Viterbi algorithm

As usual.

4 Results

5 Discussion

6 Acknowledgments

7 Figure Legends

8 Appendix

8.1 Exponential distribution

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

Rate parameter κ.

8.2 Gamma distribution

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

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).

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