1. Directional STTC

To incorporate the temporal order of the firing events of two neurons, we extended the STTC as follows: the fraction of the number of the firing events of A which fall within Δt before each firing event of B by the number of firing events of A is computed (P_A^{B-}). The firing events that have this property increase the positive correlation (Fig. 1). Similarly, the fraction of the number of firing events of B that fall within Δt after each firing event of A by the number of firing events of B is estimated(P_B^{A+}). In this way we estimate the correlation between spike trains for the spikes of B that follows spikes of A and the spikes of A that proceeds spikes of B.

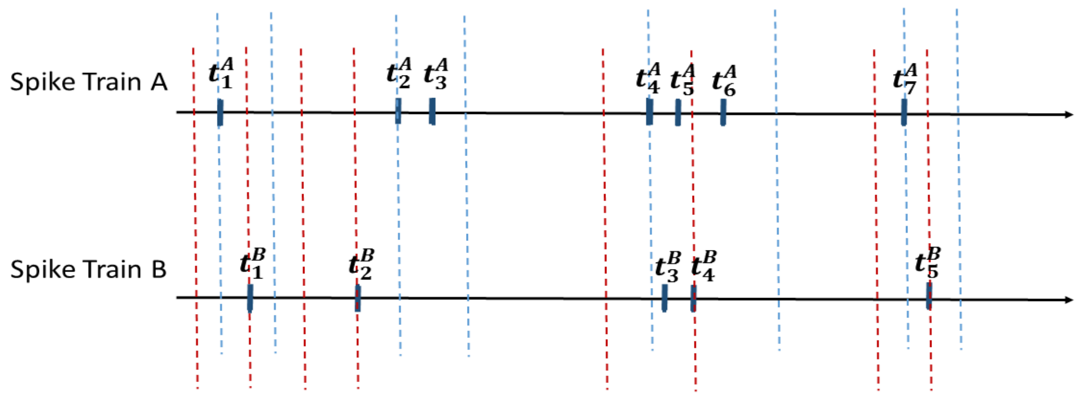


Figure 1: Directional STTC for spike trains A and B. The blue color dotted lines represent the Δt time interval after each firing event of A. The red color dotted lines represent the Δt time interval before each firing event of B. In this example P_A^{B-} is 4/7 and P_B^{A+} is 4/5.

$\boldsymbol{t_x^y}$ is the moment t of the firing event x of spike train y. E.g., in Fig. 1 t_5^A is the 5th firing event of the spike train A.

$\boldsymbol{T_{A^+}}$ is the fraction of the total recording time which is covered by the tiles Δt after each spike of A. Additional, $\boldsymbol{T_{B^-}}$ is the fraction of the total recording time which is covered by the tiles Δt before each spike of B.

$$STTC_{AB} = \frac{1}{2}\left(\frac{P_A^{B^-} - T_{B^-}}{1 - P_A^{B^-} T_{B^-}} + \frac{P_B^{A^+} - T_{A^+}}{1 - P_B^{A^+} T_{A^+}}\right) \qquad (1)$$

Some of the directional STTC(A,B) properties are:

- The metric is bounded taking values [-1, 1]. High values indicate positive correlation.
- This metric is firing independent as we consider the fractions P_A^{B-} andP_B^{A+}.
- It does not correlate silent intervals. Common silent intervals between spike trains A and B does not indicate positive correlation.

2. Conditional STTC of two neurons, given the firing of a third one

To estimate the temporal correlation of two neurons, given that a third neuron is firing, we defined the conditional STTC as follows: we identify the firing events of A which follow within an interval of Δt of a firing event of C (Fig. 2). This new sequence of firing events of A forms the "reduced" spike train A. The number of firing events of B that falls within the tiles Δt after the firing events of the reduced spike train A ($\boldsymbol{N^{CA}_{A^+B}}$) and the number of firing events of the reduced spike train A that falls within the tiles Δt after the firing events of spike train B is estimated ($\boldsymbol{N^{CA}_{B^-A}}$). The spikes that have this property increase the positive correlation between A and B given the spike train C.

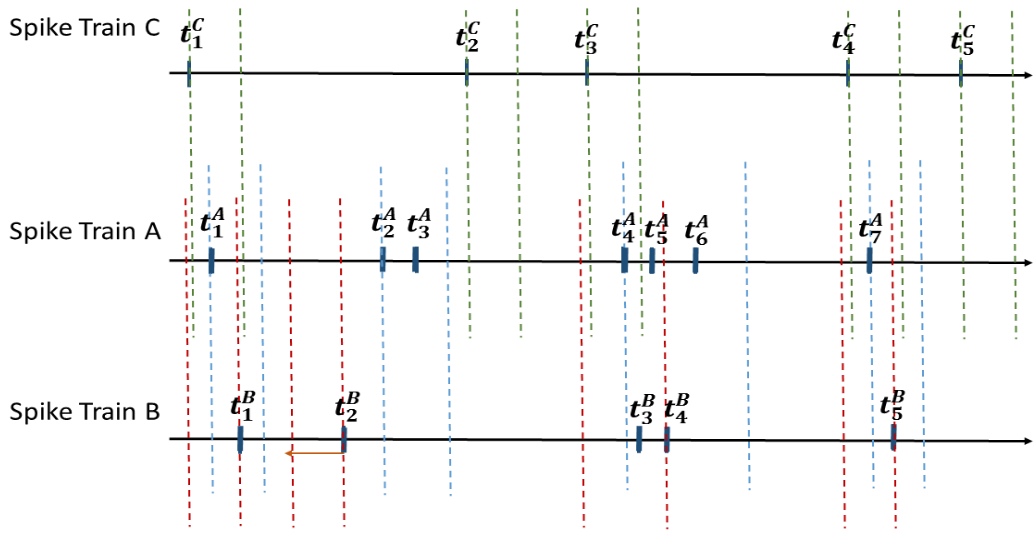


Figure 2: Conditional STTC A -> B|C. The green and blue color dotted lines represent the Δt time interval after each firing event of C and A, respectively. The red color dotted lines represent the Δt time interval before each firing event of B. The firing event of spike train A at the moment $\boldsymbol{t_5^A}$ does not fall within a tile of Δt after a firing event of C. So even it fall within a Δt tile before a firing event of spike train B, it does not increase the correlation between spike trains A and B.

$$STTC^{C}_{AB} = \frac{1}{2}\left(\frac{\frac{N^{CA}_{B-A}}{N_A} - T_{B^-}}{1 - \frac{N^{CA}_{B-A}}{N_A}T_{B^-}} + \frac{\frac{N^{CA}_{A+B}}{N_B} - T_{A^+}}{1 - \frac{N^{CA}_{A+B}}{N_B}T_{A^+}}\right) \tag{2}$$

$\boldsymbol{t_x^y}$ is the moment t of the firing event x of spike train y. E.g., in Fig. 1 t_6^A is the 6th firing event of the spike train A.

N

$\mathbf{N_A}$ is the number of firing event in A & $\mathbf{N_B}$ is the number of firing event in B.

$\boldsymbol{T_{A^+}}$ is the fraction of the total recording time which is covered by the tiles +Δt after each spike of A, that fall within the tiles Δt after each spike of C.

$\boldsymbol{T_{B^-}}$ is the fraction of the total recording time which is covered by the tiles Δt before each spike of B.

3. Analysis

3.1 Significant pairs and triplets

We estimate the conditional STTC for each possible triplet for the 183 neurons of the dataset. Given a STTC triplet (e.g., A->B|C), we distinguish eight different motifs (Table 1), based on the presence of statistical significant directional STTC of the pairs, e.g., C->A, C->B, A->B. E.g., for a triplet that corresponds to motif 6 there are two significant directional STTC pairs C->A and C->B.

Table 1: The coding of different motifs.

Motif	Coding	Edges
0	000	
1	001	A->B
2	010	C->B
3	011	C->B, A->B
4	100	C->A
5	101	C->A, A->B
6	110	C->A, C->B
7	111	C->A, C->B, A->B

In order to identify the motifs we use the directional STTC and the null distribution testing. When the null distribution test reports that the directional STTC is statistically significant, an edge is considered, and the corresponding bit of the motif is set to 1; otherwise it is set to 0.

Unique threshold null distribution test for directional STTC

To evaluate whether a directional STTC (A,B) value is significant we form a distribution based on the histogram of values, as follows:

For each neuron A of the set we circular shift the spike train of the neuron A (X') and estimate the directional STTC between the circular shifted spike train and all the other neurons of the set.

The histogram of the null distribution test is based on all the aforementioned directional STTC values. The significant threshold corresponds to the 0.99999 value of the normalized histogram. Thus, if the directional STTC value of two neurons is greater than the threshold, then we consider the edge between this pair as significant.

In this approach we set **one significant threshold value** based on all the produced directional values and compare each pair (A, B) with this unique threshold value.

Per pair threshold null distribution test for directional STTC

For a given pair (A,B) we circular shift the spike train of the neuron A 50 times and estimate the directional STTC between the circular shifted spike trains A and the spike train B . Based on these 50 values we estimate the mean value (mean_sttc_direct) and the standard deviation (std_sttc_direct). The significant threshold corresponds to:

Significant threshold = mean_sttc_direct + 3 std_sttc_direct

If the directional STTC value of the given pair (A, B) is greater than the threshold, then we consider the edge between this pair as significant. In this approach we set one significant threshold value per pair, based on the 50 produced values and compare each pair (A,B) with the corresponding significant threshold value.

Null distribution for conditional STTC

For a given triplet A->B|C we circular shift the spike train of the neuron C 50 times and estimate the conditional STTC between A->B and the circular shifted spike trains C. Based on these 50 values we estimate the mean value (mean_sttc_cond) and the standard deviation (std_sttc_cond). The significant threshold corresponds to:

Significant threshold = mean_sttc_cond + 3 std_sttc_cond

A second limitation in order to consider a triplet as significant is that the number of firing events of A that follows ΔT after each spike of C ('reduced A').
If the conditional STTC of the given triplet is greater than the significant threshold and the number of firing events of 'reduced A' is greater than 5, then we consider this triplet as significant.
In this approach we set one significant threshold value per triplet, based on the 50 produced values and compare each triplet (A-> B)|C with the corresponding significant threshold value.

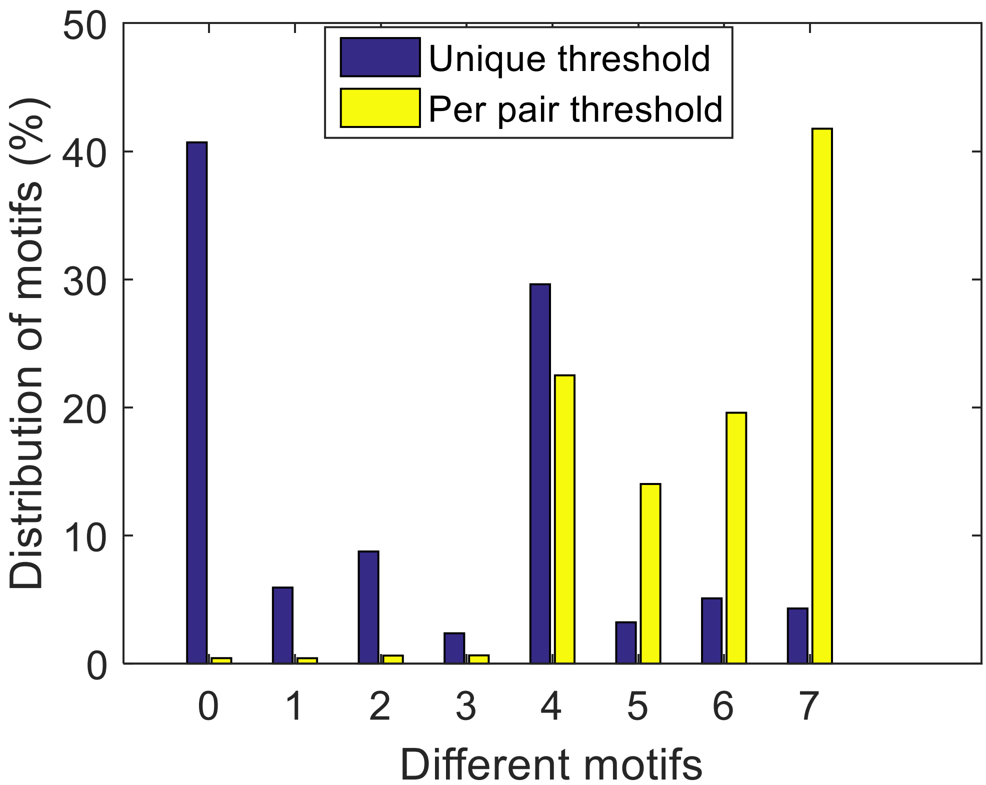


Figure 3: Distribution of the frequencies per motif using the unique threshold approach (blue color bars) and the per pair threshold approach (yellow color) of the null distributions testing.

Table 2: Number of triplets per motif considering the 2 approaches for the directional STTC

Motif	Unique threshold Significant Triplets	Per pair threshold Significant Triplets
0	122,663	1,285
1	17,895	1,268
2	26,388	1,884
3	7,135	1,938
4	89,273	67,844
5	9,718	42,266
6	15,357	59,037
7	12,977	125,884

- We observe that these two approaches give different distributions of the motifs.
- In the first approach the majority of the triplets appears to the motif 0 this could be due to the fact that in the first null distribution we set only one significant threshold and compare the

population of pairs with it. So we identify a high number of pairs that do not have a significant edge.

- For the second approach of the null distribution test we set a significant threshold value for each pair (A, B) and the majority of triplets appears on the motif 7. Also, we observe that the majority of the triplets appear for the motifs that there is an edge C->A (e.g., motifs 4, 5, 6 and 7).

For the significant pairs of the directional STTC based on the unique threshold approach we estimate the degree of connectivity for each neuron (Fig. 4). We consider an outgoing edge for a given pair (A, B) when the firing events of the spike train A procced the firing events of the spike train B. Similarly, an incoming edge is consider when the firing events of spike train A follow the firing events of the spike train B. The neurons that have degree of connectivity higher than 23, for the incoming or outgoing edges, we set them as hubs. We identify 12 and 5 hubs given the outgoing and incoming edges, respectively.

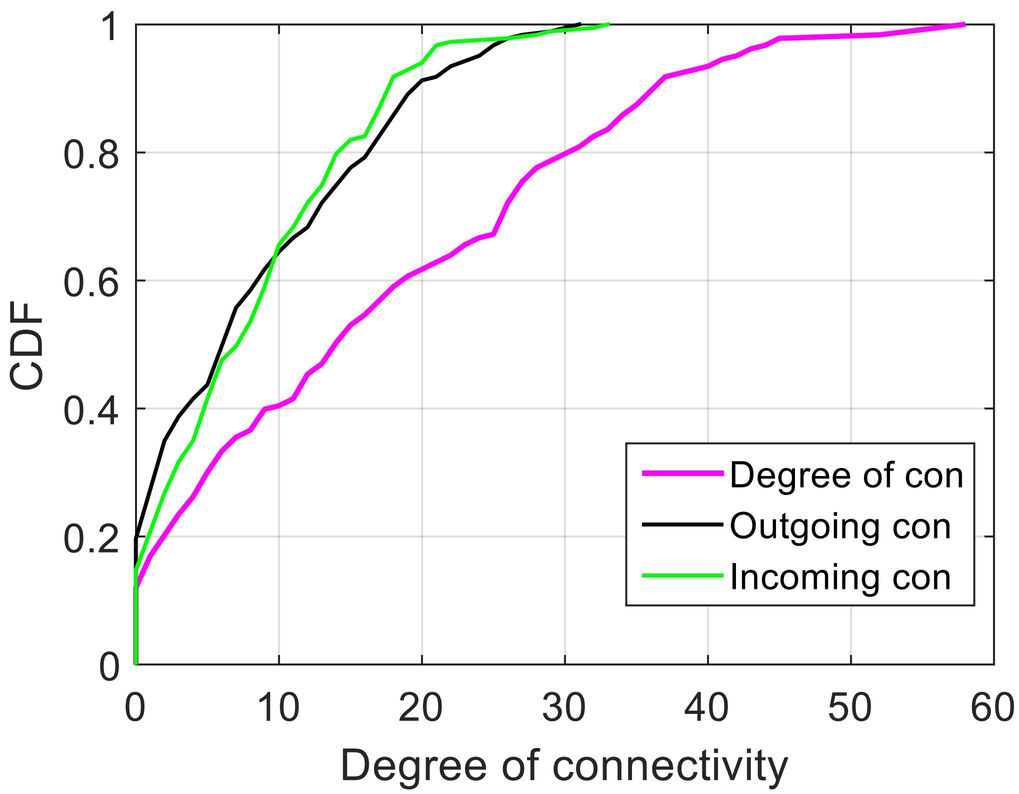
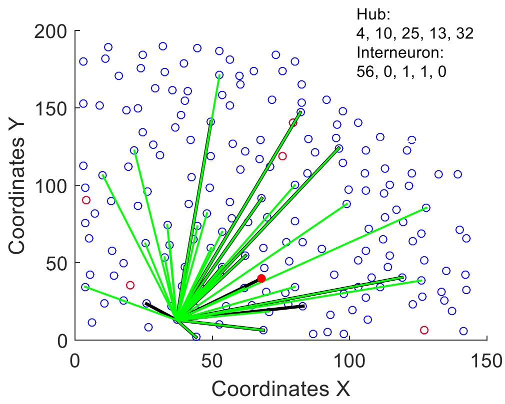
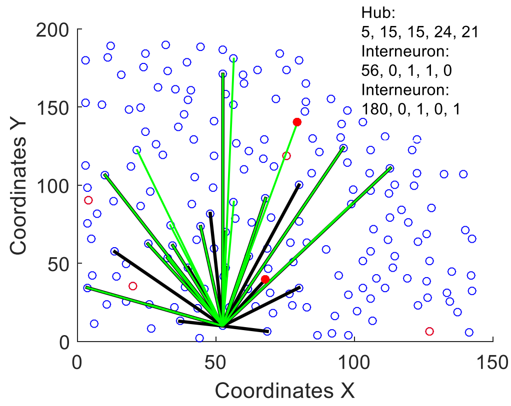
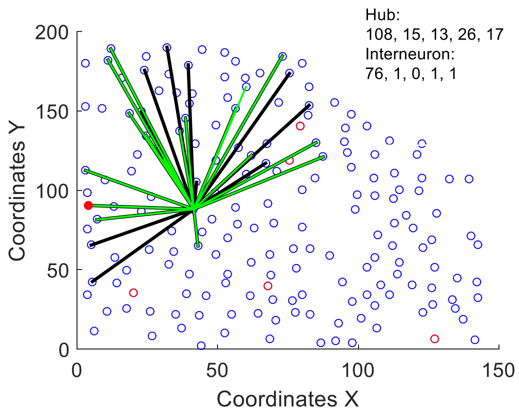
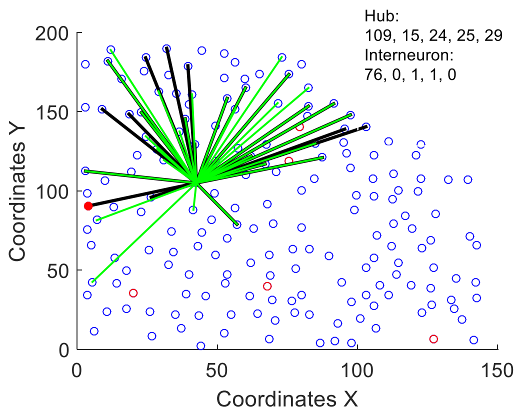


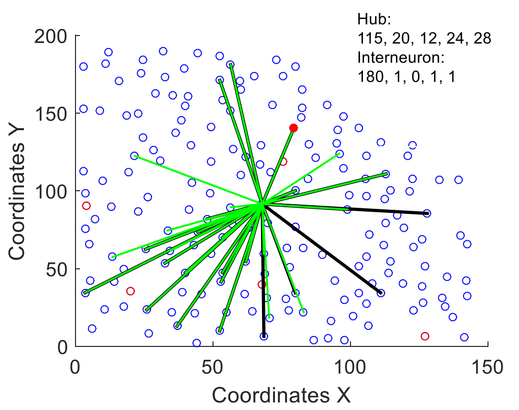
Figure 4: Degree of connectivity for the significant edges of the directional STTC.

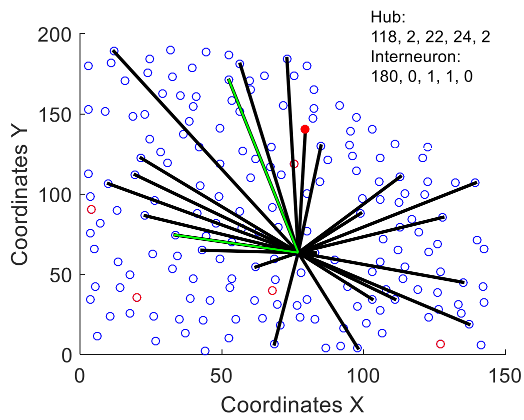

Hub:
4, 10, 25, 13, 32
Interneuron:
56, 0, 1, 1, 0
Coordinates Y
Coordinates X


Hub:
5, 15, 15, 24, 21
Interneuron:
56, 0, 1, 1, 0
Interneuron:
180, 0, 1, 0, 1
Coordinates Y
Coordinates X


Hub:
108, 15, 13, 26, 17
Interneuron:
76, 1, 0, 1, 1
Coordinates Y
Coordinates X


Hub:
109, 15, 24, 25, 29
Interneuron:
76, 0, 1, 1, 0
Coordinates Y
Coordinates X


Hub:
115, 20, 12, 24, 28
Interneuron:
180, 1, 0, 1, 1
Coordinates Y
Coordinates X


Hub:
118, 2, 22, 24, 2
Interneuron:
180, 0, 1, 1, 0
Coordinates Y
Coordinates X

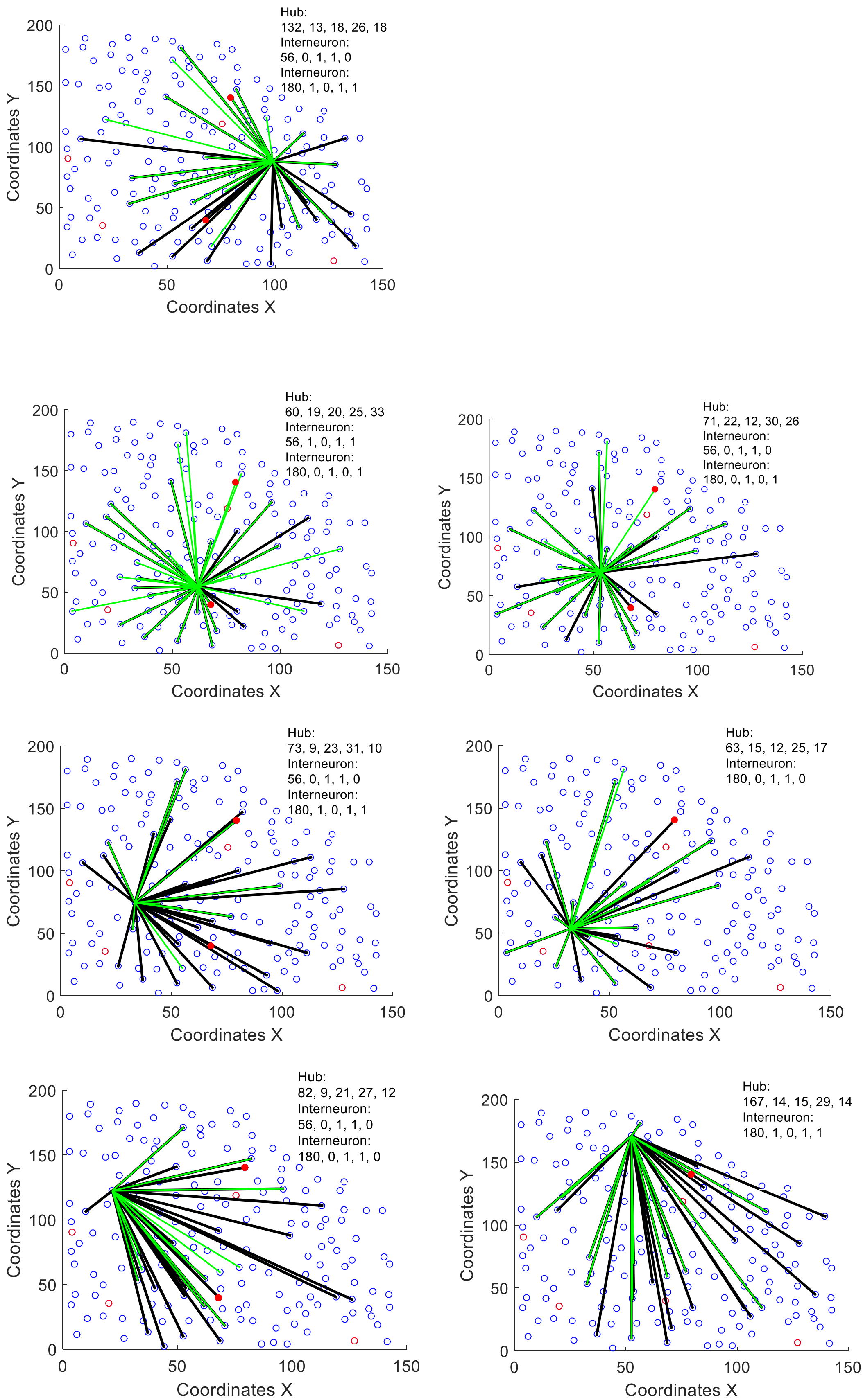


Figure 5: Network of the hubs the numbers on the legegend corresponds to [Hub id, bidirectional edges, one-way edges, outgoing, incoming], the same numbers appear for the

connected to the hub interneurons. The green and black color lines represent incoming and outgoing edges, respectively.

We observe some similarities based on the connections for hubs (Fig. 5):

- 4 – 5
- 109 – 108
- 115 – 118
- 60 – 71 – 73

While interneurons 56 and 76 appear high number of incoming and outgoing edges for several of the hubs.

3.2 Distribution of the motifs

Distribution of the frequency of triplets per motif for all triplets (Fig. 6) and the significant triplets (Fig. 7). Number of triplets per motif (Fig. 8).

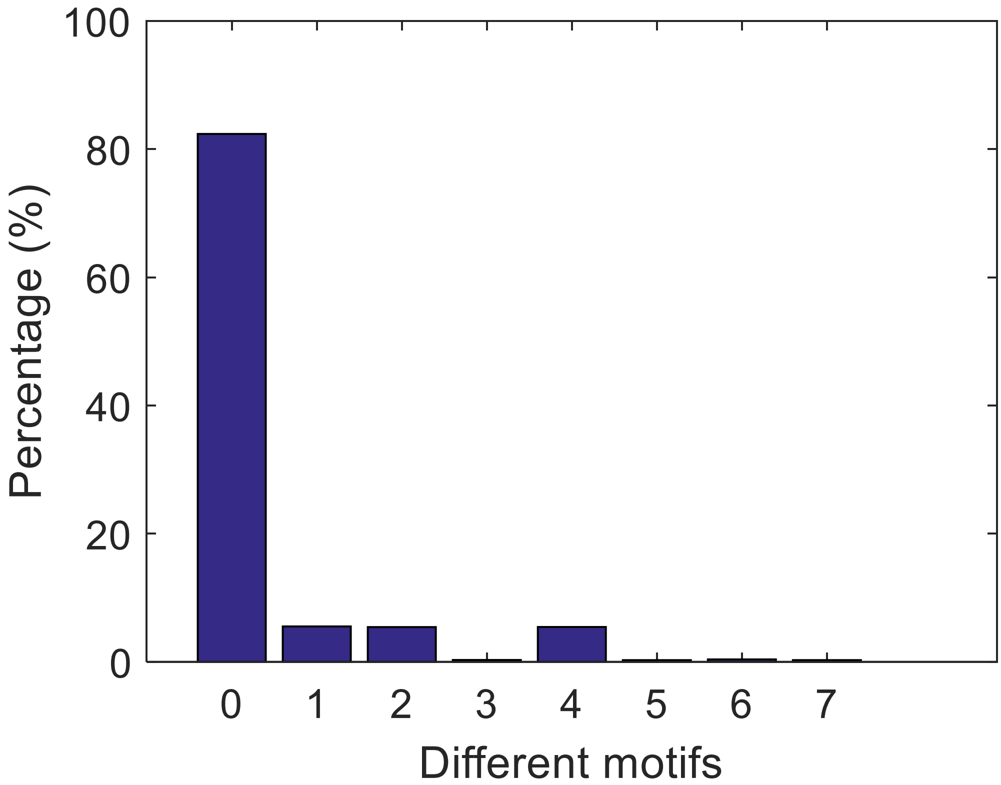


Figure 6: Distribution of the frequencies per motif, across all triplets.

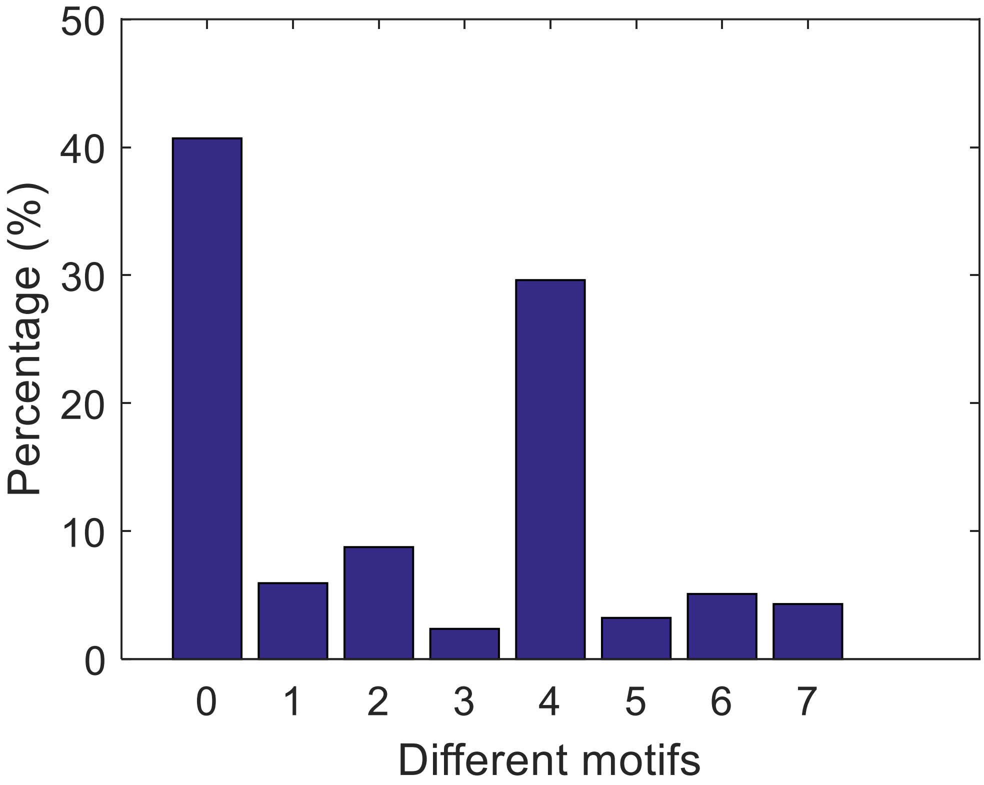


Figure 7: Distribution of the frequencies per motif, across significant triplets.

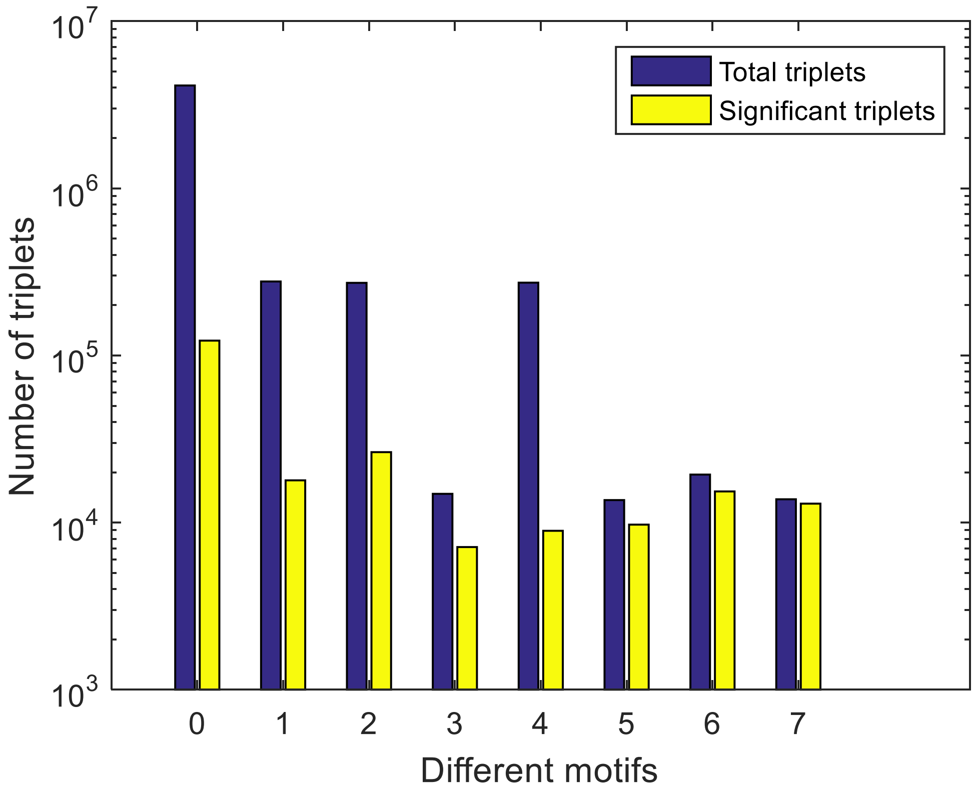


Figure 8: Distribution of the number of triplets per motif, across all triplets (blue bars) & significant triplets (yellow bars). Axis y is in log scale.

Table 2: Number of triplets per motif considering the entire dataset and the significant triplets

Motif	All Triplets (total number 5,007,834)	Significant Triplets (total number 301,406)
0	4,124,669	122,663
1	277,060	17,895
2	271,850	26,388
3	14,858	7,135
4	272,615	89,273
5	13,629	9,718
6	19,370	15,357
7	13,783	12,977

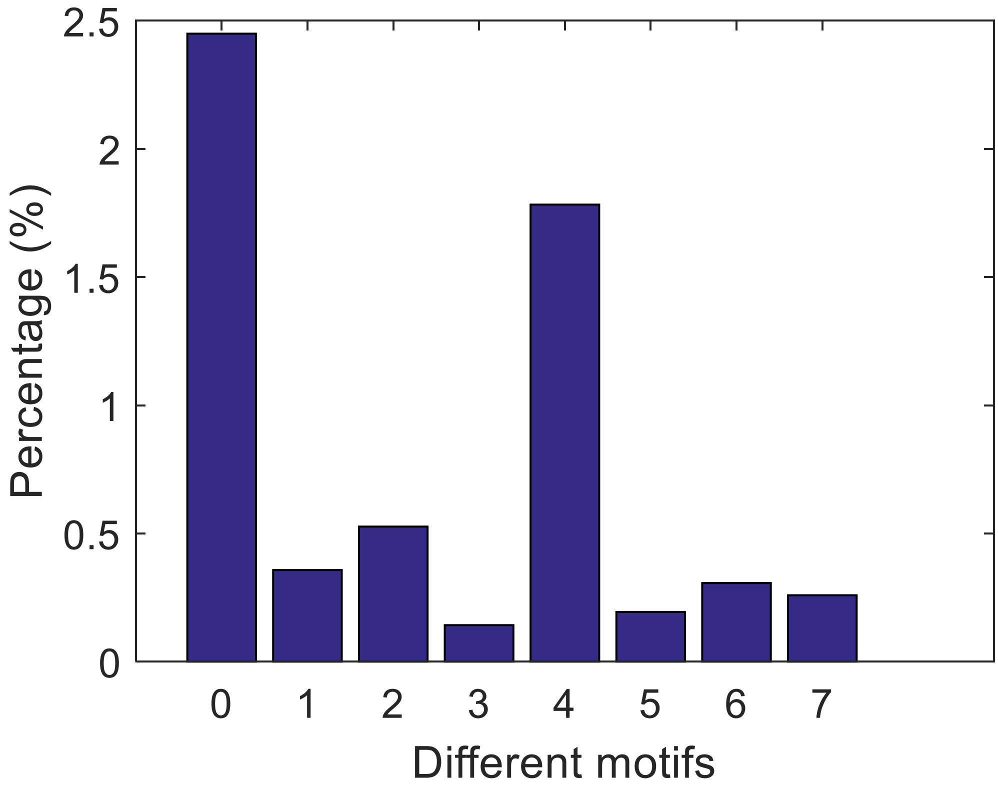


Figure 9: Distribution of the frequencies of the significant triplets per motif, across the entire dataset.

4. Neuron C across significant triplets

For each one of the neurons we estimate the frequency of appearance at the position C in the triplet (A->B)|C, considering **only the significant triplets**.

Type 3: PercC(i) = (Number of times that neuron i appears at position C / the number of significant triplets) * 100

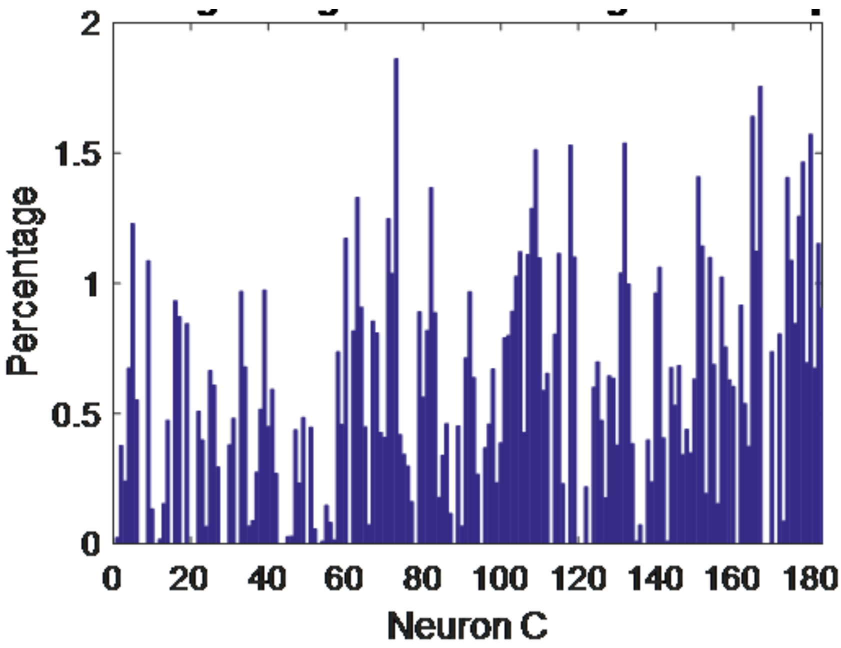


Figure 10: Percentages of the frequency of appearance at the position C for each neuron**.** E.g., neuron 5 has a frequency of appearance at the position C 1.24%, across all significant triplets.

Table 3: Statistics on percentages of the frequency of appearance for each neuron at the position C

	Min	**Max**	**Mean**	**Median**
Significant triplets	0	1.8619	0.5464	0.4618
Motif 0	0	1.7617	0.5464	0.5535
Motif 1	0	2.3079	0.5464	0.5141
Motif 2	0	2.6262	0.5464	0.2653
Motif 3	0	1.9481	0.5464	0.4205
Motif 4	0	2.0353	0.5464	0.4301
Motif 5	0	1.9140	0.5464	0.4631
Motif 6	0	4.8056	0.5464	0.1563
Motif 7	0	3.0978	0.5464	0.1541

Type 4: PercCperMotif(i,j) = (Number of times that neuron i appears at position C for the triplets that correspond to the motif j / the number of significant triplets of the motif j) * 100

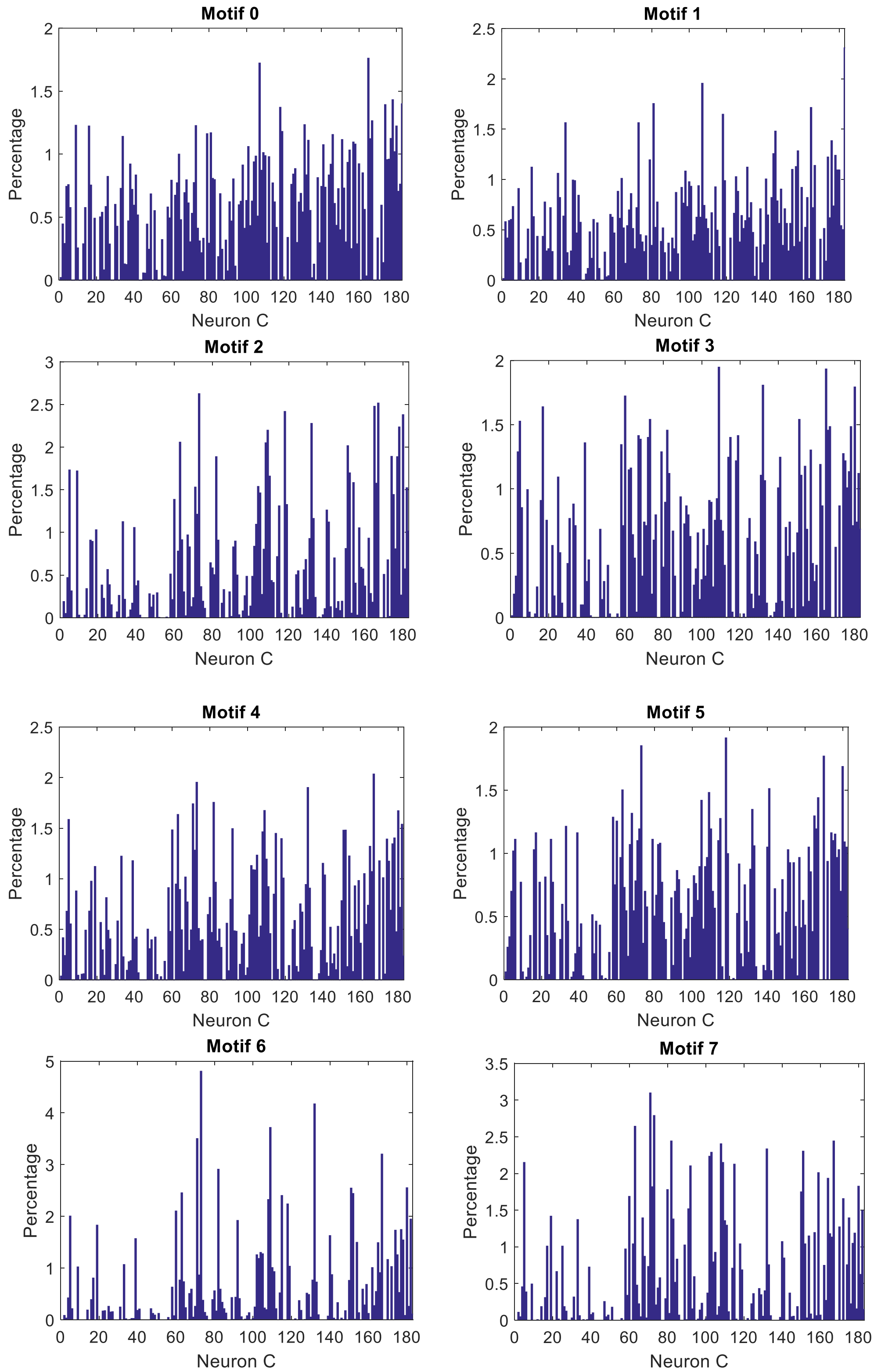


Figure 11: Percentages of the frequency of appearance at the position C for each neurons, per motif.

The CCDFs for all significant triplets, considering the same percentages applying type 1 for each neuron.

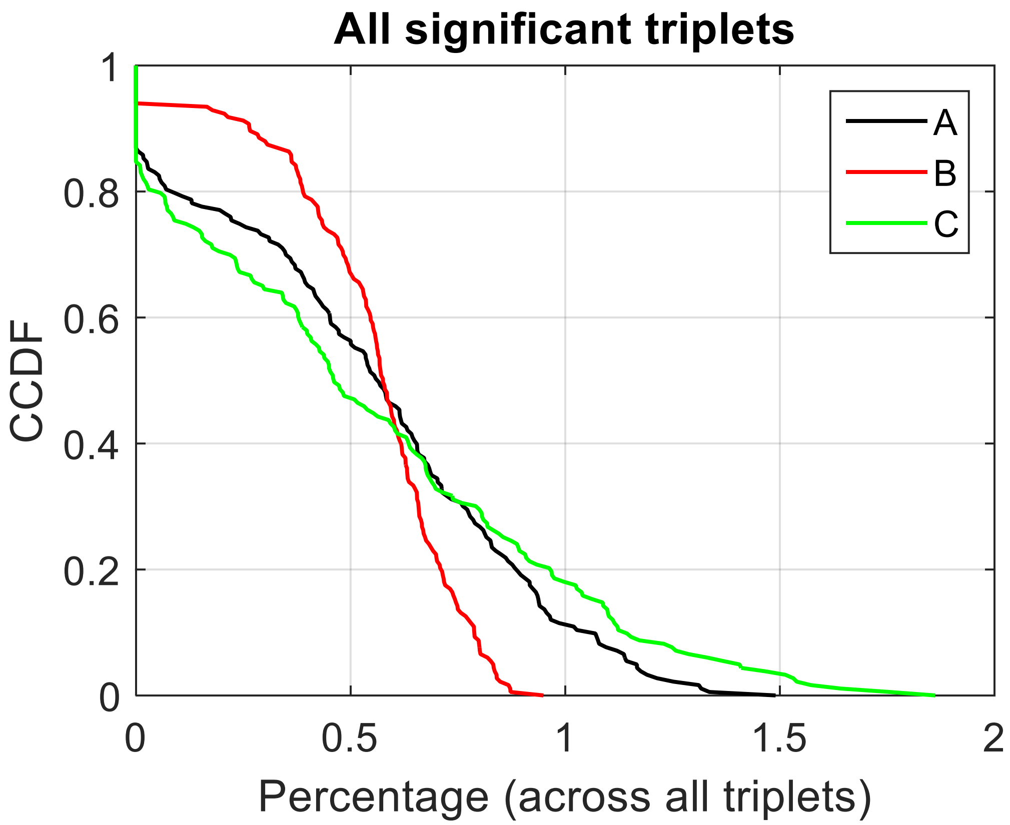


Figure 12: Percentages of the frequency of appearance for each neuron at the positions A, B & C of the triplet, for all significant triplets. E.g., the 50% of the neurons have frequency of appearance at position A higher than 0.6 % for all significant triplets.

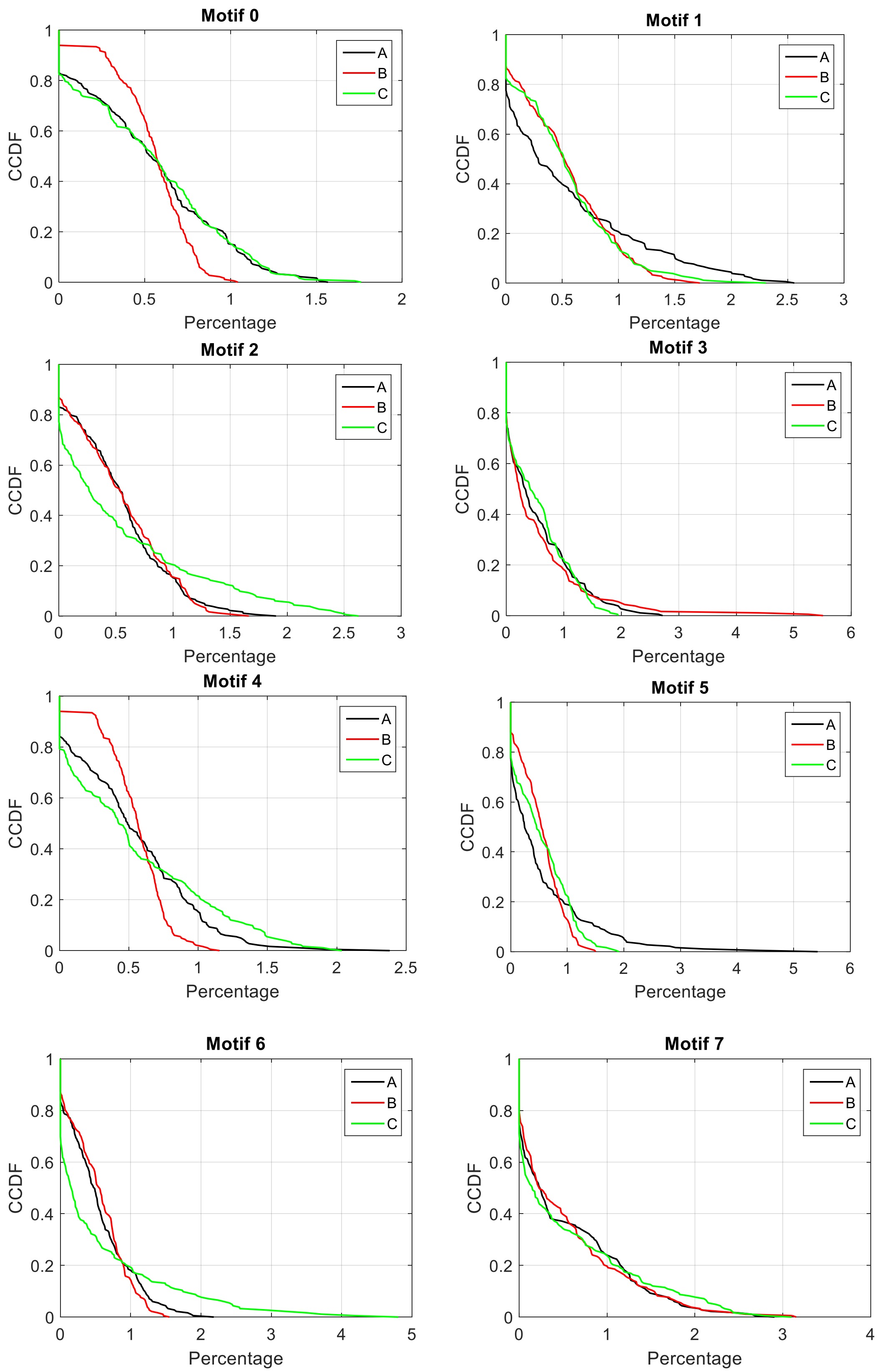


Figure 13: Percentages of the frequency of appearance for each neuron at the positions A, B & C of the triplet, per motif (for the significant triplets).

5. Clustering

5.1.1 Clustering of the neurons at position C for the 8 motifs
For the position C, considering the **percentages** applying type 2 for the 8 motifs:

Type 4: PercCperMotif(I,j) = (Number of times that neuron i appears at position C for the triplets that correspond to the motif j / the number of significant triplets of the motif j) * 100

Number of tested clusters k = 2:20

Best clustering k = 2
Cluster 1: 66 neurons (36.07 %)
Cluster 2: 117 neurons (63.93 %)

Table 4: Centroids of the 2 clusters for the 8 motifs

	Motif 0	**Motif 1**	**Motif 2**	**Motif 3**	**Motif 4**	**Motif 5**	**Motif 6**	**Motif 7**
Centroid 1	0.8983	0.8100	1.2700	1.1221	1.1336	1.0738	1.3603	1.2799
Centroid 2	0.3479	0.3978	0.1383	0.2217	0.2153	0.2490	0.0874	0.1327

- In the first cluster belongs the neurons with higher percentages for all the 8 motifs, they participate often at the position C.
- While in the second cluster belongs the neurons that they don't participate often at the position C in the significant triplets.

5.1.2 Clustering of the neurons at position C for 4 motifs
For the position C, considering the **percentages** applying type 4 for the 4 motifs, that there are edge A->B (for the directional STTC).
Number of tested clusters k = 2:20

Best clustering k = 2
Cluster 1: 101 neurons (55.19 %)
Cluster 2: 82 neurons (44.81 %)

Table 5: Centroids of the 2 clusters for the 4 motifs

	Motif 1	**Motif 3**	**Motif 5**	**Motif 7**
Centroid 1	0.3288	0.1435	0.1795	0.0839
Centroid 2	0.8145	1.0428	0.9984	1.1161

We observe the same trend as the previous clustering 2.1.1 with the 2 clusters the first one the neurons that they don't participate often at the position C, while the second one with the neurons that they participate often at the position C.

5.2 Clustering of the neurons at position A, B & C
By applying type 4 for each neuron we estimate the percentages not only for position C but also for A and B for all the significant triplets.

Number of tested clusters k = 2:20
Best clustering k = 2
Cluster 1: 101 neurons (55.19 %)
Cluster 2: 82 neurons (44.81 %)

Table 6: Centroids of the 2 clusters for the positions A, B & C

	A	**B**	**C**
Centroid 1	0.8196	0.6725	0.8641
Centroid 2	0.2100	0.3912	0.1551

Same trend for the two clusters as clustering 5.1.1 & 5.1.2.

5.3 Clustering of the neurons at position A, B & C
For each neuron we estimate the:
NumofApp: number of times that a neuron i appears at all positions A, B & C
Type 5: percentage of times that a neuron i appears at each position across the NumofApp(i)

Number of tested clusters k = 2:20
Best clustering k = 2
Cluster 1: 143 neurons (83.14 %)
Cluster 2: 29 neurons (16.86 %)   Interneurons: 10 & 28

Table 7: Centroids of the 2 clusters for the positions A, B & C

	A	**B**	**C**
Centroid 1	33.95	33.83	32.20
Centroid 2	6.46	90.21	3.31

- In the first cluster belongs the neurons that participate equally at each position.
- While in the second cluster belongs the neurons that participate more at position, than at the other positons.

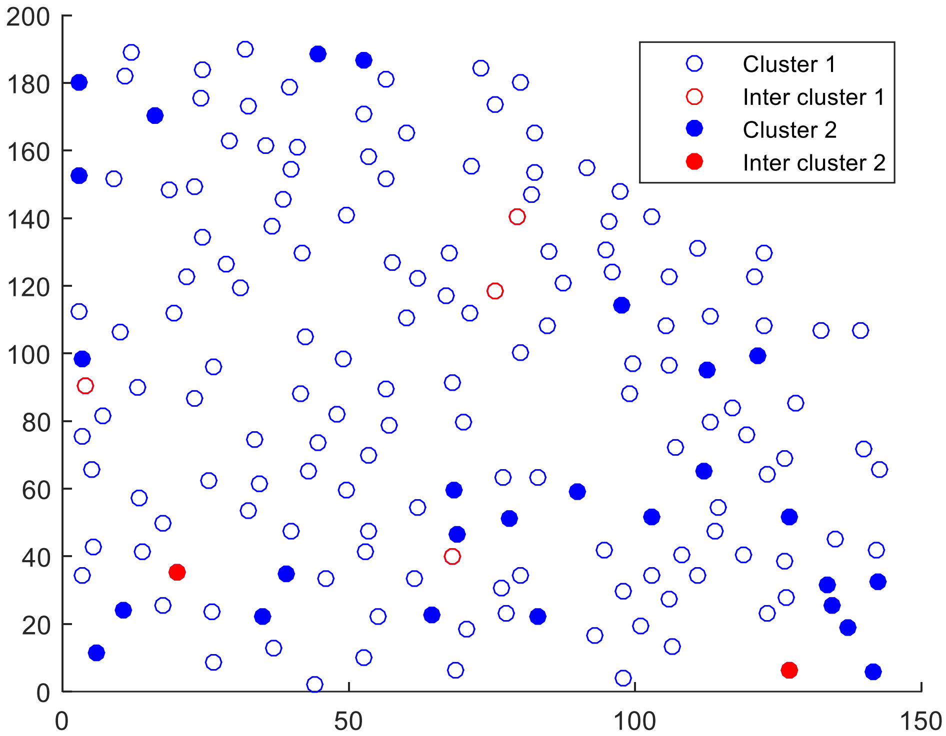


Figure 14: Network of the 2 clusters considering all the significant triplets

5.4 Clustering of the neurons at position A, B & C per motif
By applying the type 5 for each neuron we estimate the percentages per motif (considering the triplets that corresponds in each motif).
Best clustering k = 2
Cluster 1: neurons (69.77 %), interneurons [10 76 180]
Cluster 2: neurons (30.23 %), interneurons [28 56 149]

Table 8: Centroids of the 2 clusters for the positions A, B & C

	Motif 0			**Motif 1**			**Motif 2**			**Motif 3**		
	A	**B**	**C**	**A**	**B**	**C**	**A**	**B**	**C**	**A**	**B**	**C**
Cen1	33.75	30.66	35.58	32.39	31.25	36.34	35.31	35.57	32.10	35.93	26.88	37.17
Cen2	16.62	71.78	11.58	3.27	55.22	28.04	32.32	50.34	1.94	9.61	49.41	8.28

	Motif 4			**Motif 5**			**Motif 6**			**Motif 7**		
	A	**B**	**C**	**A**	**B**	**C**	**A**	**B**	**C**	**A**	**B**	**C**
Cen1	32.41	31.99	35.59	28.48	32.50	39.01	33.38	33.46	32.32	32.24	31.64	34.44
Cen2	22.08	73.39	4.51	6.54	69.14	9.01	36.20	45.62	0.86	8.97	47.73	2.91

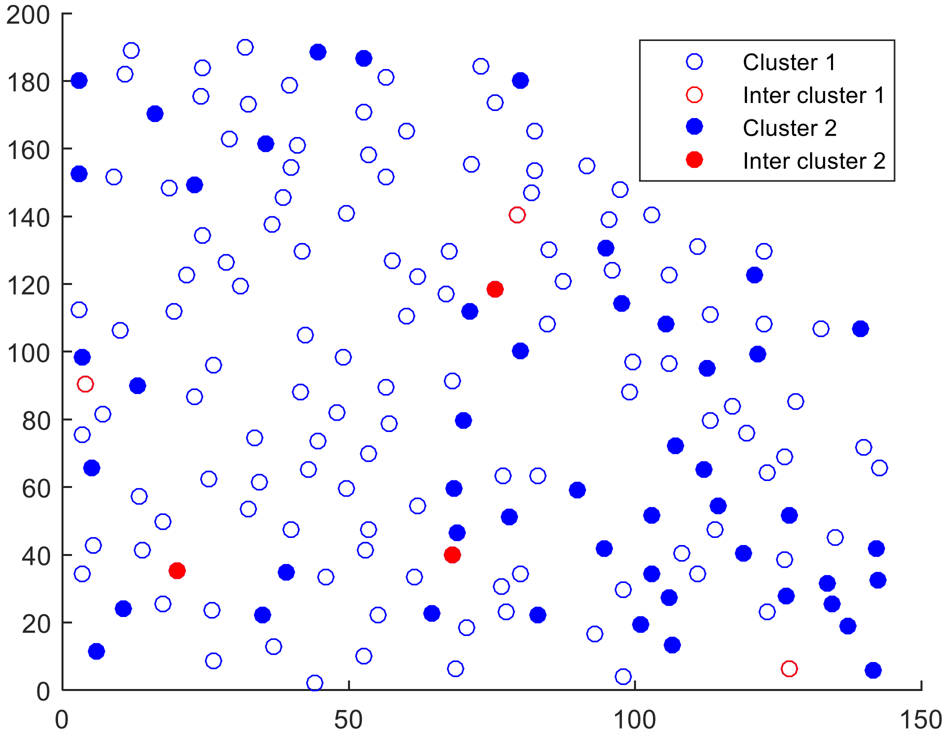


Figure 15: Network of the 2 clusters considering the different motifs

Clustering of the entire dataset vs. clustering per motif

- The number of neurons that belongs in the second cluster increases for the clustering per motif
- For the clustering per motif 3 interneurons belongs in the first cluster & 3 other in the second

5.5 Clustering of the edges

For the different pairs A->B (significant edges for directional STTC), we estimate the occurrences of this pair on the significant triplets of each scenario.
Number of tested clusters k = 2:20

Best clustering k = 5
Cluster 1: 355 pairs (18.91 %)
Cluster 2: 347 pairs (18.49 %)
Cluster 3: 401 pairs (21.36 %)
Cluster 4: 485 pairs (25.84 %)
Cluster 5: 289 pairs (15.40 %)

Table 9: Centroids of the 5 clusters for the 4 motifs

	Motif 1	**Motif 3**	**Motif 5**	**Motif 7**
Centroid 1	8.5352	9.0056	3.1549	6.8704
Centroid 2	6.9308	2.5620	3.1326	13.2853
Centroid 3	17.0948	3.3117	6.0773	5.9077
Centroid 4	6.1320	2.2928	3.0969	3.3505
Centroid 5	9.1038	2.1073	12.3599	6.6920

Cluster 4: low level of occurrences for all motifs
Cluster 1: High occurrences for Motif 3, medium for all others
Cluster 2: High occurrences for Motif 7, medium for all others
Cluster 3: High occurrences for Motif 1, medium for all others
Cluster 2: High occurrences for Motif 5, medium for all others

6. Interneurons & coverage of the network

6.1 Interneurons in the triplets

Considering the significant triplets that correspond at each motif,
Type 6: the number of the triplets that they have an interneuron at position A / number of significant triplets of this motif
The same calculation is performed for positions B & C.

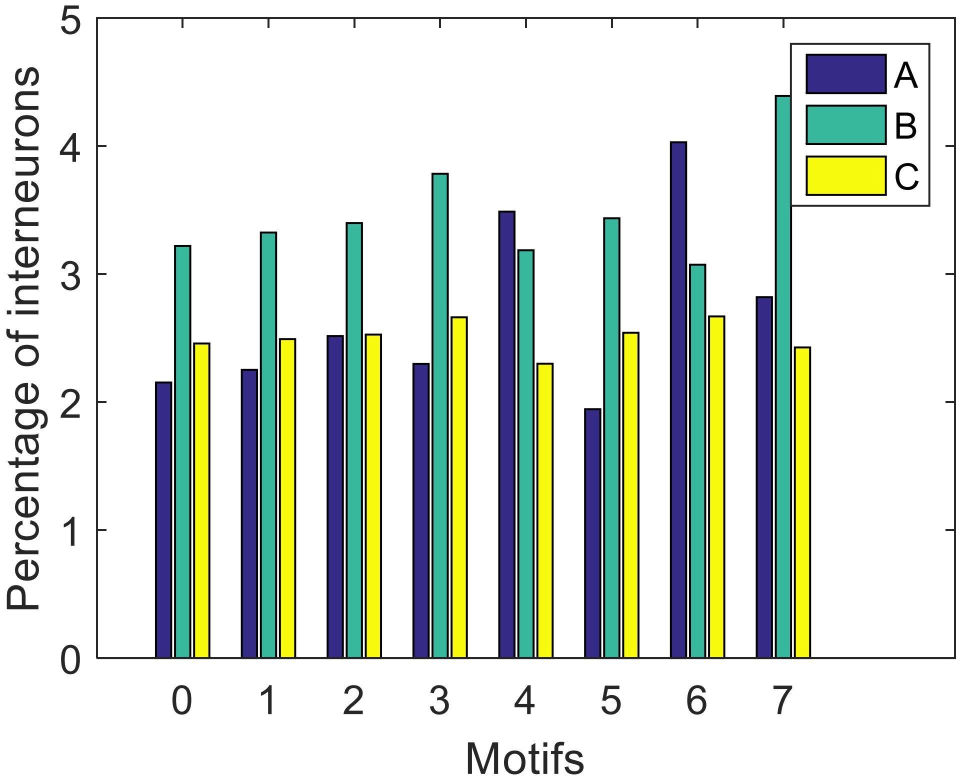


Figure 16: Percentages of triplets that have an interneuron at positions A or B or C per motif (for the significant triplets). E.g., for motif 1 2.5% of the triplets have an interneuron at position C.

Table 10: The interneurons that appear at least one time at a position of the triplet, per motif

	A	B	C
Motif 0	10 56 76 149 180	10 28 56 76 149 180	10 56 76 149 180
Motif 1	10 56 76 180	28 56 76 149 180	10 56 76 149 180
Motif 2	10 56 76 149 180	28 56 76 149 180	10 56 76 180
Motif 3	10 56 76 180	28 56 76 149 180	10 56 76 180
Motif 4	56 76 149 180	10 28 56 76 149 180	10 56 76 180
Motif 5	56 76 180	28 56 76 149 180	10 56 76 180
Motif 6	56 76 149 180	28 56 76 149 180	56 76 180
Motif 7	56 76 180	56 76 149 180	56 76 180

- The interneurons in this dataset are: 10 28 56 76 149 180.
- Interneuron 28 does not appear at positions A & C.
- At positions A & C appear less interneurons than in B, for the most of the motifs (0, 3 ,4, 5, 6, 7)

6.2 Coverage of the network

For each the positions of the triplet we estimate how many different neurons appeared at least one time.

- For the motifs 0, 4 and all significant triplets (full) at position B appeared all the neurons of the network.
- For all motifs at position B appeared the highest number of different neurons.

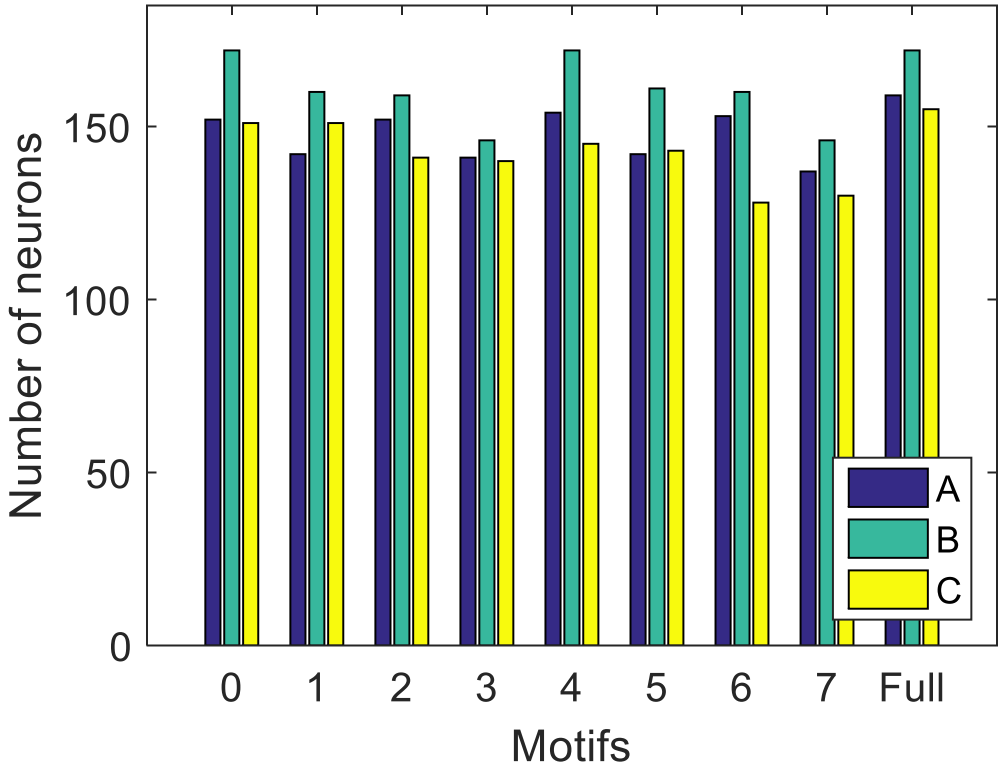


Figure 17: Number of the different neurons that appeared at the positions A, B & C of the triplet, per motif & for the significant triplets (full). E.g., for motif 7 at position A appear 137 different neurons.

7. Edges A->B

For the different pairs A->B, we estimate the number of neuron C that they are connected, for the significant triplets.

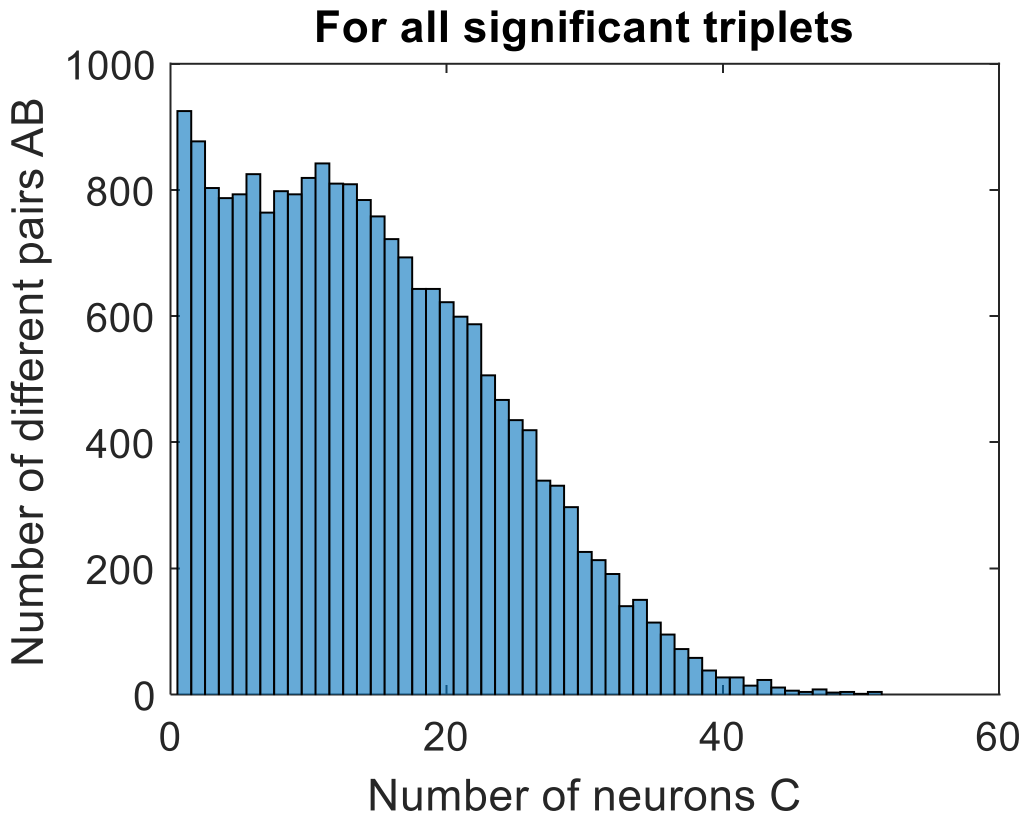


Figure 18: Number of neuron C that they are connected with different A->B for the significant triplets. E.g., there are more than 900 different pairs that they are connected with at least one neuron C.

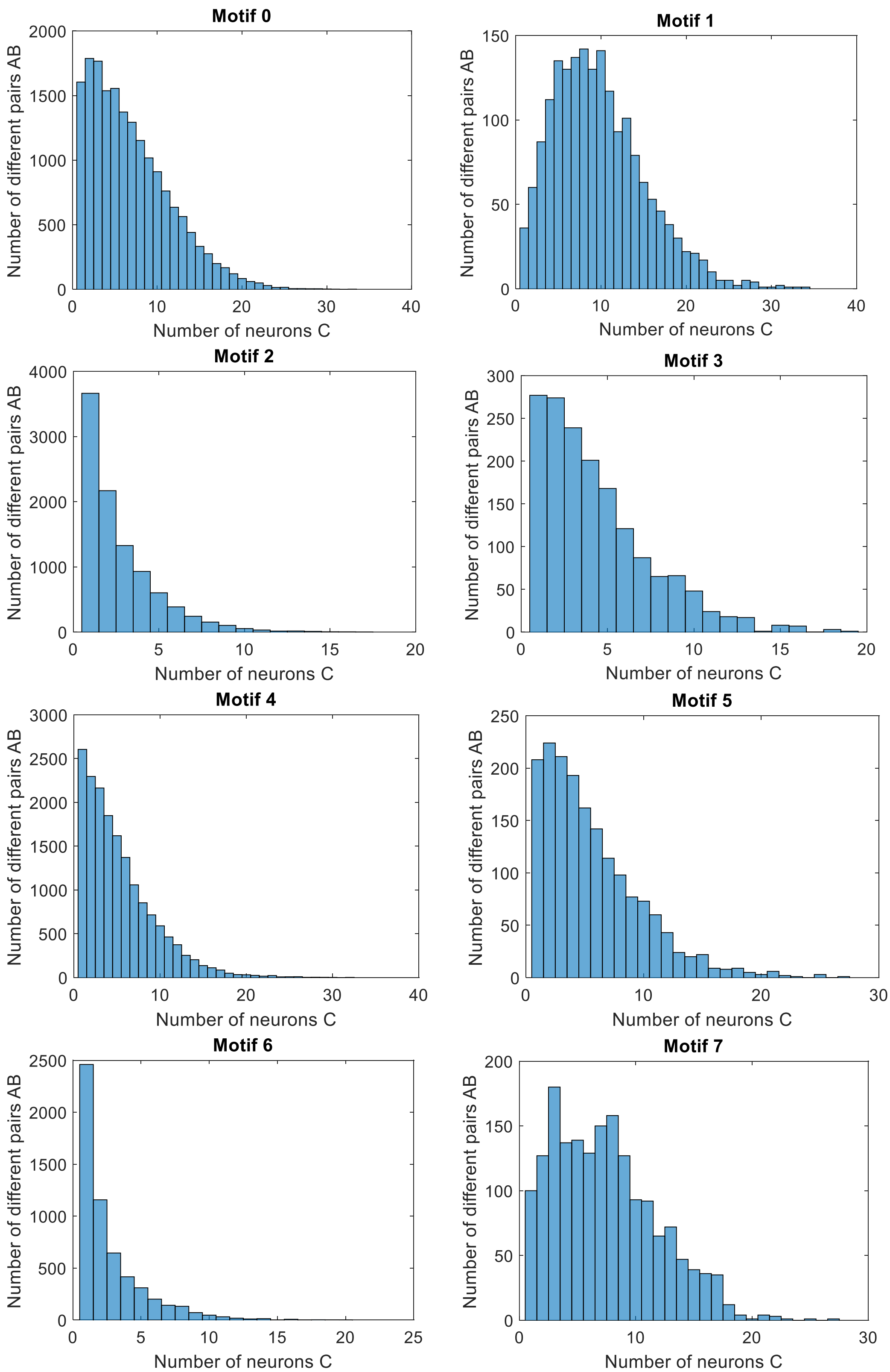


Figure 19: Number of neuron C that they are connected with different A->B per motif (considering the significant triplets).

- For the motifs 2, 3, 4 & 6 we observe that the highest number of different triplets are connected with one neuron C.

8. Euclidean distance of pairs

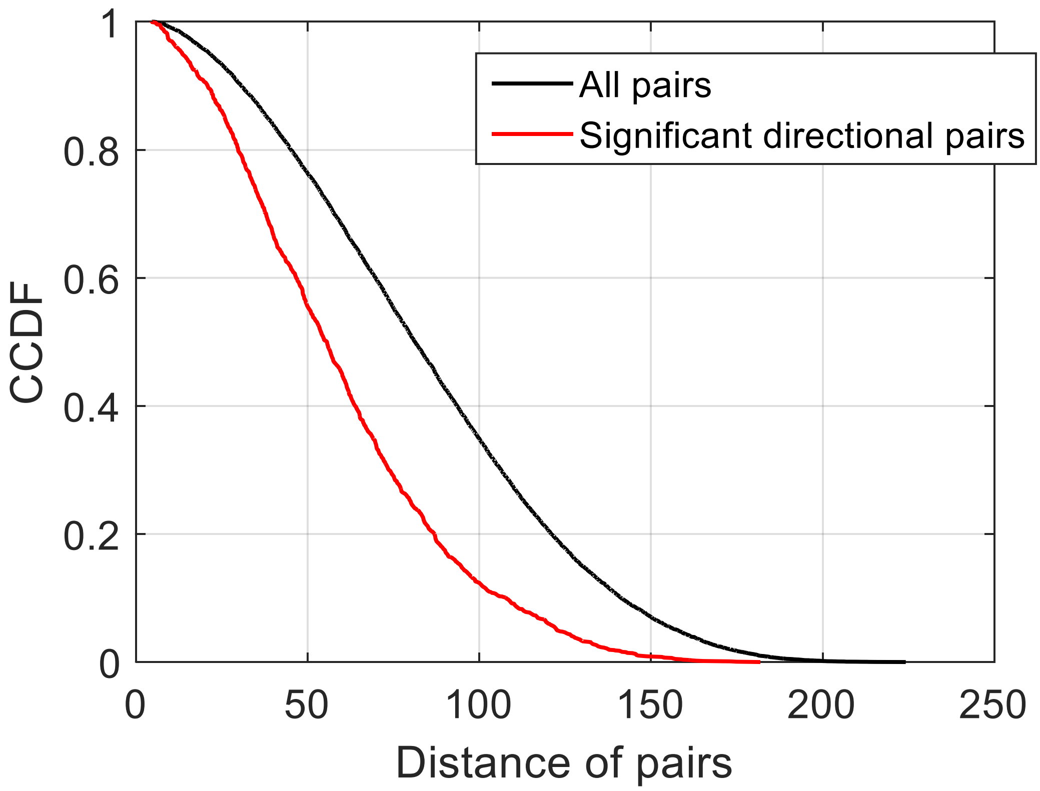


Figure 20: Distance among all pairs of the entire dataset & the significant directional pairs. E.g., 50% of all possible pairs have Euclidean distance higher than 85.

Table 11: Statistics on the distances

	Min	Max	Mean	Median
All pairs	4.5637	224.1897	84.1741	81.2989
Signif dir pairs	4.5637	181.8399	59.6294	55.6256

5.1 Distance of significant pairs & among all pairs of neurons at position C

For each motif we consider all different pairs A->B that they have more than 1 neuron C, then we estimate the distance between A & B and the distance among all possible pairs of the C.

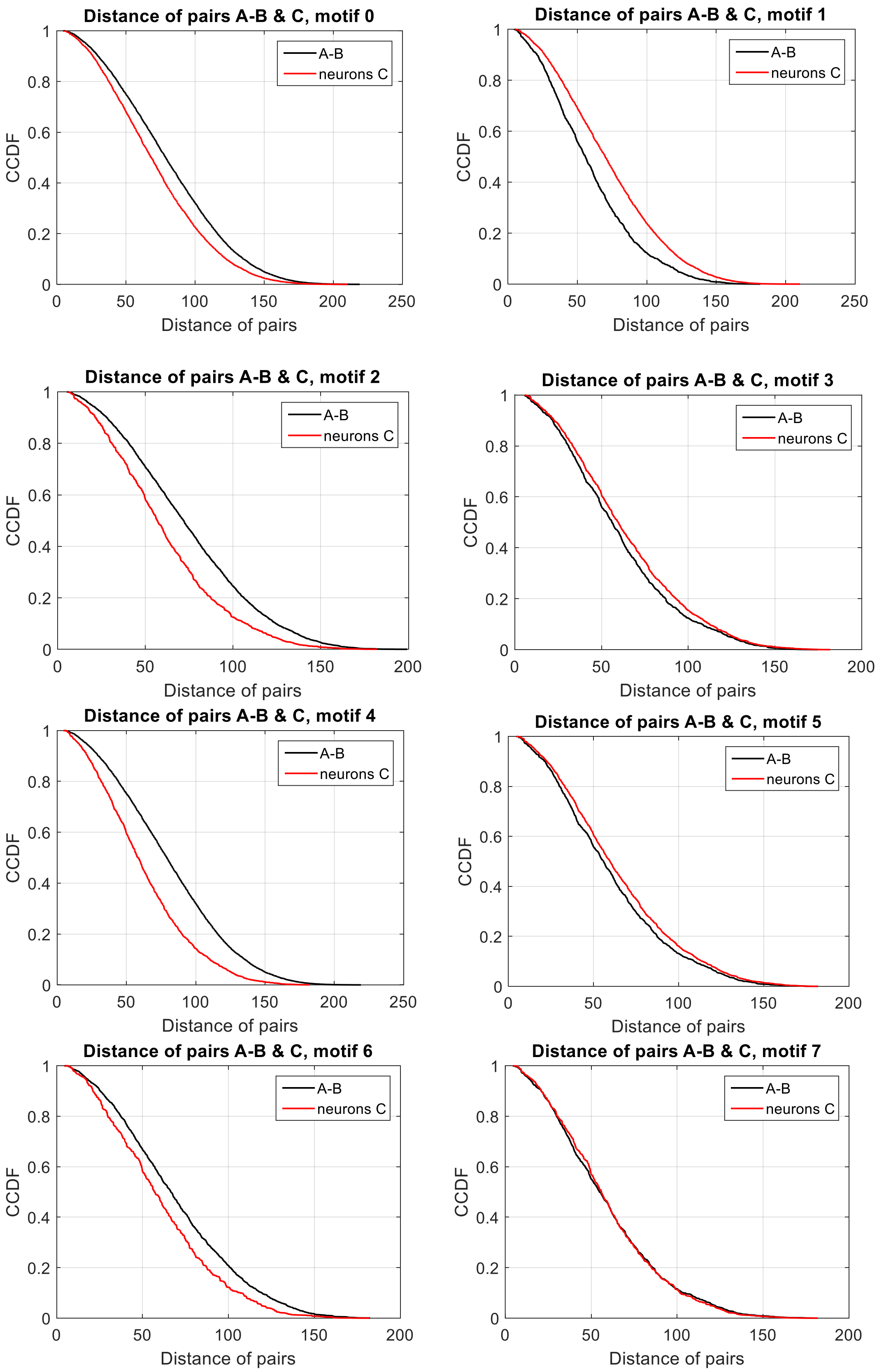


Figure 21: Distance of significant pairs & distance among all pairs of neurons at position C.

Table 11: Statistics on the distances of significant pairs & distance among all pairs of neurons at position C

Motif	Pairs	Min	Max	Mean	Median
0	**A->B**	4.5637	219.12	81.11	78.84
	Neurons C	5.2439	210.4081	71.7130	68.3533
1	**A->B**	5.2439	199.3173	74.2764	71.8415
	Neurons C	5. 2439	210.4081	73.0941	70.0647
2	**A->B**	5.2439	219.1292	81.2370	79.1844
	Neurons C	5.7462	182.0628	60.8695	56.7445
3	**A->B**	4.5637	182.2752	69.8314	66.4777
	Neurons C	5.7462	181.8399	63.9582	59.6191
4	**A->B**	4.5637	181.8399	59.7582	55.8195
	Neurons C	14.9005	182.0628	62.5833	58.5035
5	**A->B**	5.7462	174.9209	60.1573	55.9977
	Neurons C	4.5637	181.8399	64.3392	59.7126
6	**A->B**	5.7462	181.8399	60.3638	55.9131
	Neurons C	4.5637	181.8399	60.7964	57.0026
7	**A->B**	4.5637	181.8399	59.2206	54.8579
	Neurons C	4.5900	181.4142	59. 4472	55.9131