



PAPER

Smash++: finding rearrangements

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Some Mathematics Sample

Let X_1, X_2, \dots, X_n be a sequence of independent and identically distributed random variables with $E[X_i] = \mu$ and $\text{Var}[X_i] = \sigma^2 < \infty$, and let

$$S_n = \frac{X_1 + X_2 + \dots + X_n}{n} = \frac{1}{n} \sum_{i=1}^n X_i \quad (1)$$

denote their mean. Then as n approaches infinity, the random variables $\sqrt{n}(S_n - \mu)$ converge in distribution to a normal

$\mathcal{N}(0, \sigma^2)$.

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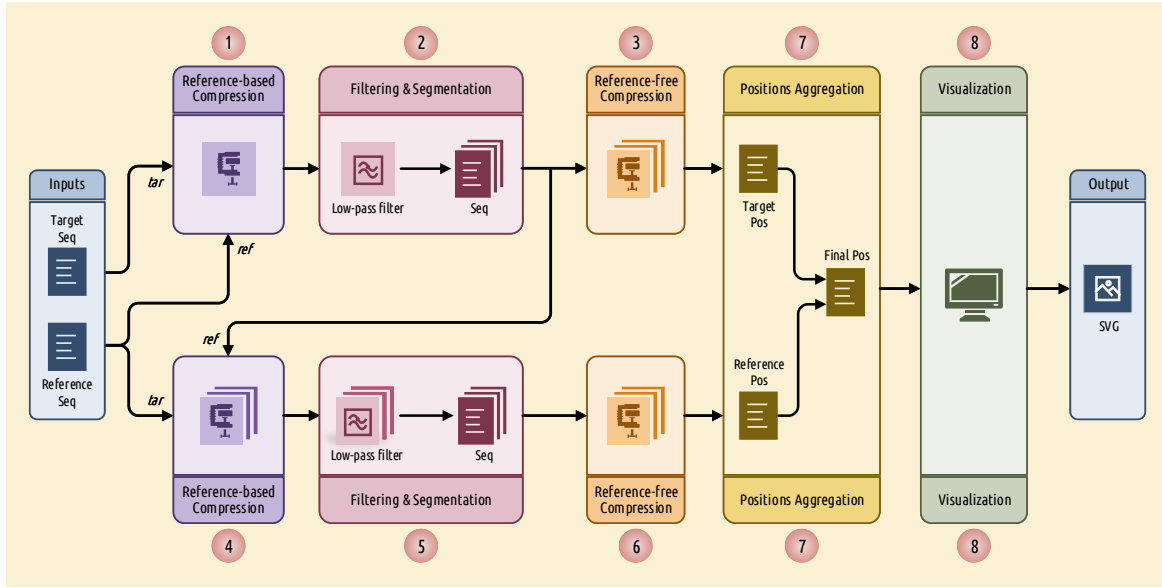


Figure 1. The schema of Smash++. The process of finding similar regions in reference and target sequences and also, computing redundancy in each region includes eight stages. Finally, Smash++ outputs a *.pos file that includes the positions of the similar regions, and can be then visualized, resulting in an SVG image.

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Methods

The schema of the proposed method is illustrated in Figure 1. Smash++ takes as inputs a reference and a target file and produces as output a position file, which is then fed to the Smash++ visualizer to produce an SVG image. This process has eight major stages: (1) compression of the original target file, based on the model of original reference file, (2) filtering and segmentation of the compressed file, (3) reference-free compression of the segmented files, obtained by the previous stage, (4) compression of the original reference file, based on the model of segmented files obtained by stage 2, (5) filtering and segmentation of the compressed files, (6) reference-free compression of the segmented files, that are obtained by the stage 5, (7) aggregating positions, generated by stages 3 and 6, and (8) visualizing the positions. The following sections describe the process in detail.

Data modeling

Smash++ works on the basis of cooperation between finite-context models (FCMs) and substitutional tolerant Markov models (STMMs). Applying these models on various contexts provides probability and weight values, illustrated in Figure 2a, which are then mixed (by multiplication and addition, shown in Figure 2b) to provide the final probability (P) of occurring an input symbol. The following subsections describe FCMs and STMMs in detail.

Finite-context model (FCM)

A finite-context model considers Markov property to estimate the probability of the next symbol in an information source, based on the past k symbols (a context of size k) [? 4?]. Denoting the context as $c_{k,i} = s_{i-k}s_{i-k+1} \dots s_{i-2}s_{i-1}$, the probability of the next symbol s_i in an information source S , which is posed

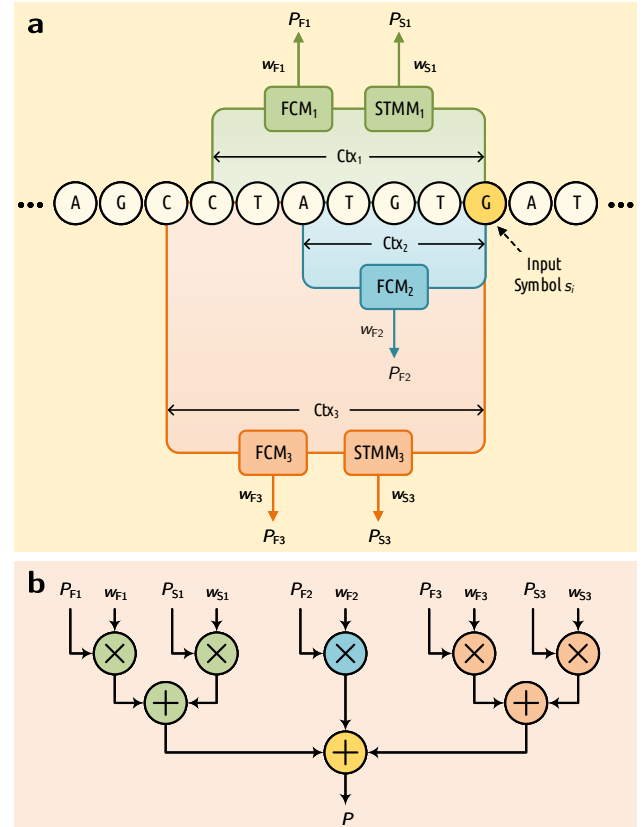


Figure 2. Data modelling by Smash++. (a) cooperation between finite-context models (FCMs) and substitutional-tolerant Markov models (STMMs). Note that each STMM needs to be associated with an FCM. (b) probability of an input symbol is estimated by employing the probability and weight values that have been obtained from processing previous symbols.

at i , can be estimated as

$$P_m(s_i|c_{k,i}) = \frac{N(s_i|c_{k,i}) + \alpha}{N(c_{k,i}) + \alpha|\Theta|}, \quad (2)$$

in which m stands for model (FCM in this case), $N(s_i|c_{k,i})$ shows the number of times that the information source has generated symbol s_i in the past, $|\Theta|$ denotes size of the alphabet Θ , $N(c_{k,i}) = \sum_{b \in \Theta} N(b|c_{k,i})$ represents the total number of events occurred for the context $c_{k,i}$ and α allows to keep a balance between the maximum likelihood estimator and the uniform distribution. Eq. 2 turns to the Laplace estimator, for $\alpha = 1$, and also behaves as a maximum likelihood estimator, for large number of events i [5].

Substitutional tolerant Markov model (STMM)

A substitutional tolerant Markov model [6] is a probabilistic-algorithmic model that assumes at each position, the next symbol in the information source is the symbol which has had the highest probability of occurrence in the past. This way, an STMM ignores the real next symbol in the source. Denoting the past k symbols as $c_{k,i} = s_{i-k} s_{i-k+1} \dots s_{i-2} s_{i-1}$, the probability of the next symbol s_i , can be estimated as

$$P_m(s_i|c'_{k,i}) = \frac{N(s_i|c'_{k,i}) + \alpha}{N(c'_{k,i}) + \alpha|\Theta|}, \quad (3)$$

where N represents the number of occurrences of symbols, that is saved in memory, and $c'_{k,i}$ is a copy of the context $c_{k,i}$ which is modified as

$$c'_{k,i} = \arg \max_{b \in \Theta} P_m(b|c'_{k,i}). \quad (4)$$

STMMs can be used along with FCMs to modify the behavior of Smash++ in confronting with nucleotide substitutions in genomic sequences. These models have the potential to be disabled, to reduce the number of mathematical calculations and consequently, increase the performance of the proposed method. Such operation is automatically performed using an array of size k (the context size), named history, which preserves the past k hits/misses. Seeing a symbol in the information source, the memory is checked for the symbol with the highest number of occurrences. If they are equal, a hit is saved in the history array; otherwise, a miss is inserted into the array. Before getting to store a hit/miss in the array, it is checked for the number of misses and in the case they are more than a predefined threshold t , the STMM will be disabled and also the history array will be reset. This process is performed for each symbol in the sequence.

This example shows the distinction between a finite-context model and a substitutional tolerant Markov model. Assume, the current context at position i is $c_{11,i} = \text{GGCTAACGTAC}$, and the number of occurrences of symbols saved in memory is $A = 10$, $C = 12$, $G = 13$ and $T = 11$. Also, the symbol to appear in the sequence is T . An FCM would consider the next context as $c_{11,i+1} = \text{GCTAACGTACT}$, while an STMM would consider it as $c'_{11,i+1} = \text{GCTAACGTACG}$, since the base G is the most probable symbol, based on the number of occurrences stored in memory.

Cooperation of FCMs and STMMs

When FCMs and STMMs are in cooperation, the probability of the next symbol s_i in an information source S , at position i , can be estimated as

$$P(s_i) = \sum_{m \in M_F} P_m(s_i|c_{k,i}) w_{m,i} + \sum_{m \in M_S} P_m(s_i|c'_{k,i}) w'_{m,i}, \quad \forall s_i \in S, 1 \leq i \leq |S|, 1 \leq k \leq i-1, \quad (5)$$

in which M_F and M_S denote sets of FCMs and STMMs, respectively, $P_m(s_i|c_{k,i})$ shows the probability of the next symbol estimated by the FCM, $P_m(s_i|c'_{k,i})$ represents this probability es-

timated by the STMM, and $w_{m,i}$ and $w'_{m,i}$ are weights assigned to each model based on its performance. We have

$$\begin{aligned} \forall m \in M_F : w_{m,i} &\propto (w_{m,i-1})^{\gamma_m} P_m(s_i|c_{k+1,i-1}), \\ \forall m \in M_S : w'_{m,i} &\propto (w'_{m,i-1})^{\gamma'_m} P_m(s_i|c'_{k+1,i-1}), \end{aligned} \quad (6)$$

where γ_m and $\gamma'_m \in [0, 1)$ are forgetting factors predefined for each model. Also,

$$\sum_{m \in M_F} w_{m,i} + \sum_{m \in M_S} w'_{m,i} = 1. \quad (7)$$

By experimenting different forgetting factors for models, we have found that higher factors should be assigned to models that have higher context-order sizes (less complexity) and vice versa. As an example, when the context size $k = 6$, γ_m or $\gamma'_m \simeq 0.9$ and when $k = 18$, γ_m or $\gamma'_m \simeq 0.95$ would be appropriate choices. These values show that forgetting factor and complexity of a model are inversely related.

Storing models in memory

The FCMs and STMMs include, in fact, count values which need to be saved in memory. For this purpose, four different data structures have been employed considering the context-order size k , as follows:

- table of 64 bit counters, for $k \in [1, 11]$,
- table of 32 bit counters, for $k = \{12, 13\}$,
- table of 8 bit approximate counters, for $k = 14$, and
- Count-Min-Log sketch of 4 bit counters, for $k \geq 15$.

The table of 64 bit counters, that is shown in Figure 3a, simply saves number of events for each context. The table of 32 bit counters saves in each position the number of times that the associated context is observed. When a counter reaches to the maximum value $2^{32} - 1 = 4294967295$, all the counts will be renormalized by dividing by two, as shown in Figure 3b.

The approximate counting is a method that employs probabilistic techniques to count large number of events, while using small amount of memory [7]. Figure ?? shows the algorithm for two major functions associated with this method, Update and Query. In order to update the counter, a pseudo-random number generator (PRNG) is used the number of times of the counter's current value to simulate flipping a coin. If it comes up 0/Heads each time or 1/Tails each time, the counter will be incremented. Figure 3c shows the difference between arithmetic and approximate counting, and also the values which are actually stored in memory. Note that since an approximate counter represents the actual count by an order of magnitude estimate, one only needs to save the exponent. For example, if the actual count is 8, we store it in memory as $\log_2 8 = 3$.

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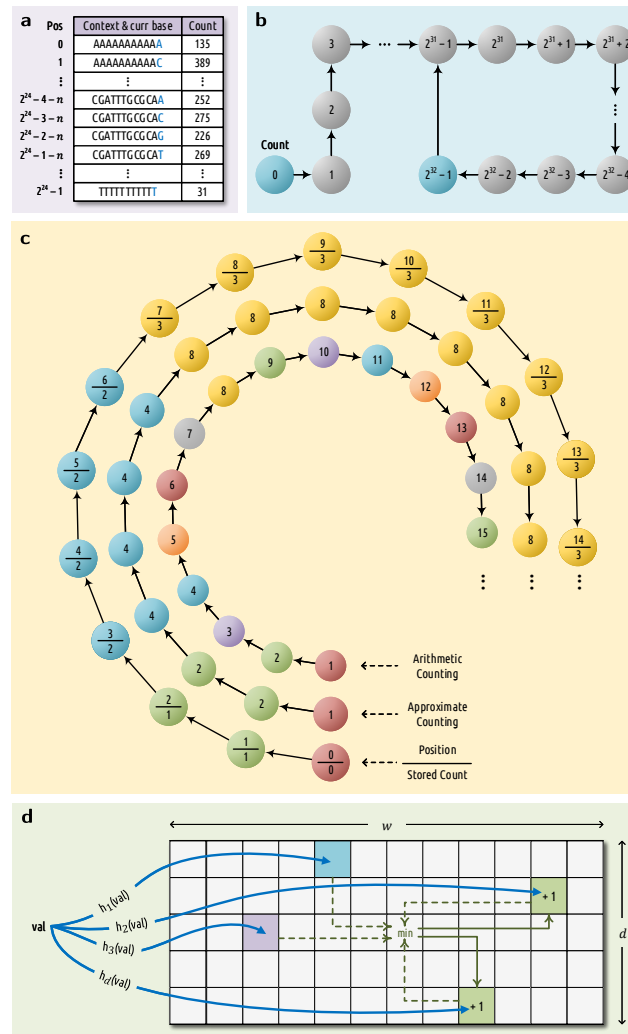


Figure 3. The data structures used by Smash++ to store the models in memory. (a) table of 64 bit counters that uses up to 128 MB of memory, (b) table of 32 bit counters that consumes at most 960 MB of memory, (c) table of 8 bit approximate counters with memory usage of up to 1 GB and (d) Count-Min-Log sketch of 4 bit counters which consumes up to $\frac{1}{2}w \times d$ B of memory, e.g., if $w = 2^{30}$ and $d = 4$, it uses 2 GB of memory.

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Declarations

List of abbreviations

CPU: central processing unit; FCM: finite-context model; RAM: random access memory; STMM: substitutional-tolerant Markov model;

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The authors declare that they have no competing interests.

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