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, 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.

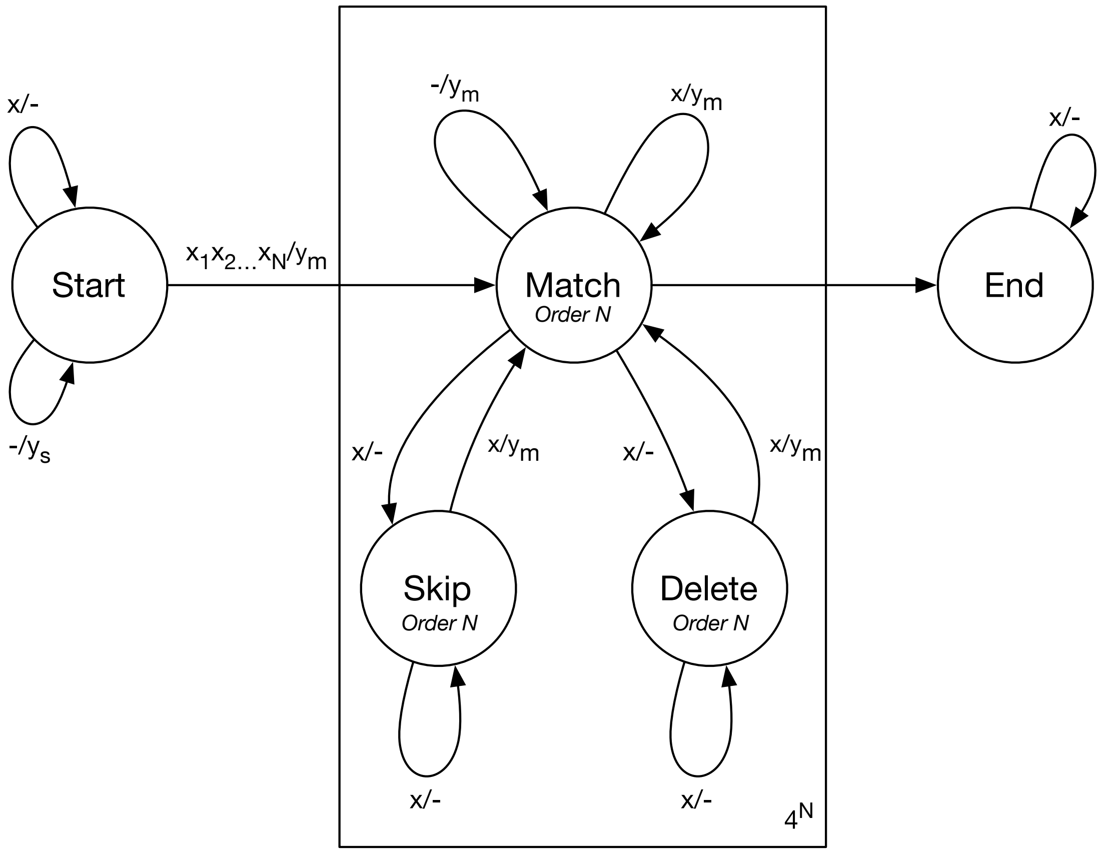
3.1 Null model

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

- K current samples (*ticks*). Sequence is $y_1 \ldots y_K$
  - partitioned into a sequence of L *events*: $E_1 \ldots E_L$
- Parameters: $p^{\mathrm{NullEvent}}, p^{\mathrm{NullTick}}, \mu^{\mathrm{Null}}, \tau^{\mathrm{Null}}$
- Gaussian emissions: $y_n \sim \mathrm{Normal}(\mu^{\mathrm{Null}}, \tau^{\mathrm{Null}})$
- Probability is

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

3.2 Homology model

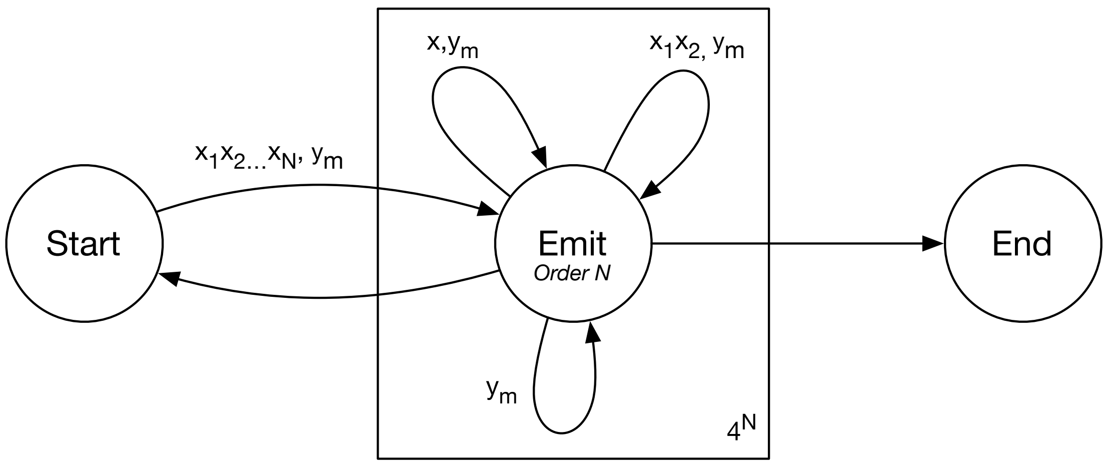


- Order-N Mealy transducer.
- Input alphabet: $\Omega = \{A, C, G, T\}$ (nucleotides)
- Output alphabet: real numbers partitioned into events, as with null model
- States: Start, End, $\{$ $\text{Match}_{x_1 \ldots x_N}$, $\text{Delete}_{x_1 \ldots x_N}$: $x_1 \ldots x_N \in \Omega^N\}$
- Parameters: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

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).

The transition weights for this transducer are shown in Section 8.4.

3.3 Basecalling model



- Order-N HMM.
- Unobserved transition labels: $\Omega = \{A, C, G, T\}$ (nucleotides)
- Output alphabet: real numbers partitioned into events, as with null & transducer models
- States: Start, End, { $\text{Emit}_{x_1 \ldots x_N}$
- Parameters: same as transducer model, plus length parameter p^{Emit}, and kmer probability distribution $q(x_1 \ldots x_N)$ together with associated conditional distributions $q(x_{N+1}|x_2 \ldots x_N)$ and $q(x_{N+1}, x_{N+2}|x_2 \ldots x_N) = q(x_{N+1}|x_2 \ldots x_N) q(x_{N+2}|x_3 \ldots x_{N+1})$. Also define

$$
\begin{aligned}
p^{\text{LongDelete}} &= p^{\text{Emit}} p^{\text{BeginDelete}} p^{\text{ExtendDelete}} \\
p^{\text{ShortDelete}}_{x_1 \ldots x_N} &= p^{\text{Emit}} \left(p^{\text{BeginDelete}} (1 - p^{\text{ExtendDelete}}) + (1 - p^{\text{BeginDelete}}) p^{\text{Skip}}_{x_1 \ldots x_N} \right) \\
p^{\text{NoDelete}}_{x_1 \ldots x_N} &= p^{\text{Emit}} (1 - p^{\text{BeginDelete}}) (1 - p^{\text{Skip}}_{x_1 \ldots x_N})
\end{aligned}
$$

The transition weights for this HMM are shown in Section 8.5.

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).

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

8.4 Transition table for nanopore transducer

The following table gives the transition weights for the transducer introduced in Section 3.2.

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

8.5 Transition table for basecalling HMM

The following table gives the transition weights for the transducer introduced in Section 3.3.

Source	Destination	Weight	Unobserved	Observed
Start	$\mathrm{Emit}_{x_1 \ldots x_N}$	$q(x_1 \ldots x_N)$	$x_1 \ldots x_N \in \Omega^N$	$\{y_m^{(k)} : 1 \le k \le K_m\}$,
		$\times (p^{\mathrm{MatchTick}}_{x_1 \ldots x_N})^{K_m} (1 - p^{\mathrm{MatchTick}}_{x_1 \ldots x_N})$		$K_m \sim \mathrm{Geometric}(p^{\mathrm{MatchTick}}_{x_1 \ldots x_N})$,
		$\times \prod_{k=1}^{K_m} P(y_m^{(k)} \vert \mu^{\mathrm{Match}}_{x_1 \ldots x_N}, \tau^{\mathrm{Match}}_{x_1 \ldots x_N}) dy_m^{(k)}$		$y_m^{(k)} \sim \mathrm{Normal}(\mu^{\mathrm{Match}}_{x_1 \ldots x_N}, \tau^{\mathrm{Match}}_{x_1 \ldots x_N})$
$\mathrm{Emit}_{x_1 \ldots x_N}$	$\mathrm{Emit}_{x_1 \ldots x_N}$	$p^{\mathrm{MatchEvent}}_{x_1 \ldots x_N}$		$\{y_m^{(k)} : 1 \le k \le K_m\}$,
		$\times (p^{\mathrm{MatchTick}}_{x_1 \ldots x_N})^{K_m} (1 - p^{\mathrm{MatchTick}}_{x_1 \ldots x_N})$		$K_m \sim \mathrm{Geometric}(p^{\mathrm{MatchTick}}_{x_1 \ldots x_N})$,
		$\times \prod_{k=1}^{K_m} P(y_m^{(k)} \vert \mu^{\mathrm{Match}}_{x_1 \ldots x_N}, \tau^{\mathrm{Match}}_{x_1 \ldots x_N}) dy_m^{(k)}$		$y_m^{(k)} \sim \mathrm{Normal}(\mu^{\mathrm{Match}}_{x_1 \ldots x_N}, \tau^{\mathrm{Match}}_{x_1 \ldots x_N})$
$\mathrm{Emit}_{x_1 \ldots x_N}$	$\mathrm{Emit}_{x_2 \ldots x_{N+1}}$	$(1 - p^{\mathrm{MatchEvent}}_{x_1 \ldots x_N})$	$x_{N+1} \in \Omega$	$\{y_m^{(k)} : 1 \le k \le K_m\}$,
		$\times q(x_{N+1} \vert x_2 \ldots x_N) p^{\mathrm{NoDelete}}_{x_2 \ldots x_{N+1}}$		$K_m \sim \mathrm{Geometric}(p^{\mathrm{MatchTick}}_{x_2 \ldots x_{N+1}})$,
		$\times (p^{\mathrm{MatchTick}}_{x_2 \ldots x_{N+1}})^{K_m} (1 - p^{\mathrm{MatchTick}}_{x_2 \ldots x_{N+1}})$		$y_m^{(k)} \sim \mathrm{Normal}(\mu^{\mathrm{Match}}_{x_2 \ldots x_{N+1}}, \tau^{\mathrm{Match}}_{x_2 \ldots x_{N+1}})$
		$\times \prod_{k=1}^{K_m} P(y_m^{(k)} \vert \mu^{\mathrm{Match}}_{x_2 \ldots x_{N+1}}, \tau^{\mathrm{Match}}_{x_2 \ldots x_{N+1}}) dy_m^{(k)}$		
$\mathrm{Emit}_{x_1 \ldots x_N}$	$\mathrm{Emit}_{x_3 \ldots x_{N+2}}$	$(1 - p^{\mathrm{MatchEvent}}_{x_1 \ldots x_N})$	$x_{N+1} x_{N+2} \in \Omega^2$	$\{y_m^{(k)} : 1 \le k \le K_m\}$,
		$\times q(x_{N+1}, x_{N+2} \vert x_2 \ldots x_N) p^{\mathrm{ShortDelete}}_{x_2 \ldots x_{N+1}}$		$K_m \sim \mathrm{Geometric}(p^{\mathrm{MatchTick}}_{x_3 \ldots x_{N+2}})$,
		$\times (p^{\mathrm{MatchTick}}_{x_3 \ldots x_{N+2}})^{K_m} (1 - p^{\mathrm{MatchTick}}_{x_3 \ldots x_{N+2}})$		$y_m^{(k)} \sim \mathrm{Normal}(\mu^{\mathrm{Match}}_{x_3 \ldots x_{N+2}}, \tau^{\mathrm{Match}}_{x_3 \ldots x_{N+2}})$
		$\times \prod_{k=1}^{K_m} P(y_m^{(k)} \vert \mu^{\mathrm{Match}}_{x_3 \ldots x_{N+2}}, \tau^{\mathrm{Match}}_{x_3 \ldots x_{N+2}}) dy_m^{(k)}$		
$\mathrm{Emit}_{x_1 \ldots x_N}$	Start	$p^{\mathrm{LongDelete}}$		
$\mathrm{Emit}_{x_1 \ldots x_N}$	End	$1 - p^{\mathrm{Emit}}$		