Today’s Lecture

- Dynamic programming to find highest weight paths
- Weighted linked lists
  - Sequence graphs
  - WLLs for “motif clusters” & numerical data
  - Statistical issues

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').

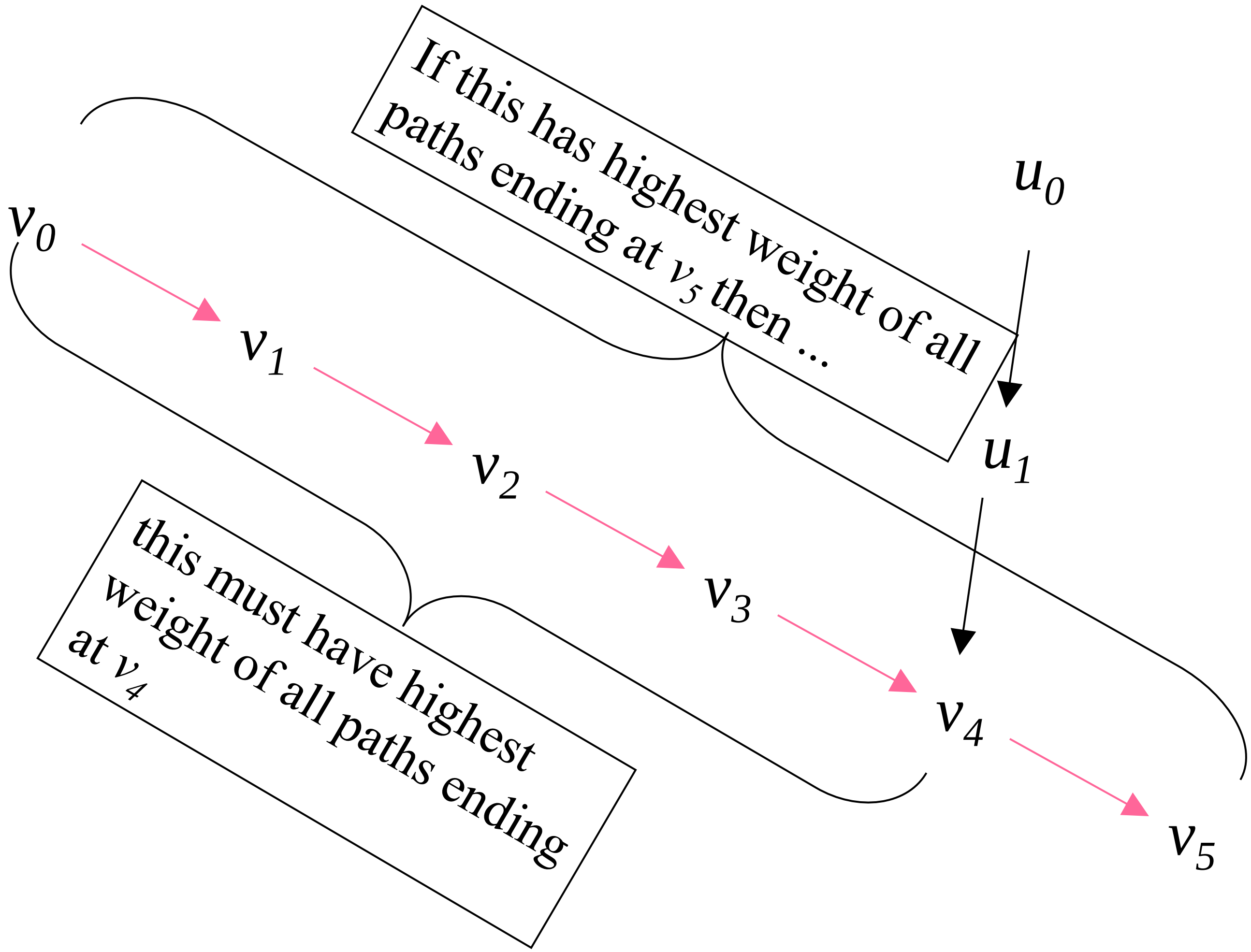
Highest Weight Paths on WDAGs (cont'd)

- 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:



Highest Weight Paths on WDAGs (cont'd)

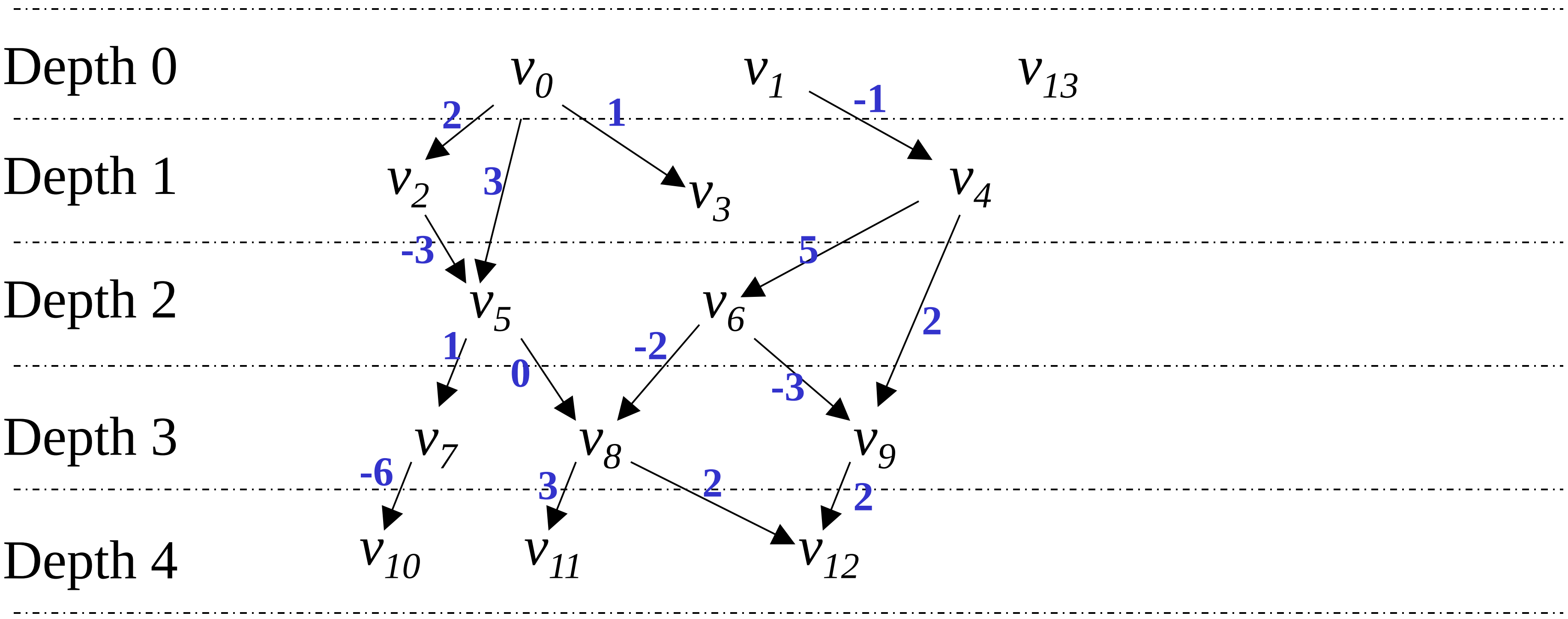
- So generalize the problem as follows:
- find, for *each* vertex v, the highest weight of all paths ending at v – call this $w(v)$
- Can find $w(v)$ in single pass through V, as follows:
  - process the v in depth order (*or any order in which parents precede children*)
  - if v has no parents, $w(v) = 0$ (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

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

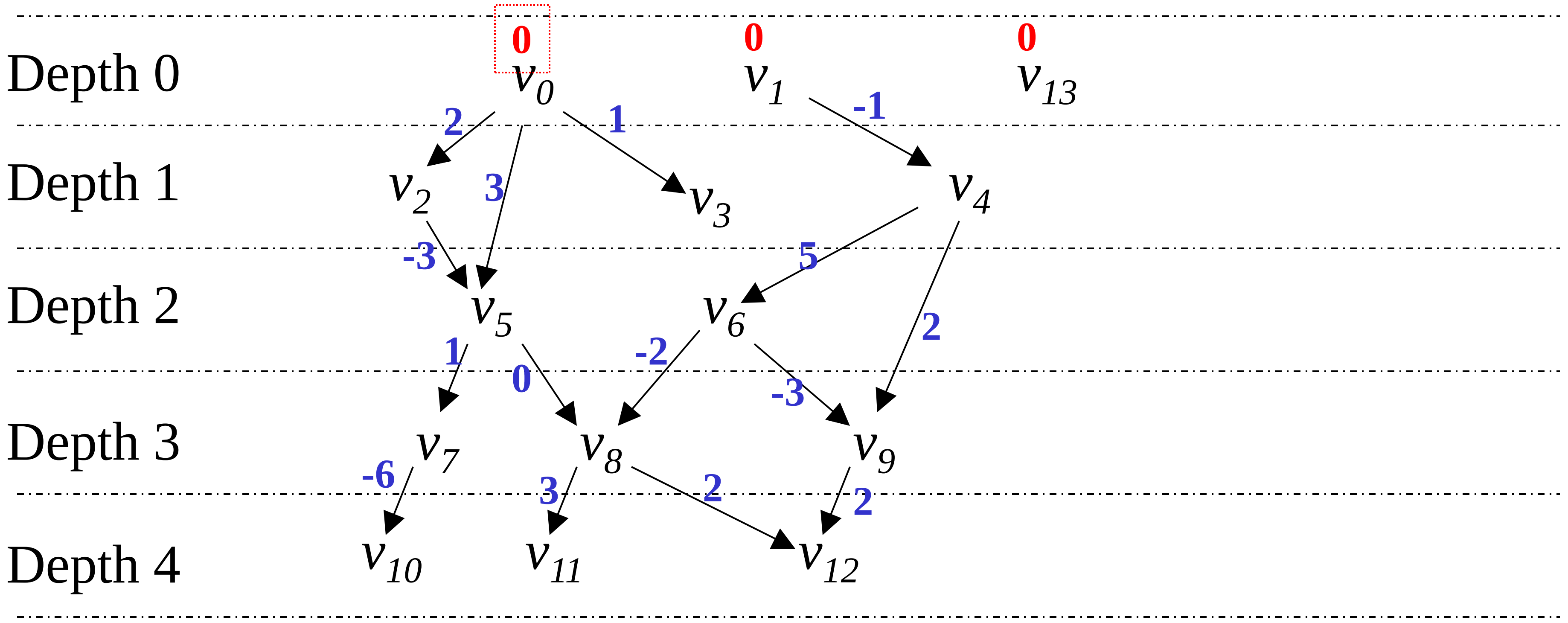
  with equality for an appropriate choice of v_i.
  - Therefore we may compute $w(v)$ as

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

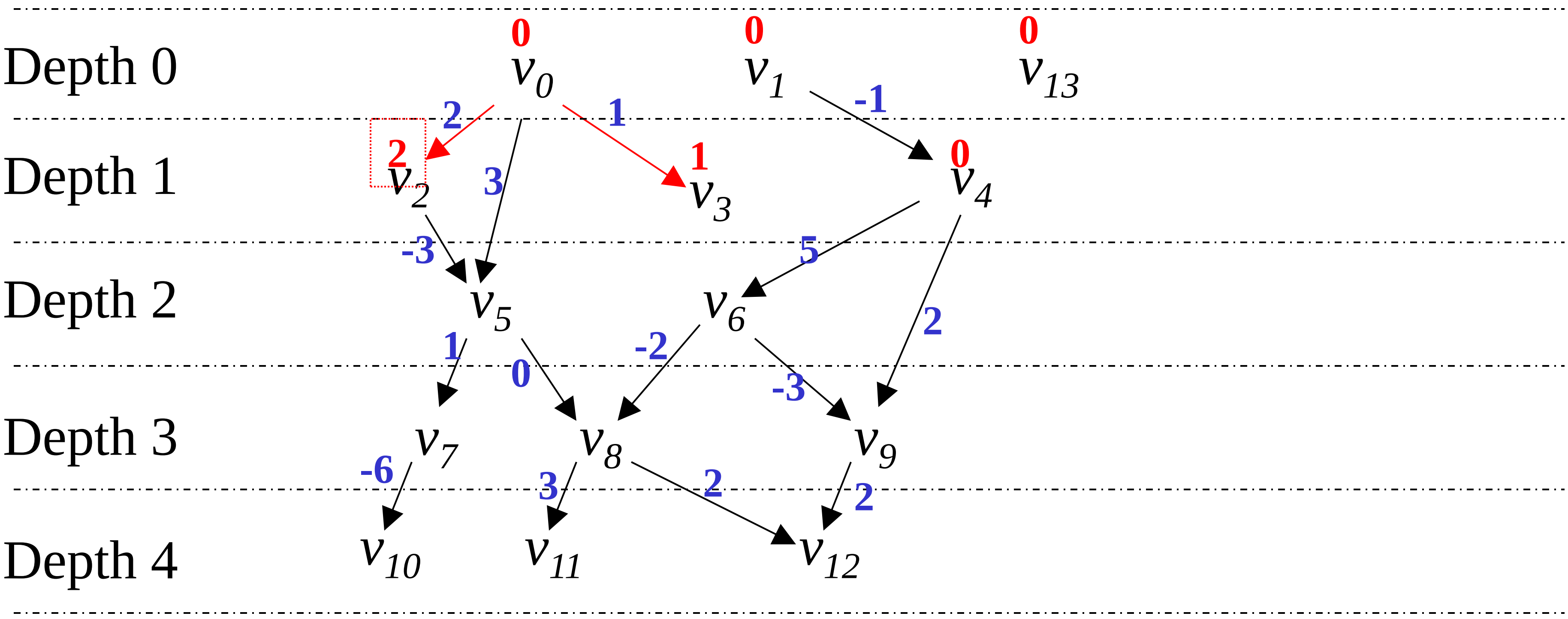
Example


Depth 0
Depth 1
Depth 2
Depth 3
Depth 4
v0
v1
v13
v2
v3
v4
v5
v6
v7
v8
v9
v10
v11
v12
2
1
3
-1
-3
5
2
1
0
-2
-3
-6
3
2
2

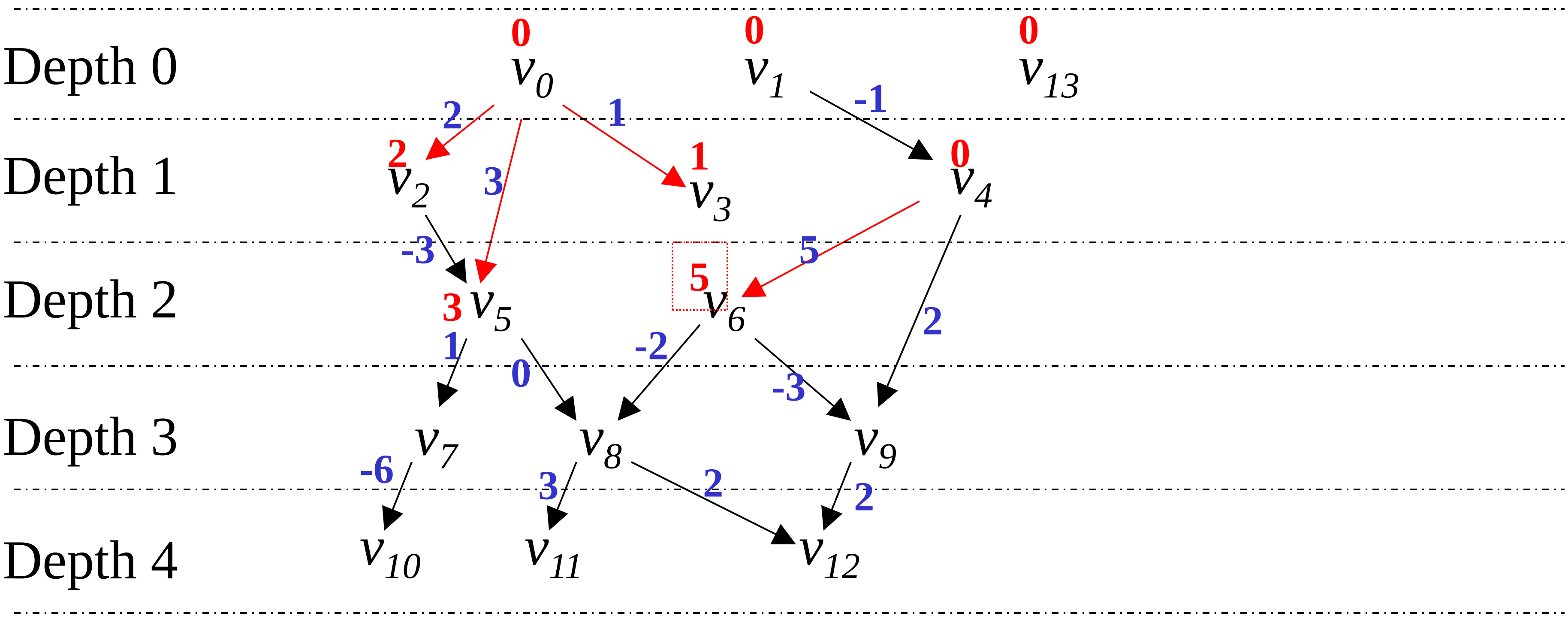
$w(v)$ – depth 0 nodes



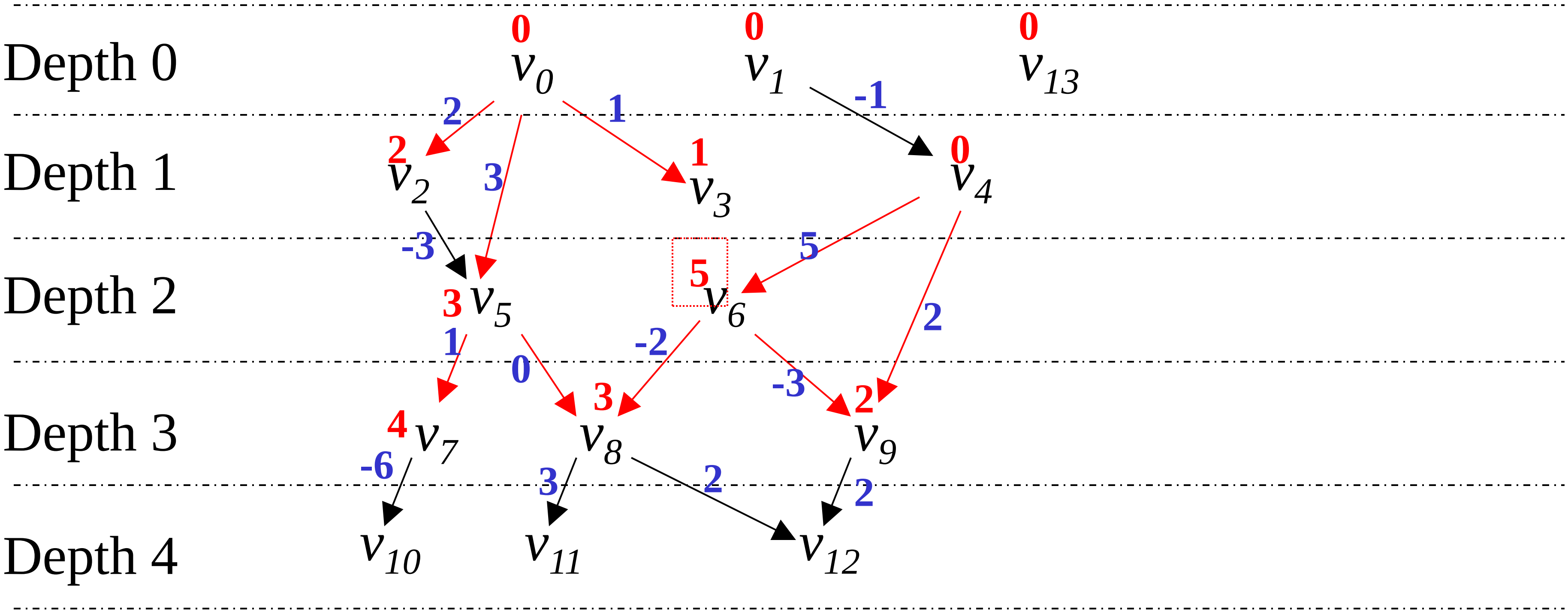
$w(v)$ – depth 1 nodes



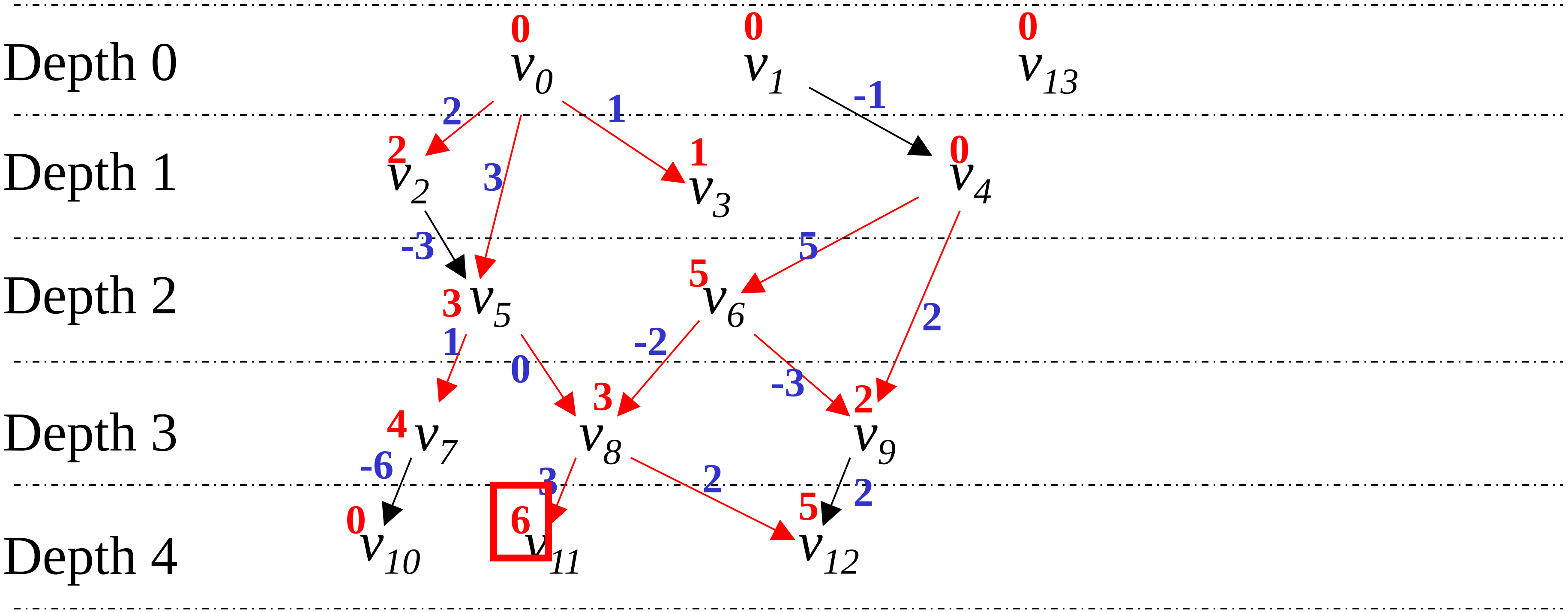
$w(v)$ – depth 2 nodes



$w(v)$ – 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

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

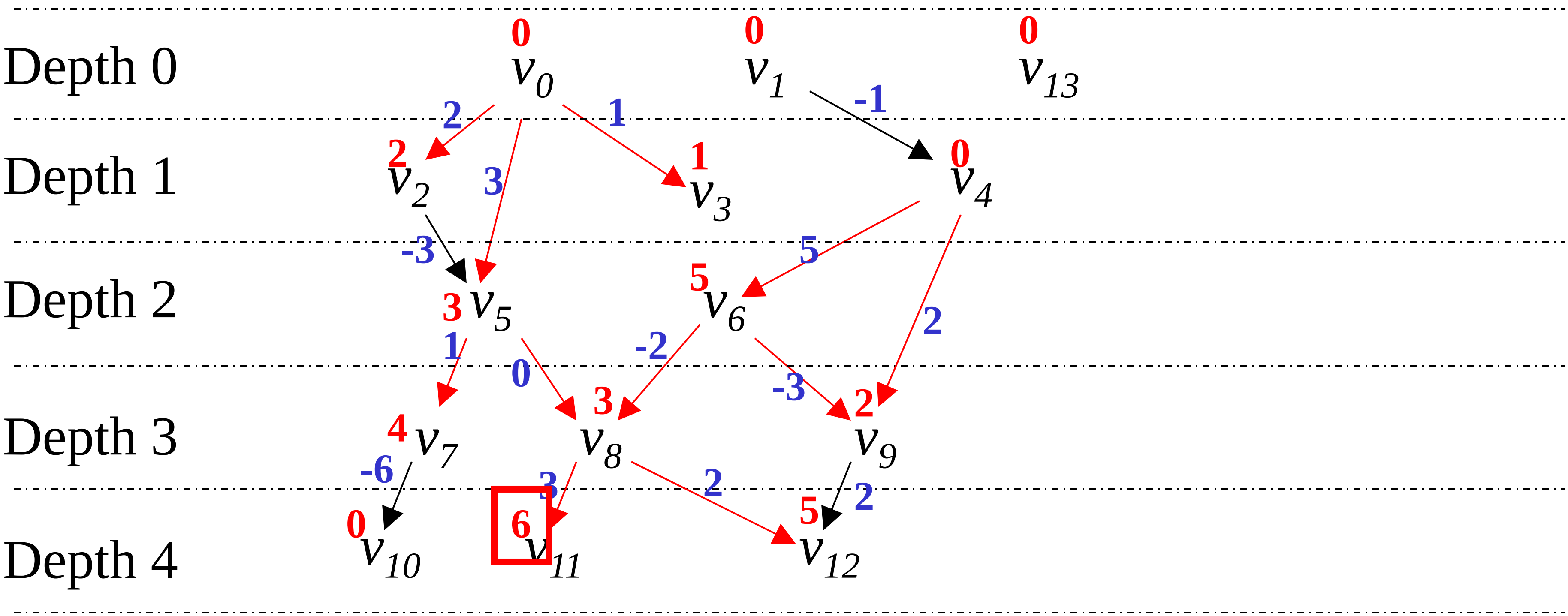
  - updated as each node is visited
    - indicated by $\boxed{}$ in preceding graph –

  and so doesn't require additional pass through vertices

- if $u = \text{argmax}_{v \in V} (w(v))$, 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 $\ll O(|V|)$.
  - If want path itself, must store $T(v)\ \forall\ v$
    - space = $O(|V|)$
    - $\exists$ 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:

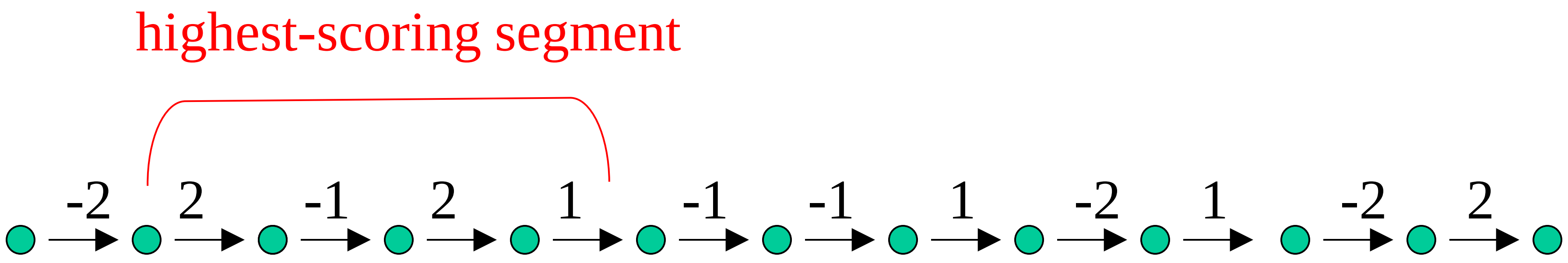
1. Highest product weight path (if weights are ≥ 0)
2. Highest weight path that
   - *starts* in particular subset V' of vertices,
     - don't consider paths that start outside V' :

       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.

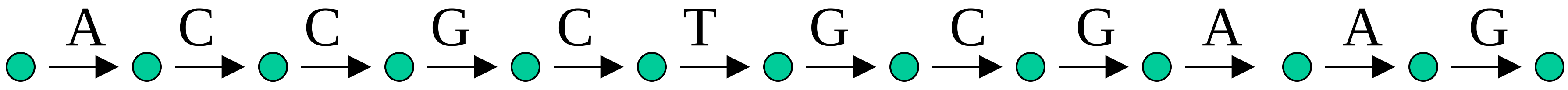


WLLs: Computational Issues

- 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

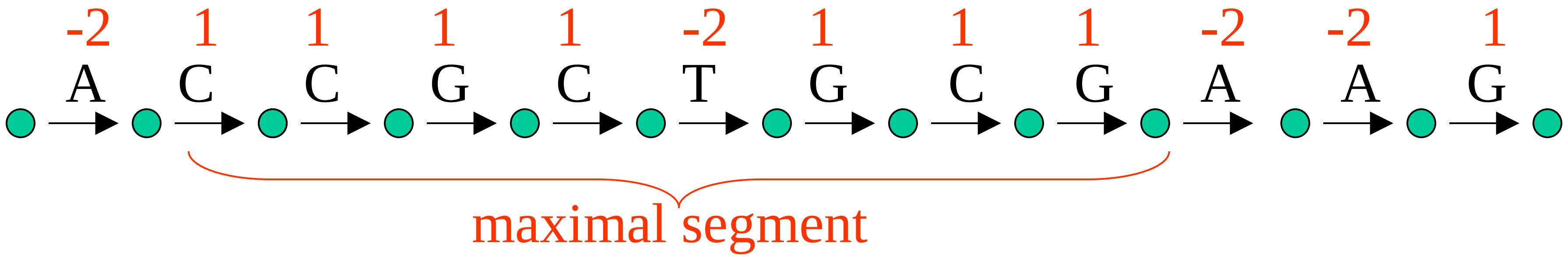
Applications to Sequences

- 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

Non-sequence-based scoring

- Can also assign scores to each genomic position based on other quantitative info:
  - Next-gen read frequency, e.g.
    - CNVs (Homework 3)
    - Hypersensitive sites
    - CHIP-seq
  - Other measurements?

Important issues!

- What is best scoring system to detect the 'target regions'?
  - Short answer: $s(r) = \log(t_r / b_r)$ where
    - t_r , b_r are freqs of residue (or motif) r in target and background
    - (if unknown, can sometimes estimate iteratively)
- When is the score of a segment 'significant'?
  - ∃ theory (due to Karlin & Altschul) for score dist'n for highest-scoring segments in a random sequence
- Will revisit both issues later.