## Note S1 Methods

The schema of the proposed method is illustrated in Fig. S1. Smash++ takes a reference and a target file, as inputs, and produces a position file, as output, 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 that are 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 which are obtained by the stage 5, (7) aggregating positions based on the results of stages 3 and 6, and (8) visualizing the positions. The following sections describe the process in detail.

**Fig. S1.** The schema of Smash++.

### S1.1 Data modeling

Smash++ works on the basis of cooperation between finite-context models (FCMs) and substitutional tolerant Markov models (STMMs), as illustrated in Fig. S2. Applying these models on various contexts, seen in the past, provides probability and weight values, which are then mixed to provide the final probability ($P$) of the next symbol, G in this case. The following subsections describe FCMs and STMMs in detail.

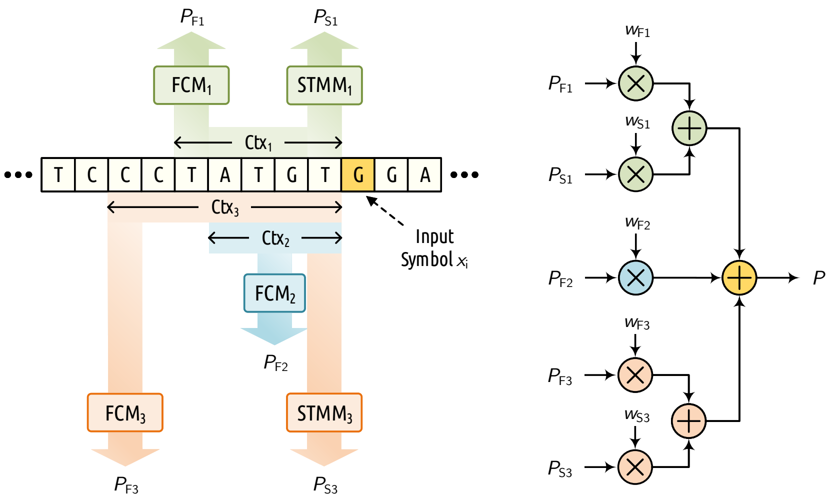

**Fig. S2.** model.

**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 $k$) [1–3]. Denoting the context as $x_{i-k}^{i-1} = x_{i-k}x_{i-k+1}\cdots x_{i-2}x_{i-1}$, the probability of the next symbol $s$, which is posed at $i$, can be estimated as

$$P_m(s|x_{i-k}^{i-1}) = \frac{N(s|x_{i-k}^{i-1}) + \alpha}{N(x_{i-k}^{i-1}) + \alpha|\Theta|}, \qquad \textbf{(Eq. S1)}$$

in which $m$ stands for model (FCM in this case), $N(s|x_{i-k}^{i-1})$ shows the number of times that the information source has generated symbol $s$ in the past, $|\Theta|$ denotes size of the alphabet $\Theta$, $N(x_{i-k}^{i-1}) = \sum_{j\in\Theta} N(j|x_{i-k}^{i-1})$ represents the total number of events occurred for the context $x_{i-k}^{i-1}$ and $\alpha$ allows to keep a balance between the maximum likelihood estimator and the uniform distribution. Eq. S1 turns to the Laplace estimator, for $\alpha = 1$, and also behaves as a maximum likelihood estimator, for large number of events $i$ [4].

**Substitutional tolerant Markov model (STMM)** A substitutional tolerant Markov model [5] 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 $x_{i-k}^{i-1} = x_{i-k}x_{i-k+1}\cdots x_{i-2}x_{i-1}$, the probability of the next symbol $s$, at position $i$, can be estimated as

$$P_m(s|{x'}_{i-k}^{i-1}) = \frac{N(s|{x'}_{i-k}^{i-1}) + \alpha}{N({x'}_{i-k}^{i-1}) + \alpha|\Theta|}, \qquad \textbf{(Eq. S2)}$$

where $N$ represents the number of occurrences of symbols, that is saved in memory, and ${x'}_{i-k}^{i-1}$ is a copy of the context $x_{i-k}^{i-1}$ which is modified as

$$x'_i = \operatorname*{argmax}_{\forall s\in\Theta} P_m(s|{x'}_{i-k}^{i-1}). \qquad \textbf{(Eq. S3)}$$

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 $c_0$ = 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 $c_1$ = GCTAACGTACT, while an STMM would consider it as $c'_1$ = 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 $s$, at position $i$, can be estimated as

$$P(s_i) = \sum_{m\in\mathcal{F}} P_m(s|x_{i-k}^{i-1})\, w_{m,i} + \sum_{m\in\mathcal{S}} P_m(s|{x'}_{i-k}^{i-1})\, w'_{m,i}, \qquad \textbf{(Eq. S4)}$$

in which $\mathcal{F}$ and $\mathcal{S}$ denote sets of FCMs and STMMs, respectively, $P_m(s|x_{i-k}^{i-1})$ shows the probability of the next symbol estimated by the FCM, $P_m(s|{x'}_{i-k}^{i-1})$ represents this probability estimated by the STMM, and $w_{m,i}$ and $w'_{m,i}$ are weights assigned to each model based on its performance. We have

$$\begin{aligned} \forall m \in \mathcal{F}: &\quad w_{m,i} \propto (w_{m,i-1})^{\gamma_m} P_m(s|x_{i-k-1}^{i-2}) \\ \forall m \in \mathcal{S}: &\quad w'_{m,i} \propto (w'_{m,i-1})^{\gamma'_m} P_m(s|{x'}_{i-k-1}^{i-2}), \end{aligned} \qquad \textbf{(Eq. S5)}$$

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

$$\sum_{m\in\mathcal{F}} w_{m,i} + \sum_{m\in\mathcal{S}} w'_{m,i} = 1. \qquad \textbf{(Eq. S6)}$$

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 $k = 6$, $\gamma_m$ or $\gamma'_m \simeq 0.9$ and when $k = 18$, $\gamma_m$ or $\gamma'_m \simeq 0.95$ would be appropriate choices. These values show that forgetting factor and complexity of a model are inversely related.

**data structures**

## S1.2 Finding similar regions

In order to smooth the profile information, we use Hann window [6], which is a discrete window function given by

$$w[n] = 0.5 - 0.5\ \cos\left(\frac{2\pi n}{N}\right) = \sin^2\left(\frac{\pi n}{N}\right), \qquad \textbf{(Eq. S7)}$$

in which, $0 \leq n \leq N$ and length of the window is $N + 1$ (Fig. S3).

**Fig. S3.** Hann window for 101 samples.

## S1.3 Computing complexities

## S1.4 The software

Besides Hann window, that is used as default to filter the profile information obtained by the reference-based compression, we have implemented several other window functions (Fig. S4), including Blackman [6], Hamming [7], Nuttall [8], rectangular [9], sine [10], triangular [11] and Welch [12] windows. These functions are given by

$$\begin{aligned}
&w[n] = 1, && \text{(rectangular)}\\
&w[n] = 1 - \left|\tfrac{n-N/2}{L/2}\right|, \quad L = N, && \text{(triangular/Bartlett)}\\
&w[n] = 1 - \left(\tfrac{n-N/2}{N/2}\right)^2, && \text{(Welch)}\\
&w[n] = \sin\left(\tfrac{\pi n}{N}\right), && \text{(sine)}\\
&w[n] = 0.54348 - 0.45652\ \cos\left(\tfrac{2\pi n}{N}\right), && \text{(Hamming)}\\
&w[n] = 0.42659 - 0.49656\ \cos\left(\tfrac{2\pi n}{N}\right) + 0.07685\ \cos\left(\tfrac{4\pi n}{N}\right), && \text{(Blackman)}\\
&w[n] = 0.35577 - 0.48740\ \cos\left(\tfrac{2\pi n}{N}\right) + 0.14423\ \cos\left(\tfrac{4\pi n}{N}\right) - 0.01260\ \cos\left(\tfrac{6\pi n}{N}\right). && \text{(Nuttall)}\\
& && \textbf{(Eq. S8)}
\end{aligned}$$

**Fig. S4.** Window functions.

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