

COMPARING THE 3D SPATIAL DISTRIBUTION OF MOUSE AND HUMAN HIPPOCAMPAL CA1 SINAPSES

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Abstract

Three-dimensional spatial organization of synapses in hippocampal CA1 field is still unknown. The combination of focused ion beam milling and scanning electron microscopy (FIB/SEM) allows detailed three-dimensional reconstructions of synaptic junctions. Recent research has analyzed the three-dimensional spatial distribution of synapses in all six layers of the rat somatosensory cortex, where random sequential adsorption (RSA) point process was found to fit the data. In this work we focus on the hippocampal CA1 field and compare human versus mice synapses fully reconstructed using FIB/SEM. We analyze a total of 7,965 mice synapses (from three animals) and 5,562 human synapses (from four subjects), in both cases from three layers, from the deepest level to the surface: *stratum oriens*, *stratum radiatum* and *stratum lacunosum-moleculare*. Different samples, layers, animals/subjects were aggregated using RSA replicated spatial point processes. Humans versus mice were finally compared which is important in translational inter-species comparisons. The results show that mice have more synapses per unit volume than humans, smaller synaptic junction shapes and individual samples fit RSA processes more easily in humans than in mice, although in both this is often the case. There are differences between layers. First, log-normality of Feret's diameters is not rejected only in layer I of mice. Mean and variance estimates are homogeneous between layers for humans but is decreasing from layer I to III in mice. Second, synaptic density is much higher in layer II in humans but increases from layer I to III in mice. Third, layer III fits an RSA process both in humans and mice but layer I only complies with RSA in humans. Finally, human synapse distributions are more prone to form clustered patterns than in mice, which present per-layer repulsion-followed-by-clustered patterns.

OUTLINE

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- Per-layer analysis
- Per-animal analysis
- Altogether
- Tabular summaries

HUMAN

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- Per-sample analysis
- Per-layer analysis
- Per-subject analysis
- Altogether
- Tabular summaries

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ACKNOWLEDGMENTS

REFERENCES

INTRODUCTION

Previous research has analyzed the three-dimensional spatial distribution of synapses in all six layers of the rat somatosensory cortex (Anton-Sánchez et al, 2014). In human hippocampal CA1 field, some descriptive statistics about synaptic organization have been studied in Montero-Crespo et al. (2020). However, there is no work on modeling the synaptic 3D spatial distribution in humans and mice and its subsequent comparison. This is the contribution of this paper.

We study whether each spatial synaptic pattern conforms to an RSA process. In these processes, synaptic junctions would be distributed almost randomly in space, with the only constraint that they cannot overlap. The overlapping stems from the volume occupied by the synapse, that is a random variable. Thus, we first fit a lognormal distribution to the Feret's diameters, assuming then that synaptic junction volume may be approximated as a sphere. We also study the (different) synaptic densities. Per-sample, per-layer, per-animal/subject and per-species comparisons are made. When grouping samples as e.g., in the per-layer study, replicated spatial point processes must be considered and the corresponding summary functions have to be aggregated, having into account the number of synapses for each sample in each group. See Anton-Sánchez et al. (2014) and Merchán-Pérez et al. (2014) for further details on the statistical procedure.

The analyses were performed with the 3DSynapsesSA, a web-based tool developed by the Computational Intelligence Group at the Universidad Politécnica de Madrid (Spain), supported by European Union's Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 604102 (Human Brain Project) and by the European Union's Horizon 2020 Framework Programme for Research and Innovation under the Specific Grant Agreement No. 785907 (Human Brain Project SGA2). The tool is freely available at: <https://neurosuites.com:3838/apps//3DSynapsesSA/>

The results shown below have three different outputs. First, for fitting the Feret's diameters to a log-normal distribution we report its estimated parameters, the observed histogram versus expected density curve as well as the p-value of the one sample Kolmogorov-Smirnov goodness-of-fit-test. Second, for fitting an RSA process, we report the process intensity (mean number of synapses/ μm^3) and simulation-based envelopes to test the RSA null hypothesis. RSA envelopes (in green) are approximated from 198 RSA simulations (99 for computing the average L function as an estimate of the theoretical mean value of the L summary statistic for the RSA model; and other 99 for obtaining the global envelope width). The L function of the experimentally observed samples are shown in blue. For groups of replicates (layers, animals...), the aggregated L function is shown as the solid blue curve, whereas the L function of each observed sample within the group are the dashed blue line curves. The theoretical L function for the CSR model is the red curve, shown for visual comparison only. Third, the F, G, K and L summary functions are plotted to visually compare the experimentally observed sample (blue) and the tested (simulated-based) functions of the RSA model (green) as well as the exact functions of the CSR model (red).

MOUSE

Data samples

Data come from Javier DeFelipe's lab and correspond to three c57 mice identified as ID2, ID4 and ID28. One stack was obtained from the three hippocampal layers and animals, except for ID2 where two stacks of serial sections were obtained from each layer, *stratum lacunosum-moleculare* (layer I), *stratum radiatum* (II), and *stratum oriens* (III). The *stratum pyramidale* layer was not included because it lacks neuropil. This gives a total of 12 samples. The data set contained the 3D spatial position of the centroids of the synaptic junctions, an estimation of their sizes using the Feret's diameter (diameter of the smallest sphere circumscribing the synaptic junction) and whether each was included/excluded within/from the unbiased counting frame (CF). There was also information about whether the synapse was excitatory (asymmetric or AS) or inhibitory (symmetric or SS), although we considered all as a whole due to the small percentage of symmetric synapses (around 3.6% of the total number of synapses). After filtering synapses within the CF, we obtained 7,965 synapses, see the table.

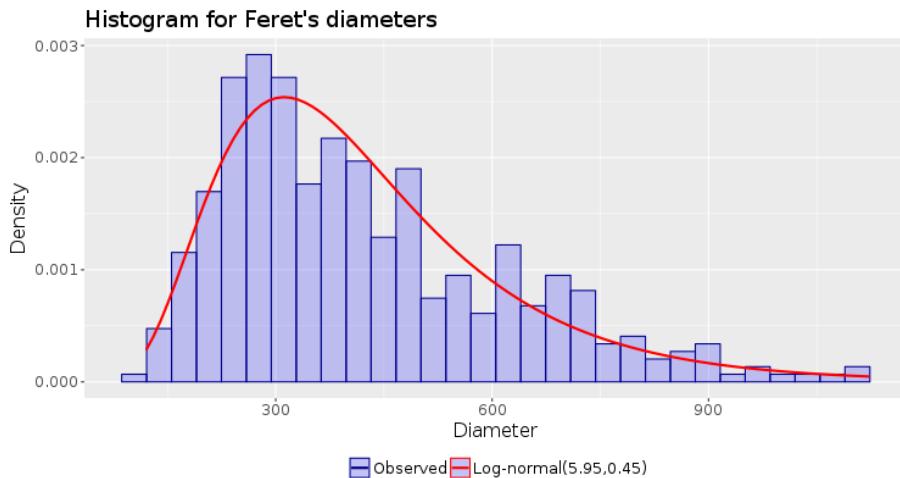
Layer	Sample	Animal	No. of AS	No. of SS	No. of AS within CF	No. of SS within CF	No. of valid synapses
LacMol (I)	1 (LacMol2)	ID2	595	47	393	33	426
	2 (LacMol3)	ID2	721	60	230	28	258
	3	ID4	688	62	474	35	509
	4	ID28	650	55	439	40	479
Radiatum (II)	5	ID2	828	27	544	16	560
	6 (Radiatum2)	ID2	1468	37	676	19	695
	7	ID4	1225	23	686	21	707
	8 (Radiatum-soma)	ID28	1758	36	1079	28	1107
Oriens (III)	9	ID2	1368	24	1003	18	1021
	10 (Oriens2)	ID2	2096	29	489	3	492
	11	ID4	1322	31	886	27	913
	12	ID28	1645	40	777	21	798
TOTAL	12	3	14364	471	7676	289	7965

PER-SAMPLE ANALYSIS (I 1-to-4, II 1-to-4 and III 1-to-4):

Sample1-Layer I:

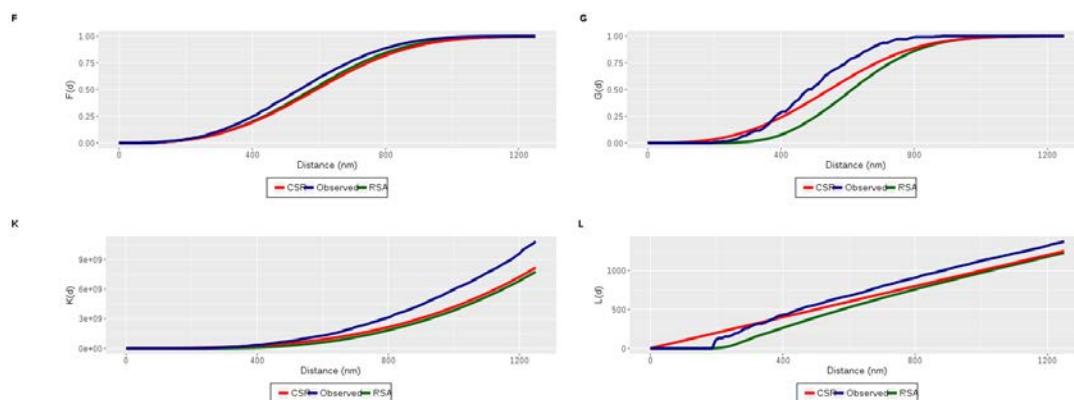
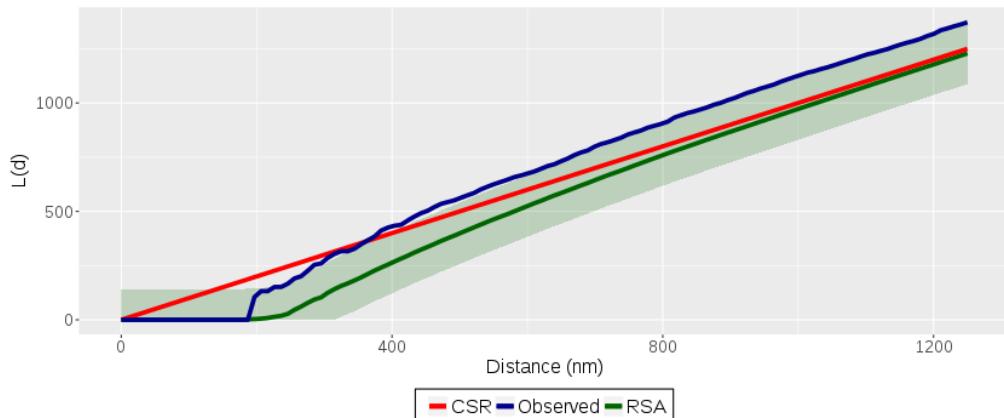
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9487
- **Log standard deviation :** 0.4545
- **Test p-value:** : 0.3416 (One-sample Kolmogorov-Smirnov test). **NOT REJECTED**



Envelope and results based on 198 simulations:

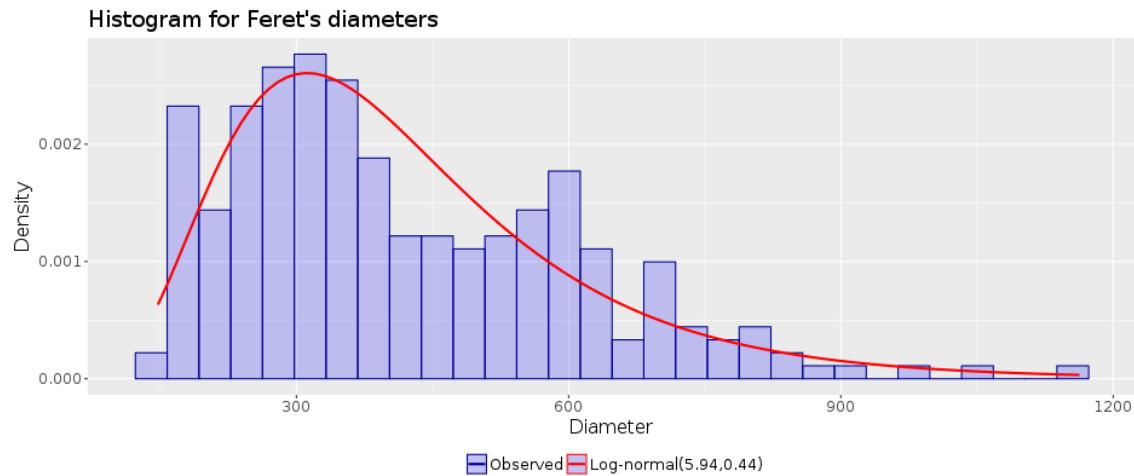
- **Feret diameter log mean:** 5.9487
- **Feret diameter log standard deviation:** 0.4545
- **Process intensity:** 1.0165 synapses/ μm^3



Sample2-Layer I:

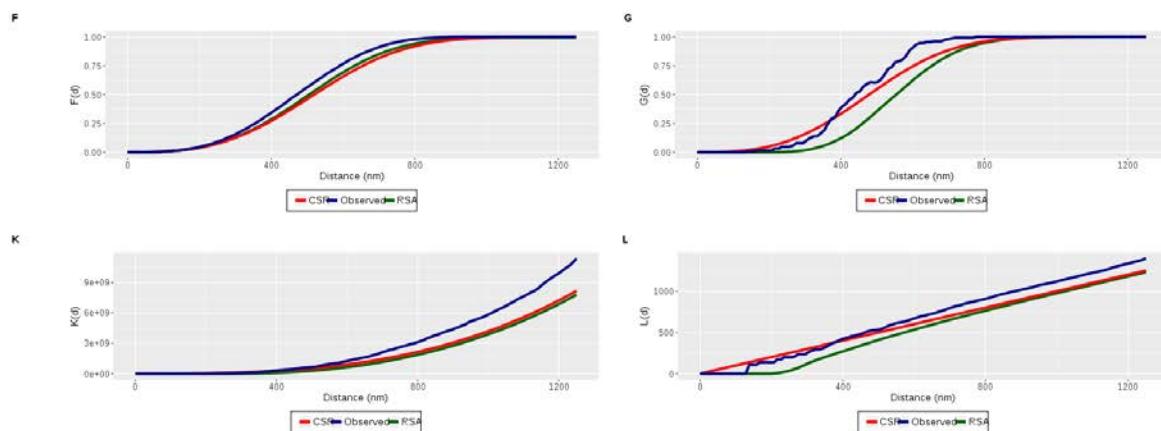
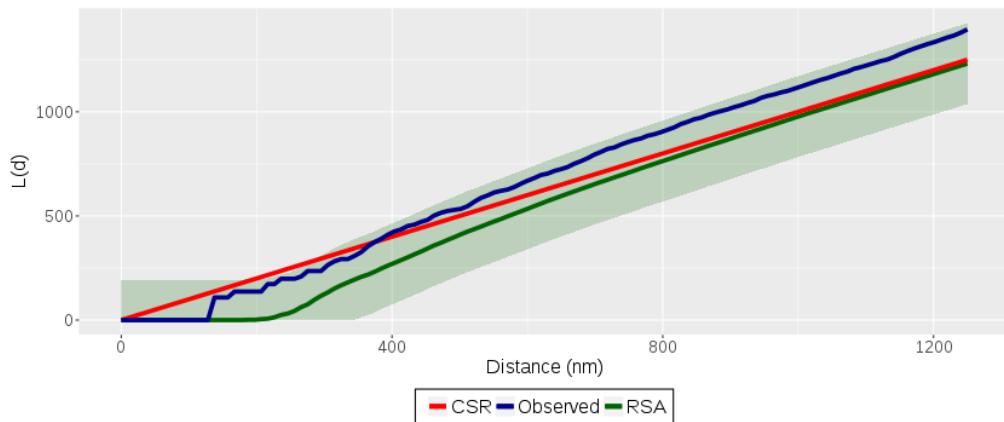
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9400
- **Log standard deviation :** 0.4448
- **Test p-value:** : 0.2628 (One-sample Kolmogorov-Smirnov test). **NOT REJECTED**



Envelope and results based on 198 simulations:

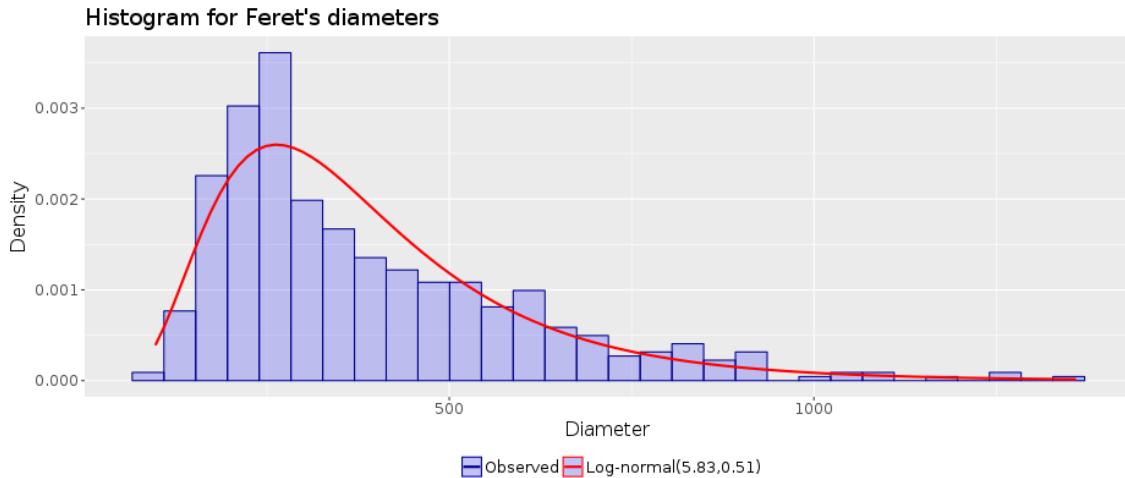
- **Feret diameter log mean:** 5.9400
- **Feret diameter log standard deviation:** 0.4448
- **Process intensity:** 1.5100 synapses/ μm^3



Sample3-Layer I:

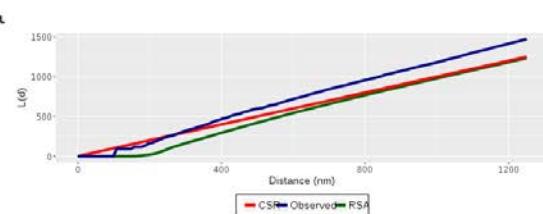
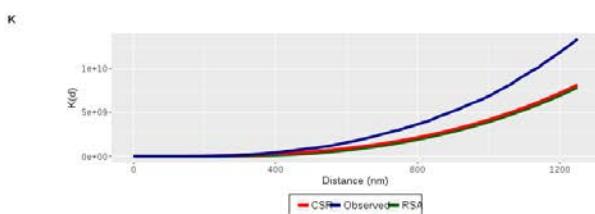
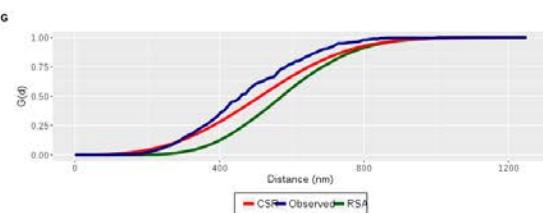
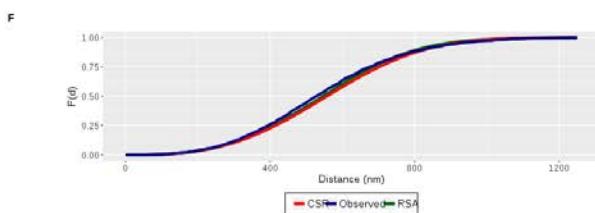
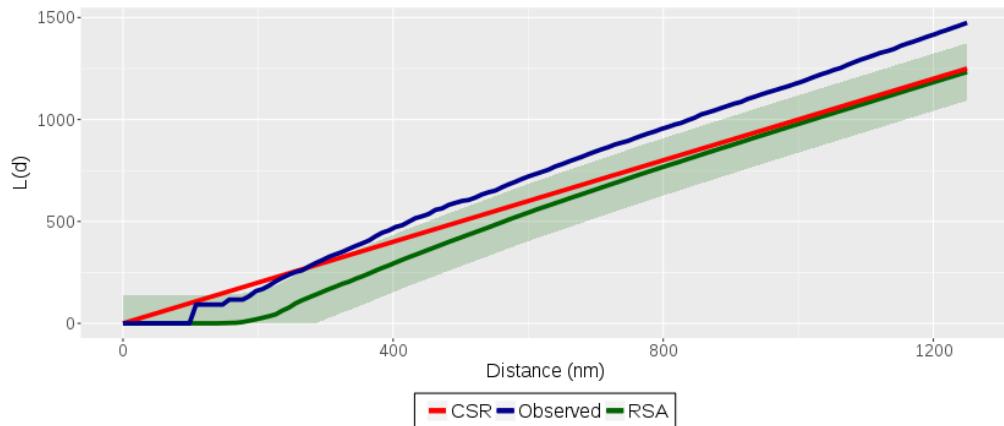
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.8346
- **Log standard deviation :** 0.5119
- **Test p-value:** : 0.0128 (One-sample Kolmogorov-Smirnov test) **REJECTED**



Envelope and results based on 198 simulations:

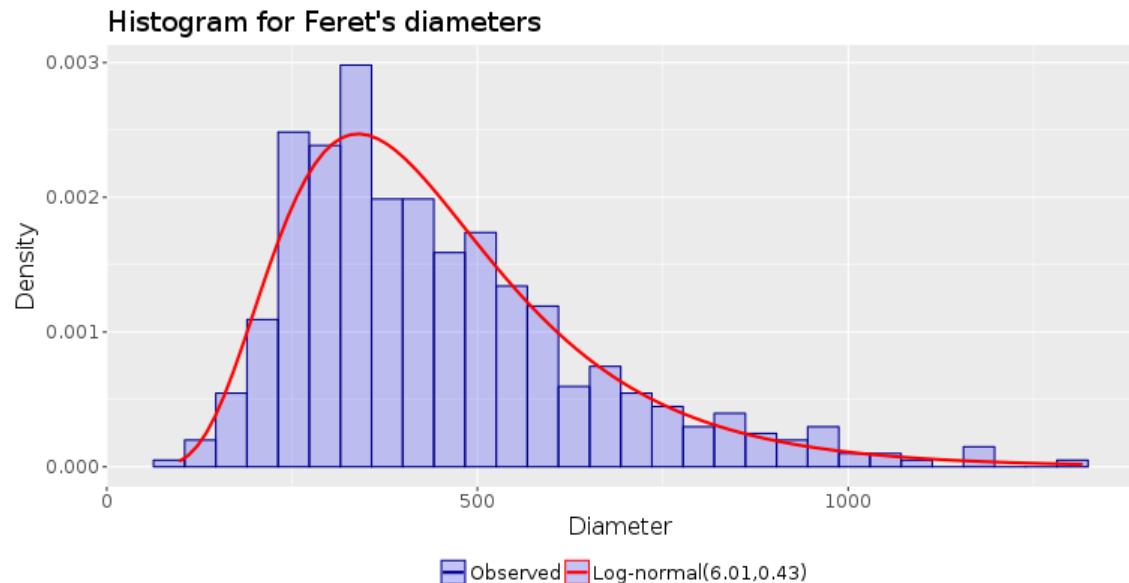
- **Feret diameter log mean:** 5.8346
- **Feret diameter log standard deviation:** 0.5119
- **Process intensity:** 1.2208 synapses/ μm^3



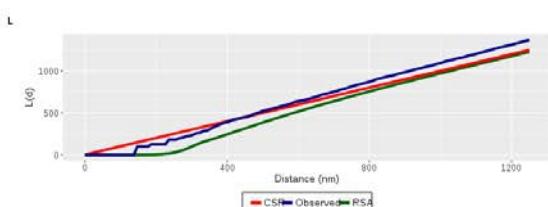
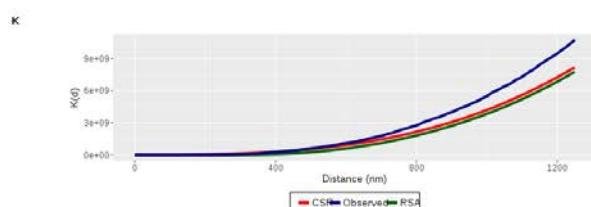
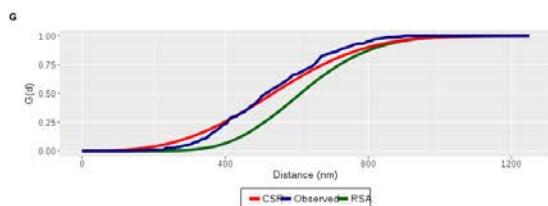
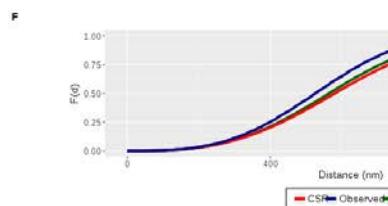
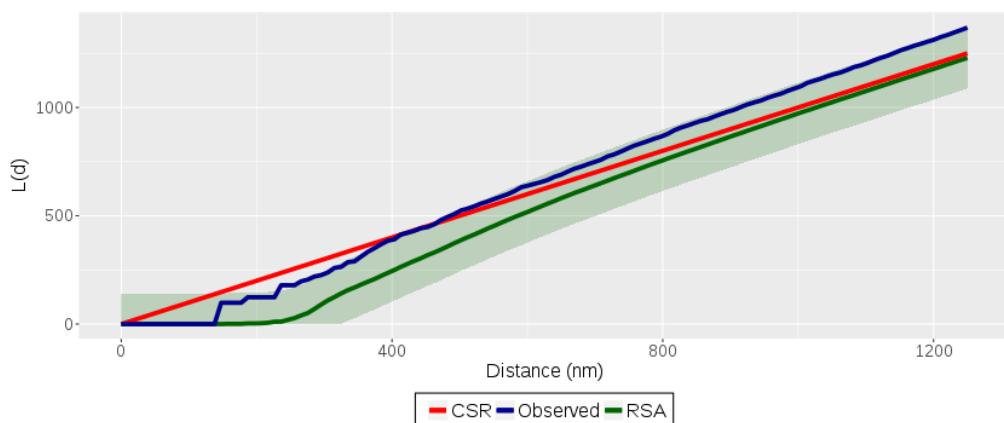
Sample4-Layer I:

Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 6.0141
- **Log standard deviation :** 0.4335
- **Test p-value:** : 0.5659 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



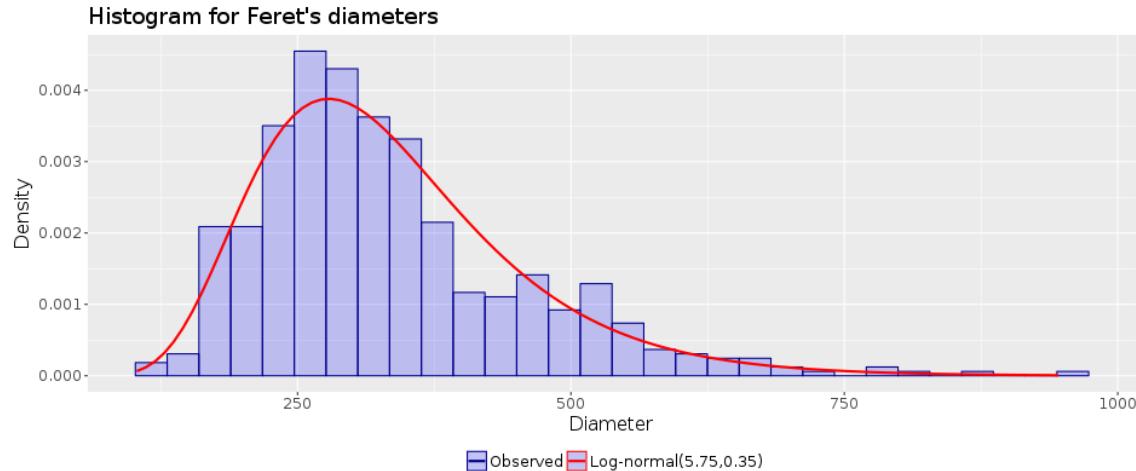
- **Feret diameter log mean:** 6.0141
- **Feret diameter log standard deviation:** 0.4335
- **Process intensity:** 1.0863 synapses/ μm^3



Sample1-Layer II:

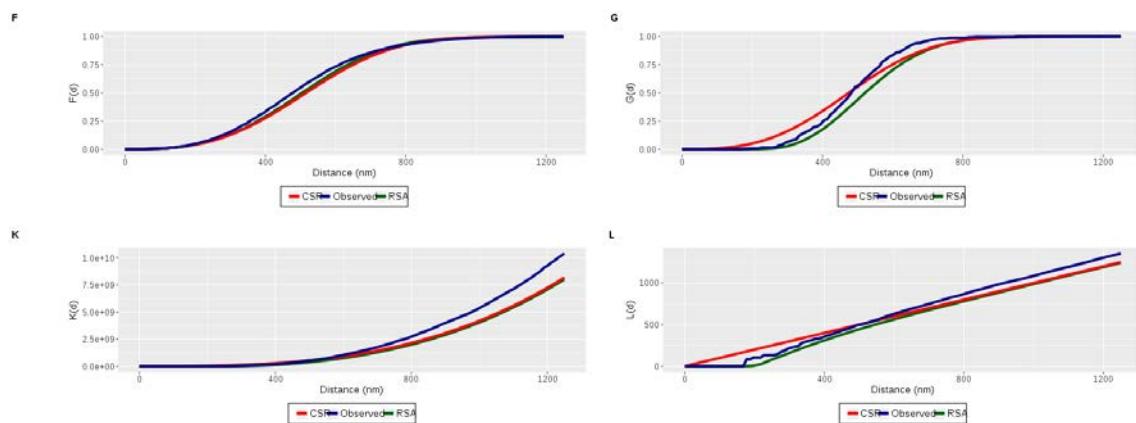
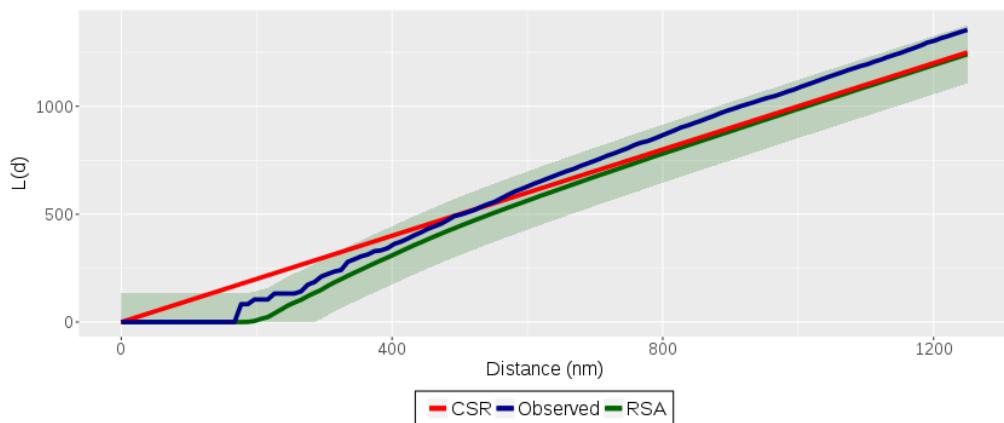
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.7504
- **Log standard deviation :** 0.3475
- **Test p-value:** : 0.3331 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

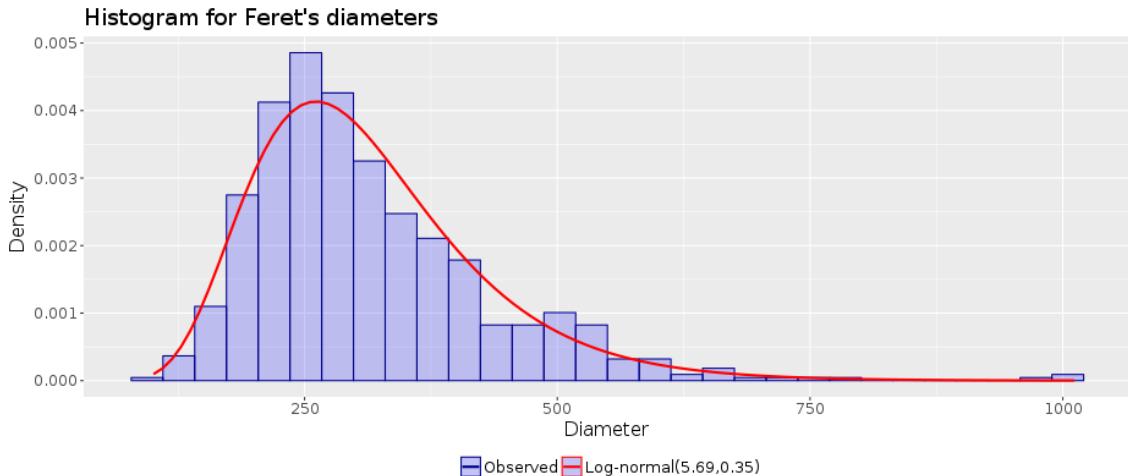
- **Feret diameter log mean:** 5.7504
- **Feret diameter log standard deviation:** 0.3475
- **Process intensity:** 1.5432 synapses/ μm^3



Sample2-LayerII:

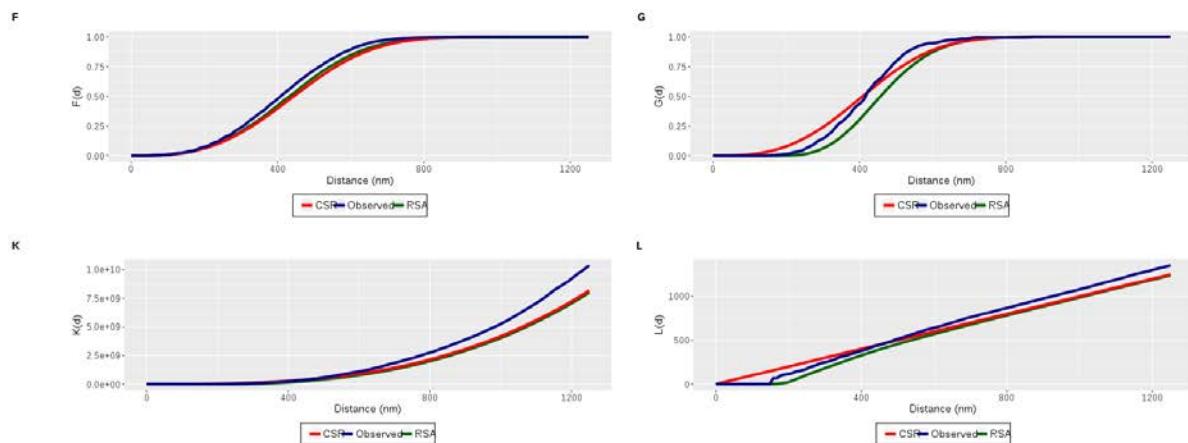
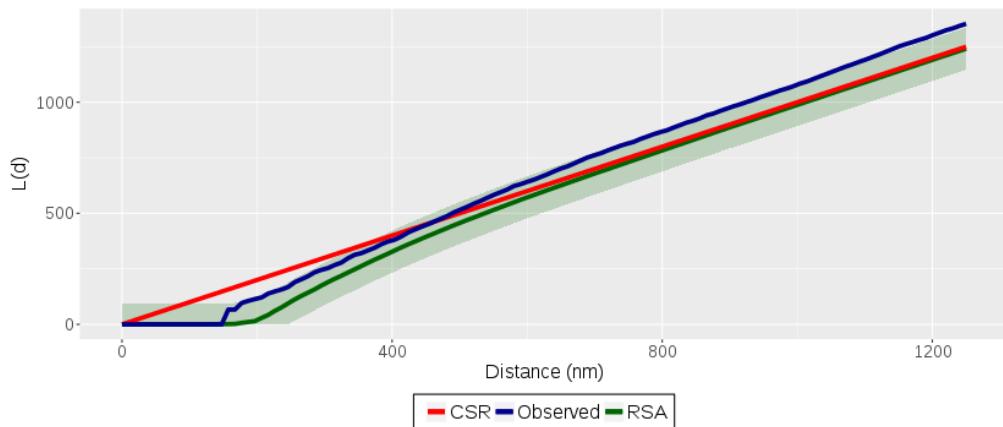
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.6861
- **Log standard deviation :** 0.3478
- **Test p-value:** : 0.0193 (One-sample Kolmogorov-Smirnov test) **REJECT**



Envelope and results based on 198 simulations:

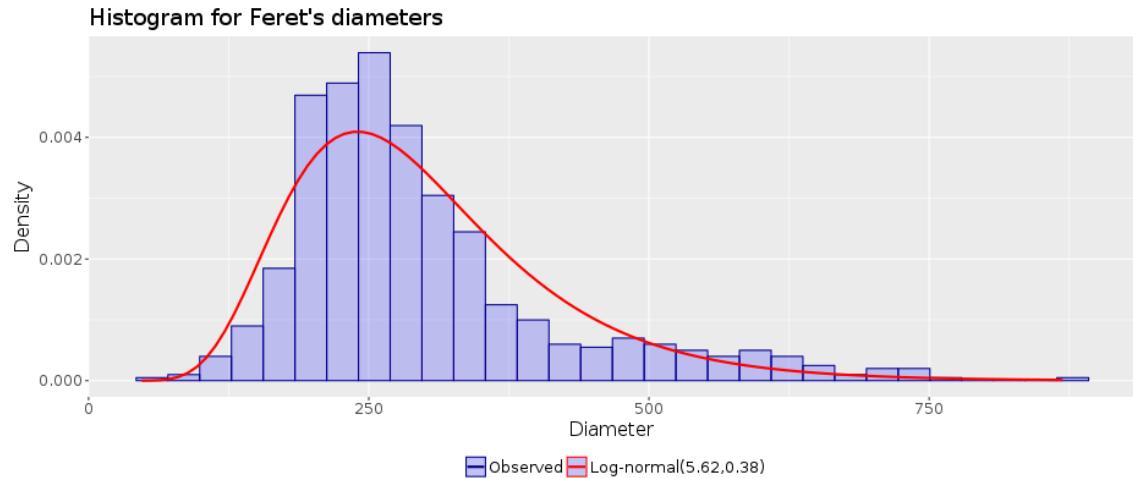
- **Feret diameter log mean:** 5.6861
- **Feret diameter log standard deviation:** 0.3478
- **Process intensity:** 2.4204 synapses/ μm^3



Sample3-Layer II:

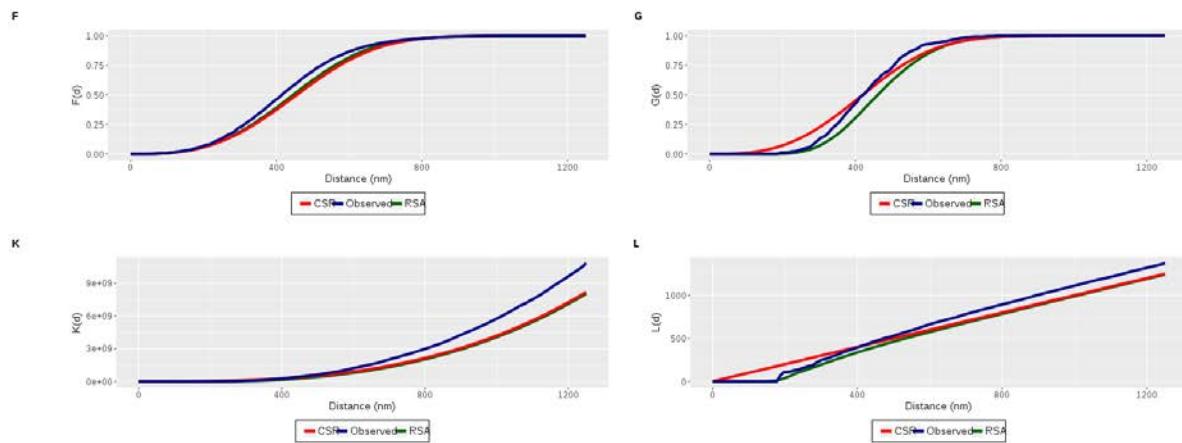
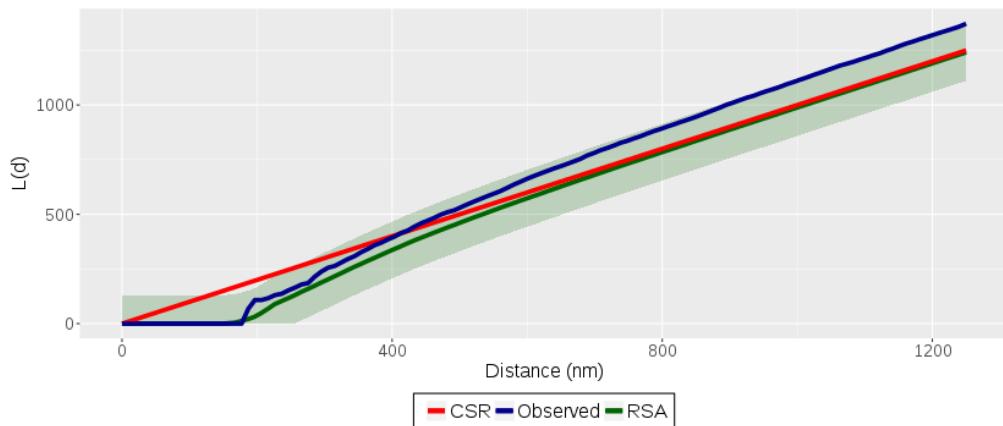
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.6232
- **Log standard deviation :** 0.3782
- **Test p-value:** : 0.0048 (One-sample Kolmogorov-Smirnov test) **REJECT**



Envelope and results based on 198 simulations:

- **Feret diameter log mean:** 5.6232
- **Feret diameter log standard deviation:** 0.3782
- **Process intensity:** 2.2338 synapses/ μm^3

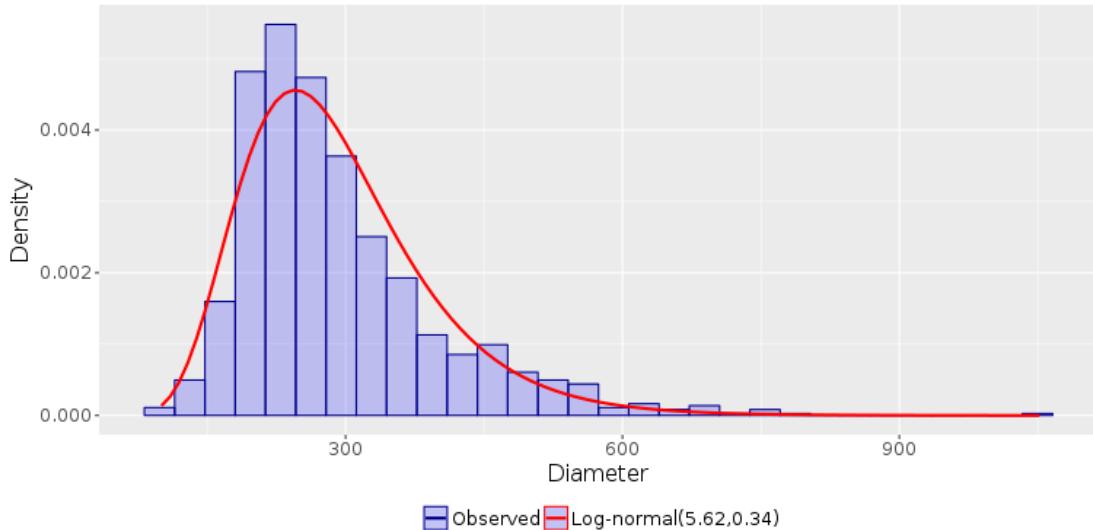


Sample4-Layer II:

Feret diameter distribution has been fitted to a log-normal distribution with parameters:

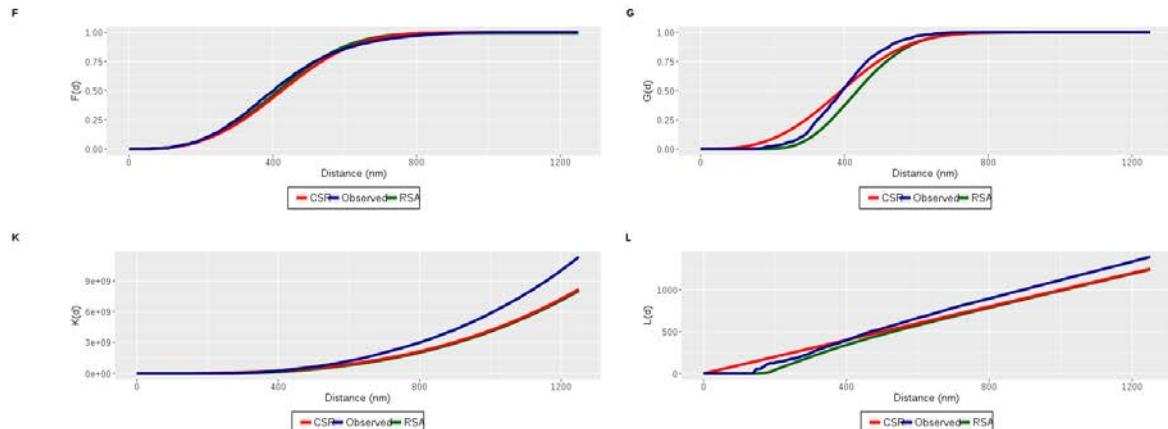
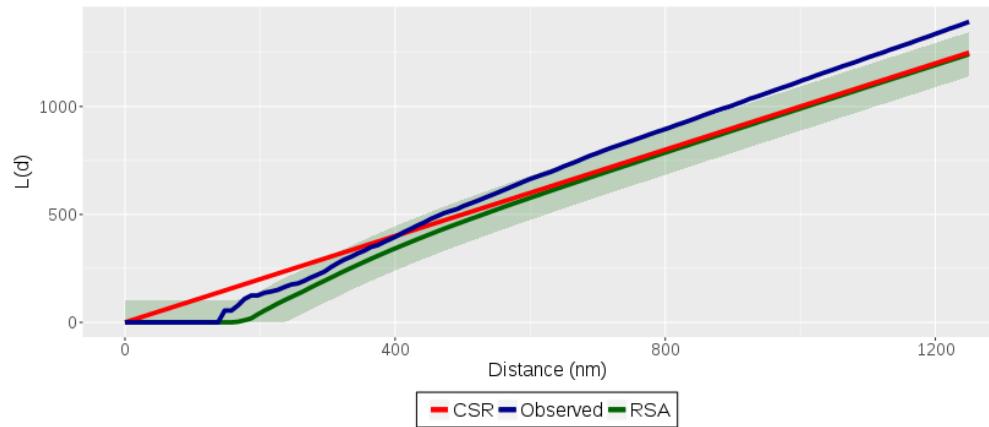
- **Log mean :** 5.6164
- **Log standard deviation :** 0.3368
- **Test p-value:** : 0.0007 (One-sample Kolmogorov-Smirnov test) **REJECT**

Histogram for Feret's diameters



Envelope and results based on 198 simulations:

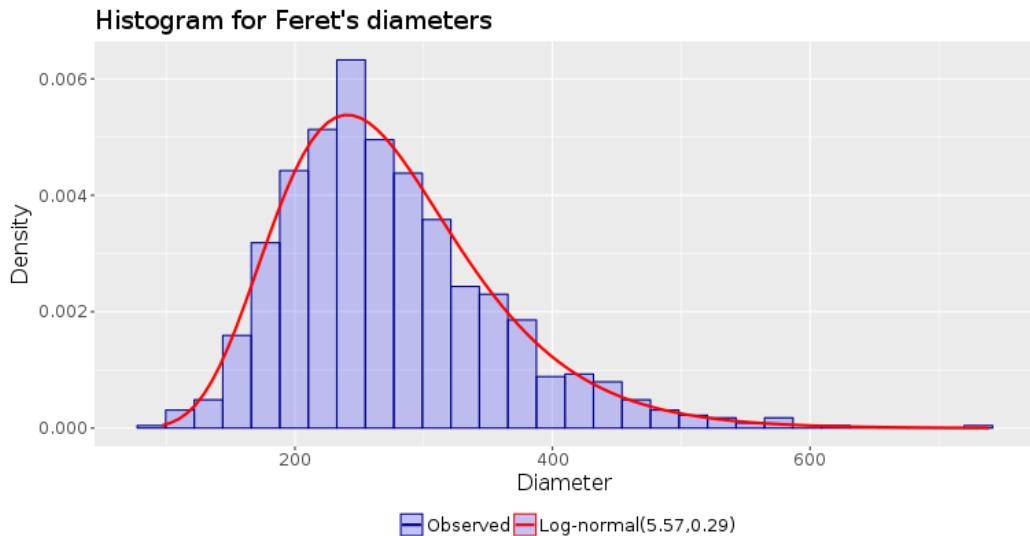
- **Feret diameter log mean:** 5.6164
- **Feret diameter log standard deviation:** 0.3368
- **Process intensity:** 2.7631 synapses/ μm^3



Sample1-Layer III:

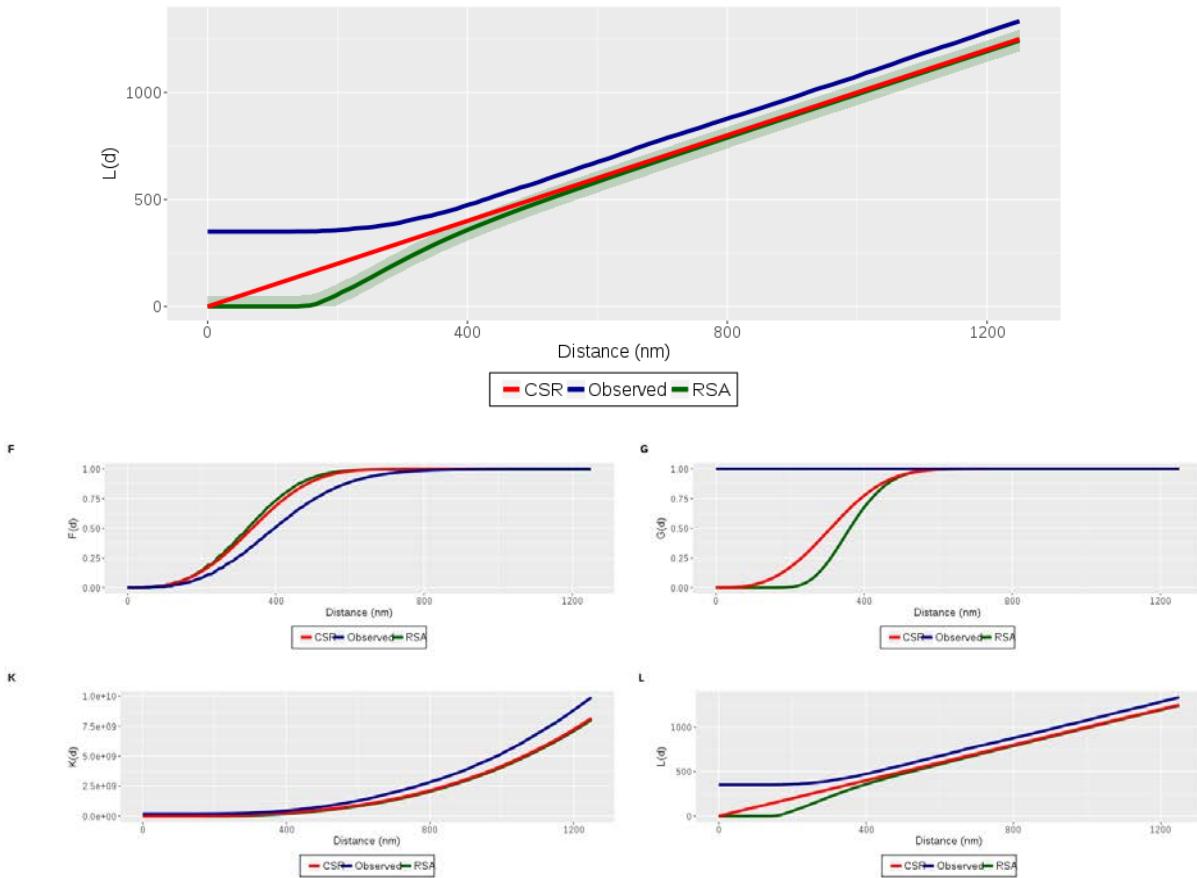
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.5705
- **Log standard deviation :** 0.2949
- **Test p-value:** : 0.1989 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

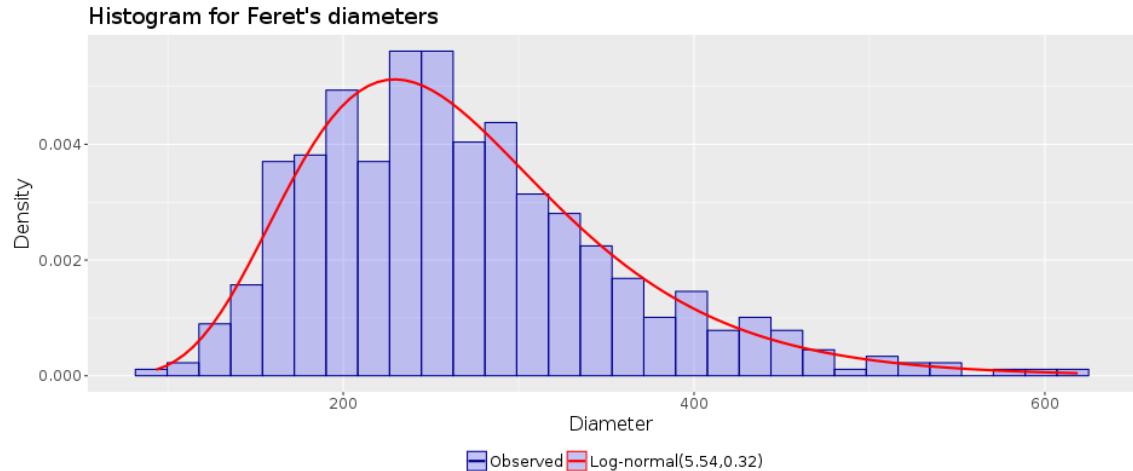
- **Feret diameter log mean:** 5.5705
- **Feret diameter log standard deviation:** 0.2949
- **Process intensity:** 5.5675 synapses/ μm^3



Sample2-Layer III:

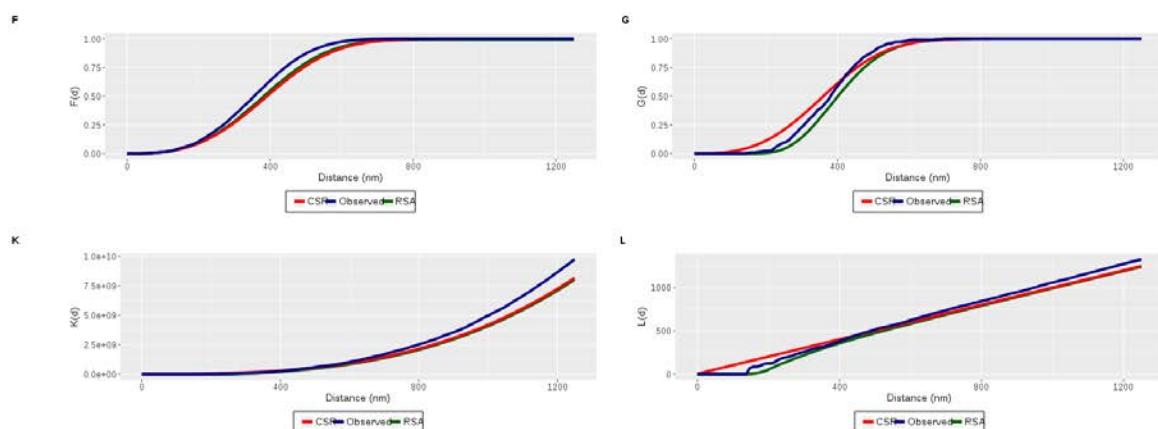
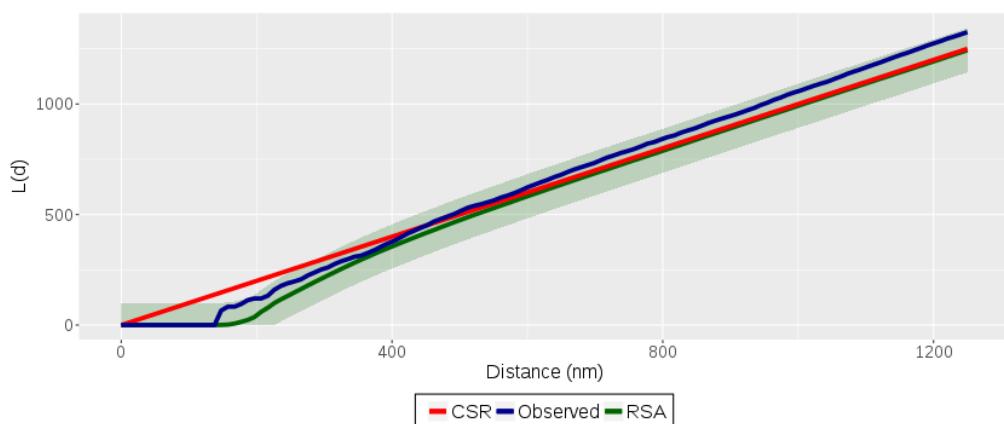
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.5393
- **Log standard deviation :** 0.3223
- **Test p-value:** : 0.9976 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

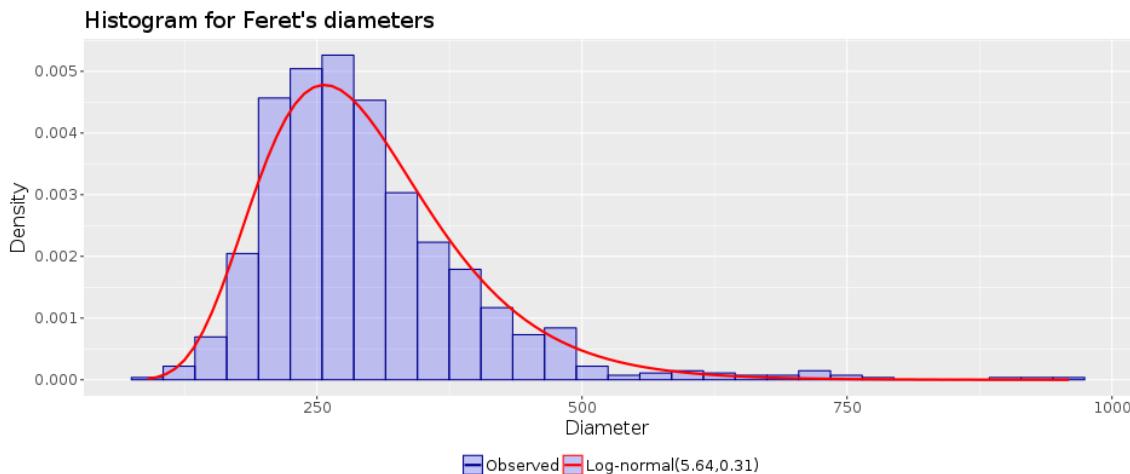
- **Feret diameter log mean:** 5.5393
- **Feret diameter log standard deviation:** 0.3223
- **Process intensity:** 3.5328 synapses/ μm^3



Sample3-Layer III:

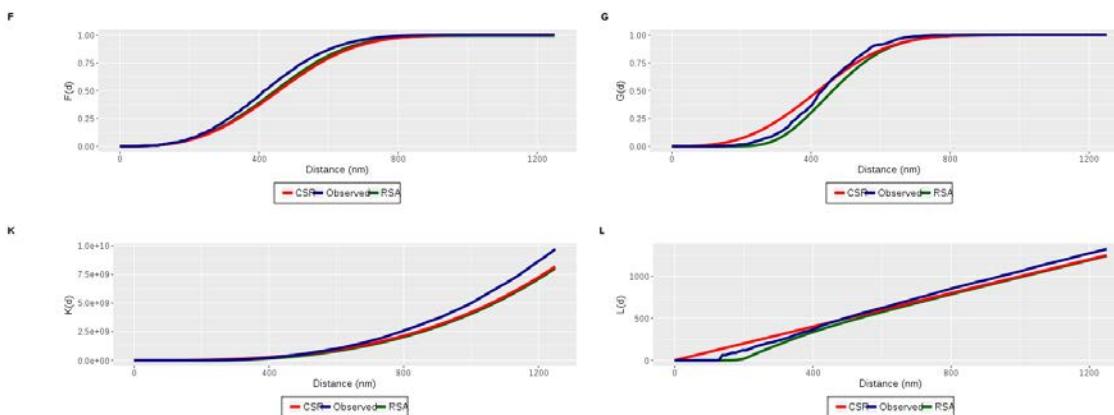
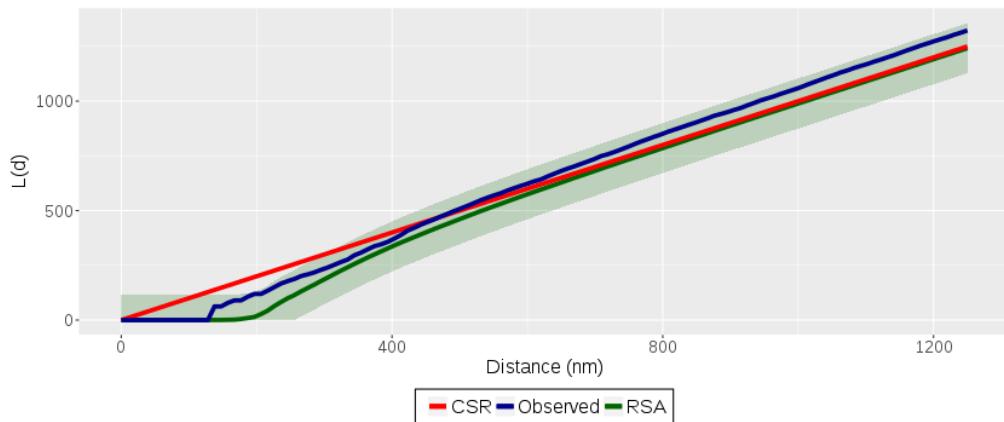
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.6446
- **Log standard deviation :** 0.3097
- **Test p-value:** : 0.0749 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

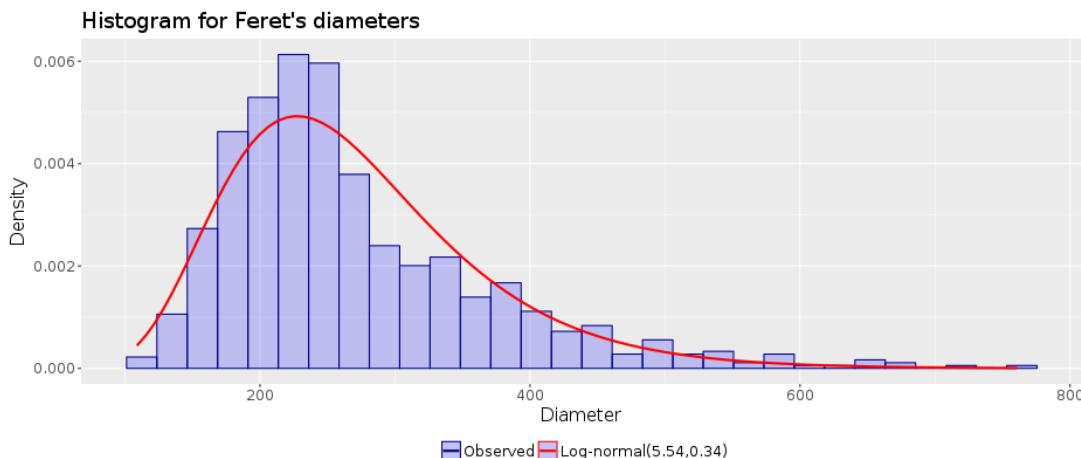
- **Feret diameter log mean:** 5.6446
- **Feret diameter log standard deviation:** 0.3097
- **Process intensity:** 2.2239 synapses/ μm^3



Sample4-Layer III:

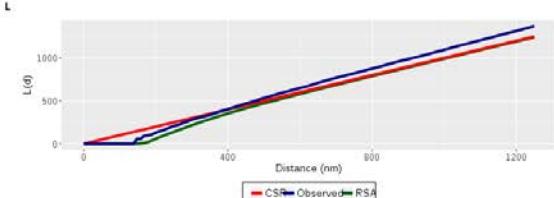
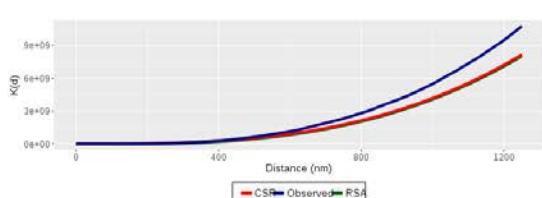
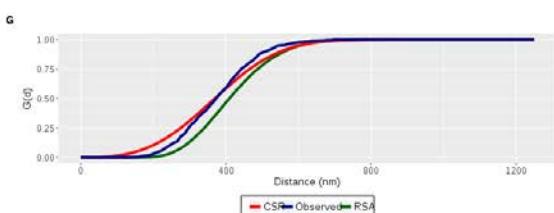
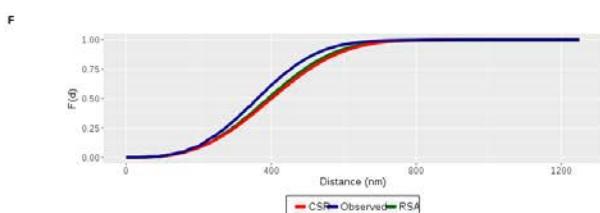
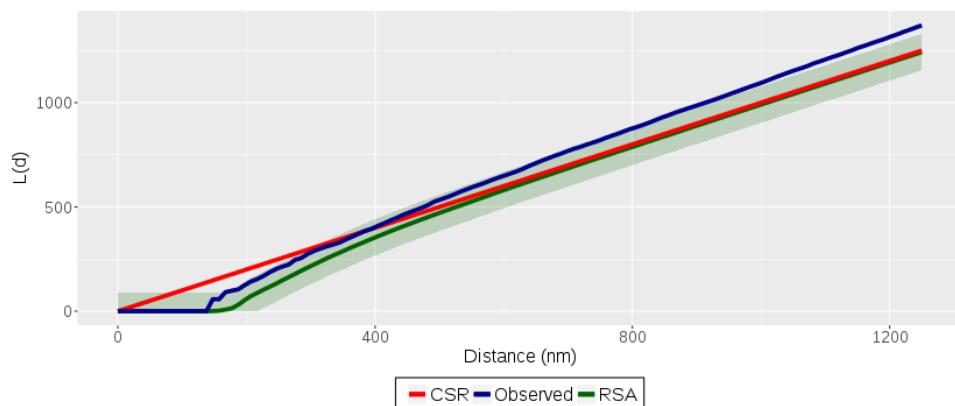
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.5404
- **Log standard deviation :** 0.3363
- **Test p-value:** : 0.0007 (One-sample Kolmogorov-Smirnov test) **REJECT**



Envelope and results based on 198 simulations:

- **Feret diameter log mean:** 5.5404
- **Feret diameter log standard deviation:** 0.3363
- **Process intensity:** 3.2841 synapses/ μm^3

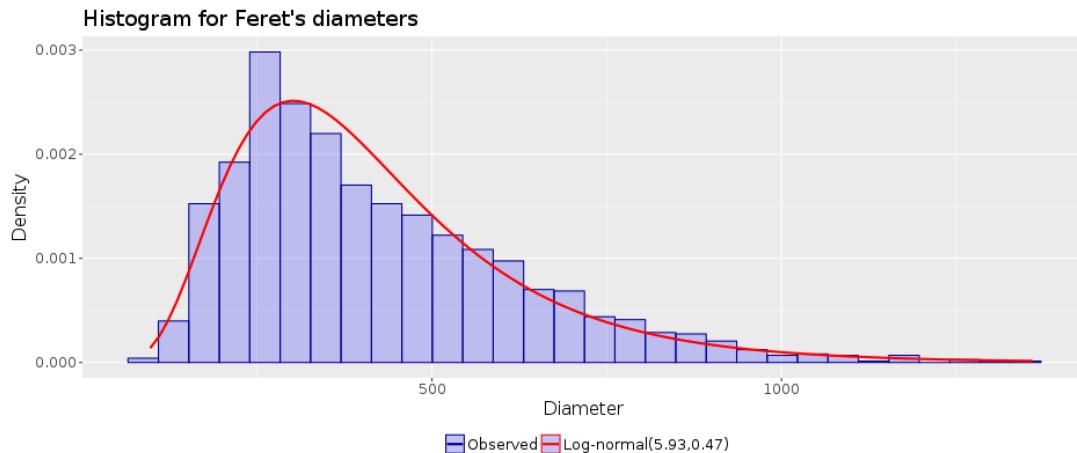


PER-LAYER ANALYSIS (I, II and III, 4 samples per analysis):

Layer I (LACUNOSUM):

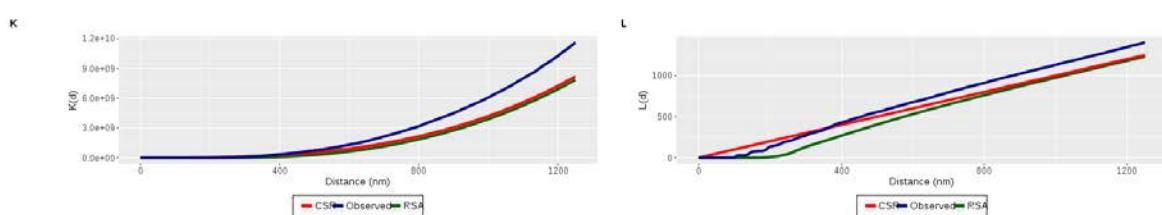
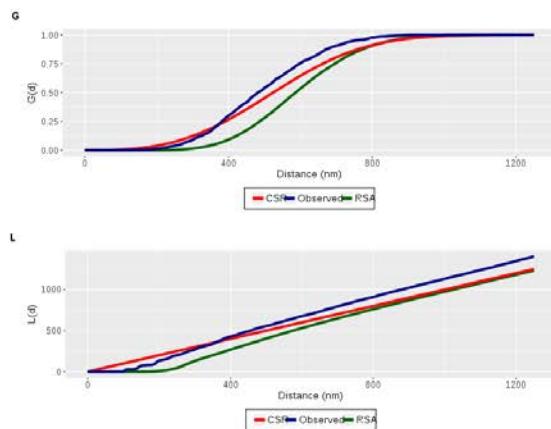
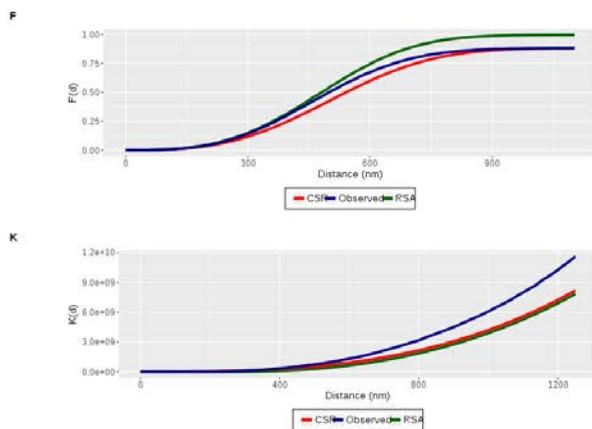
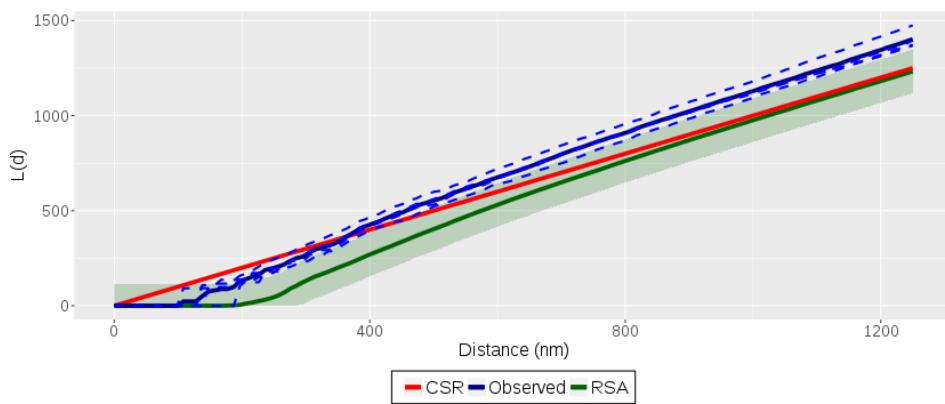
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9313
- **Log standard deviation :** 0.4708
- **Test p-value:** : 0.0603 (One-sample Kolmogorov-Smirnov test) **NOT REJECT**



Envelope and results based on 198 simulations:

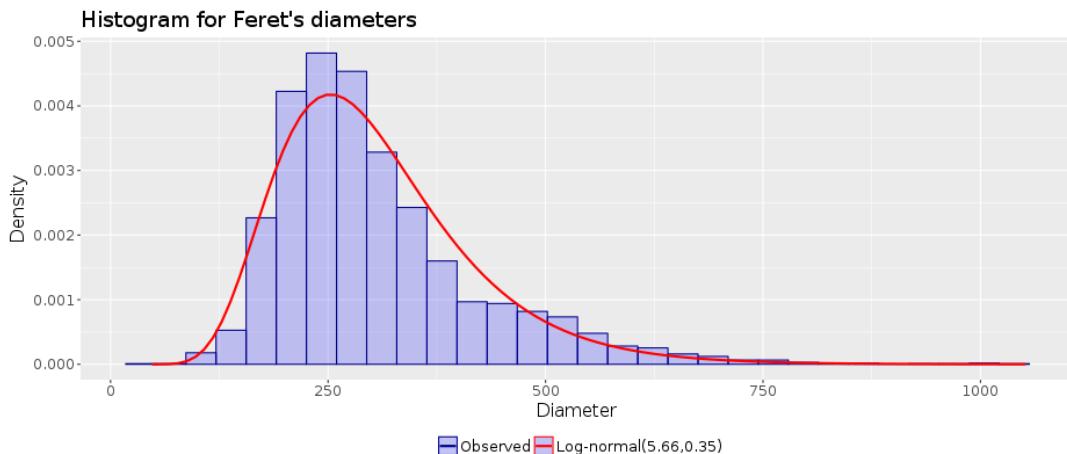
- **Feret diameter log mean:** 5.9313
- **Feret diameter log standard deviation:** 0.4708
- **Process intensity:** 1.2084 synapses/ μm^3



LayerII (RADIATUM):

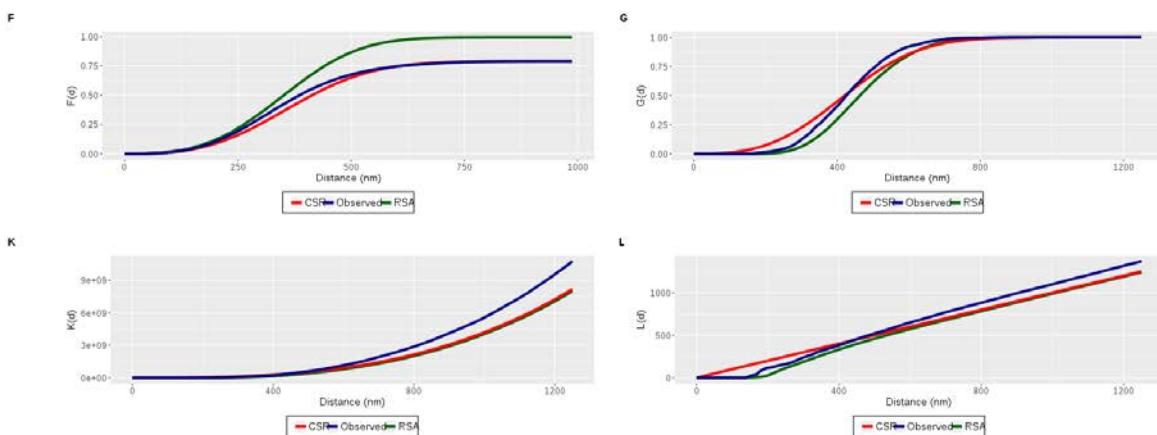
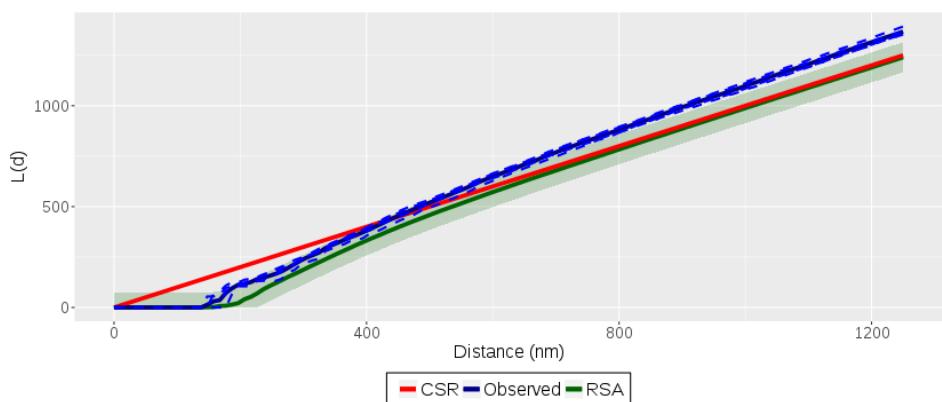
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.6582
- **Log standard deviation :** 0.3549
- **Test p-value:** : 0.0000 (One-sample Kolmogorov-Smirnov test) **REJECT**



Envelope and results based on 198 simulations:

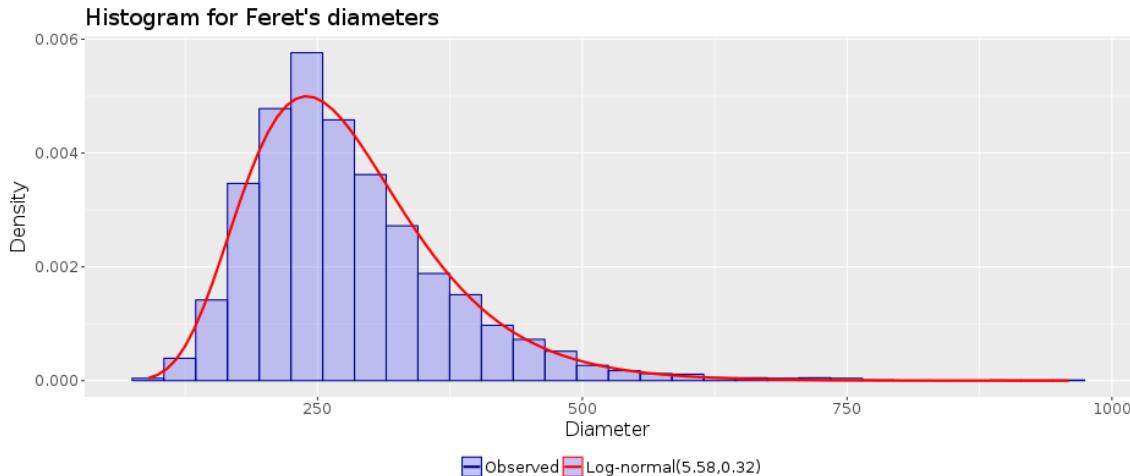
- **Feret diameter log mean:** 5.6582
- **Feret diameter log standard deviation:** 0.3549
- **Process intensity:** 2.2401 synapses/ μm^3



LayerIII (ORIENS):

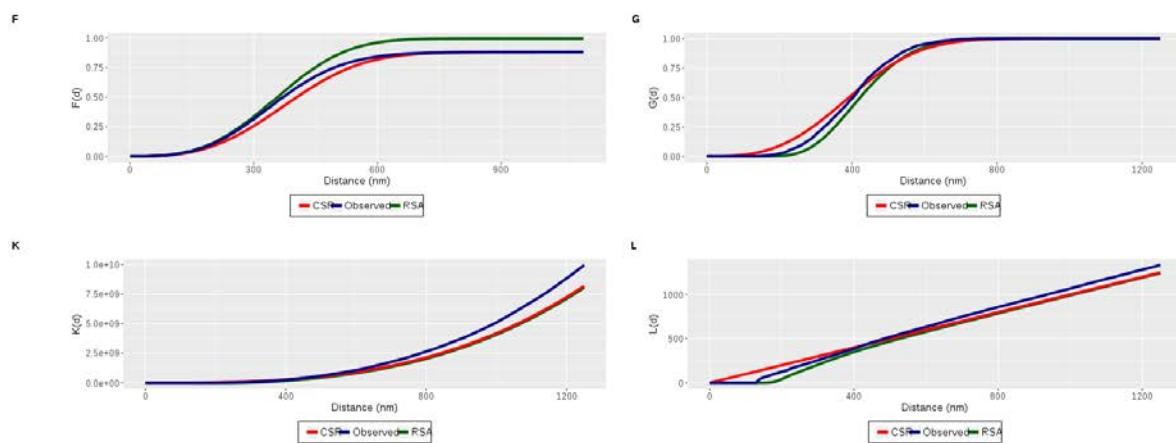
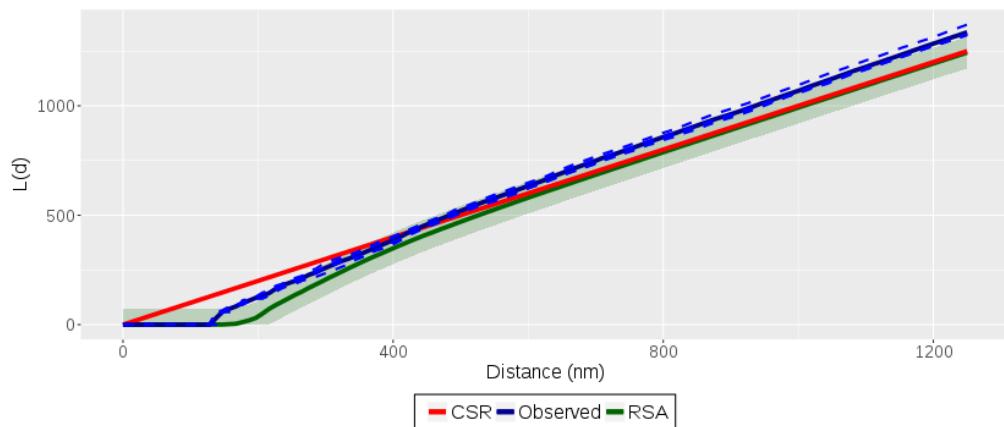
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.5793
- **Log standard deviation :** 0.3168
- **Test p-value:** : 0.0105 (One-sample Kolmogorov-Smirnov test) **REJECT**



Envelope and results based on 198 simulations:

- **Feret diameter log mean:** 5.5793
- **Feret diameter log standard deviation:** 0.3168
- **Process intensity:** 2.9561 synapses/ μm^3

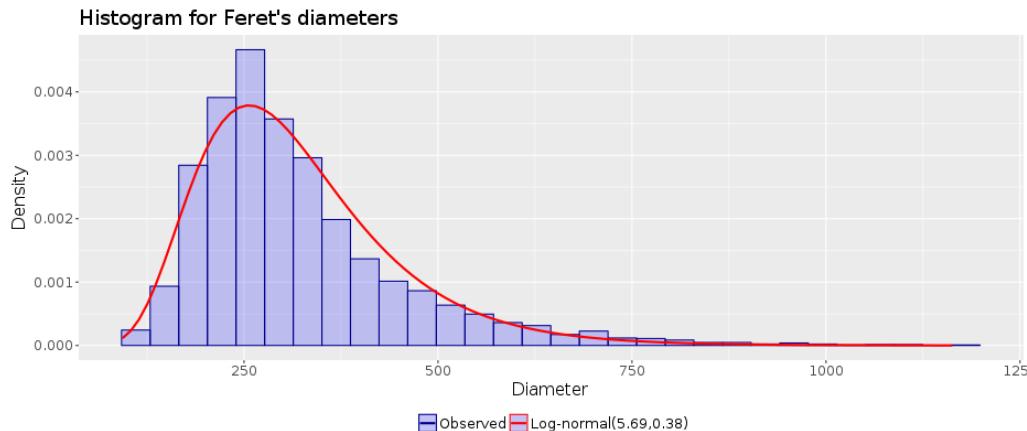


PER-ANIMAL ANALYSIS (ID2, ID4 and ID28):

ID2 (6 samples):

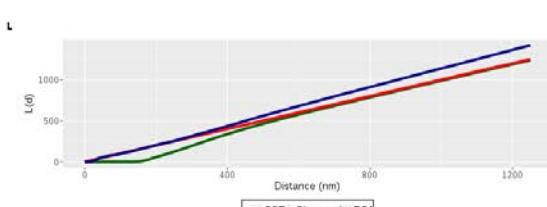
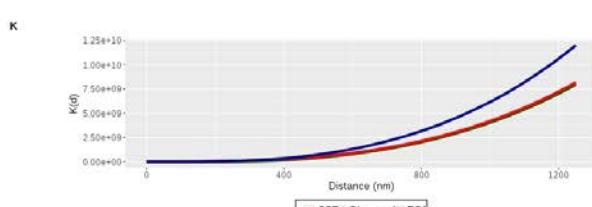
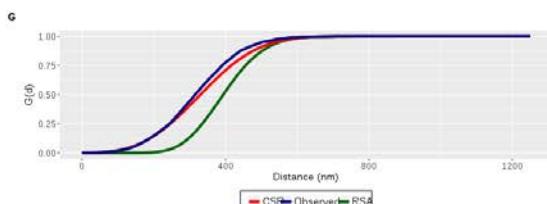
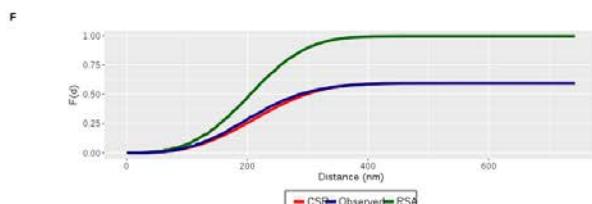
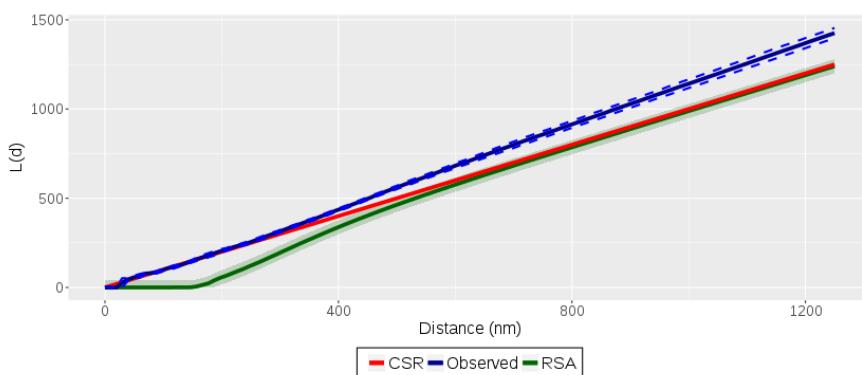
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.6928
- **Log standard deviation :** 0.3817
- **Test p-value:** : 0.0000 (One-sample Kolmogorov-Smirnov test) **REJECT**



Envelope and results based on 198 simulations:

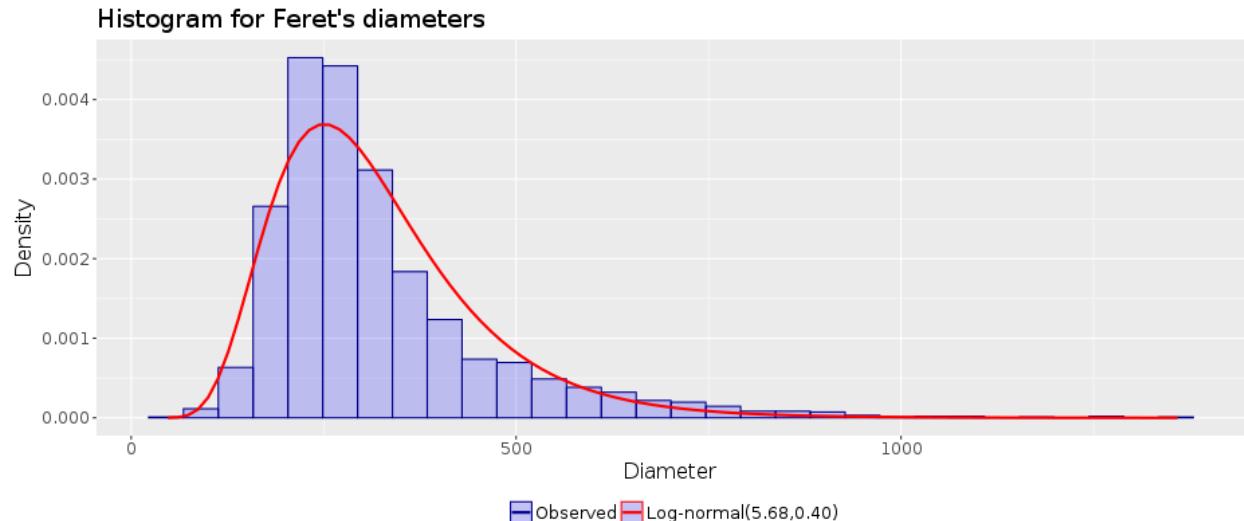
- **Feret diameter log mean:** 5.6928
- **Feret diameter log standard deviation:** 0.3817
- **Process intensity:** 4.6071 synapses/ μm^3



ID4 (3 samples):

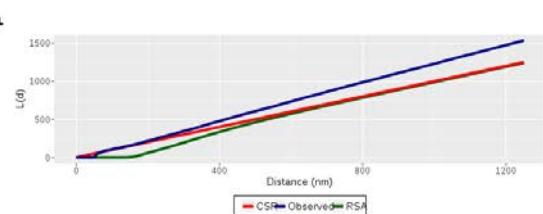
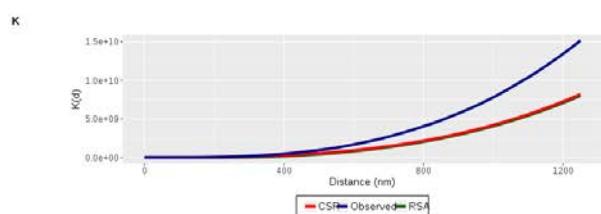
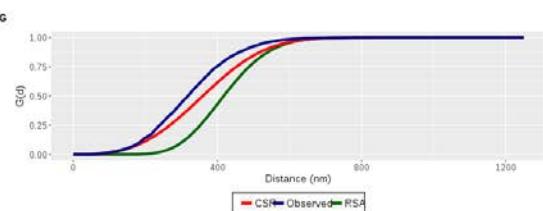
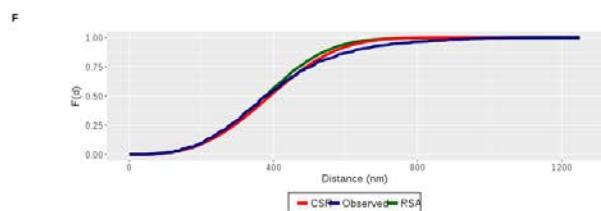
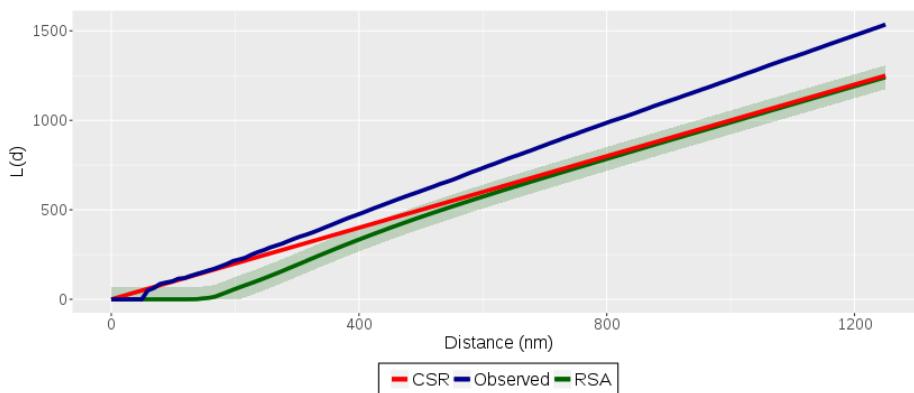
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.6829
- **Log standard deviation :** 0.3982
- **Test p-value:** : 0.0000 (One-sample Kolmogorov-Smirnov test) **REJECT**



Envelope and results based on 198 simulations:

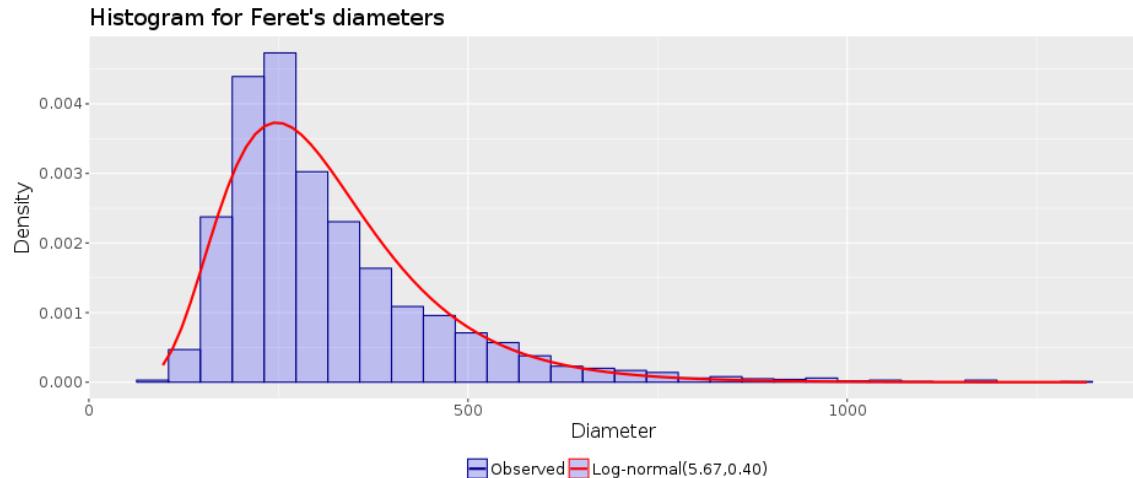
- **Feret diameter log mean:** 5.6829
- **Feret diameter log standard deviation:** 0.3982
- **Process intensity:** 3.5656 synapses/ μm^3



ID28 (3 samples):

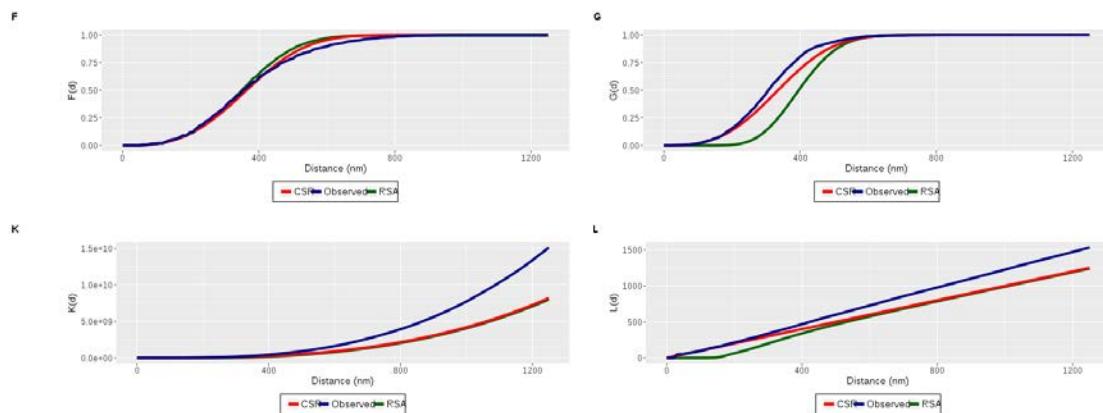
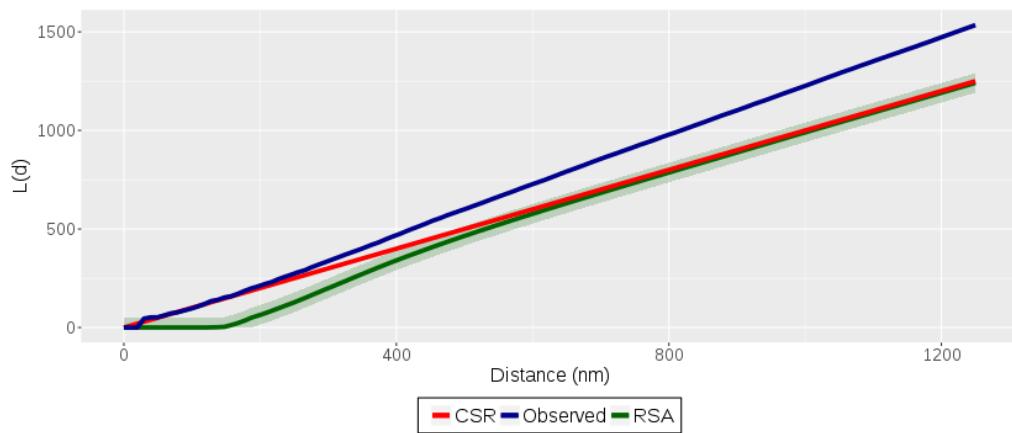
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.6709
- **Log standard deviation :** 0.3988
- **Test p-value:** : 0.0000 (One-sample Kolmogorov-Smirnov test) **REJECT**



Envelope and results based on 198 simulations:

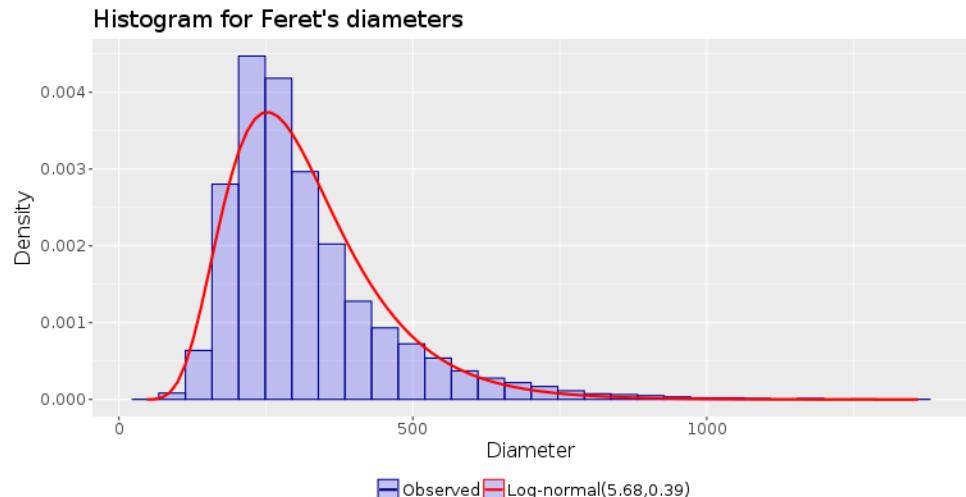
- **Feret diameter log mean:** 5.6709
- **Feret diameter log standard deviation:** 0.3988
- **Process intensity:** 4.3942 synapses/ μm^3



ALTOGETHER:

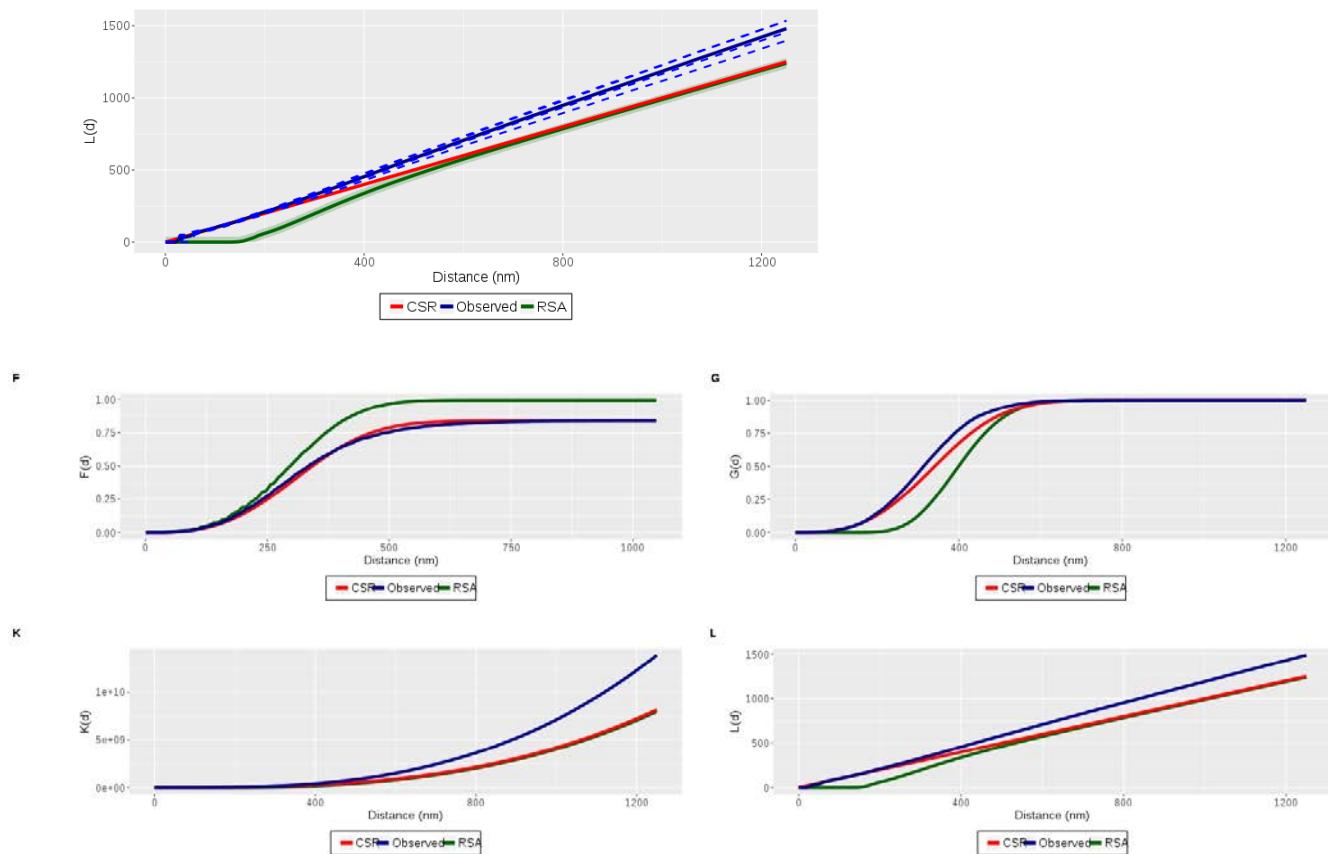
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.6836
- **Log standard deviation :** 0.3914
- **Test p-value:** : 0.0000 (One-sample Kolmogorov-Smirnov test) **REJECT**



Envelope and results based on 198 simulations:

- **Feret diameter log mean:** 5.6836
- **Feret diameter log standard deviation:** 0.3914
- **Process intensity:** 4.2935 synapses/ μm^3



PER-SAMPLE SUMMARY:

Layer	Animal	Sample.no.	Is Feret diam LogNormal?	Mean Feret diam ± SD	Synapses/mu m^3	Summary functions suggest	RSA?
LacMol (I)	ID2	1	OK	424.96 ± 203.56	1.0165	Regular (d<300nm) and clustered (>300)	~YES
	ID2	2	OK	419.44 ± 196.19	1.51	Regular (d<400nm) and clustered (>400)	YES
	ID4	3	Reject	389.79 ± 213.35	1.2208	Regular (d<300nm) and clustered (>300)	NO
	ID28	4	OK	449.47 ± 204.37	1.0863	Regular (d<400nm) and clustered (>400)	YES
Radiatum (II)	ID2	1	OK	333.42 ± 117.99	1.5432	Regular (d<550nm) and clustered (>550)	YES
	ID2	2	Reject	313.12 ± 112.28	2.4204	Regular (d<500nm) and clustered (>500)	YES
	ID4	3	Reject	297.29 ± 116.58	2.2338	Regular (d<400nm) and clustered (>400)	YES
	ID28	4	Reject	290.94 ± 100.83	2.7631	Regular (d<400nm) and clustered (>400)	YES
Oriens (III)	ID2	1	OK	274.23 ± 82.66	5.5675	Clustered	NO
	ID2	2	OK	268.07 ± 88.69	3.5328	Regular (d<400nm) and clustered (>400)	YES
	ID4	3	OK	296.65 ± 94.12	2.2239	Regular (d<500nm) and clustered (>500)	YES
	ID28	4	Reject	269.63 ± 93.39	3.2841	Regular (d<500nm) and clustered (>500)	~YES

PER-LAYER SUMMARY:

Layer	Is Feret diam LogNormal?	Mean Feret diam ± SD	Synapses/mu m^3	Summary functions suggest	RSA?
LacMol (I)	OK	420.79 ± 209.61	1.2084	Regular (d<400nm) and clustered (>400)	NO
Radiatum (II)	Reject	305.26 ± 111.84	2.2401	Regular (d<500nm) and clustered (>500)	NO
Oriens (III)	Reject	278.52 ± 90.50	2.9561	Regular (d<500nm) and clustered (>500)	YES?

PER-ANIMAL SUMMARY:

Animal	Is Feret diam LogNormal?	Mean Feret diam ± SD	Synapses/mu m^3	Summary functions suggest	RSA?
ID2	Reject	319.15 ± 126.39	4.6071	Clustered	NO
ID4	Reject	318.04 ± 131.83	3.5656	Clustered	NO
ID28	Reject	314.32 ± 130.50	4.3942	Clustered	NO

ALTOGETHER:

Animal	Is Feret diam LogNormal?	Mean Feret diam ± SD	Synapses/mu m^3	Summary functions suggest	RSA?
All	Reject	317.41 ± 129.15	4.2935	Clustered	NO

HUMAN

Data samples

Data come from Javier DeFelipe's lab and is a subset of the data in Montero-Crespo et al (2020). The data correspond to four human brain autopsies identified as AB1, AB2, AB3 and M17. Three stacks were obtained per individual and layer. This gives a total of 36 samples. The data set contained the 3D spatial position of the centroids of the synaptic junctions, an estimation of their sizes using the Feret's diameter (diameter of the smallest sphere circumscribing the synaptic junction) and whether each was included/excluded within/from the unbiased counting frame (CF). There was also information about whether the synapse was excitatory (asymmetric or AS) or inhibitory (symmetric or SS), although we considered all as a whole due to the small percentage of symmetric synapses (around 6.7% of the total number of synapses). After filtering synapses within the CF, we obtained 5,562 synapses, see the table.

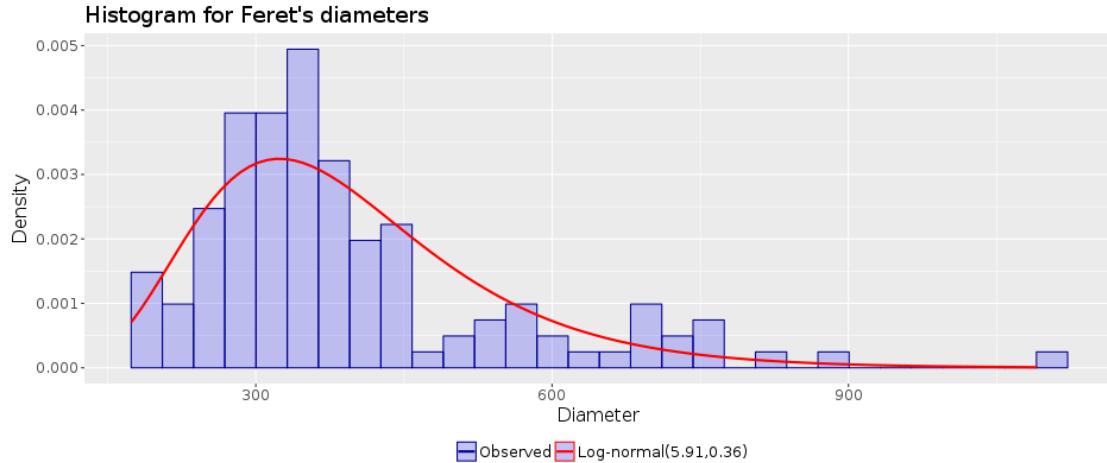
Layer	Sample	Subject	No. of AS	No. of SS	No. of AS within CF	No. of SS within CF	No. of valid synapses	
LacMol (I)	S1	AB1	203	18	120	8	128	
	S2	AB1	170	16	99	10	109	
	S3	AB1	195	17	98	13	111	
	S1	AB2	293	17	69	7	76	
	S2	AB2	243	13	143	10	153	
	S3	AB2	200	17	122	13	135	
	S1	AB3	235	25	128	20	148	
	S2	AB3	335	30	163	16	179	
	S3	AB3	307	23	171	11	182	
Radiatum (II)	S1	M17	253	41	96	21	117	
	S2	M17	206	33	127	25	152	
	S3	M17	240	38	118	25	143	
	S1	AB1	293	12	105	5	110	
	S2	AB1	277	10	107	2	109	
	S3	AB1	288	7	146	3	149	
	S1	AB2	355	13	193	7	200	
	S3	AB2	506	4	183	2	185	
	S4	AB2	375	13	216	11	227	
Oriens (III)	S1	AB3	383	8	169	5	174	
	S2	AB3	573	18	273	7	280	
	S4	AB3	330	19	177	16	193	
	S1	M17	282	13	204	10	214	
	S2	M17	287	12	159	9	168	
	S3	M17	299	21	226	19	245	
	S1	AB1	200	6	98	4	102	
	S2	AB1	172	7	115	6	121	
	S3	AB1	158	11	91	5	96	
	S1	AB2	376	14	116	7	123	
	S2	AB2	321	17	170	8	178	
	S3	AB2	501	23	251	11	262	
	S1	AB3	171	24	105	15	120	
	S2	AB3	245	13	156	11	167	
	S3	AB3	186	6	91	4	95	
	S1	M17	269	8	178	6	184	
	S2	M17	191	21	107	10	117	
	S3	M17	182	20	98	12	110	
TOTAL	36		4	10100	608	5188	374	5562

PER-SAMPLE ANALYSIS (I 1-to-12, II 1-to-12 and III 1-to-12):

Sample1-Layer I:

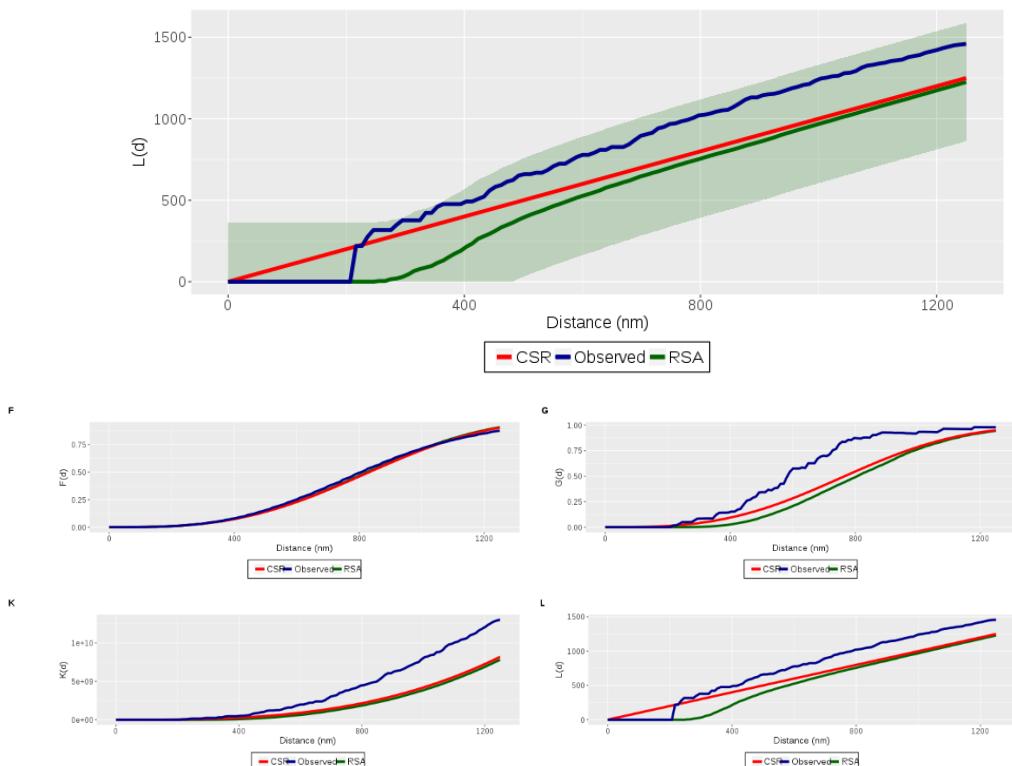
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9076
- **Log standard deviation :** 0.3563
- **Test p-value:** : 0.1353 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

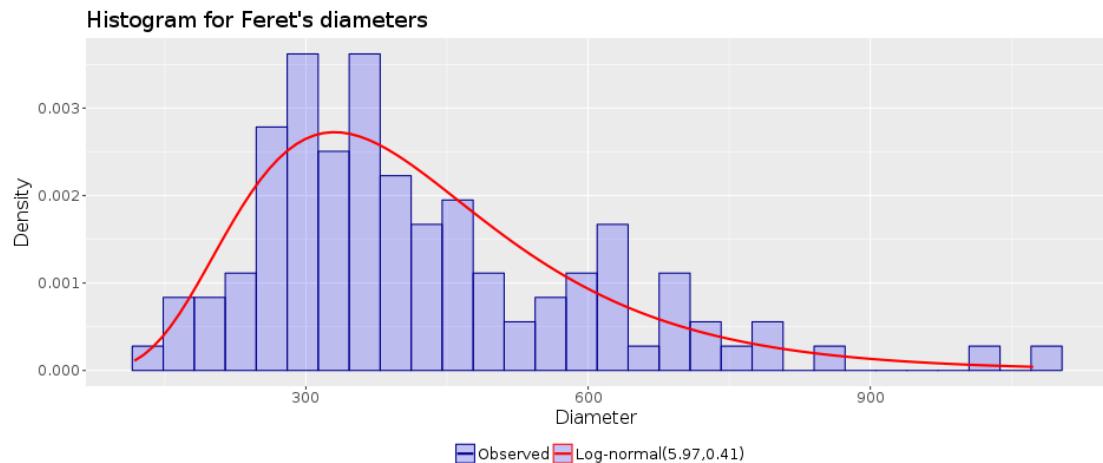
- **Feret diameter log mean:** 5.9076
- **Feret diameter log standard deviation:** 0.3563
- **Process intensity:** 0.3683 synapses/ μm^3



Sample2-Layer I:

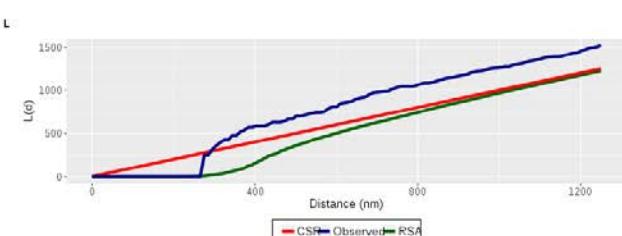
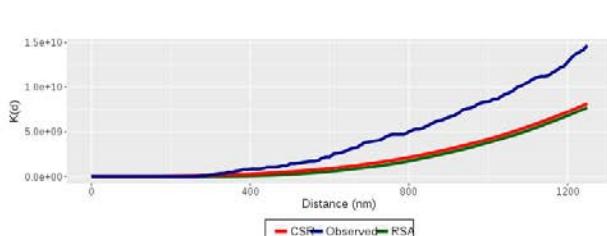
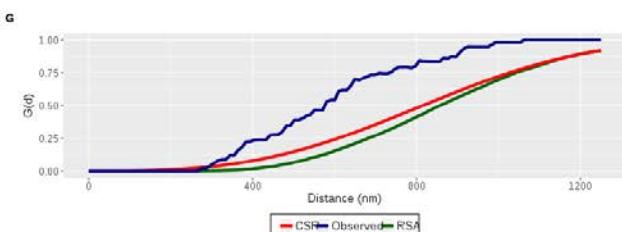
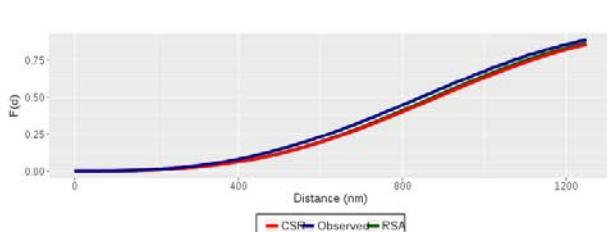
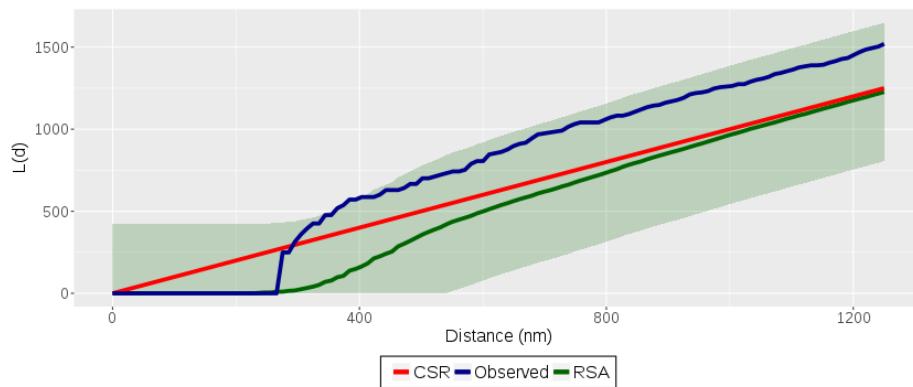
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9663
- **Log standard deviation :** 0.4079
- **Test p-value:** : 0.8113 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

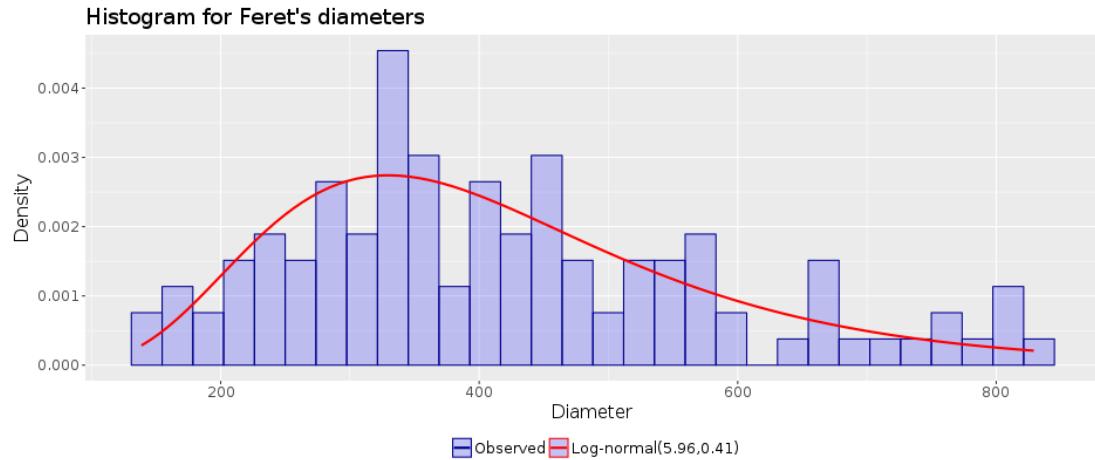
- **Feret diameter log mean:** 5.9663
- **Feret diameter log standard deviation:** 0.4079
- **Process intensity:** 0.3046 synapses/ μm^3



Sample3-Layer I:

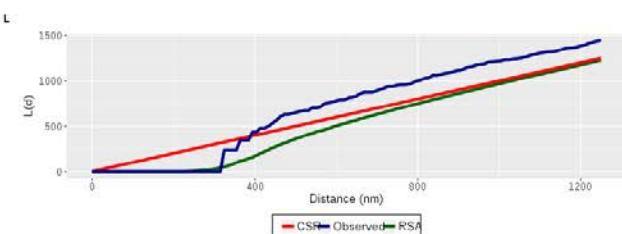
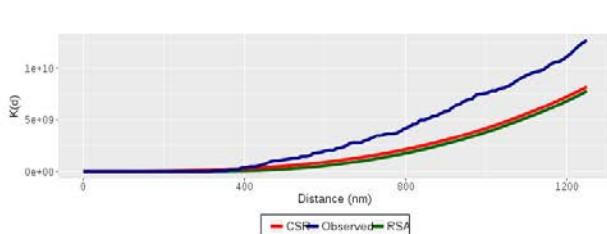
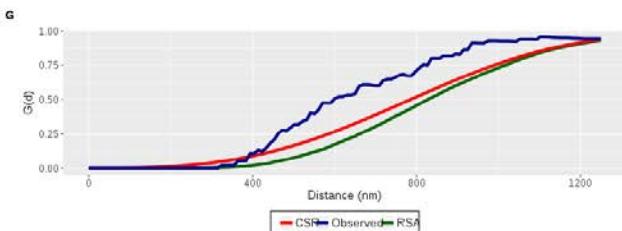
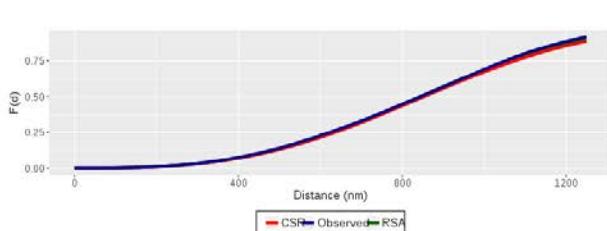
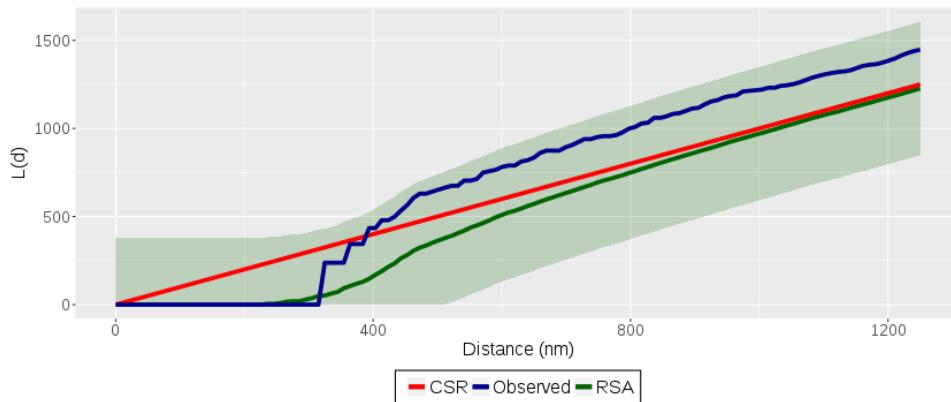
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9632
- **Log standard deviation :** 0.4065
- **Test p-value:** : 0.9739 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

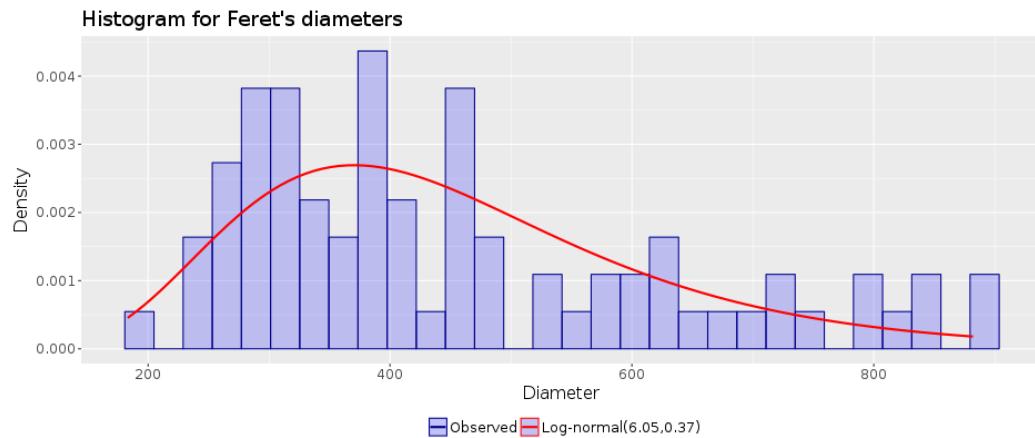
- **Feret diameter log mean:** 5.9632
- **Feret diameter log standard deviation:** 0.4065
- **Process intensity:** 0.3412 synapses/ μm^3



Sample4-Layer I:

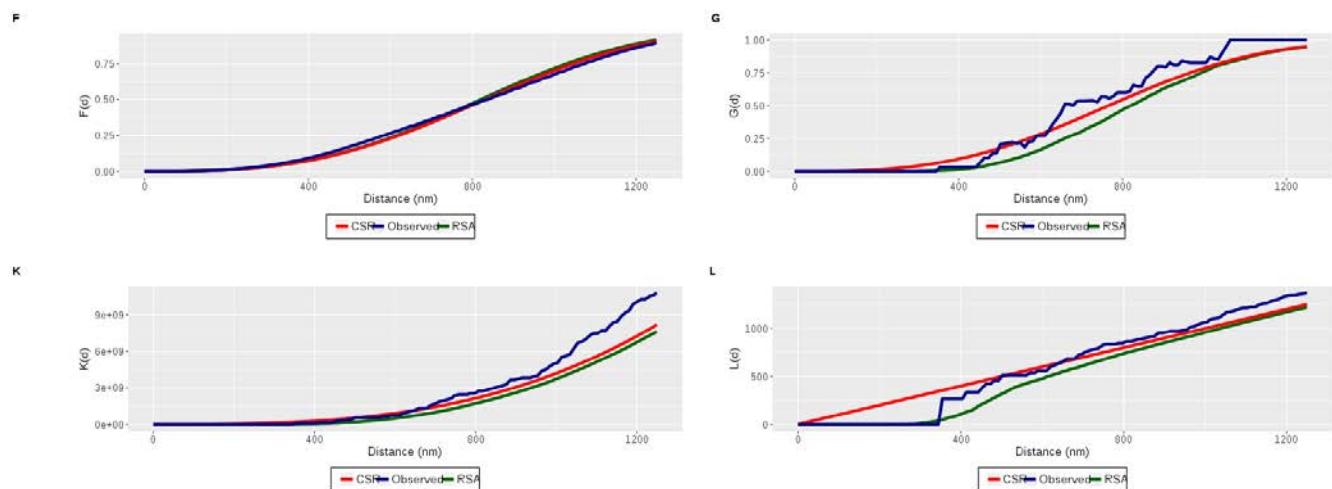
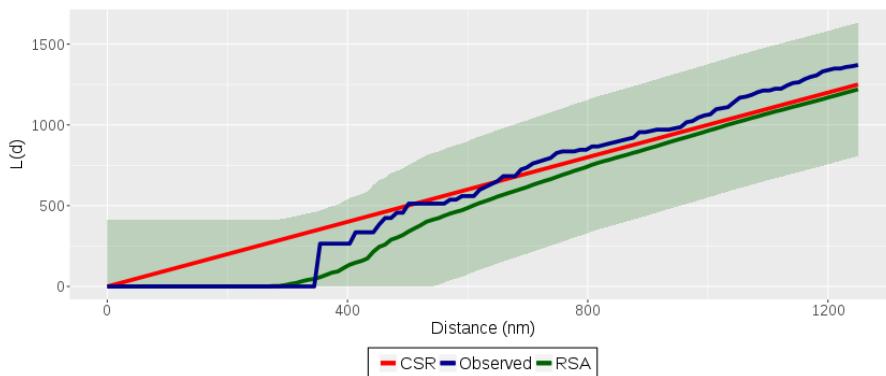
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 6.0534
- **Log standard deviation :** 0.3731
- **Test p-value:** : 0.6226 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

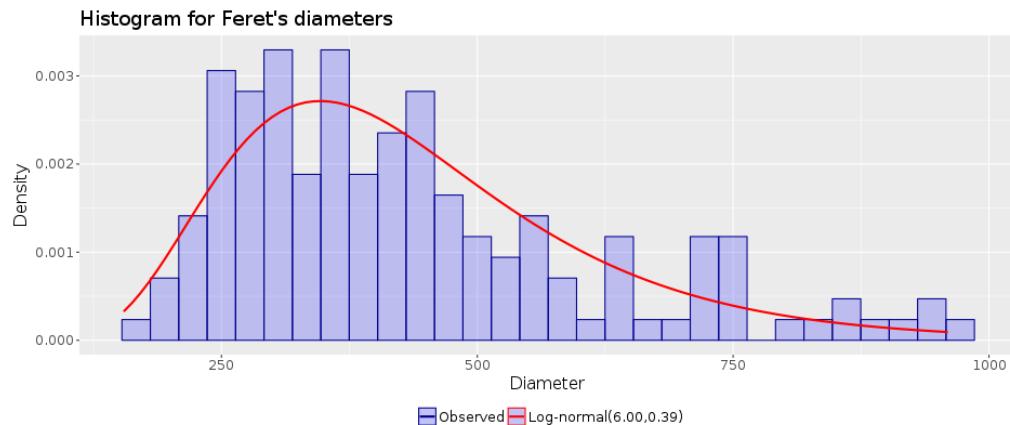
- **Feret diameter log mean:** 6.0534
- **Feret diameter log standard deviation:** 0.3731
- **Process intensity:** 0.3680 synapses/ μm^3



Sample5-Layer I:

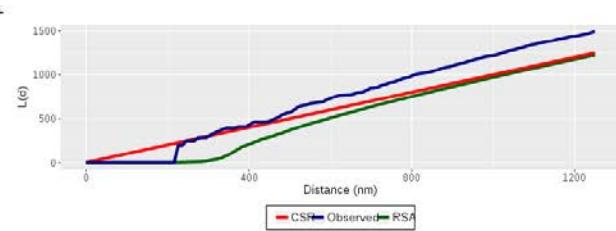
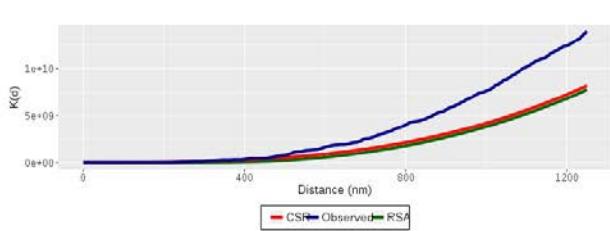
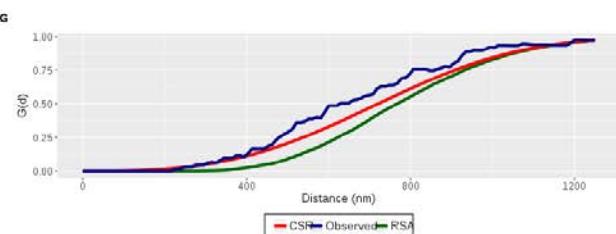
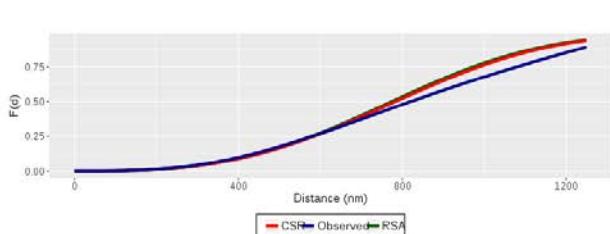
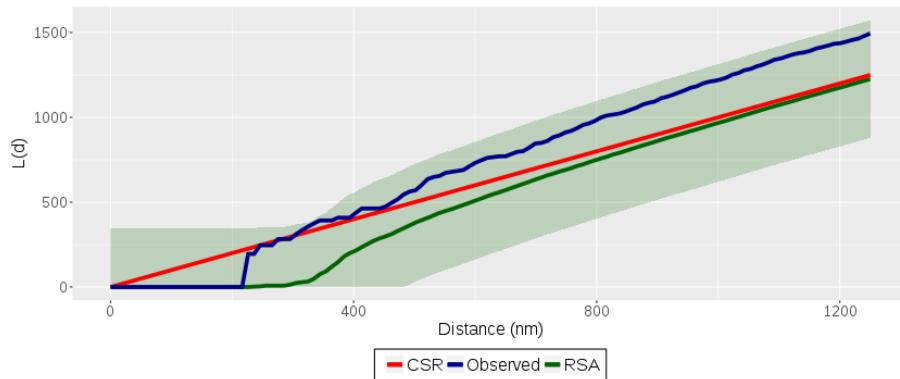
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 6.0022
- **Log standard deviation :** 0.3926
- **Test p-value:** : 0.7854 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

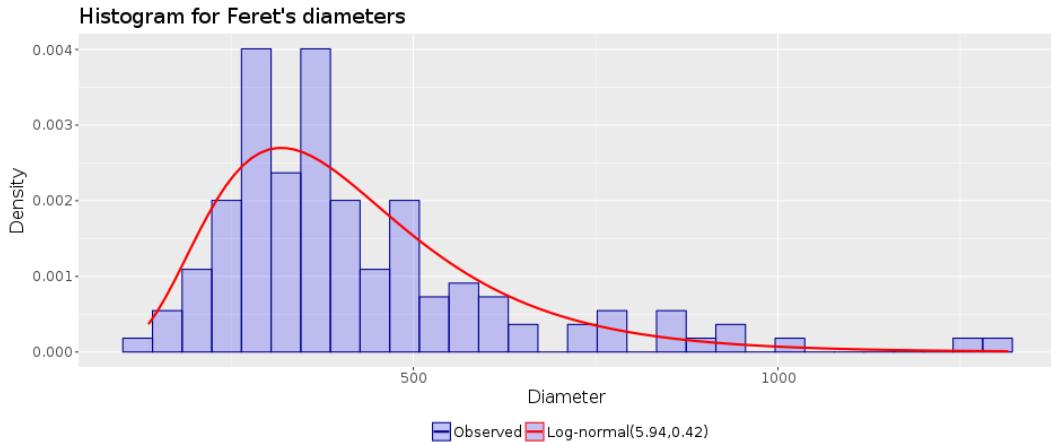
- **Feret diameter log mean:** 6.0022
- **Feret diameter log standard deviation:** 0.3926
- **Process intensity:** 0.4416 synapses/ μm^3



Sample6-Layer I:

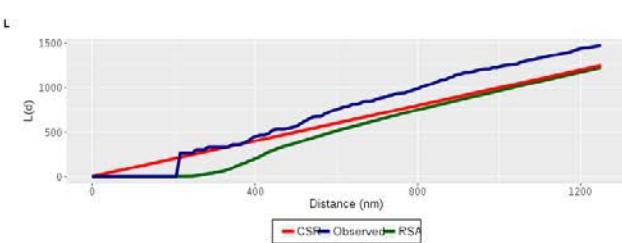
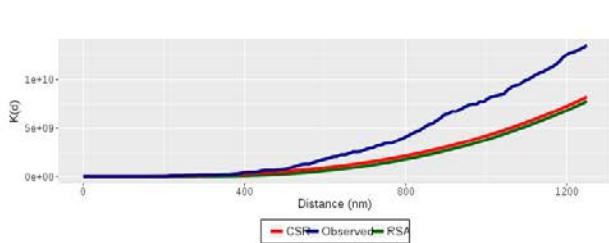
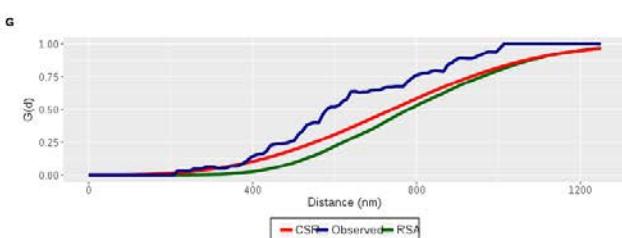
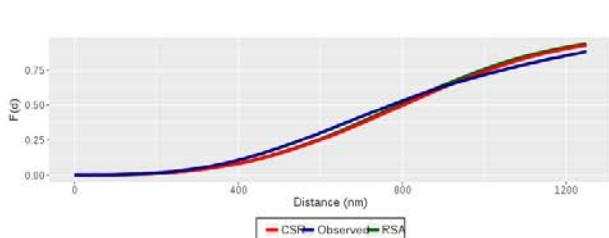
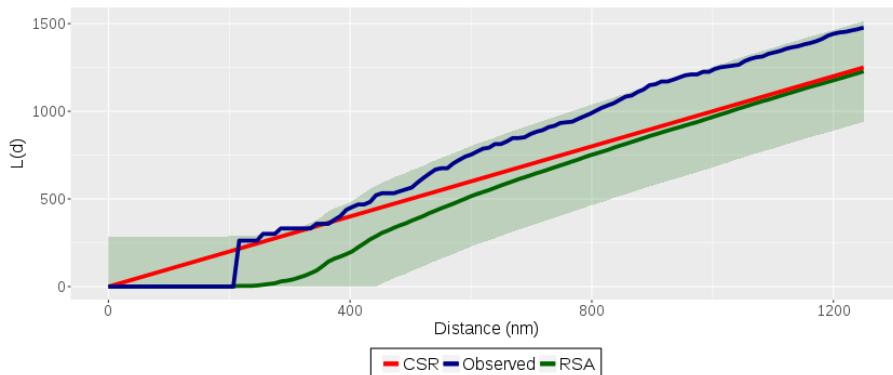
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9442
- **Log standard deviation :** 0.4237
- **Test p-value:** : 0.1786 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

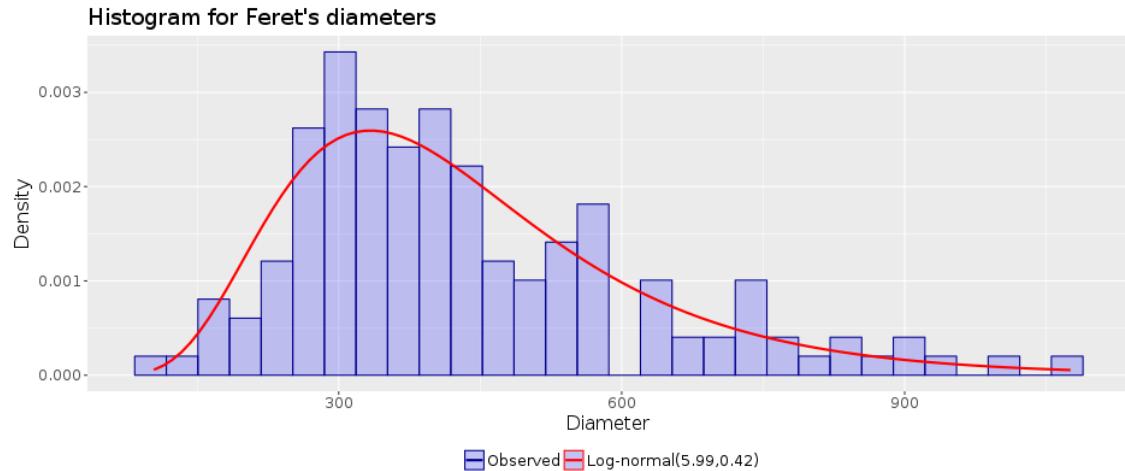
- **Feret diameter log mean:** 5.9442
- **Feret diameter log standard deviation:** 0.4237
- **Process intensity:** 0.4082 synapses/ μm^3



Sample7-Layer I:

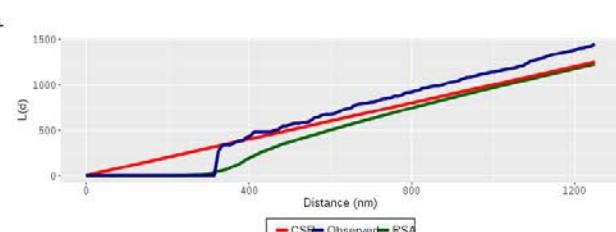
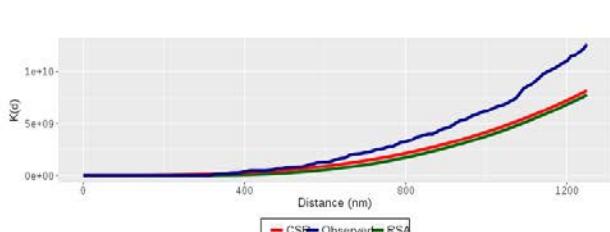
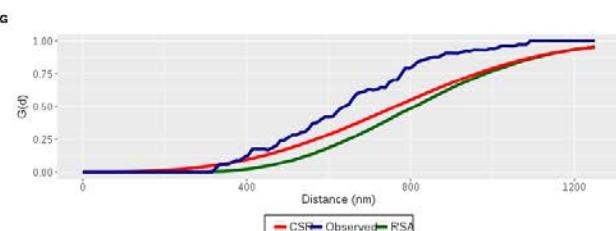
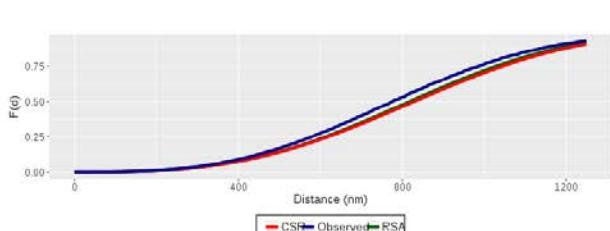
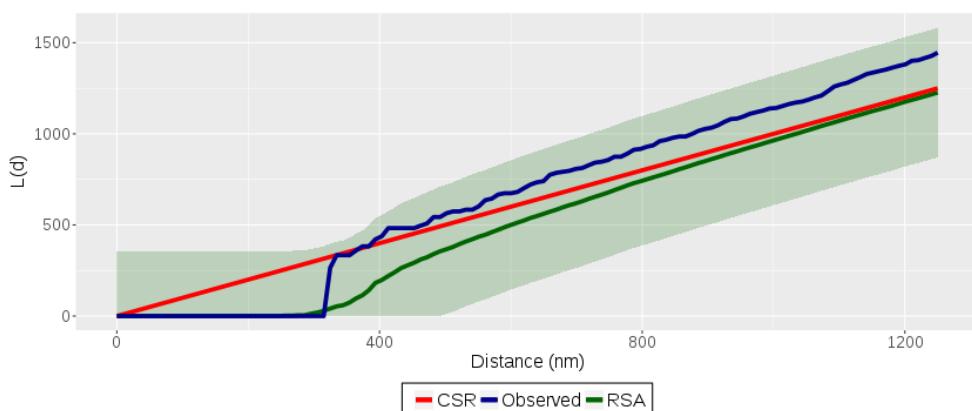
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9874
- **Log standard deviation :** 0.4219
- **Test p-value:** : 0.8967 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

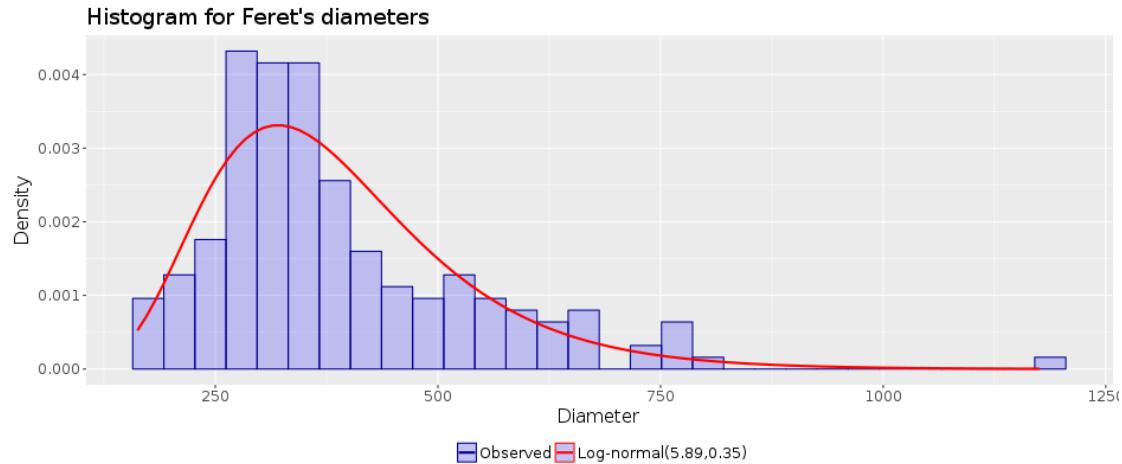
- **Feret diameter log mean:** 5.9874
- **Feret diameter log standard deviation:** 0.4219
- **Process intensity:** 0.3717 synapses/ μm^3



Sample8-Layer I:

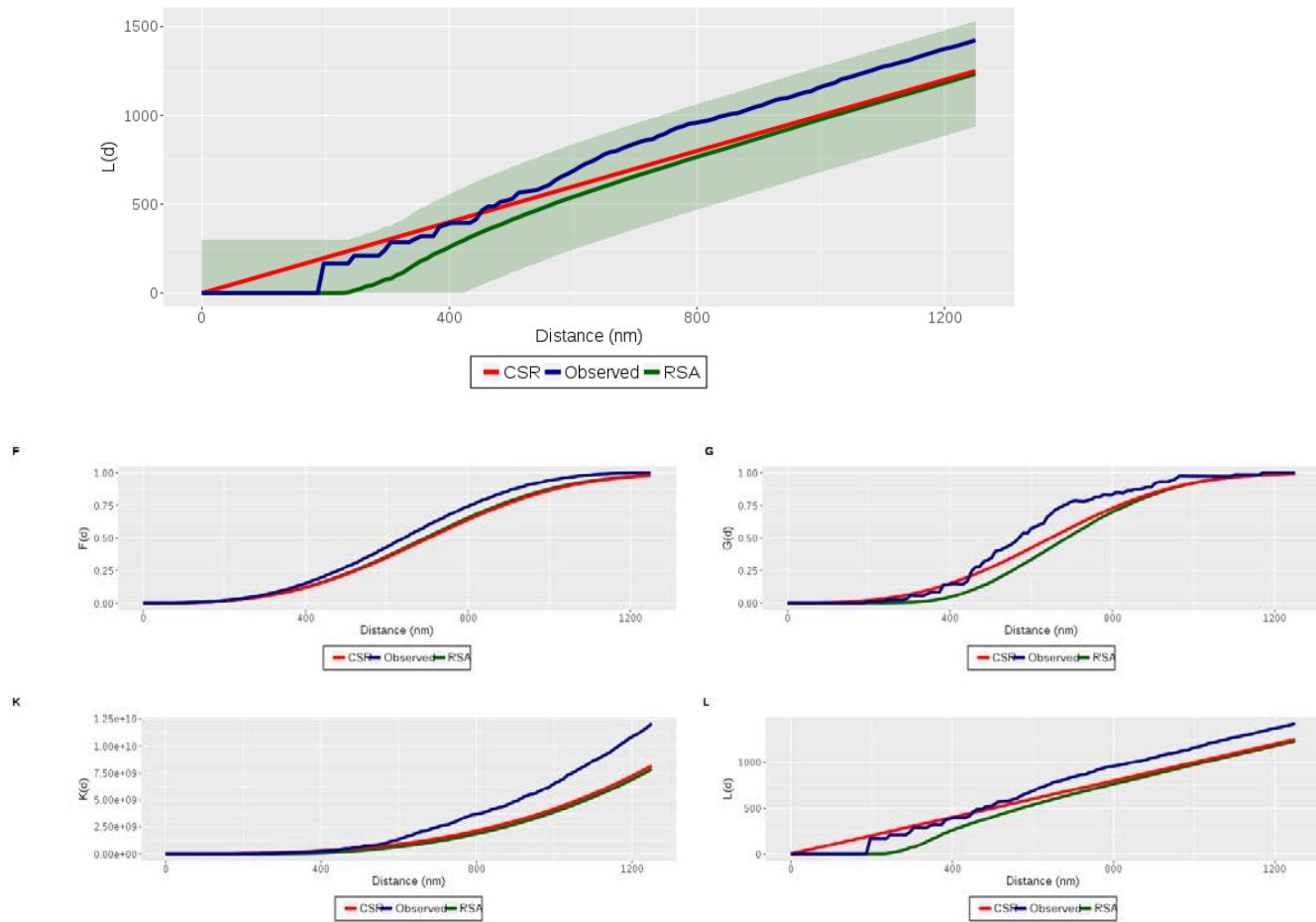
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.8942
- **Log standard deviation :** 0.3532
- **Test p-value:** : 0.1518 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

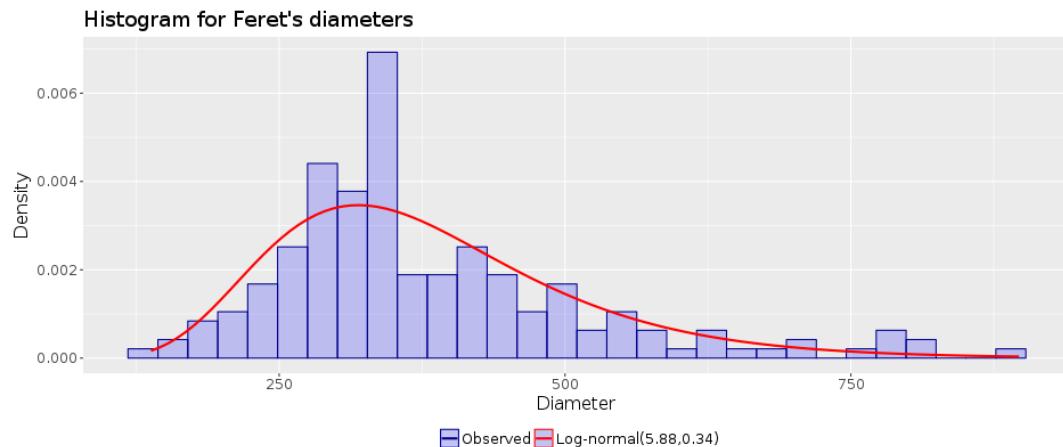
- **Feret diameter log mean:** 5.8942
- **Feret diameter log standard deviation:** 0.3532
- **Process intensity:** 0.6079 synapses/ μm^3



Sample9-Layer I:

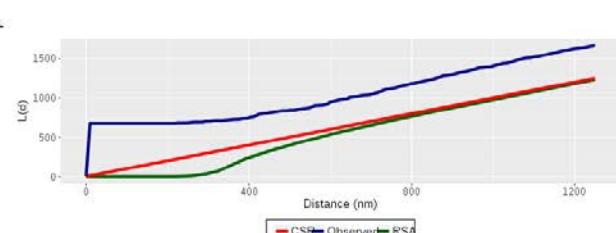
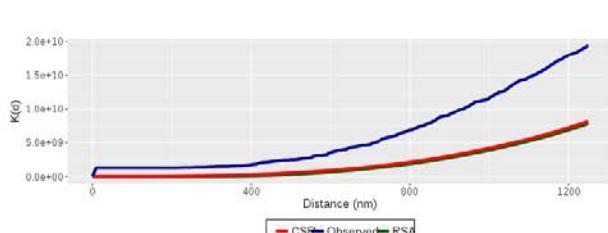
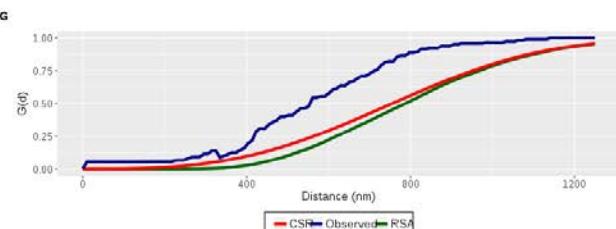
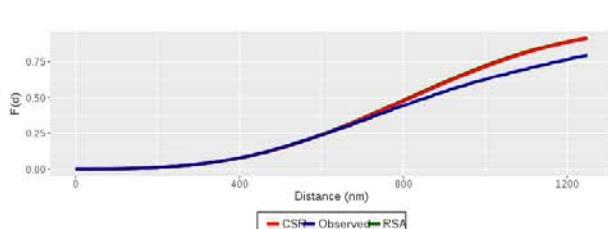
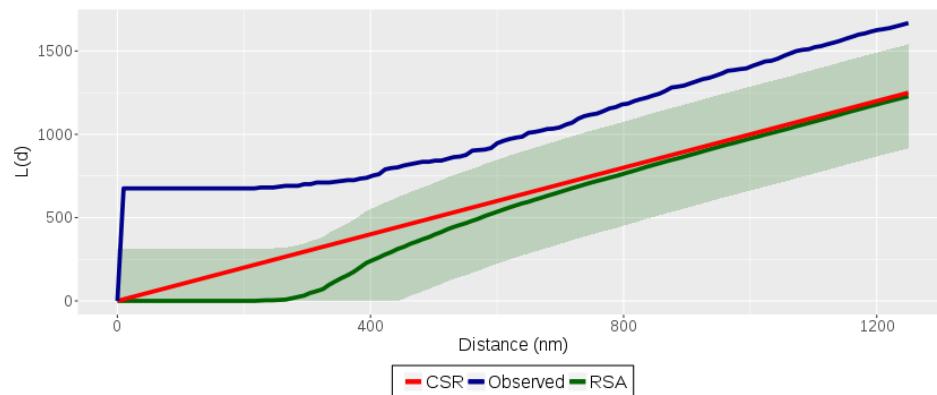
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.8818
- **Log standard deviation :** 0.3404
- **Test p-value:** : 0.0775 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

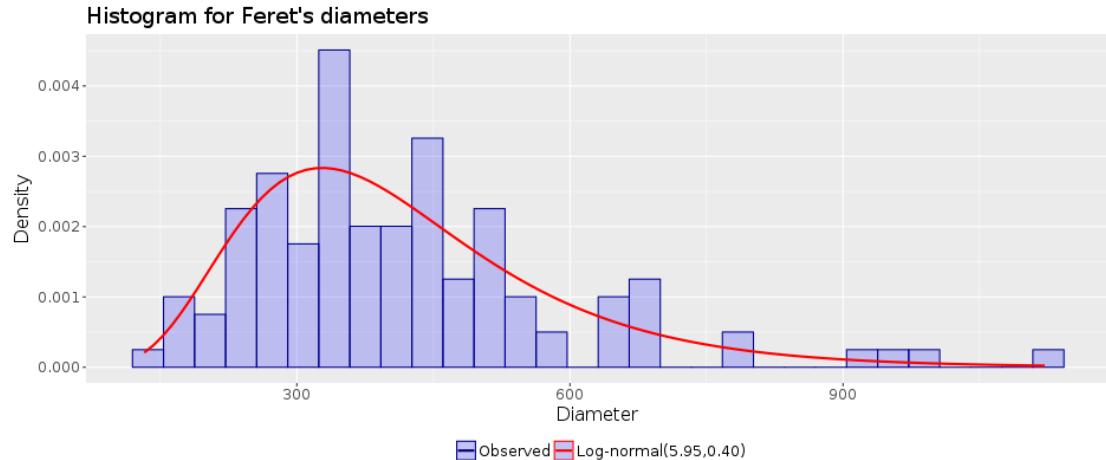
- **Feret diameter log mean:** 5.8818
- **Feret diameter log standard deviation:** 0.3404
- **Process intensity:** 0.3832 synapses/ μm^3



Sample10-Layer I:

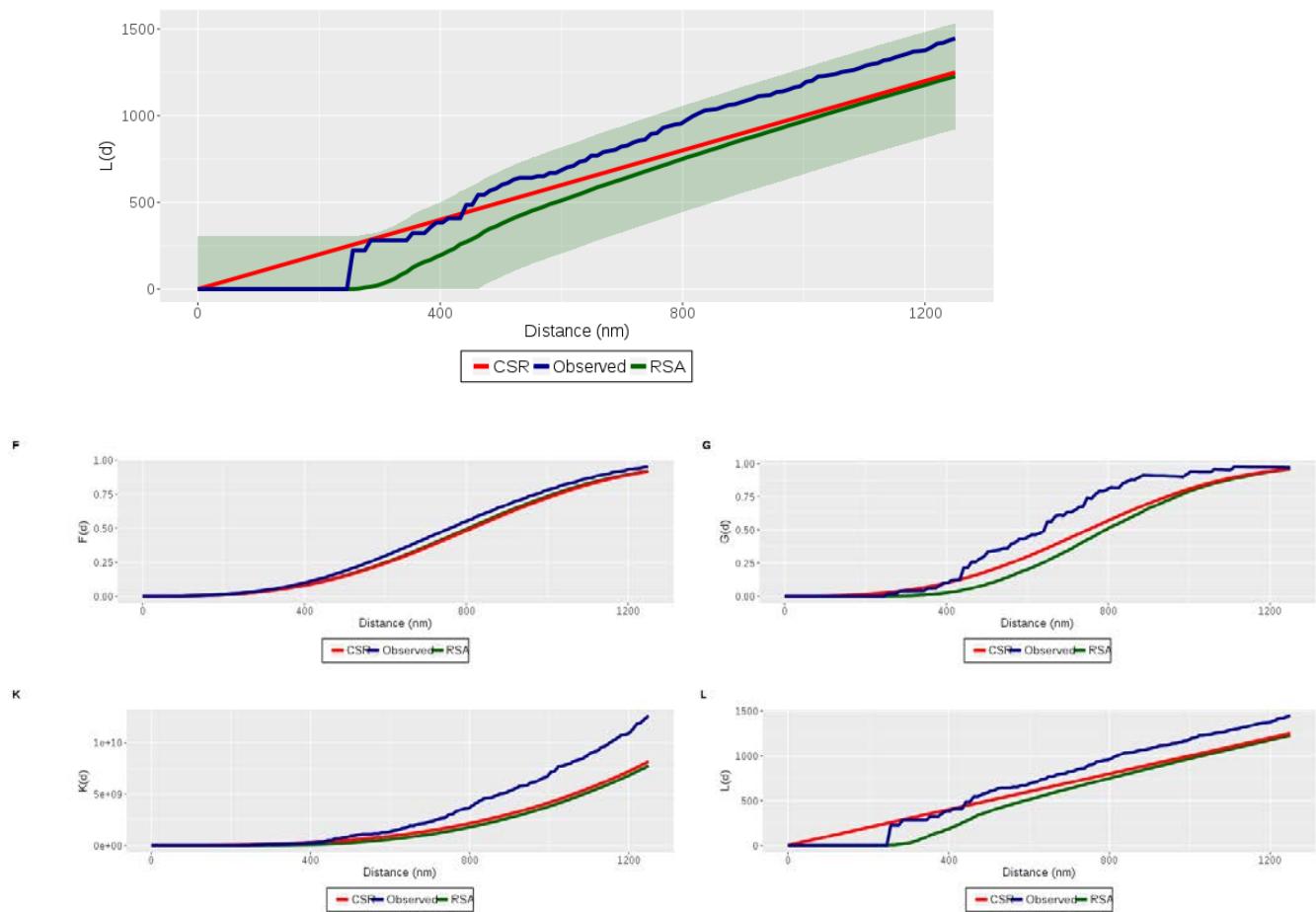
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9497
- **Log standard deviation :** 0.3970
- **Test p-value:** : 0.9325 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

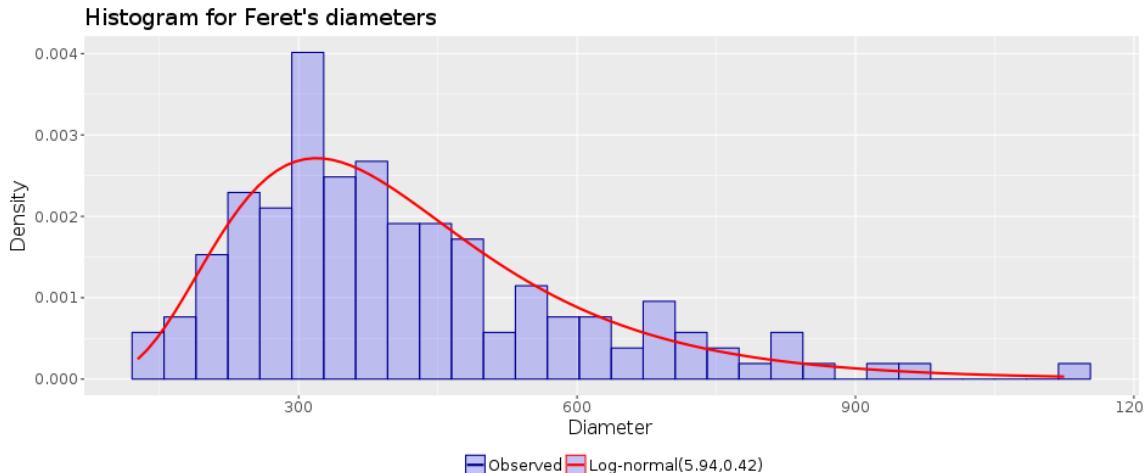
- **Feret diameter log mean:** 5.9497
- **Feret diameter log standard deviation:** 0.3970
- **Process intensity:** 0.3929 synapses/ μm^3



Sample11-Layer I:

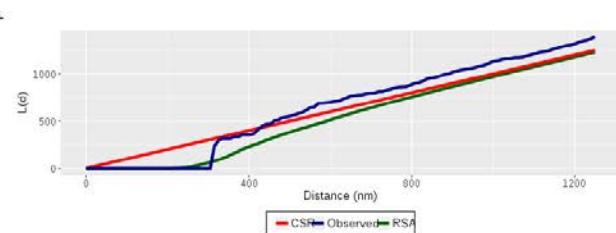
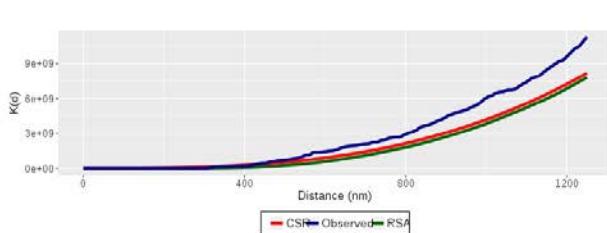
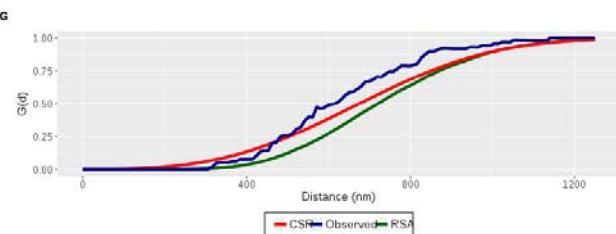
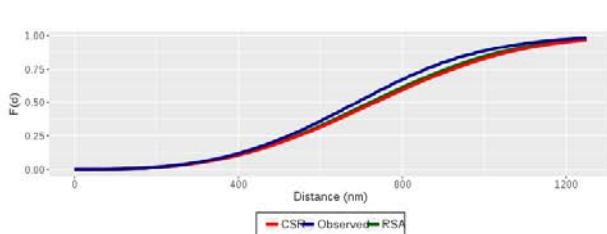
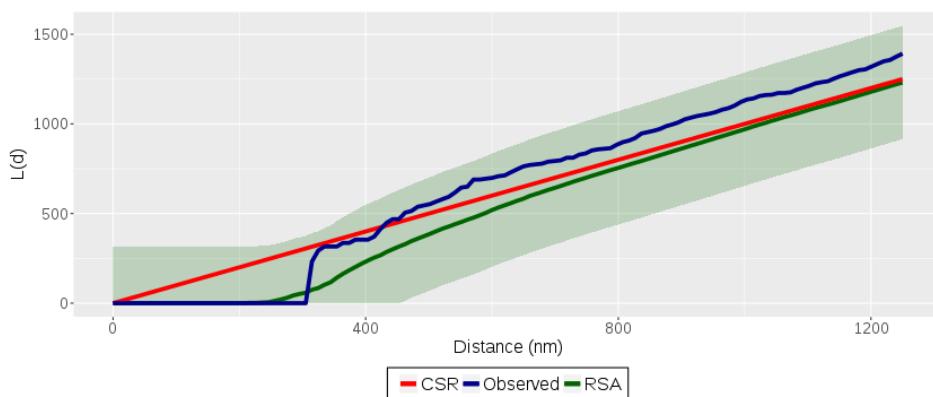
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9432
- **Log standard deviation :** 0.4213
- **Test p-value:** : 0.9830 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

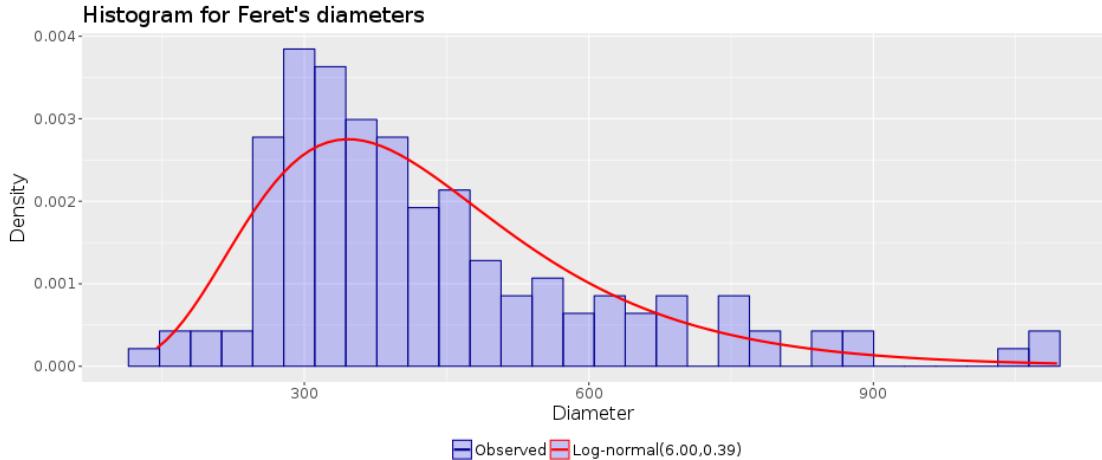
- **Feret diameter log mean:** 5.9432
- **Feret diameter log standard deviation:** 0.4213
- **Process intensity:** 0.5379 synapses/ μm^3



Sample12-Layer I:

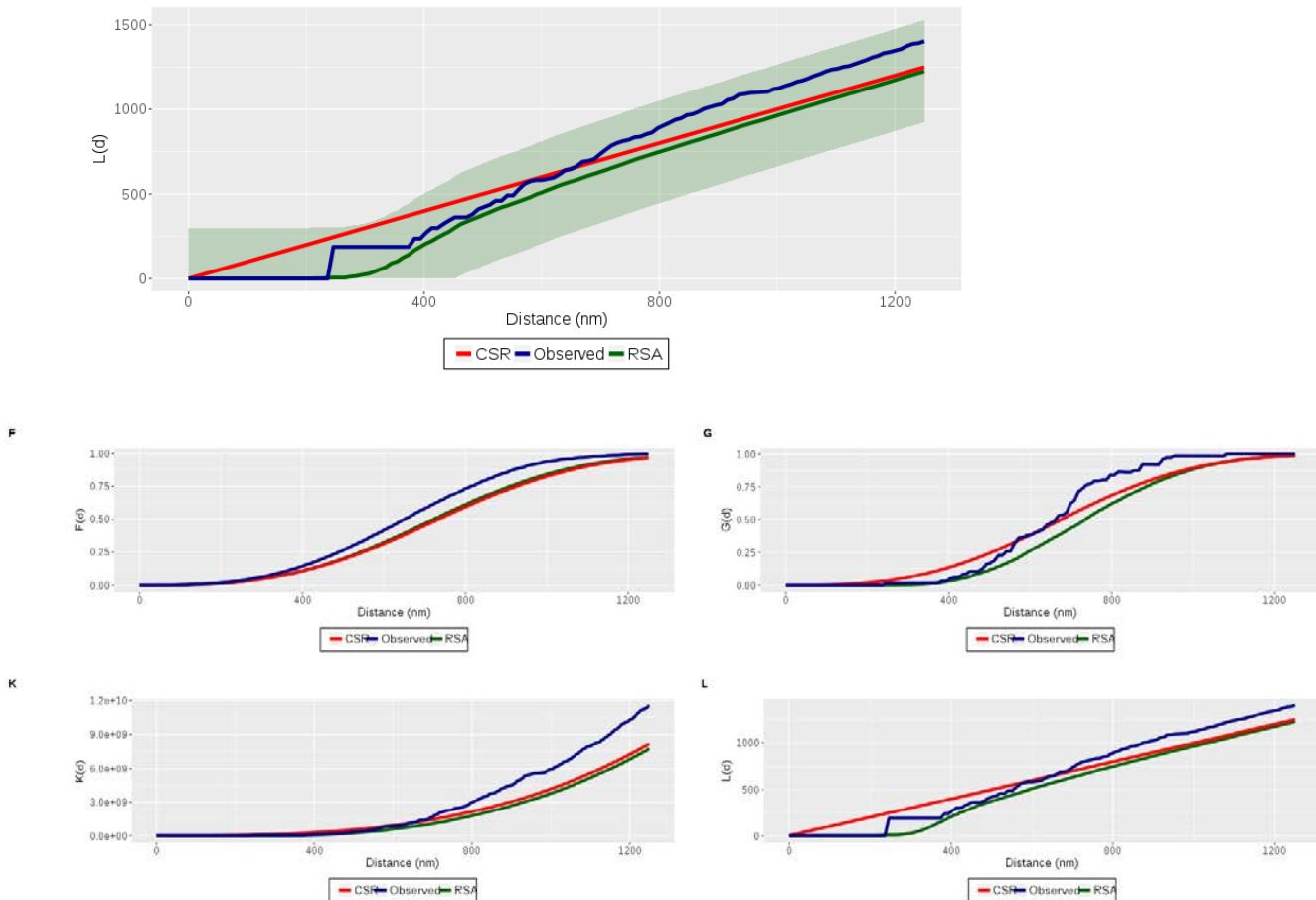
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9977
- **Log standard deviation :** 0.3884
- **Test p-value:** : 0.5635 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

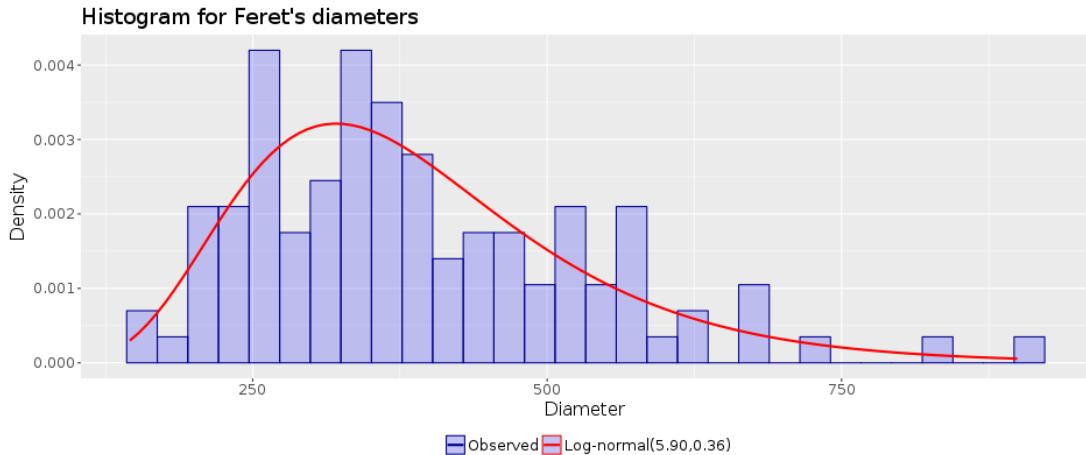
- **Feret diameter log mean:** 5.9977
- **Feret diameter log standard deviation:** 0.3884
- **Process intensity:** 0.5345 synapses/ μm^3



Sample1-Layer II:

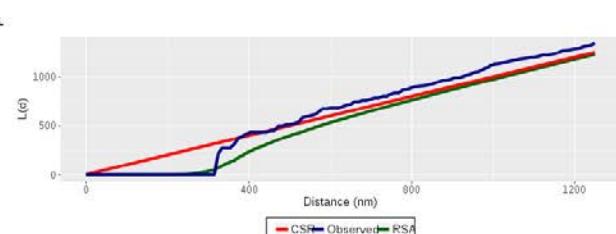
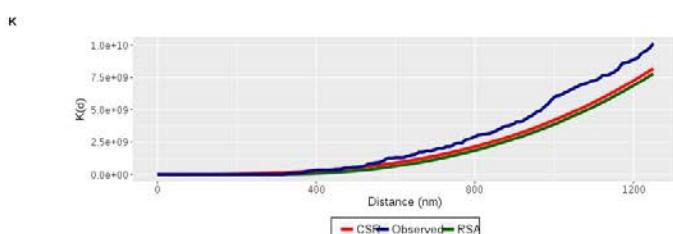
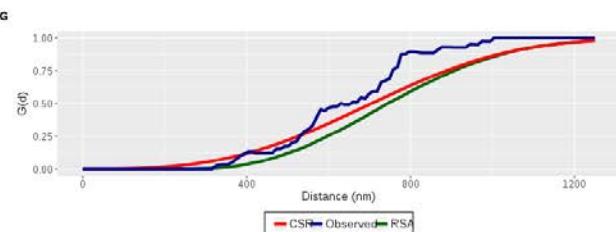
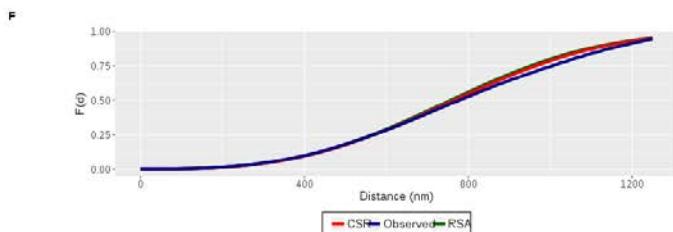
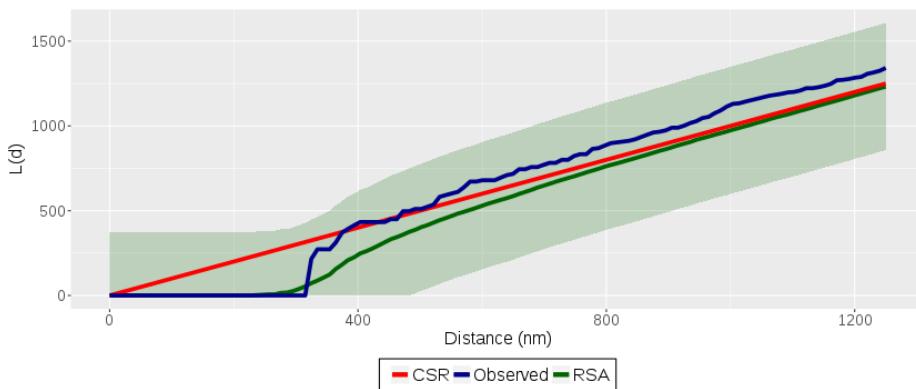
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9021
- **Log standard deviation :** 0.3625
- **Test p-value:** : 0.8631 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

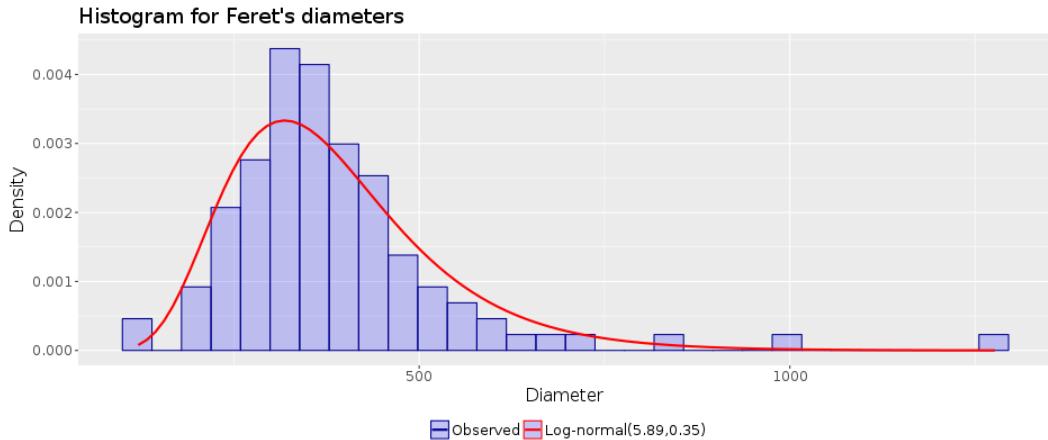
- **Feret diameter log mean:** 5.9021
- **Feret diameter log standard deviation:** 0.3625
- **Process intensity:** 0.4721 synapses/ μm^3



Sample2-Layer II:

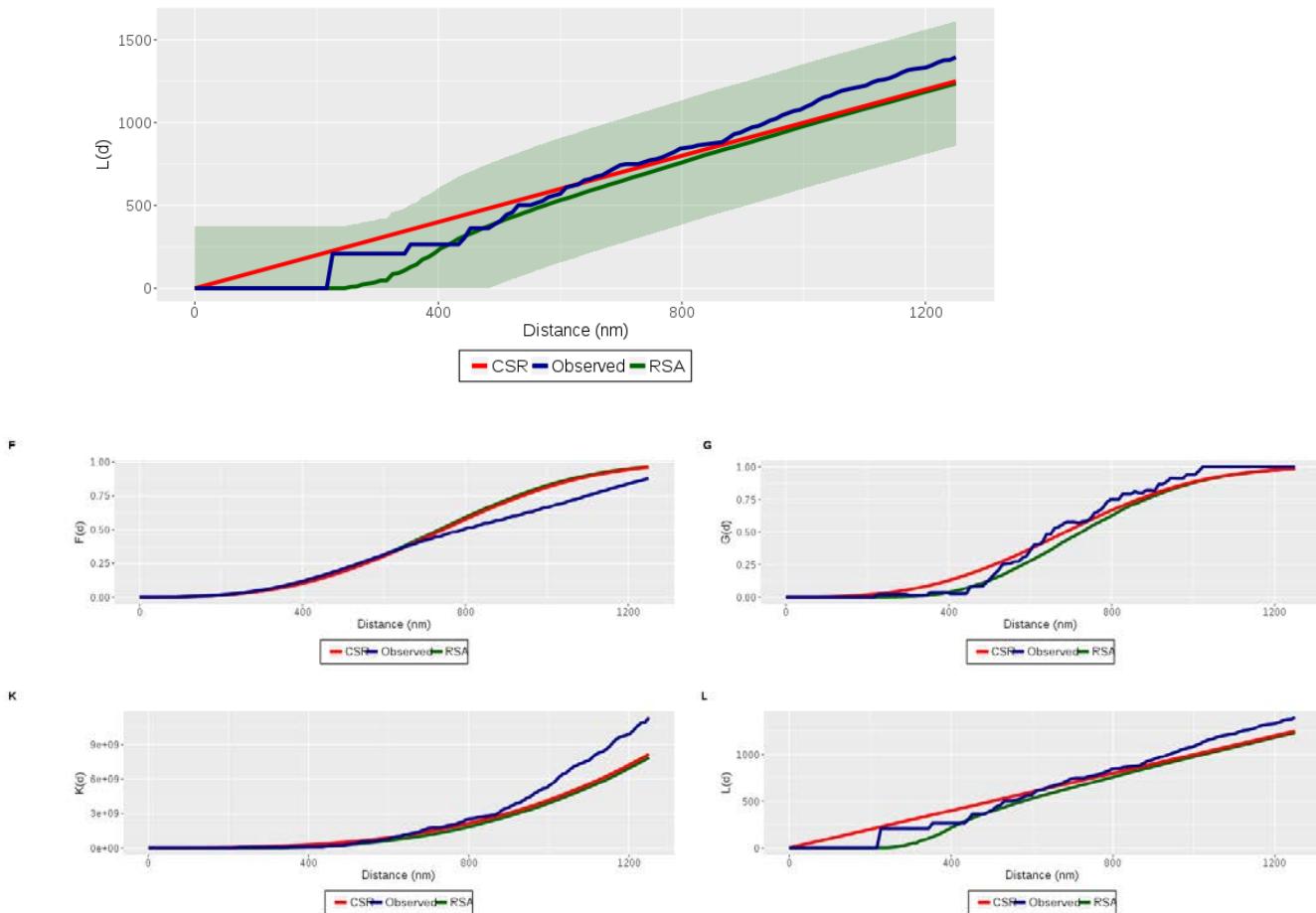
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.8881
- **Log standard deviation :** 0.3532
- **Test p-value:** : 0.7104 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

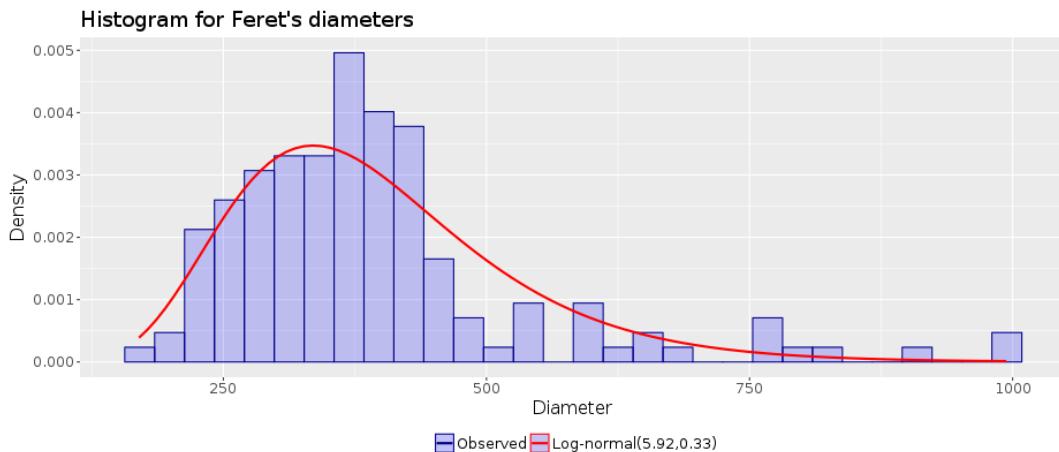
- **Feret diameter log mean:** 5.8881
- **Feret diameter log standard deviation:** 0.3532
- **Process intensity:** 0.5113 synapses/ μm^3



Sample3-Layer II:

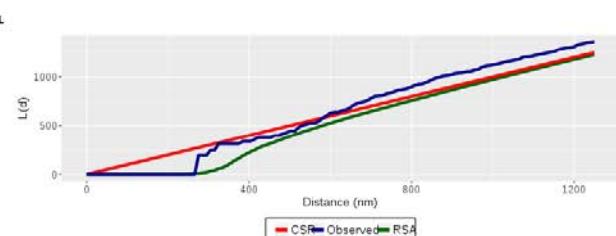
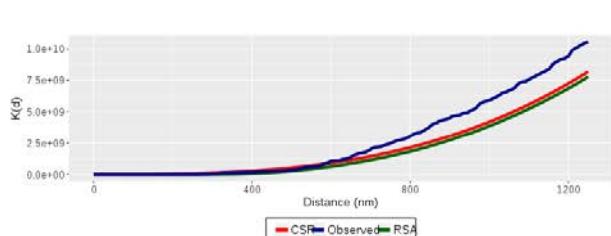
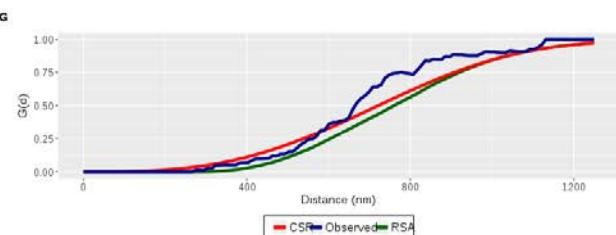
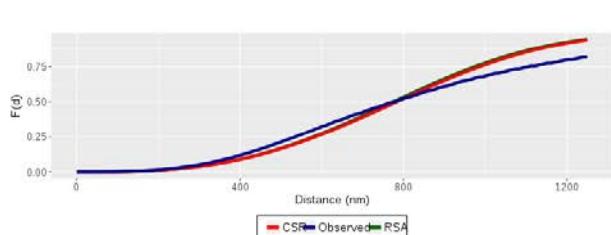
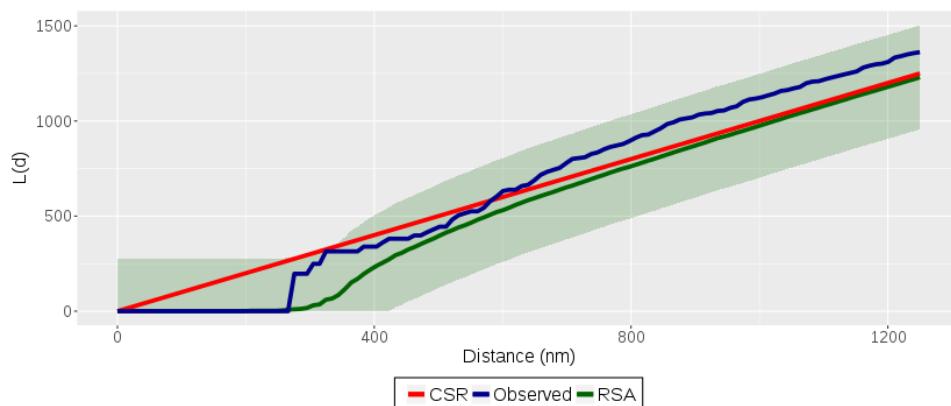
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9207
- **Log standard deviation :** 0.3251
- **Test p-value:** : 0.0451 (One-sample Kolmogorov-Smirnov test) **REJECT**



Envelope and results based on 198 simulations:

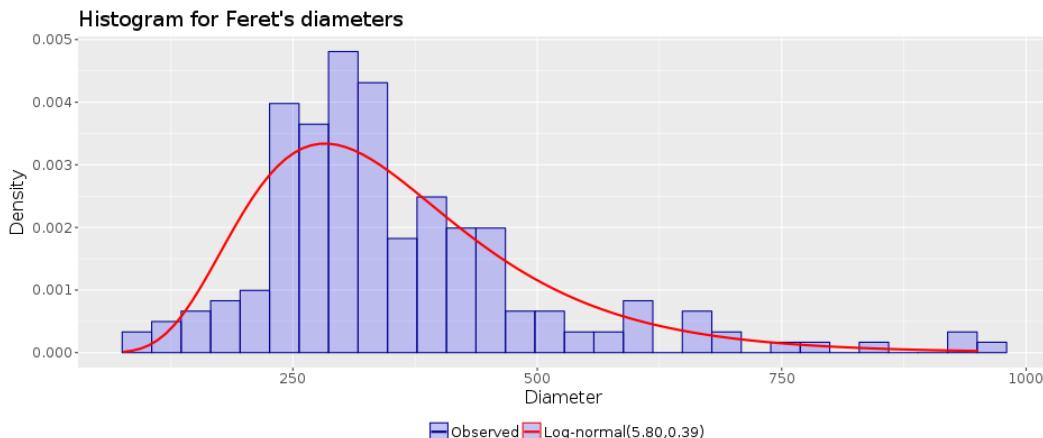
- **Feret diameter log mean:** 5.9207
- **Feret diameter log standard deviation:** 0.3251
- **Process intensity:** 0.4408 synapses/ μm^3



Sample4-Layer II:

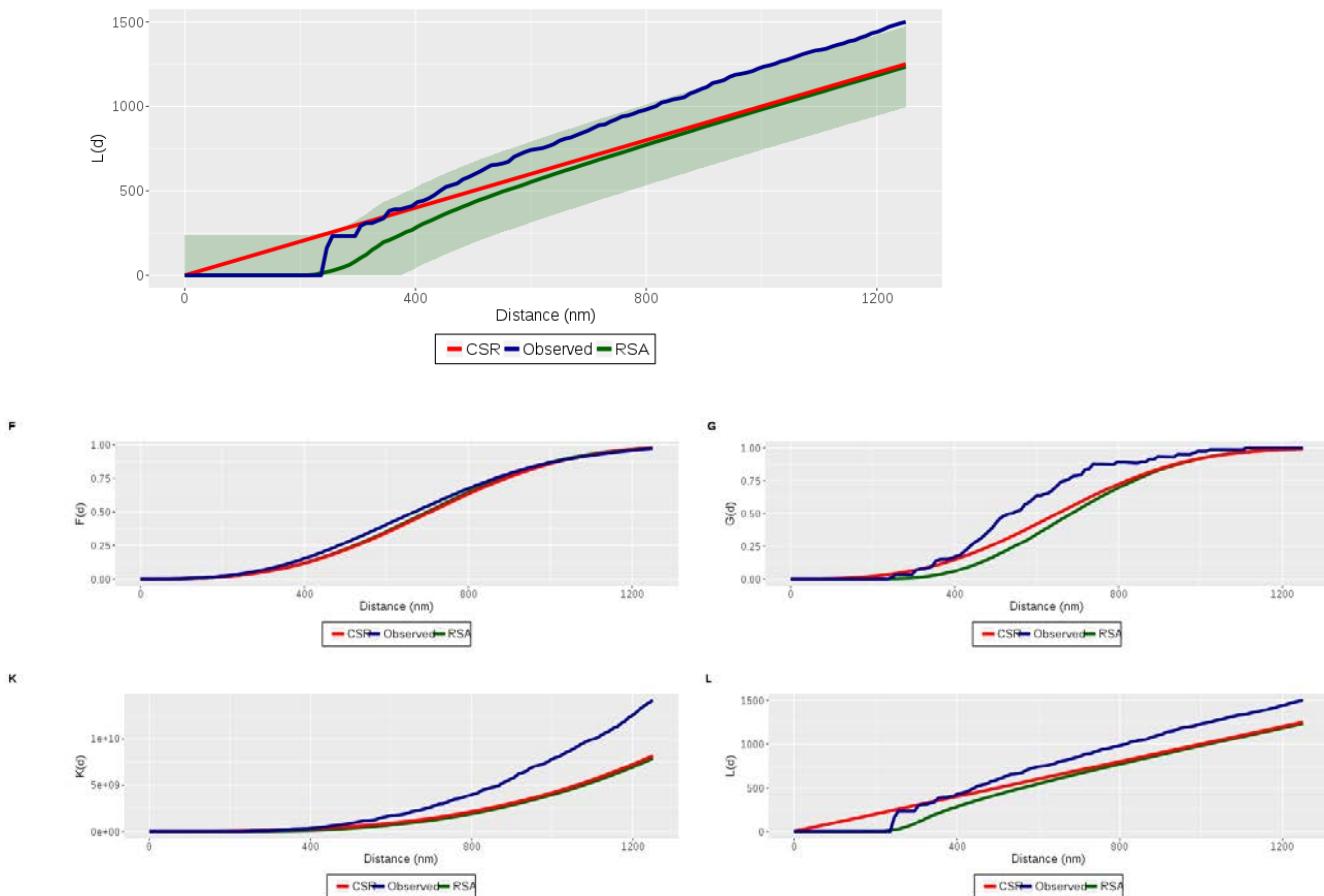
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.7976
- **Log standard deviation :** 0.3914
- **Test p-value:** : 0.2539 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

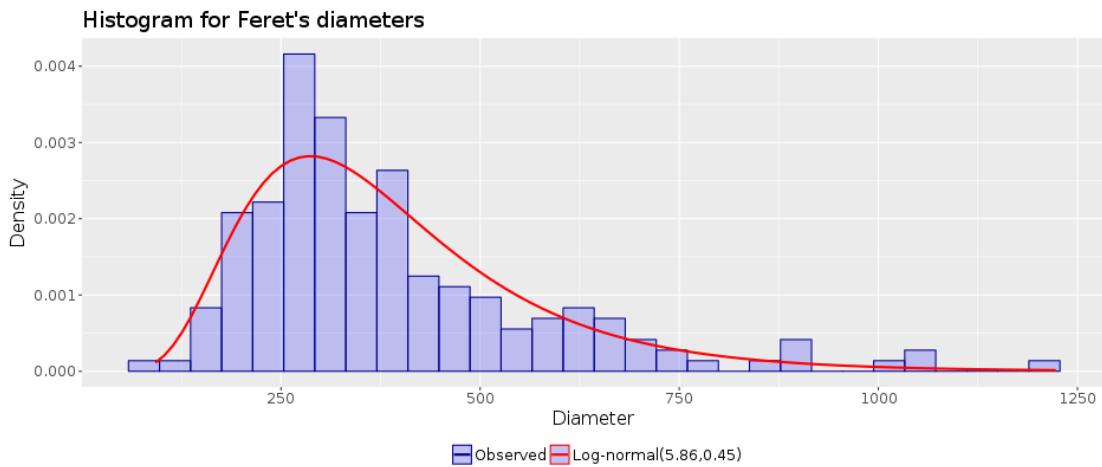
- **Feret diameter log mean:** 5.7976
- **Feret diameter log standard deviation:** 0.3914
- **Process intensity:** 0.5989 synapses/ μm^3



Sample5-Layer II:

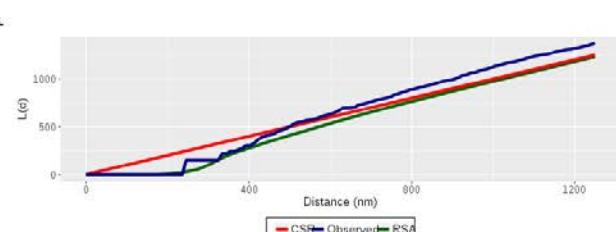
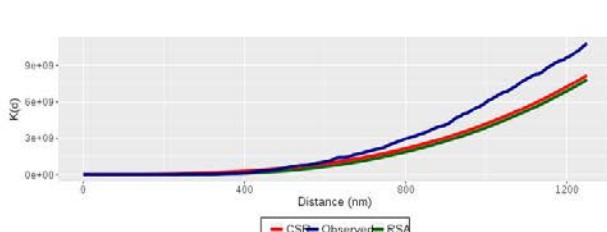
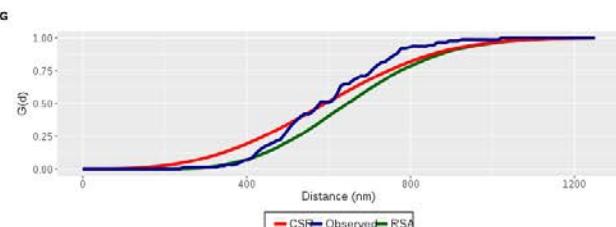
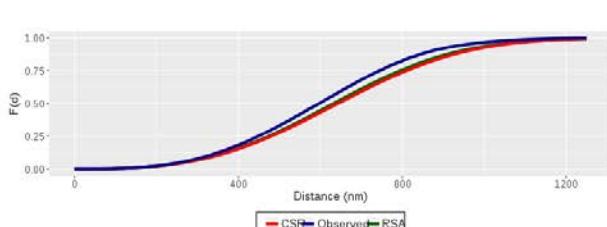
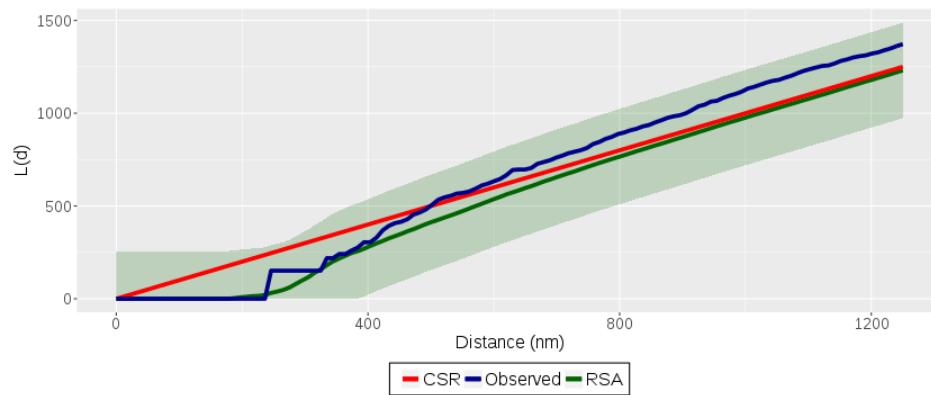
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.8582
- **Log standard deviation :** 0.4463
- **Test p-value:** : 0.4976 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

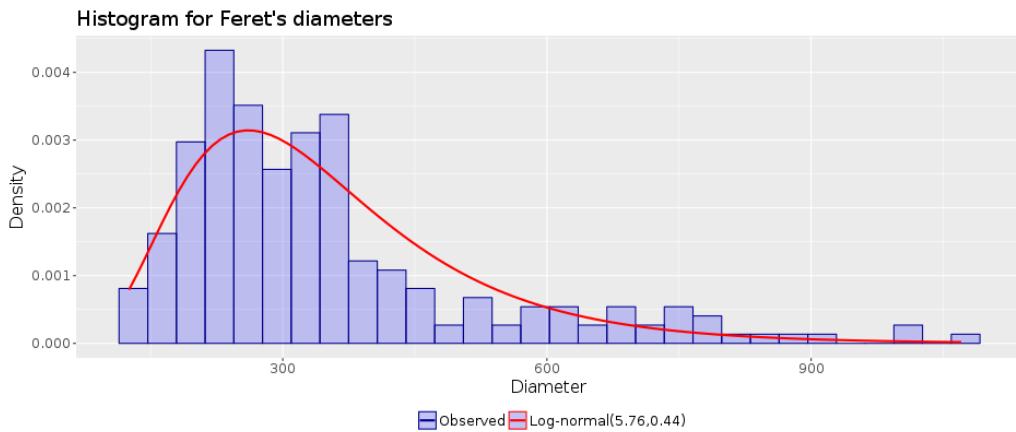
- **Feret diameter log mean:** 5.8582
- **Feret diameter log standard deviation:** 0.4463
- **Process intensity:** 0.7970 synapses/ μm^3



Sample6-Layer II:

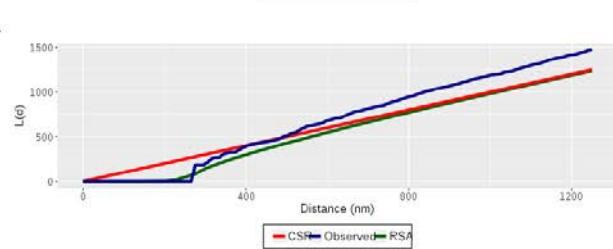
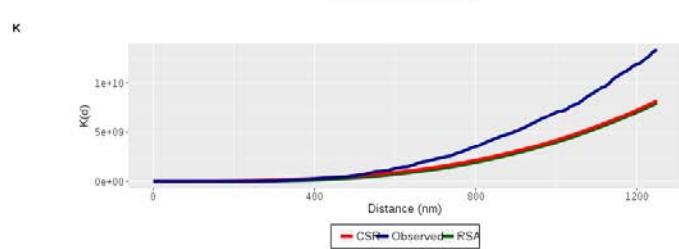
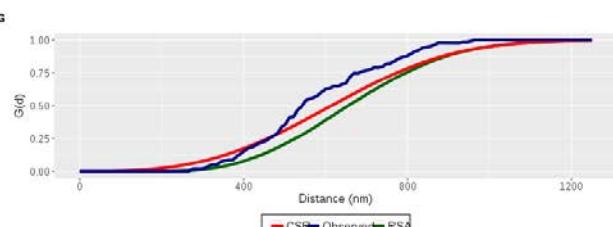
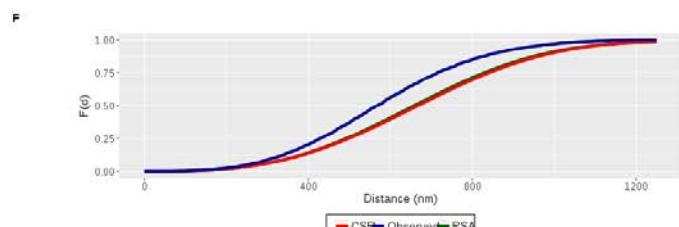
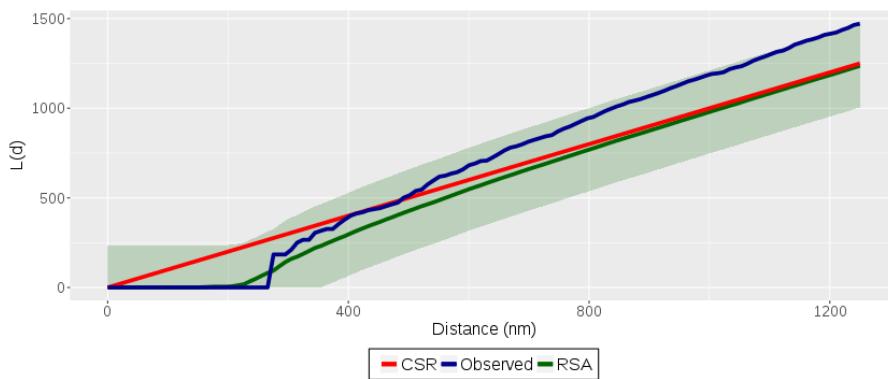
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.7588
- **Log standard deviation :** 0.4412
- **Test p-value:** : 0.1070 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

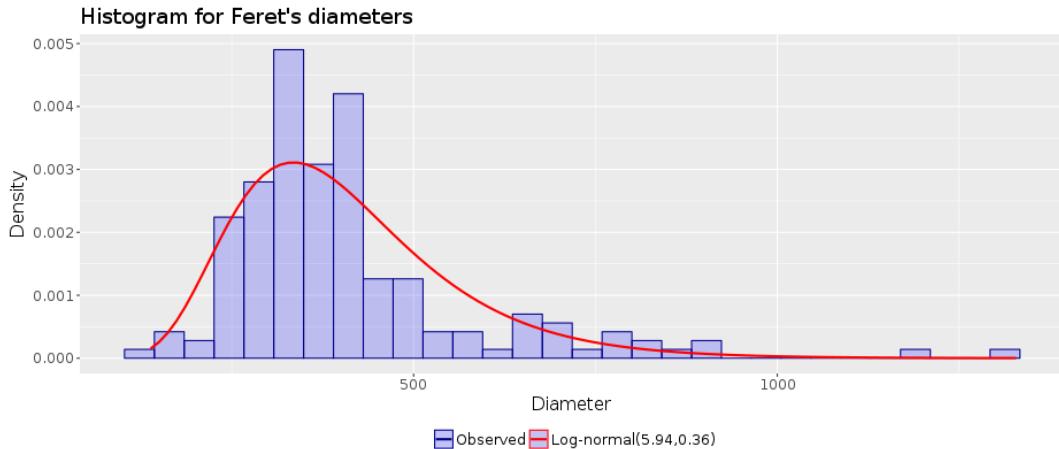
- **Feret diameter log mean:** 5.7588
- **Feret diameter log standard deviation:** 0.4412
- **Process intensity:** 0.7132 synapses/ μm^3



Sample7-Layer II:

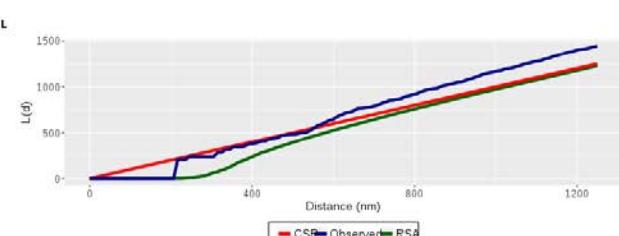
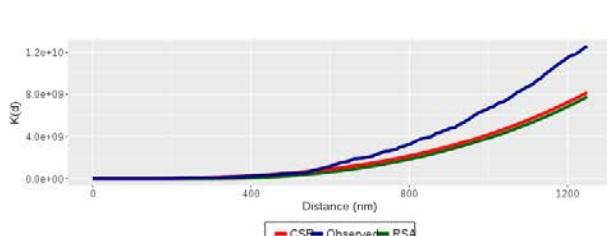
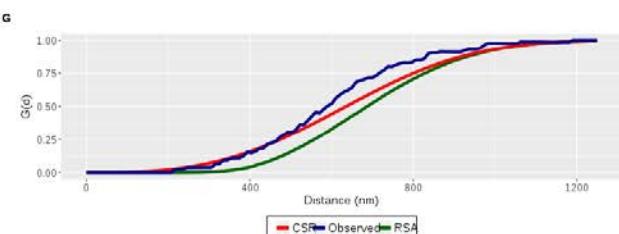
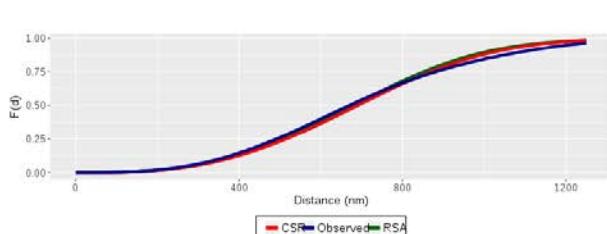
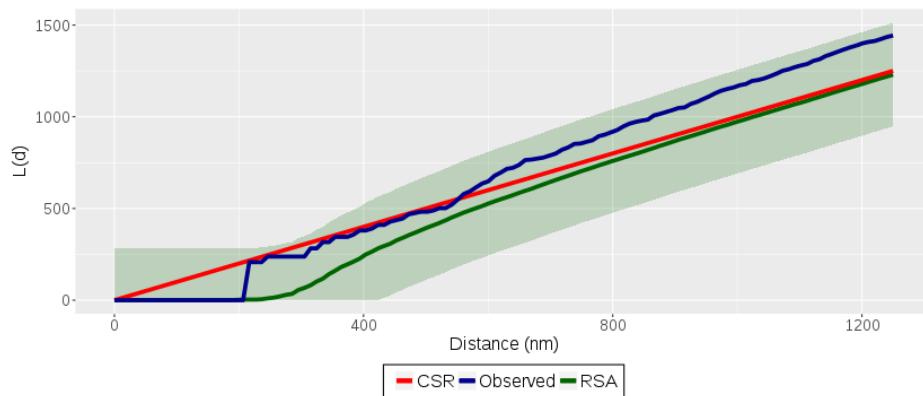
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9424
- **Log standard deviation :** 0.3592
- **Test p-value:** : 0.0311 (One-sample Kolmogorov-Smirnov test) **REJECT**



Envelope and results based on 198 simulations:

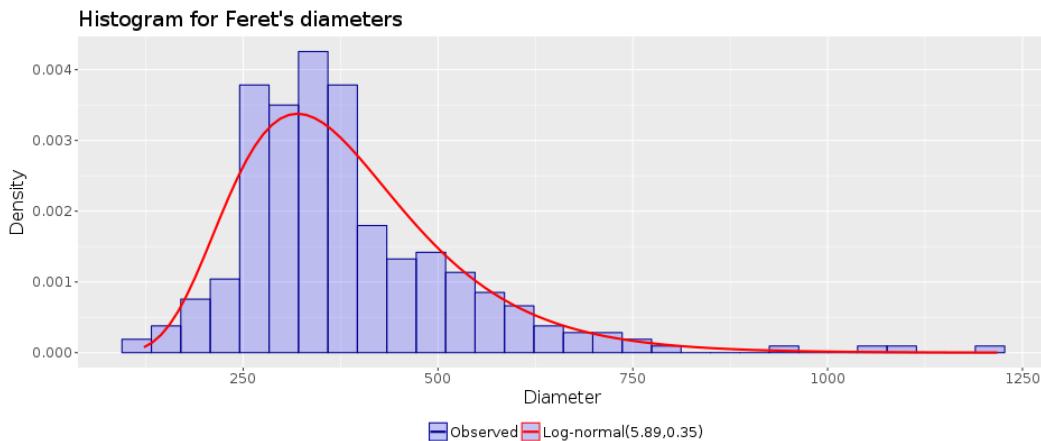
- **Feret diameter log mean:** 5.9424
- **Feret diameter log standard deviation:** 0.3592
- **Process intensity:** 0.6445 synapses/ μm^3



Sample8-Layer II:

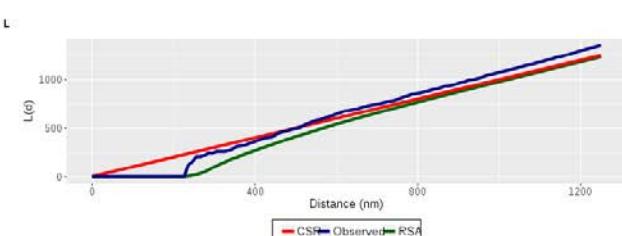
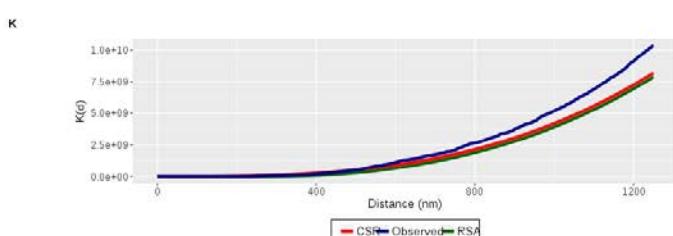
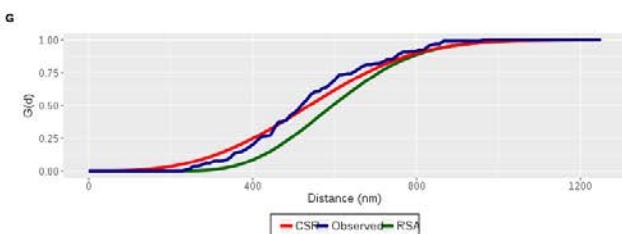
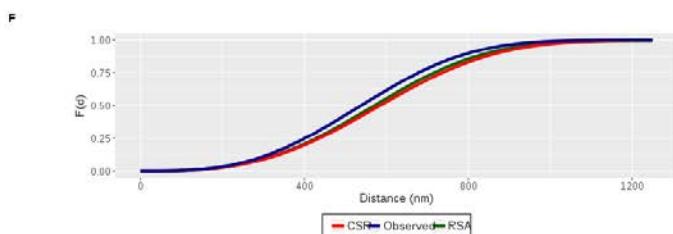
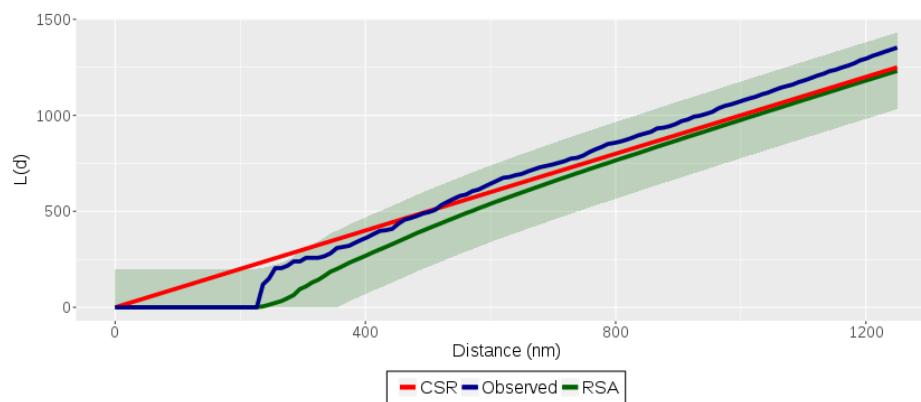
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.8880
- **Log standard deviation :** 0.3479
- **Test p-value:** : 0.1283 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

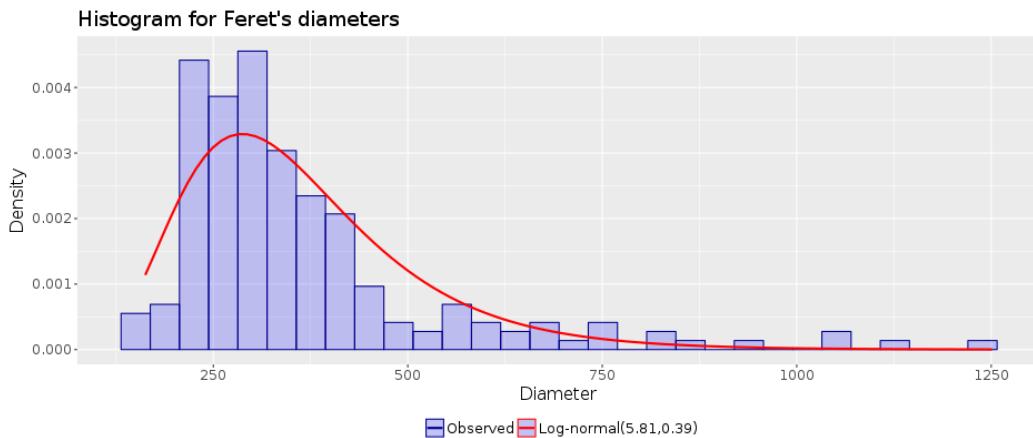
- **Feret diameter log mean:** 5.8880
- **Feret diameter log standard deviation:** 0.3479
- **Process intensity:** 1.0601 synapses/ μm^3



Sample9-Layer II:

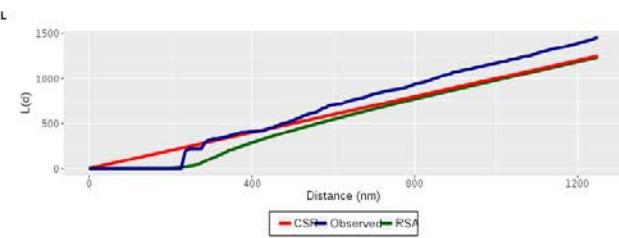
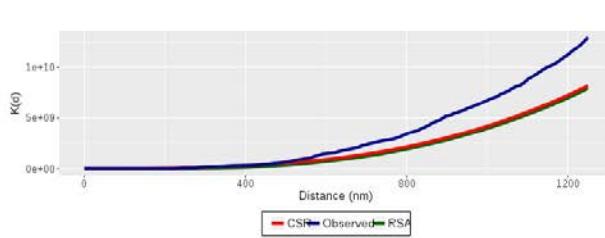
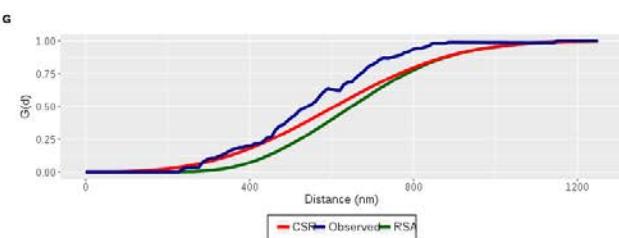
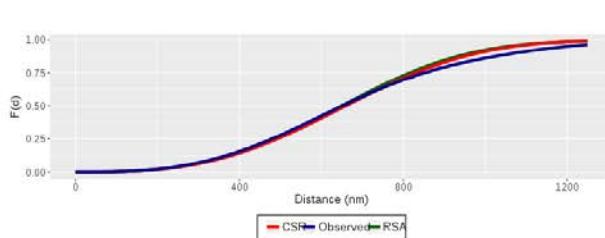
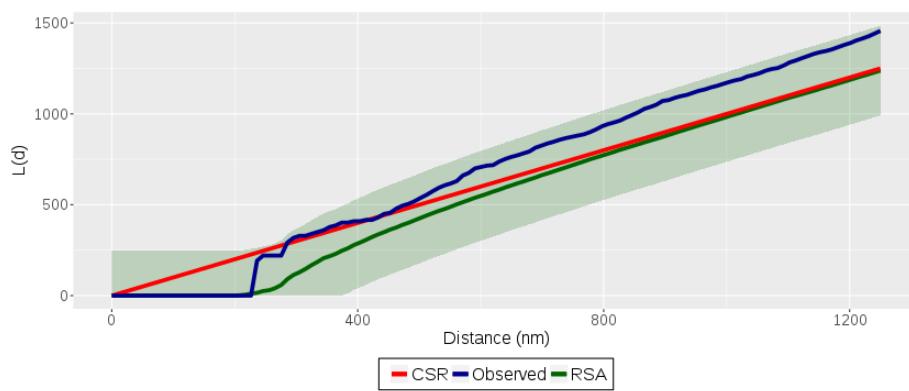
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.8132
- **Log standard deviation :** 0.3910
- **Test p-value:** : 0.0652 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

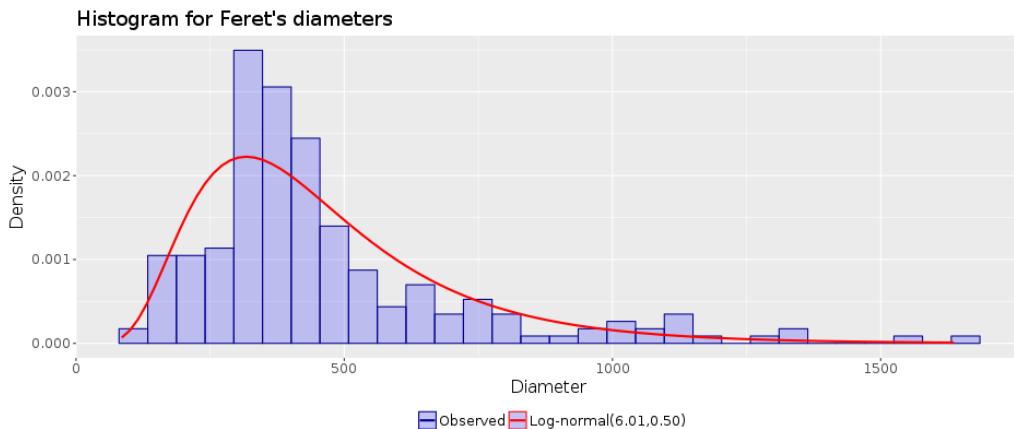
- **Feret diameter log mean:** 5.8132
- **Feret diameter log standard deviation:** 0.3910
- **Process intensity:** 0.7384 synapses/ μm^3



Sample10-Layer II:

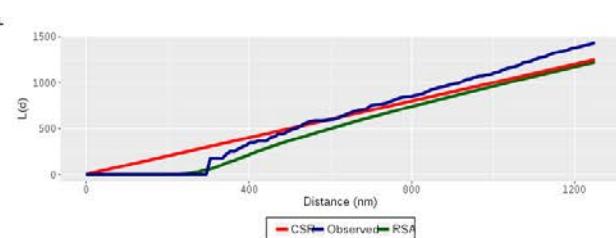
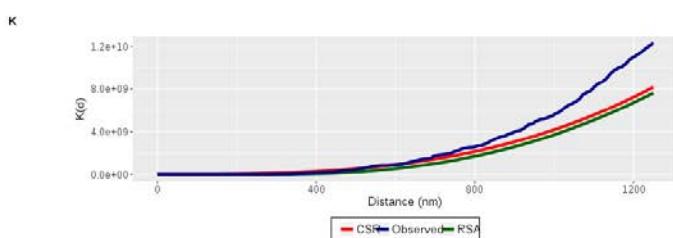
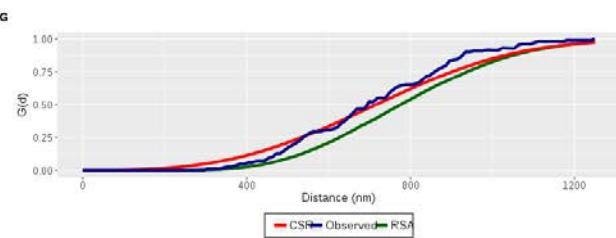
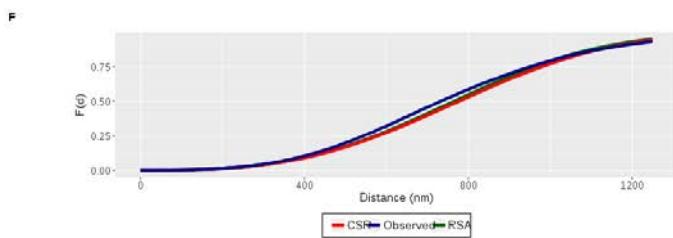
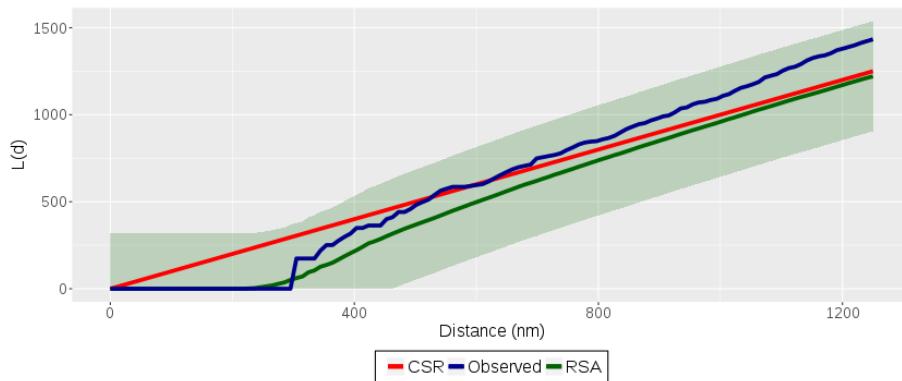
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 6.0091
- **Log standard deviation :** 0.4986
- **Test p-value:** : 0.0969 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

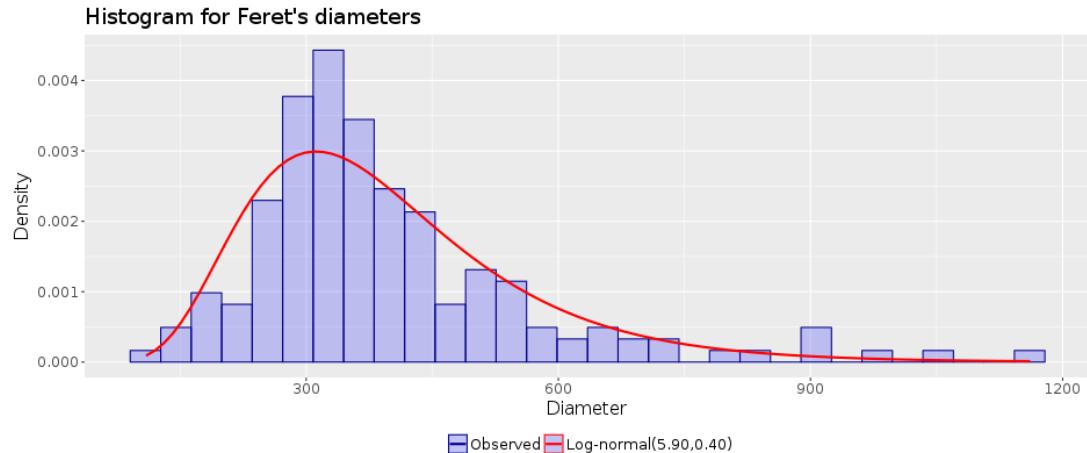
- **Feret diameter log mean:** 6.0091
- **Feret diameter log standard deviation:** 0.4986
- **Process intensity:** 0.4514 synapses/ μm^3



Sample11-Layer II:

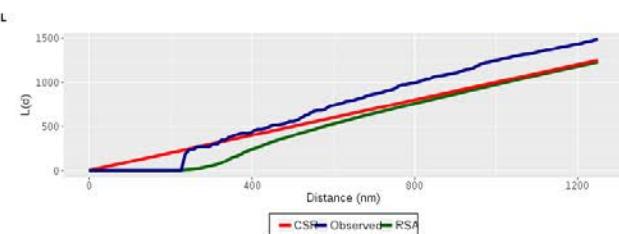
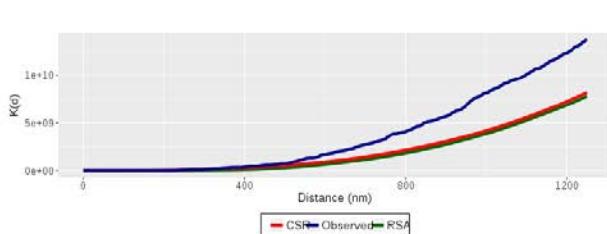
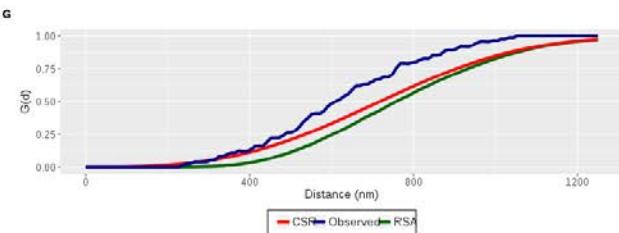
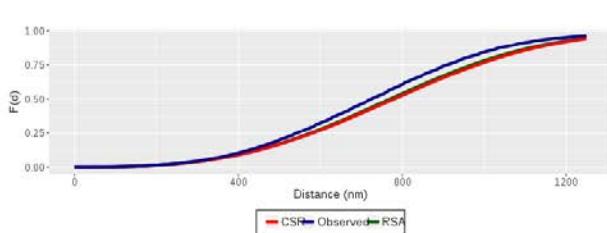
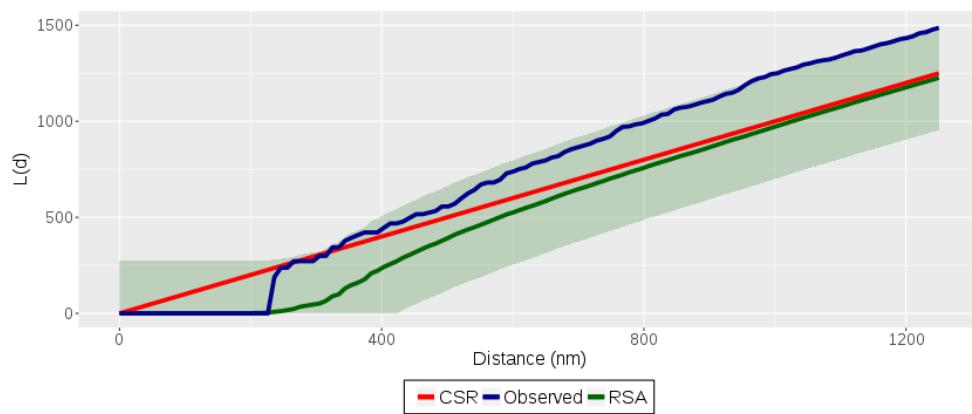
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.8984
- **Log standard deviation :** 0.3956
- **Test p-value:** : 0.4128 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

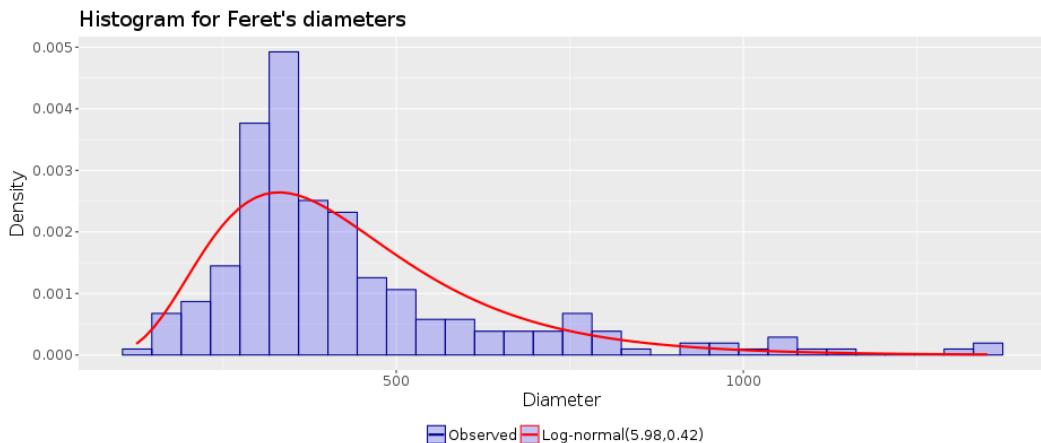
- **Feret diameter log mean:** 5.8984
- **Feret diameter log standard deviation:** 0.3956
- **Process intensity:** 0.4463 synapses/ μm^3



Sample12-Layer II:

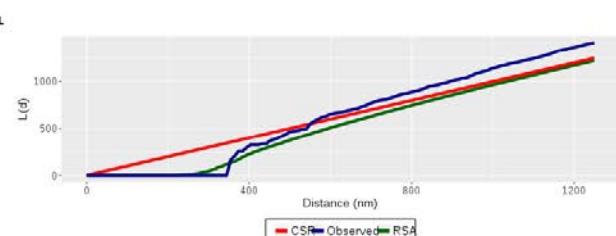
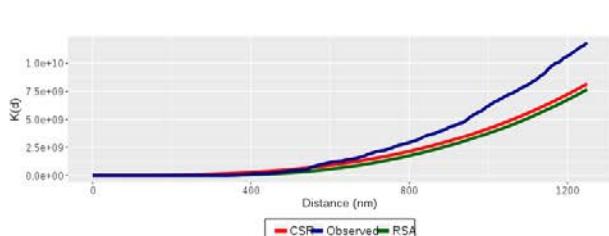
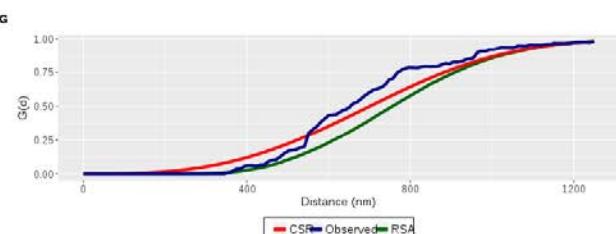
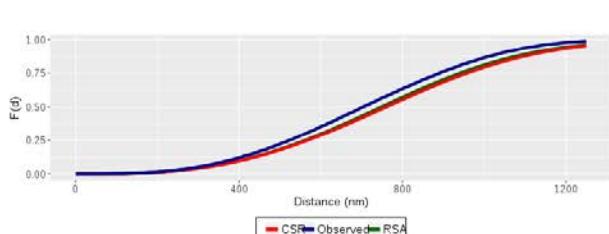
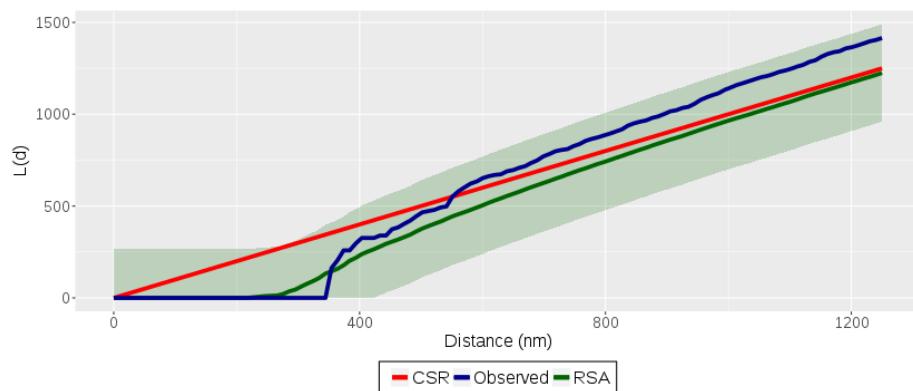
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9769
- **Log standard deviation :** 0.4180
- **Test p-value:** : 0.0172 (One-sample Kolmogorov-Smirnov test) **REJECT**



Envelope and results based on 198 simulations:

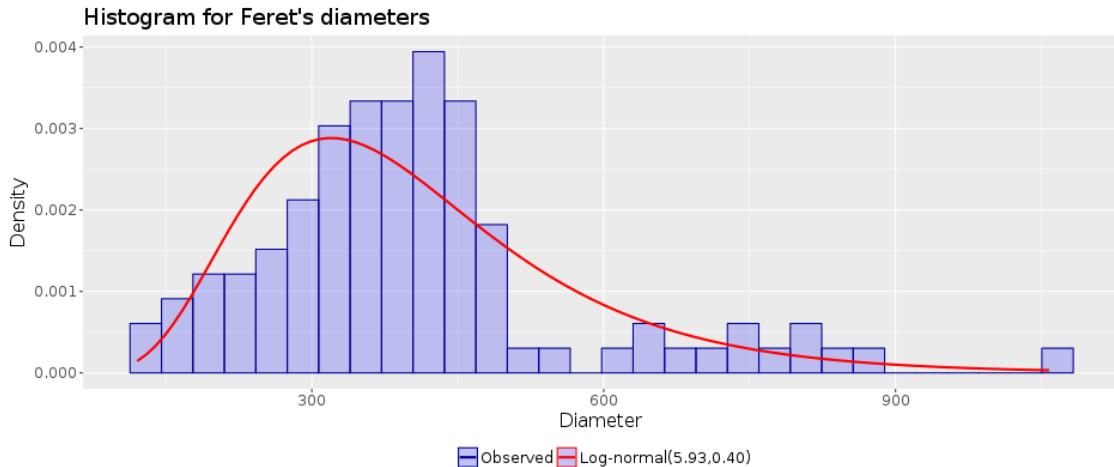
- **Feret diameter log mean:** 5.9769
- **Feret diameter log standard deviation:** 0.4180
- **Process intensity:** 0.4814 synapses/ μm^3



Sample1-Layer III:

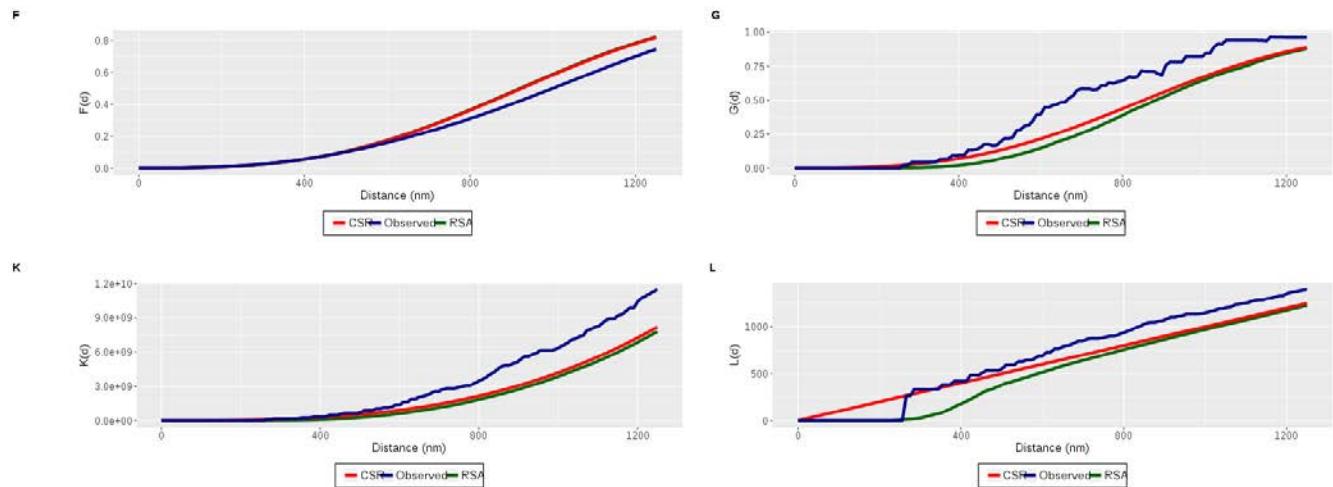
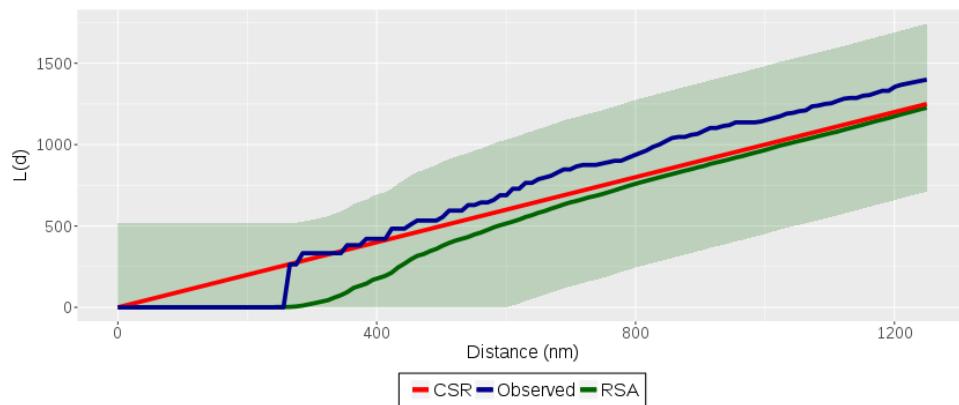
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9274
- **Log standard deviation :** 0.3994
- **Test p-value:** : 0.1202 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

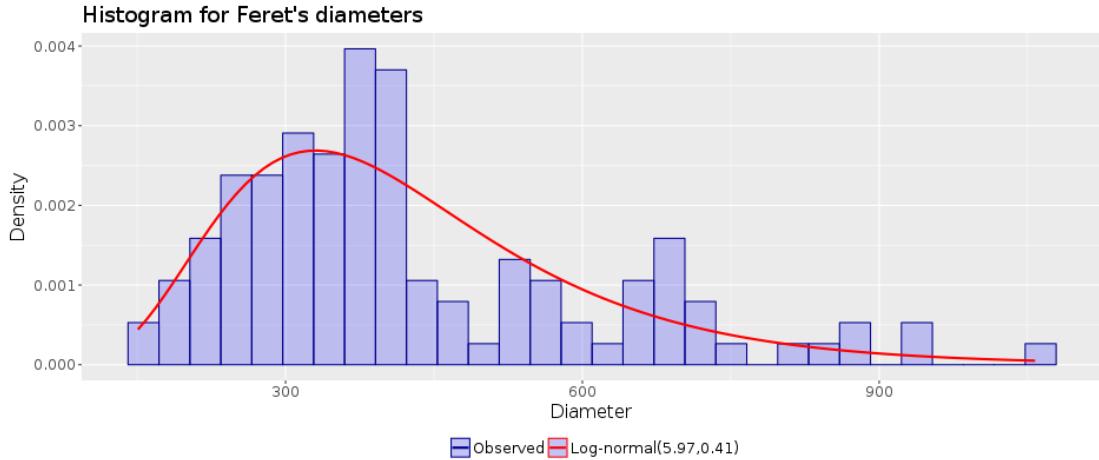
- **Feret diameter log mean:** 5.9274
- **Feret diameter log standard deviation:** 0.3994
- **Process intensity:** 0.2678 synapses/ μm^3



Sample2-Layer III:

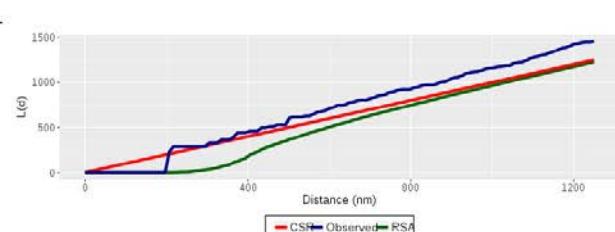
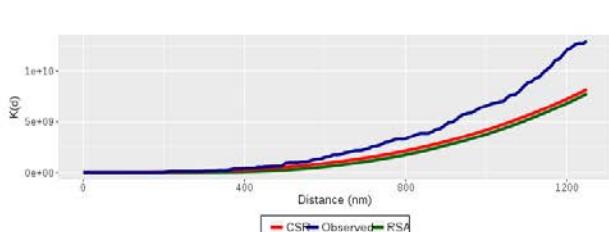
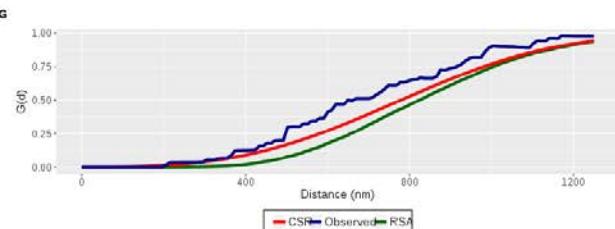
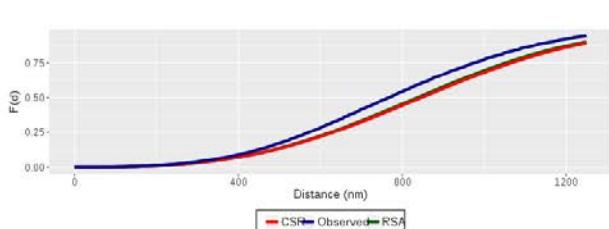
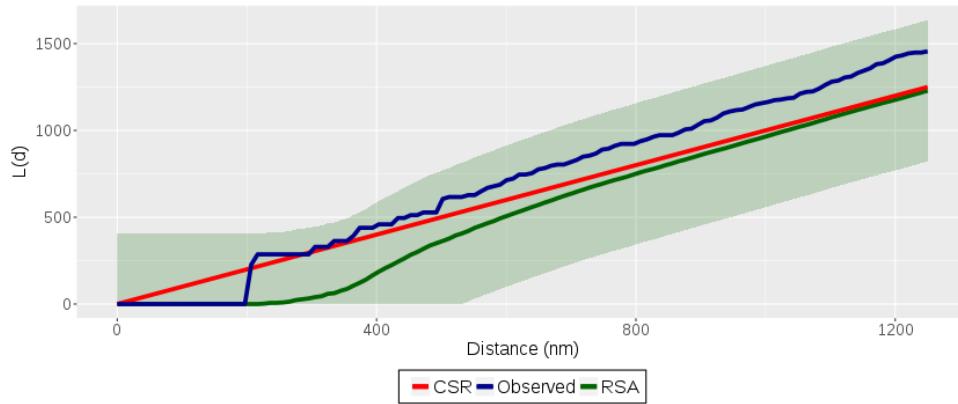
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9703
- **Log standard deviation :** 0.4128
- **Test p-value:** : 0.1957 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

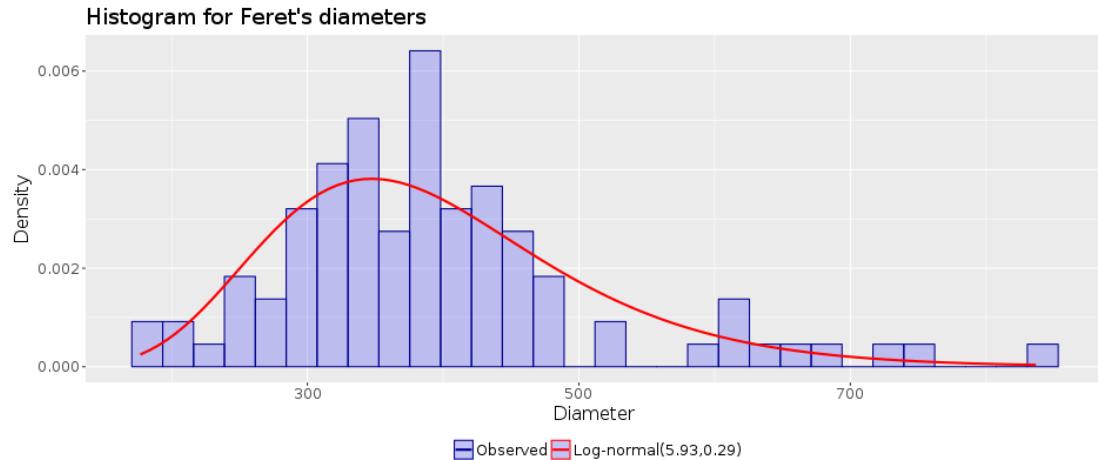
- **Feret diameter log mean:** 5.9703
- **Feret diameter log standard deviation:** 0.4128
- **Process intensity:** 0.3497 synapses/ μm^3



Sample3-Layer III:

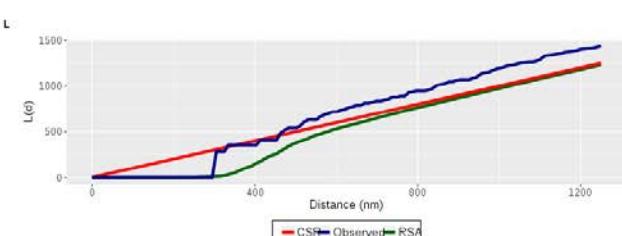
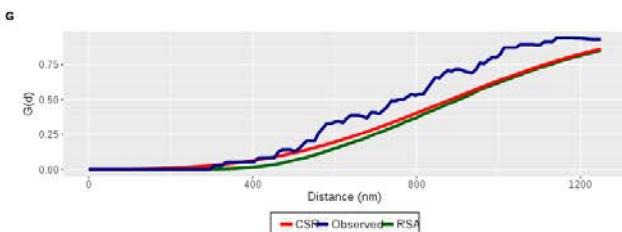
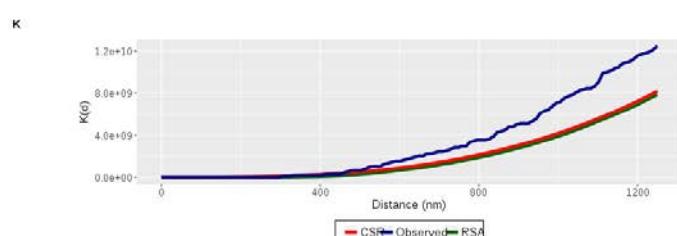
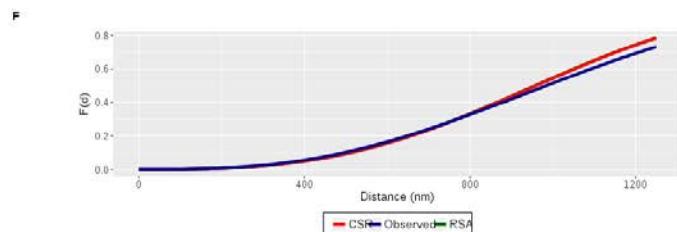
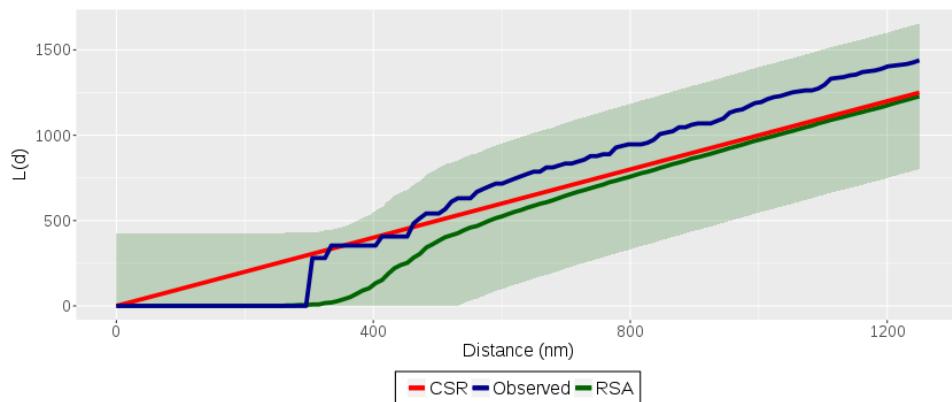
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9340
- **Log standard deviation :** 0.2888
- **Test p-value:** : 0.6323 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

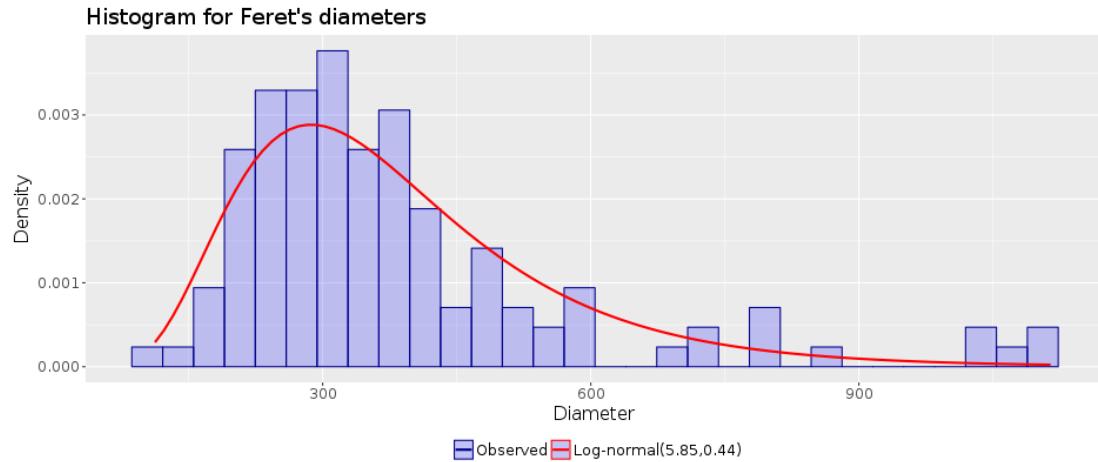
- **Feret diameter log mean:** 5.9340
- **Feret diameter log standard deviation:** 0.2888
- **Process intensity:** 0.2401 synapses/ μm^3



Sample4-Layer III:

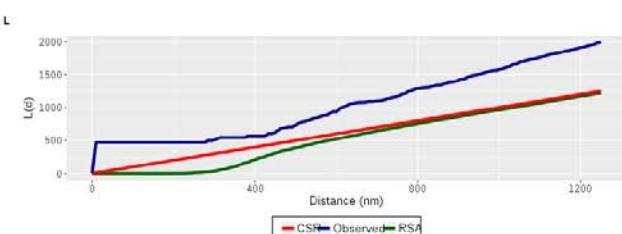
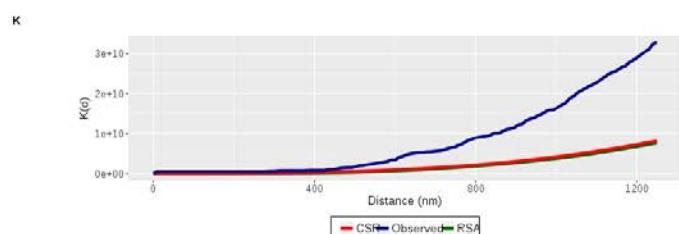
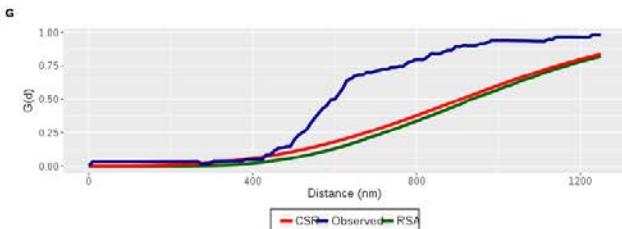
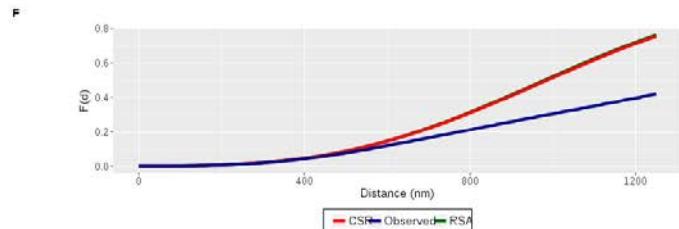
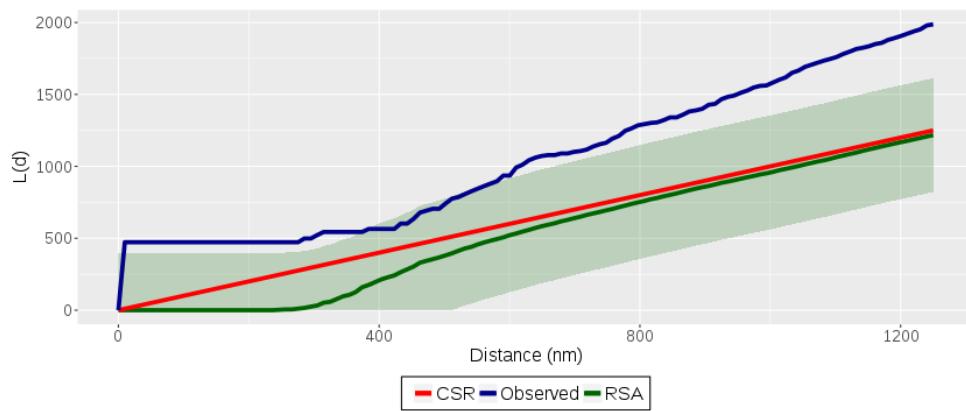
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.8512
- **Log standard deviation :** 0.4379
- **Test p-value:** : 0.2987 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

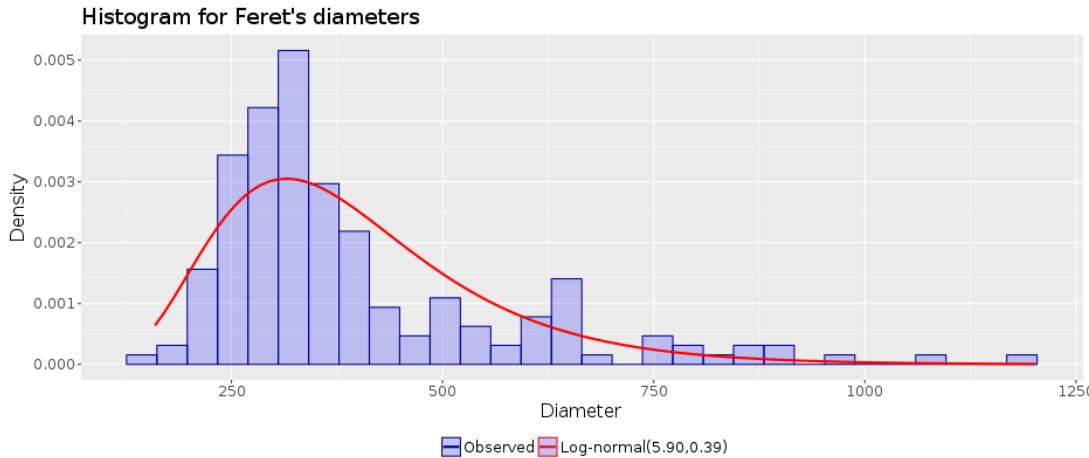
- **Feret diameter log mean:** 5.8512
- **Feret diameter log standard deviation:** 0.4379
- **Process intensity:** 0.2209 synapses/ μm^3



Sample5-Layer III:

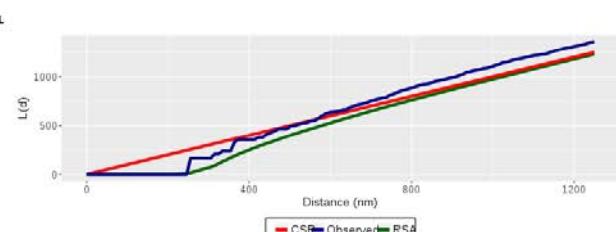
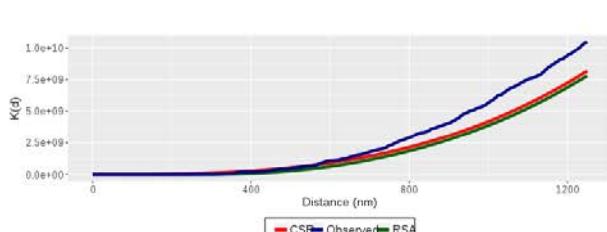
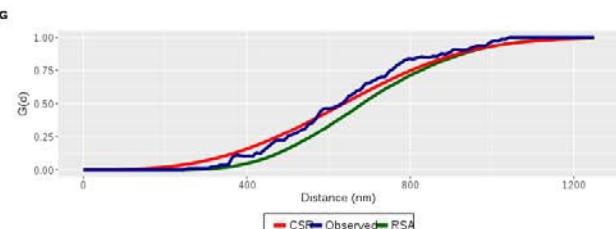
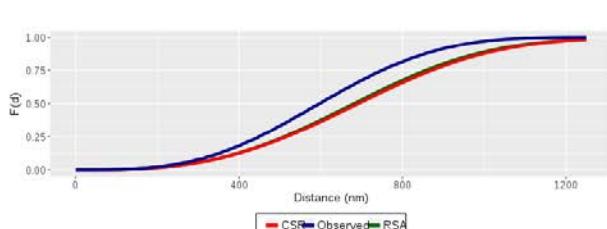
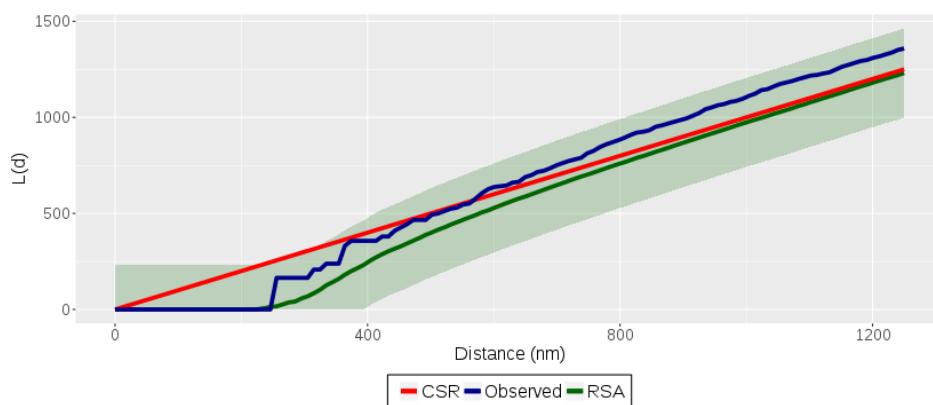
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9014
- **Log standard deviation :** 0.3851
- **Test p-value:** : 0.0048 (One-sample Kolmogorov-Smirnov test) **REJECT**



Envelope and results based on 198 simulations:

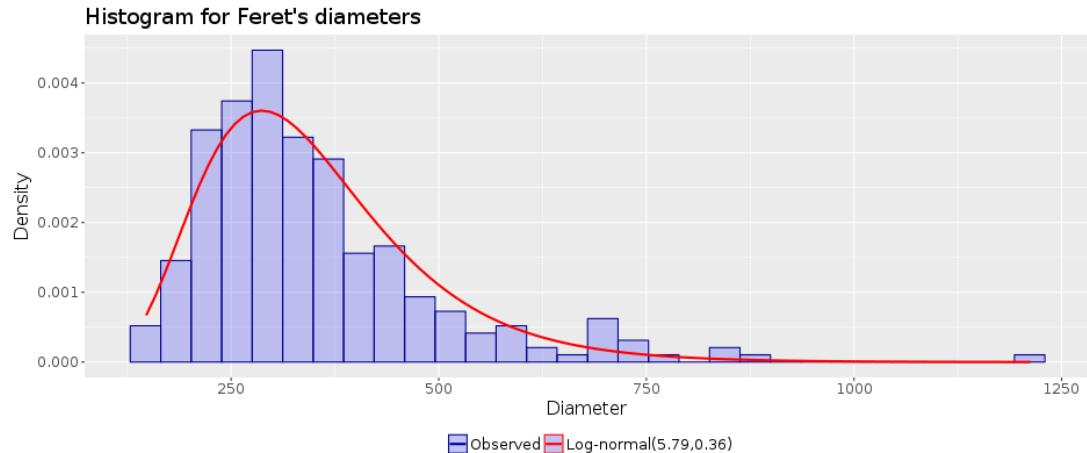
- **Feret diameter log mean:** 5.9014
- **Feret diameter log standard deviation:** 0.3851
- **Process intensity:** 0.6407 synapses/ μm^3



Sample6-Layer III:

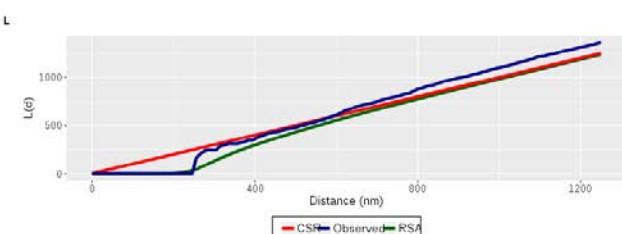
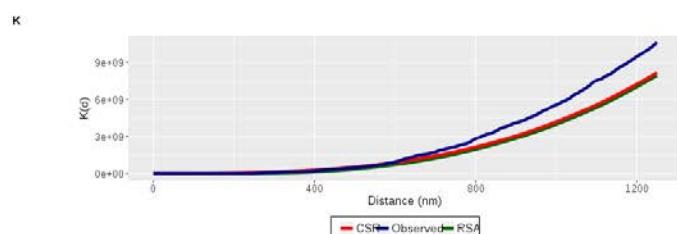
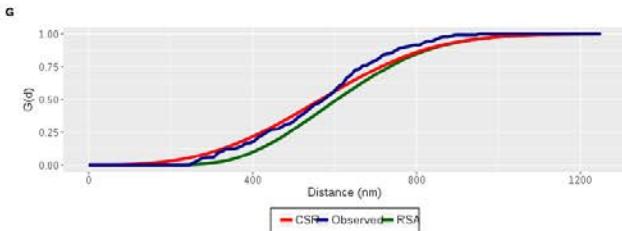
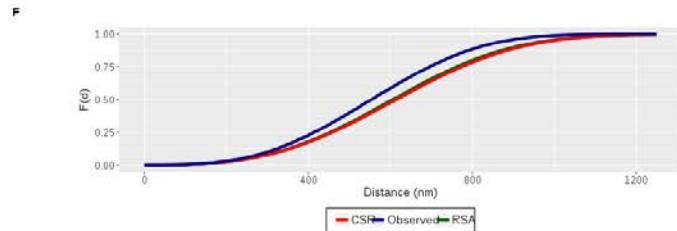
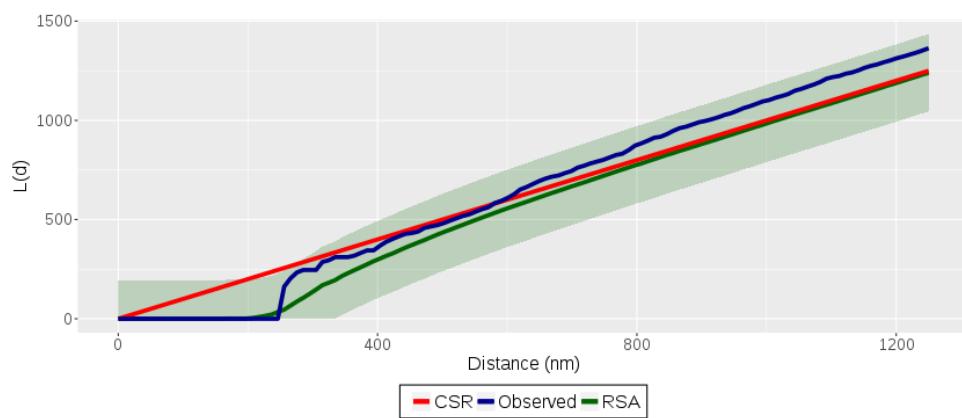
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.7893
- **Log standard deviation :** 0.3616
- **Test p-value:** : 0.2591 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

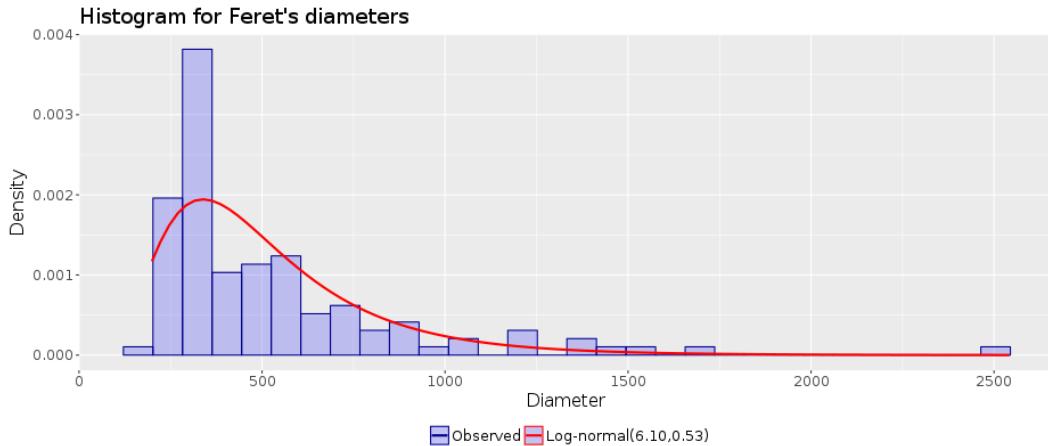
- **Feret diameter log mean:** 5.7893
- **Feret diameter log standard deviation:** 0.3616
- **Process intensity:** 0.9109 synapses/ μm^3



Sample7-Layer III:

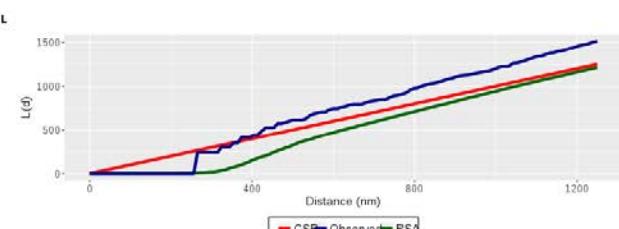
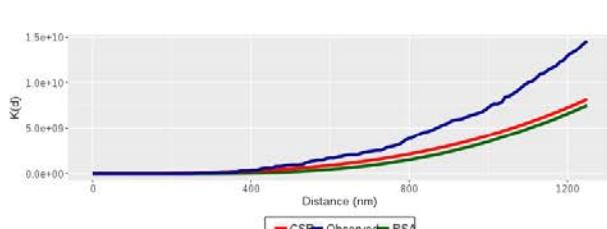
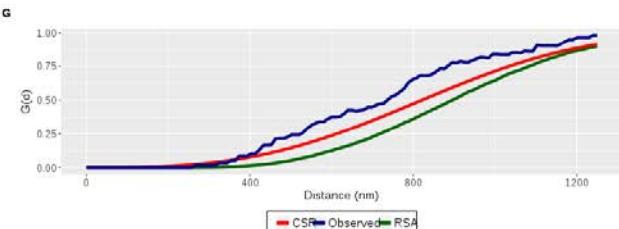
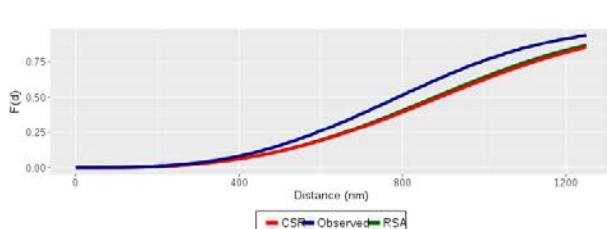
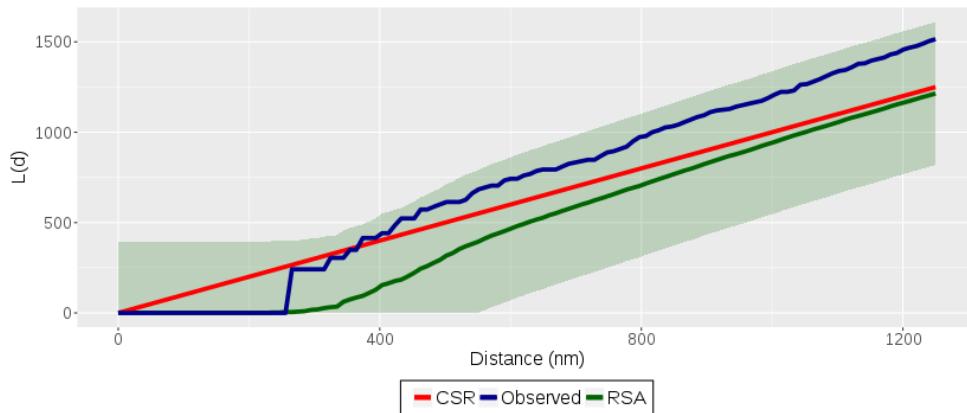
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 6.1032
- **Log standard deviation :** 0.5273
- **Test p-value:** : 0.0278 (One-sample Kolmogorov-Smirnov test) **REJECT**



Envelope and results based on 198 simulations:

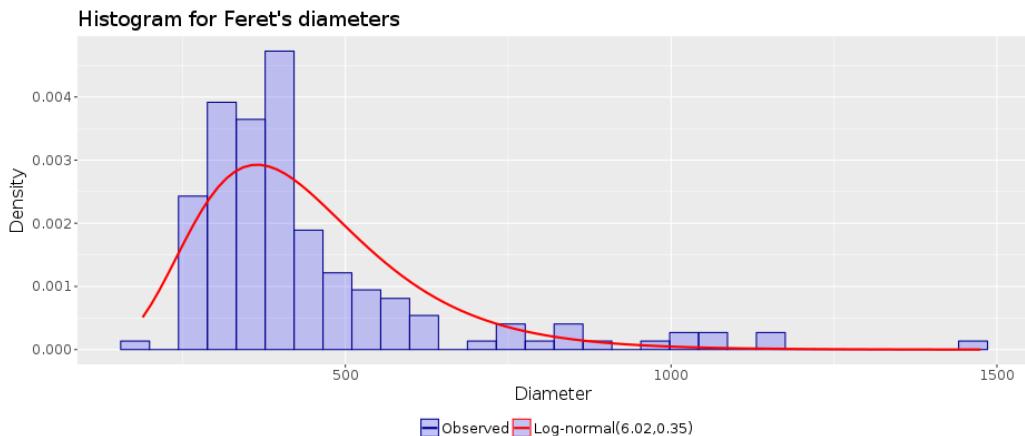
- **Feret diameter log mean:** 6.1032
- **Feret diameter log standard deviation:** 0.5273
- **Process intensity:** 0.2995 synapses/ μm^3



Sample8-Layer III:

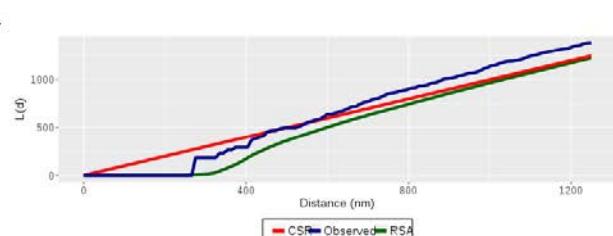
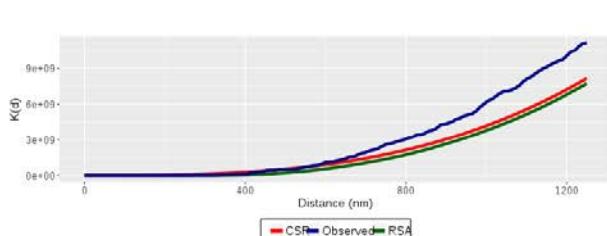
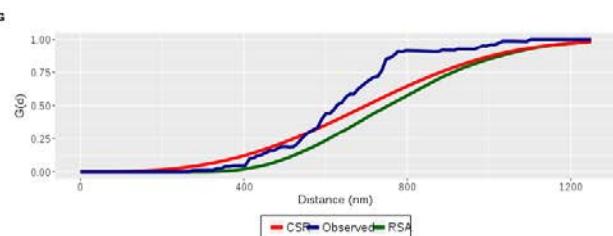
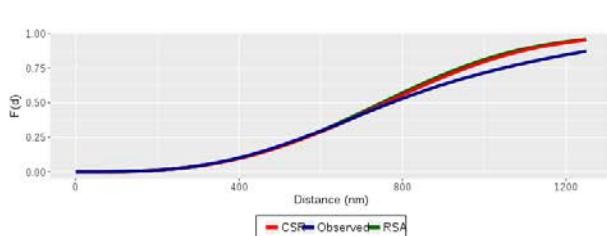
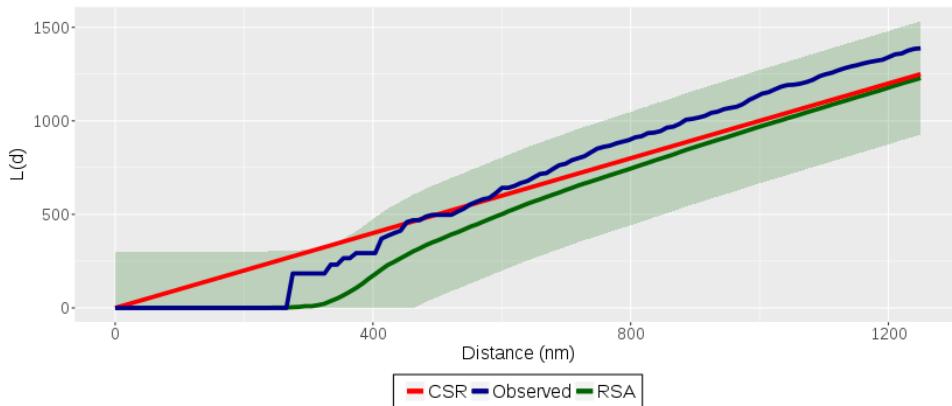
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 6.0219
- **Log standard deviation :** 0.3514
- **Test p-value:** : 0.0020 (One-sample Kolmogorov-Smirnov test) **REJECT**



Envelope and results based on 198 simulations:

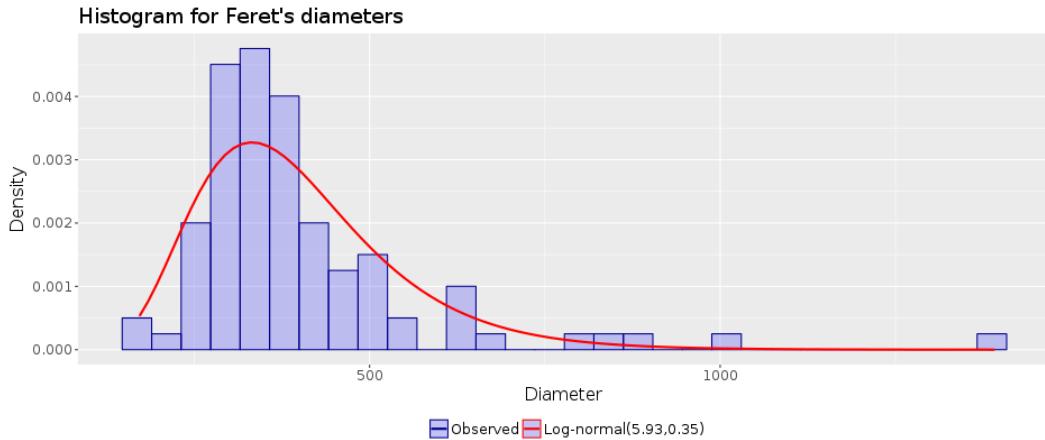
- **Feret diameter log mean:** 6.0219
- **Feret diameter log standard deviation:** 0.3514
- **Process intensity:** 0.4843 synapses/ μm^3



Sample9-Layer III:

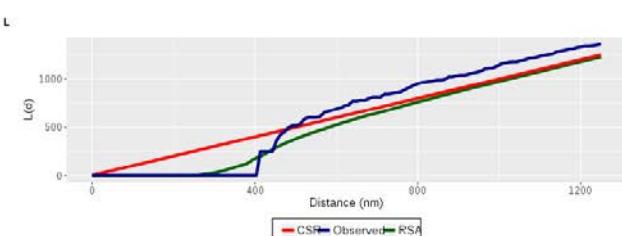
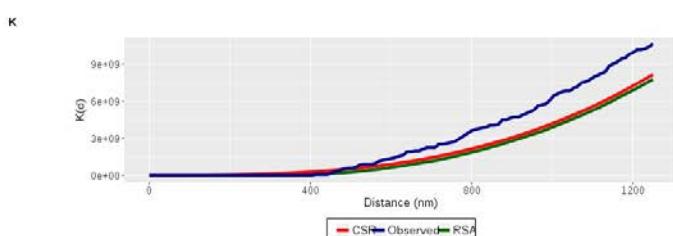
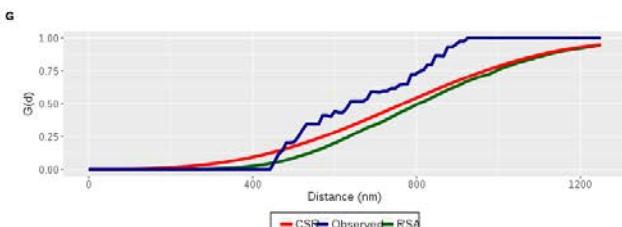
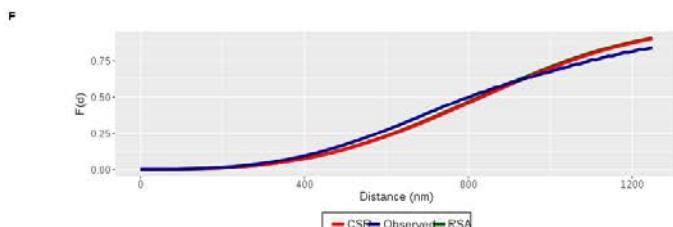
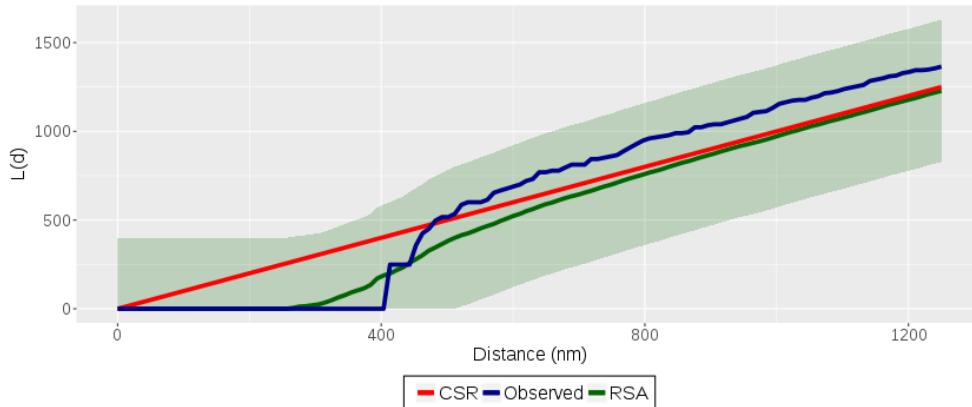
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9251
- **Log standard deviation :** 0.3455
- **Test p-value:** : 0.1528 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

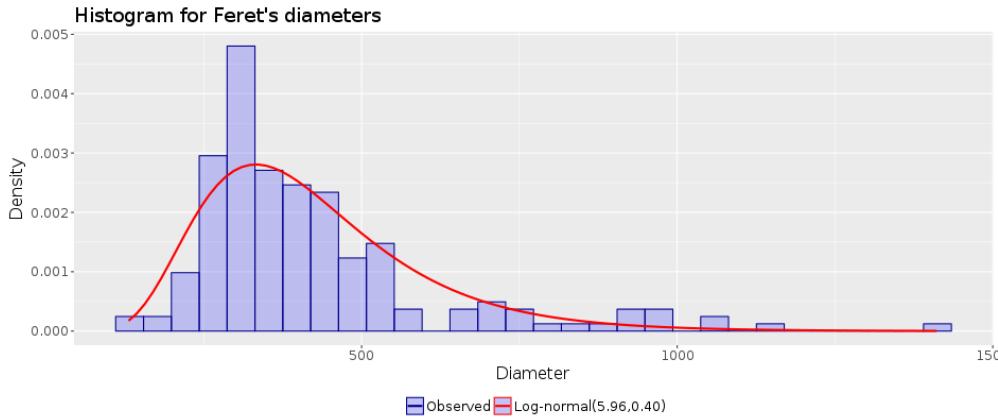
- **Feret diameter log mean:** 5.9251
- **Feret diameter log standard deviation:** 0.3455
- **Process intensity:** 0.3658 synapses/ μm^3



Sample10-Layer III:

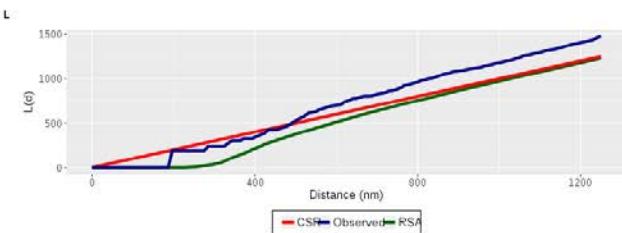
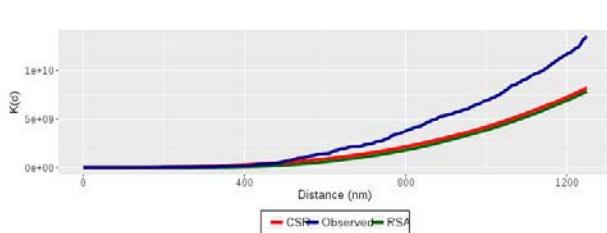
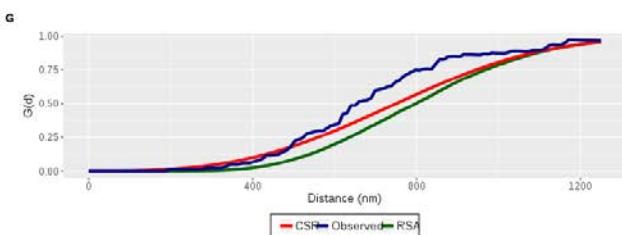
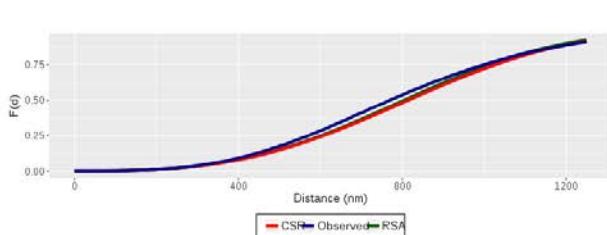
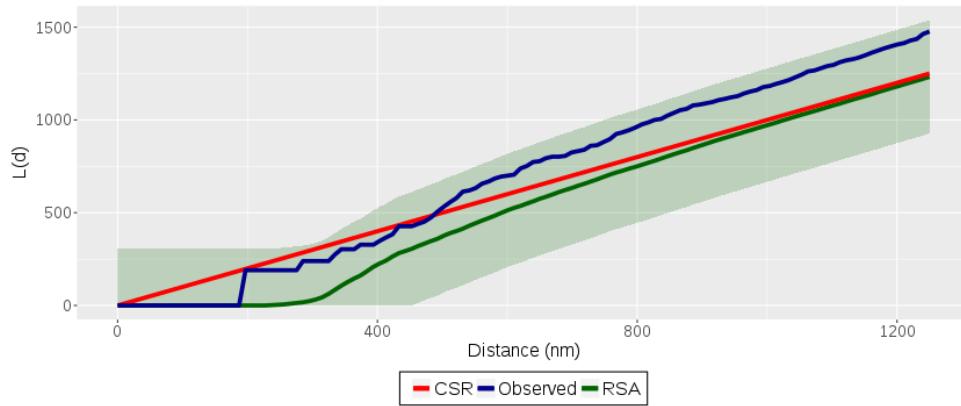
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9627
- **Log standard deviation :** 0.3954
- **Test p-value:** : 0.2296 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

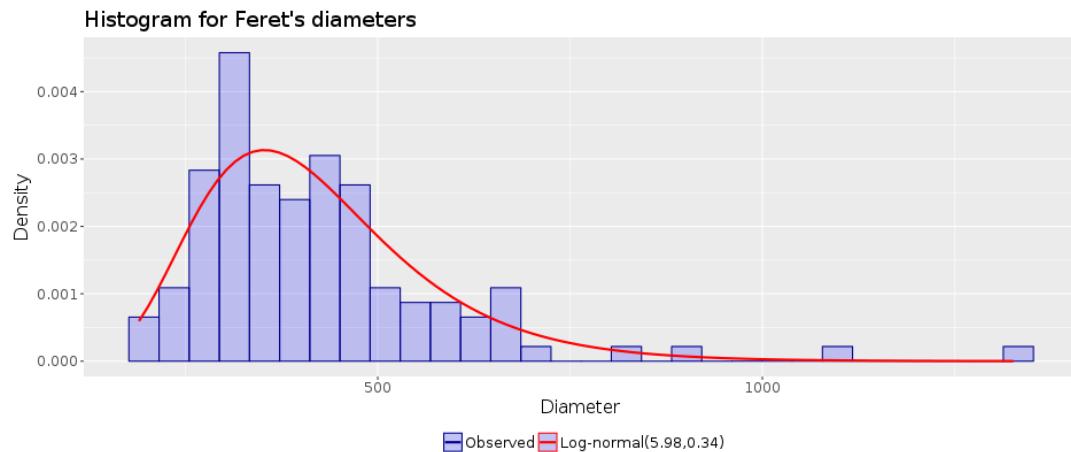
- **Feret diameter log mean:** 5.9627
- **Feret diameter log standard deviation:** 0.3954
- **Process intensity:** 0.3924 synapses/ μm^3



Sample11-Layer III:

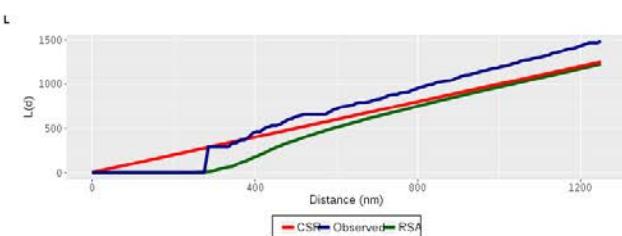
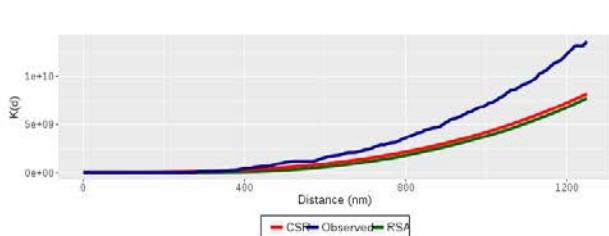
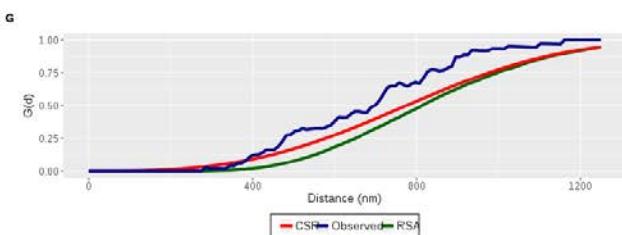
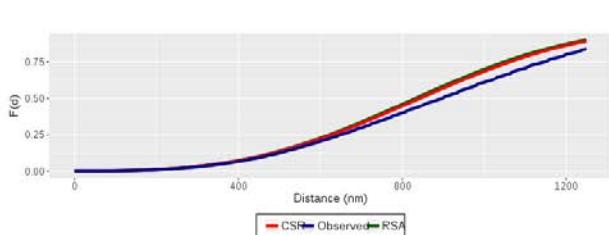
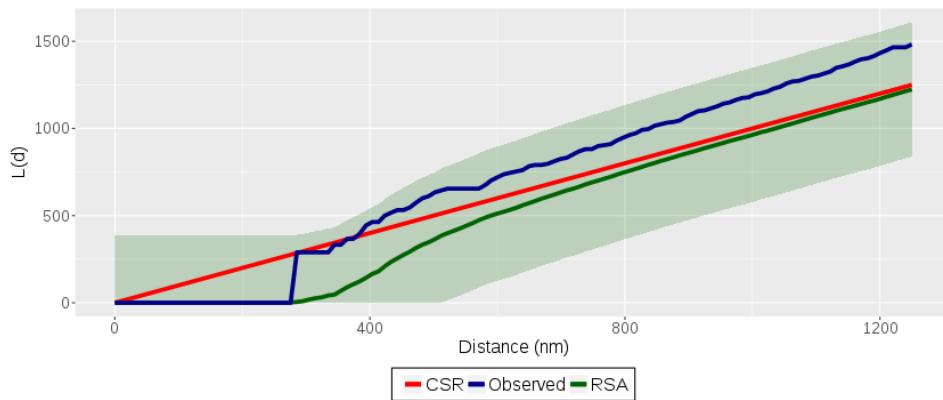
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9814
- **Log standard deviation :** 0.3407
- **Test p-value:** : 0.7587 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

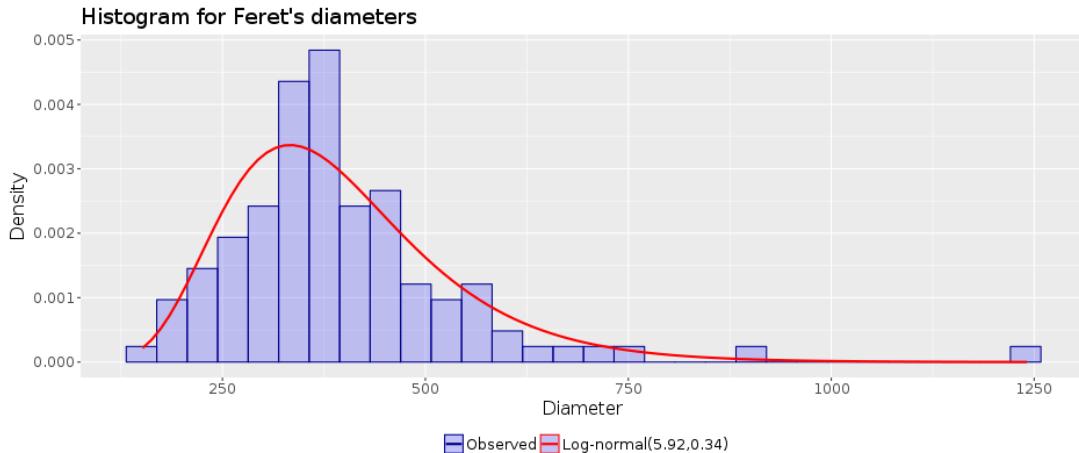
- **Feret diameter log mean:** 5.9814
- **Feret diameter log standard deviation:** 0.3407
- **Process intensity:** 0.3541 synapses/ μm^3



Sample12-Layer III:

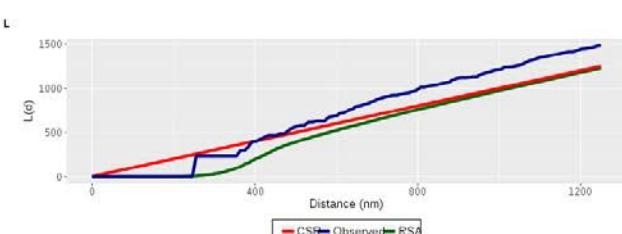
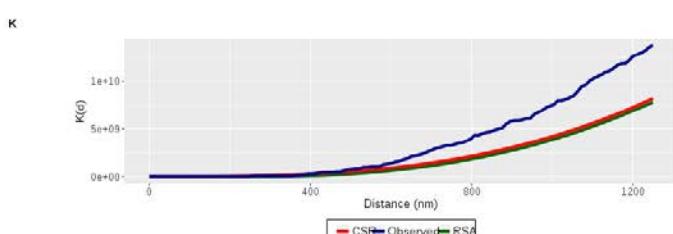
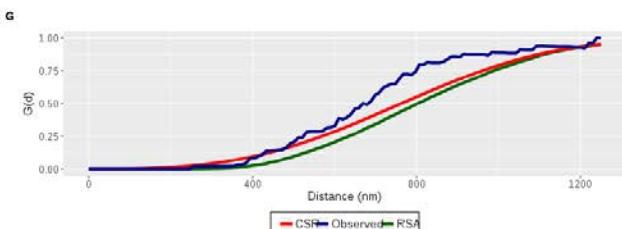
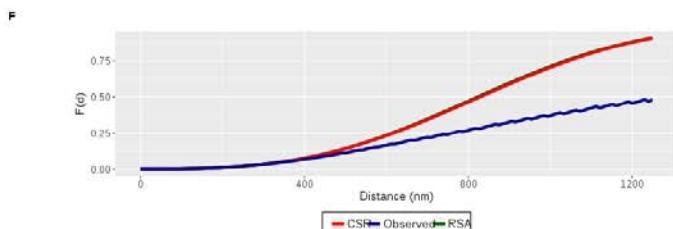
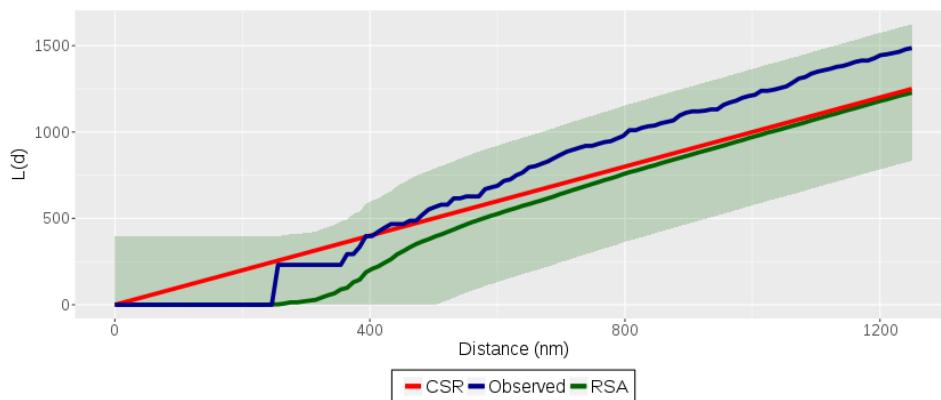
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9215
- **Log standard deviation :** 0.3359
- **Test p-value:** : 0.5004 (One-sample Kolmogorov-Smirnov test) **NOT REJECTED**



Envelope and results based on 198 simulations:

- **Feret diameter log mean:** 5.9215
- **Feret diameter log standard deviation:** 0.3359
- **Process intensity:** 0.3722 synapses/ μm^3

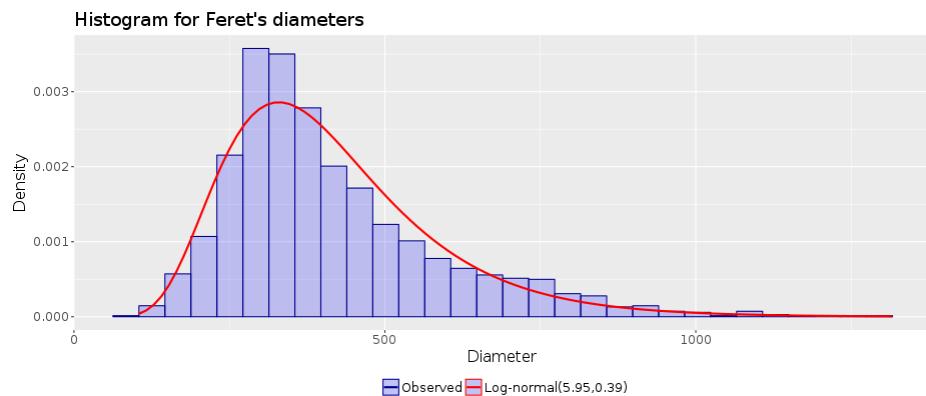


PER-LAYER ANALYSIS (I, II and III, 12 samples per analysis):

Layer I (LACUNOSUM):

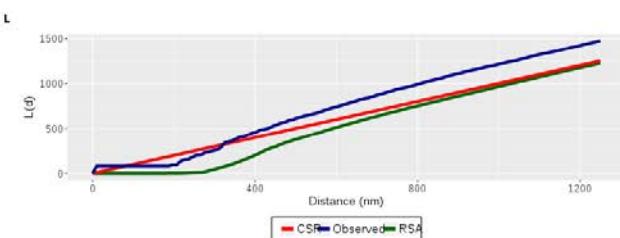
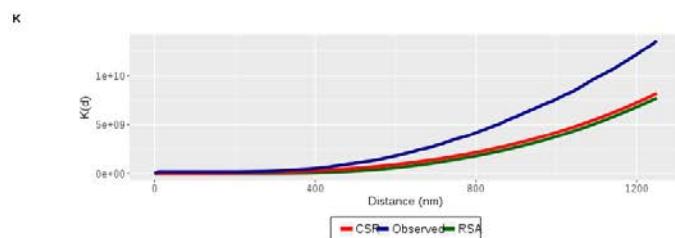
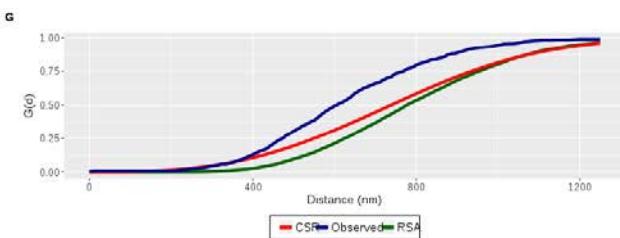
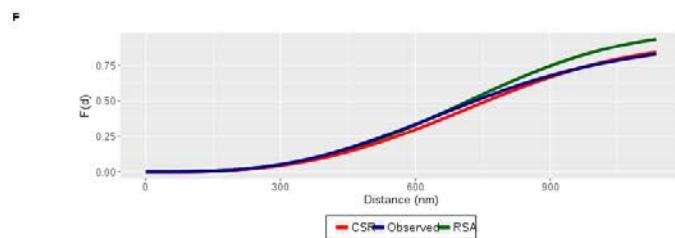
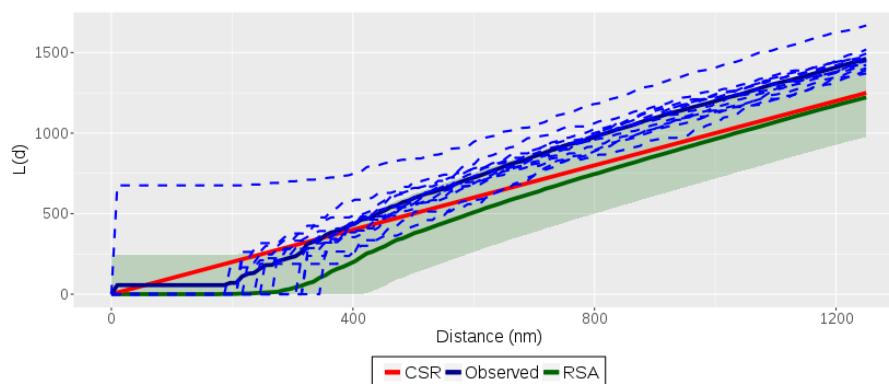
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9511
- **Log standard deviation :** 0.3923
- **Test p-value:** : 0.0016 (One-sample Kolmogorov-Smirnov test) **REJECT**



Envelope and results based on 198 simulations:

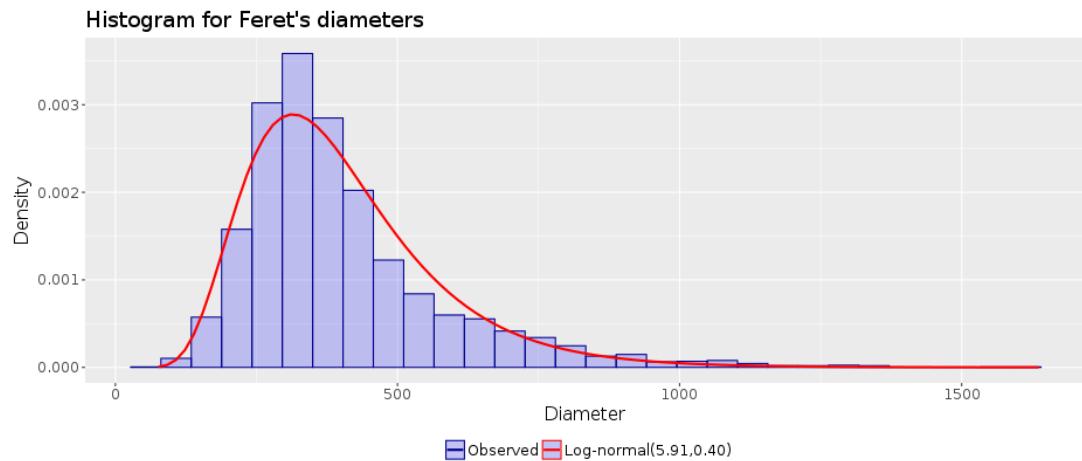
- **Feret diameter log mean:** 5.9511
- **Feret diameter log standard deviation:** 0.3923
- **Process intensity:** 0.4217 synapses/ μm^3



LayerII (RADIATUM):

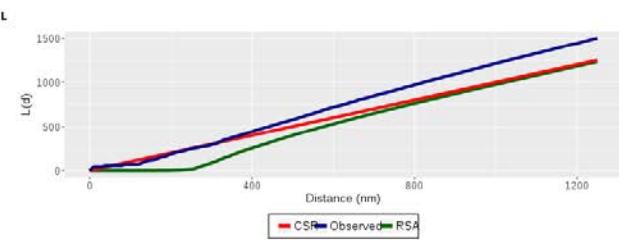
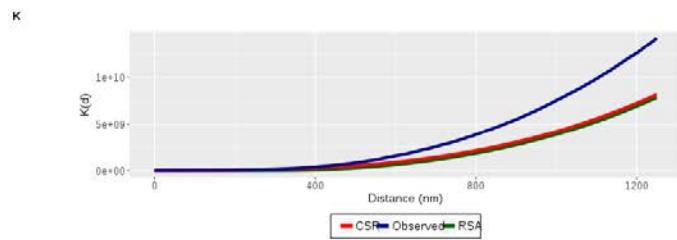
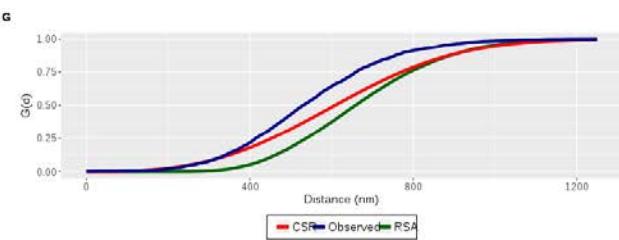
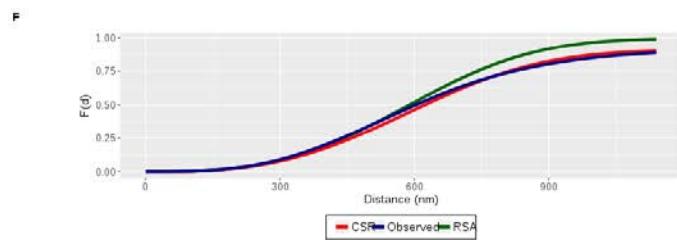
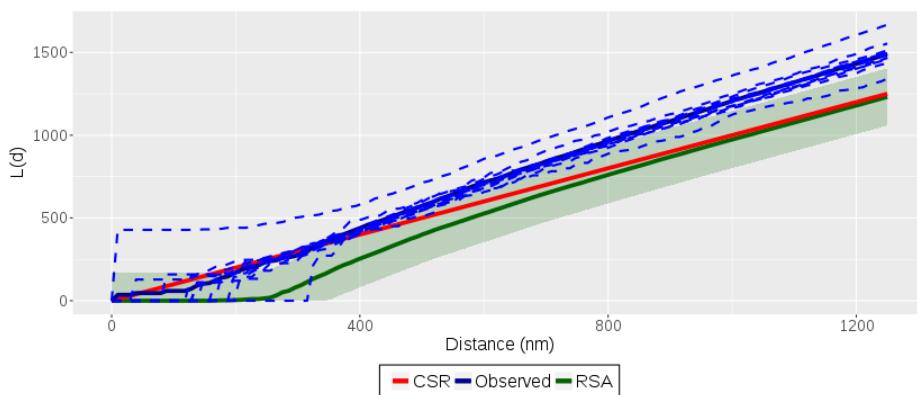
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9142
- **Log standard deviation :** 0.4045
- **Test p-value:** : 0.0000 (One-sample Kolmogorov-Smirnov test) **REJECT**



Envelope and results based on 198 simulations:

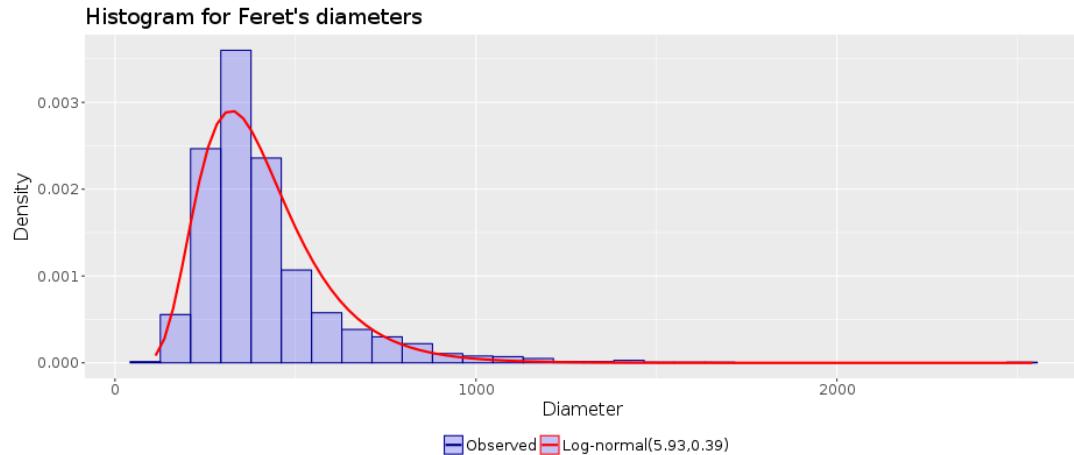
- **Feret diameter log mean:** 5.9142
- **Feret diameter log standard deviation:** 0.4045
- **Process intensity:** 0.7400 synapses/ μm^3



LayerIII (ORIENS):

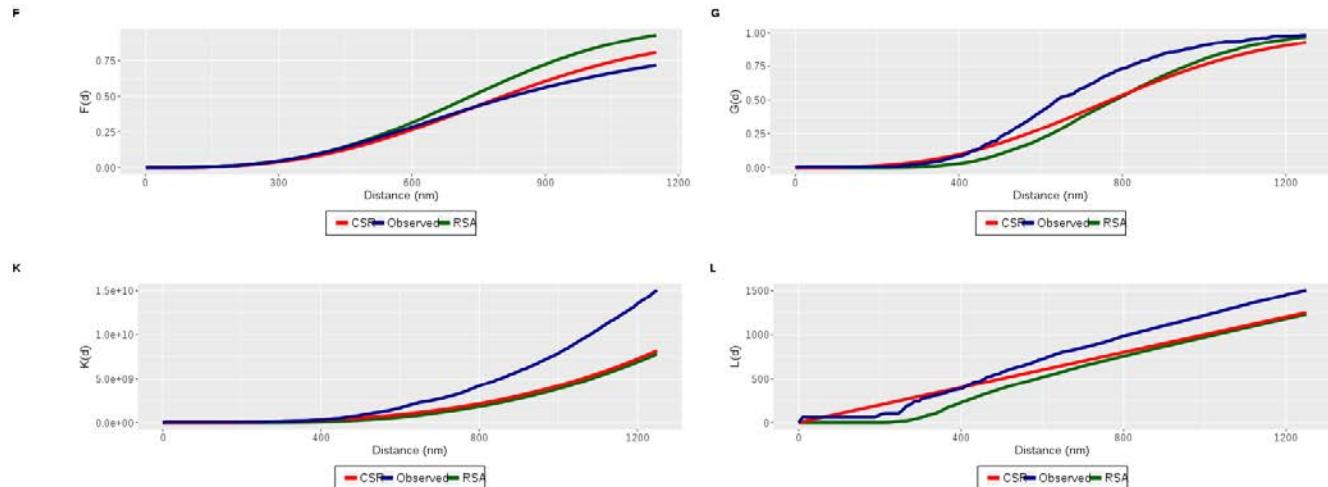
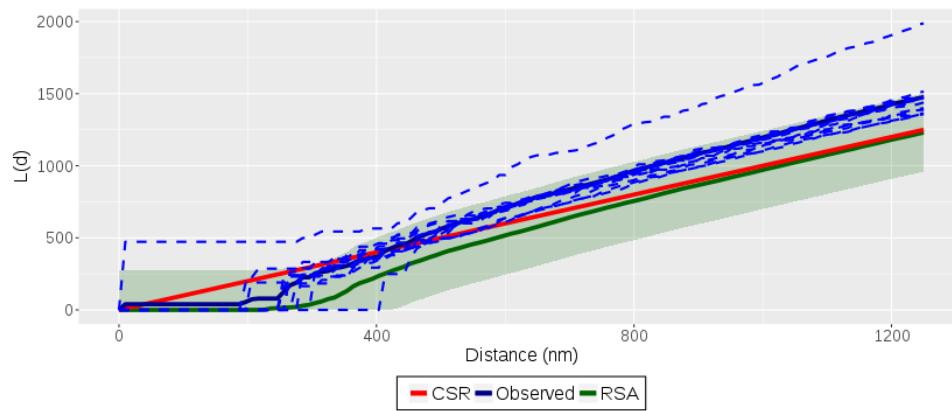
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9301
- **Log standard deviation :** 0.3948
- **Test p-value:** : 0.0000 (One-sample Kolmogorov-Smirnov test) **REJECT**



Envelope and results based on 198 simulations:

- **Feret diameter log mean:** 5.9301
- **Feret diameter log standard deviation:** 0.3948
- **Process intensity:** 0.4082 synapses/ μm^3

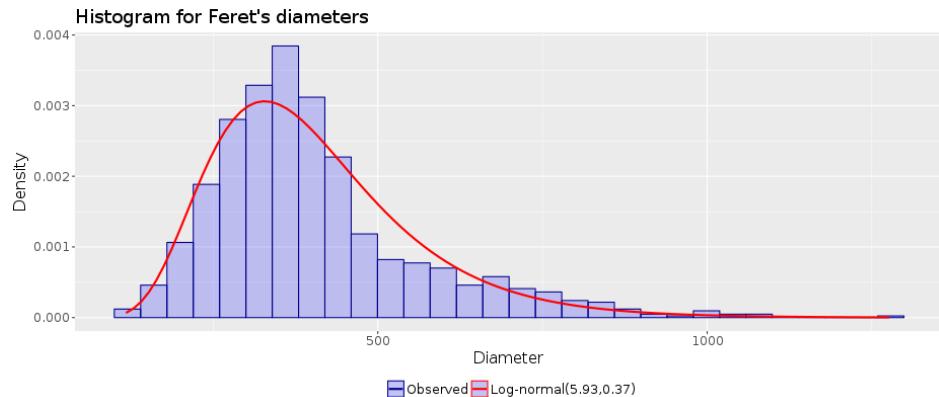


PER-SUBJECT ANALYSIS (AB1, AB2, AB3 and M17):

AB1 (9 samples):

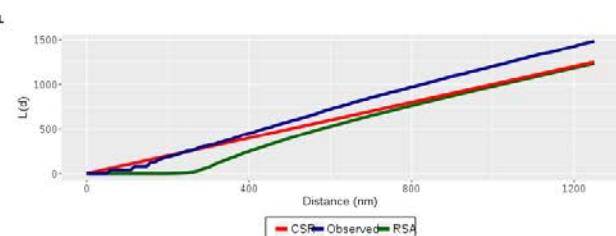
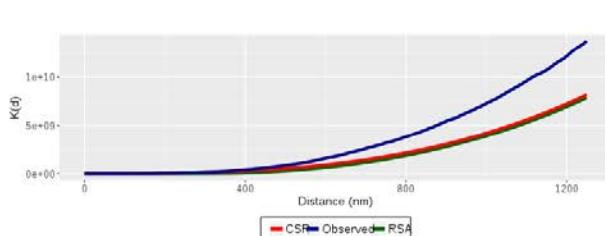
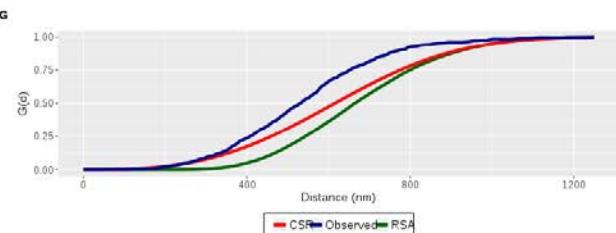
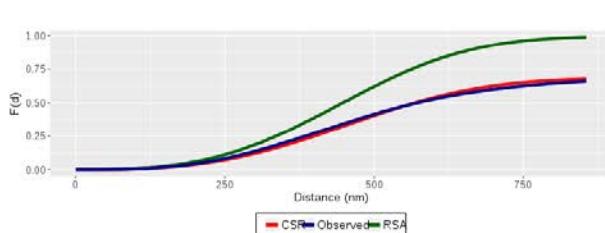
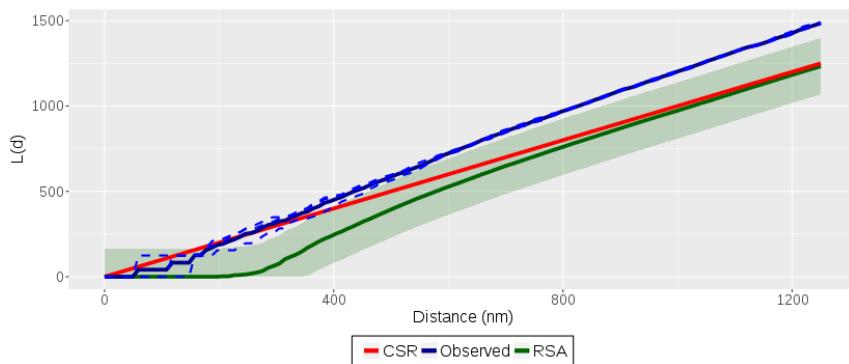
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9307
- **Log standard deviation :** 0.3707
- **Test p-value:** : 0.0032 (One-sample Kolmogorov-Smirnov test) **REJECT**



Envelope and results based on 198 simulations:

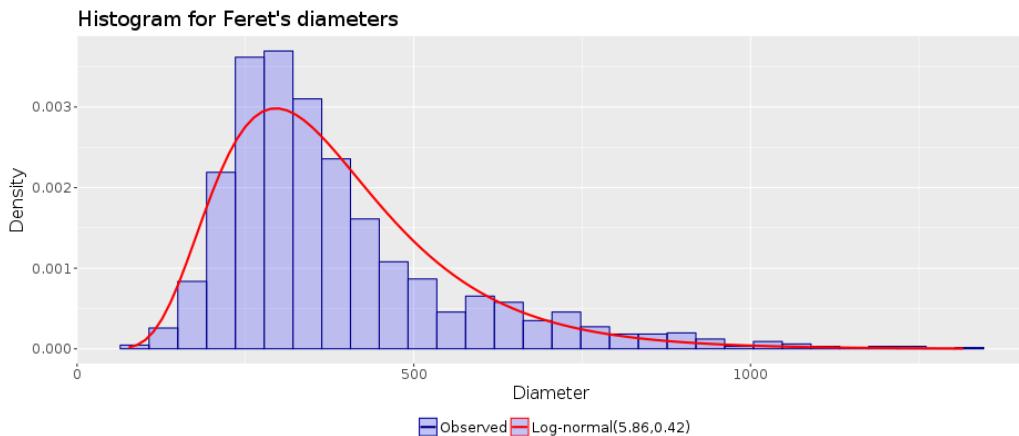
- **Feret diameter log mean:** 5.9307
- **Feret diameter log standard deviation:** 0.3707
- **Process intensity:** 0.7128 synapses/ μm^3



AB2 (9 samples):

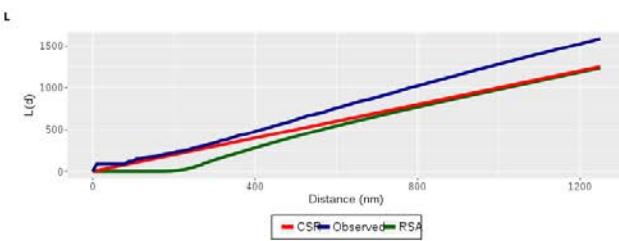
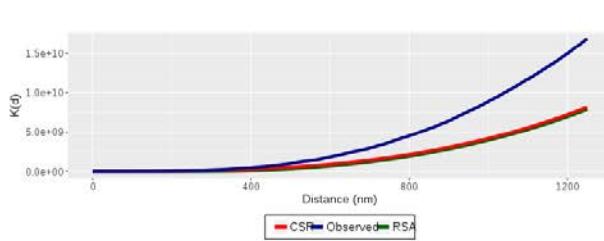
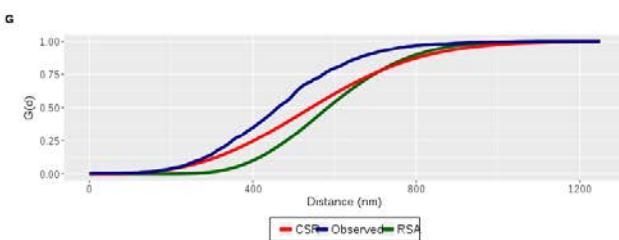
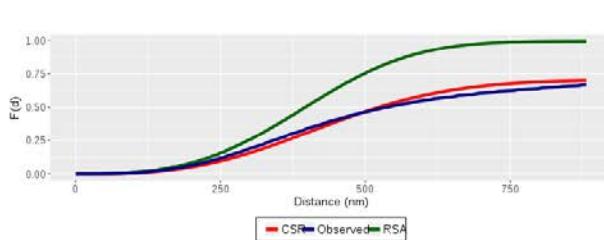
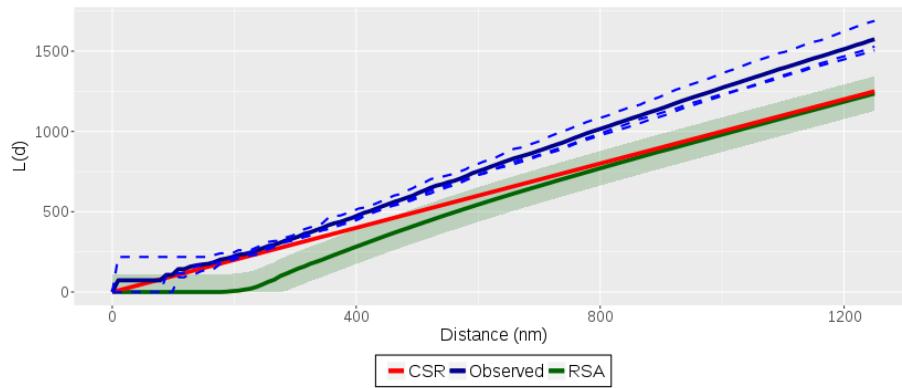
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.8599
- **Log standard deviation :** 0.4157
- **Test p-value:** : 0.0000 (One-sample Kolmogorov-Smirnov test) **REJECT**



Envelope and results based on 198 simulations:

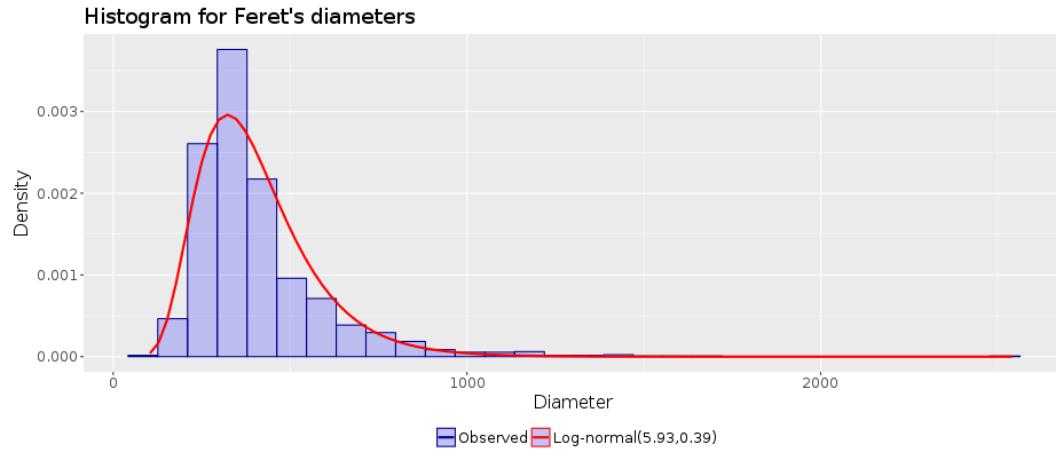
- **Feret diameter log mean:** 5.8599
- **Feret diameter log standard deviation:** 0.4157
- **Process intensity:** 1.1179 synapses/ μm^3



AB3 (9 samples):

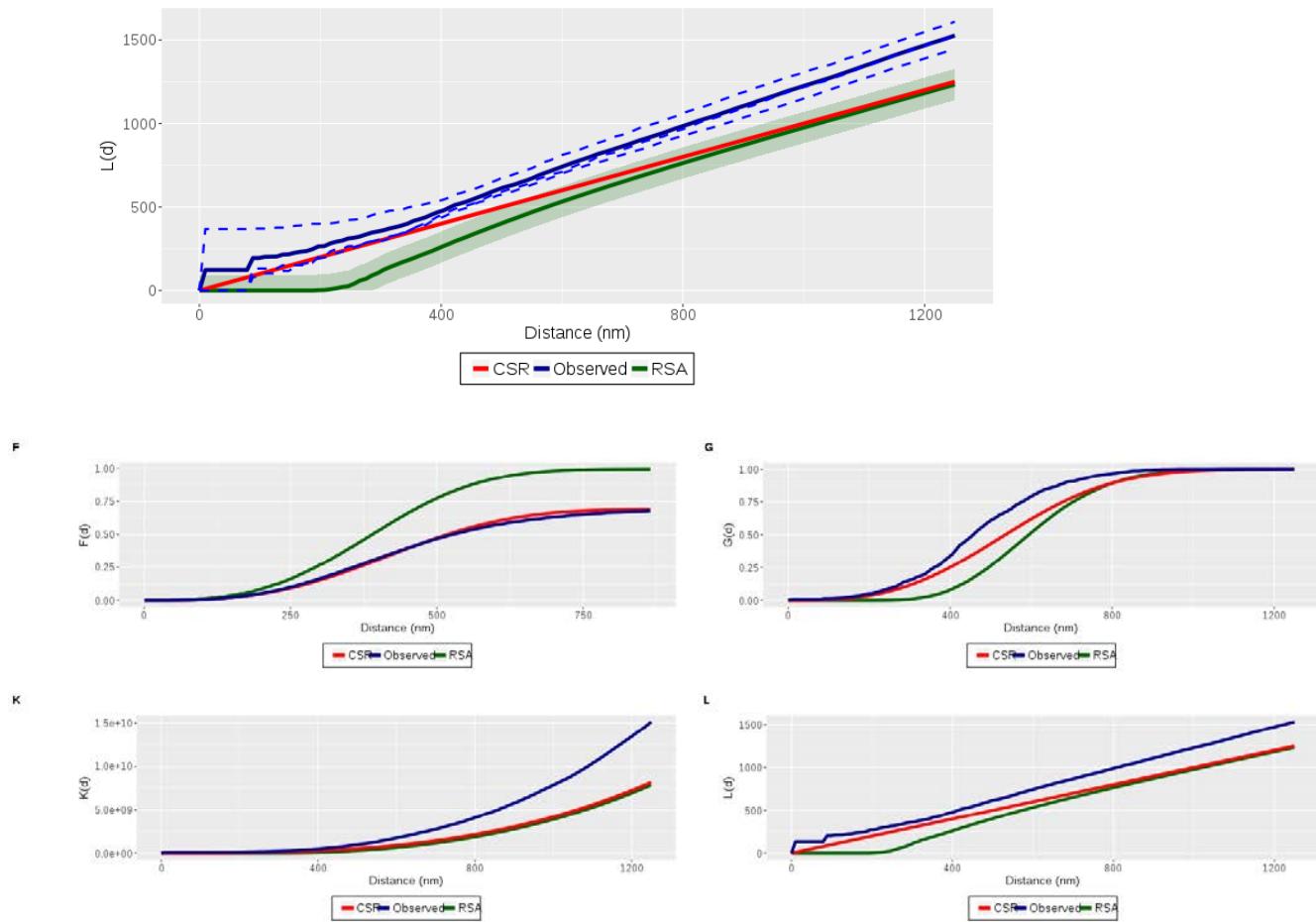
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9279
- **Log standard deviation :** 0.3869
- **Test p-value:** : 0.0000 (One-sample Kolmogorov-Smirnov test) **REJECT**



Envelope and results based on 198 simulations:

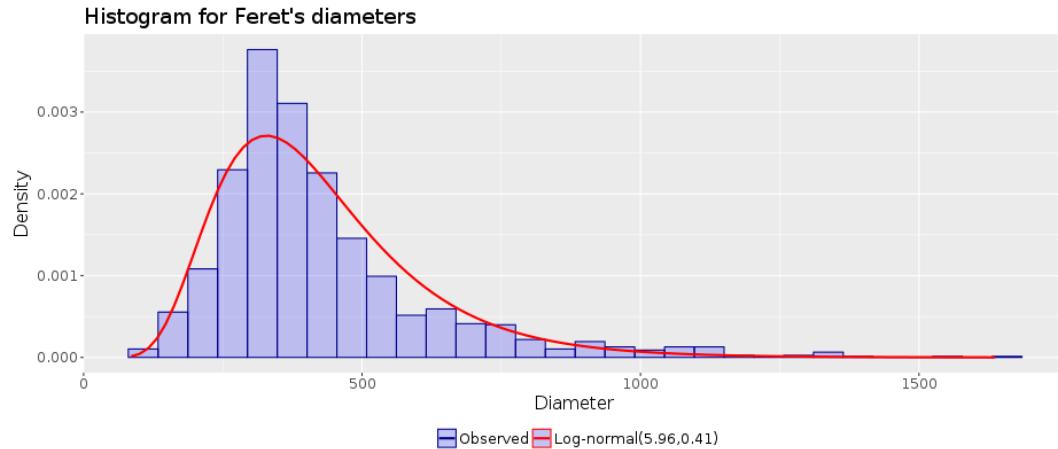
- **Feret diameter log mean:** 5.9279
- **Feret diameter log standard deviation:** 0.3869
- **Process intensity:** 1.1050 synapses/ μm^3



M17 (9 samples):

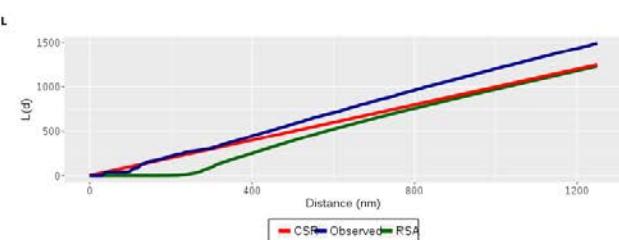
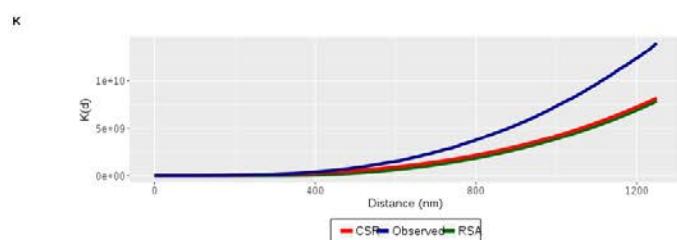
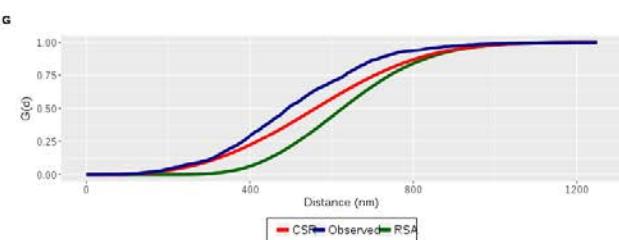
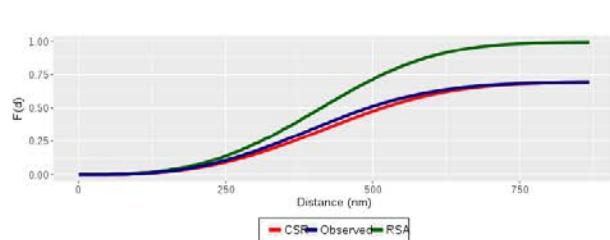
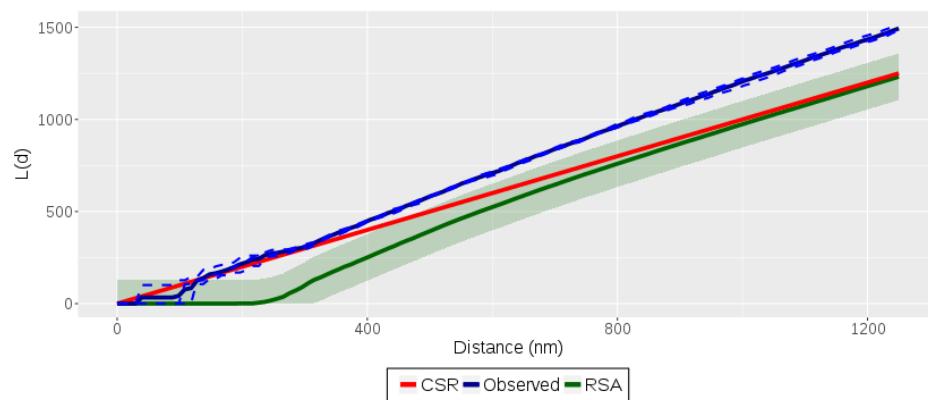
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9633
- **Log standard deviation :** 0.4117
- **Test p-value:** : 0.0001 (One-sample Kolmogorov-Smirnov test) **REJECT**



Envelope and results based on 198 simulations:

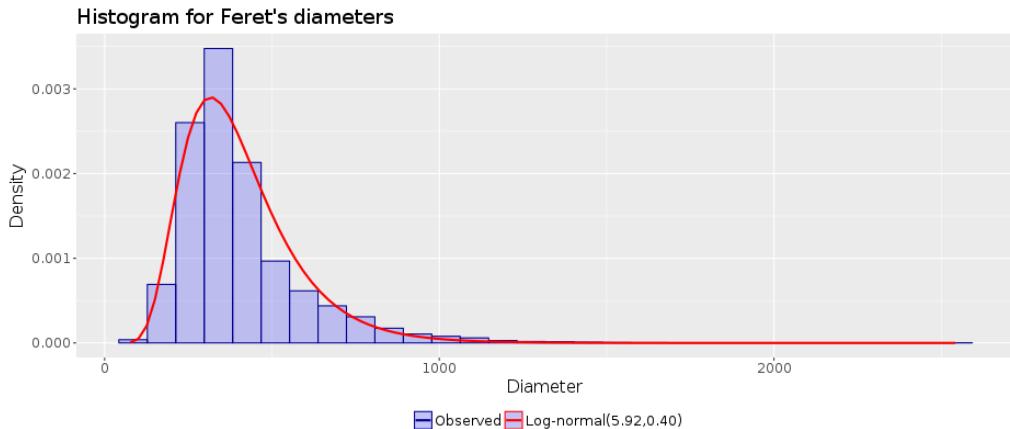
- **Feret diameter log mean:** 5.9633
- **Feret diameter log standard deviation:** 0.4117
- **Process intensity:** 0.9416 synapses/ μm^3



ALTOGETHER:

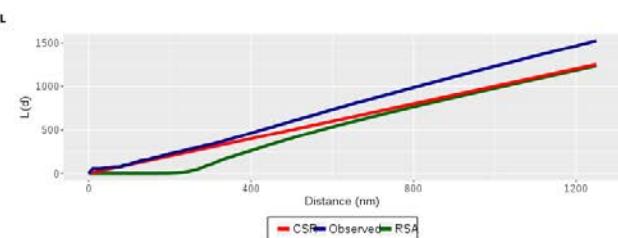
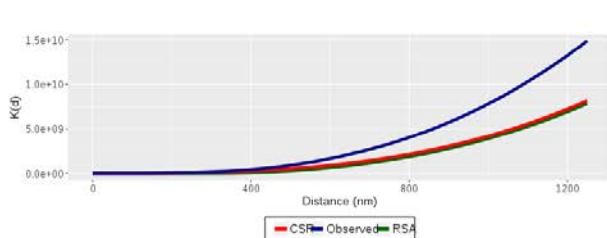
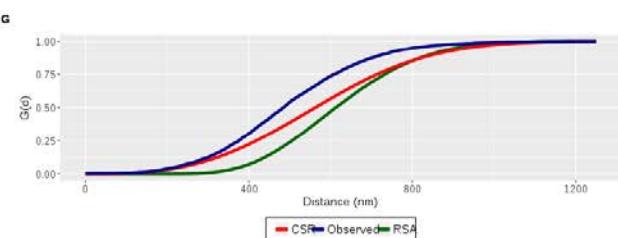
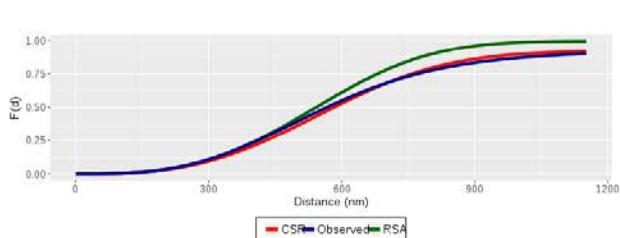
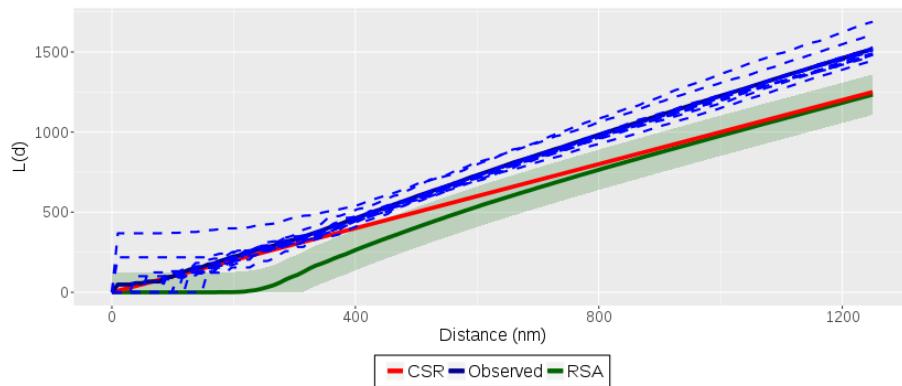
Feret diameter distribution has been fitted to a log-normal distribution with parameters:

- **Log mean :** 5.9188
- **Log standard deviation :** 0.4006
- **Test p-value:** : 0.0000 (One-sample Kolmogorov-Smirnov test) **REJECT**



Envelope and results based on 198 simulations:

- **Feret diameter log mean:** 5.9188
- **Feret diameter log standard deviation:** 0.4006
- **Process intensity:** 0.9693 synapses/ μm^3



PER-SAMPLE SUMMARY:

Layer	Sub-ject	Sam-ple.no.	Is Feret diam LogNormal?	Mean Feret diam ± SD	Synapses/mu m^3	Summary functions suggest	RSA?
LacMol (I)	AB1	1	OK	391.93 ± 144.19	0.3683	Clustered	YES
	AB1	2	OK	423.90 ± 180.36	0.3046	Clustered	YES
	AB1	3	OK	422.34 ± 179.03	0.3412	Clustered	YES
	AB2	4	OK	456.23 ± 176.32	0.3680	Clustered	YES
	AB2	5	OK	436.71 ± 178.28	0.4416	Clustered	YES
	AB2	6	OK	417.36 ± 185.08	0.4082	Clustered	YES
	AB3	7	OK	435.46 ± 192.21	0.3717	Clustered	YES
	AB3	8	OK	383.28 ± 140.80	0.6079	Regular (d<500nm) and clustered (>500)	YES
	AB3	9	OK	379.83 ± 133.13	0.3832	Clustered (not hard core!)	NO
	M17	10	OK	415.01 ± 171.50	0.3929	Regular (d<450nm) and clustered (>450)	YES
	M17	11	OK	416.53 ± 183.56	0.5379	Regular (d<400nm) and clustered (>400)	YES
	M17	12	OK	434.04 ± 175.14	0.5345	Regular (d<700nm) and clustered (>700)	YES
Radiatum (II)	AB1	1	OK	390.65 ± 146.39	0.4721	Clustered	YES
	AB1	2	OK	383.94 ± 139.95	0.5113	Regular (d<600nm) and clustered (>600)	YES
	AB1	3	Reject	292.90 ± 131.18	0.4408	Regular (d<600nm) and clustered (>600)	YES
	AB2	4	OK	355.74 ± 144.74	0.5989	Clustered	YES
	AB2	5	OK	386.76 ± 181.57	0.7970	Regular (d<500nm) and clustered (>500)	YES
	AB2	6	OK	349.37 ± 161.96	0.7132	Regular (d<500nm) and clustered (>500)	YES
	AB3	7	Reject	406.23 ± 150.75	0.6445	Regular (d<500nm) and clustered (>500)	YES
	AB3	8	OK	383.18 ± 137.45	0.1283	Regular (d<500nm) and clustered (>500)	YES
	AB3	9	OK	361.28 ± 146.83	0.7384	Clustered	YES
	M17	10	OK	461.00 ± 244.91	0.4514	Regular (d<600nm) and clustered (>600)	YES
	M17	11	OK	394.12 ± 162.22	0.4463	Clustered	YES
	M17	12	Reject	430.21 ± 187.97	0.4814	Regular (d<550nm) and clustered (>550)	YES
Oriens (III)	AB1	1	OK	406.33 ± 168.98	0.2678	Clustered	YES
	AB1	2	OK	426.45 ± 183.81	0.3497	Clustered	YES
	AB1	3	OK	393.74 ± 116.13	0.2401	Clustered	YES
	AB2	4	OK	382.63 ± 175.92	0.2209	Clustered (not hard core!)	NO
	AB2	5	Reject	393.68 ± 157.41	0.6407	Regular (d<600nm) and clustered (>600)	YES
	AB2	6	OK	348.86 ± 130.39	0.9109	Regular (d<600nm) and clustered (>600)	YES
	AB3	7	Reject	514.00 ± 291.01	0.2995	Regular (d<400nm) and clustered (>400)	YES

	AB3	8	Reject	438.62 ± 159.02	0.4843	Regular (d<600nm) and clustered (>600)	YES
	AB3	9	OK	397.34 ± 141.48	0.3658	Clustered	YES
	M17	10	OK	420.26 ± 172.88	0.3924	Regular (d<450nm) and clustered (>450)	YES
	M17	11	OK	419.66 ± 147.23	0.3541	Regular (d<400nm) and clustered (>400)	YES
	M17	12	OK	394.62 ± 136.38	0.3722	Regular (d<400nm) and clustered (>400)	YES

PER-LAYER SUMMARY:

Layer	Is Feret diam LogNormal?	Mean Feret diam ± SD	Synapses/mu m^3	Summary functions suggest	RSA?
LacMol (I)	Reject	414.91 ± 169.24	0.4217	Clustered	YES
Radiatum (II)	Reject	401.82 ± 169.42	0.7400	Clustered	NO
Oriens (III)	Reject	406.68 ± 167.02	0.4082	Clustered	YES

PER-SUBJECT SUMMARY:

Subject	Is Feret diam LogNormal?	Mean Feret diam ± SD	Synapses/mu m^3	Summary functions suggest	RSA?
AB1	Reject	403.19 ± 154.75	0.7128	Clustered	NO
AB2	Reject	382.43 ± 166.06	1.1179	Clustered	NO
AB3	Reject	404.54 ± 162.56	1.1050	Clustered	NO
M17	Reject	423.29 ± 181.92	0.9416	Clustered	NO

ALTOGETHER:

Subject	Is Feret diam LogNormal?	Mean Feret diam ± SD	Synapses/mu m^3	Summary functions suggest	RSA?
All	Reject	403.04 ± 168.16	0.9693	Clustered	NO

CONCLUSIONS

For mice:

1. Most samples in mice follow an RSA model (10 out of 12 samples passed the envelope test, a 83.3%). Clustered patterns were observed in many samples and other patterns combined clustered behavior with a repulsion pattern at short distances (400-500nm).
2. Log-normality of Feret's diameters is less than half the times rejected (5 out of 12 rejections or 41.6%). Log-normal distribution parameters were different.
3. Mean synaptic densities were statistically different among samples.
4. Per-layers: log-normal distribution for Feret's diameters is not rejected only in layer I (stratum lacunosum moleculare). Mean and variance estimates decrease from layer I to III, whereas the synaptic density increases from layer I to III. Only layer III follows an RSA model. Patterns of repulsion at short distance and clustered at larger distances are observed for all layers.
5. Per-animals: log-normal distribution for Feret's diameters is always rejected. Mean and variance estimate are not rather different. Synaptic density is higher in ID2 and then ID28 (higher than the overall mean) and finally ID4. None of the subject patterns fit an RSA model and a clustered pattern is suggested.

For humans:

1. For humans, observation 1 above (although short distances are in the range 400-600nm) also holds (34 out of 36 passed the RSA envelope test, a 94.4%).
2. Log-normality of Feret's diameters is more often verified (only 6 rejections out of 36 or 16.6%). Log-normal distribution parameters were different.
3. Mean synaptic densities were statistically different among samples.
4. Per-layers: log-normal distribution for Feret's diameters is always rejected. Mean and variance estimates are not so different. However, the synaptic density is statistically higher for layer II (stratum radiatum). Unlike the other two layers, this layer II does not follow an RSA model.
5. Per-subjects: as in mice, log-normal distribution for Feret's diameters is always rejected. Mean and variance estimate are not rather different (M17 has the highest figures, then AB3/AB3 and finally AB2). Synaptic density is higher in AB2/AB3 (higher than the overall mean) and then M17 and finally AB1. None of the subject patterns fit an RSA model and a clustered pattern is suggested.

Mice vs. humans:

1. When comparing species, mice have higher synaptic densities (mean of 4.29 synapses/ μm^3) than humans (0.96 synapses/ μm^3). This finding agrees with that in Montero-Crespo et al. (2020).
2. Feret's diameters of mice are smaller (317nm) than for humans (403nm).
3. Mice tend to present per-layer repulsion-followed-by-clustered patterns rather than RSA models. Some layers (I and III) in humans comply with an RSA process. This is true only for layer III in mice.

ACKNOWLEDGMENTS

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