## A Pseudocode

### A.1 A* algorithm for match pruning

We present our variant of A* (Hart *et al.*, 1968) that supports match pruning (Algorithm 1). All computed values of $g$ are stored in a hash map, and all *open* states are stored in a bucket queue of tuples $(v, g(v), f(v))$ ordered by increasing $f$. Line 14 prunes (removes) a match and thereby increases some heuristic values before that match. As a result, some $f$-values in the priority queue may become outdated. Line 11 solves this problem by checking if the $f$-value of the state about to be expanded was changed, and if so, line 12 pushes the updated state to the queue, and proceeds by choosing a next best state. This way, we guarantee that the expanded state has minimal updated $f$. To reconstruct the best alignment we traceback from the target state using the hash map $g$ (not shown).

### A.2 Diagonal transition for A*

For a given distance $g$, the diagonal transition method only considers the *farthest-reaching* (f.r.) state $u{=}\langle i,j\rangle$ on each diagonal $k{=}i{-}j$ at distance $g$. We use $F_{gk} := i{+}j$ to indicate the antidiagonal[4] of the farthest reaching state. Let $X_{gk}$ be the farthest state on diagonal $k$ adjacent to a state at distance $g{-}1$, which is then *extended* into $F_{gk}$ by following as many matches as possible. The edit distance is the lowest $g$ such that $F_{g,n-m} \geq n + m$, and we have the recursion

$$X_{gk} := \max(F_{g-1,k-1}{+}1, F_{g-1,k}{+}2, F_{g-1,k+1}{+}1), \tag{3}$$

$$F_{gk} = X_{gk} + \mathrm{LCP}\left(A_{\geq(X_{gk}+k)/2}, B_{\geq(X_{gk}-k)/2}\right). \tag{4}$$

The base case is $X_{0,0}{=}0$ with default value $F_{gk}{=}{-}\infty$ for $k{>}|g|$, and LCP is the length of the longest common prefix of two strings. Each edge in a traceback path is either a match created by an extension (4), or a mismatch starting in a f.r. state (3). We call such a path an *f.r. path*.

[4] Previous works indicate the column $i$ of $u$, but using the antidiagonal $i{+}j$ keeps the symmetry between insertions and deletions.

**Implementation.** In Algorithm 2 we further modify the A* algorithm to only consider f.r. paths. We replace the map $g$ that tracks the best distance by a map $F_{gk}$ that tracks f.r. states (lines 4, 18, and 19). Instead of $g(u)$ decreasing over time, we now ensure that $F_{g,k}$ increases over time. Each time a state $u$ is opened or expanded, the check whether $g(u)$ decreases is replaced by a check whether $F_{gk}$ increases (line 9). This causes the search to skip states that are known to not be farthest reaching. The proof of correctness (Thm. 2) still applies.

Alternatively, it is also possible to implement A* directly in the diagonal-transition state-space by pushing states $F_{gk}$ to the priority queue, but for simplicity we keep the similarity with the original A*.

### A.3 Implementation notes

Here we list implementation details on performance and correctness.

**Bucket queue.** We use a hashmap to store all computed values of $g$ in the A* algorithm. Since the edit costs are bounded integers, we implement the priority queue using a *bucket queue* (Bertsekas, 1991). Unlike heaps, this data structure has amortized constant time push and pop operations since the value difference between consecutive pop operations is bounded.

**Greedy matching of letters.** From a state $\langle i,j\rangle$ where $a_i = b_j$, it is sufficient to only consider the matching edge to $\langle i{+}1, j{+}1\rangle$ (Allison, 1992; Ivanov *et al.*, 2020), and ignore the insertion and deletion edges to $\langle i, j{+}1\rangle$ and $\langle i{+}1, j\rangle$. During alignment, we greedily match as many letters as possible within the current seed before inserting only the last open state in the priority queue, but we do not cross seed boundaries in order to not interfere with match pruning. This optimization is superseded by the DT-optimization. We include greedily matched states in the reported number of expanded states.

**Priority queue offset.** Pruning the last remaining match in a layer may cause an increase of the heuristic in all states preceding the start $u$ of the match. This invalidates $f$ values in the priority queue and causes reordering. We skip most of the update operations by storing a global offset to the $f$-values in the priority queue, which we update when all states in the priority queue precede $u$.

**Algorithm 1** A* algorithm with match pruning.
Lines added for pruning (11, 12, and 14) are marked in **bold**.

```
1:  Input: Sequences $A$ and $B$ and pruning heuristic $h$
2:  Output: Edit distance between $A$ and $B$
3:  function ASTAR($A$, $B$, $h$)
4:      $g(v_s) \leftarrow 0$                     ▷ Hashmap of distances; default $+\infty$
5:      $q \leftarrow BucketQueue()$              ▷ Bucket queue of open states
6:      $q.push((v_s, g{=}0, f{=}0))$
7:      repeat
8:          $(u, g_u, f_u) \leftarrow q.pop()$    ▷ Pop $u$ with minimal $f$
9:          if $g_u > g(u)$ then
10:             continue                          ▷ $u$ was already expanded
11:         else if $f_u < g(u) + h(u)$ then      ▷ $h(u)$ has increased
12:             $q.push((u, g_u, g(u) + h(u)))$   ▷ Reorder $u$
13:         else                                  ▷ Expand $u$
14:             $Prune(u)$
15:             for successors $v$ of $u$ do
16:                 $g_v \leftarrow g_u + \mathrm{d}(u, v)$
17:                 $v \leftarrow Extend(v)$      ▷ Greedy matching within seed
18:                 if $g_v < g(v)$ then          ▷ Open $v$
19:                     $g(v) \leftarrow g_v$
20:                     $q.push((v, g_v, g_v + h(v)))$
21:     until $v_t$ is expanded
22:     return $g(v_t)$
```

**Algorithm 2** A*-DT algorithm with match pruning.
Lines changed for diagonal transition (4, 9, 18, and 19) are in **bold**.

```
1:  Input: Sequences $A$, $B$ and pruning heuristic $h$
2:  Output: Edit distance between $A$ and $B$
3:  function ASTAR-DT($A$, $B$, $h$)
4:      $F_{0,0} \leftarrow 0$                    ▷ Hashmap of f.r. point per $g$ and $k$; default $-\infty$
5:      $q \leftarrow BucketQueue()$              ▷ Bucket queue of open states
6:      $q.push((v_s, g{=}0, f{=}0))$
7:      repeat
8:          $(u, g_u, f_u) \leftarrow q.pop()$    ▷ Pop $u$ with minimal $f$
9:          if $i_u{+}j_u < F_{g_u, i_u - j_u}$ then
10:             continue                          ▷ $u$ is not farthest reaching
11:         else if $f_u < g(u) + h(u)$ then      ▷ $h(u)$ has increased
12:             $q.push((u, g_u, g(u) + h(u)))$   ▷ Reorder $u$
13:         else                                  ▷ Expand $u$
14:             $Prune(u)$
15:             for successors $v$ of $u$ do
16:                 $g_v \leftarrow g_u + \mathrm{d}(u, v)$
17:                 $v \leftarrow Extend(v)$      ▷ Greedy matching in seed
18:                 if $i_v{+}j_v > F_{g_v, i_v - j_v}$ then   ▷ Open $v$
19:                     $F_{g_v, i_v - j_v} \leftarrow i_v{+}j_v$
20:                     $q.push((v, g_v, g_v + h(v)))$
21:     until $v_t$ is expanded
22:     return $g(v_t)$
```

**Split vector for layers.** Pruning a match may trigger the removal of one or more layers of matches in $L$, and the shifting down of higher layers. To efficiently remove layers, we use a *split vector* data structure consisting of two stacks. In the first stack we store the layers before the last deleted layer, and in the second stack the remaining layers in reverse order. Before deleting a layer, we move layers from the top of one of the stacks to the top of the other, until the layer to be deleted is at the top of one of the stacks. Removing layers in decreasing order of $\ell$ takes linear total time.

**Binary search speedup.** Instead of using binary search to determine the layer/score $S_p(u)$ (Algorithm 3), we first try a linear search around either the score of the parent of $u$ or a known previous score at $u$. This linear search usually finds the correct layer in a few iterations, or otherwise we fall back to binary search.

In practice, most pruning happens near the tip of the search, and the number of layers between the start $v_s$ and an open state $u$ rarely changes. Thus, to account for changing scores, we store a *hint* of value $S_p(v_s) - S_p(u)$ in a hashmap and start the search at $S_p(v_s) - hint$.

**Code correctness.** Our implementation A*PA is written in Rust, contains many assertions testing e.g. the correctness of our A* and layers data structure implementation, and is tested for correctness and performance on randomly-generated sequences. Correctness is checked against simpler algorithms (Needleman-Wunsch) and other aligners (EDLIB, BIWFA).

## A.4 Computation of the heuristic

Algorithm 3 shows how the heuristic is initialized, how $S_p(u)$ and $h(u)$ are computed, and how matches are pruned.

**Algorithm 3** Computation of the heuristic.

```
1: **Input:** Sequences $A$ and $B$
2: **Output:** Heuristic $h$
3: function INITIALIZEHEURISTIC($A$, $B$, $k$)
4:     $S \leftarrow$ Non-overlapping $k$-mers of $A$                         ▷ Seeds
5:     $H \leftarrow$ Map of all $k$-mers (and $k\pm1$-mers for $r=2$) of $B$
6:     $\mathcal{M}_s \leftarrow \bigcup_{s':\,\mathrm{ed}(s,s')<r} H[s']$                  ▷ Seed matches
7:     $\mathcal{M} \leftarrow \bigcup_{s\in\mathcal{S}} \mathcal{M}_s$                            ▷ Matches
8:     $P(i) \leftarrow r\cdot|S_{\geq i}|$ for all $i\in[0,|A|]$               ▷ Potentials
9:     $L[0] = \{m_\omega\}$                                         ▷ Layers
10:    for $m\in\mathcal{M}$ in decreasing order of $\preceq_p$ do
11:        $\ell \leftarrow \mathrm{score}(m) + S_p(\mathrm{end}(m))$
12:        if $m \preceq_p m_\omega$ then                 ▷ If $m$ precedes the target
13:            $L[\ell].push(m)$

14: function $S_p(u)$
15:    function TEST($\ell$)
16:        for $\ell' \in [\ell, \ell+r)$ do
17:            if $u \preceq_p m$ for some $m \in L[\ell']$ then
18:                return $True$
19:        return $False$
20:    return $\max\{\ell \mid \mathtt{TEST}(\ell)\}$        ▷ Binary search the highest $\ell$

21: function $h_s(u)$                                             ▷ SH
22:    return $P(u) - S_i(u)$

23: function $h_{cs}(u)$                                            ▷ CSH
24:    return $P(u) - S_\leq(u)$

25: function $h_{gcs}(u)$                                          ▷ GCSH
26:    return $\max(P(u) - S_T(u), c_{\mathrm{gap}}(u, v_t))$

27: function PRUNE($u$)
28:    $\ell_u \leftarrow S_p(u)$
29:    for all $m\in\mathcal{M}$: $start(m) = u$ or $end(m) = u$ do
30:        if $h \neq h_{gcs}$ or $\mathcal{M}\backslash\{m\}$ is consistent then
31:            Remove $m$ from $\mathcal{M}$
32:            for $\ell \in [S_p(start(m)) - r + 1, S_p(start(m))]$ do
33:                Remove $m$ from $L[\ell]$ if present
34:    for $\ell \in [\ell_u + 1, S_p\langle 0,0\rangle]$ do
35:        for all $m \in L[\ell]$ do
36:            $\ell' \leftarrow S_p(m)$
37:            if $\ell' \neq \ell$ then
38:                Move $m$ from $L[\ell]$ to $L[\ell']$
39:        if $r$ consecutive layers unchanged then
40:            return
41:        if $r{-}1{+}\ell{-}\ell'$ consecutive layers shifted exactly $\ell{-}\ell'$ then
42:            Remove empty layers $L[\ell'{+}1], \ldots, L[\ell]$
                                              ▷ Shift higher layers down
43:            return
```

## B Proofs

### B.1 Admissibility

Our heuristics are not *consistent*, but we show that a weaker variant holds for states *at the start of a seed*.

**Definition 5** (Start of seed)**.** *A state $\langle i, j\rangle$ is at the start of some seed when $i$ is a multiple of the seed length $k$, or when $i = n$.*

**Lemma 1** (Weak triangle inequality)**.** *For states $u$, $v$, and $w$ with $v$ and $w$ at the starts of some seeds, all $\gamma \in \{c_{\text{seed}}, c_{\text{gap}}, c_{\text{gs}}\}$ satisfy*

$$\gamma(u, v) + \gamma(v, w) \geq \gamma(u, v).$$

*Proof.* Both $v$ and $w$ are at the start of some seeds, so for $\gamma = c_{\text{seed}}$ we have the equality $c_{\text{seed}}(u, w) = c_{\text{seed}}(u, v) + c_{\text{seed}}(v, w)$.

For $\gamma = c_{\text{gap}}$,

$$\begin{aligned} &c_{\text{gap}}(\langle i, j\rangle, \langle i', j'\rangle) + c_{\text{gap}}(\langle i', j'\rangle, \langle i'', j''\rangle) \\ &= |(i' - i) - (j' - j)| + |(i'' - i') - (j'' - j')| \\ &\geq |(i'' - i) - (j'' - j)| = c_{\text{gap}}(\langle i, j\rangle, \langle i'', j''\rangle). \end{aligned}$$

And lastly, for $\gamma = c_{\text{gs}}$,

$$\begin{aligned} &c_{\text{gs}}(u, v) + c_{\text{gs}}(v, w) \\ &= \max(c_{\text{gap}}(u, v), c_{\text{seed}}(u, v)) + \max(c_{\text{gap}}(v, w), c_{\text{seed}}(v, w)) \\ &\geq \max(c_{\text{gap}}(u, v) + c_{\text{gap}}(v, w), c_{\text{seed}}(u, v) + c_{\text{seed}}(v, w)) \\ &\geq \max(c_{\text{gap}}(u, w), c_{\text{seed}}(u, w)) = c_{\text{gs}}(u, w). \end{aligned}$$ □

**Lemma 2** (Weak consistency)**.** *Let $h \in \{h^{\mathcal{M}}_{\text{s}}, h^{\mathcal{M}}_{\text{cs}}, h^{\mathcal{M}}_{\text{gcs}}\}$ be a heuristic with partial order $\preceq_p$, and let $u \preceq_p v$ be states with $v$ at the start of a seed. When there is a shortest path $\pi^*$ from $u$ to $v$ such that $\mathcal{M}$ contains all matches of cost less than $r$ on $\pi^*$, it holds that $h(u) \leq \mathrm{d}(u, v) + h(v)$.*

*Proof.* The path $\pi^*$ covers each seed in $\mathcal{S}_{u\ldots v}$ that must to be fully aligned between $u$ and $v$. Since the seeds do not overlap, their shortest alignments $\pi^*_s$ in $\pi^*$ do not have overlapping edges. Let $u \preceq m_1 \preceq_p \cdots \preceq_p m_l \preceq_p v$ be the chain of matches $m_i \in \mathcal{M}$ corresponding to those $\pi^*_s$ of cost less than $r$ (Fig. 6). Since the matches and the paths between them are disjoint, $c_{\text{path}}(\pi^*)$ is at least the cost of the matches $c_{\text{m}}(m_{i+1}) = \mathrm{d}(\mathrm{start}(m_{i+1}), \mathrm{end}(m_{i+1}))$ plus the cost to chain these matches $\gamma(\mathrm{end}(m_i), \mathrm{start}(m_{i+1})) \leq \mathrm{d}(\mathrm{end}(m_i), \mathrm{start}(m_{i+1}))$. Putting this together:

$$\begin{aligned} &\gamma(u, m_1) + c_{\text{m}}(m_1) + \cdots + c_{\text{m}}(m_l) + \gamma(m_l, v) \\ &\leq \mathrm{d}(u, \mathrm{start}(m_1)) + \mathrm{d}(\mathrm{start}(m_1), \mathrm{end}(m_1)) + \cdots + \mathrm{d}(\mathrm{end}(m_l), v) \\ &\leq \mathrm{d}(u, v). \end{aligned}$$

Now let $v \preceq_p m_{l+1} \preceq_p \cdots \preceq_p m_{l'} \preceq_p v_t$ be a chain of matches minimizing $h(v)$ (Def. 1) with $w := \mathrm{start}(m_{l+1})$. This chain also minimizes $h(w)$ and thus $h(v) = \gamma(v, w) + h(w)$. We can now bound the cost of the joined chain from $u$ to $v$ and from $w$ to the end and get our result via $\gamma(m_l, w) \leq \gamma(m_l, v) + \gamma(v, w)$ (Lemma 1)

$$\begin{aligned} h(u) &\leq \gamma(u, m_1) + \cdots + \gamma(m_l, m_{l+1}) + c_{\text{m}}(m_{l+1}) + \cdots + \gamma(m_{l'}, v_t) \\ &= \gamma(u, m_1) + \cdots + \gamma(m_l, w) \qquad + h(w) \\ &\leq \gamma(u, m_1) + \cdots + \gamma(m_l, v) + \gamma(v, w) + (h(v) - \gamma(v, w)) \\ &\leq \mathrm{d}(u, v) + h(v). \end{aligned}$$ □

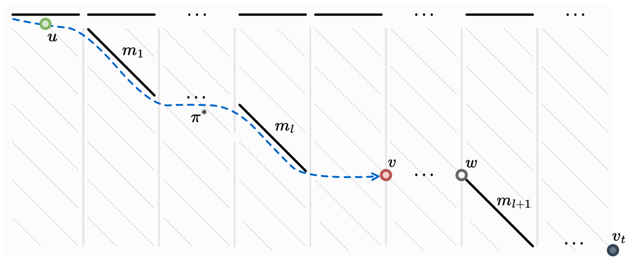


**Fig. 6. Variables of the proof of Lemma 2.**

**Theorem 1.** *The seed heuristic $h_{\text{s}}$, the chaining seed heuristic $h_{\text{cs}}$, and the gap-chaining seed heuristic $h_{\text{gcs}}$ are* admissible. *Furthermore, $h^{\mathcal{M}}_{\text{s}}(u) \leq h^{\mathcal{M}}_{\text{cs}}(u) \leq h^{\mathcal{M}}_{\text{gcs}}(u)$ for all states $u$.*

*Proof.* We will prove $h^{\mathcal{M}}_{\text{s}}(u) \overset{(1)}{\leq} h^{\mathcal{M}}_{\text{cs}}(u) \overset{(2)}{\leq} h^{\mathcal{M}}_{\text{gcs}}(u) \overset{(3)}{\leq} h^*(u)$, which implies the admissibility of all three heuristics.

(1) Note that $u \preceq v$ implies $u \preceq_i v$ and hence any $\preceq$-chain is also a $\preceq_i$-chain. A minimum over the superset of $\preceq_i$-chains is at most the minimum of the subset of $\preceq$-chains, and hence $h^{\mathcal{M}}_{\text{s}} = h^{\mathcal{M}}_{\preceq_i, c_{\text{seed}}} \leq h^{\mathcal{M}}_{\preceq, c_{\text{seed}}} = h^{\mathcal{M}}_{\text{cs}}$.

(2) The only difference between $h^{\mathcal{M}}_{\text{cs}}$ and $h^{\mathcal{M}}_{\text{gcs}}$ is that the former uses $c_{\text{seed}}$ and the latter uses the gap-seed cost $c_{\text{gs}} := \max(c_{\text{gap}}, c_{\text{seed}})$. Since $c_{\text{seed}} \leq c_{\text{gs}}$ we have $h^{\mathcal{M}}_{\text{cs}} = h^{\mathcal{M}}_{\preceq, c_{\text{seed}}} \leq h^{\mathcal{M}}_{\preceq, c_{\text{gs}}} = h^{\mathcal{M}}_{\text{gcs}}$.

(3) When $\mathcal{M}$ is the set of all matches with costs strictly less than $r$, admissibility follows directly from Lemma 2 with $v = v_t$ via

$$h^{\mathcal{M}}_{\text{gcs}}(u) \leq \mathrm{d}(u, v_t) + h^{\mathcal{M}}_{\text{gcs}}(v_t) = \mathrm{d}(u, v_t) = h^*(u).$$ □

### B.2 Match pruning

During the A* search, we continuously improve our heuristic using match pruning. The pruning increases the value of our heuristics and breaks their admissibility. Nevertheless, we prove in two steps that A* with match pruning still finds a shortest path. First, we introduce the concept of a *weakly-admissible heuristic* and show that A* using a weakly-admissible heuristic finds a shortest path (Thm. 2). Then, we show that our pruning heuristics are indeed weakly admissible (Thm. 3).

**A* with a weakly-admissible heuristic finds a shortest path.**

**Definition 6** (Fixed vertex)**.** *A vertex $u$ is* fixed *if it is expanded and A* has found a shortest path to it, that is, $g(u) = g^*(u)$.*

A fixed vertex cannot be opened again (Algorithm 1, line 18), and hence remains fixed.

**Definition 7** (Weakly admissible)**.** *A heuristic $\hat{h}$ is* weakly admissible *if at any moment during the A* search there exists a shortest path $\pi^*$ from $v_s$ to $v_t$ in which all vertices $u \in \pi^*$ after its last fixed vertex $n^*$ satisfy $\hat{h}(u) \leq h^*(u)$.*

To prove that A* finds a shortest path when used with a weakly-admissible heuristic, we follow the structure of Hart *et al.* (1968). First we restate their Lemma 1 in our notation with a slightly stronger conclusion that follows directly from their proof.

**Lemma 3** (Lemma 1 of Hart *et al.* (1968))**.** *For any unfixed vertex $n$ and for any shortest path $\pi^*$ from $v_s$ to $n$, there exists an open vertex $n'$ on $\pi^*$ with $g(n') = g^*(n')$ such that $\pi^*$ does not contain fixed vertices after $n'$.*

Next, we prove that in each step the A* algorithm can proceed along a shortest path to the target:

**Corollary 1** (Generalization of Corollary to Lemma 1 of Hart *et al.* (1968))**.** *Suppose that $\hat{h}$ is weakly admissible, and that A* has not* *terminated. Then, there exists an open vertex $n'$ on a shortest path from $v_s$ to $v_t$ with $f(n') \le g^*(v_t)$.*

*Proof.* Let $\pi^*$ be the shortest path from $v_s$ to $v_t$ given by the weak admissibility of $\hat{h}$ (Def. 7). Since A* has not terminated, $v_t$ is not fixed. Substitute $n = v_t$ in Lemma 3 to derive that there exists an open vertex $n'$ on $\pi^*$ with $g(n') = g^*(n')$. By definition of $f$ we have $f(n') = g(n') + \hat{h}(n')$. Since $\pi^*$ does not contain any fixed vertices after $n'$, the weak admissibility of $\hat{h}$ implies $\hat{h}(n') \le h^*(n')$. Thus, $f(n') = g(n') + \hat{h}(n') \le g^*(n') + h^*(n') = g^*(v_t)$. □

**Theorem 2.** *A* with a weakly-admissible heuristic finds a shortest path.*

*Proof.* The proof of Theorem 1 in Hart *et al.* (1968) applies, with the remark that instead of an arbitrary shortest path, we use the specific path $\pi^*$ given by the weak admissibility and the specific vertex $n'$ given by Corollary 1. □

**Our heuristics are weakly admissible.** A *consistent* heuristic finds the correct distance to each vertex as soon as it is expanded. While our heuristics are not consistent, this property is true for states *at the starts of seeds* (when $i$ is a multiple of the seed length $k$, or when $i = n$).

**Lemma 4.** *For $\hat{h} \in \{\hat{h}_{\text{s}}, \hat{h}_{\text{cs}}, \hat{h}_{\text{gcs}}\}$, every state at the start of a seed becomes fixed immediately when A* expands it.*

*Proof.* We use a proof by contradiction: suppose that $v$ is a state at the start of some seed that is expanded but not fixed. In other words, $f(v)$ is minimal among all open states, but the shortest path $\pi^*$ from $v_s$ to $v$ has strictly smaller length $g^*(v) < g(v)$.

Let $n^*$ be the last fixed state on $\pi^*$ before $v$, and let $u \in \pi^*$ be the successor of $n^*$. State $u$ is open because its predecessor $n^*$ is fixed and on a shortest path to $u$. Let the chain of all matches of cost less than $r$ on $\pi^*$ between $u$ and $v$ be $u \le m_1 \le \dots \le m_l \le v$. Since $n^*$ is the last fixed state on $\pi^*$, none of these matches has been pruned, and they are all in $\mathcal{M}\backslash E$ as well. This means we can apply Lemma 2 to get $h(u) \le \mathrm{d}(u,v) + h(v)$, so

$$\begin{aligned}
f(u) = g(u) + h(u) &= g^*(u) + h(u) && \pi^* \text{ is a shortest path}\\
&\le g^*(u) + \mathrm{d}(u,v) + h(v) && \text{shown above}\\
&= g^*(v) + h(v) && \pi^* \text{ is a shortest path}\\
&< g(v) + h(v) = f(v) && \text{by assumption.}
\end{aligned}$$

This proves that $f(u) < f(v)$, resulting in a contradiction with the assumption that $u$ is an open state with minimal $f$. □

**Theorem 3.** *The pruning heuristics $\hat{h}_{\text{s}}$, $\hat{h}_{\text{cs}}$, $\hat{h}_{\text{gcs}}$ are weakly admissible.*

*Proof.* Let $\pi^*$ be a shortest path from $v_s$ to $v_t$. At any point during the A* search, let $n^*$ be the farthest expanded state on $\pi^*$ that is at the start of a seed. By Lemma 4, $n^*$ is fixed. By the choice of $n^*$, no states on $\pi^*$ after $n^*$ that are at the start of a seed are expanded, so no matches on $\pi^*$ following $n^*$ are pruned. Now the proof of Thm. 1 applies to the part of $\pi^*$ after $n^*$ without changes, implying that $\hat{h}(u) \le h^*(u)$ for all $u$ on $\pi^*$ following $n^*$, for any $\hat{h} \in \{\hat{h}_{\text{s}}, \hat{h}_{\text{cs}}, \hat{h}_{\text{gcs}}\}$. □

## B.3 Computation of the (chaining) seed heuristic

**Theorem 4.** $h^{\mathcal{M}}_{p,c_{\text{seed}}}(u) = P(u) - S_p(u)$ *for any partial order $\preceq_p$ that is a refinement of $\preceq_i$ (i.e. $u \preceq_p v$ must imply $u \preceq_i v$).*

*Proof.* For a chain of matches $\{m_i\} \subseteq \mathcal{M}$, let $s_i$ and $t_i$ be the start and end states of $m_i$. We translate the terms of our heuristic from costs to potentials and match scores (Sec. 3.4):

$$\begin{aligned}
&c_{\text{seed}}(m_i, m_{i+1}) \;+\; c_{\text{m}}(m_{i+1})\\
=\;& \big(P(t_i) - P(s_{i+1})\big) \;+\; \big(P(s_{i+1}) - P(t_{i+1}) - \mathrm{score}(m_{i+1})\big)\\
=\;& P(t_i) \;-\; P(t_{i+1}) - \mathrm{score}(m_{i+1}).
\end{aligned}$$

The heuristic (Def. 1) can then be rewritten as follows:

$$\begin{aligned}
&h^{\mathcal{M}}_{p,c_{\text{seed}}}(u)\\
&= \min_{\substack{u \preceq_p m_1 \preceq_p \cdots \preceq_p m_l \preceq_p v_t\\ m_i \in \mathcal{M}}} \sum_{0 \le i \le l} \big[P(t_i) - P(t_{i+1}) - \mathrm{score}(m_{i+1})\big]\\
&= P(u) - \max_{\substack{u \preceq_p m_1 \preceq_p \cdots \preceq_p m_l \preceq_p v_t\\ m_i \in \mathcal{M}}} \sum_{0 \le i \le l} \mathrm{score}(m_{i+1})\\
&= P(u) - S_p(u).
\end{aligned}$$ □

**Lemma 5.** *Layer $\mathcal{L}_\ell$ ($\ell > 0$) is fully determined by the set of those matches $m$ for which $\ell \le S_p(m) < \ell + r$:*

$$\mathcal{L}_\ell = \{u \mid \exists m \in \mathcal{M} : u \preceq_p m \text{ and } S_p(m) \in [\ell, \ell + r)\}.$$

*Proof.* Take any state $u \in \mathcal{L}_\ell$. Its score $S_p(u) \ge \ell > 0$ implies that there is a non-empty $\preceq_p$-chain $u \preceq_p m_1 \preceq_p m_2 \preceq_p \dots$ with $\mathrm{score}(m_1) + \mathrm{score}(m_2) + \cdots \ge \ell$. The score of each match is less than $r$ and thus there must be a match $m_i$ so that the subset of the chain starting at $m_i$ has score $S_p(m_i) = \mathrm{score}(m_i) + \mathrm{score}(m_{i+1}) + \cdots +$ in the interval $[\ell, \ell + r)$. This implies that for any $u$ with score $S_p(u) \ge \ell > 0$ there is a match with score in $[\ell, \ell + r)$ succeeding $u$, as required. □

## B.4 Computation of the gap-chaining seed heuristic

In this section we prove (Thm. 5) that we can change the dependency of GCSH on $c_{\text{gs}}$ to $c_{\text{seed}}$ by introducing a new partial order $\preceq_T$ on the matches. This way, Thm. 4 applies and we can efficiently compute GCSH. Recall that the gap-seed cost is $c_{\text{gs}} = \max(c_{\text{gap}}, c_{\text{seed}})$, and that the gap transformation is:

**Definition 4** (Gap transformation)**.** *The partial order $\preceq_T$ on states is induced by comparing both coordinates after the* gap transformation

$$T: \quad \langle i, j\rangle \mapsto \big(i - j - P\langle i, j\rangle, j - i - P\langle i, j\rangle\big)$$

The following lemma allows us to determine whether $c_{\text{gap}}$ or $c_{\text{seed}}$ dominates the cost $c_{\text{gs}}$ between two matches, based on the relation $\preceq_T$.

**Lemma 6.** *Let $u$ and $v$ be two states with $v$ at the start of some seed. Then $u \preceq_T v$ if and only if $c_{\text{gap}}(u, v) \le c_{\text{seed}}(u, v)$. Furthermore, $u \preceq_T v$ implies $u \preceq v$.*

*Proof.* Let $u = \langle i, j\rangle$ and $v = \langle i', j'\rangle$. By definition, $u \preceq_T v$ is equivalent to

$$\begin{cases} i{-}j{-}P(u) \le i'{-}j'{-}P(v) \\ j{-}i{-}P(u) \le j'{-}i'{-}P(v) \end{cases} \Leftrightarrow \begin{cases} -\big((i'{-}i) - (j'{-}j)\big) \le P(u) - P(v) \\ \quad (i'{-}i) - (j'{-}j) \;\; \le P(u) - P(v). \end{cases}$$

This simplifies to

$$c_{\text{gap}}(u, v) = |(i' - i) - (j' - j)| \le P(u) - P(v) = c_{\text{seed}}(u, v),$$

where the last equality holds because $v$ is at the start of a seed.

For the second part, $u \preceq_T v$ implies $0 \le c_{\text{gap}}(u, v) \le c_{\text{seed}}(u, v) = P(u) - P(v)$ and hence $P(u) \ge P(v)$. Since $v$ is at the start of a seed, this directly implies $i \le i'$. Since seeds have length $k \ge r$ we have

$$|(i' - i) - (j' - j)| \le P(u) - P(v) = r \cdot |\mathcal{S}_{i\dots i'}| \le r \cdot (i' - i)/k \le i' - i.$$

This implies $j' - j \ge 0$ and hence $j \le j'$, as required. □

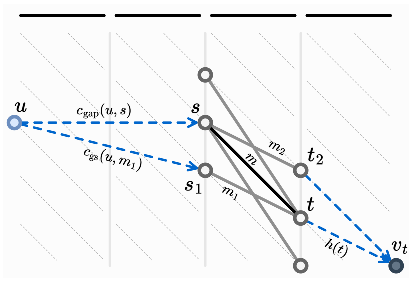


**Fig. 7. Variables in Case 2 of the proof of Lemma 7.** Match $m$ has $\text{score}(m) = 2$, so it has adjacent matches $m_1$ and $m_2$ (gray) with $\text{score}(m_i) \geq 1$.

A direct corollary is that for $u \preceq v$ with $v$ at the start of some seed, we have

$$c_{\text{gs}}(u,v) = \begin{cases} c_{\text{seed}}(u,v) & \text{if } u \preceq_T v, \\ c_{\text{gap}}(u,v) & \text{if } u \npreceq_T v. \end{cases} \tag{5}$$

A second corollary is that $\text{start}(m) \preceq_T \text{end}(m)$ for all matches $m \in \mathcal{M}$, since a match from $u$ to $v$ satisfies $c_{\text{gap}}(u,v) < r = c_{\text{seed}}(u,v)$ by definition.

**Lemma 7.** *When the set of matches $\mathcal{M}$ is consistent, $h^{\mathcal{M}}_{\text{gcs}}(u)$ can be computed using $\preceq_T$-chains only:*

$$h^{\mathcal{M}}_{\text{gcs}}(u) := h^{\mathcal{M}}_{\preceq, c_{\text{gs}}}(u) = \begin{cases} h^{\mathcal{M}}_{\preceq_T, c_{\text{gs}}}(u) & \textit{if } u \preceq_T v_t, \\ c_{\text{gap}}(u, v_t) & \textit{if } u \npreceq_T v_t. \end{cases}$$

*Proof.* We write $h := h^{\mathcal{M}}_{\text{gcs}} = h^{\mathcal{M}}_{\preceq, c_{\text{gs}}}$ (Def. 1) and $h' := h^{\mathcal{M}}_{\preceq_T, c_{\text{gs}}}$.

Case 1: $u \npreceq_T v_t$. Let $u \preceq m_1 \preceq \cdots \preceq m_l \preceq v_t$ be a chain minimizing $h(u)$ in Def. 1, so

$$h(u) = c_{\text{gs}}(u, m_1) + c_{\text{m}}(m_1) + c_{\text{gs}}(m_1, m_2) + \cdots + c_{\text{gs}}(m_l, v_t).$$

By definition, $c_{\text{gs}} \geq c_{\text{gap}}$, and $c_{\text{m}}(m_i) \geq c_{\text{gap}}(\text{start}(m_i), \text{end}(m_i))$, so the weak triangle inequality (Lemma 1) for $c_{\text{gap}}$ gives

$$h(u) \geq c_{\text{gap}}(u, m_1) + c_{\text{gap}}(m_1) + \cdots + c_{\text{gap}}(m_l, v_t) \geq c_{\text{gap}}(u, v_t).$$

Since $u \npreceq_T v_t$, the empty chain $u \preceq v_t$ has cost $h(u) \leq c_{\text{gs}}(u, v_t) = c_{\text{gap}}(u, v_t)$. Combining the two inequalities, $h(u) = c_{\text{gap}}(u, v_t)$.

Case 2: $u \preceq_T v_t$. First rewrite $h$ and $h'$ recursively as

$$h(u) = \min_{\substack{m \in \mathcal{M} \\ u \preceq m \preceq v_t}} \left( c_{\text{gs}}(u,m) + c_{\text{m}}(m) + h(\text{end}(m)) \right) \tag{6}$$

$$h'(u) = \min_{\substack{m \in \mathcal{M} \\ u \preceq_T m \preceq_T v_t}} \left( c_{\text{gs}}(u,m) + c_{\text{m}}(m) + h'(\text{end}(m)) \right), \tag{7}$$

both with base case $h(v_t) = h'(v_t) = 0$ after eventually taking $m_\omega$. We will show that

$$h(u) = \min_{\substack{m \in \mathcal{M} \\ u \preceq_T m \preceq_T v_t}} \left( c_{\text{gs}}(u,m) + c_{\text{m}}(m) + h(\text{end}(m)) \right), \tag{8}$$

which is exactly the recursion for $h'$, so that by induction $h(u) = h'(u)$.

By Lemma 6, every $\preceq_T$-chain is a $\preceq$-chain, so $h(u) \leq h'(u)$. To prove $h(u) = h'(u)$, it remains to show the reverse inequality, $h'(u) \leq h(u)$. To this end, choose a match $m$ that

(priority 0) minimizes $h(u)$ in Eq. (6), and among those, has
(priority 1) maximal $c_{\text{seed}}(u,m)$, and among those, has
(priority 2) minimal $c_{\text{gap}}(u,m)$, and among those, has
(priority 3) minimal $c_{\text{gap}}(m, v_t)$.

We show that $u \preceq_T m$ (in 2.A) and $m \preceq_T v_t$ (in 2.B), which proves Eq. (8).

Part 2.A: $u \preceq_T m$. Let $s$ and $t$ be the begin and end of $m$ (Fig. 7), and let $m'$ be a match minimizing $h(t)$ in Eq. (6) so

$$h(t) = c_{\text{gs}}(t, m') + c_{\text{m}}(m') + h(\text{end}(m')).$$

Since $m'$ comes after $t$ we have $c_{\text{seed}}(u, m') > c_{\text{seed}}(u, m)$ (p.1) and hence $m'$ does not minimize $h(u)$ (p.0):

$$h(u) < c_{\text{gs}}(u, m') + c_{\text{m}}(m') + h(\text{end}(m')).$$

Using the minimality of $m$, the non-minimality of $m'$, and the triangle inequality we get

$$\begin{aligned} c_{\text{gs}}(u,s) + c_{\text{m}}(m) + h(t) &= h(u) \\ &< c_{\text{gs}}(u, m') \qquad\qquad + c_{\text{m}}(m') + h(\text{end}(m')) \\ &\leq c_{\text{gs}}(u,t) + c_{\text{gs}}(t, m') + c_{\text{m}}(m') + h(\text{end}(m')) \\ &= c_{\text{gs}}(u,t) + h(t) \end{aligned}$$

so we have

$$c_{\text{gs}}(u,m) + c_{\text{m}}(m) < c_{\text{gs}}(u,t). \tag{9}$$

From the triangle inequality for $c_{\text{gap}}$, from $c_{\text{gap}}(u,s) \leq c_{\text{gs}}(u,s)$, and from $c_{\text{gap}}(s,t) \leq c_{\text{m}}(m)$, and from Eq. (9) we obtain

$$c_{\text{gap}}(u,t) \leq c_{\text{gap}}(u,s) + c_{\text{gap}}(s,t) \leq c_{\text{gs}}(u,s) + c_{\text{m}}(m) < c_{\text{gs}}(u,t).$$

This implies $c_{\text{gs}}(u,t) = c_{\text{seed}}(u,t)$ and hence reusing Eq. (9)

$$\begin{aligned} c_{\text{gap}}(u,s) + c_{\text{m}}(m) &\leq c_{\text{gs}}(u,s) + c_{\text{m}}(m) \\ &< c_{\text{seed}}(u,t) = c_{\text{seed}}(u,s) + c_{\text{seed}}(s,t). \end{aligned}$$

We have $c_{\text{m}}(m) = c_{\text{seed}}(s,t) - \text{score}(m)$, so the above simplifies to $c_{\text{gap}}(u,s) < c_{\text{seed}}(u,s) + \text{score}(m)$ and since these are integers $c_{\text{gap}}(u,s) \leq c_{\text{seed}}(u,s) + \text{score}(m) - 1$.

When $\text{score}(m) = 1$, this implies $c_{\text{gap}}(u,s) \leq c_{\text{seed}}(u,s)$ and $u \preceq_T s = \text{start}(m)$ by Lemma 6.

When $\text{score}(m) > 1$, suppose that $c_{\text{gap}}(u,s) > c_{\text{seed}}(u,s) \geq 0$. That means that $u$ is either above or below the diagonal of $s$. Let $s_1 = \langle s_i, s_j \pm 1 \rangle$ be the state adjacent to $s$ on the same side of this diagonal as $u$. This state exists since $u \preceq s_1 \preceq t$. Then $c_{\text{gap}}(u, s_1) = c_{\text{gap}}(u,s) - 1$, and by consistency of $\mathcal{M}$ there is a match $m_1$ from $s_1$ to $t$ with $c_{\text{m}}(m_1) \leq c_{\text{m}}(m) + 1$. Then

$$\begin{aligned} & c_{\text{gs}}(u, s_1) + c_{\text{m}}(m_1) + h(t) \\ & \leq c_{\text{gs}}(u,s) - 1 + c_{\text{m}}(m) + 1 + h(t) = h(u), \end{aligned}$$

showing that $m_1$ minimizes $h(u)$ (p.0). Also $c_{\text{seed}}(u, m_1) = c_{\text{seed}}(u, m_1)$ (p.1) and $c_{\text{gap}}(u, m_1) < c_{\text{gap}}(u, m)$ (p.2), so that $m_1$ contradicts the minimality of $m$. Thus, $c_{\text{gap}}(u,s) > c_{\text{seed}}(u,s)$ is impossible and $u \preceq_T s$.

Part 2.B: $m \preceq_T v_t$. When there is some match $m'$ succeeding $m$ in the chain, we have $m \preceq m' \preceq v_t$ and hence $m \preceq v_t$. Thus, suppose that $m$ is the only match in the chain $u \preceq m \preceq v_t$ minimizing $h(u)$. We repeat the proofs of Part 2.A in the reverse direction to show that $m \preceq_T v_t$.

Since $c_{\text{seed}}(u, m)$ is maximal, $h(u) < c_{\text{gs}}(u, m_\omega)$ and thus

$$h(u) = c_{\text{gs}}(u, s) + c_{\text{m}}(m) + c_{\text{gs}}(m, v_t) < c_{\text{gs}}(u, v_t).$$

By assumption we have $u \preceq_T v_t$ and thus $c_{\text{gs}}(u, v_t) = c_{\text{seed}}(u, v_t)$. This gives

$$\begin{aligned} &c_{\text{seed}}(u, s) + c_{\text{seed}}(s, t) - \text{score}(m) + c_{\text{gap}}(t, v_t) \\ &\qquad < c_{\text{seed}}(u, v_t) = c_{\text{seed}}(u, s) + c_{\text{seed}}(s, t) + c_{\text{seed}}(t, v_t). \end{aligned}$$

Cancelling terms we obtain $c_{\text{gap}}(t, v_t) < c_{\text{seed}}(t, v_t) + 1$ and since they are integers $c_{\text{gap}}(t, v_t) \leq c_{\text{seed}}(t, v_t) + \text{score}(m) - 1$. When $\text{score}(m) = 1$, this implies $t \preceq_T v_t$, as required.

When $\text{score}(m) > 1$, suppose that $c_{\text{gap}}(t, v_t) > c_{\text{seed}}(t, v_t)$. Let $t_2 = \langle t_i, t_j \pm 1\rangle$ be the state adjacent to $t$ on the same side of the diagonal as $v_t$. By consistency of $\mathcal{M}$ there is a match $m_2$ from $s$ to $t_2$ with $\text{score}(m_2) \geq \text{score}(m) - 1$ and $c_{\text{gap}}(t_2, v_t) = c_{\text{gap}}(t, v_t) - 1$. Then $m_2$ minimizes $h(u)$ (p.0)

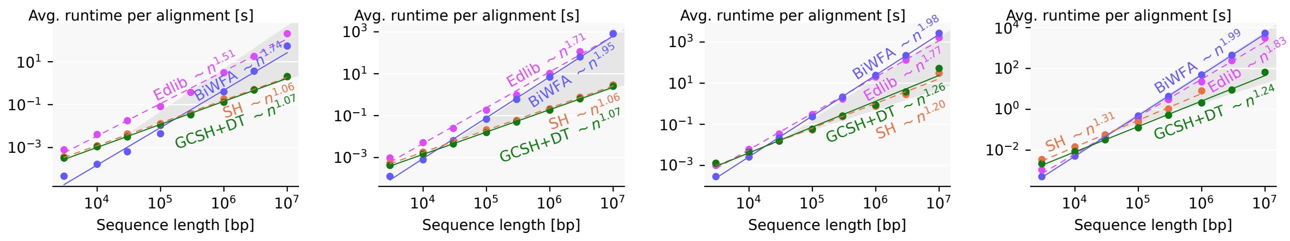
$$\begin{aligned} &c_{\text{gs}}(u, s) + \; c_{\text{m}}(m_2) \; + \; c_{\text{gs}}(t_2, v_t) \\ \leq \; &c_{\text{gs}}(u, s) + c_{\text{m}}(m) + 1 + c_{\text{gs}}(t, v_t) - 1 = h(u), \end{aligned}$$

and furthermore $c_{\text{seed}}(u, m_2) = c_{\text{seed}}(u, m)$ (p.1), $c_{\text{gap}}(u, m_2) = c_{\text{gap}}(u, m)$ (p.2), and $c_{\text{gap}}(m_2, v_t) < c_{\text{gap}}(m, v_t)$ (p.3), contradicting the choice of $m$, so $c_{\text{gap}}(t, v_t) > c_{\text{seed}}(t, v_t)$ is impossible and $t \preceq_T v_t$. □

**Theorem 5.** *Given a* consistent *set of matches* $\mathcal{M}$*, the gap-chaining seed heuristic can be computed using scores in the transformed domain:*

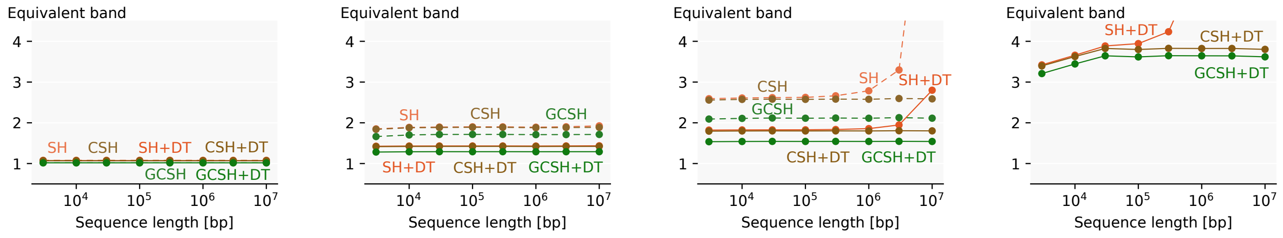
$$h^{\mathcal{M}}_{\text{gcs}}(u) = \begin{cases} P(u) - S_T(u) & \text{if } u \preceq_T v_t, \\ c_{\text{gap}}(u, v_t) & \text{if } u \npreceq_T v_t. \end{cases}$$

*Proof.* Write $h := h^{\mathcal{M}}_{\text{gcs}}$ and $h' := h^{\mathcal{M}}_{\preceq_T, c_{\text{gs}}}$. When $u \npreceq_T v_t$, $h(u) = c_{\text{gap}}(u, v_t)$ by Lemma 7. Otherwise, when $u \preceq_T v_t$, we have $h(u) = h'(u)$. Let $u \preceq_T m_1 \preceq_T \dots \preceq_T v_t$ be a $\preceq_T$-chain for $h'$ as in Def. 1. All terms in $h'$ satisfy $\text{end}(m_i) \preceq_T \text{start}(m_{i+1})$, so $c_{\text{gap}} \leq c_{\text{seed}}$ and by Lemma 6 $c_{\text{gs}}(m_i, m_{i+1}) = c_{\text{seed}}(m_i, m_{i+1})$. Thus, $h' = h_{\preceq_T, c_{\text{seed}}}$, and $h^{\mathcal{M}}_{\text{gcs}}(u) = P(u) - S_T(u)$ by Thm. 4. □



(a) $d$=1%, exact matches (b) $d$=4%, exact matches (c) $d$=8%, inexact matches (d) $d$=12%, inexact matches

**Fig. 8. Runtime scaling with sequence length on synthetic data.** Log-log plots comparing our simplest heuristic (SH) and our most accurate heuristic (GCSH, with DT) with EDLIB and BIWFA. The slopes of the bottom (top) of the dark-grey cones correspond to linear (quadratic) growth. The seed length is $k$=15 and for $d$≥8% the heuristics use inexact matches ($r$=2). Averages are over total $N$=$10^7$ bp. The missing data points for SH at $d$=12% are due to exceeding the 32 GiB memory limit.



(a) $d$=1%, exact matches (b) $d$=4%, exact matches (c) $d$=8%, inexact matches (d) $d$=12%, inexact matches

**Fig. 9. Equivalent band scaling with sequence length on synthetic data.** ($k$=15, $r$=2 for $d$≥8%). The equivalent band is the number of expanded states per bp for aligning synthetic sequences. Averages are over total $N$=$10^7$ bp. At $d$=12%, the bands of non-DT methods are ≥ 3× wider.

## C Further results

### C.1 Tool comparison on synthetic data

In Fig. 8 we compare our A* heuristics with EDLIB and BIWFA in terms of runtime scaling with sequence length $n$ and divergence $d$.

### C.2 Expanded states and equivalent band

The main benefit of an A* heuristic is a lower number of expanded states, which translates to faster runtime. Instead of evaluating the runtime scaling with length (Fig. 8), we can judge how well a heuristic approximates the edit distance by directly measuring the *equivalent band* (Fig. 9) of each alignment: the number of expanded states divided by sequence length $n$, or equivalently, the number of expanded states per base pair. The theoretical lower bound is an equivalent band of 1, resulting from expanding only the states on the main diagonal.

The equivalent band tends to be constant in $n$, indicating that the number of expanded states is linear on the given domain. The equivalent band of SH starts to grow around $n \geq 10^6$ at divergence $d$=8%, and around $n \geq 10^5$ at $d$=12%. Because of the chaining, CSH and GCSH cope with spurious matches and remain constant in equivalent band (i.e. linear expanded states with $n$). The equivalent band for GCSH is slightly lower than CSH due to better accounting for indels. The DT variants expand fewer states by skipping non-farthest reaching states.

### C.3 Human data results

Statistics on our human data are presented in Table 2. We compare all our heuristics in Fig. 10.

For ONT reads without genetic variation, SH is faster than other methods in median, but slower for sequences with high divergence and larger gaps. CSH is slightly slower than SH due to additional bookkeeping without significant benefit for the heuristic. Penalizing indels with GCSH improves performance several times.

| | | **Length** [kbp] | | | **Divergence** [%] | | | **Max gap** [kbp] | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Dataset** | **Cnt** | min | mean | max | min | mean | max | min | mean | max |
| ONT | 50 | 500 | 594 | 849 | 2.7 | 6.3 | 18.0 | 0.02 | 0.1 | 1 |
| ONT+gen.var. | 48 | 502 | 632 | 1053 | 4.4 | 7.4 | 19.8 | 0.05 | **1.9** | **42** |

**Table 2. Human datasets statistics.** ONT reads only include short gaps, while genetic variation also includes long gaps. **Cnt**: number of sequence pairs. **Max gap**: longest gap in the reconstructed alignment.

When genetic variation is included, SH and CSH do not sufficiently penalize long gaps, and A* with GCSH estimates the remaining edit distance significantly better. The diagonal transition optimization considerably speeds up the alignment of long indels where the search regresses to quadratic.

### C.4 Memory usage

Table 3 compares memory usage of aligners on synthetic sequences of length $n$=$10^6$. Alignments with inexact matches ($d$≥8%) use significantly more memory than those with exact matches because more $k$-mer hashes need to be stored to find inexact matches. Table 4 compares memory usage on the human data sets.

### C.5 Scaling with divergence

Figure 12 shows the runtime scaling with divergence for various heuristics. The heuristics using inexact matches ($r$=2) are slower for low-divergence sequences due to spending relatively a lot of time on the initialization of the heuristic, which requires finding all inexact matches.

The threshold for near-constant runtime is near 10% = $1/k$ for exact matches and near 20% = $2/k$ for inexact matches. As the divergence approaches this threshold, the runtime (and number of expanded states) starts to grow. This can be explained as follows.

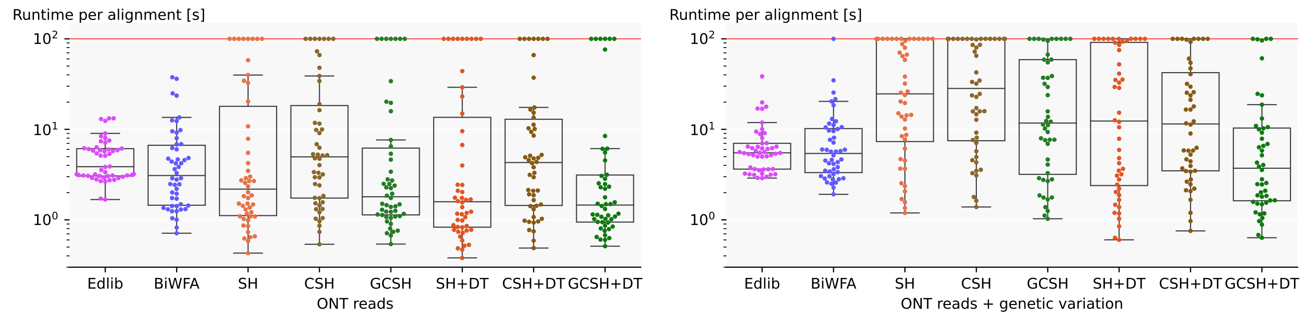
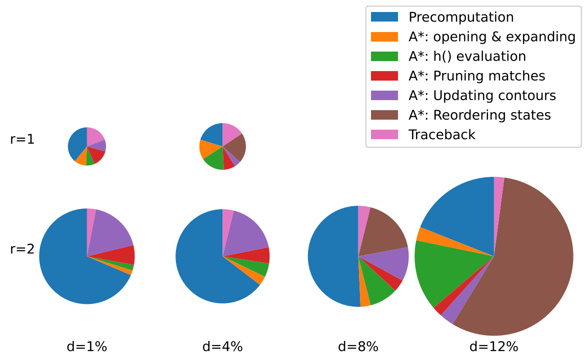
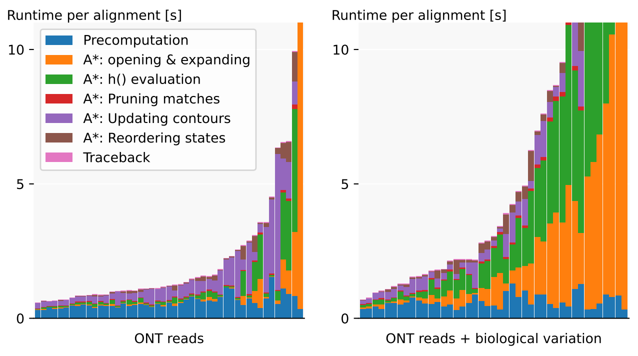


**Fig. 10. Runtime on long reads of human data** (logarithmic, $\geq 500\,\mathrm{kbp}$). Each dot corresponds to an alignment of a sequence pair. The ONT reads are without (left) and with (right) genetic variation. Runtime is capped at $100\,\mathrm{s}$.



(a) Synthetic data



(b) Human data

**Fig. 11. Runtime distributions per stage of A*PA (GCSH with DT)** (stages do not overlap). Stage *A** includes expanding and opening states. *Pruning matches* includes consistency checks. *Updating contours* includes updating of contours after pruning. (a) On synthetic data ($n{=}10^6\ \mathrm{bp}$, $N{=}10^7\ \mathrm{bp}$ total). The circle area is proportional to the total runtime. Figures for $r{=}1$ and $d{\geq}8\%$ are skipped due to timeouts ($100\,\mathrm{s}$). (b) On human data ($r{=}2$). Alignments are sorted by total runtime (timeouts not shown).

| | Memory usage [MB] | | | |
|---|---|---|---|---|
| **Aligner** | $d{=}1\%$ | $d{=}4\%$ | $d{=}8\%$ | $d{=}12\%$ |
| EDLIB | 2 | 1 | 2 | 2 |
| BIWFA | 15 | 13 | 14 | 18 |
| **SH** | 50 | 59 | 151 | 480 |
| **CSH** | 52 | 59 | 151 | 261 |
| **GCSH** | 49 | 50 | 151 | 255 |
| **SH + DT** | 49 | 49 | 151 | 150 |
| **CSH + DT** | 49 | 49 | 151 | 150 |
| **GCSH + DT** | 48 | 46 | 152 | 150 |

**Table 3. Memory usage per algorithm** (synthetic data, $n{=}10^6$). Exact matches are used when $d \leq 4\%$, and inexact matches when $d \geq 8\%$.

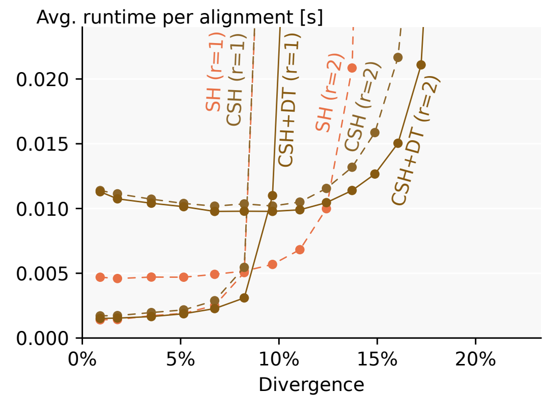


**Fig. 12. Runtime scaling with divergence (zoomed)** (linear, synthetic, $n{=}10^4$, $10^6\ \mathrm{bp}$ total, $k{=}10$). The figure shows the same results as Fig. 4c, but zoomed in to small runtimes where the scaling with $n$ degrades from linear to quadratic. $r{=}1$ and $r{=}2$ indicate exact and inexact matches, respectively.

| | ONT reads | | + genetic var. | |
|---|---|---|---|---|
| **Aligner** | Median | Max | Median | Max |
| EDLIB | 2 | 5 | 2 | 6 |
| BIWFA | 11 | 19 | 15 | 24 |
| **A*PA (GCSH + DT)** | 160 | 3478 | 270 | 6926 |

**Table 4. Memory usage [MB] of aligners on human data.** Medians are over all alignments; maximums are over alignments not timing out.

For each error that is not accounted for by a heuristic, A* needs to increase its best estimate $f$ of the total cost by 1. This means it needs to *backtrack* and expand more states with this higher $f$ value, including states before the search tip. Pruning compensates for this by increasing $h$ before the tip. However, the more unaccounted errors occur, the more pruned matches are needed. Once the total cost is equal to the potential, *all* pruned matches are needed to compensate. At that point, each edit that is not accounted for effectively increases the band width by 2.

### C.6 Runtime of A*PA internals

Figures 11a and 11b compare the time used by stages of A*PA.

### C.7 Linear mode without matches

States are penalized by the number of remaining seeds that cannot be matched. So, curiously, matches are not always needed to direct the A* search to an optimal path. In fact, when each seed contains exactly one mutation seed heuristic scales linearly even though there are no matches, as shown by the artificial example in Fig. 13.

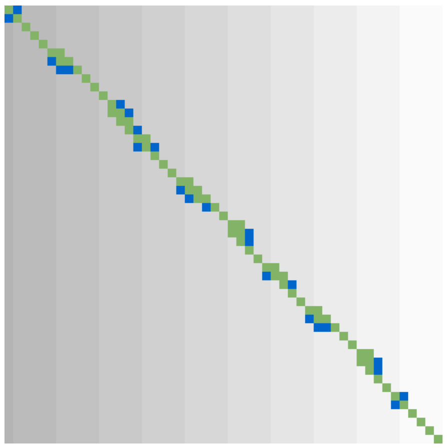
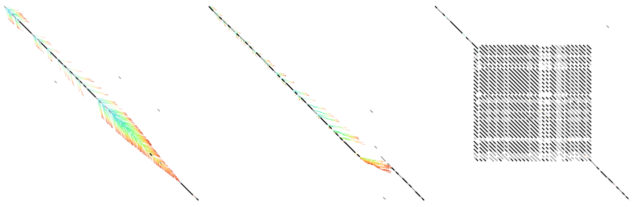


**Fig. 13. Artificial example of A* with seed heuristic with no matches** ($n$=$m$=50, $r$=1, $k$=5, 80% similarity, 1 mutation per seed alternating substitution, insertion, and deletion). The background colour indicates $h_s(u)$ with higher values darker. Expanded states are green (🟩), open states blue (🟦).

### C.8 Complex cases



(a) High divergence (b) Long indel (c) Short repeats

**Fig. 14. Quadratic exploration behavior for complex alignments** (GCSH with DT, $r$=2, $k$=10, synthetic sequences, $n$=1000). (a) A highly divergent region, (b) a deletion, and (c) a short repeated pattern inducing a quadratic number of matches. The colour corresponds to the order of expansion, from blue to red.

### C.9 Comparison of heuristics and techniques

Figure 15 shows the effect of our heuristics and optimizations for aligning complex short sequences. The effect of pruning is most noticeable for CSH and GCSH without DT. GCSH is our most accurate heuristic, so, as expected, it leads to the lowest number of expanded states.

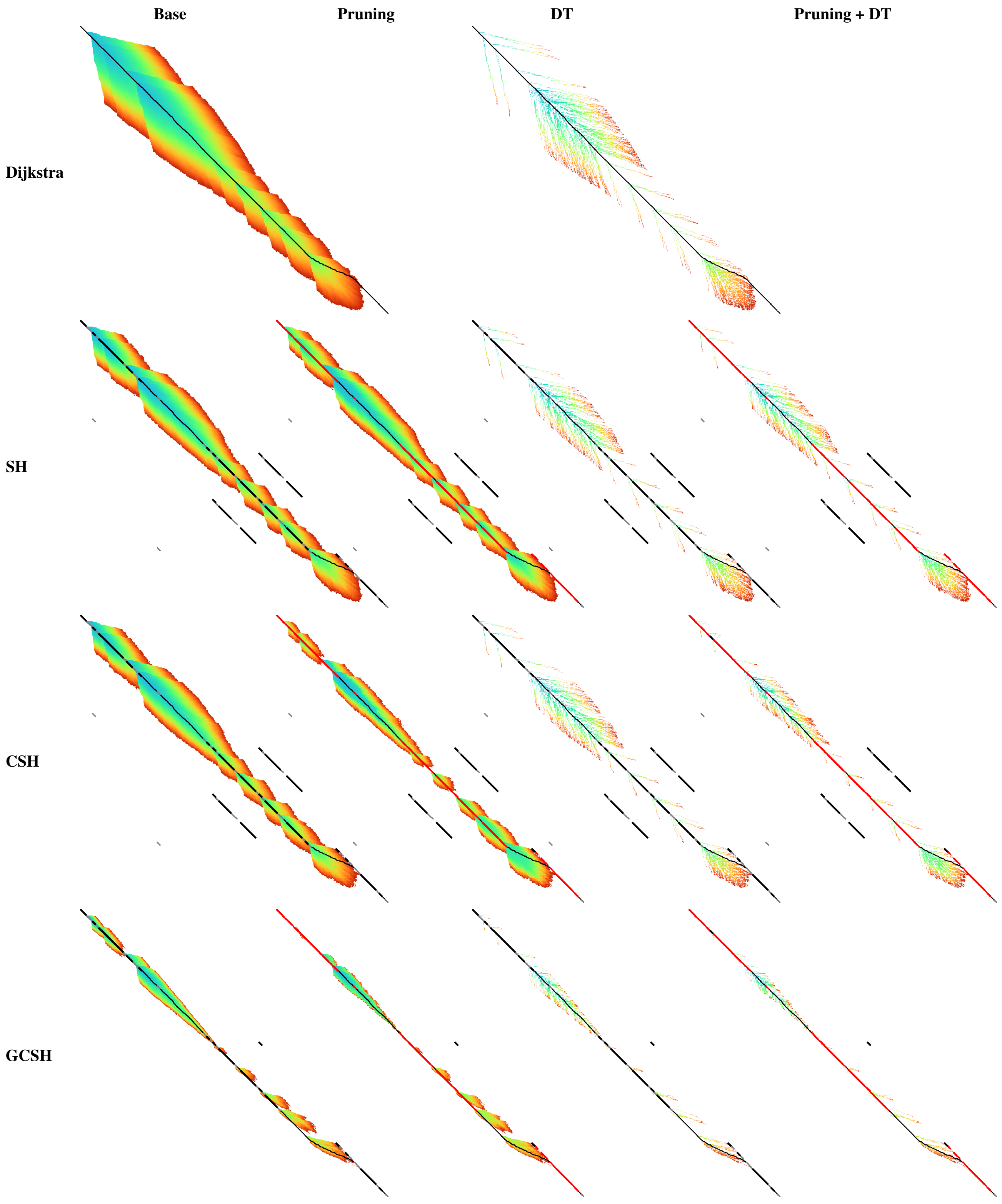


**Fig. 15. Expanded states for various heuristics and techniques, on a sequence containing a noisy region, a repeat, and an indel** ($n$=1000, $d$=17.5%). The colour shows the order of expanding, from blue to red. The sequences include a highly divergent region, a repeat, and a gap. Matches are shown as **black diagonals**, with inexact matches in grey and pruned matches in red. The final path is **black**. Dijkstra does not have pruning variants, and Dijkstra with DT is equivalent to WFA. More accurate heuristics reduce the number of expanded states by more effectively punishing repeats (CSH) and gaps (GCSH). Pruning reduces the number of expanded states before the pruned matches, and diagonal transition reduces the density of expanded states in quadratic regions.

## D Notation

| Object | Notation |
|---|---|
| **Sequences** | |
| Alphabet | $\Sigma = \{\texttt{A},\texttt{C},\texttt{G},\texttt{T}\}$ |
| Sequences | $A = \overline{a_0a_1\dots a_i\dots a_{n-1}} \in \Sigma^*$ |
| | $B = \overline{b_0b_1\dots b_j\dots b_{m-1}} \in \Sigma^*$ |
| Substring | $A_{i..i'} = \overline{a_i\dots a_{i'-1}}$ |
| Prefix | $A_{<i} = \overline{a_0\dots a_{i-1}}$ |
| Suffix | $A_{\geq i} = \overline{a_i\dots a_{n-1}}$ |
| Edit distance | $\mathrm{ed}(A,B)$ |
| Divergence | $d = \mathrm{ed}(A,B)/n$ |
| Error rate | $e$ |
| **Alignment graph** | |
| Graph | $G = (V, E)$ |
| Vertices (states) | $u, v \in V = \{\langle i,j\rangle \mid 0 \leq i \leq n, 0 \leq j \leq m\}$ |
| Edges | match/substitution $\langle i,j\rangle \to \langle i{+}1, j{+}1\rangle$ |
| | deletion $\langle i,j\rangle \to \langle i{+}1, j\rangle$ |
| | insertion $\langle i,j\rangle \to \langle i, j{+}1\rangle$ |
| Distance | $\mathrm{d}(u,v)$ |
| Path, shortest path | $\pi$, $\pi^*$ |
| Cost | $\mathrm{c}_{\mathrm{path}}(\pi)$ |
| **Diagonal transition** | |
| Farthest-reaching state | $F_{gk} = i{+}j$ on diagonal $k{=}i{-}j$ |
| **A*** | |
| Start and target state | $v_s = \langle 0,0\rangle$, $v_t = \langle n,m\rangle$ |
| Distance from $v_s$ | $g^* = \mathrm{d}(v_s, \cdot)$ |
| Distance to $v_t$ | $h^* = \mathrm{d}(\cdot, v_t)$ |
| Heuristic | $h$ |
| Best distance from start | $g$ |
| Estimated distance | $f = g + h$ |
| Admissible heuristic | $h \leq h^*$ |
| Consistent heuristic | $h(u) \leq \mathrm{d}(u,v) + h(v)$ |
| Expanded states | $E$ |

| Object | Notation |
|---|---|
| **Seeds and matches** | |
| Seed length | $k$ |
| Seed potential | $r$ |
| Seeds | $s \in \mathcal{S}$, $s_l = A_{lk..lk+k}$ |
| Seeds in suffix | $\mathcal{S}_{\geq i} = \{s_l \in \mathcal{S} \mid lk \geq i\}$ |
| Alignment of seed | $\pi_s$ |
| Matches (per seed) | $m \in \mathcal{M}$, $\mathcal{M}_s$ |
| Terminal match | $m_\omega$ from $v_t$ to $v_t$ |
| Cost of match | $0 \leq \mathrm{c_m}(m) < r$ |
| Score of match | $0 < \mathrm{score}(m) = r - \mathrm{c_m}(m) \leq r$ |
| Score of seed | $\mathrm{score}(s) = \max_{m \in \mathcal{M}_s} \mathrm{score}(m)$ |
| **Chains** | |
| Preceding states | $\langle i,j\rangle \preceq \langle i',j'\rangle$ when $i \leq i'$ and $j \leq j'$ |
| Preceding matches | $m \preceq m'$ when $\mathrm{end}(m) \preceq \mathrm{start}(m')$ |
| | $u \preceq m$ when $u \preceq \mathrm{start}(m)$ |
| Partial order | $u \preceq_p v$ when $p(u) \leq p(v)$ |
| $i$-order | $\langle i,j\rangle \preceq_i \langle i',j'\rangle$ when $i \leq i'$ |
| $\preceq_p$-chain | $m_1 \preceq_p \cdots \preceq_p m_l \preceq_p v_t$ |
| **Chaining costs** | |
| Chaining cost | $\gamma(m, m')$ |
| Gap cost | $c_{\mathrm{gap}}(\langle i,j\rangle, \langle i',j'\rangle) := \lvert(i'{-}i){-}(j'{-}j)\rvert$ |
| Seed cost | $c_{\mathrm{seed}}(u,v) = r \cdot \mathcal{S}_{u\dots v}$ |
| Gap-seed cost | $c_{\mathrm{gs}} = \max(c_{\mathrm{gap}}, c_{\mathrm{seed}})$ |
| **Scores** | |
| Potential | $P\langle i,j\rangle = r \cdot \lvert\mathcal{S}_{\geq i}\rvert$ |
| Chain score | $S_p(m) = \max_{m \preceq_p m_1 \preceq_p \cdots \preceq_p v_t} \mathrm{score}(m) + \dots$ |
| | $S_p(u) = \max_{u \preceq_p m \preceq_p v_t} S_p(m)$ |
| Computation | $h_{p,c_{\mathrm{seed}}}(u) = P(u) - S_p(u)$ |
| **Heuristics** | |
| SH | $h_{\mathrm{s}}(u) = P(u) - S_i(u)$ |
| CSH | $h_{\mathrm{cs}}(u) = P(u) - S_{\preceq}(u)$ |
| GCSH | $h_{\mathrm{gcs}}(u) = \max(c_{\mathrm{gap}}(u, v_t), P(u) - S_T(u))$ |
| | $T : \langle i,j\rangle \mapsto (i{-}j{-}P\langle i,j\rangle, j{-}i{-}P\langle i,j\rangle)$ |
| Pruning heuristic | $\hat{h}^{\mathcal{M}}$ |
| **Layers** | |
| Layer | $\mathcal{L}_\ell = \{u \mid S_p(u) \geq \ell\}$ |
| Dominant state | $u \in \mathcal{L}_\ell$ s.t. $\{v \in \mathcal{L}_\ell \mid u \preceq v\} = \{u\}$ |