SUPPLEMENTAL DIGITAL CONTENT

Analysis of the spatial distribution of the synapses

Briefly, we tested the Complete Spatial Randomness (CSR) hypothesis (see 1, for further details). This hypothesis implies that points follow a Poisson distribution with no interaction among them. Thus, the position of each point is totally independent of the position of any other point in the sample. That is the most important constraint of CSR, since in the real data, a minimum distance between synapses is inevitable due to its synaptic volume. As a result, our approach belongs to the so-called Random Sequential Adsorption (RSA; 2, 3, 4). Thus, in order to demonstrate the spatial random distribution of the synapses with the constraint of non-overlapping synaptic volumes, it is necessary to obtain several populations of simulated synapses, using an RSA process.

To simulate synapse volume, a sphere representation was used. Firstly, the distribution of the feret diameters' density was analyzed, using the *Fitdistplus* package of R-Project (5, 6). The "feret diameter" is defined as the value of the minimum sphere diameter that circumscribes the object measured in physical units A hundred RSA simulations per sample were then performed. Then, using the *Spatstat* package of R-Project (7), the F, G and K functions (8) were calculated in order to compare each actual sample with the RSA simulations. All functions were compared by means of Kolgomorov-Smirnov two-sided test.

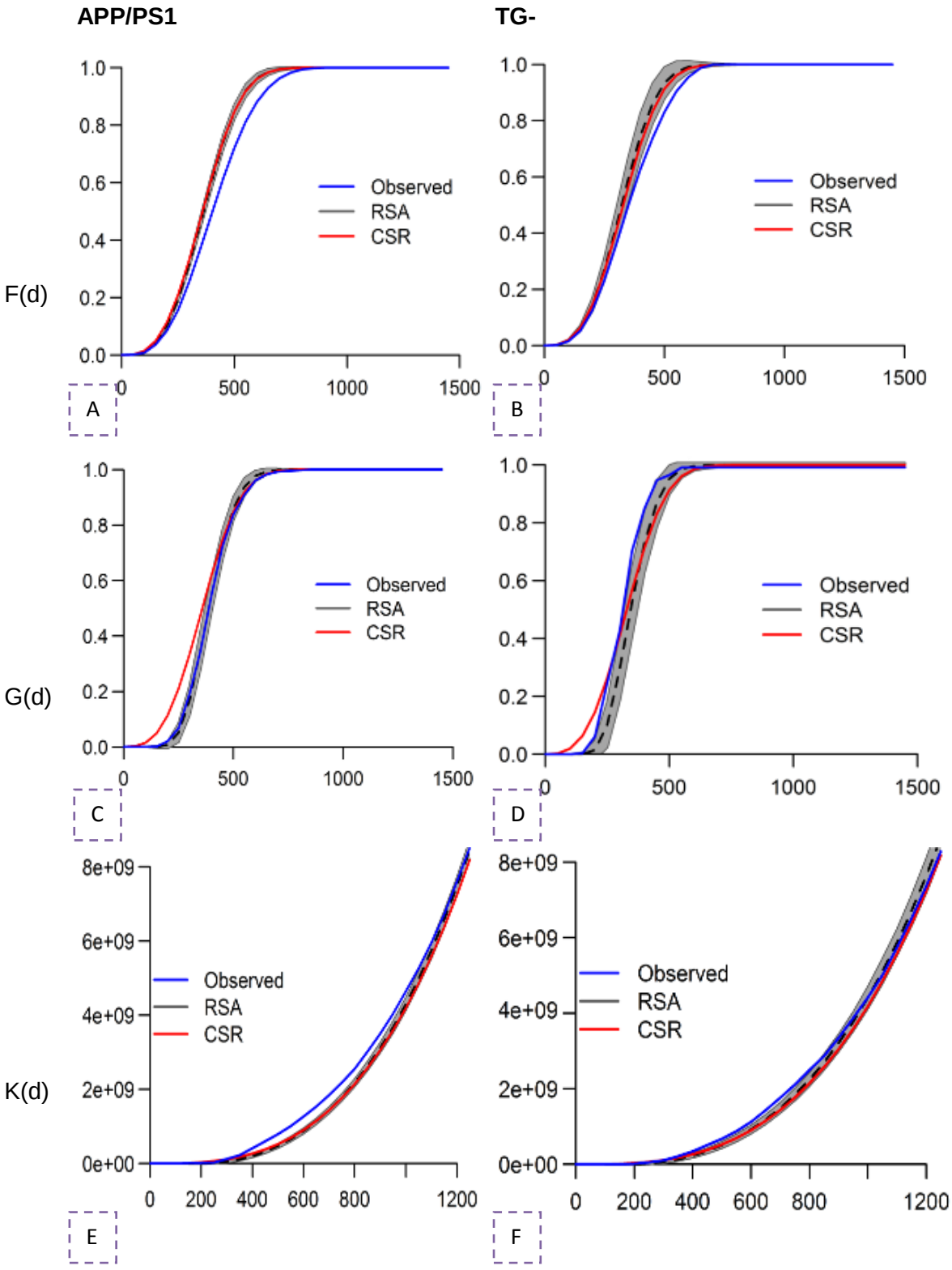
APP/PS1
TG-
F(d)
G(d)
K(d)
Observed
RSA
CSR
A
B
C
D
E
F

Figure S1. Graphs showing the F, G and K functions of two FIB/SEM samples (APP/PS1-1 and TG-2), as examples. In the case of F functions (A, B), the Poisson curve and the mean curve of RSA simulations were very similar, with the Observed curve positioned slightly to the right of the RSA range. G functions were very similar for the Observed and RSA simulations, however, the Poisson curve tended to locate slightly to the left of the RSA curves, particularly at the beginning (C, D). K functions were also very similar for the Poisson and RSA simulations with the observed curve lying slightly to the left.

Table S1. Results of the KS two-sided test: all comparisons indicate a clear fit to the RSA (p-values over 0.95).

Sample	**P-value**		
	F(d)	**G(d)**	**K(d)**
TG-(1)	0.952	1.000	1.000
TG-(2)	0.999	0.999	0.999
TG-(3)	0.998	1.000	0.995
APP/PS1 (1)	0.998	0.999	0.999
APP/PS1 (2)	0.998	0.999	0.999
APP/PS1 (3)	0.952	0.999	0.999
APP/PS1 (4)	0.952	0.999	1.000
APP/PS1 (5)	0.998	1.000	1.000

Equation for the simple sampling of postsynaptic elements:

$$n = \frac{N Z_{\alpha/2}^2 \, P(1-P)}{(N-1)e^2 + Z_{\alpha/2}^2 \, P(1-P)}$$

Where $Z_{\alpha/2}$ is the Z-score associated with the confidence level, P is the proportion of one category of class, e is the maximum error and N the total population size.

References

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