Sassy: Searching Short DNA Strings in the 2020s

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Abstract

Motivation. Approximate string matching (ASM) is the problem of finding all occurrences of a pattern P in a text T while allowing up to k errors. ASM was researched extensively around the 1990s, but with the rise of large-scale datasets, focus shifted towards inexact approaches based on *seed-chain-extend*. These methods often provide large speedups in practice, but do not guarantee finding all matches with $\leq k$ errors. However, many applications, such as CRISPR off-target detection, require exhaustive results with no false negatives.
Methods. We introduce Sassy, a library and tool for ASM of short (up to ≈1000 bp) patterns in large texts. Sassy builds on earlier tools that use Myers' bitpacking, such as Edlib. Algorithmically, the two main novelties are to split each sequence into 4 parts that are searched in parallel, and to use bitvectors in the text direction (*horizontally*) rather than the pattern direction (*vertically*). This allows significant speedups for short queries, especially when k is small, as has complexity $O(k\lceil n/W\rceil)$ when searching random text, where $W = 256$ is the SIMD width. Practically speaking, Sassy is the only recent index-free tool that is designed specifically for ASM, rather than the more common semi-global alignment. In addition, Sassy supports the IUPAC alphabet, which is essential for primer design and for matching ambiguous bases in assemblies.
Separately, we also introduce the concept of *overhang cost*: a variant of 'overlap' alignment where e.g. a suffix of the pattern is matched against a prefix of the text, where each character of the pattern that extends beyond the text incurs a cost of e.g. $\alpha = 0.5$. This is important when matches are near contig or read ends.
Results. Compared to Edlib, Sassy is $4\times$ to $15\times$ faster for sequences up to length 1000, and has throughputs exceeding 2 GB/s, whereas Edlib remains below 130 MB/s. Likewise, Sassy is up to $10\times$ faster than parasail when searching short strings. Sassy is also readily applicable to biological problems such as CRISPR off-target detection. When searching 61 guide sequences in a human genome, Sassy is $100\times$ faster than SWOffinder and only slightly slower (for $k \leq 3$) than CHOPOFF, for which building its index takes 20 minutes. Sassy also scales well to larger $k \in \{4, 5\}$, unlike CHOPOFF whose index took over 10 hours to build.
Availibility. Sassy is available as Rust library and binary at https://github.com/RagnarGrootKoerkamp/sassy.

Key words: Approximate string matching, pattern matching, fuzzy string searching, semi-global alignment, edit distance, bitpacking, SIMD, DNA

1. Introduction

Approximate string matching (ASM) is the problem of finding all matches of a pattern P of length m in a text T of length n with at most k errors [Navarro, 2001]. In this paper, we consider errors under the unit-cost edit distance, also known as Levenshtein distance [Levenshtein et al., 1966]. ASM has applications in many different fields. Specifically in bioinformatics, instances of ASM are CRISPR off-target detection [Yaish et al., 2024, Roux et al., 2025] and searching barcodes for demultiplexing [Cheng et al., 2024].

Recent years have seen a large number of papers on speeding up the related problem of global alignment by using faster implementations (bitpacking, SIMD), faster algorithms (A*), and better banding heuristics. Simultaneously, there is a lot of research on *mapping*: aligning, say, 1 Kbp reads against static text indices that can range from megabases to gigabases in size, without the guarantee of finding *all* matches. We identify that there is an unfilled niche of a modern, SIMD-based tool for ASM. Sassy (SIMD Approximate String Searcher)[1] fills this gap.

1.1. Contributions

Sassy is a conceptually simple but highly efficient command line tool and Rust library for approximate string matching. Sassy targets patterns with length up to around a thousand characters. It supports both ASCII and (IUPAC) DNA sequences and comes with C and Python bindings. The underlying algorithm is *online* and does not require a text index. This makes it especially suitable for e.g. searching a pattern while streaming DNA reads, one-off searches in assembled genomes, and reference-free analysis.

[1] Or, as anagram: Searching Short DNA Strings in the 2020s.

On a high level, our main contributions are:

1. We argue that while similar, semi-global alignment, mapping, and ASM are all distinct problems, and that for certain applications, exact methods for ASM are required and currently not available.
2. We define what it means to "report all matches", and choose to report only local minima by default. We note that matching reversed inputs can give different results (Figure 2).
3. We develop an efficient implementation of ASM. Algorithmically this has two small novelties: 1) bit-packing in the text direction, rather than the pattern direction, and 2) intra-sequence parallellism by splitting the text into 4 chunks that are processed in parallel using $W = 256$ bit SIMD. This leads to expected-case complexity $O(k\lceil n/W\rceil)$ when matching against random text, and $O(m\lceil n/W\rceil)$ in the worst-case when excluding the time for tracebacks.
4. We introduce an *overhang cost* $\alpha = 0.5$ that allows and controls the cost of *overhanging* alignments extending beyond the text.
5. Sassy is $4-15\times$ faster than Edlib for sequences up to length 1000 with up to 5% divergence.
6. Sassy is $100\times$ faster than Swoffinder for CRISPR off-target detection, and equally fast or faster than the index-based CHOPOFF while reporting identical matches.

1.2. Previous work

ASM has been extensively studied between 1980 and 2000, mostly concluding in the bit-packing algorithm of Myers [1999]. For word size $w = 64$, this has worst-case complexity $O(\lceil m/w\rceil n)$, or expected-case complexity $O(\lceil k/w\rceil n)$ on random text. Since then, research has shifted to other types of pairwise alignment. Indeed, both *global alignment* and *mapping* are very active areas of research on similar but slightly different problems. Some methods developed for those problems can also be applied to ASM. Unfortunately, they usually do not guarantee to return all matches, either because they only return best matches, as in *semi-global alignment*, or because of their heuristic nature in case of mappers. Before discussing the older results on ASM itself in detail, we first cover some recent work on these related problems, so that the differences can be appreciated.

Global alignment. In *global alignment*, the pattern P is aligned against the *entire* text T. The lengths $m := |P|$ and $n := |T|$ are typically relatively close to each other, and may range from tens to millions of bases. The classical Needleman-Wunsch [Needleman and Wunsch, 1970] (or Wagner-Fischer/Levenshtein [Wagner and Fischer, 1974, Levenshtein et al., 1966]) algorithm requires $O(nm)$ time and space, although space can be reduced to $O(\min(m,n))$ when only the alignment trace is needed. While no worst-case algorithm breaks the $O(n^{2-\varepsilon})$ barrier under SETH [Backurs and Indyk, 2015], many practical methods achieve sub-quadratic performance on typical inputs. For instance, Ukkonen's band-doubling method [Ukkonen, 1985b] runs in $O(ns)$ time, where s is the edit distance, and diagonal-transition approaches Myers [1986], Ukkonen [1985a] attain $O(n+s^2)$ both in expectation on random texts and in practice. A recent implementation of this (for affine costs) is in WFA [Marco-Sola et al., 2021] and its extension BiWFA [Marco-Sola et al., 2023] with reduced memory usage. Another key technique in accelerating global alignment is bit-packing, pioneered by Myers in 1999 [Myers, 1999]. Rather than processing each DP cell individually, cost differences can be stored in word-size $w = 64$ bit vectors, allowing the processing of 64 DP states at once. This reduced the time complexity to $O(n\lceil m/w\rceil)$, or $O(n\lceil s/w\rceil)$ with banding. This bit-packing is implemented in the commonly used tool Edlib [Šošić and Šikić, 2017]. Modern CPUs can process more than 64 bits in SIMD registers (e.g. 256 bits for avx2). To effectively use parallelization, the DP matrix is often broken into smaller regions [Farrar, 2006, Wozniak, 1997, Liu and Steinegger, 2021], allowing parallel processing such as in KSW2 Li [2018], Suzuki and Kasahara [2018], BSAlign [Zhang et al., 2019], and SeqMatcher [Espinosa et al., 2024]. Additionally, unlike for ASM, heuristics such as X-drop can be employed to reduce the search space [Altschul et al., 1990, Suzuki and Kasahara, 2018, Liu and Steinegger, 2021, Walia et al., 2024, Doblas et al., 2025], while losing the guarantee that the best alignment is found. A*PA and A*PA2 instead bound the search region by using A*, and retaining the guarantee that an optimal alignment is found [Groot Koerkamp and Ivanov, 2024, Groot Koerkamp, 2024].

Semi-global alignment. In *semi-global* alignment, a pattern P is aligned to a *substring* of a longer text T, and gaps at the start and end of T do not incur a penalty. Like in global alignment, only the alignment(s) with the lowest number of errors are reported. Semi-global alignment can either be between a short pattern and a much longer text ($m \ll n$, e.g. searching a read in a reference genome), or between two sequences of similar length ($m \approx n$, e.g. refining a mapped read). This approach was first introduced by Sellers [1979, 1980], and later termed *semi-global*[2] by Gotoh [1999], who also termed *global* alignment. It is implemented in tools such as Parasail [Daily, 2016], SeqAn [Reinert et al., 2017], Edlib [Šošić and Šikić, 2017], and more recently Ish [Stadick, 2025]. When $m \approx n$, semi-global alignment can benefit from adaptive banding methods as developed for global alignment, but this is not the case when $m \ll n$. There, some methods (parasail, Seqan, Ish) simply compute the entire $O(mn)$ DP matrix, while others (Edlib, Sassy) often only compute the top $O(k)$ rows [Myers, 1999]. Thus, these two regimes lead to completely different algorithms.

Cost models. A *cost model* defines what constitutes an *error* and the cost associated to each error. This concept originated in the early 1900s with systems designed to detect misspelled names by sound [Odell and Russell, 1918]. In the 1950s, Hamming distance was introduced for binary codes, measuring the number of differing bit positions [Hamming, 1950], or in the context of DNA, the number of mismatches between two equal-length strings. Around a decade later, the Levenshtein distance was formalized [Damerau, 1964, Levenshtein et al., 1966], that allows insertions and deletions alongside substitutions. Importantly, Levenshtein distance uses a *unit cost* model, assigning a cost of 1 to each edit, making it computationally efficient. However, this assumption is unrealistic for large insertions or deletions, as deleting or inserting long segments often represents a single biological event. This led to the development of gap-affine models, where gap opening and extension have different costs [Gotoh, 1982, Altschul and Erickson, 1986, Marco-Sola et al., 2021]. For Sassy, we use unit-cost edit distance for its computational efficiency and the assumption that long indels are rare when aligning relatively short patterns.

[2] Confusingly, the term semi-global is sometimes also used for different variants of alignment. Parasail [Daily, 2016] uses it for all types of alignment that are not exactly global alignment, while [Suzuki and Kasahara, 2018] uses it for *extension* alignment where the pattern has to match at the start of the text.

Approximate string matching. As mentioned before, the goal of ASM is to find all matches of a pattern P in a text T with $\leq k$ errors [Galil and Giancarlo, 1988, Navarro, 2001]. The key distinction from semi-global alignment is that not just the single best match should be reported, but that *all* matches with $\leq k$ errors should be reported. We first discuss *online* (streaming) algorithms, where the text is not known in advance, as opposed to *offline* algorithms that build an index on T. Moreover, we focus on the *k-difference* variant that uses edit distance rather than the *k-mismatch* variant that uses Hamming distance [Chhabra et al., 2025, Fiori et al., 2021, Gottlieb and Reinert, 2025].

Searching exact matches of patterns became popular through algorithms such as Knuth-Morris-Pratt [Knuth et al., 1977] and Boyer-Moore [Boyer and Moore, 1977]. With the development of different cost models in the 1980s, algorithms were created to detect inexact matches with k errors. Initially, *approximate string matching* described comparison of two strings [Ukkonen, 1983, Hall and Dowling, 1980], but later also described searching for a pattern as a substring of a text with $\leq k$ errors [Landau and Vishkin, 1985]. Sellers proposed an $O(mn)$ time algorithm [Sellers, 1980], which was improved to $O(m^2 + k^2 n)$ [Landau and Vishkin, 1985], and then $O(kn)$ [Ukkonen, 1985a]. The introduction of bit-parallelism [Baeza-Yates and Gonnet, 1992] led to complexities involving the word size w, such as $O(k\lceil m/w \rceil n)$ [Wu and Manber, 1992] in the famous agrep tool, $O(mn \log(\sigma)/w)$ [Wright, 1994], and eventually $O(\lceil m/w \rceil n)$ in Myers' algorithm [Myers, 1999]. Later optimizations targeted specific scenarios: short patterns or small k [Baeza-Yates and Navarro, 1999, Navarro and Baeza-Yates, 1999, Bille, 2011], fixed pattern lengths [Iliopoulos et al., 2001, Ho et al., 2017], and periodic texts [Cole and Hariharan, 2002]. Some were optimized for multi-pattern search [Muth and Manber, 1996, Baeza-Yates and Navarro, 1997], though here we focus on a single pattern.

Additionally, many offline algorithms leverage text pre-processing and indexing, such as text compression [Mäkinen et al., 2003, Kärkkäinen et al., 2000], suffix arrays [Landau and Vishkin, 1986, Manber and Myers, 1993, Huynh et al., 2004], and suffix trees [Ukkonen, 1993]. Others use pre-filtering with n-grams [Owolabi and McGregor, 1988, Jokinen and Ukkonen, 1991, Ukkonen, 1992, Sutinen and Tarhio, 1995, Bingmann et al., 2019], inexact hashing [Yao et al., 2010, McCauley, 2021], heuristics [Koehn and Senellart, 2010, Salmela et al., 2009], or search schemes on top of a birectional FM-index [Renders et al., 2022, 2024]. Such offline methods thus implement completely different algorithms than we focus on in this paper, and are suitable for different applications.

SIMD parallellism. Overall, the complexity of index-free methods did not improve beyond Myers' $O(\lceil m/w \rceil n)$. Practical speedups emerged with larger SIMD word sizes with $W = 256$ or $W = 512$ bits. Improvements then involved optimal utilization of W. For example, BGSA [Zhang et al., 2019] uses inter-sequence parallelism to compare multiple sequences to the same pattern, since intra-sequence parallelism is limited when $m \leq W$ [Zhang et al., 2019]. An alternative approach is taken by A*PA2 [Groot Koerkamp, 2024], where the dependency between SIMD lanes is broken by tiling them diagonally. Yet another approach is taken by SeqMatcher [Espinosa et al., 2024], where AVX512 instructions are used to effectively use 512-bit integers. In contrast, Sassy splits the text into 4 chunks that are processed in parallel, somewhat similar to Farrar's striped method [Farrar, 2006] and as also used by SimdMinimizers [Groot Koerkamp and Martayan, 2025], for a complexity of $O(m\lceil n/W \rceil)$. This way, intra-sequence parallelism is maximized.

Mapping. In modern applications, the text is often an assembled genome of many gigabases, and the number of patterns (reads) to be searched is very large. This means that index-free methods are infeasible, and in practice, *mappers* drop the guarantee to find all matches in favour of speed. Thus, we consider mapping to be approximate[3] ASM.

In the 1980s, with increasing sequence availability and the release of GenBank [Bilofsky et al., 1986] previous exact methods were no longer fast enough. Early mapping methods performed *exact* substring matches between the pattern P and database sequences, beginning with Wilbur and Lipman [1983] and followed by others using similar approaches [Lipman and Pearson, 1985, Ning et al., 2001, Wu and Watanabe, 2005] such as BLAST [Altschul et al., 1990].

Some methods controlled sensitivity based on the pigeonhole principle [Weese et al., 2012], while others tried to identify similar regions between P and the database sequences through spaced seeds [Ma et al., 2002, Rumble et al., 2009] or locality-sensitive hashing [Buhler, 2001]. As sequences got longer, also the number of seeds increased, leading to algorithms that reduced the number of seeds being stored, such as minimizers (e.g. Minimap2) [Li, 2018, Jain et al., 2020], strobemers (e.g. StrobeAlign) [Tolstoganov et al., 2024], or by hashing subsequences instead of substrings (e.g. SubseqHash2) [Li et al., 2024].

However, in benchmarks these mappers do not detect all mapping locations: they can achieve over 99% sensitivity but not full coverage [Banović Đeri et al., 2024], and their performance heavily depends on parameter settings such as the seed length [Oliva et al., 2021].

Biological applications of ASM. The earliest methods for ASM, developed in the 1980s, proved directly useful for biological problems. For example, Myers [1986] used ASM to find a 16-nucleotide binding site of the LexA protein in a 48 kb virus genome. Today, ASM supports diverse applications, including read demultiplexing [Cheng et al., 2024], genome polishing [Tonkin-Hill et al., 2020], and CRISPR off-target searching [Chaudhari et al., 2020].

We focus on the latter due to its clinical relevance. CRISPR and its associated Cas proteins form an adaptive immune system in bacteria and archaea, evolved to defend against foreign nucleic acids such as bacteriophage and plasmid DNA [Mojica et al., 2009]. In this system, foreign DNA is precisely cut using a template called single guide RNA (sgRNA). When the target DNA is flanked by a protospacer adjacent motif (PAM) — for example, 5'-NGG-3' in *Streptococcus pyogenes* — the CRISPR-Cas complex binds and cleaves the DNA, thereby neutralizing the invader. By modifying the sgRNA sequence, the CRISPR-Cas system can be programmed to cut virtually any DNA sequence. This technology has been applied to treat genetic diseases [Ledford, 2019], enhance crop traits [Jaganathan et al., 2018], and engineer microorganisms [Shapiro et al., 2018]. For an in-depth review, see Koonin and Makarova [2019]. Notably, on May 15th, 2025, CRISPR was used for the first time as a personalized treatment for a baby with

[3] ASM is *approximate* in the sense that matches are allowed up to k errors. Mapping is *approximate* in the sense that it is an approximate algorithm that does not guarantee to find *all* such matches.

carbamoyl phosphate synthetase 1 (CPS1) deficiency, a rare and life-threatening condition [Musunuru et al., 2025].

When CRISPR is engineered to target a specific sequence it is crucial that no other, unintended sequences are cut. This is called *off-target* cutting. Hence, computational tools to screen for such off-target sites have been developped. These include Cas-OFFinder [Bae et al., 2014], CRISPRitz [Cancellieri et al., 2020], SWOffinder [Yaish et al., 2024], and CHOPOFF [Labun et al., 2025], with the latter two representing the current state-of-the-art.

While CHOPOFF is much faster than SWOffinder, it requires a time-consuming step of building an index before searching. Given that human genetic variation affects off-target profiles [Scott and Zhang, 2017], we argue that with the advancement of personalized CRISPR therapies, there is a need for fast, index-free tools that are user friendly and robust to ambiguous bases.

2. Methods

We now describe our tool, Sassy. We start with some brief notation. Throughout the paper, we assume that we are given a *pattern* P of length $m := |P|$, and a *text* $T = t_0 \dots t_{n-1}$ of length $n := |T|$, which are both strings over an alphabet Σ of size $\sigma := |\Sigma|$. We write $T[i \dots j] := t_i \dots t_{j-1}$ for a right-exclusive substring of T, and we use $d(P, T[i \dots j])$ for the edit distance between P and $T[i \dots j]$. We write $\mathsf{rev}(T) := t_{n-1} \dots t_1 t_0$ for the reverse of T, and for DNA sequences, we define the *complement* $\mathsf{comp}(T)$ as the sequence where each base is replaced by its complement ($\mathsf{A} \leftrightarrow \mathsf{T}$ and $\mathsf{C} \leftrightarrow \mathsf{G}$, extended to IUPAC as well). The *reverse complement* is then $\mathsf{rc}(T) := \mathsf{rev}(\mathsf{comp}(T))$.

2.1. Approximate String Matching

We define approximate string matching following Navarro [2001], but restrict ourselves to edit distance only.

Definition 1 (Approximate String Matching, ASM.) Let P be a *pattern* of length $m := |P|$, and let T be a *text* of length $n := |T|$. Further, let $k \in \mathbb{N}_{\geq 0}$ be the maximum number of errors allowed. The problem of *approximate string matching*, $\mathsf{search}(P, T, k)$, is to find *all* end positions $j \in \{0, \dots, n\}$ in the text such that there exists an $i \in \{0, \dots, j\}$ such that the edit distance $d(P, T[i \dots j])$ between P and $T[i \dots j]$ is at most k.

What is a match? As defined above, a *match* is a position j in the text where an alignment of cost $\leq k$ ends. In practice, one might rather care about all *substrings* of T that have edit distance $\leq k$ to the pattern, i.e., all tuples (i, j) such that $d(P, T[i \dots j]) \leq k$ [Sellers, 1980, Definition 1]. Or, even more exhaustively, one could consider all *alignments* of P to substrings of T, where an alignment is a specific sequence of edits transforming P into $T[i \dots j]$.

In Sassy, we choose the first option: we find all end positions, and then do a *single* traceback for each of them.

When do we have a match? In practice, one is usually not quite interested in *all* matches. In particular, if there is an exact match ending in position j, all positions in $j - k$ to $j + k$ will have a cost $\leq k$ (see Figure 2). Thus, there are numerous options for which matches to report:

1. **All.** Report (matches ending in) *all* end positions with cost $\leq k$.
2. **Single best.** Report only a *single best* end position (if $\leq k$). Supported by Seqan.
3. **All best.** Report *all* positions where a match of *globally optimal* cost ends (if $\leq k$) as done in semi-global alignment as defined by Sellers [1980] and supported by Edlib and Seqan.
4. **Non-overlapping.** Report only end positions that are at least (roughly) m apart.

In Sassy, we take a different approach, that we argue is more principled:

5. **Local minima.** Report only *rightmost local minima* $\leq k$.

This is similar to the idea of Sellers [1980] to report all substrings $T[i \dots j]$ that can not be shrunk nor grown into a substring with lower edit distance, with the difference that we only report end positions, and that we only report a single match for each plateau of local minima.

ASM is not reverse-invariant. We note here that when reporting end positions, it is typically hard to guarantee that the matches reported by $\mathsf{search}(P, T, k)$ are in one-to-one correspondence with those reported by $\mathsf{search}(\mathsf{rev}(P), \mathsf{rev}(T), k)$, since the number of (local/global minima) end positions $\leq k$ can differ in the forward and reverse case, as exemplified in Figure 2. Reporting all substrings $T[i \dots j]$ would avoid this.

Sassy *is* invariant to reverse complements: when enabled, we search P in T and $\mathsf{rc}(T)$[4], so that both searches are in the natural direction of the text. Searching $\mathsf{rc}(P)$ in T would instead change the set of matches if the reverse-complement was taken of both P and T.

Traceback. Given the set of end positions that define a match, we can run a traceback from each of them to obtain both the position in the text where the match starts, and the full corresponding alignment. Sassy simply recomputes the part of the DP matrix preceding each end position and traces back through that.

2.2. Bitpacking and SIMD tiling

Figure 1 shows how Sassy applies both Myers' bitpacking [Myers, 1999] and SIMD. Using bitpacking, a *block* of $w = 64$ states of the DP matrix can be computed in parallel. Whereas other methods typically tile these bitvectors in the direction of the pattern, we tile them in the direction of the text. Algorithm 1 shows corresponding pseudocode of the main search function of Sassy.

SIMD. We use 256 bit AVX2 SIMD instructions to compute 4 *lanes* of 64 bit words in parallel. We avoid dependency between SIMD lanes by splitting the text into 4 chunks of $\lceil n/256 \rceil$ blocks each. Each lane then processes one chunk: we iterate over the 64 character blocks of each chunk, and then for each block, compute the m rows of the matrix.

As with Farrar's striped method [Farrar, 2006], there may be some "patching up" to do when a good alignment crosses the boundary between two chunks. In our case, we extend each chunk to the right (overlapping with the next chunk) as long as there is a partial alignment of cost $\leq k$ that started inside the original chunk. Especially when the text is long (so that $\lceil n/W \rceil \approx n/W$), this intra-sequence parallellism is near-optimal.

[4] As an implementation detail, we actually search $\mathsf{comp}(P)$ against $\mathsf{rev}(T)$, so that we can avoid taking the complement of T. Invariance under complements is trivial.

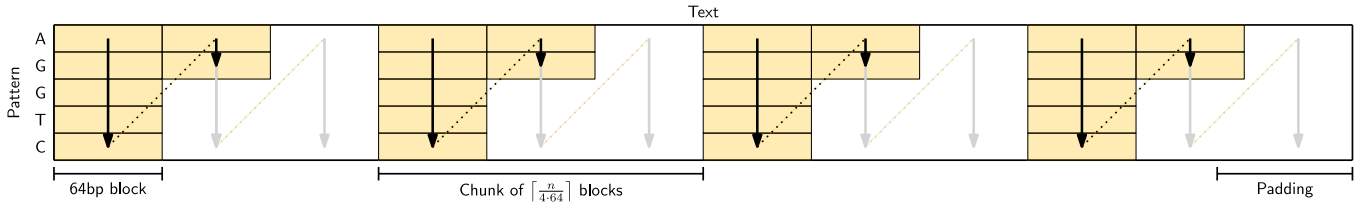

Fig. 1: The tiling strategy used by Sassy. The text is first split into word-size blocks of 64 bases. Then, the list of blocks is split into 4 chunks that are processed in parallel, with one SIMD lane per chunk. The text is implicitly padded as needed. Within a chunk, filling the matrix proceeds block-by-block. For each block, all (up to, see Section 2.3 and Figure 3) $m = |P|$ rows are computed before proceeding to the next block. Each chunk is extended into the succeeding chunk as long as there is a sufficiently good "in progress" alignment (not shown).

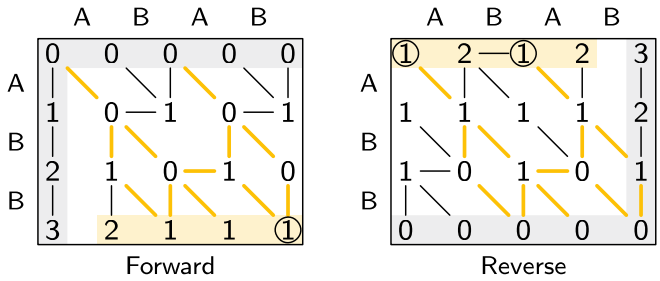

Fig. 2: Approximate string matching. An example of finding all occurrences of ABB in ABAB. On the left, the forward search initializes the top and left of the matrix (shaded in grey). Then, it shows all optimal paths to each state. On the bottom, the final distances are highlighted, and all optimal alignments of cost 1 are highlighted in yellow. By default, Sassy only starts a trace in the circled 1, a rightmost local minimum. The right figure shows the reverse alignment, where the matrix is filled from the bottom right to the top left. Note that the set of optimal alignments is the same, but that the number of local minima (1 vs 2) and global minima (3 vs 2) both differ.

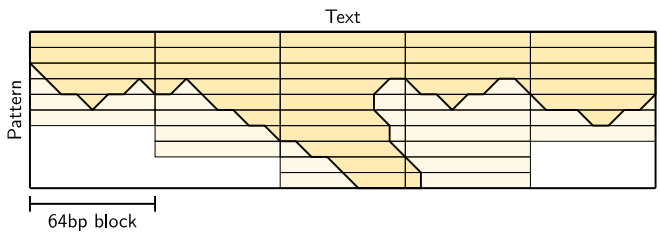

Fig. 3: Early break. We are only interested in entries of the DP matrix with value $\leq k$, as shown in the bold-outlined area. As soon as all entries in a row are $> k$, we can stop processing that block of text, as in the first and second block. Then, we only reach the bottom of the matrix when matches are present, as in the third block. One exception is shown in the fourth block: when there are states at the end of the previous block at distance $\leq k$, we must continue at least one row beyond that point. Since we use SIMD to process 4 chunks in parallel (not shown here), in practice we continue until the values in all 4 lanes are $> k$.

Alg. 1: Pseudocode for Sassy's main Search function, that takes as input the pattern P of length m and text T of length n, and returns a list of end-positions in the text where alignments of cost $\leq k$ end. Some of the operations operate on SIMD registers such as $[0, 0, 0, 0]$. ComputeBlock applies Myers' bitpacking algorithm to SIMD registers. Details of Eq, AllAboveK and FindEndPositionsAtMostK can be found in Appendix A.

```
1:  function Search(P, T, k)
2:      B ← ⌈n/(4 · 64)⌉                ▷ Number of 64bp blocks per chunk.
3:      j_{≤k} ← 0                      ▷ Last row in previous block ending in a value ≤ k.
4:      j_max ← 0                       ▷ Last computed row in previous block.
5:      v⁺ ← [[1, 1, 1, 1]; m]          ▷ Initialize list of SIMD of +1 deltas.
6:      v⁻ ← [[0, 0, 0, 0]; m]          ▷ Modified when α < 1 for overhang.
7:      M ← [[], [], [], []]            ▷ Matches (pos, cost) per lane.
8:      for i ∈ {0, ..., B + ⌈(m + k)/64⌉ − 1} do
9:          i_max ← i
10:         h⁺, h⁻ ← [0, 0, 0, 0]       ▷ Deltas in current row.
11:         d_s, d_e ← [0, 0, 0, 0]     ▷ Dist to start and end of each block.
12:         j'_{≤k}, j'_max ← 0
13:         for j ∈ {0, ..., m − 1} do
14:             d_s ← d_s + v⁺[j] − v⁻[j]
15:             for ℓ ∈ {0, 1, 2, 3} do
16:                 ▷ Profile determines a bitmask indicating equal chars. ◁
17:                 eq[ℓ] ← Eq(P[j], T[B · ℓ + 64 · i ... B · ℓ + 64 · i + 64])
18:             ComputeBlock(v⁺[j], v⁻[j], h⁺, h⁻, eq) ▷ Myers bitpacking.
19:             d_e ← d_e + v⁺[j] − v⁻[j]
20:             if min_ℓ d_e[ℓ] ≤ k then
21:                 j'_{≤k} ← j
22:             j'_max ← j
23:             ▷ Check if all 256 values are > k. ◁
24:             if j > j_{≤k} and AllAboveK(d_s, h⁺, h⁻, k) then
25:                 for j' ∈ {j + 1, ..., j_max} do
26:                     v⁺[j'] ← [1, 1, 1, 1]   ▷ Reset "dirty" skipped rows.
27:                     v⁻[j'] ← [0, 0, 0, 0]
28:                 j_max ← j'_max
29:                 j_{≤k} ← j'_{≤k}
30:                 if i ≥ B and 64 · (i − B) − j > k then
31:                     Goto 35, break out of i.   ▷ Done with chunk overlap.
32:                 Goto 8, continue with next i   ▷ Early break.
33:         ▷ Find (local minima) end positions with cost ≤ k. ◁
34:         FindEndPositionsAtMostK(M, d_s, h⁺, h⁻, k)
35:     for ℓ ∈ {1, 2, 3} do            ▷ Prune duplicate matches in overlap.
36:         M[ℓ] ← {x ∈ M[ℓ] : x ≥ B · ℓ + 64 · (i_max + 1)}
37:     return M
```

2.3. Early break

The complexity of computing the entire DP matrix as described so far is $O(m(\lceil n/W \rceil + m/w))$, where the final $+m/w$ accounts for overlaps between chunks. In ASM, we only care about matches with a cost at most k, and thus, parts of the DP matrix where values are $> k$ can be skipped [Ukkonen, 1983, 1985b, Myers, 1986], as shown in Figure 3. In particular, the edit distance between two uniform random and equal-length DNA sequences is typically around 45% of their length, so that most of the time, the cost of aligning a prefix of length $2 \cdot k$ of the pattern already incurs a cost $> k$. More formally, Chang and Lampe [1992] proved

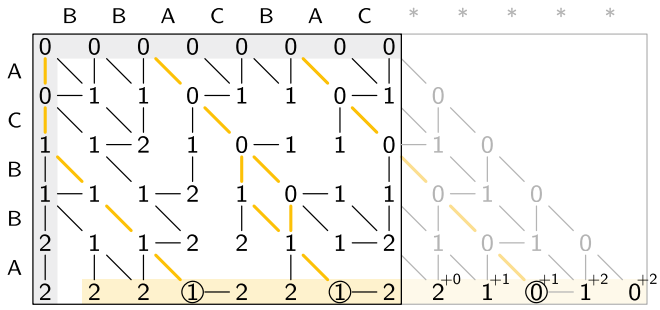

Fig. 4: Overhang alignment of ACBBA against BBACBAC, with overhang cost $\alpha = 0.5$. On the left, the state in row i is initialized with cost $\lfloor i\alpha \rfloor$, and a left-overhanging alignment (highlighted) is found where BBA matches and AC extends beyond the text for a cost of $\lfloor 2/2 \rfloor = 1$. On the right, the text is padded with m wildcard symbols, so that the costs on the right side of the matrix are replicated in the bottom row. Then, for each extended state in columns $j > n$, $\lfloor (j-n)\alpha \rfloor$ is added to the cost. This finds a right-overhanging alignment where AC matches and BBA extends beyond the text for a cost of $\lfloor 3/2 \rfloor = 1$.

that the number of states with cost $\leq k$ is $O(kn)$ when searching a random text.

Thus, as soon as all W columns corresponding to a SIMD vector contain a value $> k$, and additionally there are no remaining states with cost $\leq k$ at the end of the preceding blocks, we can stop with the current four blocks and move on to the next.

2.4. Overhang alignments

In some applications, it is useful to not only find occurrences of the pattern that are fully contained in the text, but also those that extend beyond the text. For example, this is the case for reads that may only partially contain a barcode, or in case of fragmented assemblies [Abramova et al., 2024]. Following Abrahamson [1987], we call these *overhanging* matches.

Definition 2 (Overhanging match) Given pattern P of length m and text T of length n:

1. there is a *left-overhanging* match when a suffix $P[l \dots m]$ matches a prefix of T,
2. there is a *right-overhanging* match when a prefix $P[0 \dots m-l]$ matches a suffix of T.

In either case, each of the l overhanging (unmatched) characters of P incurs a cost of $0 \leq \alpha \leq 1$, for a total *overhang cost* of $\lfloor l \cdot \alpha \rfloor$.

Figure 4 shows an example with $\alpha = 0.5$ (Sassy's default) with three matches of cost 1: a left-overhanging match, a non-overhanging match, and a right-overhanging match. When $\alpha = 1$, this corresponds to semi-global alignment and ASM, whereas $\alpha = 0$ corresponds to *overlap* alignments.

Sassy only needs a slight modification to find overlapping matches: the left of the DP matrix is initialized with cost $\lfloor i\alpha \rfloor$ instead of i, and on the right we extend the text with m "wildcard" symbols, so that the costs in the right column of the matrix are "copied" to the bottom row. Then, we manually add the overhang cost for those extended states. In practice, we use the IUPAC alphabet for this, and simply append N characters.

2.5. Tool

The main entrypoint of the Sassy Rust library is a function `search(pattern, text, k)` that returns one match for each rightmost local minium endpoint. It can optionally return matches for *all* endpoints, and supports reverse complements. The input can be either (case insensitive) ASCII text, simple ACGT DNA, or more general IUPAC-encoded DNA where sequences (*both* the pattern and the text) may contain bases such as N (matching ACTG), Y (matching CT), and R (matching AG). This is handled by selecting a *profile* (Appendix A.1). In case of simple DNA, we provide a function to validate that no non-ACGT bases are present. We provide both C and Python bindings.

We also provide a simple command line tool for searching a sequence in all records of a Fasta file, that can be installed using `cargo install sassy -config 'build.rustflags="-C target-cpu=native"'` (This ensures that AVX2 instructions are used when supported by the architecture.) Examples of commands are:

```
sassy search --alphabet dna --no-rc -k 0 --pattern CAT data.fa
sassy search --alphabet iupac -k 1 -f patterns.fa genome.fa.gz
sassy crispr -k 5 --guide guides.fa ref.fa
```

The first searches for an exact match of CAT in all records of `data.fa`. The second searches each record of `patterns.fa` in `genome.fa.gz`, while allowing up to 1 error and also searching the reverse-complement text. The last searches each of the guides in `guides.fa` against `ref.fa` while allowing at most 5 errors. Here, PAM sequences must match exactly and the preceding sgRNA can contain up to 5 errors.

Whereas the library is single-threaded, the command line tool maintains a queue of (P, T) tuples that are distributed (in batches) over all threads. Further details on the implementation can be found in Appendix A.

3. Results

We compare Sassy against Edlib [Šošić and Šikić, 2017] in two metrics: throughput of searching random DNA sequences without matches, and the throughput of finding and tracing matches. Section 4 shows specific applications of Sassy. The code and data for the benchmarks can be found in the `evals` directory at `https://github.com/RagnarGrootKoerkamp/sassy`. These experiments were run on an Intel Core i7-10750H with 6 cores with AVX2 support, running at a fixed frequency of 3.6 GHz with hyperthreading disabled.

Throughput of text searching. In Figure 5, we show the throughput of Sassy and Edlib when searching relatively short random DNA patterns ($20 \leq m \leq 1000$) against a long random texts ($n = 10^5$), for varying error thresholds ($0 \leq k \leq 50 = 0.05 \cdot 1000$).

Sassy is faster across all m and all k. For queries of length 20, Sassy reaches throughput over 2 GB/s whereas the throughput of Edlib does not exceed 130 MB/s. Since both the pattern and text are random, no matches occur, and the early break causes Sassy to have complexity $O(k\lfloor n/W \rfloor)$. Indeed, for constant k the throughput is constant in m, while it decreases when $k = 0.05 \cdot m$. Edlib, on the other hand, has throughput nearly independent of k: in nearly all cases we have $k \leq 20$, so that crossing the first $w = 64$ rows of the DP matrix already incurs a cost $> k$. This matches the complexity of $O(\lceil k/w \rceil n)$.

The throughput when searching ASCII (slightly faster) or IUPAC (slightly slower) text is within 5% compared to DNA.

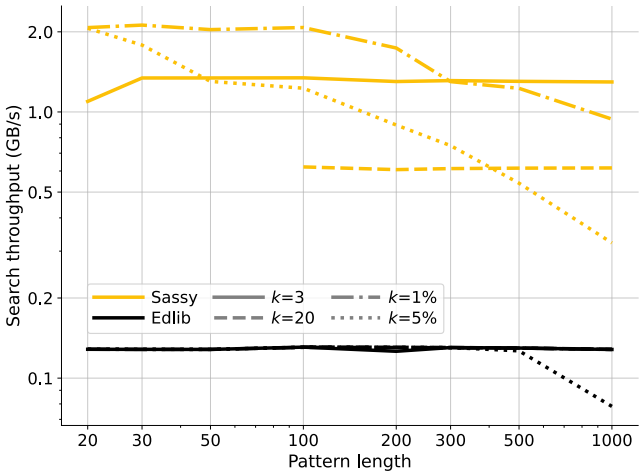

Fig. 5: Throughput of searching a random text. The pattern length m (x-axis) ranges from 20 to 1000, and the error threshold k (line style) is either fixed at 3 or 20, or computed as $m/100$ or $m/20$, rounded towards the nearest integer. Only points with $m > 3{*}k$ are shown to avoid spurious matches. All points are computed by averaging over 1000 random patterns and texts of length $n = 10^5$, and then converting to throughput. Note that this does not include searching the reverse-complement strand. Sassy has up to $10\times$ higher throughput when k is small.

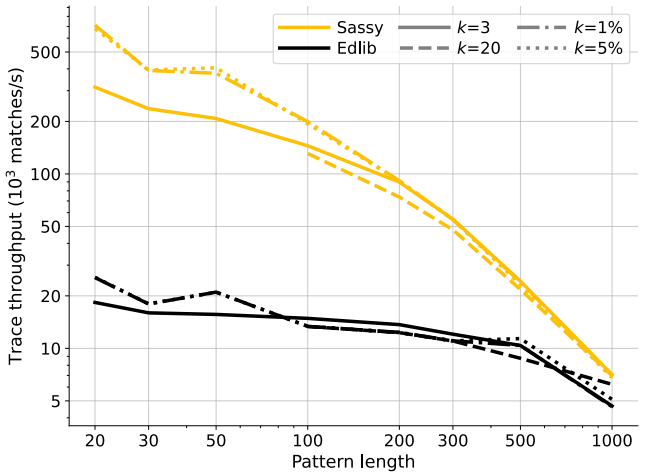

Fig. 6: Throughput of finding matches. When the text contains a match, this causes a larger part of the matrix to be computed since the early break does not trigger. Later, this part of the matrix is recomputed in full and stored in $O(m^2/w)$ words of memory so that a traceback can be done. To measure the total time it takes to process a match, we use the same setup as in fig. 5 with the addition of a single copy of the pattern planted at the end of the text. We measure the time difference with the version without match and report the corresponding throughput.

Affine-cost aligners. Sassy is over $10\times$ faster than tools implementing affine-cost alignments. For example, Sassy needs 4.5 seconds to search a pattern of length 23 in a human genome (with up to $k = 4$ errors, excluding searching the reverse-complement). For the same task, parasail [Daily, 2016] in semi-global mode with default cost parameters takes 53 to 69 seconds, depending on the exact configuration (8 or 16 bit values, and SSE4.1 vs AVX2), reporting up to 1.45 GCUPS (giga cell updates per second). lsh [Stadick, 2025] with default parameters takes 69 seconds (SSE4.1) to 110 seconds (AVX2). Running parasail with the same costs as lsh takes 81 seconds to 198 seconds. These methods are slower both because they store larger values (instead of bitpacking), and because they compute two additional *affine layers* of the DP matrix.

We propose that fast edit-distance alignments could be used to identify candidate regions which can then be refined with affine-cost methods.

Throughput of tracing. In Figure 6, we show the throughput of finding matches. This includes the time to locally compute all rows of the matrix (rather than just the top $O(k)$ rows), the time to recompute the matrix region containing the match, and the time for tracing through the filled matrix. We use the same setup as in previous experiments, and "plant" a single match at the end of the text. We then compared the run time of the same text with and without match.

Placing the match at the end avoids triggering the dynamic reduction of k in Edlib: Since Edlib performs semi-global alignment and only searches matches with the minimum edit distance, it reduces k whenever it finds a match with cost $< k$. If the match were placed earlier in the text, this reduction would confound the measurement by timing both the tracing time and its k reduction strategy. By placing the match at the end of the text, we largely isolate the tracing cost from the k reduction strategy.

For short patterns, Sassy is over $10\times$ faster per match than Edlib. For longer patterns, Sassy's throughput goes down quadratically as it naively computes the $O(m^2/w)$ words to fill the part of the matrix where a match is. Edlib does not slow down as much, likely due to $O(ns)$ banding, but is nevertheless still slower than Sassy for patterns up to length $m \leq 1000$.

4. Application: Finding CRISPR off-targets

Finding short sequences has many important applications, with CRISPR off-target searching being of particular recent interest [Musunuru et al., 2025]. SWOffinder [Yaish et al., 2024] and CHOPOFF [Labun et al., 2025] are currently among the fastest and most accurate tools for identifying off-target sequences. We extended Sassy with CRISPR off-target searching, enabling the search for PAM motifs—such as the Cas9 NGG motif—preceded by a guide RNA (gRNA) sequence [Ran et al., 2013].

4.1. Searching 61 guide RNAs in the human genome

First, we briefly summarize the algorithms used by the benchmarked tools. SWOffinder uses Smith-Waterman alignment to fill the entire $m \times n$ matrix, identifying all end positions with $\leq k$ edits. It then post-processes these alignments [Yaish et al., 2024]. CHOPOFF takes a different approach by first indexing all PAM locations in the target genome and storing their prefixes i.e. the sgRNA flank. Then they precompute all the edit distance paths, within k, through these prefixes. This allows instant lookup of sgRNA sequences with at most k edits of previously identified PAM sites. These indexes range from 3.2GB ($k = 0$) to 4.5GB ($k = 4$) for the human genome. The prefix edit paths are shipped with CHOPOFF for $k \leq 4$. However, computing this for $k = 5$ did not finish in 10 hours. Sassy's algorithm is similar to its regular search, but with an additional filter prior to traceback: when

	Sassy		CHOPOFF		SWOffinder	
k	Time	Matches	Time	Matches	Time	Matches
0	0:19	62	0:18 (19:47)	62	40:21	62
1	0:20	127	0:19 (23:53)	127	42:07	155
2	0:23	1,284	0:19 (23:59)	1,284	39:54	1,411
3	0:28	32,033	0:26 (23:39)	32,033	40:34	35,434
4	0:30	405,401	2:23 (23:56)	405,401	41:38	471,395
5	0:44	4,093,387	–	–	40:43	1,476,640

Table 1. Time (mm:ss) to search 61 sgRNAs in Human genome CHM13 using 16 threads, and number of matches. For CHOPOFF the time to build the index is shown in parentheses, and was terminated after 10 hours for $k = 5$. SWOffinder has different counts, because 1) forward and reverse searches are not equivalent (see Figure 2) and 2) it applies some post-processing, potentially "collapsing" matches for e.g. $k = 5$.

the user requests the PAM sequence to be unmutated, then the traceback is only performed when the exact PAM is present.

To compare Sassy to the other off-target search tools we used the benchmark from the CHOPOFF paper [Labun et al., 2025]. This queries 61 guide sequences with the NGG PAM against the human genome. Experiments were run on a Intel(R) Xeon(R) Gold 6240, using 16 threads for each job. Results are in Table 1.

For large values of k, Sassy outperforms both competitors by a wide margin. In fact, for $k \geq 4$, Sassy is more than 100× faster than SWOffinder and over 4× faster than the index-based CHOPOFF. Notably, Sassy completes the $k = 5$ search in just 44s, whereas CHOPOFF's index building for $k = 5$ exceeded 10hours (and was therefore omitted). For smaller values ($k \leq 3$), Sassy and CHOPOFF have comparable performance, with Sassy trailing by only a few seconds. We do note that CHOPOFF is faster when there are substantially more sgRNA queries, as most time is spent on loading the index, which is not parallellized over multiple threads.

We note that full support for IUPAC bases, as Sassy and CHOPOFF have, is important for this application, since human genome assemblies may not always be fully resolved—see Appendix B.

Thus, Sassy is an extremely fast tool that does not require building an index, making it ideal for personalized, reference-free, off-target screening.

5. Discussion

Sassy solves approximate string matching, and allows fast searching for short DNA sequences without using an index. The main algorithmic novelty is to use *horizontal* bitpacking of deltas, and intra-sequence parallellism using SIMD (Figure 1), leading to a complexity of $O(k \cdot \lceil n/W \rceil)$ when searching random text. This improved complexity allows searching text at up to 2 GB/s, and up to 15× speedup over Edlib.

Practically speaking, Sassy is a simple-to-use tool with many applications. Since Sassy is index-free, it easily supports IUPAC characters in both the pattern and text. It is significantly faster than other index-free methods for searching CRISPR off-target matches, and is being integrated into other tools such as CRISPRapido[5], which uses Sassy as a pre-filter for off-target detection with a more fine-grained (affine-cost) cost model, and Barbell, a work-in-progress demultiplexer.

[5] `https://github.com/pinellolab/crisprapido`

Future work. Sassy is primarily designed to search for short patterns (small m), and includes a quadratic $O(m^2/w)$ component. In particular, the traceback currently recomputes a full m^2 matrix, whereas a band of width k around the diagonal would be sufficient. Similarly, during the initial pass over the matrix, each match induces an "upper triangle" of computed states (Figure 3), whereas it would be possible to separate this into a band of size k around the match and a band of size $O(k)$ at the top of the matrix. Furthermore, we currently do not use SIMD to fill a traceback matrix, since intra-sequence parallellism does not work here. Instead, the diagonally strided technique of A*PA2 [Groot Koerkamp, 2024] could be used.

6. Acknowledgments

We thank Erik Garrison for encouraging us to build Sassy, and Rob Patro for feedback on this paper. We thank Seth Stadick for help with the evaluation of parasail and lsh.

RB is financed by ZonMw [541003001]. RGK is financed by ETH Research Grant ETH-17 21-1 to Gunnar Rätsch.

Conflict of Interest: none declared.

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A. Implementation Notes

We now provide some more details on the functions used in Algorithm 1.

AllAboveK(d_s, h^+, h^-, k)**.** This function takes as input the distance d_s to the start of 4 blocks, a threshold k, and the bit-encoded horizontal differences in each block. It then checks if the represented values in all blocks are $> k$. In practice, this function is slightly slow, and we call it not every row (as shown in the pseudocode), but only at most every 8 rows.

It processes each lane ℓ independently. First, we *pack* the bits of $h^+[\ell]$ and $h^-[\ell]$ into p (using `_pext_u64` available in BMI2) to remove positions where the delta is 0 and both have an indicator bit of 0. Then, a 1 in p indicates -1 and a 0 indicates $+1$ (with $+1$ padding at the end). We split the 64-bit value p into bytes, and do a precomputed table lookup that gives the total delta across the byte, and the minimum prefix sum in the byte. The we do a rolling sum over the bytes to compute the minimum overall prefix.

FindEndPositionsAtMostK(M, d_s, h^+, h^-, k)**.** This function again works lane-by-lane. Unlike **AllAboveK**, this function is only called at most once per block of text, when the iteration over j reaches the end of the pattern. Thus, it is less performance critical, and we implement it by simply iterating through the 64 bits of the bitmasks and keeping a rolling sum for the current score in each column. Then, each time a value $\leq k$ is seen, the index of the text and the corresponding cost are pushed to the list of matches.

A.1. Profiles

The job of a *profile* is to take a single character $P[j]$ of the pattern and a slice of 64 text characters, and determine a bitmask **Eq**$(P[j], T[x \dots y])$ indicating which of the text characters equal $P[j]$ [Rognes and Seeberg, 2000].

We recommend having a look at the code, in the `src/profiles` directory of the git repository. Currently we only support AVX2, and thus, this is subject to change.

ASCII. For the ASCII profile, we implement this as follows. For each block of text, we precompute a 256 long array of 64-bit words, so that the mask for each ASCII (In fact, ASCII characters are < 128, but this way we can handle any raw data.) character of the pattern can simply be looked up. The array is filled by using 256-bit SIMD instructions to compare each byte up to 256 to both the first 32 characters (`[u8; 32]` is 256 bits) and last 32 characters of the text slice, and merging the two 32-bit values.

For efficiency, we first compute a list of all distinct bytes in the pattern, and then only fill table rows corresponding to those bytes.

Case-insensitive ASCII. In this case, we first lowercase all text and pattern characters before doing the equality check. This is done by xor'ing the value of all uppercase bytes by 32.

DNA. DNA only has 4 characters, and so we precompute a table of size 4. Each **ACTG** character is encoded into an integer in $\{0, 1, 2, 3\}$ by first shifting right 1 bit and then only looking at the bottom 2 bits.

Optionally, it can first be checked that the text only contains valid bases in **ACTG**. This is done by ensuring that each position case-insensitively equals one of **ACTG**.

IUPAC. Here, we start by building a table that maps each IUPAC character to a 4-bit mask indicating which subset of **ACTG** it matches. Since only letters are allowed input, it is sufficient to only consider the low 5 bits of each input character leaving 32 possible values. This automatically collapses upper and lower case values. We would now like to use a `[u8; 32]` SIMD register as a lookup table (via shuffle instructions), but unfortunately cross-128-bit lane byte shuffles are not supported on AVX2. We work around this: each byte only contains 4 bits of data, and thus, we can merge them, so that byte i in a `[u8; 16]` contains the 4 bits of both i (low half) and $i+16$ (high half). Then, we can use this as a lookup table on the low 4 bits of each text character, and use the 5th bit to select either the low or high half of the returned byte.

From here, we proceed similar to before: we first build a list of characters occurring in the profile. Then we encode each character to its 4-bit representation, and find the text characters that this "intersects" with.

B. Support for ambiguous bases

Depending on their quality, human genome assemblies can contain over 10% ambiguous bases, as seen in GRCh38 [Nurk et al., 2022]. In search applications with clinical implications, such as CRISPR off-target analysis, it is crucial to report matches in regions containing ambiguous bases (e.g., **N**), as these indicate sequence uncertainty and may harbor unintended cut sites. To evaluate tool performance in such scenarios, we searched for the sgRNA **GGAAGACACACTGGCAGAAANGG** with $k = 0$ against a mock sequence where the sgRNA base at position 14 (**C**) was replaced by **N** in one version of a text, and by **Y** in another. **Sassy** implements the IUPAC profile for CRISPR off-target searches and returned all matches according to IUPAC base pairing. **CHOPOFF** requires a user to specificy the max number of ambiguous bases (we used `-ambig-max=23`) and did also return all matches. **SWOffinder** does not have a command line option but a hardcoded boolean flag (default is `false`) which we set to `true` and recompiled. It did find the **N** version but not the **Y** version. Therefore, both **Sassy** and **CHOPOFF** have IUPAC support, and **SWOffinder** only supports **N** with source code modification. This result underscores the importance of selecting tools that correctly handle ambiguous bases in clinically relevant analyses.