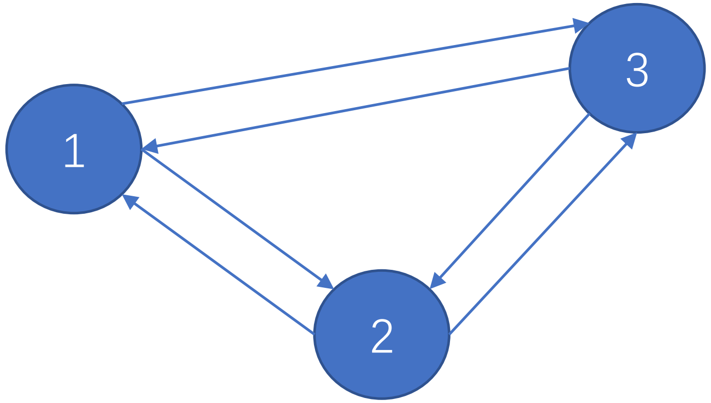
Intron Splicing Order Matrix

The intron number is labeled. Filling each row the read count support that this intron is spliced before other introns. Then naturally the read counts in the column represent this intron is spliced after other introns.

For example: Row 2 represents the read count support that intron 2 spliced before intron 1,3. While column 2 represents the read count support that intron 2 spliced after intron 1,3.

	1	2	3
1	0	2	2
2	3	0	1
3	7	4	0



Intron Splicing Oder Graph

In graph theory, matrix and graph are tightly connected. Every Bayesian network can be convert into a DAG, so as the above matrix.

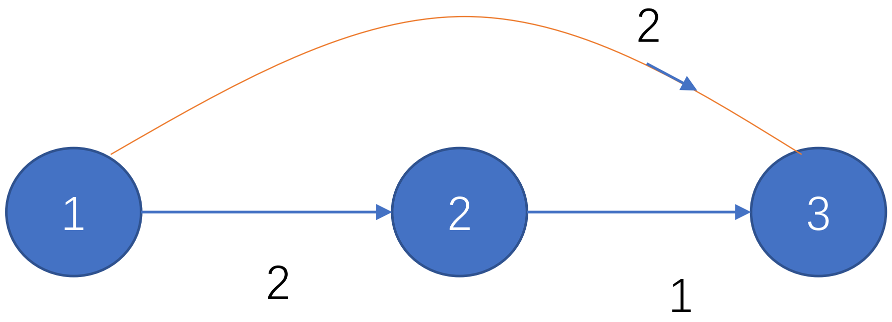
Most likely Order

For each order, a probability can be calculated, the path with highest likelihood is the most likely order (MLO).

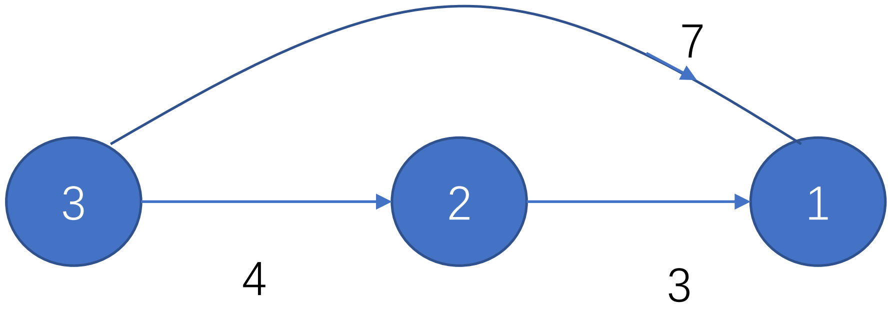
	1	2	3
1	0	2	2
2	3	0	1
3	7	4	0

Every order can form a DAG, multiply each edge's probability.

$$P(2\ spliced\ before\ 1) = \frac{3}{3+2} = 0.6$$
$$P(1\ spliced\ before\ 2) = \frac{2}{3+2} = 0.4$$
$$P(3\ spliced\ before\ 1) = \frac{7}{7+2} = 0.78$$
$$P(1\ spliced\ before\ 3) = \frac{2}{7+2} = 0.22$$
$$P(3\ spliced\ before\ 2) = \frac{4}{4+1} = 0.8$$
$$P(2\ spliced\ before\ 3) = \frac{1}{4+1} = 0.2$$



probability value= 0.0176



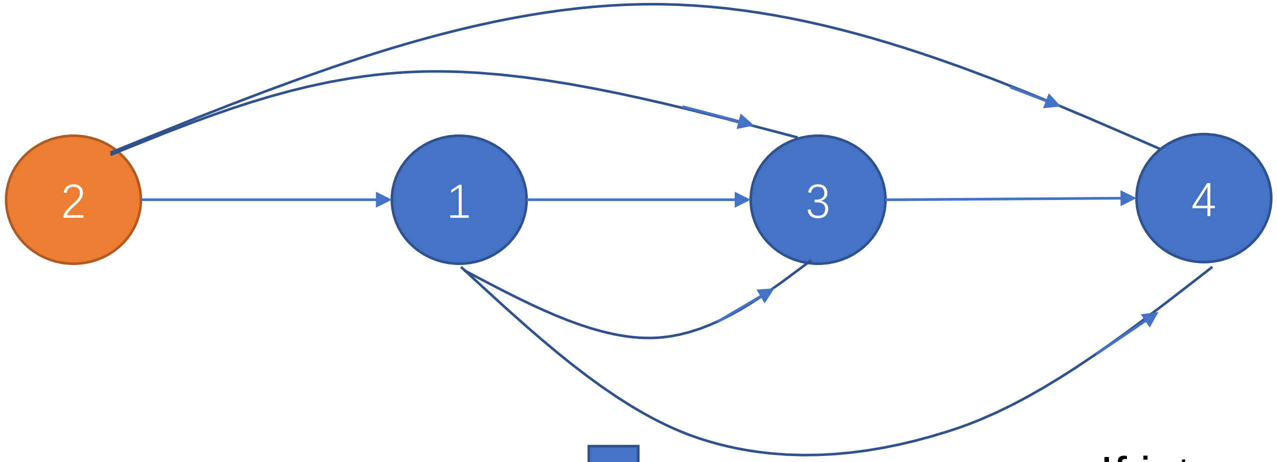
probability value=0.374

p-value of in order splicing
Likelihood ratio test
-2*log(0.0176 /0.374)~X, df=n*(n-1)/2

P-value=0.89

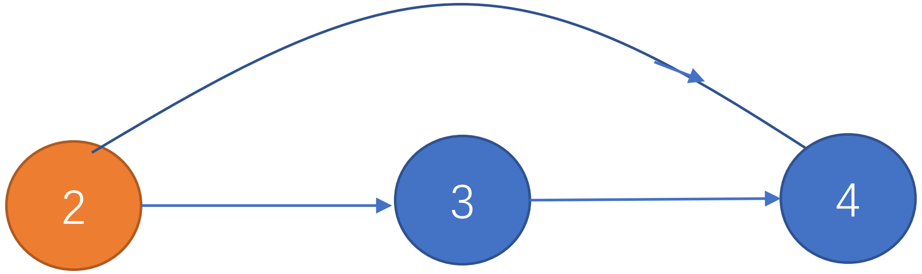
Most likely Order

Find MLO is N!, difficult for intron number > 10
*Row i represent the frequency of each intron spliced after i.
*Column i represent the frequency of each intron spliced before i.



	1	2	3	4
1	0	0	1	1
2	1	0	1	1
3	0	0	0	1
4	0	0	0	0

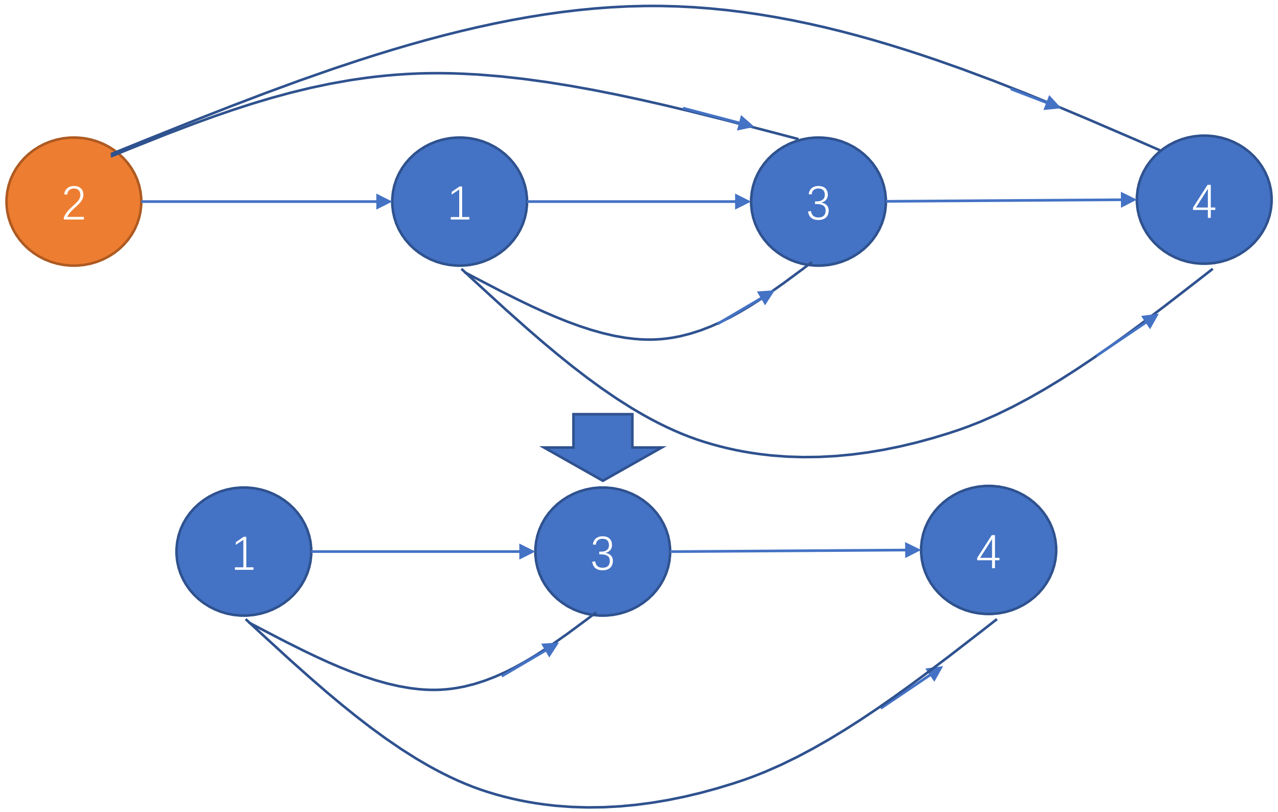
If intron 2 is the left node (first spliced), then the sum of Row 2 is maximum in the right.
Reverse this process we can got a algorithm to estimate the order.



Remove one node doesn’t change the order of the rest.
Correspond to remove row I and column i doesn’t change the order when opti rest in matrix,
Thus make iteration possible

Most likely Order

For each isoform got the frequency matrix D as above described.	1
Find potential most left intron using D, by which.max(rowsum) = q_1	2
Find 2nd, 3rr, 4th maximum rowsum row number: q_2,q_3,q_4.	3
For i in vector (q_1, q_2,q_3,q_4)	4
Remove column i and row i in D and repeat step 1.	5
Stop if the number of orders calculated reach 5,000.	6
After got all the potential best orders, calculate probability for each order and return the best.	7



Matrix A

	1	2	3	4
1	0	0.1	0.6	0
2	0.9	0	0.4	0.9
3	0.4	0.6	0	0
4	0	0.1	0	0

remove intron 2

Matrix D

	1	3	4
1		0.6	
3	0.4		
4			

$$D_{i,j} + D_{j,i} = 1$$

Splicing unit

Some introns tends to spliced simultaneously.
Two introns are spliced together, if their spliced rate relative to other introns are similar.
i.e. column i and column j are correlated or say row j and row i are correlated.
We used DBscan algorithm with pearson correlation as distance measure to find unit.

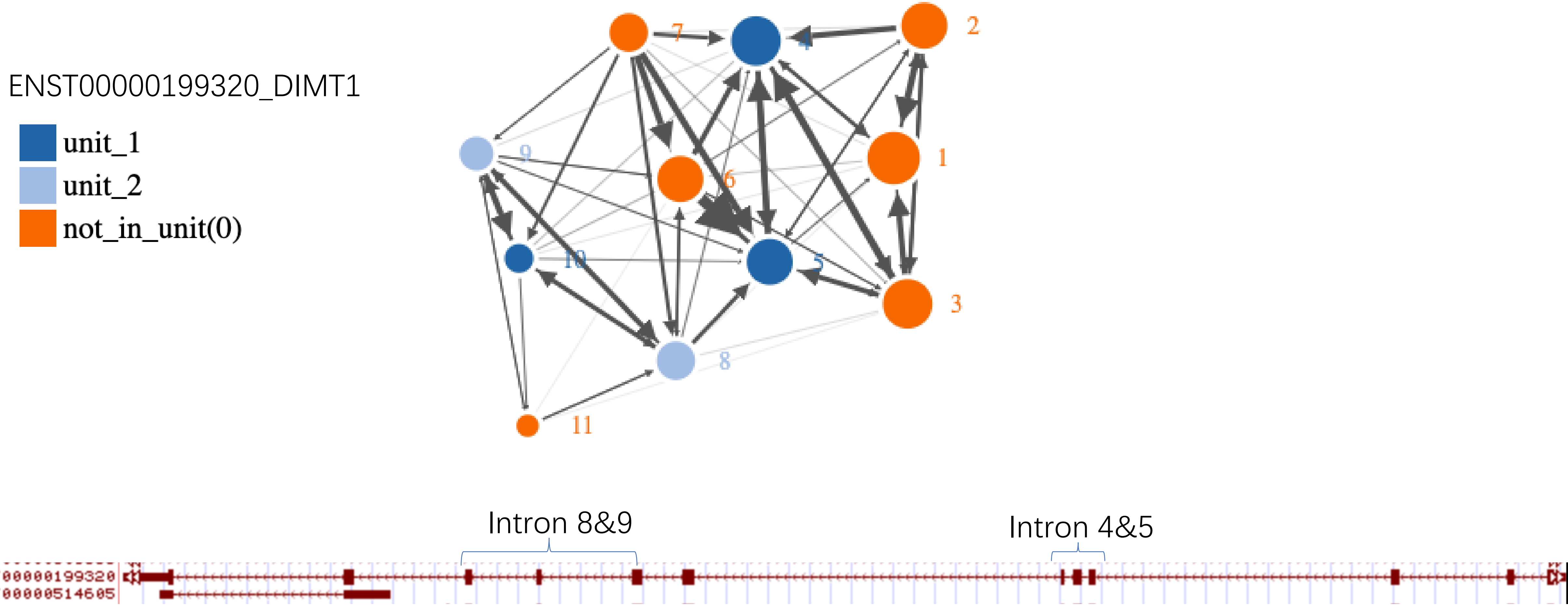
	1	2	3	4
1	0.5	0.1	0.2	0.9
2	0.9	0.5	0.4	0.3
3	0.8	0.6	0.5	0.3
4	0.1	0.7	0.7	0.5

Row 2 and row 3 are similar, means their splicing rate are similar relative to others.

Thus they have higher probability tends to spliced together.
Diagonal filled with 0.5

Splicing unit

Example


ENST00000199320_DIMT1
unit_1
unit_2
not_in_unit(0)
1
2
3
4
5
6
7
8
9
10
11
Intron 8&9
Intron 4&5
ENST00000199320
ENST00000514605