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Manuscript in Preparation
Technical note

TECHNICAL NOTE

Smash++: finding rearrangements

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Abstract

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Some Mathematics Sample

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

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

denote their mean. Then as n approaches infinity, the random variables $\sqrt{n}(S_n - \mu)$ converge in distribution to a normal $\mathcal{N}(0, \sigma^2)$.

Background

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Data Description

A statement providing background and purpose for collection of these data should be presented for readers without specialist knowledge in that area. A brief description of the protocol for data collection, data curation and quality control, as well as potential uses should be included, as well as outlining how the data can be accessed if it is not deposited in our repository.

Analyses

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Discussion

The discussion should spell out the major conclusions and interpretations of the work, including some explanation on the importance and relevance of the dataset and analysis. It should not be restatement of the analyses done and their basic conclusions. The discussion section can end with a concluding paragraph that clearly states the main conclusions of the research along with directions for future work. Summary illustrations can be included.

Potential implications

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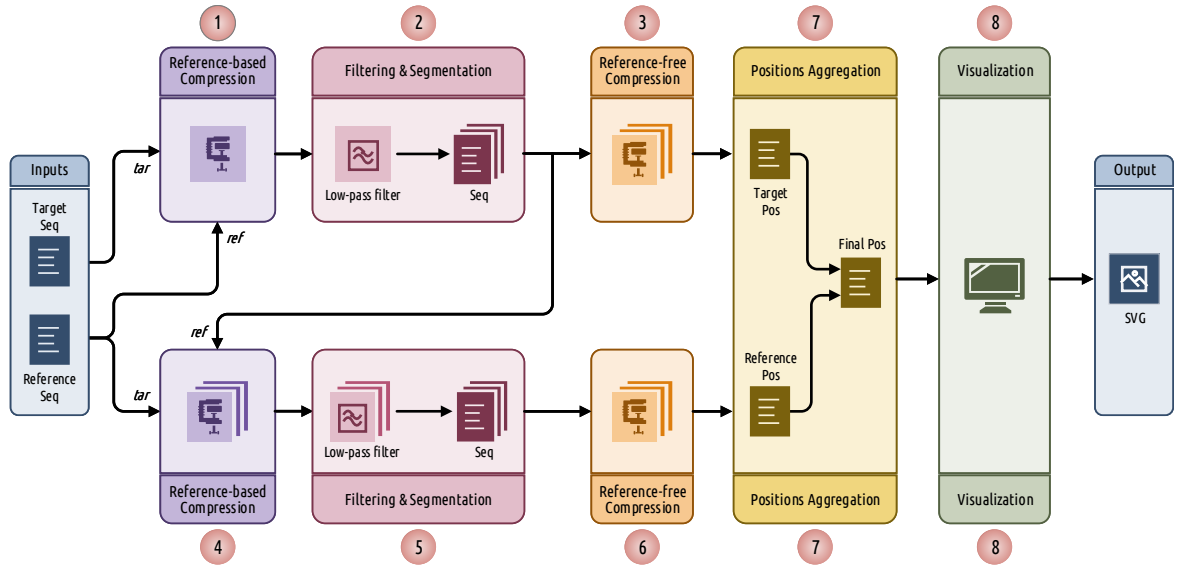

Figure 1. The schema of Smash++. The process of finding similar regions in reference and target sequences and also, computing redundancy in each region includes eight stages. Finally, Smash++ outputs a *.pos file that includes the positions of the similar regions, and can be then visualized, resulting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

manuscript, not provide speculation on how it will relate to far-reaching goals of the research area.

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 at i, can be estimated as

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

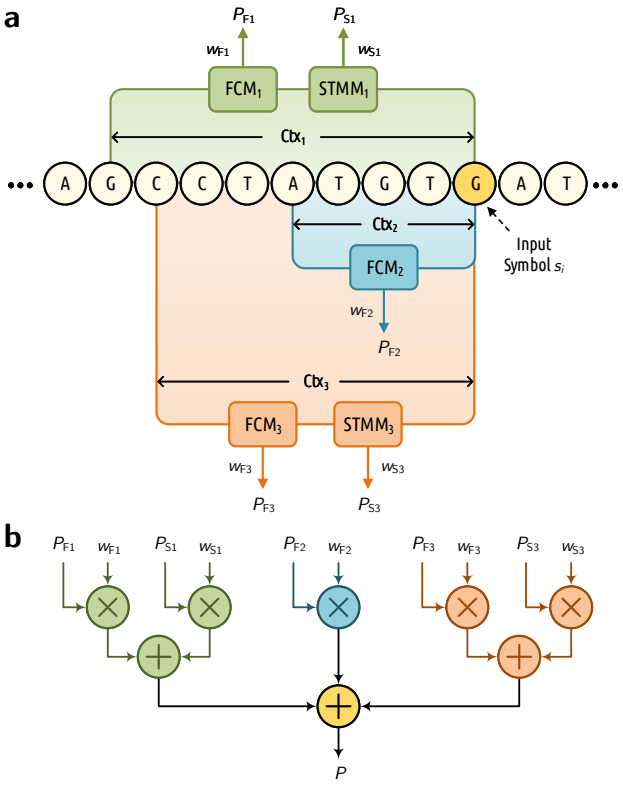

Figure 2. Data modelling by Smash++. (a) cooperation between finite-context models (FCMs) and substitutional-tolerant Markov models (STMMs). Note that each STMM needs to be associated with an FCM. (b) probability of an input symbol is estimated by employing the probability and weight values that have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

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

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

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

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

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 $c_{11,i}$ = 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 $c_{11,i+1}$ = GCTAACGTACT, while an STMM would consider it as $c'_{11,i+1}$ = 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_i in an information source S, at position i, can be estimated as

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

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

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

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

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

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 $k \ge 15$.

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 4 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 $\log_2 8 = 3$.

The Count-Min-Log Sketch (CMLS) is a probabilistic data structure to save frequency of events in a table by means of a family of independent hash functions [8]. The algorithm for updating and querying the counter is shown in Figure 5. In order to update the counter, its current value is hashed with d independent hash functions. Then, a coin is flipped the number of times of the counter's current value, employing a pseudo-random number generator. If it comes up 0/Heads each time or 1/Tails each time, the minimum hashed values (out of d values) will be updated, as shown in Figure 3d.

The CMLS requires a family of pairwise independent hash functions $H = \{h : U \to [m]\}$, in which each function h maps some universe U to m bins. To have this family, we use universal hashing by randomly selecting a hash function from a universal family in which $\forall x, y \in U,\ x \ne y:\ P_{h\in H}[h(x) = h(y)] \le \frac{1}{m}$. The hash function can be obtained by

$$h_{a,b}(x) = ((ax + b) \mod p) \mod m, \tag{8}$$

where $p \ge m$ is a prime number and a and b are randomly chosen integers modulo p with $a \ne 0$.

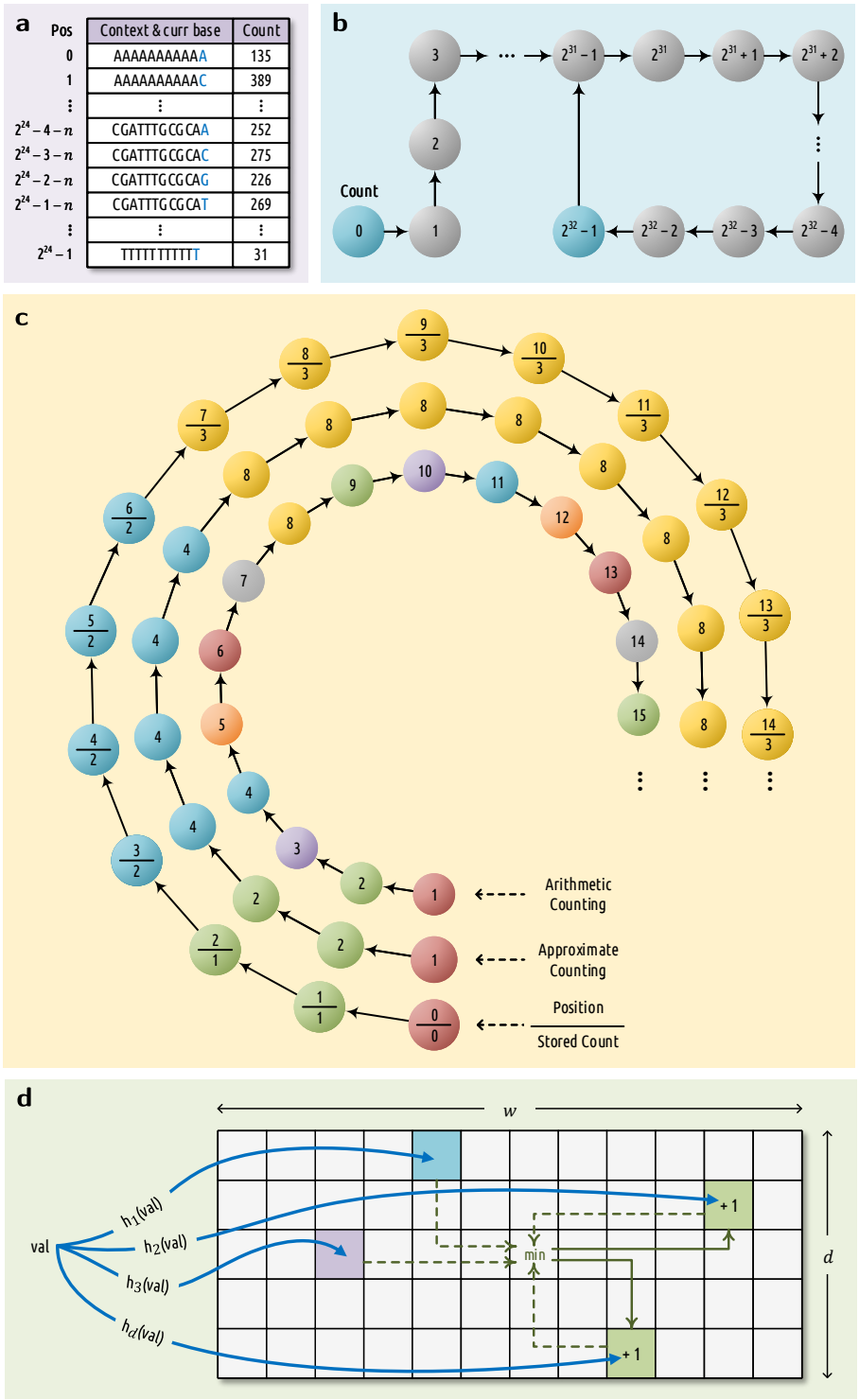

Figure 3. The data structures used by Smash++ to store the models in memory. (a) table of 64 bit counters that uses up to 128 MB of memory, (b) table of 32 bit counters that consumes at most 960 MB of memory, (c) table of 8 bit approximate counters with memory usage of up to 1 GB and (d) Count-Min-Log 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.

Finding similar regions

To find similar regions in reference and target files, a quantity is required for measuring the similarity. We use "per symbol information content" for this purpose, which can be calculated as

$$I(s_i) = -\log_2 P(s_i) \quad \text{bpb}, \quad \forall s_i \in S,\ 1 \leq i \leq |S| \qquad (9)$$

where $P(s_i)$ denotes the probability of the next symbol s_i in the information source S, obtained by Equation 5, and also "bpb" stands for bit per base.

The information content is the amount of information required to represent a symbol in the target sequence, based on the model of the reference sequence. The less the value of this measure is for two regions, the more amount of information is shared between them, and therefore, the more similar are the two regions. Note that a version of this measure has been

```
function IncreaseDecision(x)
    return True with probability 1/2^x, else False
end function

function Update(x)
    c ← table[x]
    if IncreaseDecision(c) = True then
        table[x] ← c + 1
    end if
end function

function Query(x)
    c ← table[x]
    return 2^c − 1
end function
```

Figure 4. Approximate counting update and query.

introduced in [5], which employs a single FCM to calculate the probabilities. In this paper, however, we exploit a cooperation between multiple FCMs and STMMs for highly accurate calculation of such probabilities.

The procedure of finding similar regions in a reference and a target sequence, illustrated in Figure 6, is as follows: after creating the model of the reference, the target is compressed based on that model and the information content is calculated for each symbol in the target. Then, the content of the whole target sequence is smoothed by Hann window [9], which is a discrete window function given by $w[n] = 0.5 - 0.5\cos\left(\frac{2\pi n}{N}\right)$, where $0 \leq n \leq N$ and length of the window is $N + 1$. Next, the smoothed information content is segmented considering a predefined threshold, meaning that the regions with the content greater than the threshold are filtered out. This is carried out for both regular and inverted repeat homologies and at the end, the result would be the regions in the target sequence that are similar to the reference sequence (Figure 6a). The described phase repeats for all of the target regions found, in the way that after creating the model for each region, the whole reference sequence is compressed to find those regions in the reference that are similar to each of the target regions (Figure 6b). The final result would have the form of Figure 6c.

Computing complexity

After finding the similar regions in reference and target sequences, we evaluate redundancy in each region, knowing that it is inversely related to Kolmogorov complexity, i.e., the more complex a sequence is, the less redundant it will be [10]. The Kolmogorov complexity, K, of a binary string s, of finite length, is the length of the smallest binary program p that computes s in a universal Turing machine and halts. In other words, $K(s) = |p|$ is the minimum number of bits required to computationally retrieve the string s [11, 12].

The Kolmogorov complexity is not computable, hence, an alternative is required to compute it approximately. It has been shown in the literature that a compression algorithm can be employed for this purpose [13, 14, 15]. In this paper, we employ a reference-free compressor to approximate the complexity and consequently, the redundancy of the founded similar regions in the reference and the target sequences. This compressor works based on cooperation of FCMs and STMMs, which has been previously described in detail. Note that the difference between reference-based and reference-free version of such compressor is that in the former mode, a model is first created for the reference sequence and then, the target sequence is compressed based on that model, while in the latter mode,

```
Input: sketch width w, sketch depth d, m bins, prime p ≥ m, randomly chosen integers a_{1..d} and b_{1..d} modulo p with a ≠ 0

function Hash(k, x)                    ▷ Universal hash family
    return ((a_k x + b_k) mod p) mod m
end function

function MinCount(x)
    minimum ← 15                       ▷ Biggest 4 bit number
    for k ← 1 to d do
        h ← Hash(k, x)
        if sketch[k][h] < minimum then
            minimum ← sketch[k][h]
        end if
    end for
    return minimum
end function

function IncreaseDecision(x)
    return True with probability 1/2^x, else False
end function

function Update(x)
    c ← MinCount(x)
    if IncreaseDecision(c) = True then
        for k ← 1 to d do
            h ← Hash(k, x)
            if sketch[k][h] = c then
                sketch[k][h] ← c + 1
            end if
        end for
    end if
end function

function Query(x)
    c ← MinCount(x)
    return 2^c − 1
end function
```

Figure 5. Count-Min-Log Sketch update and query.

the model is progressively created at the time of compressing the target sequence.

Experiments setup

Datasets

Results

Smash++ and several other methods have been carried out on a collection of synthetic and real sequences. The machine used for the tests had an 8-core 3.40 GHz Intel® Core™ i7-6700 CPU and 32 GB of RAM.

Availability of source code and requirements (optional, if code is present)

Lists the following:

- Project name: e.g. My bioinformatics project
- Project home page: e.g. http://sourceforge.net/projects/mged
- Operating system(s): e.g. Platform independent
- Programming language: e.g. Java

Table 1. Datasets used in the experiments.

Reference	Length (base)	Target	Length (base)	Description
Synthetic data – generated by GOOSE toolkit*				
RefS	1,000	TarS	1,000	RefS consists of four segments of size 250 bases. To build TarS, segments I and IV are inversely repeated, II is mutated 1% and III is duplicated. Read lines are 50 base long.
RefM	100,000	TarM	100,000	For building TarM, segments I and III of RefM (out of total four) are duplicated, II is inversely repeated and IV is mutated 1%. The length of read lines is 100.
RefL	5,000,000	TarL	5,000,000	RefL includes four segments, 1,250,000 bases each. Segments I and III are duplicated, II is mutated 1% and IV is inversely repeated for building TarL. Read lines are of length 100 bases.
RefXL	100,000,000	TarXL	100,000,000	RefXL is made of four segments, 25,000,000 bases each. Segment I is mutated 1%, segments II and III are inversely repeated and segment IV is duplicated to make TarXL. Read lines are 100 base long.
RefMut	60,000	TarMut	60,000	RefMut includes 60 segments. To build TarMut, the first segment (I) is mutated 1%, the second segment is mutated 2%, the third one is mutated 3%, and so on. The length of read lines is 100.
Real data				

*https://github.com/pratas/goose

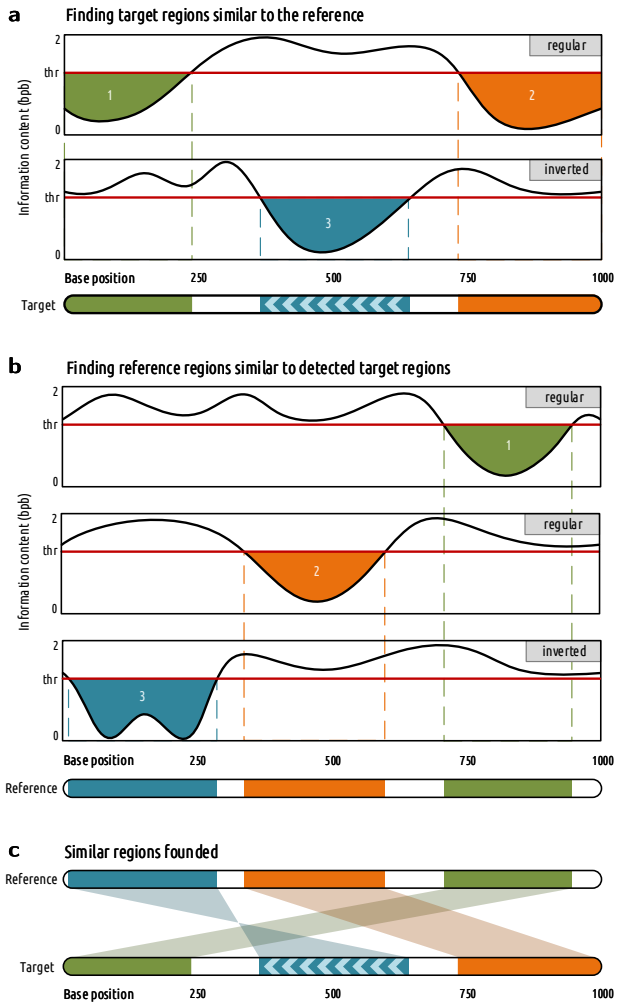

Figure 6. Finding similar regions in reference and target sequences. Smash++ finds, first, the regions in the target that are similar to the reference, and then, finds the regions in the reference that are similar to the detected target regions. This procedure is performance for both regular and inverted homologies.

- Other requirements: e.g. Java 1.3.1 or higher, Tomcat 4.0 or higher
- License: e.g. GNU GPL, FreeBSD etc. Any restrictions to use by non-academics: e.g. licence needed

This needs to be under an Open Source Initiative approved license where practicable compiled running software is made available. If the code is not hosted in a repository the *GigaScience* GitHub repository is also available for this purpose.

Availability of supporting data and materials

GigaScience requires authors to deposit the data set(s) supporting the results reported in submitted manuscripts in a publicly-accessible data repository such as *Giga*DB (see *Giga*DB database terms of use for complete details). This section should be included when supporting data are available and must include the name of the repository and the permanent identifier or accession number and persistent hyperlinks for the data sets (if appropriate). The following format is recommended:

"The data set(s) supporting the results of this article is(are) available in the [repository name] repository, [cite unique persistent identifier]."

Following the Joint Declaration of Data Citation Principles, where appropriate we ask that the data sets be cited where it is first mentioned in the manuscript, and included in the reference list. If a DOI has been issued to a dataset please always cite it using the DOI rather than the less stable URL the DOI resolves to (e.g. http://dx.doi.org/10.5524/100044 rather than http://gigadb.org/dataset/100044). For more see:

Data Citation Synthesis Group: Joint Declaration of Data Citation Principles. Martone M. (ed.) San Diego CA: FORCE11; 2014 [https://www.force11.org/datacitation]

A list of available scientific research data repositories can be found in res3data and BioSharing.

Declarations

List of abbreviations

CMLS: Count-Min-Log Sketch; CPU: central processing unit; FCM: finite-context model; GB: gigabyte; GHz: gigahertz; KB:

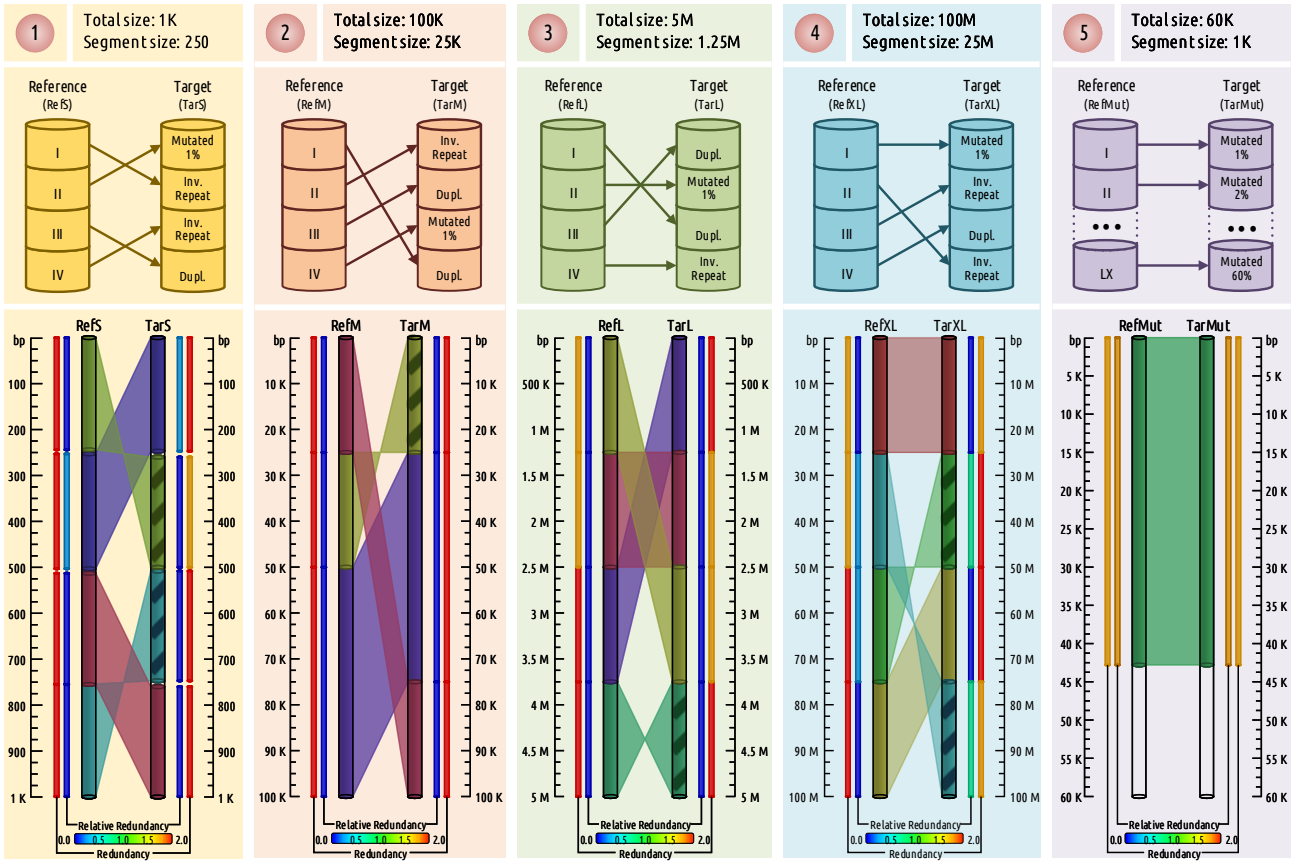

Figure 7. synthetic.

kilobyte; MB: megabyte; RAM: random access memory; PRNG: pseudo-random number generator; STMM: substitutional tolerant Markov model.

Ethical Approval (optional)

Manuscripts reporting studies involving human participants, human data or human tissue must:

- include a statement on ethics approval and consent (even where the need for approval was waived)
- include the name of the ethics committee that approved the study and the committee's reference number if appropriate

Studies involving animals must include a statement on ethics approval and have been treated in a humane manner in line with the ARRIVE guidelines.

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Competing Interests

The authors declare that they have no competing interests.

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