Statistical Segmentation of Biological Sequences

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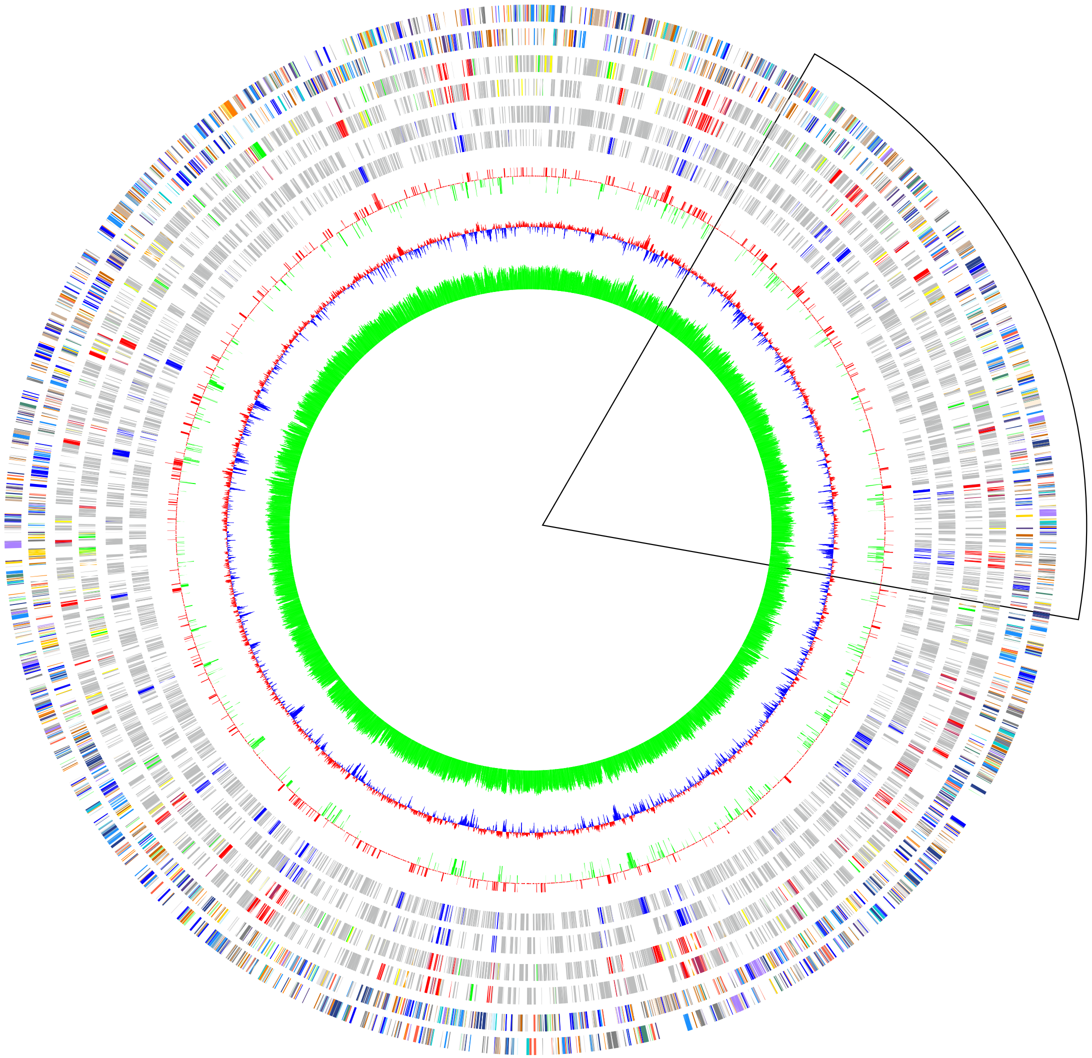
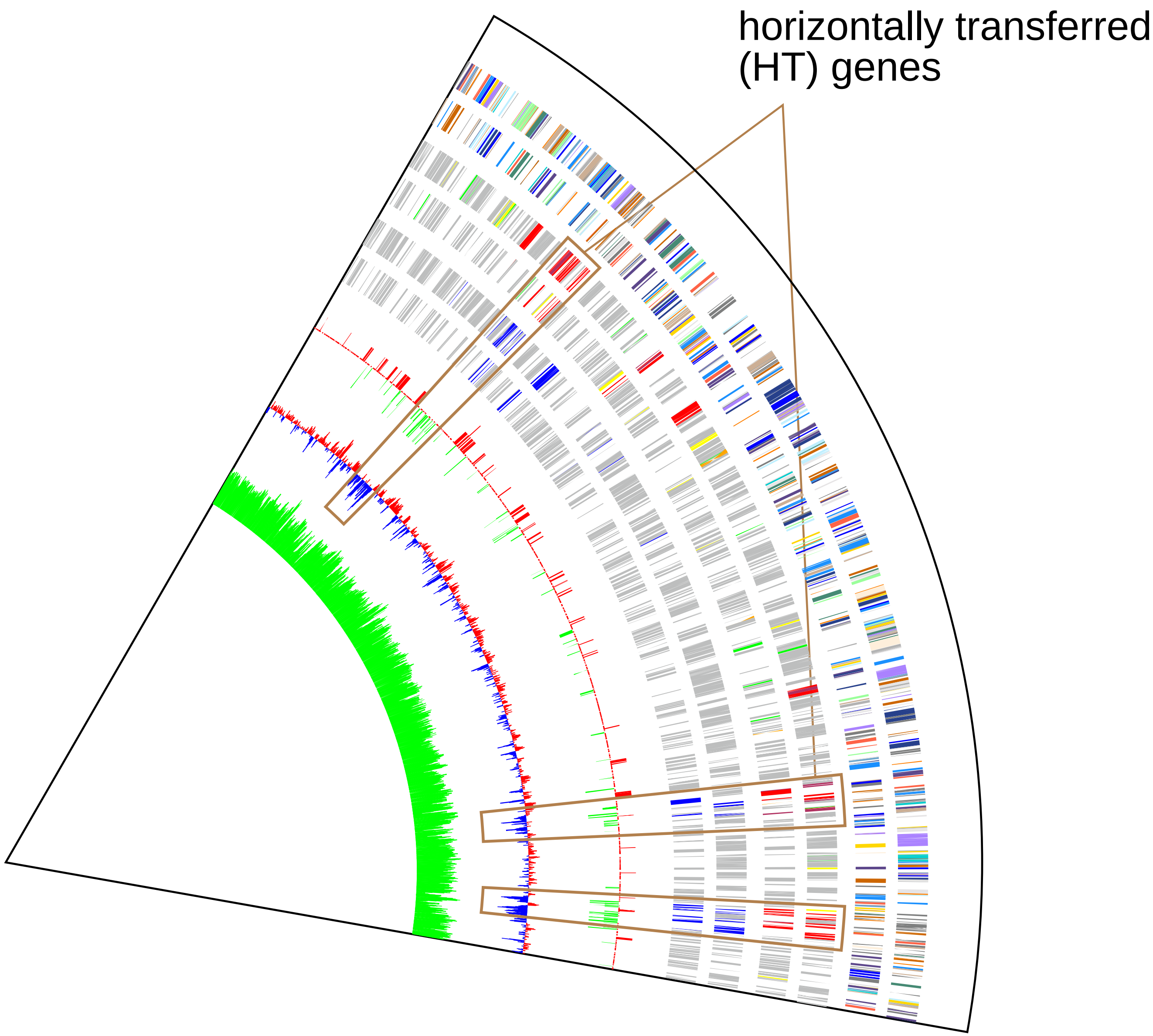
Mosaic Nature of Biological Sequences

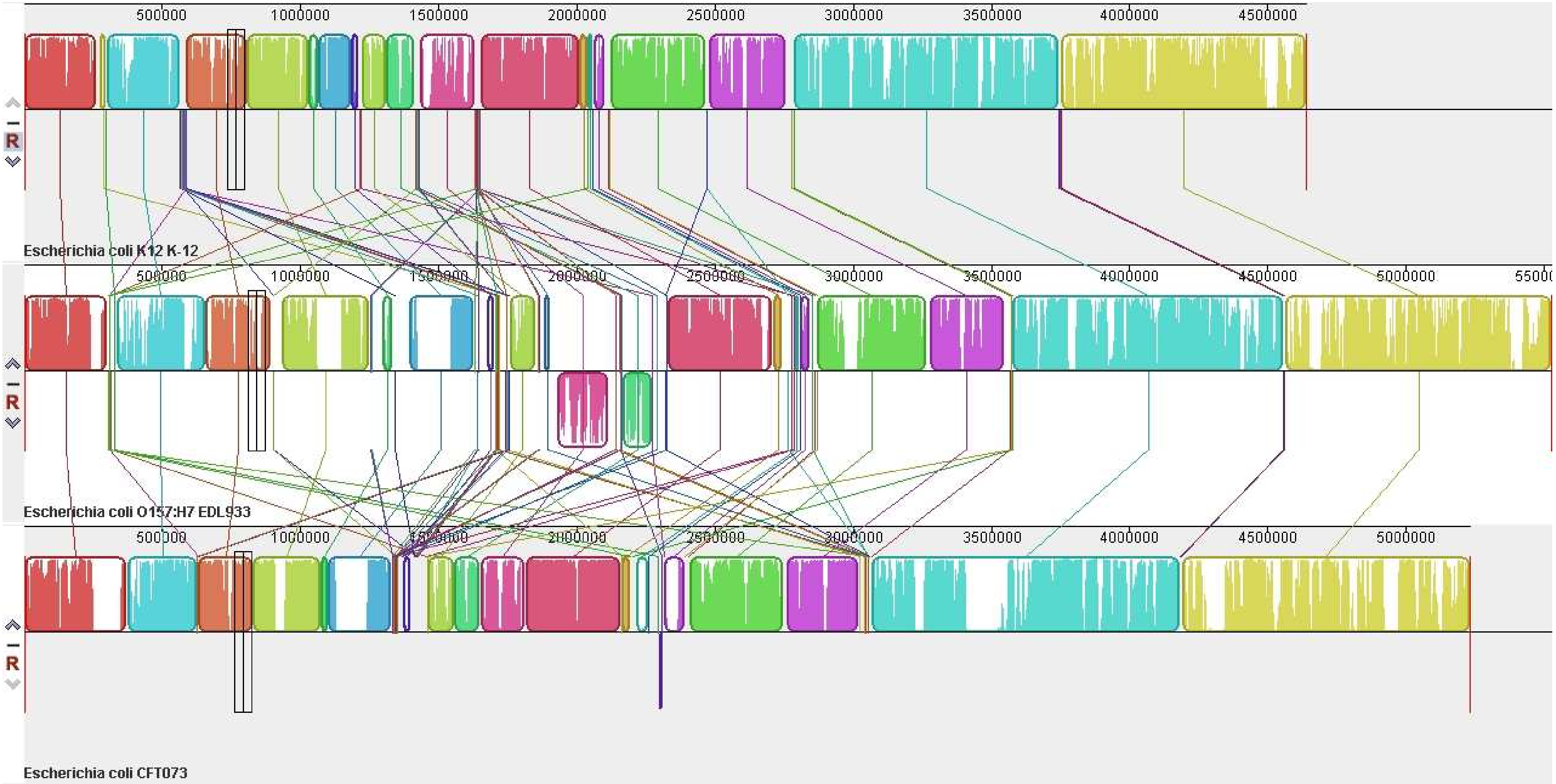


Circular map of the *Escherichia coli* K-12 MG1655 genome (N = 4639675 bp).
Reproduced from Ghai, Hain and Chakraborty, *BMC Bioinformatics* **5**, 198 (2004).

Mosaic Nature of Biological Sequences



Mosaic Nature of Biological Sequences



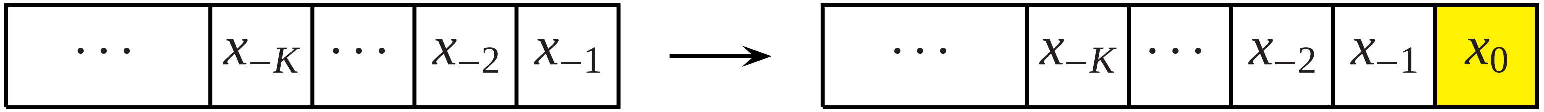
MAUVE alignment of three *E. coli* strains: K-12 MG1655, O157H7 EDL933, and CFT073.

The Biological Sequence Segmentation Problem

- Two motivating problems:
  - HT segments (genomic islands) and lineage-specific segments (backbone) in bacterial DNA.
    - HT segments have different statistics from backbone.
    - Pathogenic genes frequently found near HT segment boundaries.
    - Gene-finding algorithms do not perform well in regions where statistics differ significantly from backbone.
    - Scoring problem even more severe for computational search of short regulatory elements.
  - Mesoscopic description of genome: 'Local' statistics vary along DNA sequence. Break long sequence into intermediate length segments, based on 'discernible' changes in statistics. Coarse-grained description.
- DNA polymerization along $5' \to 3'$ direction builds directionality into sequence. Biases in dinucleotide and codon frequencies. Model as Markov chains rather than Bernoulli chains with extended alphabets.

Markov chains

- State x_i of Markov chain at sequence position i can take on values in alphabet $\mathcal{S}$ of size S. Example. For DNA sequences, $\mathcal{S} = \{A, T, C, G\}$, and $S = 4$.
- Markov chains generated probabilistically. Existing subsequence extended



by attaching x_0 to end of subsequence with transition probability

$$p(x_0|x_{-1}x_{-2}\cdots x_{-K}).$$

- Markov chain of order K if $p(x_0|x_{-1}x_{-2}\cdots x_{-K'}) = p(x_0|x_{-1}x_{-2}\cdots x_{-K})$ for all $K' \geq K$.
- Transition probabilities can be organized into transition matrix

$$\mathbb{P} = [p_{\mathbf{t}s}], \quad s = 1, \ldots, S, \quad \mathbf{t} = t_1 \cdots t_K \in S^K.$$

- Equilibrium distribution $\boldsymbol{\pi} = (P_1, \ldots, P_k, \ldots, P_{S^K})$ such that $\boldsymbol{\pi}\mathbb{P} = \boldsymbol{\pi}$, P_k = probability of finding kth K-mer in stationary Markov chain.

Classification of Segmentation Schemes

- Matrix of segmentation schemes in literature:

	single−pass	recursive	local	global
sliding window average				
DNA walk				
dynamic programming				
hidden Markov model				

- All schemes rely on entropic measure of statistical dissimilarity, whether:
  - computed directly; or
  - in the form of inner product between quantized vectors of probabilities.

The Jensen-Shannon Divergence

- Given length-N sequence $\mathbf{x} = x_1 x_2 \cdots x_N$, $x_i = A, C, G, T$, assume composed of $M \geq 1$ Markov chains with boundaries at $i_1, \ldots, i_{M-1}$. M-segment sequence likelihood given by

$$P_M(\mathbf{x}; i_1, \ldots, i_{M-1}; \hat{\mathbb{P}}_1, \ldots, \hat{\mathbb{P}}_M) = \prod_{m=1}^{M} \prod_{\mathbf{t} \in S^K} \prod_{s=1}^{S} (\hat{p}^m_{\mathbf{t}s})^{f^m_{\mathbf{t}s}}; \qquad \hat{p}^m_{\mathbf{t}s} = \frac{f^m_{\mathbf{t}s}}{\sum_{s'} f^m_{\mathbf{t}s'}}.$$

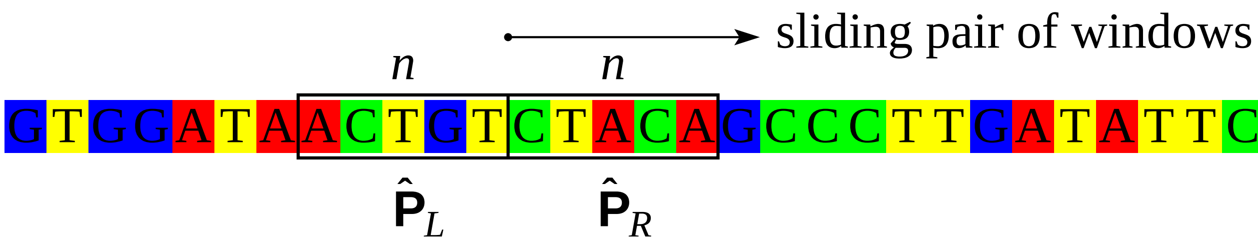
- Jensen-Shannon divergence

$$\Delta_M = \log \frac{P_M}{P_1} = -\sum_{\mathbf{t} \in S^K} \sum_{s=1}^{S} f_{\mathbf{t}s} \log \hat{p}_{\mathbf{t}s} + \sum_{m=1}^{M} \sum_{\mathbf{t} \in S^K} \sum_{s=1}^{S} f^m_{\mathbf{t}s} \log \hat{p}^m_{\mathbf{t}s};$$

$$f_{\mathbf{t}s} = \sum_{m=1}^{M} f^m_{\mathbf{t}s}, \qquad \hat{p}_{\mathbf{t}s} = \frac{f_{\mathbf{t}s}}{\sum_{s'=1}^{S} f_{\mathbf{t}s'}}$$

is symmetric relative entropy providing quantitative measure of ‘goodness-of-fit’ of M-segment model over 1-segment model.

Segmentation with a Pair of Sliding Windows



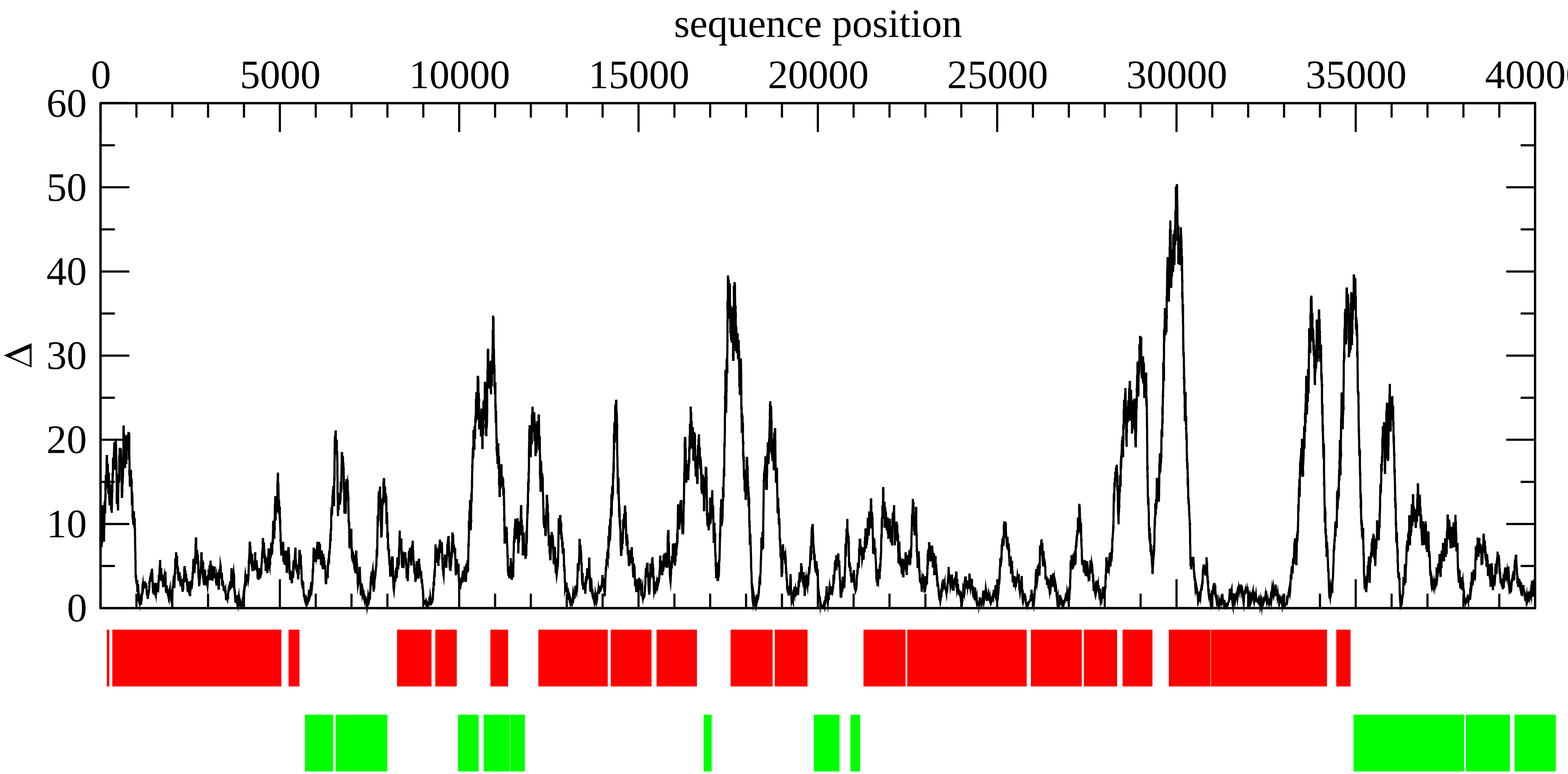
- For a single sliding window of length n, spatial resolution decreases with n while statistical significance increases with n.

- Solution: To not compromise spatial resolution, use an adjoining pair of sliding windows, each of length n.

- Compute $\Delta_2(i)$ using $\hat{\mathbb{P}}_L$ in left window and $\hat{\mathbb{P}}_L$ in right window as function of sequence position i of centre of pair of windows.

- Segment boundaries appear as peaks in $\Delta_2(i)$. Strength of peak measure of statistical difference between the segments it separates.

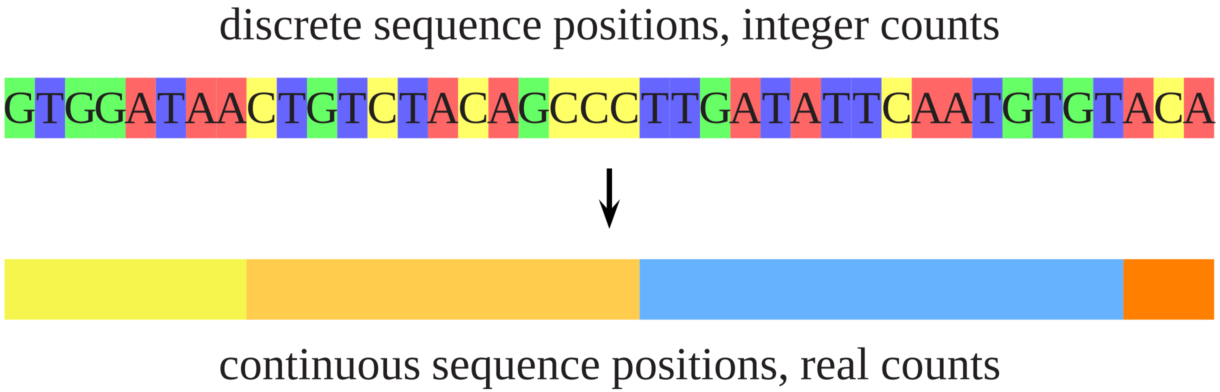
Segmentation with a Pair of Sliding Windows



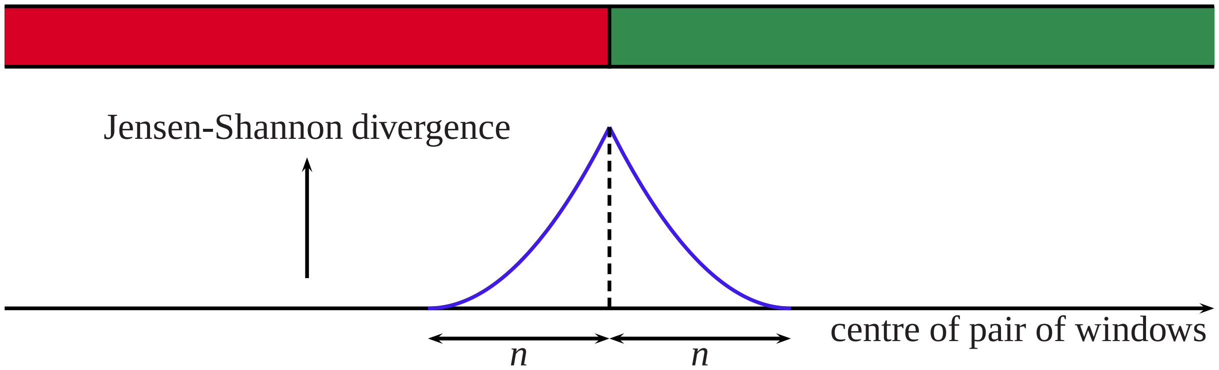
The interval $(0, 40000)$ in the *E. coli* K-12 MG1655 genome ($N = 4639675$), showing the $K = 0$ Jensen-Shannon divergence spectrum for $n = 1000$. Annotated genes on the positive (red) and negative (green) strands are shown below the graph.

Mean-Field Lineshape and Match Filtering

- Mean-field picture:

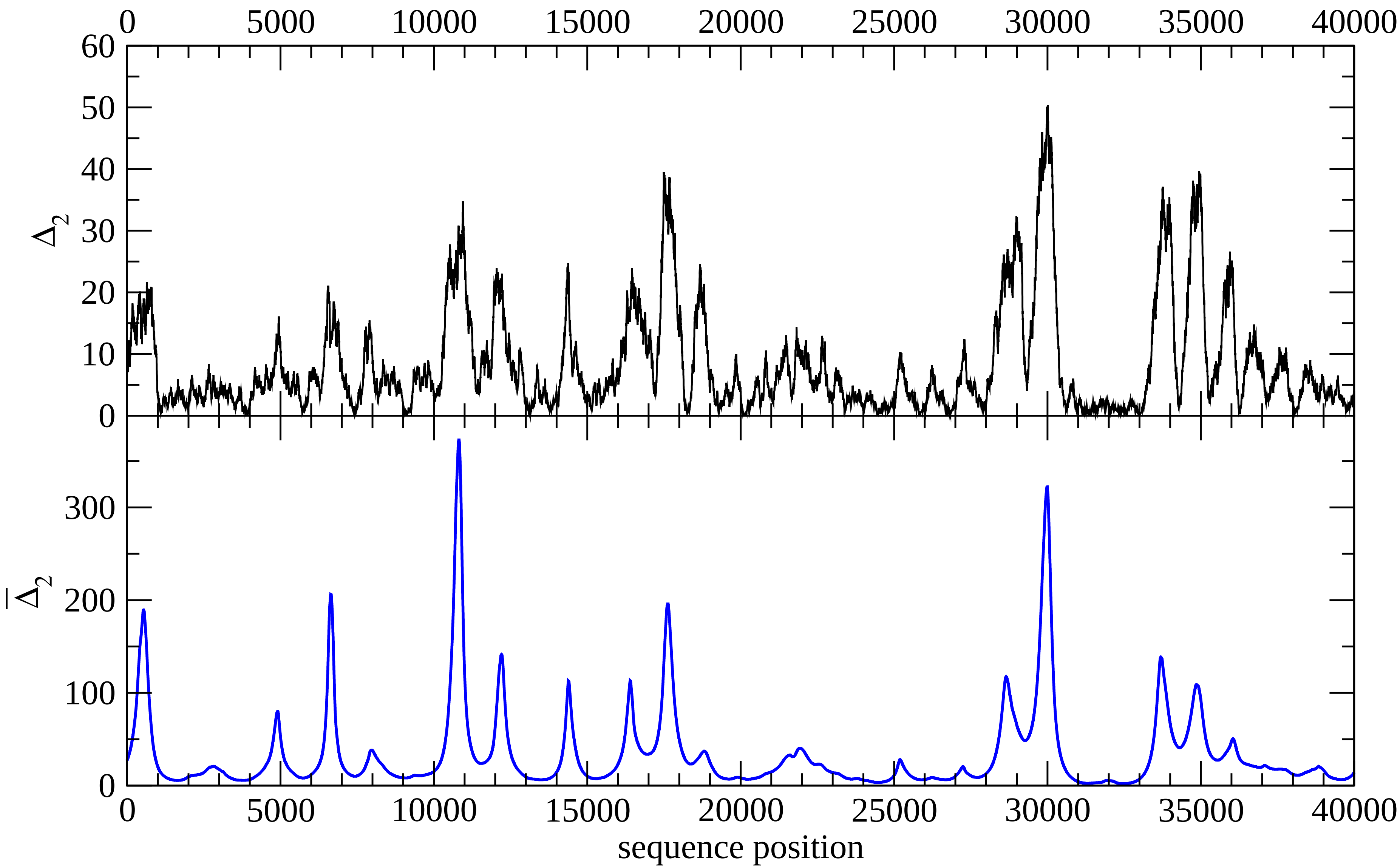


- Mean-field analysis tells us that Δ_2 reaches a maximum at boundary between red and green segments.



- Nearly piecewise quadratic mean-field lineshape can be used for match filtering.

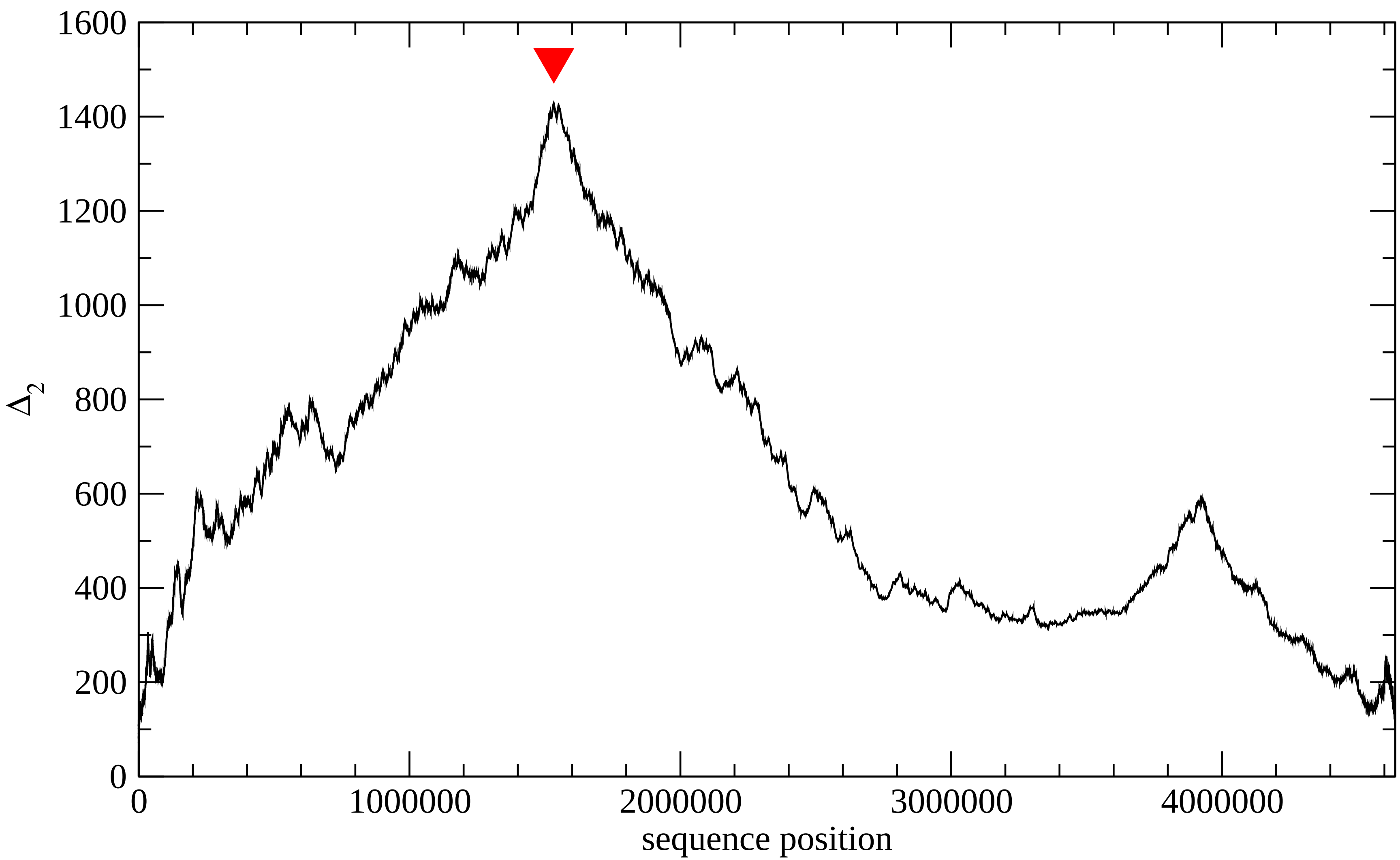
Mean-Field Lineshape and Match Filtering



Recursive Jensen-Shannon Segmentation

- STEP 1 (Segmentation):
  - Given sequence $\mathbf{x} = x_1 x_2 \cdots x_N$, compute 2-segment Jensen-Shannon divergence $\Delta_2(i)$ as function of cursor position i.
  - Find i^* such that $\Delta_2(i^*) = \max_i \Delta_2(i)$. The best 2-segment model for $\mathbf{x}$ is $\mathbf{x} = \mathbf{x}_L \mathbf{x}_R$, where $\mathbf{x}_L = x_1 \cdots x_{i^*}$ and $\mathbf{x}_R = x_{i^*+1} \cdots x_N$.
- STEP 2 (Recursion): Repeat STEP 1 for $\mathbf{x}_L$ and $\mathbf{x}_R$.
- STEP 3 (Termination): 1-segment model selected over 2-segment model if:
  - Hypothesis Testing: probability of obtaining divergence beyond observed Δ_2 greater than prescribed tolerance ϵ; or
  - Model Selection: information criterion (e.g. AIC, BIC) for 2-segment model greater than that for 1-segment model.

Recursive Jensen-Shannon Segmentation

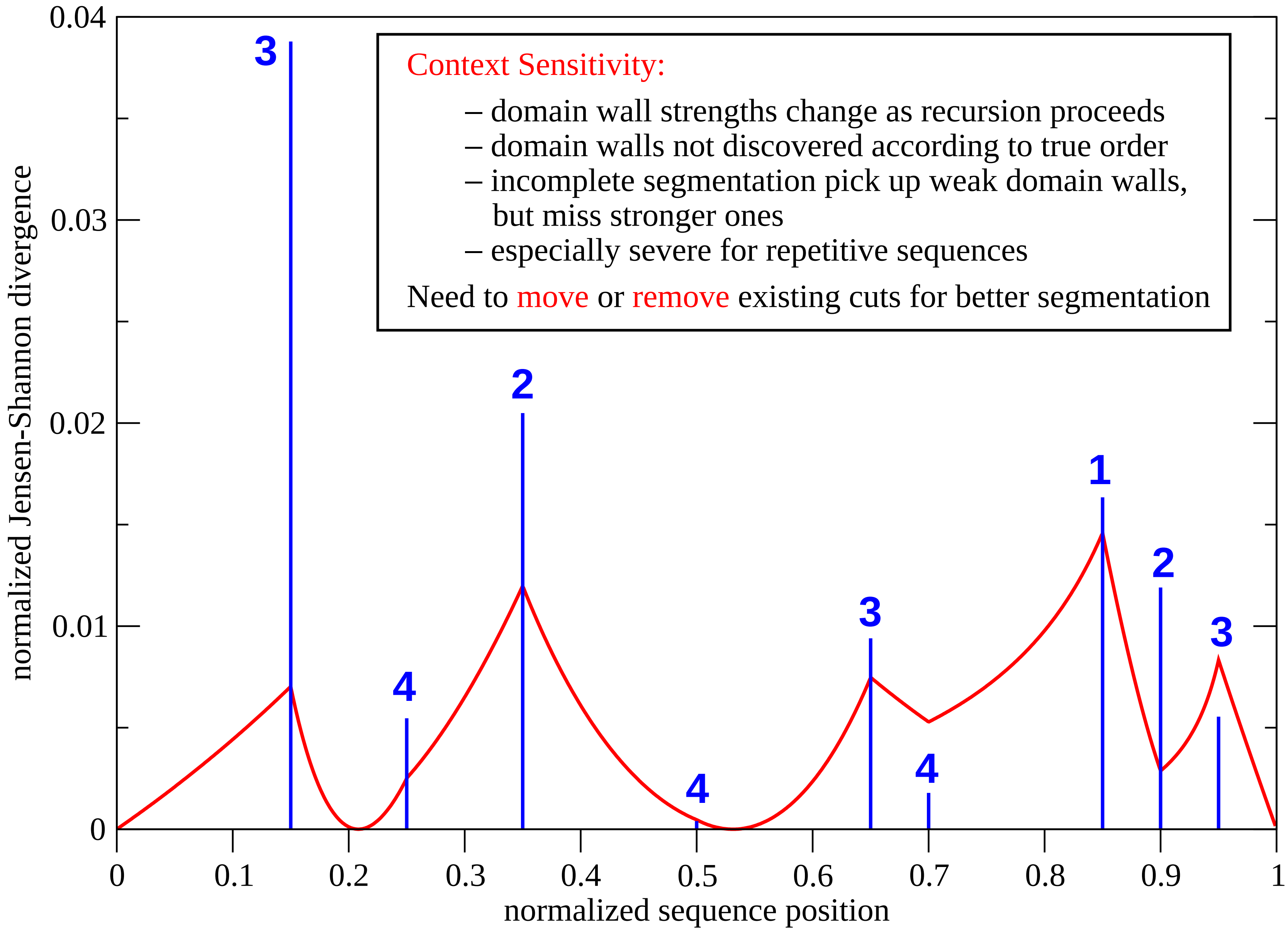


Jensen-Shannon divergence spectrum of order $K = 3$ over the entire genome of *E. coli* K-12 MG1655 ($N = 4639675$ bp). The first segment boundary to be obtained in this first stage of recursive segmentation is shown by the red arrow.

Mean-Field Analysis of Recursive Segmentation

- Analyze recursive segmentation scheme entirely within mean-field picture:
  - Peaks in mean-field divergence spectrum appear only at segment boundaries;
  - Segment boundaries also appear as kinks, or even have vanishing divergence in mean-field divergence spectrum.
  - Recursive segmentation eventually discovers all segment boundaries.
- Problem of context sensitivity:
  - Strengths of existing segment boundaries change as recursive segmentation progresses;
  - Segment boundaries not discovered according to order of true strengths in final segmentation;
  - Incomplete segmentation pick up weak segment boundaries, but miss stronger ones.
  - Problem especially severe with repetitive sequences (e.g. $abab \cdots abab$), common in biological sequences.

Pitfalls of Recursive Segmentation



Segmentation Optimization

- Two procedures to optimize segment boundary i_m if we are allowed to move only one segment boundary at a time:

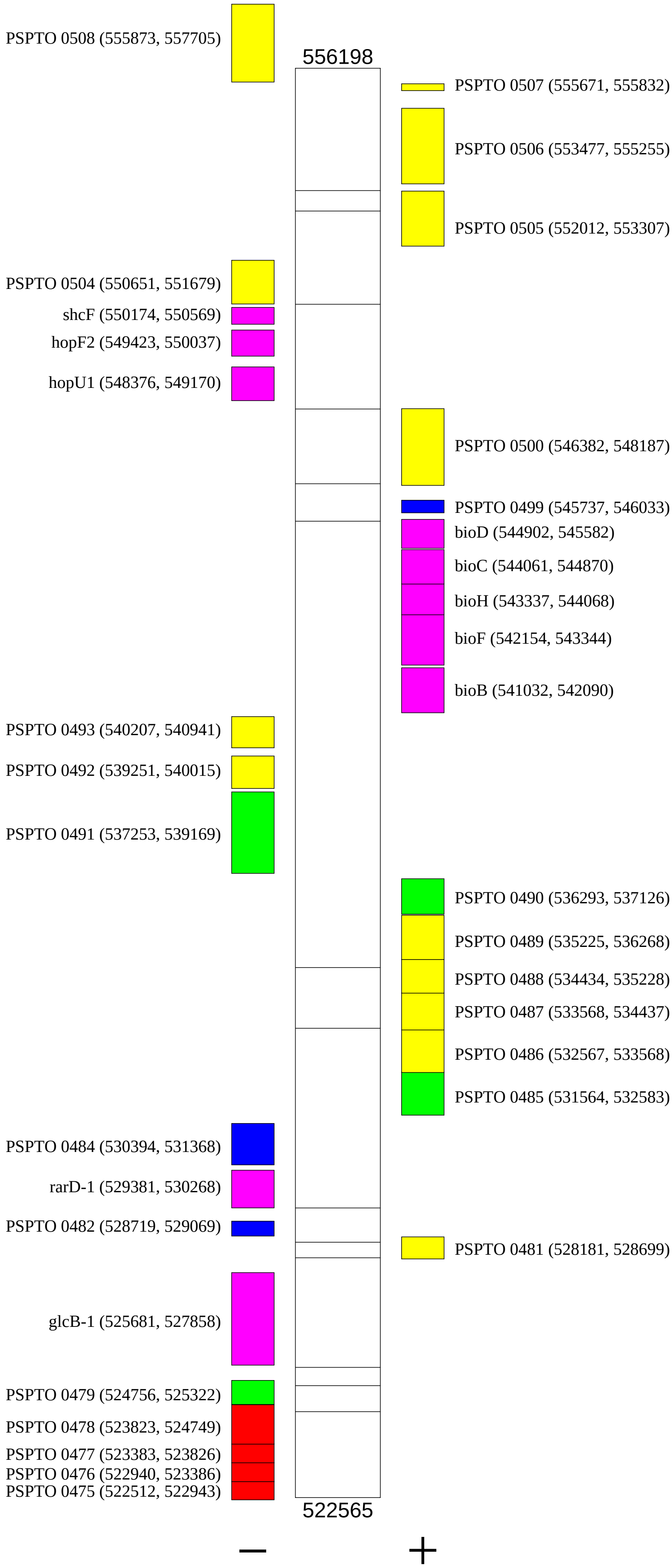
  - First-order update: Compute $\Delta_2^m(i)$ for supersegment (i_{m-1}, i, i_{m+1}), and choose $i_m = i^*$, such that $\Delta_2(i^*) = \max_{i_{m-1}<i<i_{m+1}} \Delta_2(i)$, to be new position of segment boundary.
  - Second-order update: Compute $\Delta_2^{m-1}(i)$ for supersegment (i_{m-2}, i_{m-1}, i) and $\Delta_2^{m+1}(i)$ for supersegment (i, i_{m+1}, i_{m+2}), and choose $i_m = i^*$, such that

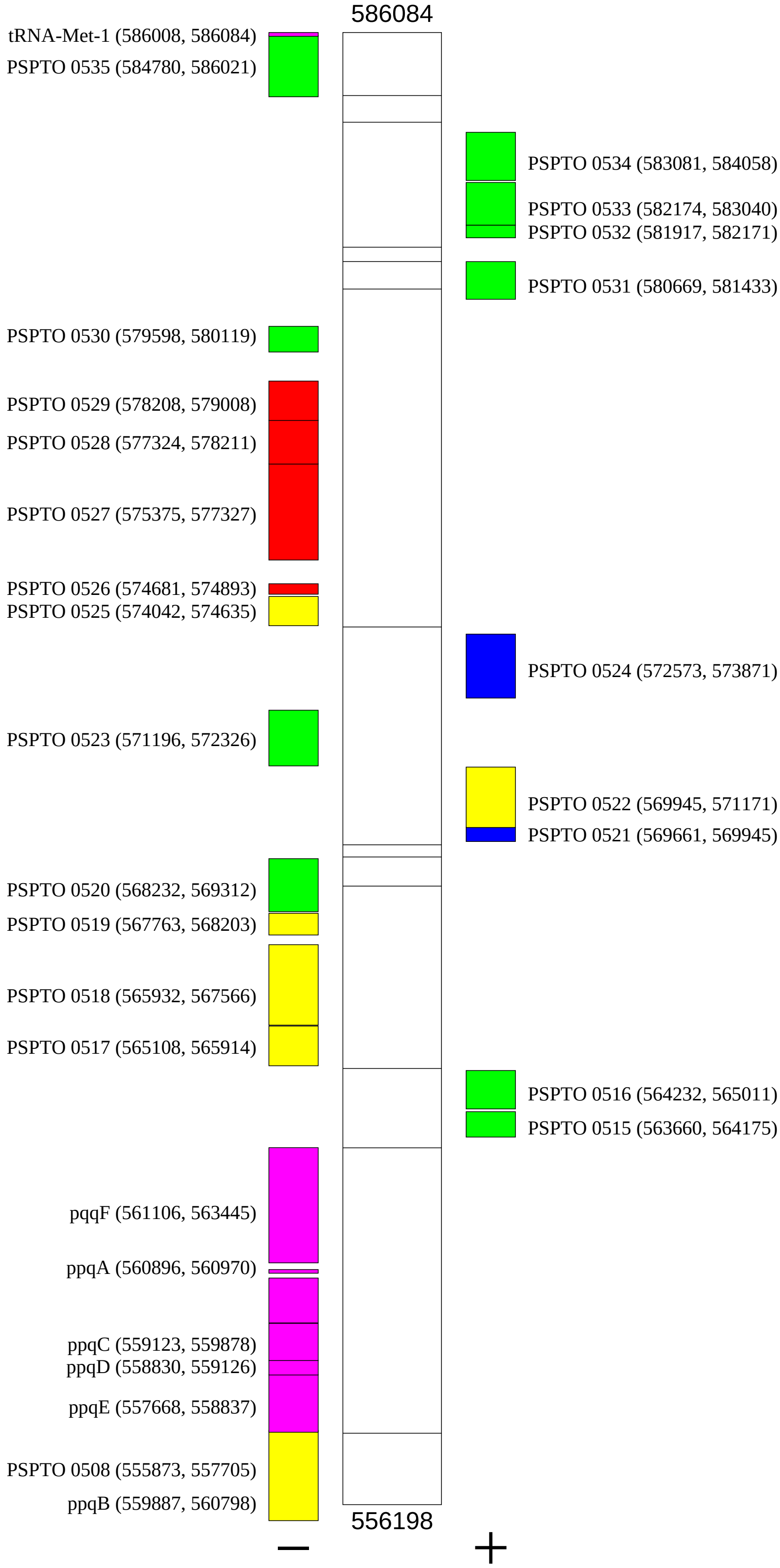
$$\Delta_2^{m-1}(i^*) + \Delta_2^{m+1}(i^*) = \max_{i_{m-1}<i<i_{m+1}} \left[\Delta_2^{m-1}(i) + \Delta_2^{m+1}(i)\right],$$

    to be new position of segment boundary.

- Segment boundaries $\{i_m\}_{m=1}^M$ updated serially, or in parallel.
- Optimized recursive segmentation: Right after STEP 1 (Segmentation), optimize segmentation using first- or second-order update algorithm.

Optimized Recursive Jensen-Shannon Segmentation




586084
tRNA-Met-1 (586008, 586084)
PSPTO 0535 (584780, 586021)
PSPTO 0534 (583081, 584058)
PSPTO 0533 (582174, 583040)
PSPTO 0532 (581917, 582171)
PSPTO 0531 (580669, 581433)
PSPTO 0530 (579598, 580119)
PSPTO 0529 (578208, 579008)
PSPTO 0528 (577324, 578211)
PSPTO 0527 (575375, 577327)
PSPTO 0526 (574681, 574893)
PSPTO 0525 (574042, 574635)
PSPTO 0524 (572573, 573871)
PSPTO 0523 (571196, 572326)
PSPTO 0522 (569945, 571171)
PSPTO 0521 (569661, 569945)
PSPTO 0520 (568232, 569312)
PSPTO 0519 (567763, 568203)
PSPTO 0518 (565932, 567566)
PSPTO 0517 (565108, 565914)
PSPTO 0516 (564232, 565011)
PSPTO 0515 (563660, 564175)
pqqF (561106, 563445)
ppqA (560896, 560970)
ppqC (559123, 559878)
ppqD (558830, 559126)
ppqE (557668, 558837)
PSPTO 0508 (555873, 557705)
ppqB (559887, 560798)
556198
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+

New Termination Criterion

- Hypothesis testing and model selection frameworks to terminate segmentation assumes statistically stationary null model.

- In practice, observer that as segmentation progress, the 1-segment null models appears less and less credible $\implies$ measure relative intrinsic statistical fluctuations instead.

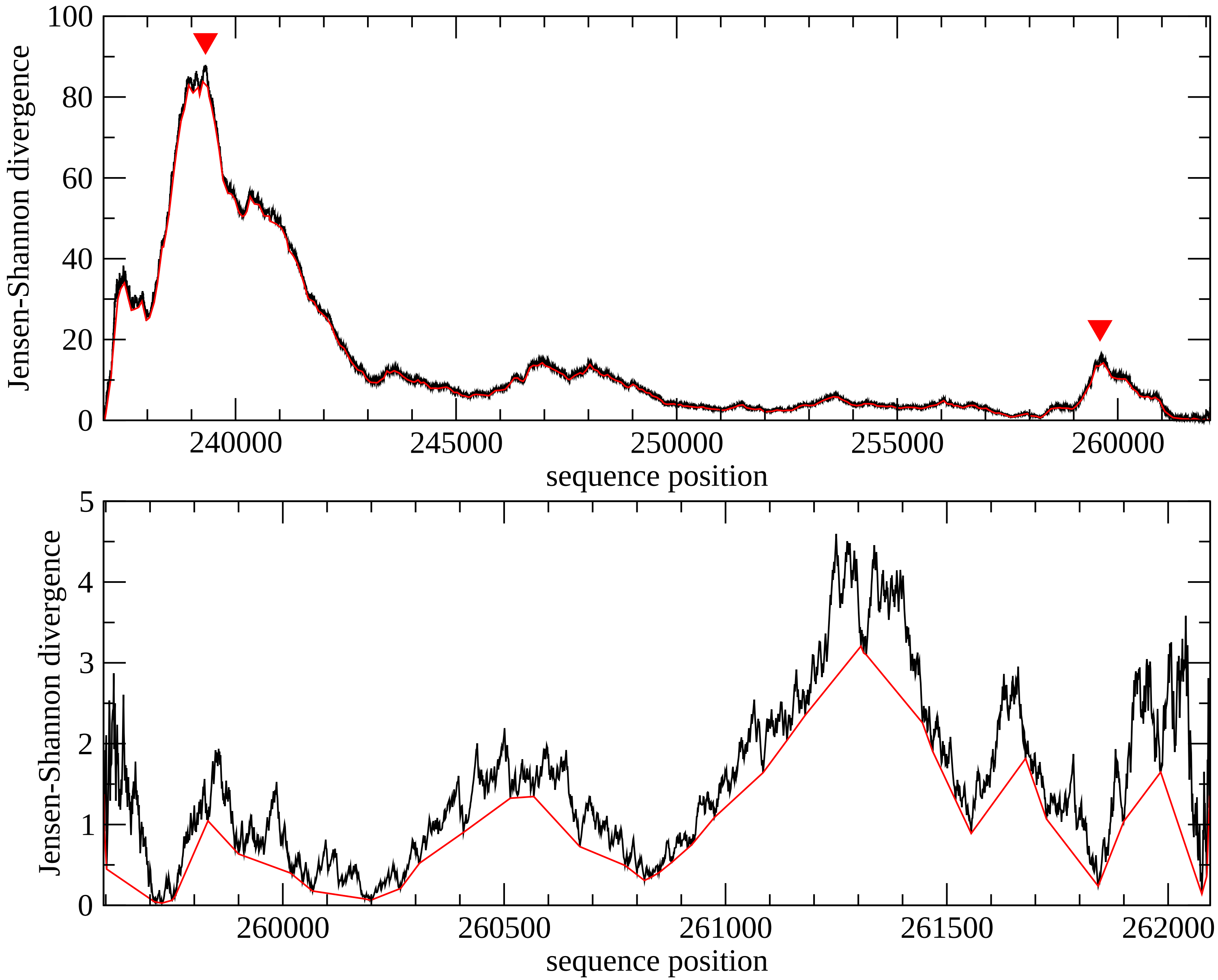
- Coarse-graining procedure developed to extract smoothed spectrum $\bar{\Delta}(i, n)$ from raw spectrum $\Delta(i)$. The parameter n is the shortest 'segment' we allow in $\bar{\Delta}(i, n)$.

- Compute

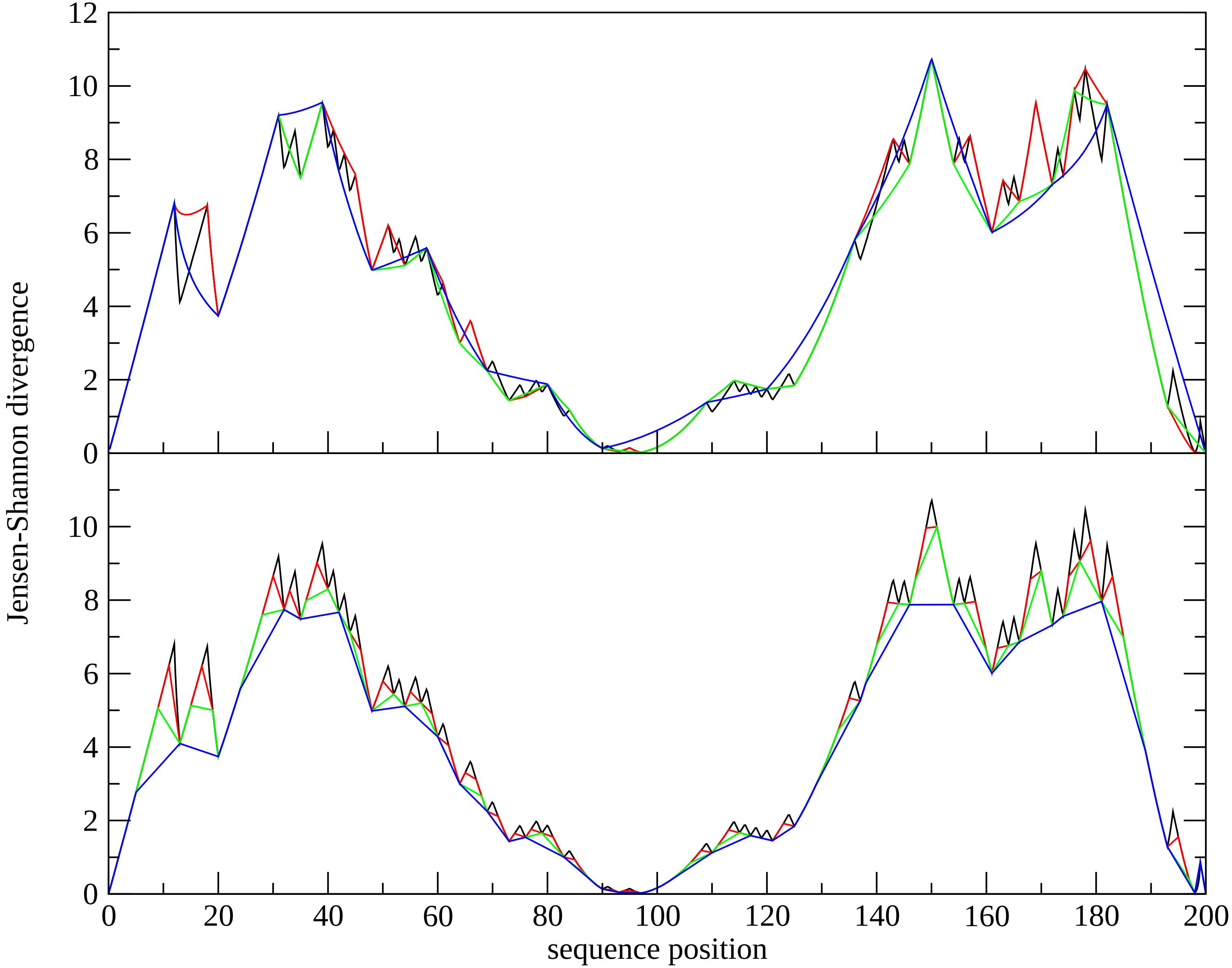
$$\delta A(n) = \int_0^N di \left|\bar{\Delta}(i, n) - \Delta(i)\right|, \quad A = \int_0^N di\, \Delta(i).$$

- Through comparison against annotation, a termination criterion of $(\delta A/A)^* = 0.30$ produces the most biologically meaningful segmentation.

New Termination Criterion



New Termination Criterion



Conclusions & Further Works

- In conclusion, we have:
  - Developed method of sliding pair of windows, and mean-field lineshape match filtering;
  - Identified problem of context sensitivity;
  - Developed optimization algorithms for recursive Jensen-Shannon segmentation scheme; and
  - Developed new termination criterion based on intrinsic statistical fluctuations.
- Further works:
  - Incomplete segmentation misleading, cluster terminal segments instead to obtain coarser scale description of genome. E.g. to distinguish lineage-specific regions arising from HGT and the genetic backbone.
  - Multiple sequence clustering for comparative, phylogenetic studies.