AND/OR Branch-and-Bound for Computational Protein Design Optimizing K* SUPPLEMENTAL MATERIALS

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1 Notation and Definitions

$\mathcal{M}$: A CPD graphical model for computing the K*MAP. More formally, $\mathcal{M} = \langle \boldsymbol{X}, \boldsymbol{D}, \boldsymbol{F} \rangle$ where:

- $\boldsymbol{X}$ is the set of all variables in the model
- $\boldsymbol{D}$ is the set of domains for all respective variables in the model
- $\boldsymbol{F}$ is the set of all functions over the variables in the model

$\boldsymbol{X}$:

- the set of all variables of the model
- $\boldsymbol{X} = \boldsymbol{R} \cup \boldsymbol{C}$
  - · $\boldsymbol{R}$
    - · "residue variables" - the set of variables corresponding to the protein residues
    - · the set of variables that will be maximized over (ie. the MAP variables)
  - · $\boldsymbol{C}$
    - · "conformation variables" - each $C \in \boldsymbol{C}$ indexes the rotamer conformation of a particular $R \in \boldsymbol{R}$
    - · the set of variables that will be summed over (ie. the SUM variables)
    - · there can be several $C \in \boldsymbol{C}$ that correspond to the same $R \in \boldsymbol{R}$. These different C's capture the rotamer conformations of their particular R when the protein is in different structural states...
    - · $\boldsymbol{C} = \cup_{\gamma \in \varphi} \boldsymbol{C_\gamma}$
      - · φ represents the set of all different substructures the protein's subunits can exist as
      - · $\varphi = B \cup U$
        - · B is the set of substructures corresponding to bound (ie. complexed) subunits corresponding to the numerator of the K^* ratio
        - · U is the set of substructures corresponding to the unbound (ie. dissociate) subunits corresponding to the denominator of the K^* ratio
      - · thus $\boldsymbol{C_\gamma}$ is the set of conformation variables corresponding to residues of substructure $\gamma \in \varphi$
        - · $C_{\gamma(i)}$ is the conformation variable for residue i when residue i's subunit is in substructure γ
- $\boldsymbol{X_\gamma} = \boldsymbol{R} \cup \boldsymbol{C_\gamma}$

$\boldsymbol{D}$**:**

- the set of domains for each variable in $\boldsymbol{X}$
- $\boldsymbol{D_\gamma}$ is the set of domains for the variables in $\boldsymbol{X_\gamma}$
- for all $R_i \in \boldsymbol{R}$, the respective $D_i = \{$ ALA, VAL, LEU, ILE, PHE, TYR, TRP, CYS, MET, SER, THR, LYS, ARG, HIP, HIE, HID, ASP, GLU, ASN, GLN, GLY$\}$

- for all $C_{\gamma(i)} \in \boldsymbol{C}$,
  - Formulation 1
    - $D_{C_{\gamma(i)}} = \{1, 2, ..., M_i\}$, where M_i is the maximum number of rotamers for any possible amino acid assignment to R_i in state $\gamma \in \varphi$.
    - the assignment to $C_{\gamma(i)}$ acts as an index to the possible side chain conformations of the amino acid assigned to R_i.
  - Formulation 2
    - $D_{C_{\gamma(i)}} = \{c \mid c$ is a rotamer in substructure γ for one of the possible amino acids of residue $R_i\}$.

$\boldsymbol{F}$**:**

- the set of all functions over the model
- $\boldsymbol{F} = \cup_{\gamma \in \varphi} F_\gamma$
  - Formulation 1
    - $F_\gamma = \boldsymbol{E^{sb}_\gamma} \cup \boldsymbol{E^{pw}_\gamma}$
      - $\boldsymbol{E^{sb}_\gamma}$ are the set of all single bodied energies over the residues and their conformations for substructure γ
      - $\boldsymbol{E^{pw}_\gamma}$ are the set of all pair-wise energies for all pairs of residues and their conformations that interact in substructure γ
  - Formulation 2
    - $F_\gamma = \boldsymbol{E^{sb}_\gamma} \cup \boldsymbol{E^{pw}_\gamma} \cup \mathscr{C}_{\boldsymbol{\gamma}}$
      - $\mathscr{C}_{\boldsymbol{\gamma}}$ are constraints ensuring that the assigned rotamer to $C_{\gamma(i)}$ belongs to the amino acid assigned to R_i.

$\mathcal{M}_\gamma$**:** The CPD graphical model $\mathcal{M}$ modified to include only components corresponding to substructure γ. Namely, $\mathcal{M}_\gamma = \langle \boldsymbol{X_\gamma}, \boldsymbol{D_\gamma}, \boldsymbol{F_\gamma} \rangle$

$\mathcal{T}$**:** Pseudo tree for $\mathcal{M}$ constrained for K*MAP computation and providing decomposition of the various substructures $\gamma \in \varphi$.

$\mathcal{T}_\gamma$**:** Pseudo tree for $\mathcal{M}_\gamma$ based on a modified $\mathcal{T}$ such that nodes corresponding to $C_{\gamma'}$, where $\gamma' \neq \gamma$, have been removed.

T**:** Full AND/OR search tree based on $\mathcal{T}$.

T_γ**:** Full AND/OR search tree of $\mathcal{M}_\gamma$ based on $\mathcal{T}_\gamma$.

π**:** Currently expanded path in T.

π_n**:** Path from the root to n in T.

$tip(\pi)$: The last node in π that was expanded to.

$OR^R, OR^C, etc.$: The set of OR nodes whose corresponding variables belong to the variable set denoted by the superscript. (Absence of superscript corresponds to all OR nodes).

$AND^R, AND^C, etc.$: The set of AND nodes of T whose corresponding variables belong to the variable set denoted by the superscript. (Absence of superscript corresponds to all AND nodes).

$LEAF_T$: The set of AND nodes that are leaves in T.

n_X: Search tree node n corresponding to a particular variable $X \in \boldsymbol{X}$.

$ch_T(n)$: Children nodes of n in the search tree indicated by its subscript.

$ch_\pi(n)$: Child of n along the π.

$ch_T^{unexp}(n)$: Children nodes of n in the search tree indicated by its subscript that have yet to be expanded to (ie. explored) by the algorithm.

$ch_T^{solved}(n)$: Children nodes of n in the search tree indicated by its subscript who have been returned to after exploration of all of their children and provably with $lb_{K^*}(n) = ub_{K^*}(n) = v^*(n)$, $v^*(n)$ being the exact K*MAP value for the subproblem rooted at n (described futher below).

$ch_T^{unsolved}(n)$: Children nodes of n in the search tree indicated by its subscript whose $lb_{K^*}(n)$ and $ub_{K^*}(n)$ values are not yet known to be exact because not all their children have been expanded to and returned from. $ch_T^{unsolved}(n) = ch_T(n) \setminus ch_T^{solved}(n)$.

$anc^{OR}(n), anc^{AND}(n), etc.$: Ordered ancestors of n in T, from most recent to eldest, that also belong to the set described by the superscript.

$c(n)$: Edge cost into n in T.

$g(n)$: Path cost from the root into n in T. Namely, $c(n) \cdot \prod_{m \in anc^{AND}(n)} c(m)$.

$v^*(n_X)$: For $X \in \boldsymbol{R}$, $v^*(n_X)$ is the K*MAP value (ie. the optimal K* value) for the problem rooted at n. For $X \in \boldsymbol{C}$, $v^*(n_X)$ is the partition function value of the problem rooted at n. Namely,

$$v^*(n) = \begin{cases} \max_{m \in ch_T(n)} v^*(m), & n \in OR^{\boldsymbol{R}} \\ \frac{(\prod_{m \in ch_T^R(n)} v^*(m))(\prod_{\gamma \in B} \prod_{m' \in ch_T^{C_\gamma}(n)} v^*(m'))}{(\prod_{\gamma \in U} \prod_{m" \in ch_T^{C_\gamma}(n)} v^*(m"))}, & n \in AND^{\boldsymbol{R}} \\ \sum_{m \in ch_T(n)} v^*(m) \cdot c(m), & n \in OR^{\boldsymbol{C}} \\ \prod_{m \in ch_T(n)} v^*(m), & n \in AND^{\boldsymbol{C}} \setminus LEAF_T \\ 1, & n \in LEAF_T \end{cases}$$

$v(n)$**:** A progressively accumulated quantity based on processing of fully solved and returned children fo a node n. $v(n)$ converges to the exact K$*$MAP value of the subproblem rooted at n once all of its children have been expanded to, solved, and returned from. Namely, if $ch_T^{solved}(n) = ch_T(n)$, then $v(n) = v^*(n)$. Formally,

$$v(n) = \begin{cases} \max_{m \in ch_T^{solved}(n)} v(m), & n \in OR^{\boldsymbol{R}} \\ \frac{(\prod_{m \in ch_T^{solved,R}(n)} v(m))(\prod_{\gamma \in B} \prod_{m' \in ch_T^{solved,C_\gamma}(n)} v(m'))}{(\prod_{\gamma \in U} \prod_{m" \in ch_T^{solved,C_\gamma}(n)} v(m"))}, & n \in AND^{\boldsymbol{R}} \\ \sum_{m \in ch_T^{solved}(n)} v(m) \cdot c(m), & n \in OR^{\boldsymbol{C}} \\ \prod_{m \in ch_T^{solved}(n)} v(m), & n \in AND^{\boldsymbol{C}} \setminus LEAF_T \\ 1, & n \in LEAF_T \end{cases}$$

$\mu^*_\gamma(n_X)$**:** For $X \in \boldsymbol{R}$, $\mu^*_\gamma(n_X)$ is the MMAP value for the problem rooted at n in T_γ. For $X \in \boldsymbol{C_\gamma}$, $v^*(n_X)$ is the partition function value of the problem rooted at n in T_γ.

$$\mu^*_\gamma(n) = \begin{cases} \max_{m \in ch_{T_\gamma}(n)} \mu^*_\gamma(m), & n \in OR^{\boldsymbol{R}} \\ \sum_{m \in ch_{T_\gamma}(n)} \mu^*_\gamma(m) \cdot c(m), & n \in OR^{\boldsymbol{C}} \\ \prod_{m \in ch_{T_\gamma}(n)} \mu^*_\gamma(m), & n \in AND \setminus LEAF_T \\ 1, & n \in LEAF_T \end{cases}$$

$\mu_\gamma(n)$**:** A progressively accumulated quantity based on the fully solved and returned children of node n in T_γ. $\mu_\gamma(n)$ converges to the exact MMAP value of the γ-subproblem rooted at n once all of its children in T_γ have been expanded to, solved, and returned from. Namely, if $ch_{T_\gamma}^{solved}(n) = ch_{T_\gamma}(n)$, then $\mu_\gamma(n) = \mu^*_\gamma(n)$. Formally,

$$\mu_\gamma(n) = \begin{cases} \max_{m \in ch_{T_\gamma^{solved}}(n)} \mu_\gamma(m), & n \in OR^{\boldsymbol{R}} \\ \sum_{m \in ch_{T_\gamma^{solved}}(n)} \mu_\gamma(m) \cdot c(m), & n \in OR^{\boldsymbol{C}} \\ \prod_{m \in ch_{T_\gamma^{solved}}(n)} \mu_\gamma(m), & n \in AND \setminus LEAF_T \\ 1, & n \in LEAF_T \end{cases}$$

$h_{K^*}(n)$**:** Precompiled WMBE-K*MAP heuristic for the problem rooted at n.

$h_{Z_\gamma}(n)$**:** Precompiled WMBE-MMAP heuristic for the problem rooted at n considering only $X \in \boldsymbol{X_\gamma} = \boldsymbol{R} \cup \boldsymbol{C_\gamma}$.

$ub_{K^*}(n)$**:** Progressively updated upper bound heuristic of the K*MAP problem rooted at n. Formally,

$$ub_{K^*}(n) = \begin{cases} max(v(n), max_{m \in ch_T^{unsolved}(n)} h_{K^*}(m)), & n \in OR^{\boldsymbol{R}} \\ v(n) \cdot \frac{(\prod_{m' \in ch_T^{unsolved,R}(n)} h_{K^*}(m'))(\prod_{\gamma \in B} \prod_{m" \in ch_T^{unsolved,C_\gamma}(n)} h_{Z_\gamma}(m"))}{(\prod_{\gamma \in U} \prod_{m'" \in ch_T^{unsolved,C_\gamma}(n)} h_{Z_\gamma}(m'"))}, & n \in AND^{\boldsymbol{R}} \\ v(n) + \sum_{m \in ch_T^{unsolved}(n)} h_{K^*}(m) \cdot c(m), & n \in OR^{\boldsymbol{C}} \\ v(n) \cdot \prod_{m \in ch_T^{unsolved}(n)} h_{K^*}(m), & n \in AND^{\boldsymbol{C}} \setminus LEAF_T \\ 1, & n \in LEAF_T \end{cases}$$

$ub_{K^*}(n, \pi)$**:** Progressively updated upper bound heuristic of the K*MAP problem rooted at n consistent with the partial search tree π. Formally,

$$ub_{K^*}(n, \pi) = \begin{cases} ub_{K^*}(n), & n \in OR^{\boldsymbol{R}} \cap tip(\pi) \\ ub_{K^*}(ch_\pi(n), \pi), & n \in OR^{\boldsymbol{R}} \cap \pi \setminus tip(\pi) \\ ub_{K^*}(n) \cdot \prod_{m \in ch_\pi(n)} \frac{ub_{K^*}(m,\pi)}{h_{K^*}(m)} & n \in AND^{\boldsymbol{R}} \cap \pi \end{cases}$$

$ub_{Z_\gamma}(n)$**:** Progressively updated upper bound of the MMAP problem for substructure γ rooted at n. Formally,

$$ub_{Z_\gamma}(n) = \begin{cases} max(\mu_\gamma(n), max_{m \in ch_{T_\gamma}^{unsolved}(n)} h_{Z_\gamma}(m)), & n \in OR^{\boldsymbol{R}} \\ \mu_\gamma(n) + \sum_{m \in ch_{T_\gamma}^{unsolved}(n)} c(m) \cdot h_{Z_\gamma}(m)), & n \in OR^{\boldsymbol{C_\gamma}} \\ \mu_\gamma(n) \cdot \prod_{ch_{T_\gamma}^{unsolved}(n)} h_{Z_\gamma}(m), & n \in AND \end{cases}$$

$MMAP_\gamma(n)$**:** The marginal map value of subunit γ conditioned on residue assignments consistent with the path from the root to n. Formally,

$$MMAP_\gamma(n) = \begin{cases} \mu^*_\gamma(n) \cdot \prod_{m \in anc^{AND}(n)} \prod_{m' \in ch_{T_\gamma(m)} \setminus \pi_n} \mu^*_\gamma(m'), & n \in \boldsymbol{R} \\ \mu^*_\gamma(n) \cdot \prod_{m \in anc^{AND^{\boldsymbol{R}}}(n)} \prod_{m' \in ch_{T_\gamma(m)} \setminus \pi_n} \mu^*_\gamma(m'), & n \in \boldsymbol{C_\gamma} \end{cases}$$

$A^{\times *}_{Z_\gamma}(n)$**:** Called the multiplicative ancestral branching mass, $A^{\times *}_{Z_\gamma}(n)$ captures the portion of $MMAP_\gamma(n)$ due to OR branchings off of n's AND ancestors. The product of $A^{\times *}_{Z_\gamma}$ and the partition function of the subtree consisting of π_n and the subtree of T_γ rooted at n is the contribution to Z_γ from all full configurations consistent with π_n. Formally,

$$A^{\times *}_{Z_\gamma}(n) = \prod_{m \in anc^{AND}(n)} \prod_{m' \in ch_{T_\gamma(m)} \setminus \pi_n} v^*_{Z_\gamma}(m')$$

$A^{\times}_{Z_\gamma}(n)$**:** Upper bound of $A^{\times *}_{Z_\gamma}$ for node n.

$$A^{\times}_{Z_\gamma}(n) = \prod_{m \in anc^{AND}(n)} v_{Z_\gamma}(m) \cdot \prod_{m' \in ch_{T_\gamma}^{unexp}(m)} h_{Z_\gamma}(m')$$

$S^*_{Z\gamma}(n)$**:** The contribution to Z_γ from all configurations not consistent with π_n.

$$S^*_{Z\gamma}(n) = \sum_{m \in anc^{OR}(n)} R^*_{Z\gamma}(m) \cdot g(m) \cdot \sum_{m' \in ch_{T_\gamma(m)} \setminus \pi_n} c(m') \cdot \mu^*_\gamma(m)$$

$S_{Z\gamma}(n)$**:** Upper bound of $S^*_{Z_\gamma}$.

$$S_{Z\gamma}(n) = \sum_{m \in anc^{OR}(n)} A^{\times}_{Z_\gamma}(m) \cdot g(m) \cdot (\mu_\gamma(m) + \sum_{m' \in ch_{T_\gamma}^{unexp}(m)} c(m') \cdot h_{Z_\gamma}(m'))$$

$UB_{Z_\gamma}(n)$**:** Progressively updated upper bound heuristic on the *entire* partition function of the substructure $\gamma \in \Phi$. Formally,

$$UB_{Z_\gamma}(n) = \Big\{ A^{\times}_{Z_\gamma}(n) \cdot g(n) \cdot ub_{Z_\gamma}(n) + S_{Z\gamma}(n), \quad n \in tip(\pi)$$

2 AOBB-K^*MAP Algorithm Details

Algorithm 1: AOBB-K*MAP

input : CPD graphical model $\mathcal{M}$; pseudo-tree $\mathcal{T}$; K^* upper-bounding heuristic function $h^{ub}_{K^*}(.)$; Z_γ upper-bounding heuristic function $h^{ub}_{Z_\gamma}(.)$; and subunit stability threshold $threshold(\gamma)$ for each subunit $\gamma \in \varphi$
output: $K^*MAP(\mathcal{M})$

begin
  Initialize $MiniSat$ with constraints from $\mathcal{M}$ // MiniSat initialization
  and generate literals via constraint propagation
  $\pi \leftarrow$ dummy AND node n_D // initialize DFS to start from dummy root node, n_D
  $ub_{K^*}(n_D) \leftarrow \prod_{m \in ch_T(n_D)} h_{K^*}(m)$ // initialize n_D with global UB on K*
  $lb_{K^*}(n_D) \leftarrow -inf$ // no solution yet found as a lower bound
  $g(n_D) \leftarrow 1$
  foreach $\gamma \in \varphi$ **do** // initialize n_D with subunit-specific UB values
    $A^{\times}_{Z_\gamma}(n_D) \leftarrow 1$
    $A^{+}_{Z_\gamma}(n_D) \leftarrow 0$
    $ub_{Z_\gamma}(n_D) \leftarrow \prod_{m \in ch_{T_\gamma}(n_D)} h_{Z_\gamma}(m)$ // initialize $ub_{Z_\gamma}(n_D)$ to the MMAP$_\gamma$ global UB value
  end
  while $n_X \leftarrow EXPAND(\pi)$ **do** // DFS Branch-and-Bound
    if $MiniSat(\pi) = false$ **then** // Constraint-Propagation Pruning (CPP)
      $PRUNE(\pi)$
    else if $\exists \gamma \in \varphi$ *s.t.* $UB_{Z_\gamma}(n_X) < threshold(\gamma)$ **then** // Subunit-Stability Pruning (SSP)
      $PRUNE(\pi)$
    else if $X \in \boldsymbol{R}$ **then**
      if $\exists a \in anc^{OR}(n)$ *s.t.* $ub_{K^*}(a, \pi) < lb_{K^*}(a)$ **then** // K*MAP Upper-Bound Pruning (UBP)
        $PRUNE(\pi)$
      end
    else if $ch^{unexp}_T(n) = \emptyset$ **then** // DFS Backtracking Step
      $BACKTRACK(\pi)$
  end
  return $ub_{K^*}(n_D) = lb_{K^*}(n_D) = K^*MAP(\mathcal{M})$
end

Algorithm 2: AOBB-K*MAP subroutine, EXPAND

input : partial search tree π
output: newly expanded node n_X of π

begin
  if $\pi = \emptyset$ **then** // signals end of DFS search
    return $null$
  else
    $n_W \leftarrow tip(\pi)$ // n_W is the node to be expanded
    $n_X \leftarrow$ next unexplored child of n_W // n_X is the next node in the DFS
    $ch_T^{unexp}(n_W) \leftarrow ch_T^{unexp}(n_W) \setminus n_X$
    if $n_X \in OR$ **then**
      foreach $\gamma \in \varphi$ *associated with* X **do**
        $A^{\times}_{Z_\gamma}(n_X) \leftarrow A^{\times}_{Z_\gamma}(n_W) \cdot ub_{Z_\gamma}(n_W) / h_{Z_\gamma}(n_X)$ // update R_{Z_γ} to include siblings of n_X
        $A^{+}_{Z_\gamma}(n_X) \leftarrow A^{+}_{Z_\gamma}(n_W)$ // no new additive ancestral branching
      end
      if $X \in \boldsymbol{R}$ **then** // for OR MAP nodes...
        $ub_{K^*}(n_X) \leftarrow \max_{m \in ch_T(n_X)} h_{K^*}(m)$
        foreach $\gamma \in \varphi$ *associated with* X **do**
          $ub_{Z_\gamma}(n_X) \leftarrow \max_{m \in ch_{T_\gamma}(n_X)} h_{Z_\gamma}(m)$
        end
      else if $X \in \boldsymbol{C_\gamma}$ **then** // for OR SUM nodes of subunit γ...
        $ub_{K^*}(n_X) \leftarrow \sum_{m \in ch_T(n_X)} c(m) \cdot h_{K^*}(m)$
        $ub_{Z_\gamma}(n_X) \leftarrow \sum_{m \in ch_T(n_X)} c(m) \cdot h_{Z_\gamma}(m)$
      end
    else if $n_X \in AND$ **then** // for SUM or MAP AND nodes...
      foreach $\gamma \in \varphi$ **do**
        $A^{\times}_{Z_\gamma}(n_X) \leftarrow A^{\times}_{Z_\gamma}(n_W)$
        $ub_{Z_\gamma}(n_X) \leftarrow \prod_{m \in ch_{T_\gamma}(n_X)} h_{Z_\gamma}(m)$
      end
      if $X \in \boldsymbol{R}$ **then**
        $$ub_{K^*}(n_X) \leftarrow \frac{(\prod_{m \in ch_T^R(n)} h_{K^*}(m))(\prod_{\gamma \in B} \prod_{m' \in ch_T^{C_\gamma}(n)} h_{Z_\gamma}(m'))}{(\prod_{\gamma \in U} \prod_{m" \in ch_T^{C_\gamma}(n)} h_{Z_\gamma}(m"))}$$
        // $ub_{K^*}(n_X)$ initialized by combining UB heuristic values of its
        // children, dividing values corresponding to dissociate subunits
        foreach $\gamma \in \varphi$ *associated with* X **do**
          $A^{+}_{Z_\gamma}(n_X) \leftarrow A^{+}_{Z_\gamma}(n_W)$ // no new additive ancestral branching
        end
      else if $X \in \boldsymbol{C_\gamma}$ **then**
        $A^{+}_{Z_\gamma}(n_X) \leftarrow A^{+}_{Z_\gamma}(n_W) + A^{\times}_{Z_\gamma}(n_W) \cdot g(n_W) \cdot (ub_{Z_\gamma}(n_W) - c(n_X) \cdot h_{Z_\gamma}(n_X))$
        // update $A^{+}_{Z_\gamma}$ to include siblings of n_X
      end
    end
    $ch_T^{unexp}(n_X) \leftarrow ch_T(n_X)$
    $\pi \leftarrow \pi \cup n_X$
    return n_X;
  end
end

Algorithm 3: AOBB-K*MAP subroutine, BACKTRACK

input : partial search tree π
output: None

begin
  if $\pi = \emptyset$ **then** // backtracked all the way through root
    return
  else
    $n_X \leftarrow tip(\pi)$ // n_X is the node we're backtracking from
    $n_W \leftarrow par_T(n_X)$ // n_W is the node we're backtracking to
    $\pi \leftarrow \pi \setminus n_X$
    if $n_W \in AND$ **then** // backtracking from OR node n_X to AND node n_W
      if $X \in \boldsymbol{C_\gamma}$ *s.t.* $\gamma \in U$ *and* $W \in \boldsymbol{R}$ **then**
        $ub_{K^*}(n_W) \leftarrow ub_{K^*}(n_W) \cdot h_{K^*}(n_X)/ub_{K^*}(n_X)$ // tighten $ub_{K^*}(n_W)$ via update of // denominator term n_X contributes to
      else
        $ub_{K^*}(n_W) \leftarrow ub_{K^*}(n_W)/h_{K^*}(n_X) \cdot ub_{K^*}(n_X)$ // tighten $ub_{K^*}(n_W)$ via update of // numerator term n_X contributes to
      end
      foreach $\gamma \in \varphi$ *associated with* X **do**
        $ub_{Z_\gamma}(n_W) \leftarrow ub_{Z_\gamma}(n_W)/h_{Z_\gamma}(n_X) \cdot ub_{Z_\gamma}(n_X)$ // update upper-bound bound on Z_γ at n_W
      end
    else if $n_W \in OR$ **then** // backtracking from AND node n_X to OR node n_W
      if $W \in \boldsymbol{R}$ **then**
        $ub_{K^*}(n_W) \leftarrow max_{m \in ch_T(n_W)} ub_{K^*}(m)$ // tighten $ub_{K^*}(n_W)$ via reevaluation of its children
        foreach $\gamma \in \varphi$ *associated with* W **do**
          $ub_{Z_\gamma}(n_W) \leftarrow max_{ch_T(n_W)} ub_{Z_\gamma}(m)$ // update upper-bound bound on Z_γ at n_W
        end
      else if $W \in \boldsymbol{C_\gamma}$ **then**
        $ub_{K^*}(n_W) \leftarrow ub_{K^*}(n_W) - c(n_X) \cdot (h_{K^*}(n_X) - ub_{K^*}(n_X))$ // tighten $ub_{K^*}(n_W)$ via update // of $ub_{K^*}(n_X)$ of summed AND child n_X
        $ub_{Z_\gamma}(n_W) \leftarrow ub_{Z_\gamma}(n_W) - c(n_X) \cdot (h_{Z_\gamma}(n_X) - ub_{Z_\gamma}(n_X))$ // tighten $ub_{Z_\gamma}(n_W)$ via update // of $ub_{Z_\gamma}(n_X)$ of summed AND child n_X
      end
    end
    if $ch_T^{unexp}(n_W) = \emptyset$ **then** // Continue Backtracking
      $BACKTRACK(\pi)$
    else if $\exists \gamma \in \varphi$ *s.t.* $UB_{Z_\gamma}(n_W) < threshold(\gamma)$ **then** // Subunit-Stability Pruning (SSP)
      $PRUNE(\pi)$
    else if $W \in \boldsymbol{R}$ **then**
      if $\exists a \in anc^{OR}(n_W)$ *s.t.* $ub_{K^*}(a, \pi) < lb_{K^*}(a)$ **then** // K*MAP Upper-Bound Pruning (UBP)
        $PRUNE(\pi)$
      end
    end
end

Algorithm 4: AOBB-K*MAP subroutine, PRUNE

input : partial search tree π
output: None

begin
  if $\pi = \emptyset$ **then** // pruned all the way through root
    return
  else
    $n_X \leftarrow tip(\pi)$ // n_X is the node we're pruning
    $n_W \leftarrow par_T(n_X)$ // n_W is the node we're backtracking to
    $\pi \leftarrow \pi \setminus n_X$ // explicitly prunes n_X from π
    if $n_W \in AND$ **then** // also prune AND parent n_W which will be missing pruned OR child n_X
      $PRUNE(\pi)$
    else if $n_W \in OR$ **then**
      if $W \in \boldsymbol{R}$ **then**
        $ub_{K^*}(n_X) \leftarrow -inf$ // implicitly marks n_X as having been pruned
        $ub_{K^*}(n_W) \leftarrow max_{m \in ch_T(n_W)} ub_{K^*}(m)$ // recompute $ub_{K^*}(n_W)$ excluding pruned child
        foreach $\gamma \in \varphi$ *associated with* W **do**
          $ub_{Z_\gamma}(n_X) \leftarrow -inf$ // implicitly marks n_X as having been pruned
          $ub_{Z_\gamma}(n_W) \leftarrow max_{ch_T(n_W)} ub_{Z_\gamma}(m)$ // recompute $ub_{Z_\gamma}(n_W)$ excluding pruned child
        end
      else if $W \in \boldsymbol{C_\gamma}$ **then**
        $PRUNE(\pi)$ // invalidity of a portion of the SUM search space implies // invalidity of the entire corresponding SUM search space
      end
      if $ch_T^{unexp}(n_W) = \emptyset$ **then** // Continue Backtracking
        $BACKTRACK(\pi)$
      else if $\exists \gamma \in \varphi$ *s.t.* $UB_{Z_\gamma}(n_W) < threshold(\gamma)$ **then** // Subunit-Stability Pruning
        $PRUNE(\pi)$
      else if $W \in \boldsymbol{R}$ **then**
        if $\exists a \in anc^{OR}(n_W)$ *s.t.* $ub_{K^*}(a, \pi) < lb_{K^*}(a)$ **then** // K*MAP Pruning
          $PRUNE(\pi)$
        end
      end
    end
  end
end