RNA Folding

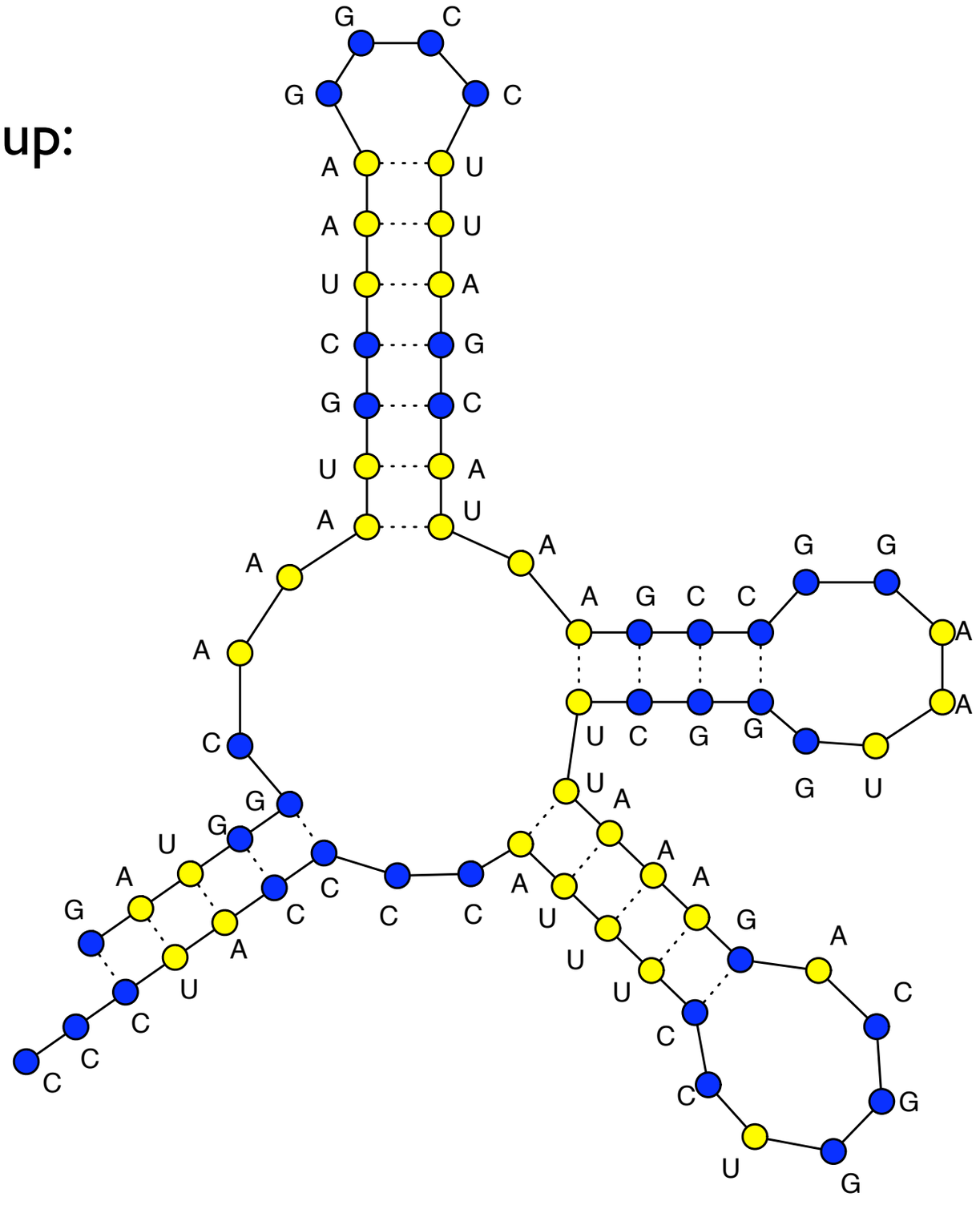
CMSC 423

Lecture by Darya Filippova

RNA Folding

RNA is single stranded and folds up:

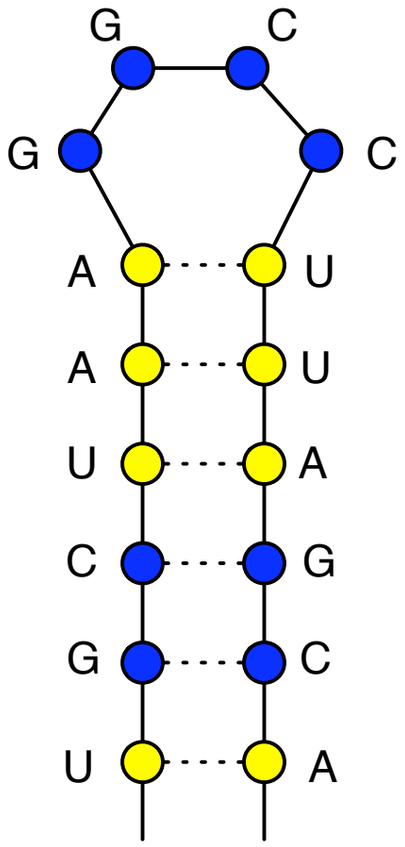
- G and C stick together
- A and U stick together

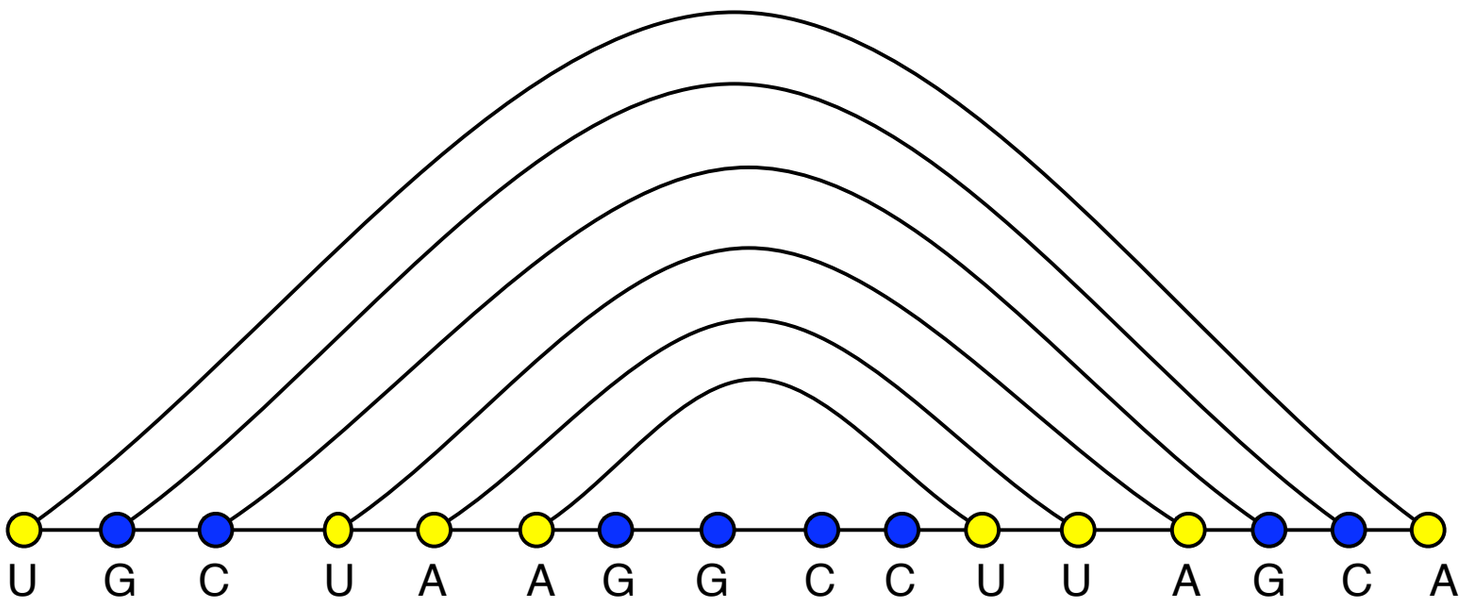


RNA Folding Rules

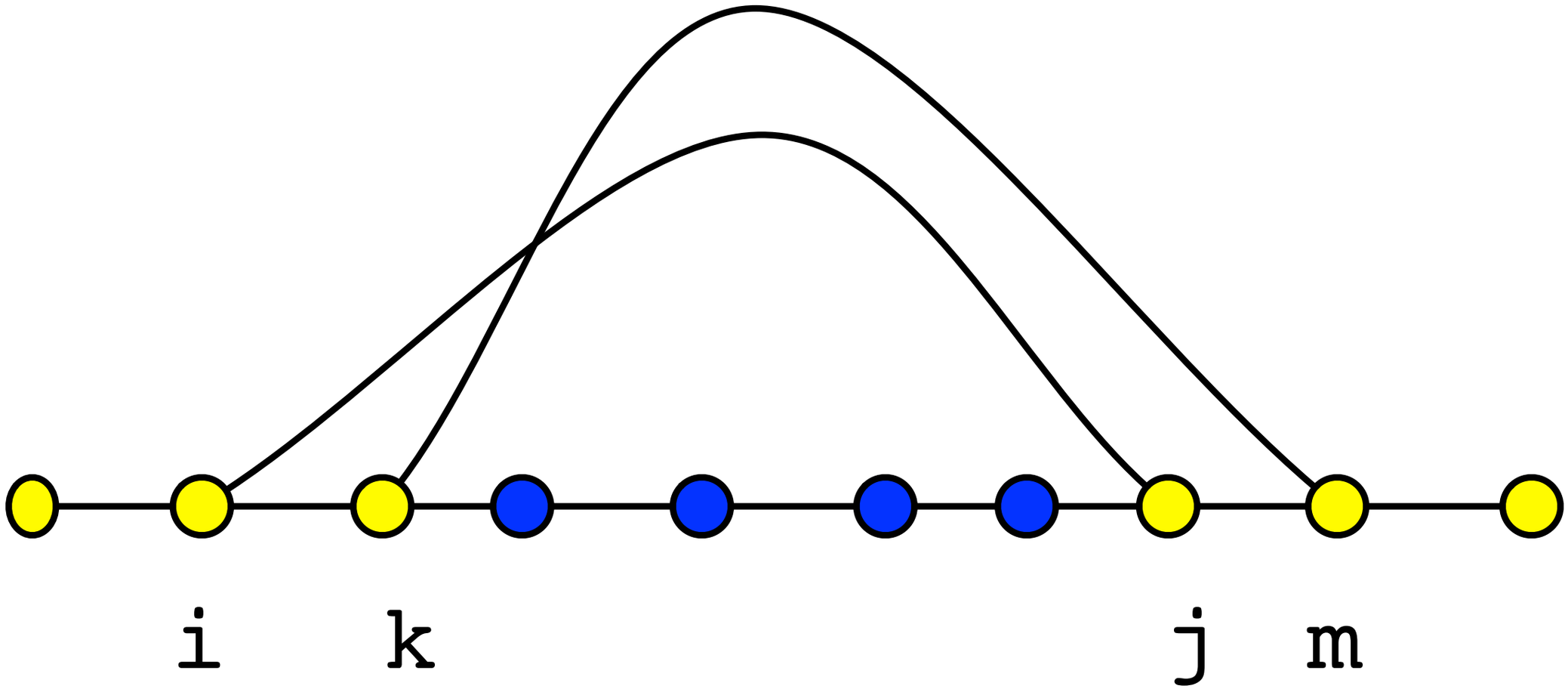
RNA folding rules:

1. If two bases are closer than 4 bases apart, they cannot pair
2. Each base is matched to at most one other base
3. The allowable pairs are {U, A} and {C, G}
4. Pairs cannot "cross."





No Crossings



If (*i*,*j*) and (*k*,*m*) are paired, we must have $i < k < m < j$.

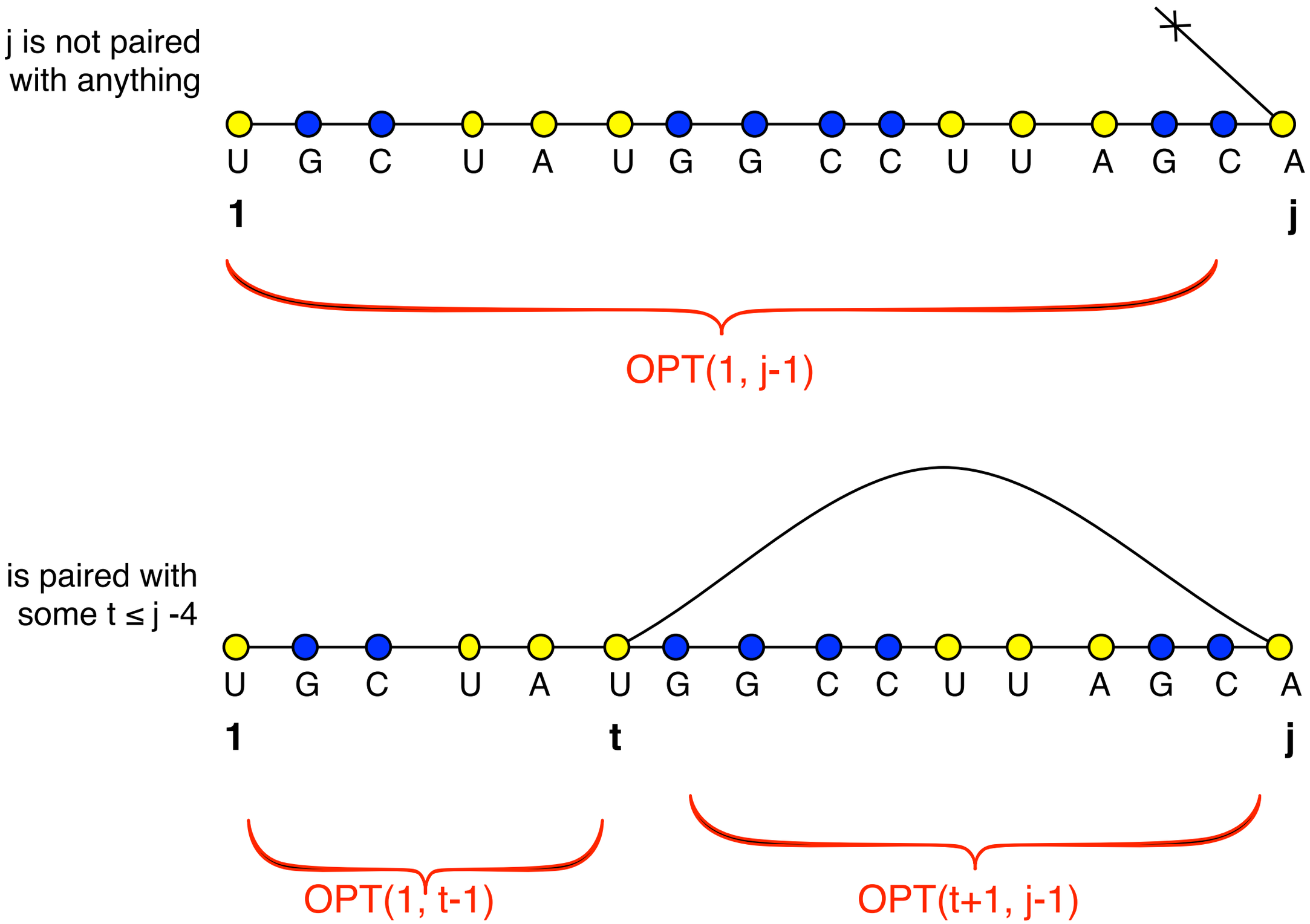
Paired bases have to be **nested.**

RNA Folding

Given: a string $r = b_1 b_2 b_3,\ldots,b_n$ with $b_i \in \{A,C,U,G\}$
Find: the largest set of pairs $S = \{(i,j)\}$, where $i,j \in \{1,2,\ldots,n\}$ that satisfies the RNA folding rules.

Goal: match as many bases as possible.

Subproblems



Recurrence

If $j - i \leq 4$:

$$OPT(i, j) = 0$$

If $j - i > 4$:

$$OPT(i, j) = \max \begin{cases} OPT(i, j-1) \\ \max_t \{1 + OPT(i, t-1) + OPT(t+1, j-1) \end{cases}$$

In the 2nd case above, we try all possible *t* with which to pair *j*.
That is, *t* runs from *i* to *j*-4.

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  for every t between i and j

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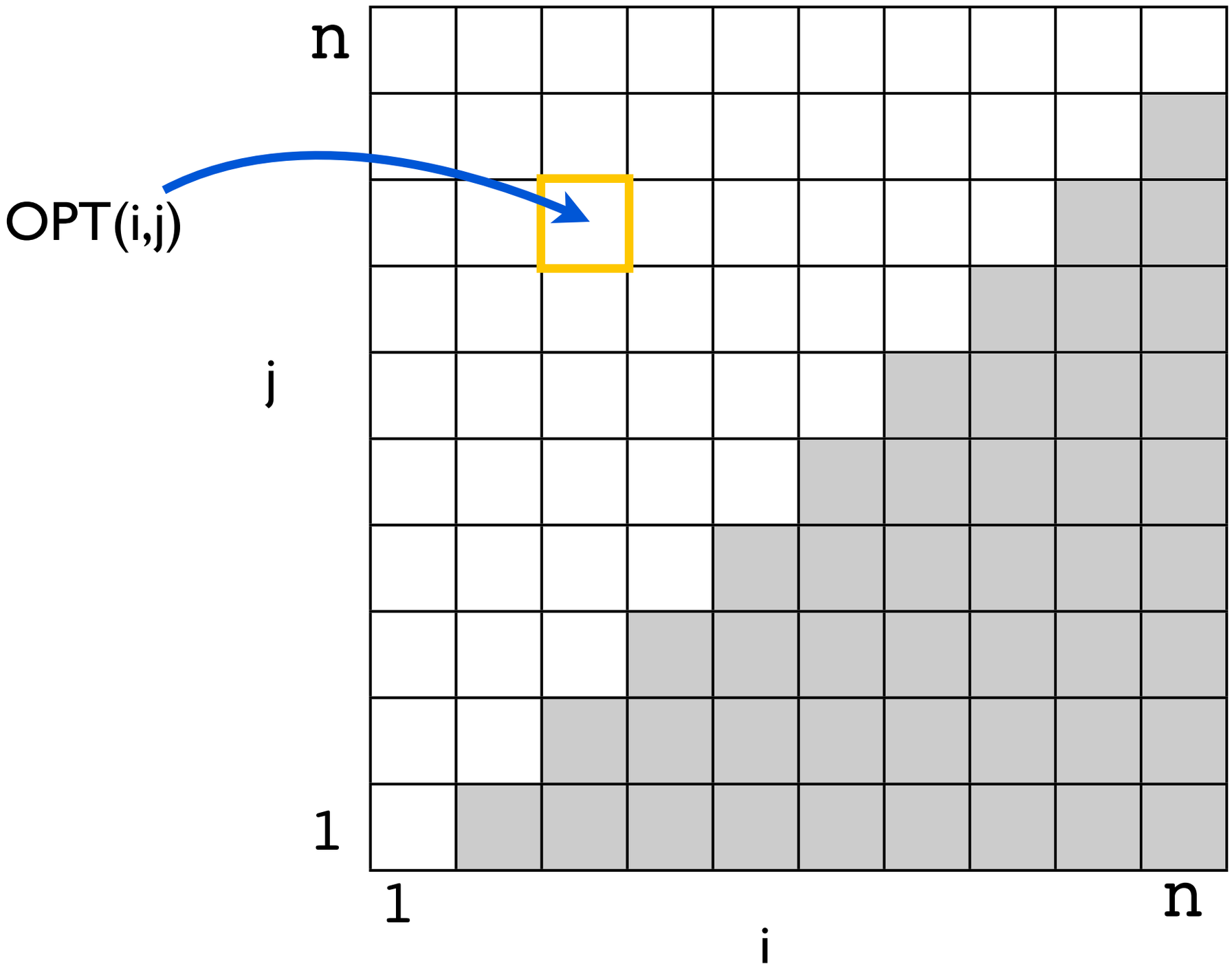
- They involve smaller intervals of the string:

  We solve $OPT(i,j)$ in order of increase value of j - i.

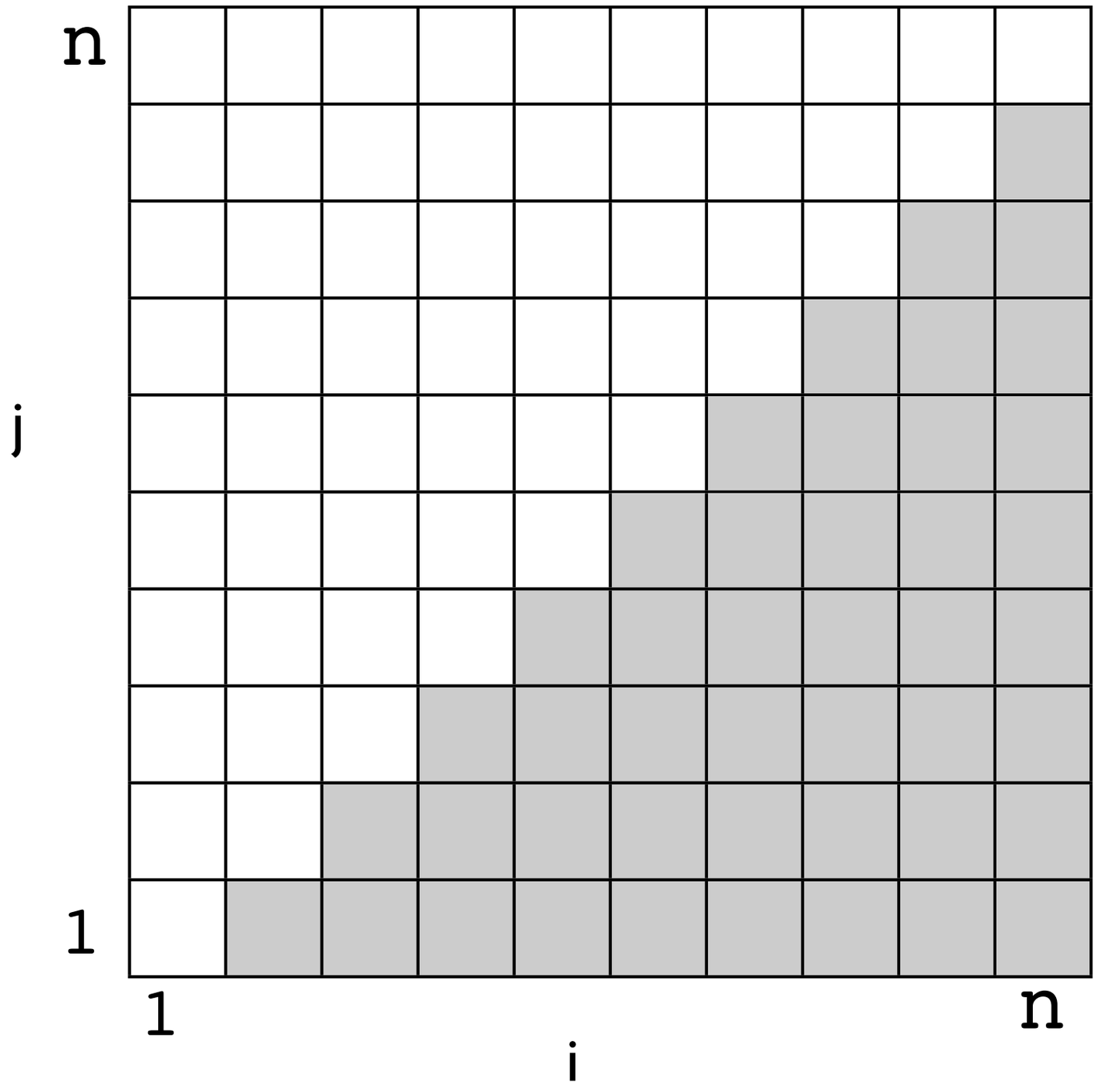
Filling in the matrix

only use half: i < j



Filling in the matrix

in order of increasing j-i



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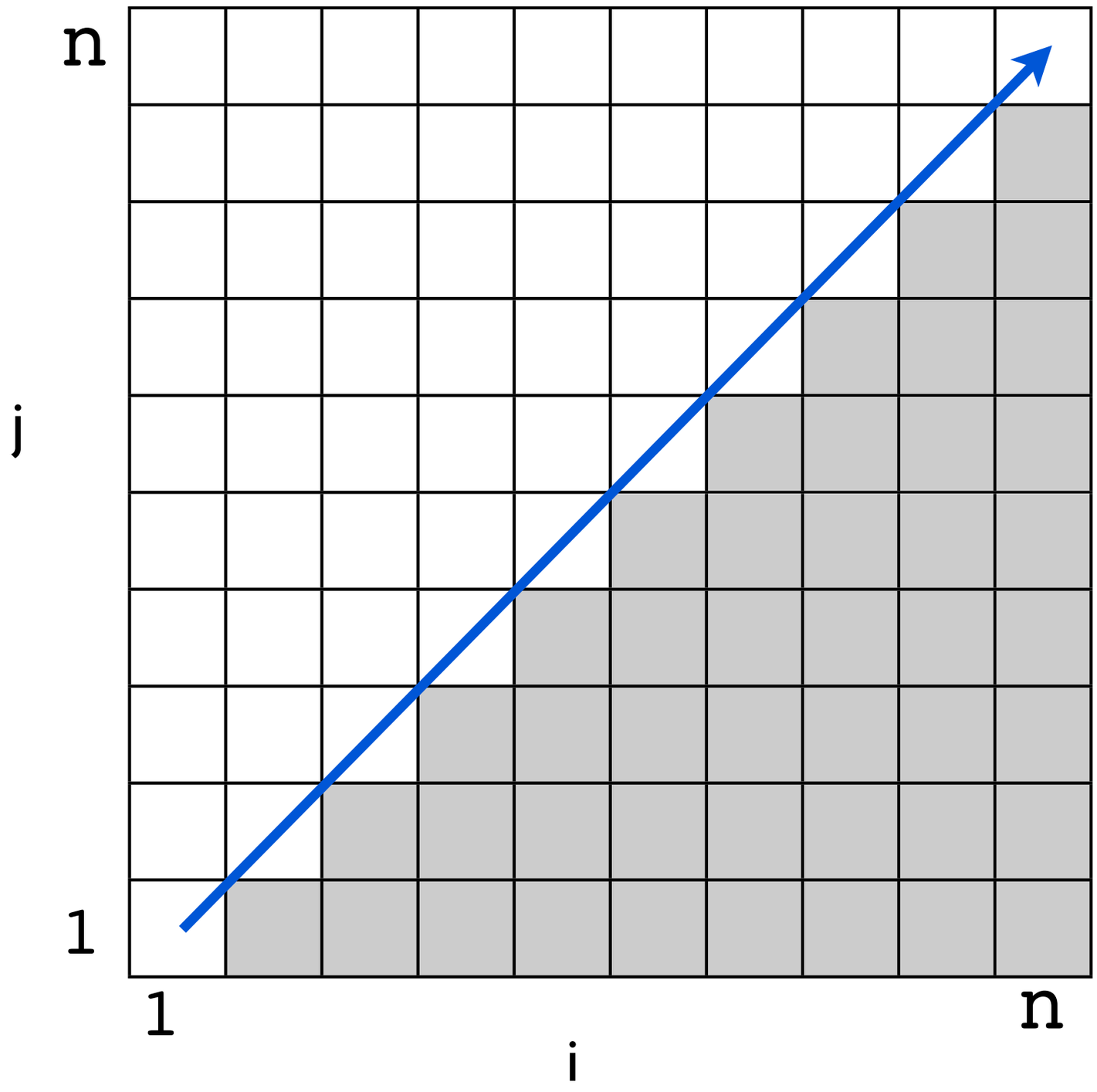

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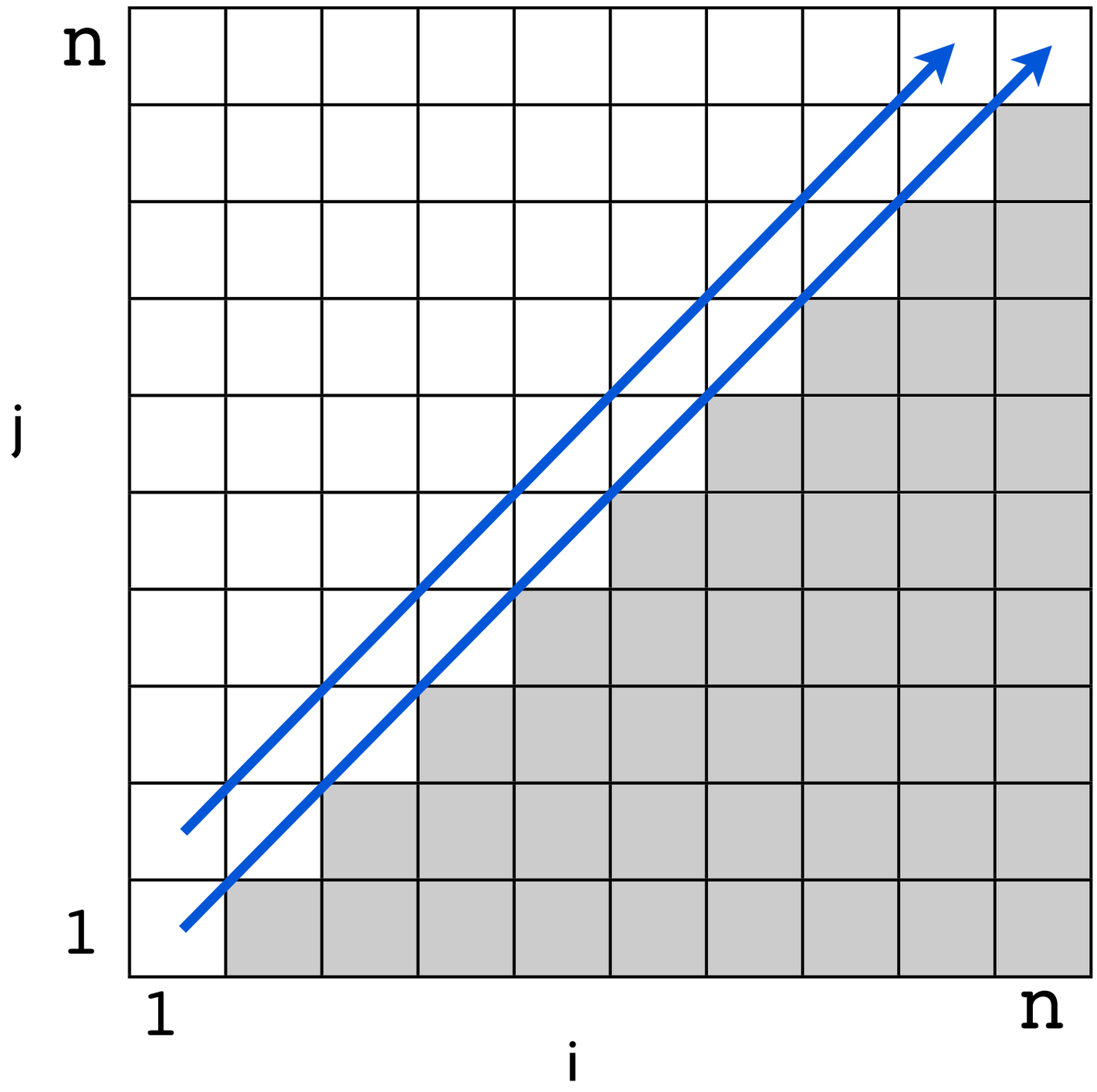

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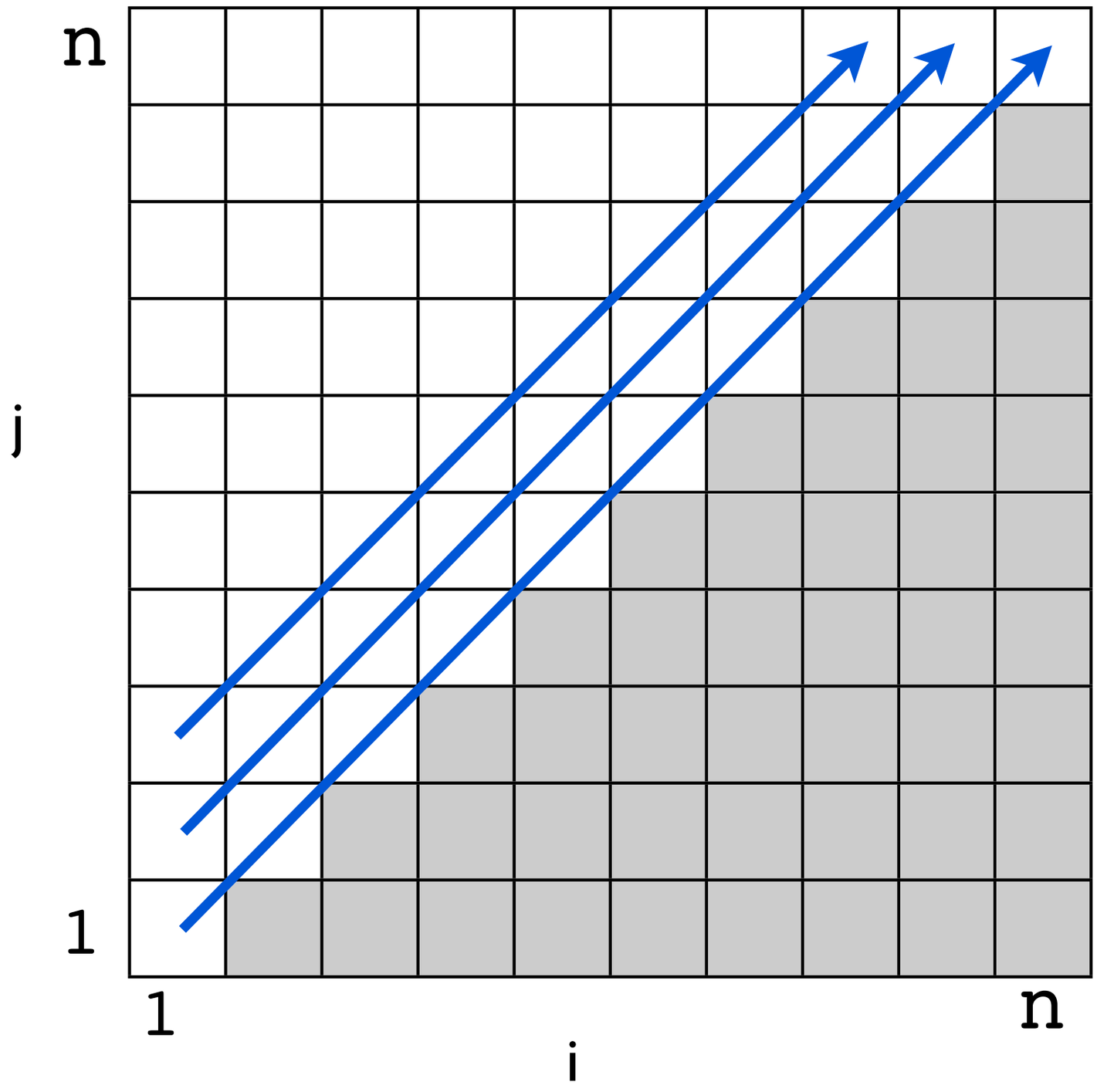

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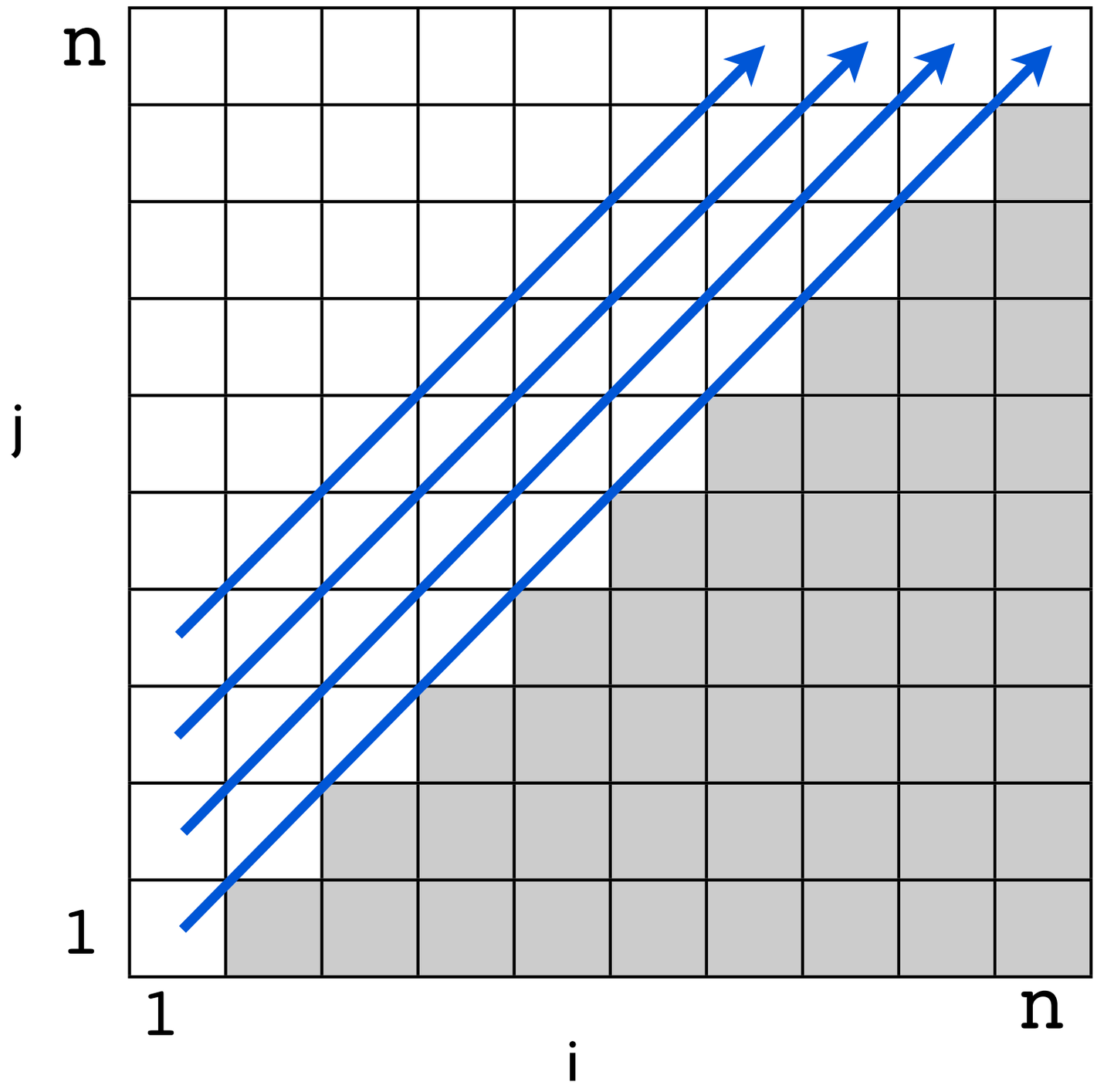
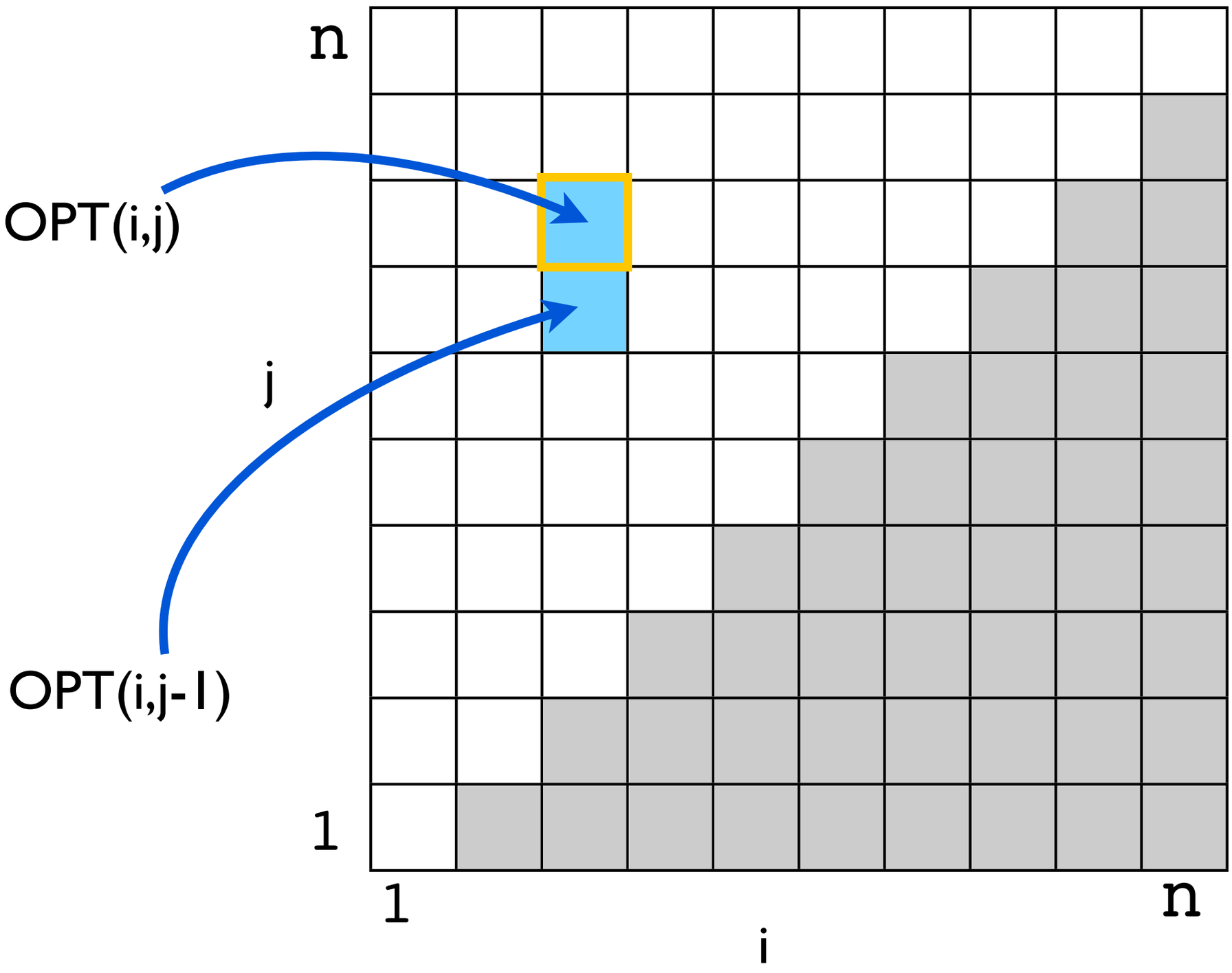


Case 1

$$OPT(i,j) = max \begin{cases} OPT(i,j-1) \\ \dots \end{cases}$$



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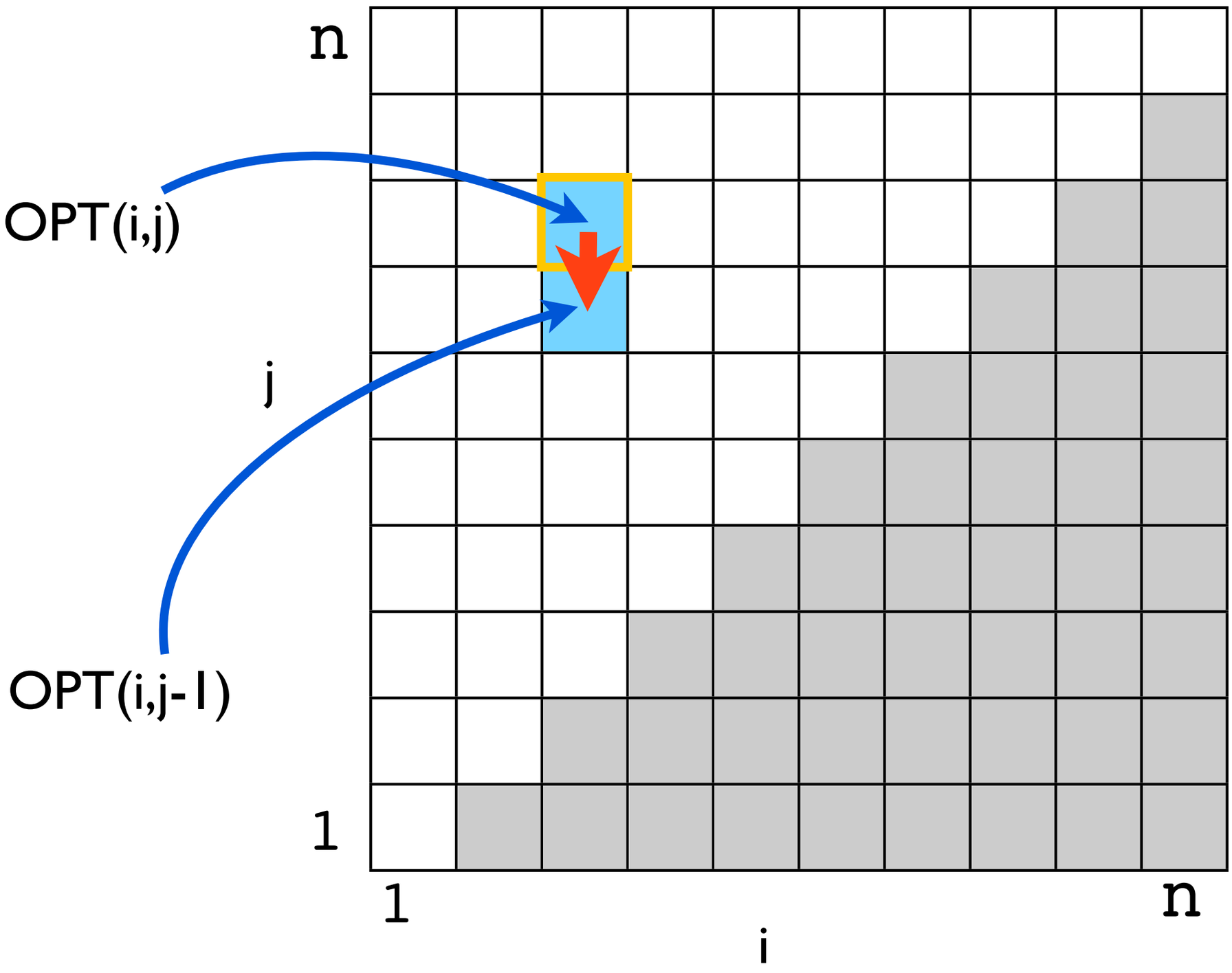
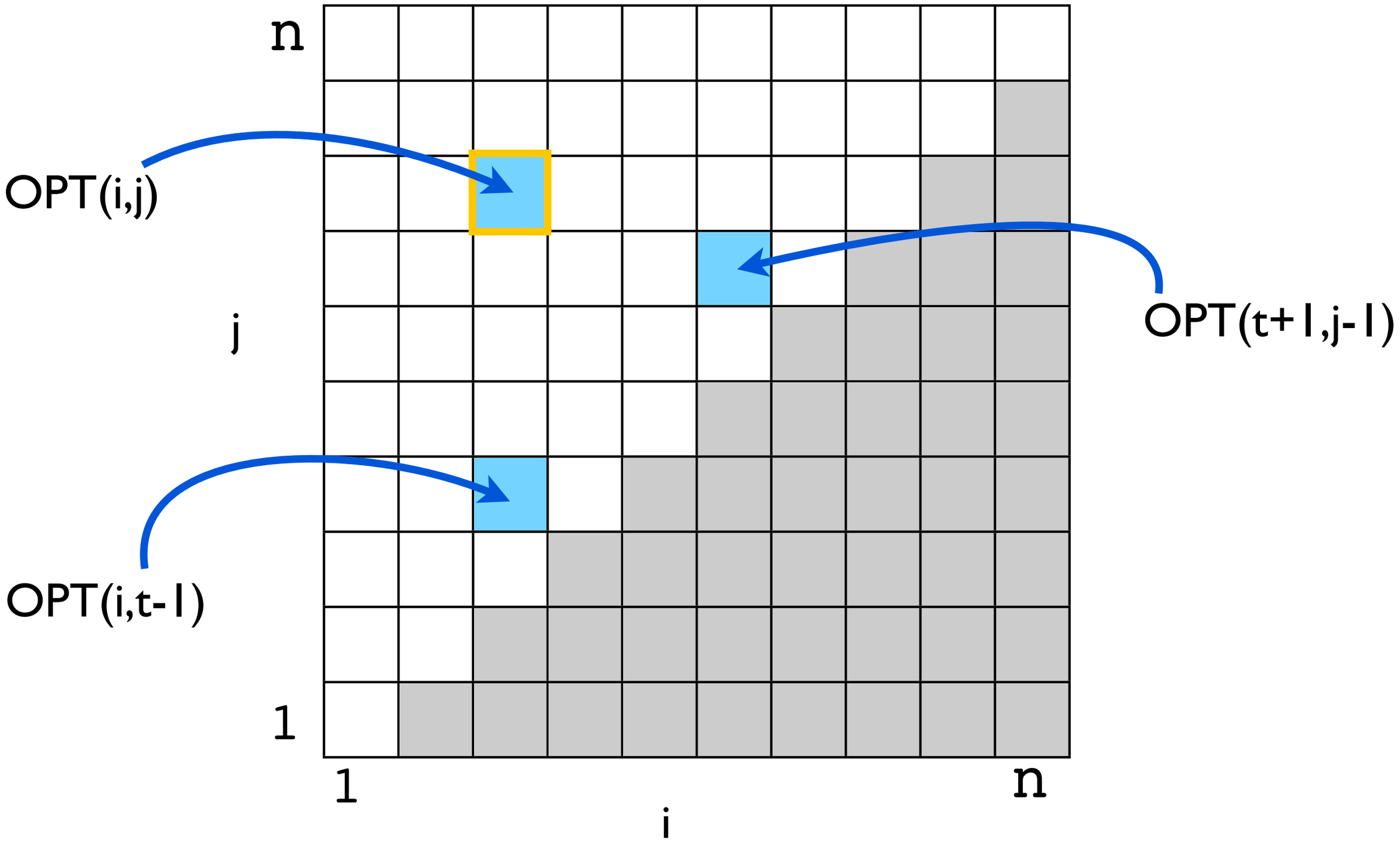


Case 2

$$OPT(i,j) = max \begin{cases} \dots \\ max_t\{1 + OPT(i, t-1) + OPT(t+1, j-1)\} \end{cases}$$



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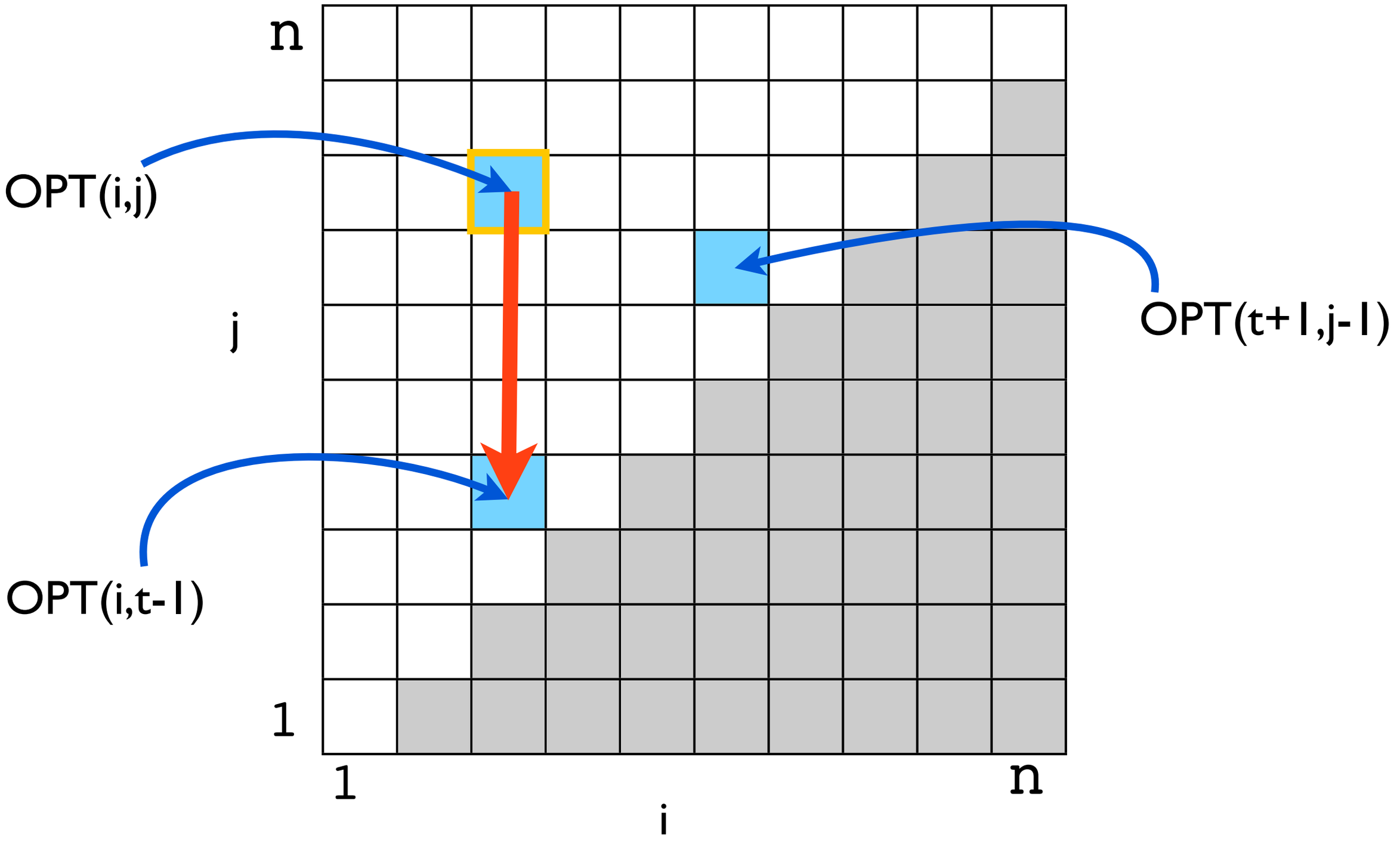

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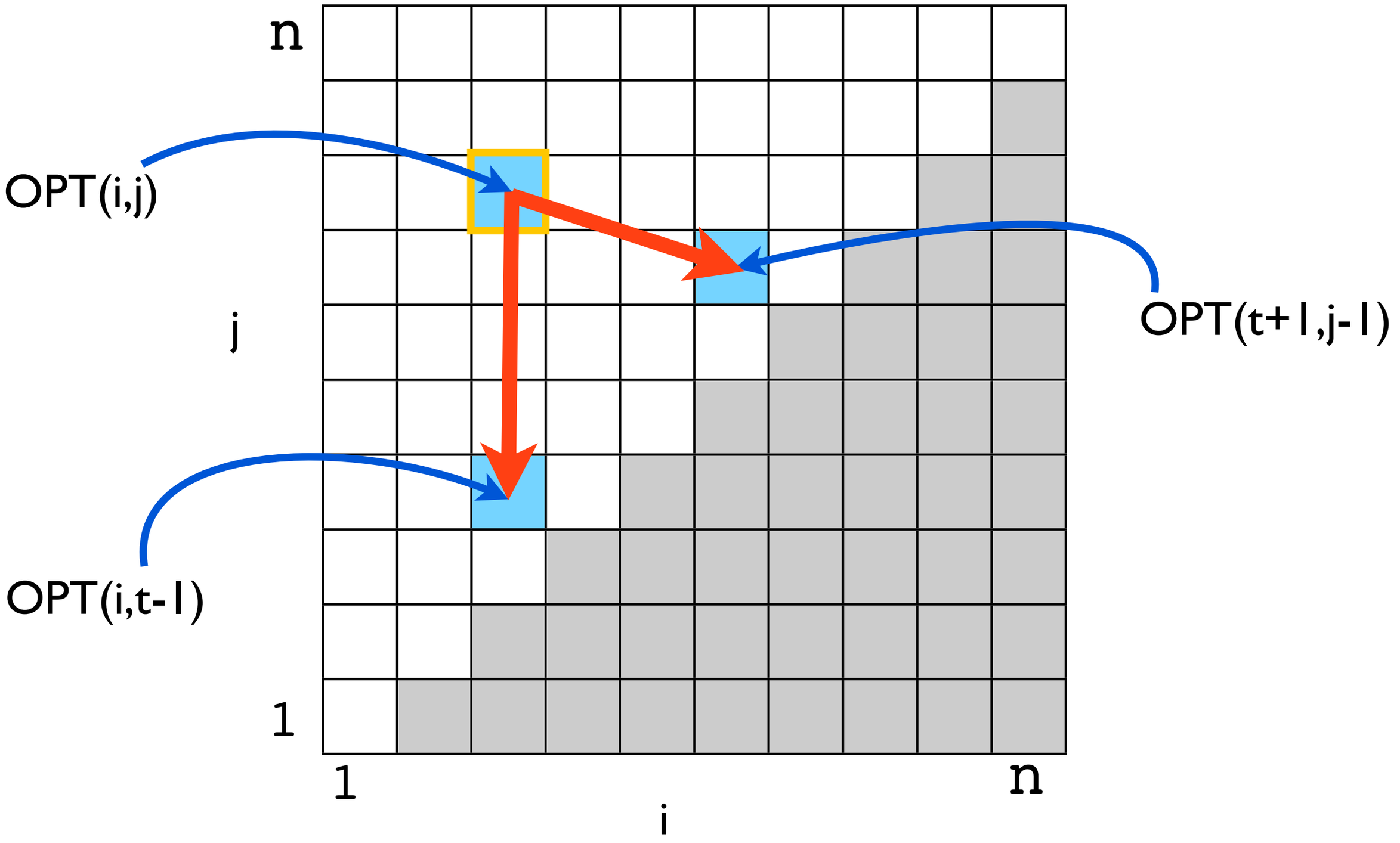

Code

```
def rnafold(rna):
    n = len(rna)
    OPT = make_matrix(n, n)
    Arrows = make_matrix(n, n)
    for k in xrange(5, n):      # interval length
        for i in xrange(n-k):  # interval start
        j = i + k              # interval end
        best_t = OPT[i][j-1]
        arrow = -1
        for t in xrange(i, j):
            if is_complement(rna[t], rna[j]):
                val = 1 + \\
                    (OPT[i][t-1] if t > i else 0) + OPT[t+1][j-1]
                if val >= best_t: best_t, arrow = val, t
        OPT[i][j] = best_t
        Arrows[i][j] = arrow
return OPT, Arrows
```

Backtrace code

```
def rna_backtrace(Arrows):
    Pairs = []  # holds the pairs in the optimal solution
    Stack = [(0, len(Arrows) - 1)]  # tracks cells we have to visit
    while len(Stack) > 0:
        i, j = Stack.pop()
        if j - i <= 4: continue       # if cell is base case, skip it
        # Arrow = -1 means we didn't match j
        if Arrows[i][j] == -1:
            Stack.append((i, j - 1))
        else:
            t = Arrows[i][j]
            Pairs.append((t, j))  # save that j matched with t
            # add the two daughter problems
            if t > i: Stack.append((i, t - 1))
            Stack.append((t + 1, j - 1))
return Pairs
```

Subproblems, 2

- We have a subproblem for every interval (*i*,*j*)
- How many subproblems are there?

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$$\binom{n}{2} = O(n^2)$$

Running Time

- $O(n^2)$ subproblems
- Each takes $O(n)$ time to solve
  (have to search over all possible choices of t)
- Total running time is $O(n^3)$.

Summary

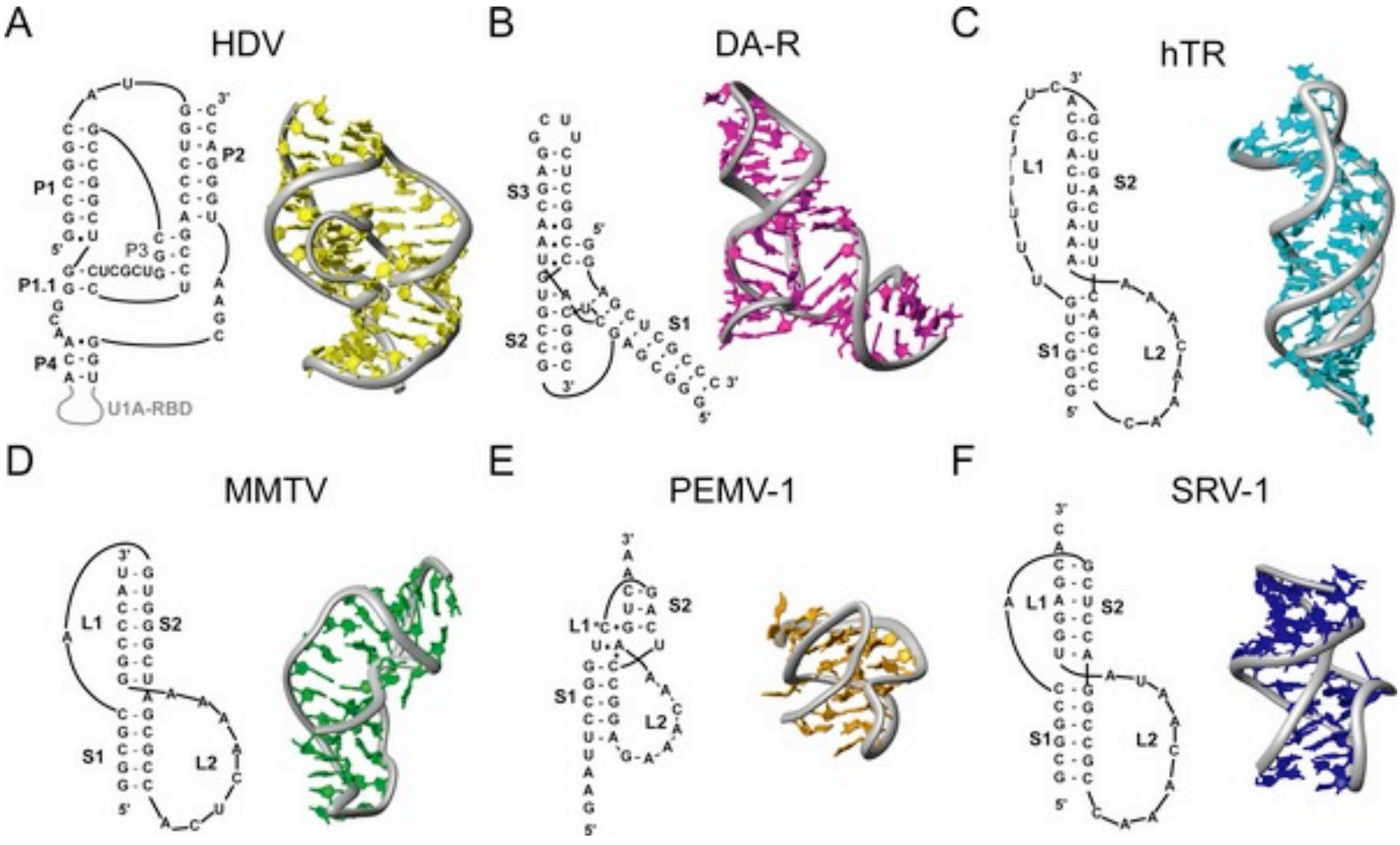
- This is essentially "Nussinov's algorithm," which was proposed for finding RNA structures in 1978.

- Same dynamic programming idea: write the answer to the full problem in terms of the answer to smaller problems.

- Still have an $O(n^2)$ matrix to fill.

- Main differences from sequence alignment:
  - We fill in the matrix in a different order: entries (i,j) in order of increasing $j - i$.
  - We have to try $O(n)$ possible subproblems inside the max. This leads to an $O(n^3)$ algorithm.

Pseudoknots



(Staple & Butcher, PLoS Biol, 2005)