Gap Penalties

CMSC 423

General Gap Penalties

```
AAAGAATTCA          AAAGAATTCA
A-A-A-T-CA    vs.   AAA----TCA
```

These have the same score, but the second one is often more plausible.

A single insertion of "GAAT" into the first string could change it into the second.

- Now, the cost of a run of k gaps is $gap \times k$
- It might be more realistic to support general gap penalty, so that the score of a run of k gaps is $\mathbf{gap}(k) < gap \times k$.
- Then, the optimization will prefer to group gaps together.

General Gap Penalties

```
AAAGAATTCA          AAAGAATTCA
A-A-A-T-CA   vs.    AAA----TCA
```

Previous DP no longer works with general gap penalties because the score of the last character depends on details of the previous alignment:

```
AAAGAAC            AAAGAATC
AAA----    vs.     AAA-----
```

Instead, we need to "know" how long a final run of gaps is in order to give a score to the last subproblem.

Three Matrices

We now keep 3 different matrices:

M[i,j] = score of best alignment of x[1..i] and y[1..j] ending with a character-character **match or mismatch**.

X[i,j] = score of best alignment of x[1..i] and y[1..j] ending with a **space in X**.

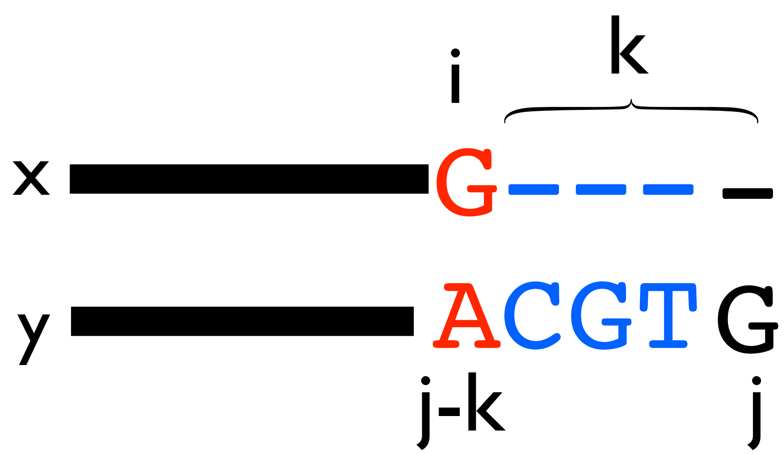
Y[i,j] = score of best alignment of x[1..i] and y[1..j] ending with a **space in Y**.

$$M[i,j] = \max \begin{cases} X[i,j] \\ M[i-1,j-1] + \mathrm{SCORE}(x[i],y[j]) \\ Y[i,j] \end{cases}$$

$$X[i,j] = \max \begin{cases} Y[i,j-k] - gap(k) \\ M[i,j-k] - gap(k) \end{cases}$$

$$Y[i,j] = \max \begin{cases} X[i-k,j] - gap(k) \\ M[i-k,j] - gap(k) \end{cases}$$

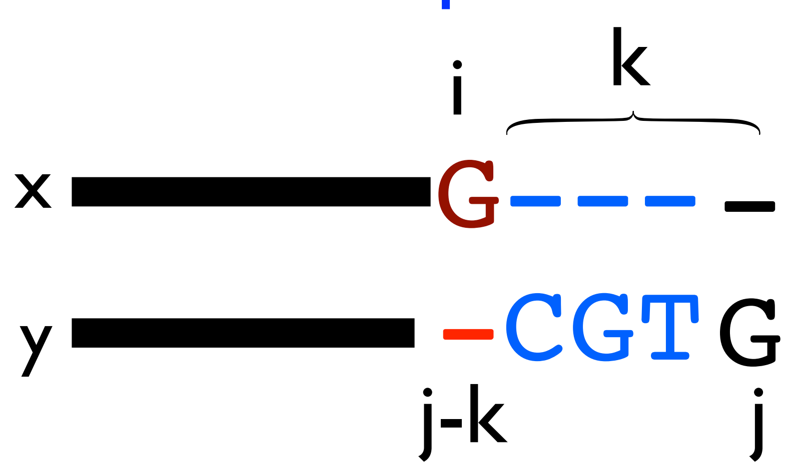
The X (and Y) matrices



k decides how long to make the gap.

We have to make the whole gap at once in order to know how to score it.

$$X[i,j] = \max \begin{cases} M[i, j-k] - \text{gap}(k) & \text{for } 1 \leq k \leq j \\ Y[i, j-k] - \text{gap}(k) & \text{for } 1 \leq k \leq j \end{cases}$$



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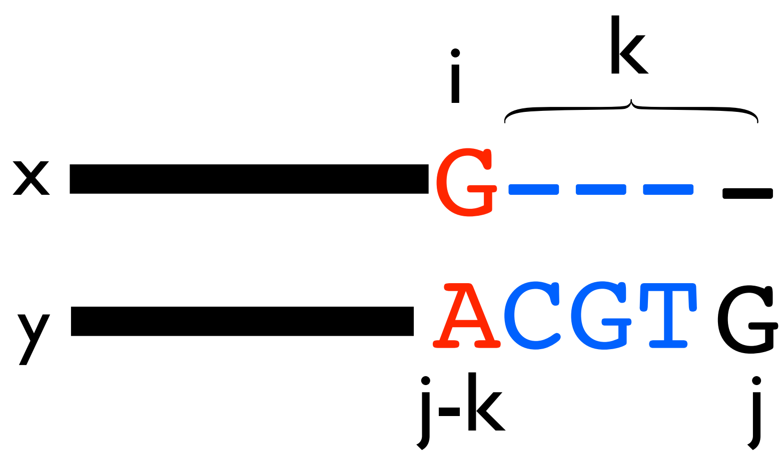

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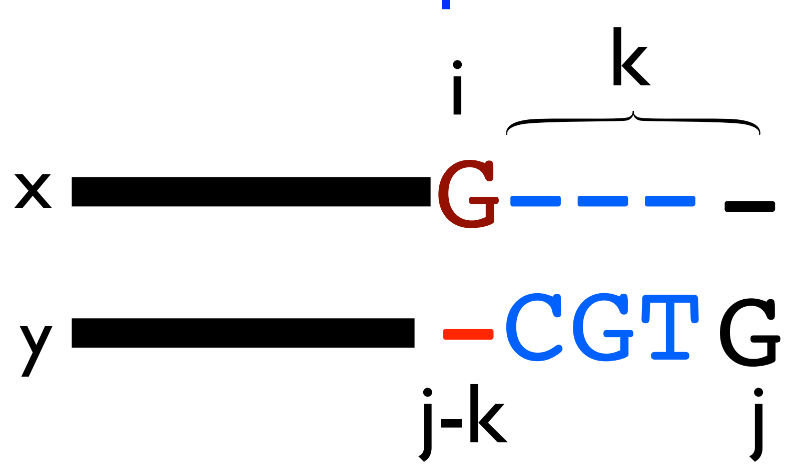
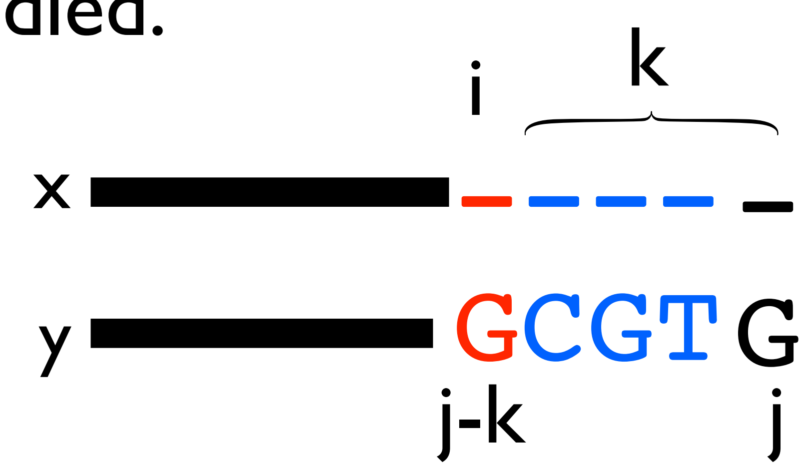


This case is automatically handled.



The M Matrix

We now keep 3 different matrices:

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Y[i,j] = score of best alignment of x[1..i] and y[1..j] ending with a **space in Y**.

$$M[i,j] = \max \begin{cases} X[i,j] \\ M[i-1,j-1] + \mathrm{SCORE}(x[i],y[j]) \\ Y[i,j] \end{cases}$$

Gaps start and end in the *M* matrix.

Running Time for Gap Penalties

$$M[i,j] = \max \begin{cases} X[i,j] \\ M[i-1,j-1] + \mathrm{SCORE}(x[i],y[j]) \\ Y[i,j] \end{cases}$$

$$X[i,j] = \max \begin{cases} Y[i,j-k] - gap(k) \\ M[i,j-k] - gap(k) \end{cases}$$

$$Y[i,j] = \max \begin{cases} X[i-k,j] - gap(k) \\ M[i-k,j] - gap(k) \end{cases}$$

Final score is max {M[n,m], X[n,m], Y[n,m]}.

How do you do the traceback?

Runtime:

- Assume |X| = |Y| = n for simplicity: $3n^2$ subproblems
- $2n^2$ subproblems take O(n) time to solve (because we have to try all k)

$\Rightarrow$ O(n^3) total time

Affine Gap Penalties

- $O(n^3)$ for general gap penalties is usually too slow...

- We can still encourage spaces to group together using a special case of general penalties called *affine gap penalties*:

  gap_start = the cost of starting a gap

  gap_extend = the cost of extending a gap by one more space

- Same idea of using 3 matrices, but now we don't need to search over all gap lengths, we just have to know whether we are starting a new gap or not.

$$gap(k) = -(\sigma + (k-1) * \epsilon)$$

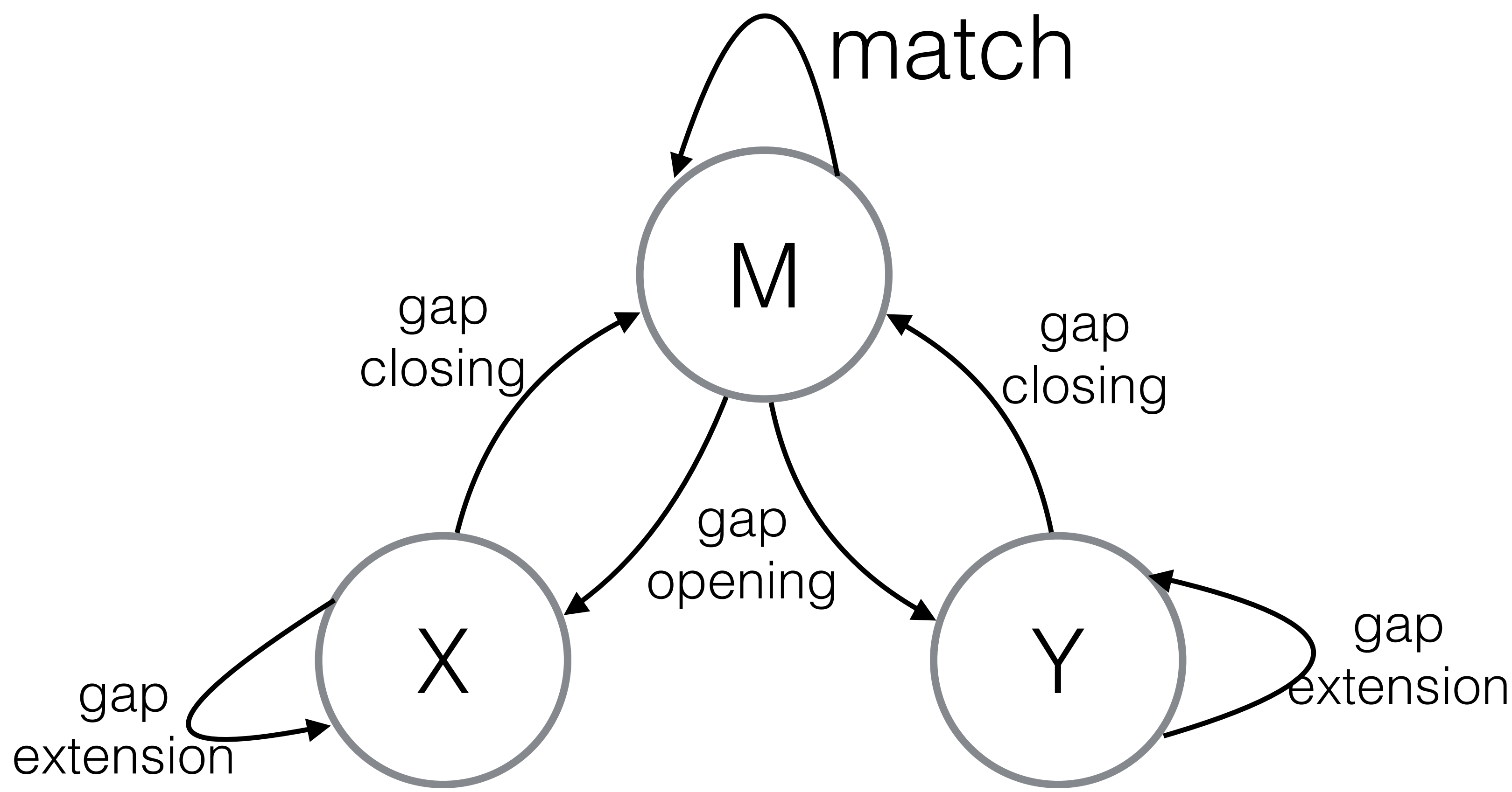
Affine Gap Penalties

$$M[i,j] = \max \begin{cases} X[i,j] & \text{gap closing} \\ M[i,j] + \mathrm{SCORE}(x[i], y[j]) \\ Y[i,j] \end{cases}$$

$$X[i,j] = \begin{cases} X[i,j-1] - \epsilon & \text{gap extension} \\ M[i,j-1] - \sigma & \text{gap opening} \end{cases}$$

$$Y[i,j] = \begin{cases} Y[i-1,j] - \epsilon \\ M[i-1,j] - \sigma \end{cases}$$

Affine gap algorithm as a finite state machine



Affine Gap Runtime

- 3*mn* subproblems
- Each one takes constant time
- Total runtime O(*mn*):
    - back to the run time of the basic running time.

Traceback

- Arrows now can point between matrices.
- The possible arrows are given, as usual, by the recurrence.
    - E.g. What arrows are possible leaving a cell in the M matrix?

Recap

- Local alignment: extra "0" case.
- General gap penalties require 3 matrices and O(n^3) time.
- Affine gap penalties require 3 matrices, but only O(n^2) time.

Global Alignment in Linear Space

- Algorithm by Hirschberg (1975): http://dl.acm.org/citation.cfm?doid=360825.360861
- Recall: Dynamic programming algorithms discussed so have $O(nm)$ time and space complexity
- Key idea:
  - We can get the optimal alignment *score* in space $O(n)$.
  - Can we *reconstruct* the optimal alignment in space $O(n)$?

Global Alignment in Linear Space

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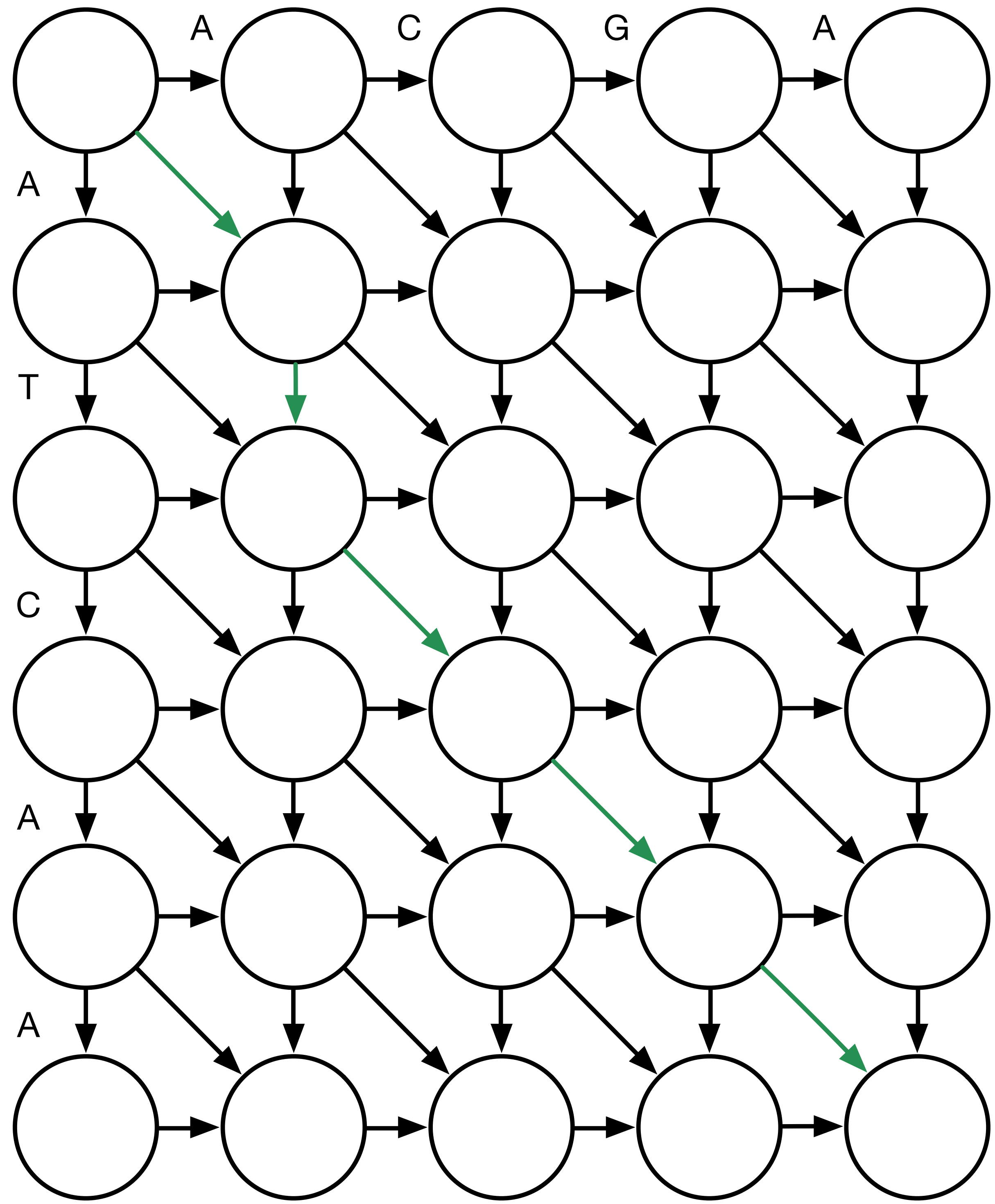
- Recall: Dynamic programming algorithms discussed so have *O(nm)* time and space complexity

- Key idea:

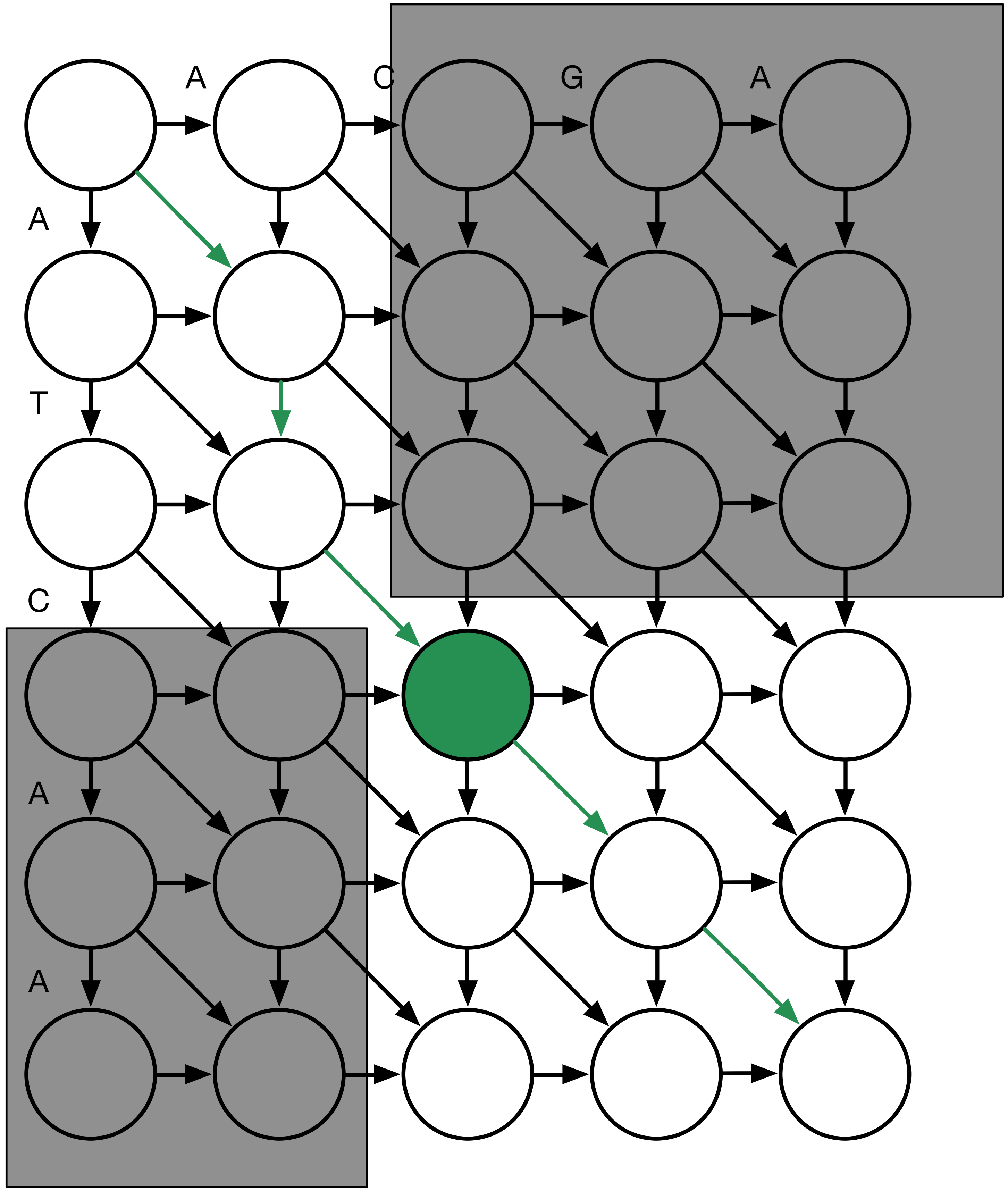
  - We can get the optimal alignment *score* in space *O(n).*

  - Can we *reconstruct* the optimal alignment in space *O(n)*?

    - Use recursion (divide and conquer) to do reconstruction.



A
C
G
A
A
T
C
A
A


A
C
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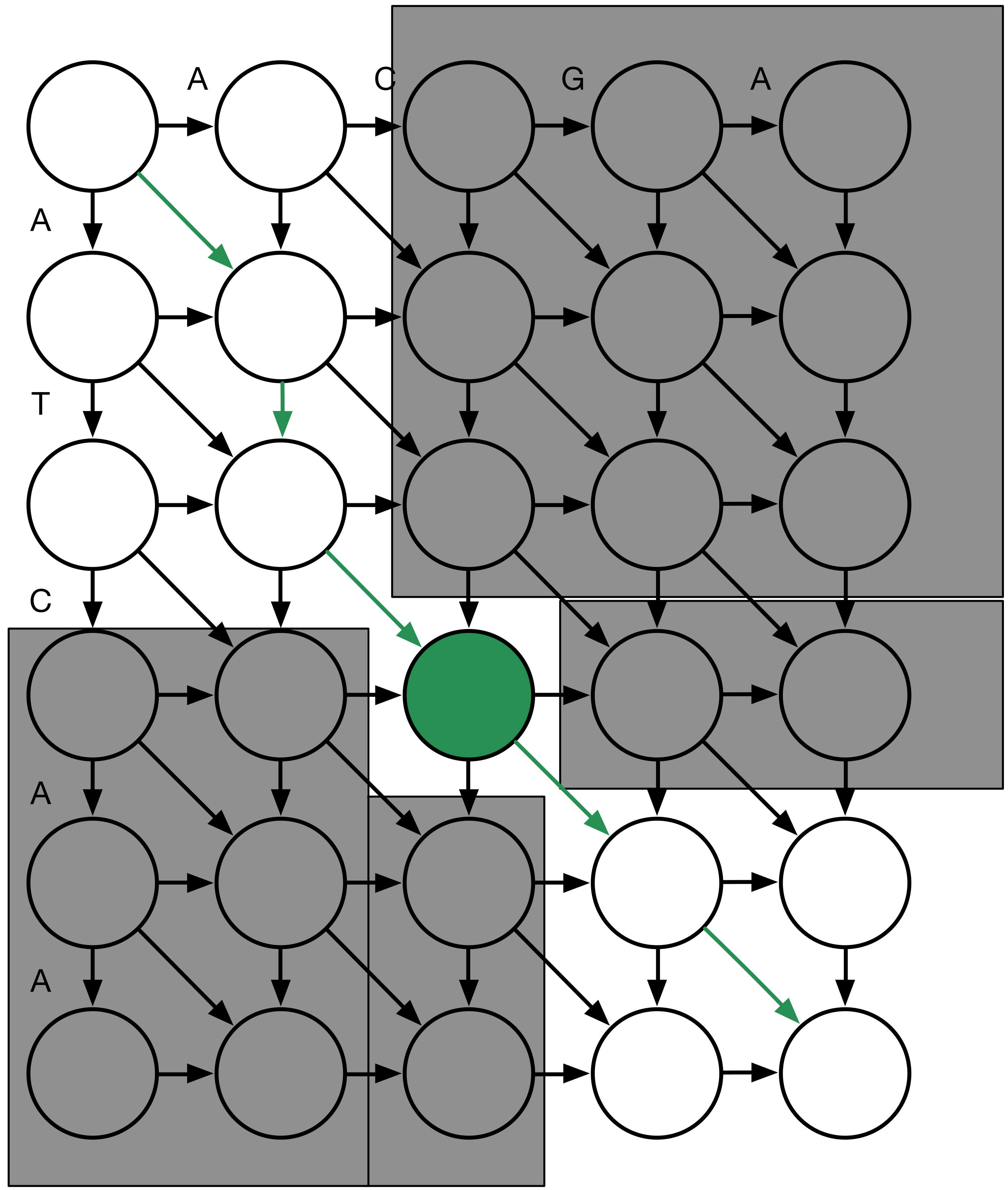
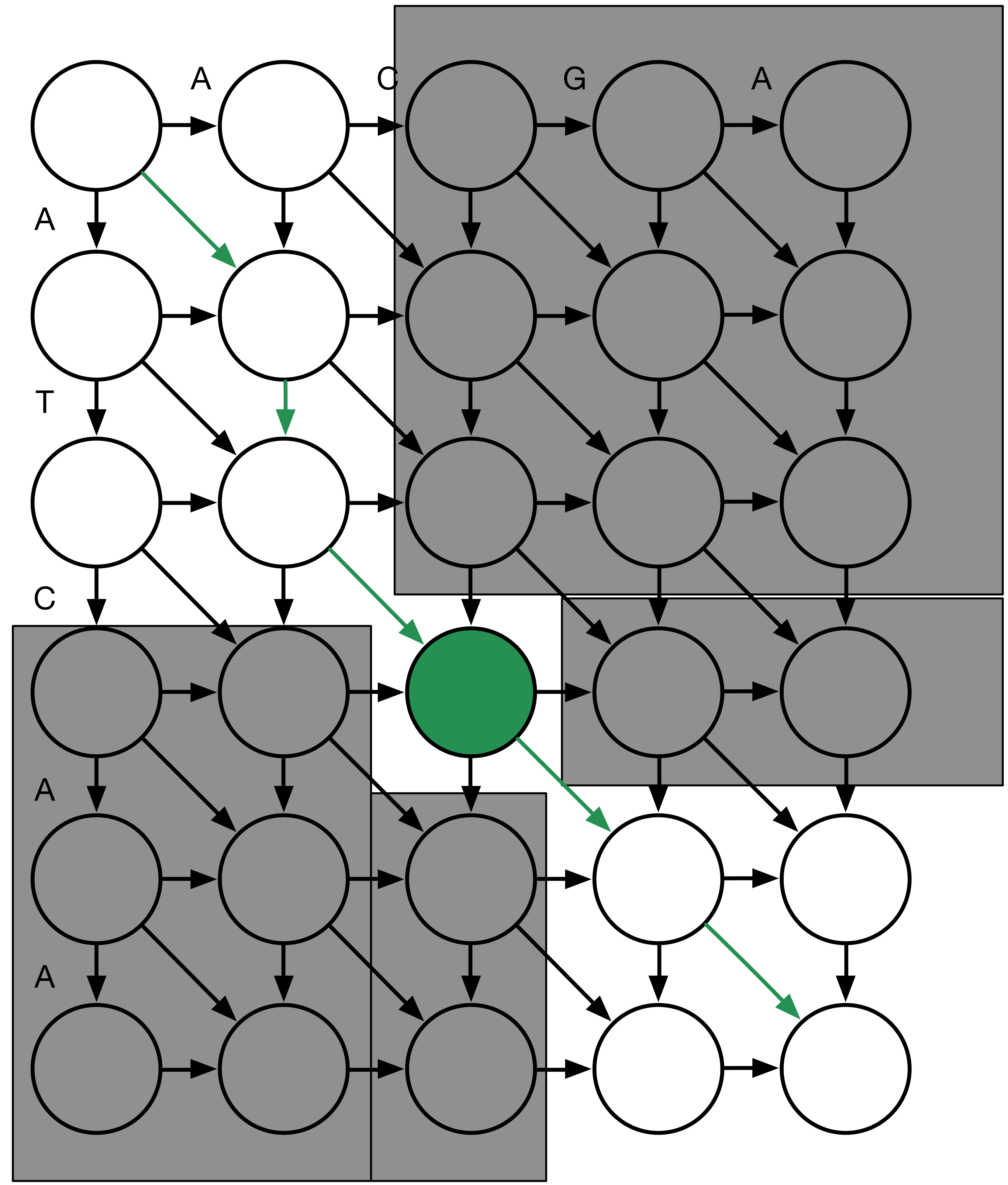
A


A
C
G
A
A
T
C
A
A

Score:
```
ATCAA
A-CGA
```
= Score:
```
ATC
A-C
```
+ Score:
```
AA
GA
```

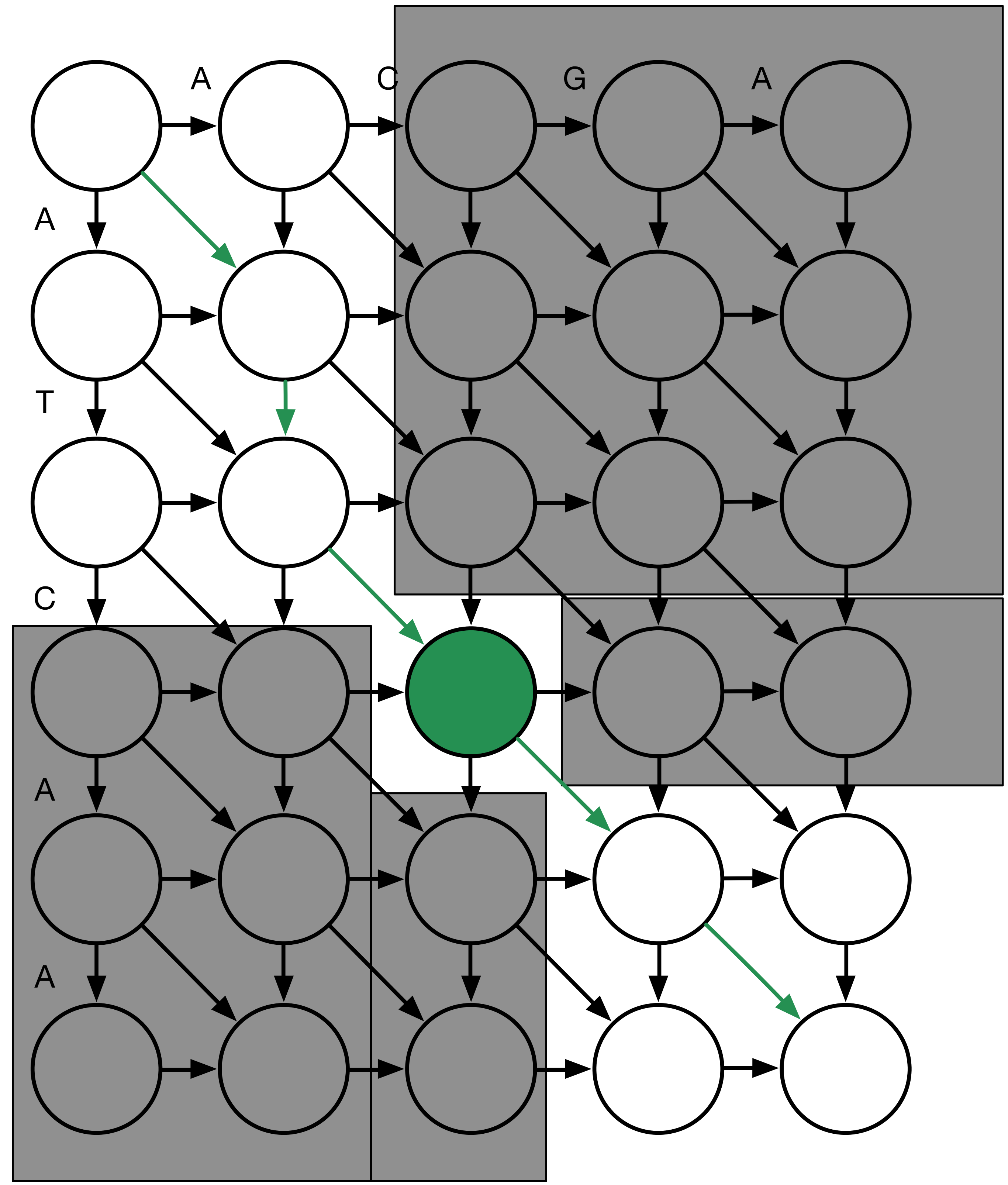
Assuming we know that optimal alignment goes through this node



Generally:

$$\mathrm{SCORE}(x_{0n}, y_{0m}) = \max_t \left[\mathrm{SCORE}(x_{0t}, y_{0\frac{m}{2}}) + \mathrm{SCORE}(x_{tn}, y_{\frac{m}{2}m})\right]$$

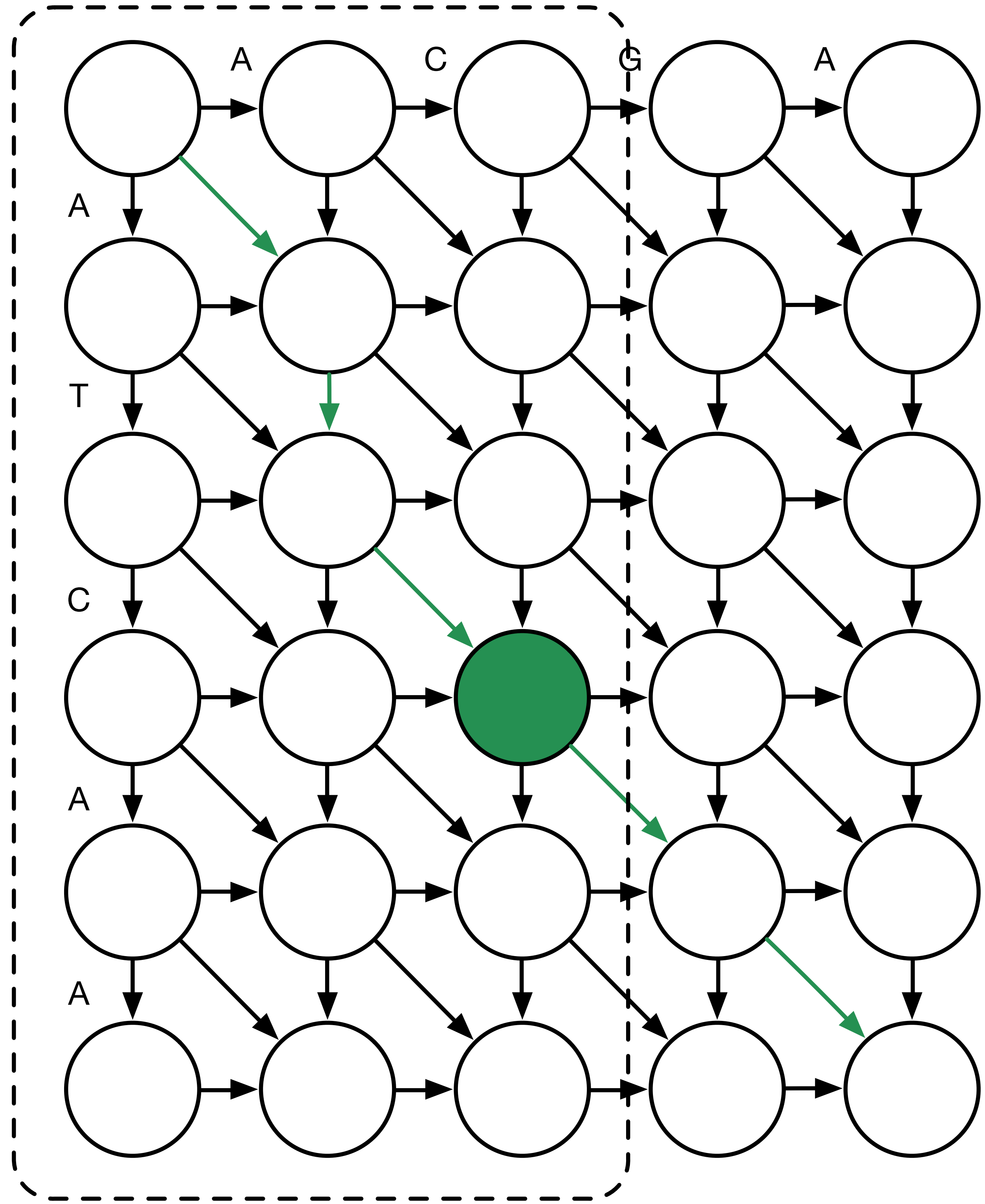
x_{ij}: substring starting at position *i* ending at position *j*



We know how to calculate first term, what about second term?

$$s_{n,m} = \max_t \left[s_{t,\frac{m}{2}} + \mathrm{SCORE}(x_{tn}, y_{\frac{m}{2}m}) \right]$$

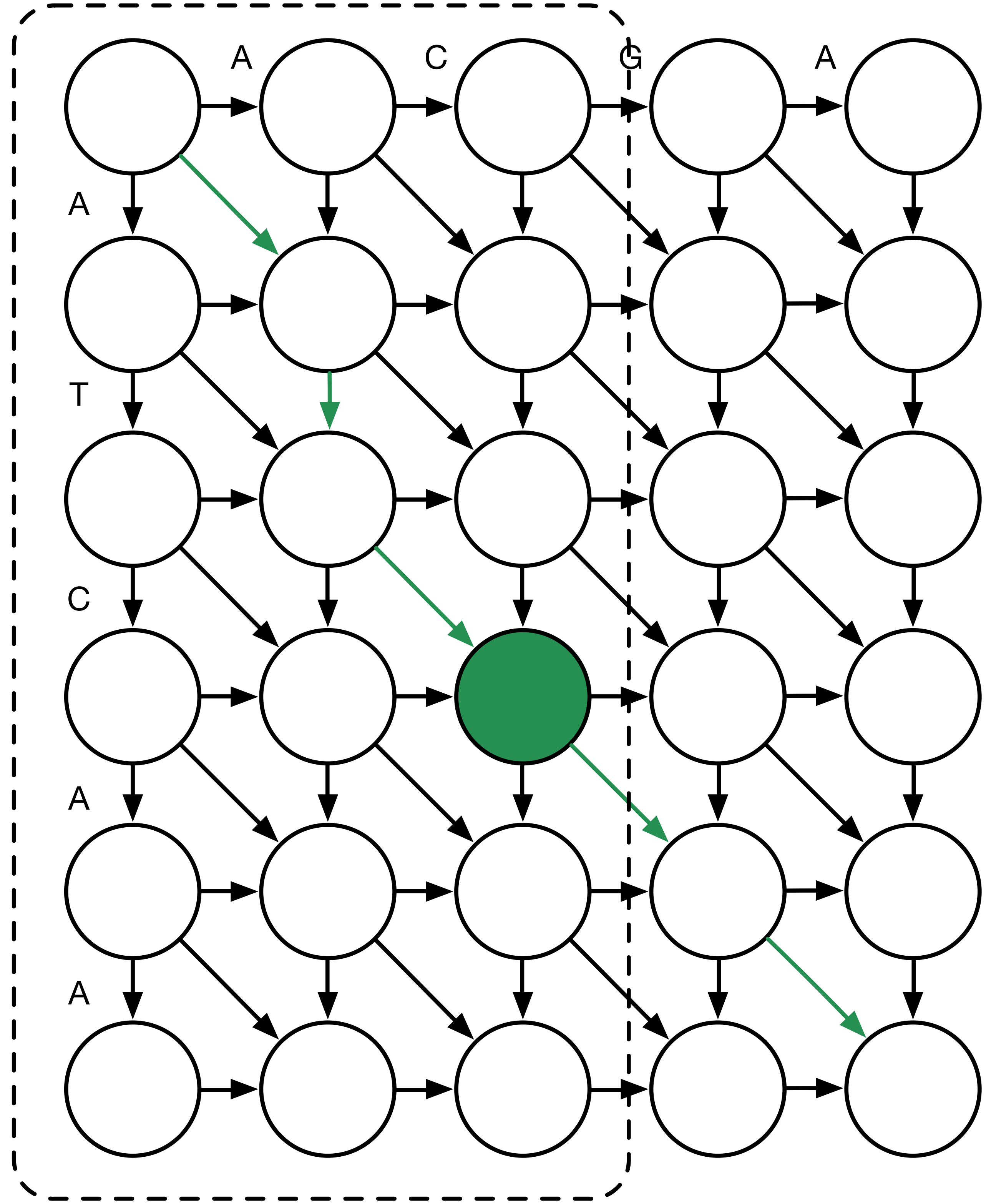
x_{ij}: substring starting at position *i* ending at position *j*

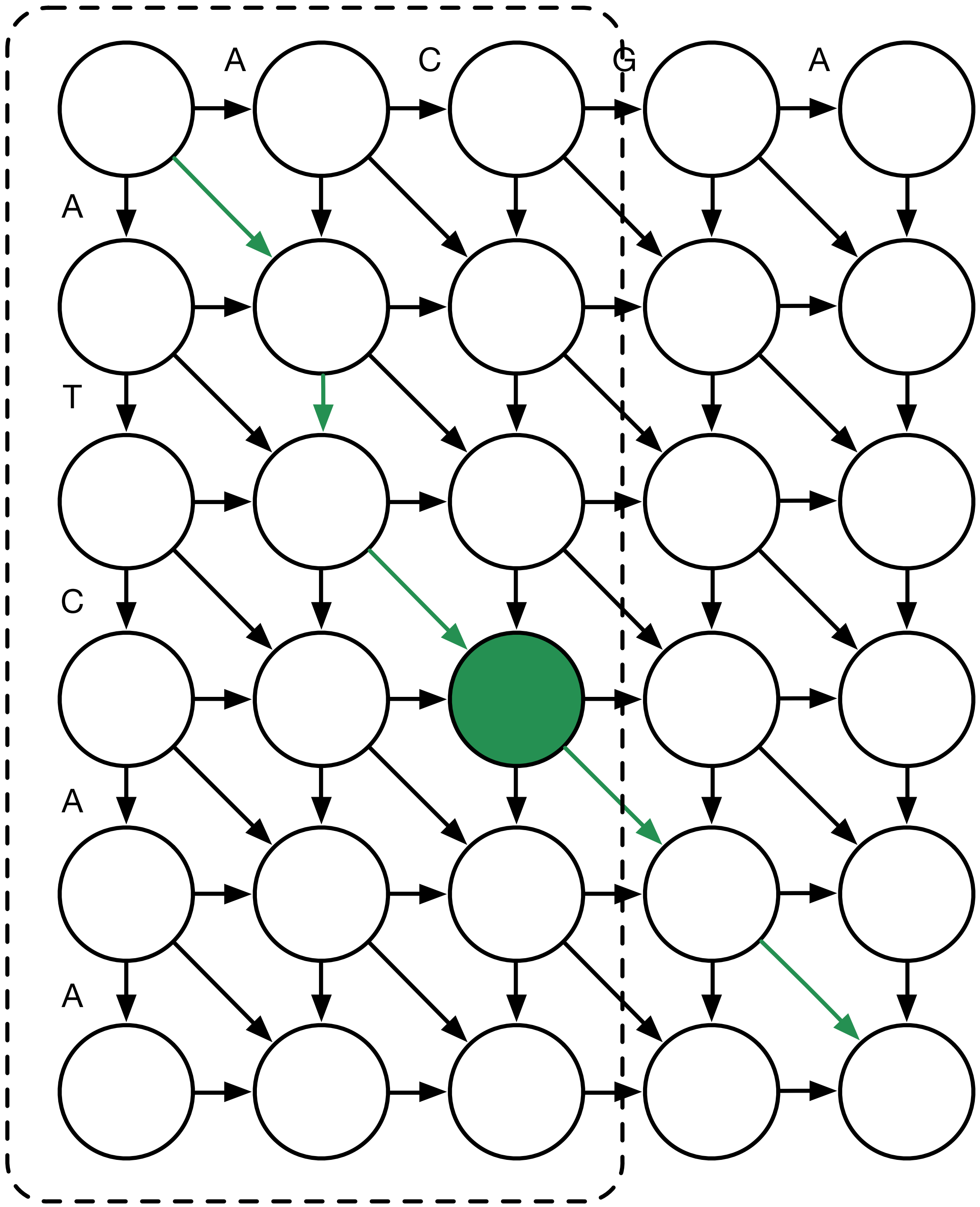


We know how to
calculate first term,
what about second term?

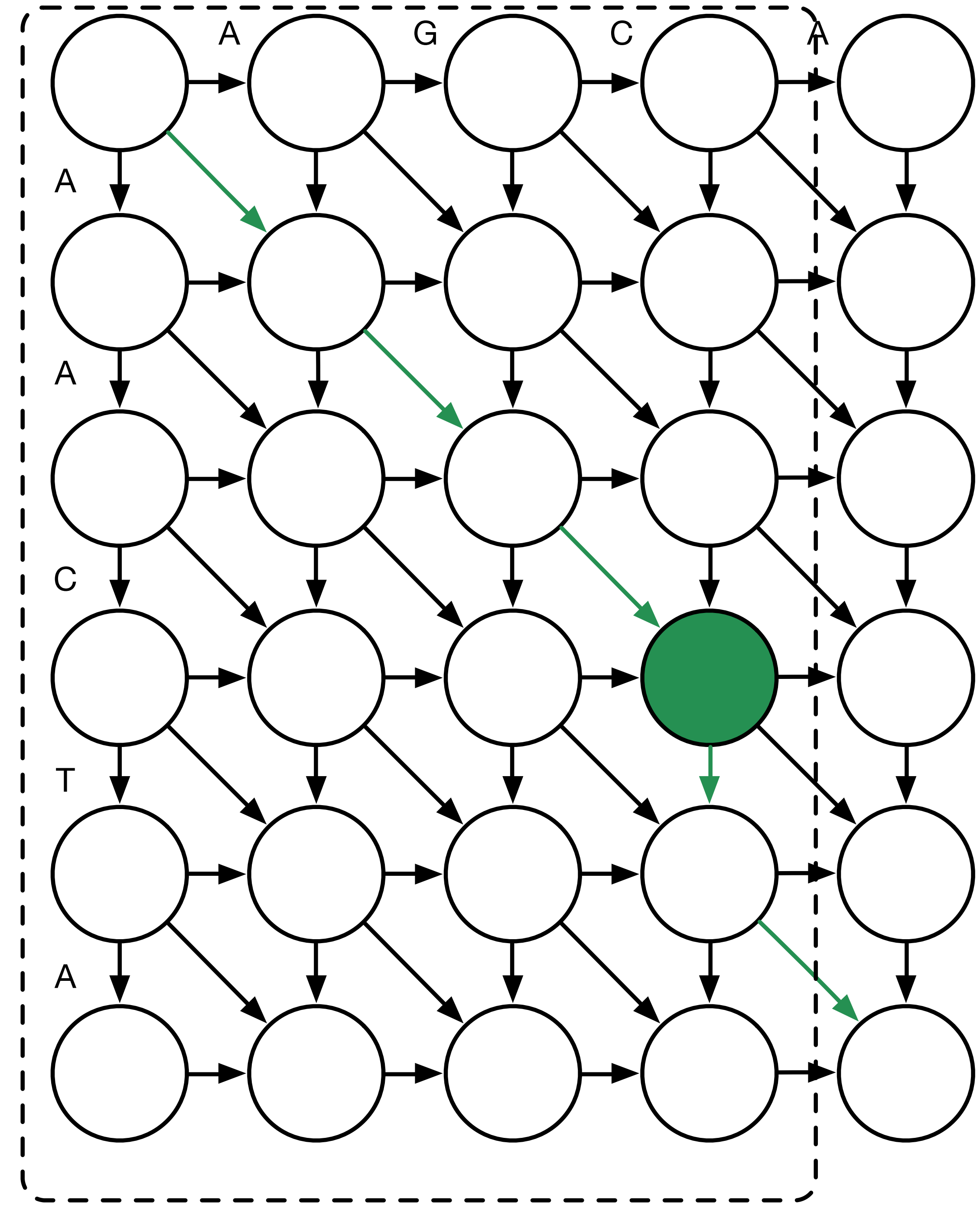
Score is invariant
to string reversal:

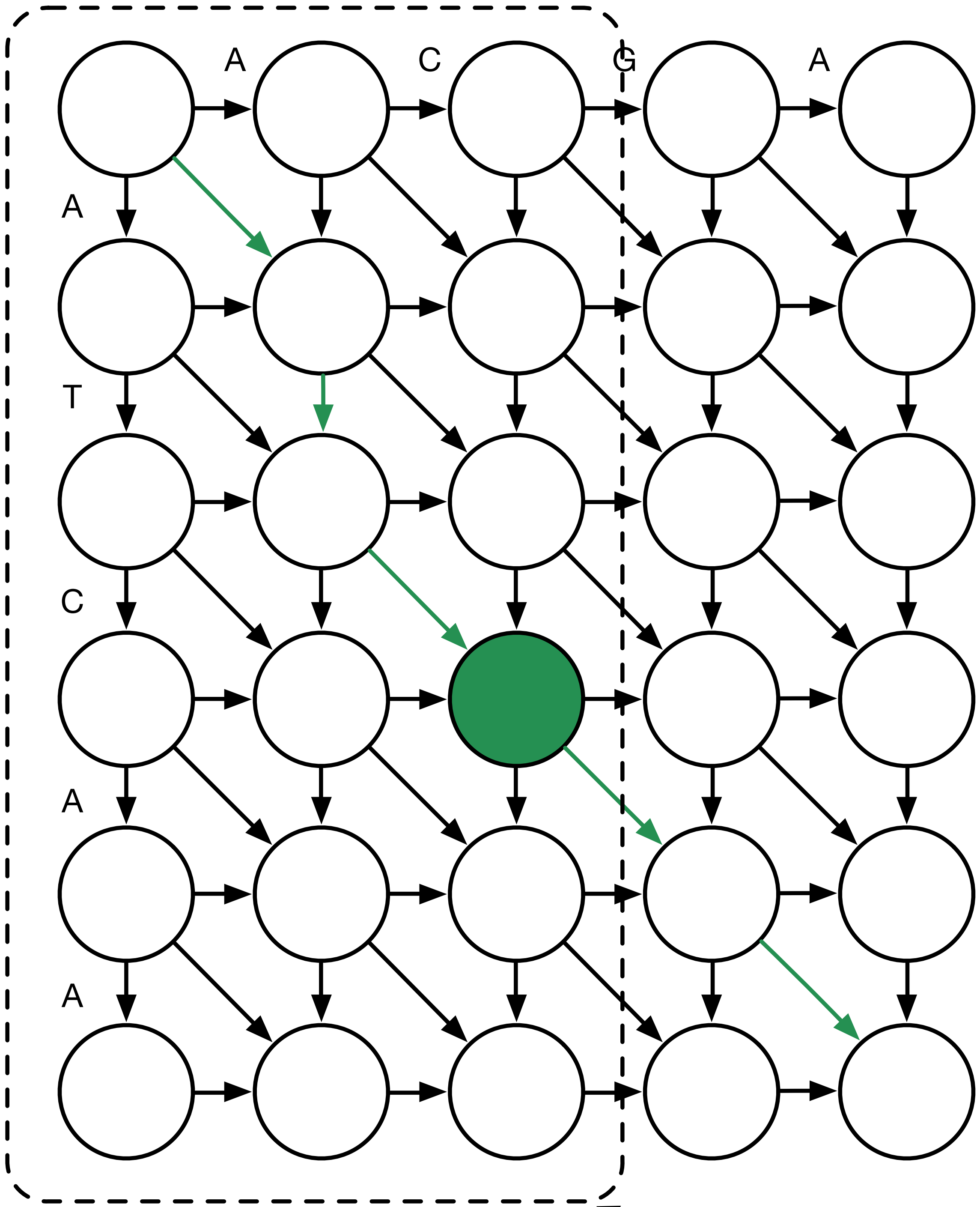
$$\mathrm{SCORE}(x_{ij}, y_{kl}) = \mathrm{SCORE}(x_{ji}, y_{lk})$$



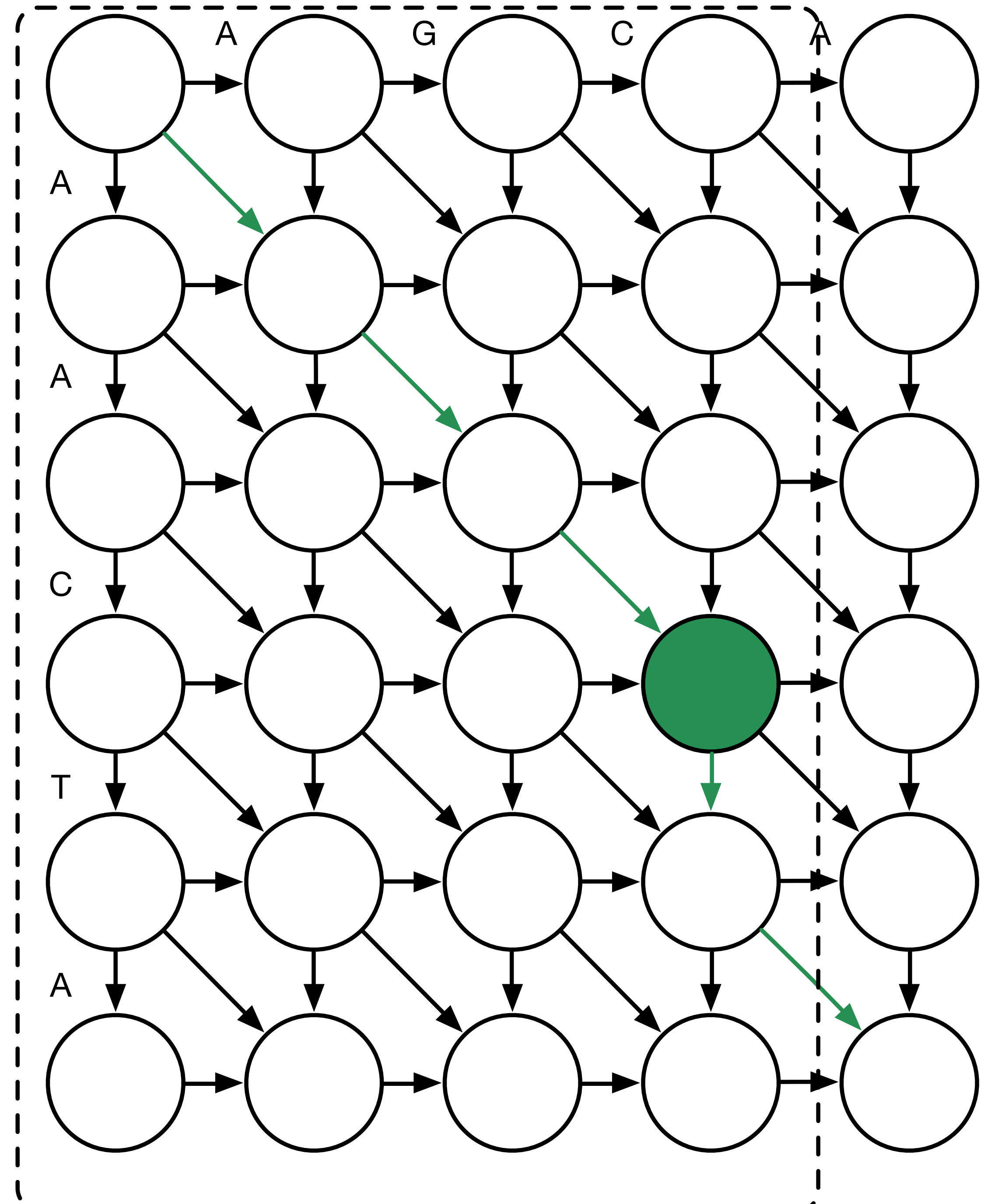


Reversed!



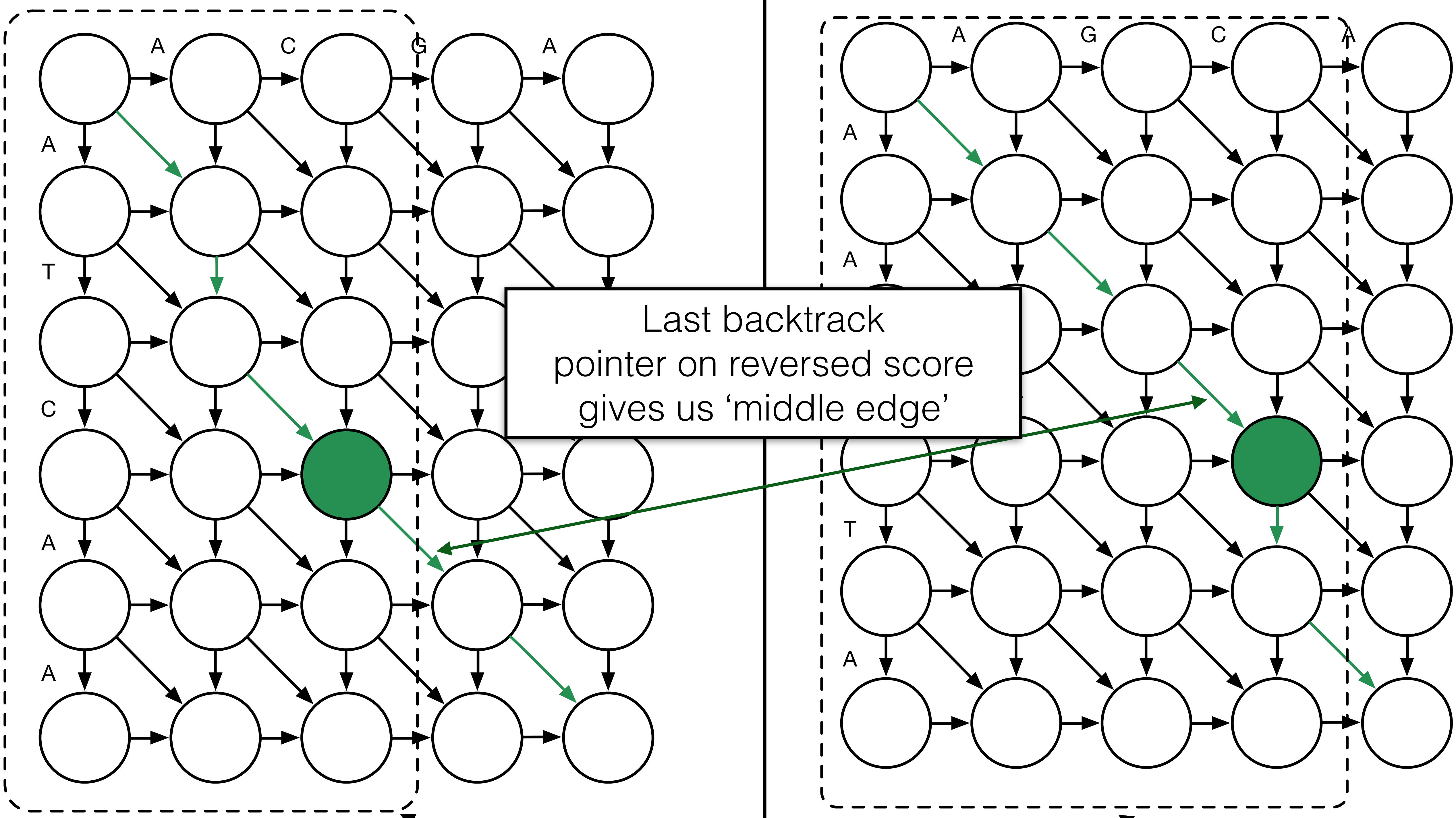


Reversed!



$$s_{n,m} = \max_t s_{t,\frac{m}{2}} + s^r_{t,\frac{m}{2}}$$

Reversed!



$$s_{n,m} = \max_t s_{t,\frac{m}{2}} + s^r_{t,\frac{m}{2}}$$

Analysis

- Space: O(n) for two columns required to compute score
- Time: O(nm) to compute all scores (there is some O(n) double counting)
- After finding 'middle edge', we have two O(nm/4) problems:
  - solve each in linear space
  - solve each in O(nm/4) time
  - so O(nm/2) time
- Overall we have O(nm + nm/2 + nm/4 + nm/8 +…) = O(nm)