Today's Lecture

- Dynamic programming to find highest weight paths

- Weighted linked lists
  - Sequence graphs
  - WLLs for "motif clusters"

Highest Weight Paths on WDAGs

- *Problem*: find a path with the highest possible weight.
- *Solution*:
  - "Brute force" approach
    - i.e. simply enumerating all possible paths and comparing their weights

  is usually impractical (too many paths!)
  - Instead, use the method of *dynamic programming* ('The Fundamental Algorithm of Computational Biology').

Highest Weight Paths on WDAGs (cont'd)

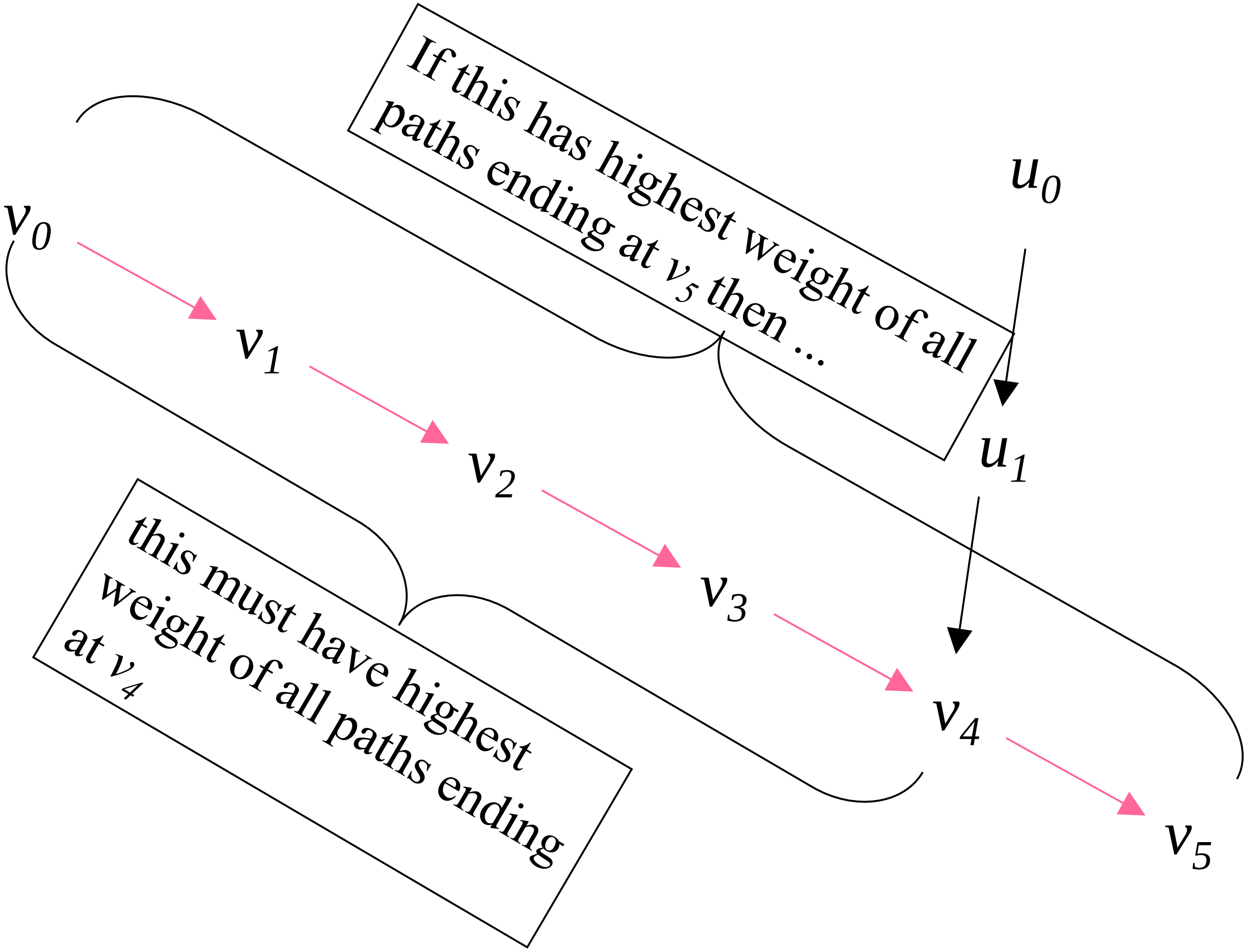
- Let $P_n = (v_0, v_1, \ldots, v_n)$ be a path of highest weight.
- Then for each $k < n$, the sub-path $P_k = (v_0, v_1, \ldots, v_k)$ must have highest weight of all paths ending at v_k, because
  - *if* $Q = (u_0, u_1, \ldots, v_k)$ were another path ending at v_k and having higher weight than P_k,
  - *then* the path $(Q, v_{k+1}, \ldots, v_n)$ would have weight

$$w((Q, v_{k+1}, \ldots, v_n)) = w(Q) + w((v_k, \ldots, v_n))$$

$$> w(P_k) + w((v_k, \ldots, v_n)) = w(P_n),$$

contradicting assumption that P_n has highest weight.

Subpaths of a highest-weight path can't be improved:


If this has highest weight of all paths ending at v_5 then ...
u_0
v_0
v_1
u_1
v_2
this must have highest weight of all paths ending at v_4
v_3
v_4
v_5

Highest Weight Paths on WDAGs (cont'd)

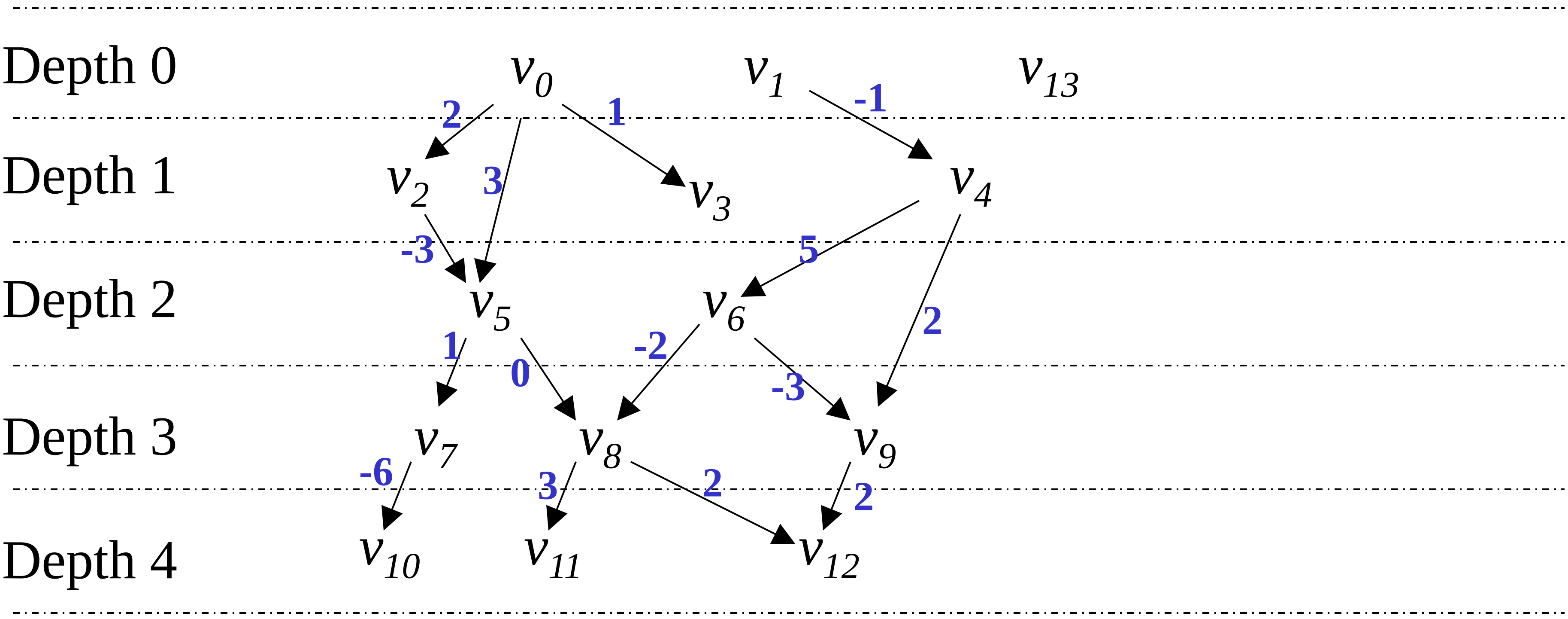
- So generalize the problem as follows:
- find, for *each* vertex *v*, the highest weight of all paths ending at *v* – call this *w*(*v*)
- Can find *w*(*v*) in single pass through *V*, as follows:
  - process the *v* in depth order (*or any order in which parents precede children*)
  - if *v* has no parents, *w*(*v*) = 0 (the only path ending at *v* is (*v*)).
  - for any other *v*, except for the path (*v*) (which has weight 0), any path ending at *v* is of form $(v_0, v_1, \ldots, v_k, u, v)$. Then
  - *u* is a parent of *v*, so *w*(*u*) has already been computed, and

    $$w((v_0, v_1, \ldots, v_k, u, v)) \leq w(u) + w((u,v))$$

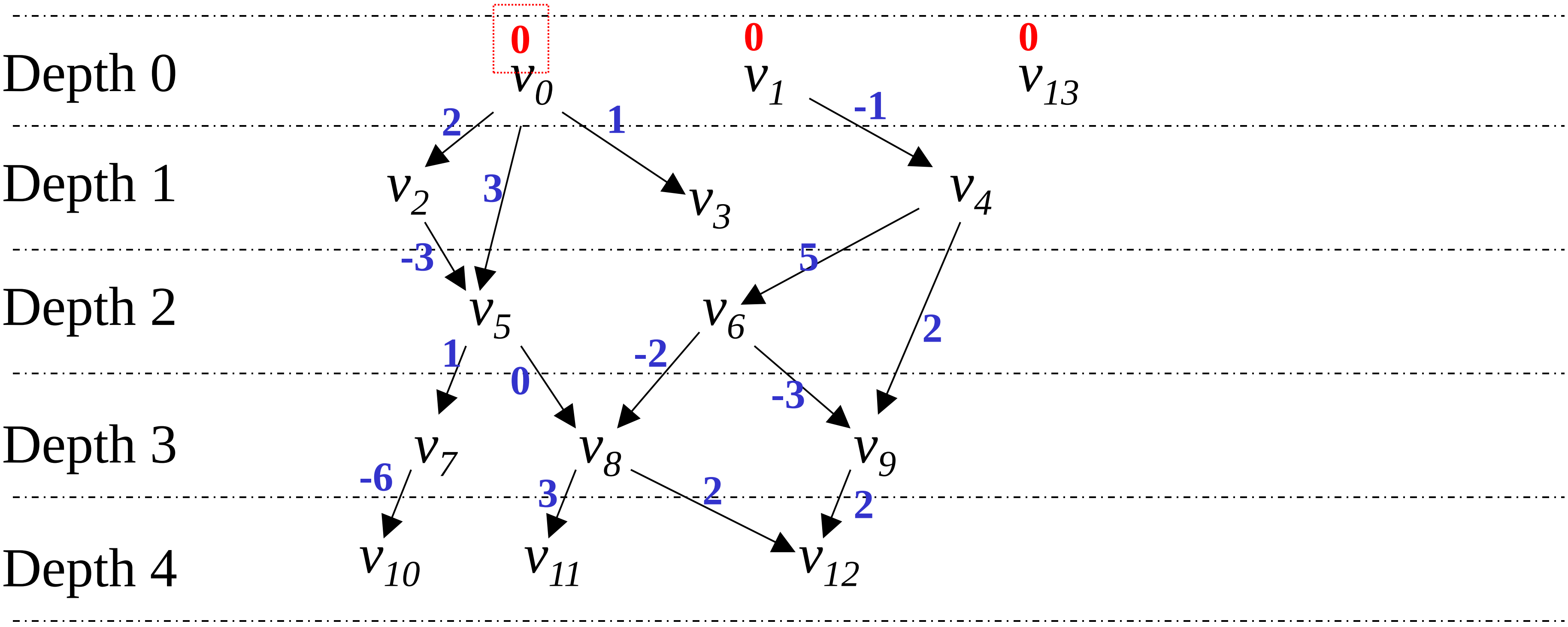
    with equality for an appropriate choice of v_i.
  - Therefore we may compute *w*(*v*) as

$$w(v) = \max(0, \max_{u \in parents(v)} (w(u) + w((u,v))))$$

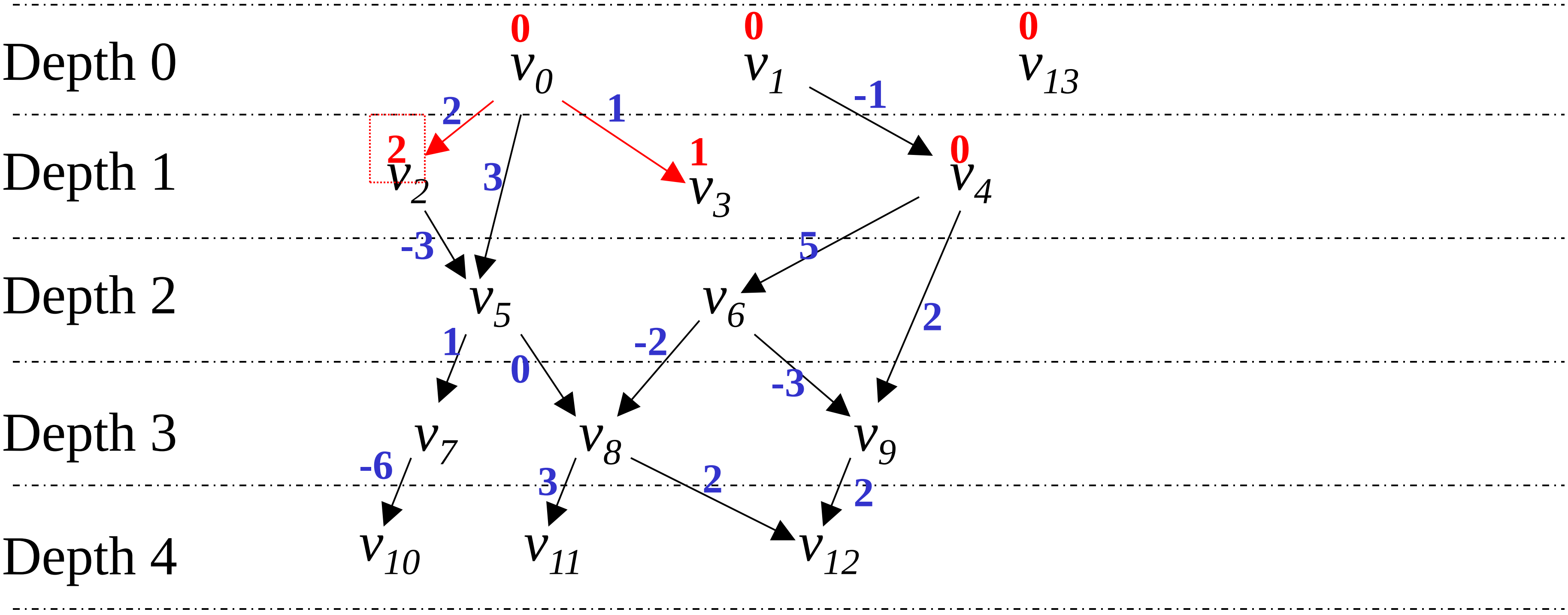
Example


Depth 0
Depth 1
Depth 2
Depth 3
Depth 4
v_0
v_1
v_{13}
2
1
3
-1
v_2
v_3
v_4
-3
5
v_5
v_6
2
1
0
-2
-3
v_7
v_8
v_9
-6
3
2
2
v_{10}
v_{11}
v_{12}

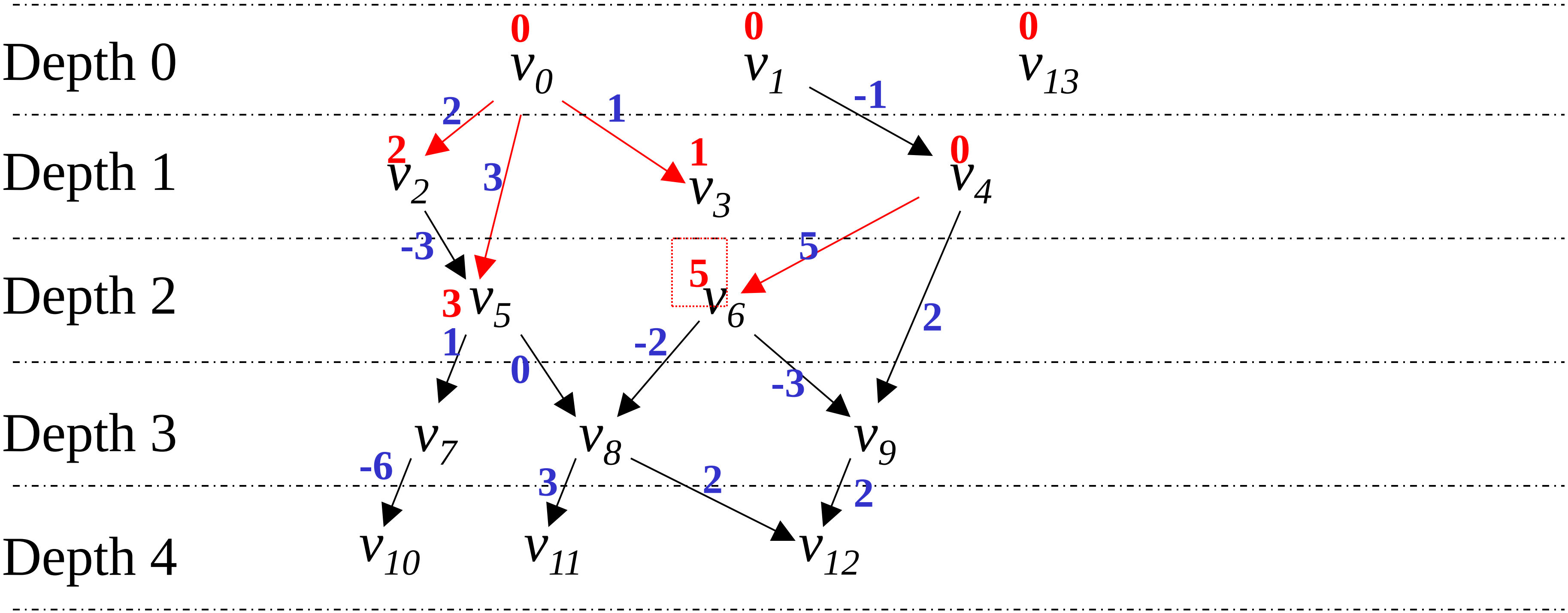
w(*v*) – depth 0 nodes



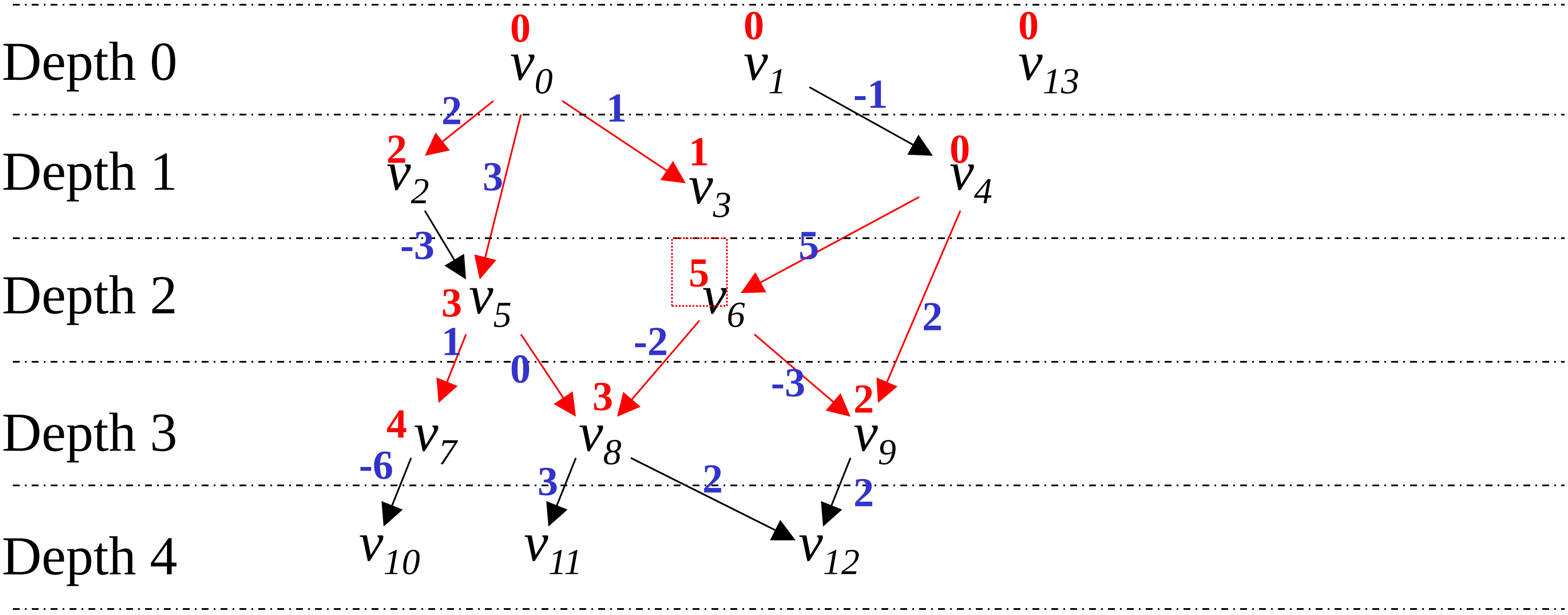
$w(v)$ – depth 1 nodes



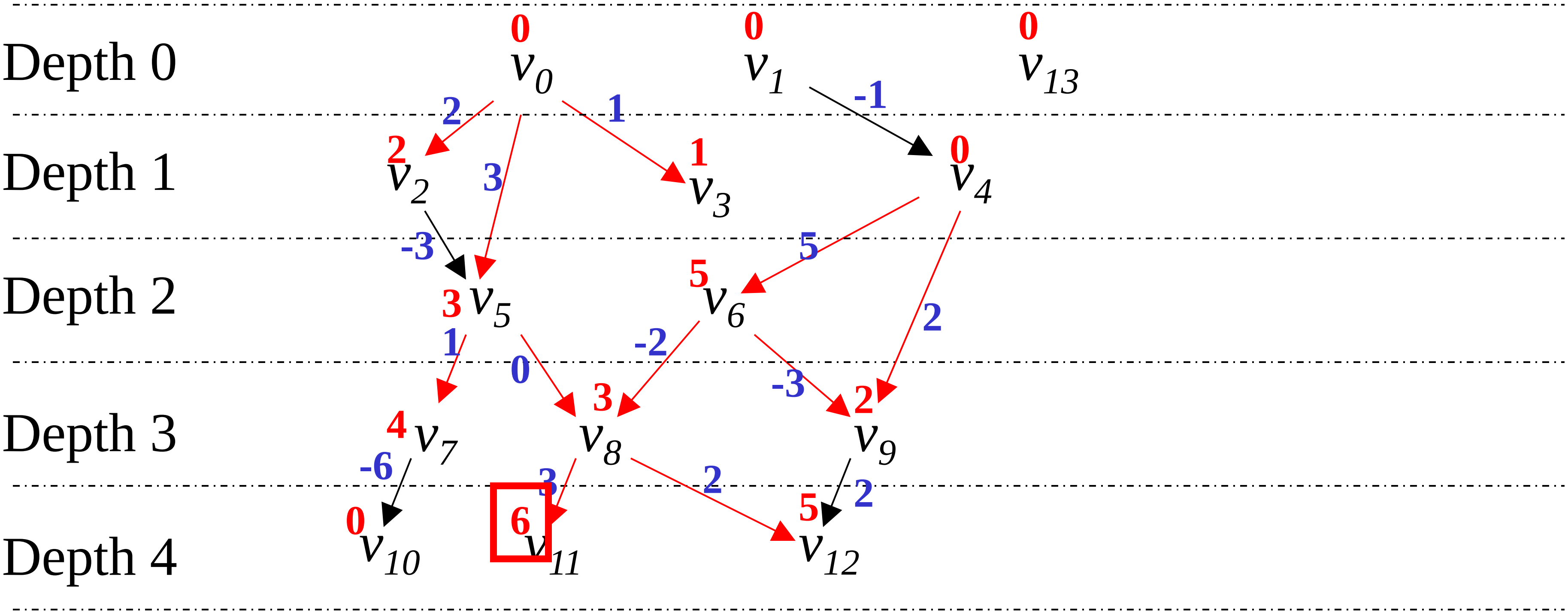
$w(v)$ – depth 2 nodes



$w(v)$ – depth 3 nodes



w(*v*) – depth 4 nodes



Highest Weight Paths on WDAGs (cont'd)

- To reconstruct best path, need "traceback" pointer to immediate predecessor of *v* in best path:

$$T(v) = \begin{cases} v & w(v) = 0 \\ \underset{u \in \text{parents}(v)}{\arg\max} \, (w(u) \; + \; w((u,v)) & w(v) \neq 0 \end{cases}$$

  - in preceding graph, *T*(*v*) is the *parent* on *red edge* coming into *v*
    - if more than one such edge, pick one at random;
    - if no such edge, *T*(*v*) = *v*
- Sometimes useful to record *beginning* of best path:

$$B(v) = \begin{cases} v & w(v) = 0 \\ B(T(v)) & w(v) \neq 0 \end{cases}$$

Highest Weight Paths on WDAGs (cont'd)

- Then highest weight of any path in graph is

$$\max_{v \in V} (w(v))$$

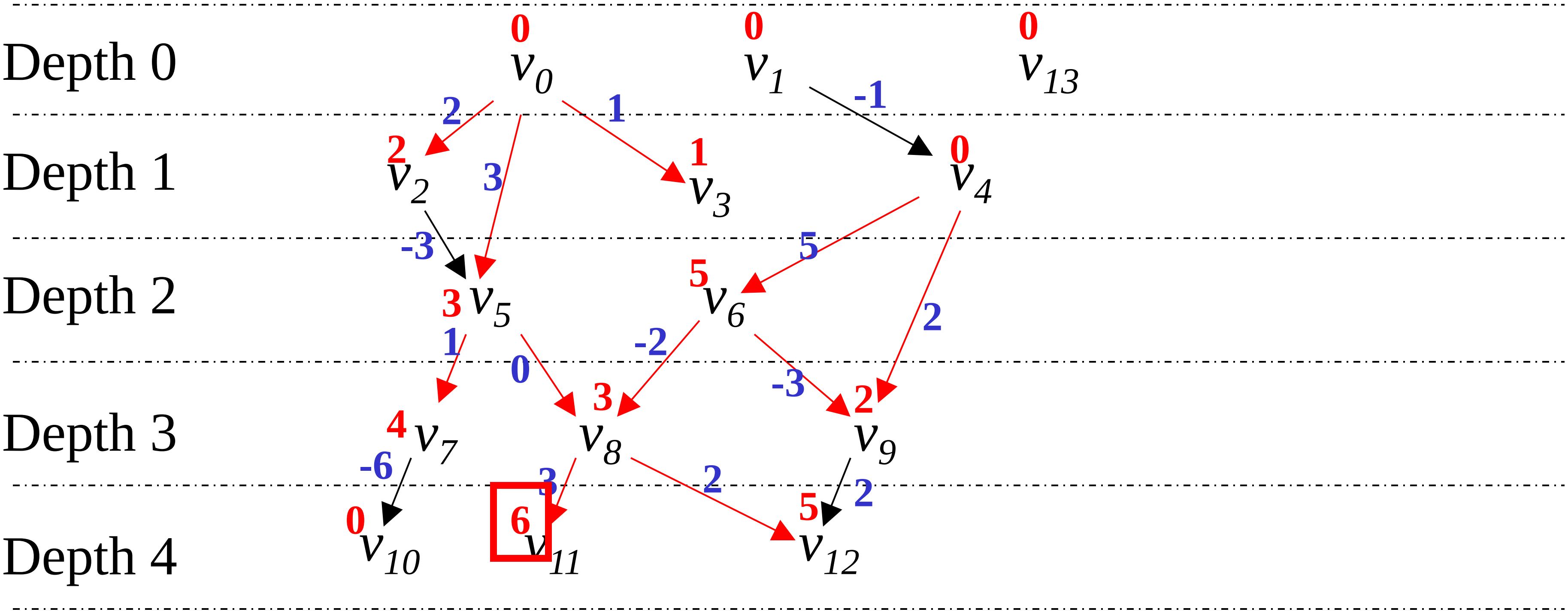
  - updated as each node is visited
    - indicated by ⬚ in preceding graph –

  and so doesn't require additional pass through vertices

- if $u = \operatorname{argmax}_{v \in V} (w(v))$, can reconstruct highest weight path by tracing back from u, using T:
  - path ends at u;
  - immediate predecessor of u is $T(u)$;
  - predecessor of $T(u)$ is $T(T(u))$; etc.
  - stop when $T(v) = v$.

- In preceding example, highest weight is 6 and $u = v_{11}$

Dynamic programming on WDAGs



Complexity of Dynamic Programming

- Time to find a best path is $O(|E|+|V|)$:
  - in initial pass, visit each node, and each edge into that node: $O(|E|+|V|)$
  - in traceback, visit subset of nodes, and unique edge from each node: $O(|V|)$

(Complexity to find *all* highest weight paths can be higher)

For very large graphs, even $O(|E|+|V|)$ may be unacceptable!

Complexity Analysis (cont'd)

- Space requirements:
  - If only want *weight* of best path, and beginning and end, then
    - don't need $T(v)$, and
    - only need retain $w(v)$ and $B(v)$ until have processed all children of v (or when best path found so far ends at v).

    Space depends on graph structure, but usually << $O(|V|)$.
  - If want path itself, must store $T(v)$ ∀ v
    - space = $O(|V|)$
    - ∃ algorithms (for some graphs) to reduce this, but may take more time.

Implementing Dynamic Programming in a Computer Program

- Storing entire graph has space complexity = $O(|V|+|E|)$
- If graph has regular structure, can often “create” and process vertices and edges on the fly, without storing in memory
  - cf. edit graph (to be defined later) for aligning sequences

Same dynamic programming approach can be used to find:

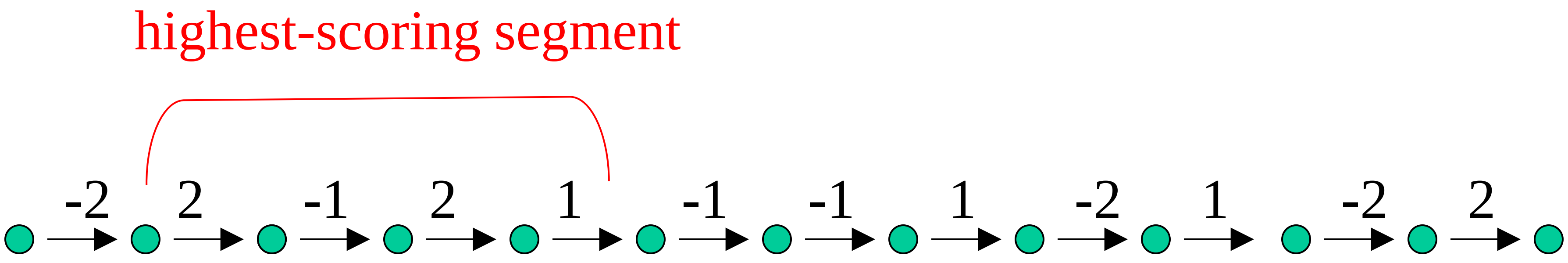
1. Highest product weight path (if weights are ≥ 0)
2. Highest weight path that
   - *starts* in particular subset *V'* of vertices,
     - don't consider paths that start outside *V'* :

       i.e. when computing $w(v)$, don't consider trivial path unless $v \in V'$
   - and/or *ends* in particular subset *V''*
     - only scan for the maximum $w(v)$ over *V''*
3. Sum of product weights of all paths ending at particular vertex
   - *sum* over all edges coming into *v*, instead of *maximizing*
   - this useful for probability calculations

- Will use the above variants later!

Weighted Linked Lists (WLLs)

- *WLL* is linked list with weights on each edge
  - – simplest kind of WDAG.
- Highest weight paths correspond to highest-scoring segments of WLL.

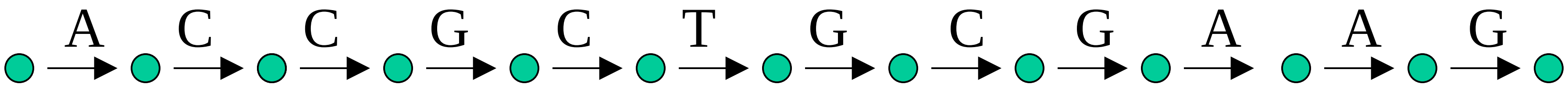


WLLs: Computational Issues

- Beginning & end of best path determine path uniquely, so
  - traceback is unnecessary
  - single pass through list suffices to find best path.
- Generally want next best path, etc.
  - Can find reasonably efficiently by repeated scans, but
  - Ruzzo-Tompa algorithm more efficient.
- Will discuss later an altered version of problem having some advantages

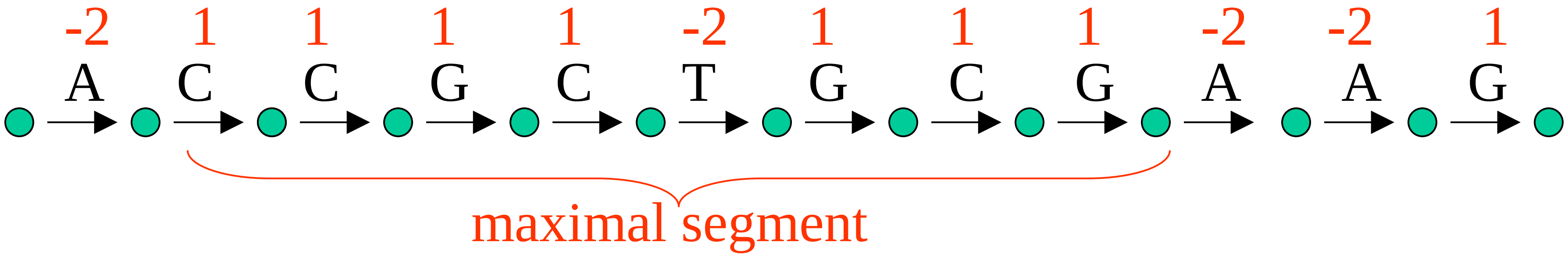
Applications to Sequences

- A *sequence graph* of a sequence is linked list whose edges are labelled by sequence residues (in order):
- e.g. graph for sequence ACCGCTGCGAAG is:



Weighted Sequence Graphs

- If attach weight to each residue, sequence graph becomes a WLL.



- Highest weight paths correspond to highest-scoring segments of sequence.
- Useful for identifying segments with “atypical composition”

- For example:
  - Gives good way to find GC-rich regions in AT-rich thermophile genomes
    - generally correspond to RNA genes (Rob Klein & Sean Eddy)
  - AT-rich, purine-rich, pyrimidine-rich regions
  - Hydrophobic, acidic, or basic regions in protein sequences

- More broadly, can find regions enriched for sequence *motifs*:
  - CpG islands in mammalian genomes
    - positive weight (e.g. +17) to the first C of each CpG, and
    - negative weight (e.g. –1) to every other base

    (This approach was used in *Nature* human genome paper).
  - *horizontally transferred* regions
  - Regions rich in (known) trranscription-factor motifs