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A SYSTEMATIC REVIEW OF SIMULATION PROCEDURES FOR fMRI CONNECTIVITY STUDIES

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Abstract

The strategies used to study functional or effective connectivity in fMRI data are mainly based on the application of correlation studies, structural equation models (SEM), dynamic causal modelling (DCM), or the Granger causality model (GCM), while some contributions focus their attention on simulation studies. Although the tradition is scarce, this increase of the latter studies has become steeper in the last five years. In this work, we present a systematic study and analysis of

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simulation studies with fMRI data for the analysis of brain connectivity. We conducted a search on the Web of Science (WoS) and PubMed and eventually we reviewed a total of 134 studies. The most remarkable finding is a lack of information on the simulation procedure. For example, 17 works did not specify the model used to generate the signal, 36 did not indicate the model's white noise addition in the signal generated, and 52 did not detail the design under which the data had been generated. Under these circumstances, it is difficult to compare the different contributions in order to identify the best strategies to simulate data for the study of brain connectivity in fMRI works. However, it is important to note the emergence of the so-called third-generation simulation models, which consider the brain as a complex, dynamical system model. This kind of model to simulate brain activity will change the state of the art in this matter, and it might be a good tool to assess the different analytical procedures to study effective connectivity.

Introduction

The use of functional Magnetic Resonance (fMRI) in the studies on computational neuroscience has seen an exponential increase in later years. If we conduct a bibliographic search on the Web of Science (WoS) database, only within the core collection, with only the keyword 'fMRI' in the title, up to December 2015, we obtain a total of 14,311 papers. One of the earliest works was published in 1993 (Miller et al. [113]), but in fact, 13,121 out of these works (91.68%) were published between 2001 and 2015 (3,466 between 2000 and 2005, 4,554 between 2006 and 2010 and, lastly, 5,101 between 2011 and 2015). The first works published in this field tried to determine which areas were activated when a person was conducting a task involved in certain cognitive domains, such as working memory (Manoach et al. [104, 105]), language processing (Carpenter et al. [21]), attention (Hillyard et al. [66]), processing speed (Waiter et al. [168]), or executive functions (Sylvester et al. [161]; Horowitz-Kraus et al. [163]). In later years, however, researchers have shown more interest in discovering how the different brain areas work together when a cognitive task is in process (Barbalat et al. [5]; Dick et al. [47]; Haase et al. [61]; Limongi and Pérez

[93]), or when the subject is in repose. Consequently, they study the resting state and, occasionally, one of the networks that appears in this situation: the default mode network (DMN) (Chiong et al. [27]; James et al. [72]; Mäki-Marttunen et al. [103]).

From a statistical point of view, we should point out that a wide range of indicators was created at the same time to estimate the connectivity level between brain areas, both – as mentioned above – upon stimuli or cognitive tasks and in a resting situation. An interesting summary of the proposals on this matter can be found in Rubinov and Sporns [136]. All the indicators are based on the joint distributions observed in the pairs of brain activity areas, both those based on the logic of covariances (s_{ij}) and correlations (r_{ij}) and those based on the study of distances or the estimations of similarities (d_{ij}), although we might understand correlation as a special case of dissimilarity. Be that as it may, all these connectivity indicators intend to summarize the behavior of the connectivity network, the symmetry between hemispheres, directionality, and entropy of the complex network, among others. It seems curious that among the different approaches conducted, some of them have been the object of statistical analysis to validate their distributions and thus establish a statistical criterion of significance, whereas others are descriptive estimations without further inferential interest. Stevenson and Körding [159] is an example of the first perspective, while Iyer et al. [71] is an example of the second. Still, it is important to note that, so far, the studies on statistical pertinence of many of these indices focus on their applied functionality, and rarely on the study of their sample distributions and inferential properties based on the usual simulation studies. This matter is still pending for analysis and data contribution.

It is important to center our attention in which techniques are used usually in order to analyse the estimation of brain connectivity using fMRI signal. First, it is important to differentiate between functional connectivity and effective connectivity. It is not a new concept but it needs to be clarified. Friston [51] defines functional connectivity as a statistical relationship (in terms of correlation coefficient r_{ij}) between the functional neuroimaging

signals in two or more brain regions. The effective connectivity is the estimation of direct effect of one brain region's activity on another region during a specified experimental condition, and it must necessarily be studied by models.

The statistical strategies used to analyse the BOLD signal in fMRI data in order to study functional or effective connectivity are, obviously, different. In the former case, the statistical techniques employed are usually based on the use of correlation with different corrections, like, for example, partial correlation in order to control the effect of other regions. Nonetheless, this correction is not problem-free because the number of possible correlations involved therein is large if we compare it to the number of scans (Sanz Leon et al. [142]). Sometimes the effect of autocorrelation is not controlled, either (Arbabshirani et al. [2]). Another strategy is the use of autoregressive vectors (Chen et al. [23]), which are based on the use of correlations as well.

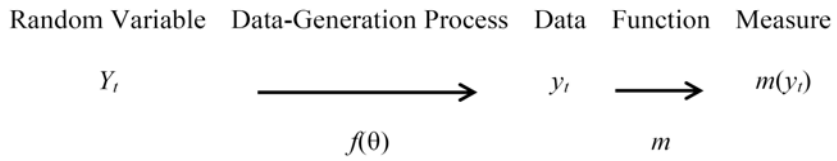
The study of effective connectivity is more complex than the study of functional connectivity and, therefore, it requires the use of more sophisticated statistical techniques, but there is no agreement on the best strategy to analyse this type of data. Indeed, it appears that the use of analysis strategies depends on the researcher and not on the type of data to be analysed. Accordingly, Poldrack [122] remarks the need to propose robust methods to study brain connectivity. The most used strategies – previously obtaining regions of interest (ROIs), using data-driven or hypothesis-driven strategies – are based on the use of structural equation models (SEM) or dynamic causal models (DCM) (de Marco et al. [36]; Friston et al. [52]; Penke and Deary [118]; Rowe [135]). The ROIs are generally obtained using principal component analysis (PCA) or independent component analysis (ICA) or, in some cases, is possible to find extractions based on other techniques as clustering. The main differences between these two analytic strategies are related to the possibility of using DCM to model the temporal correlations of a ROI, non-linearities, and also external connections (de Marco et al. [35]; Penny et al. [120]). Some authors propose modifications to the SEM to analyse effective connectivity, for example unified SEM (Gates et al. [57]), extended unified SEM (Gates et al. [58]), or exploratory SEM

(Inman et al. [70]; James et al. [72]). Other strategies to analyse effective connectivity are based on graphical theoretical modelling strategies (He and Evans [64]; Minati et al. [114]), the psychophysiological interaction (PPI) (Luchtman et al. [99]; Mason et al. [107]) or the use of Granger causality modeling (GCM) and its variants (Deshpande and Hu [41]; Deshpande et al. [43]; Deshpande et al. [44]; Miao et al. [111]; Roebroeck et al. [134]). In Barnett and Seth [6], they presented the MVGC toolbox for data simulation to analyse with the Granger causality model. In any case, Barnett and Seth [6, 7] mention that the use of Granger causality of fMRI data should be conducted with caution due to the effect of hemodynamics.

In consequence, there exists a wide range of analytic strategies, just like there are several choices of connectivity summary indicators. But which one is the best? To answer this question, previously, we should contemplate the statistical version of the different choices as their properties will determine which technique is the most adequate for one specific situation. Usually, we consider it necessary to conduct simulation studies in order to discover the efficacy of each of these analytical approaches to study brain signal. A good example of statistical simulation can be found in Bellec et al. [9], or with more complex simulations than the ones described in the dynamic model simulation in Cabral et al. [19]. The use of simulation data is essential at this point because it allows us to know in which voxels, areas, or ROIs there could be a difference in BOLD signal, given that we manipulated the generation of this information in the simulation. This situation is not true for real data because we do not know which areas are in fact activated. Actually, recently Ritter et al. [131], Sanz Leon et al. [142] and Woodman et al. [175] have all presented The Virtual Brain, a simulator of brain network dynamics; Seth [149] has described the MATLAB toolbox GCCA, Granger causal connectivity analysis; Liao et al. [92] have presented the MATLAB toolbox DynamicBC, both used to simulate the fMRI signal; and Aponte et al. [3] have presented the massively parallel dynamic causal modeling (mpdcm), a toolbox for biophysical simulations from DCM. However, to our knowledge, there are few studies assessing the suitability of the simulations performed in this area. One of these studies (Welvaert and Rosseel [173]) conducts a

systematic revision of simulations in fMRI studies in general, or the one by Deco et al. [38], which present three models to study the dynamics of the resting state with simulated data.

In any case, these toolboxes are new and we think that it is still too early to make an accurate assessment of their advantages and disadvantages because these platforms or toolboxes are not commonly used to generate the simulations in the study of functional or effective connectivity. The works using simulations to study the effectiveness of the analytical techniques to study brain connectivity – functional or effective – usually generate these simulations through their own software and models built by them, despite the mathematical properties of the simulator, the technical requirement of the software, obviously, independent of the mathematical and statistical properties of simulations functions. In fact, some authors say that in this field, researchers are currently generating their simulated data by using what has been called the third-generation of models (referred to the simulations based in dynamic complex models usually nonlinear, identifying several different functions to represent different parts of the brain represented through different density functions), which generate the brain's dynamics through, for example, the balloon model (Bellec et al. [10]). The simplest diagram to show the simulation process, could be presented as follows:



Thus, we can use a simple classification to describe the simulation procedures: (i) first generation of simulations imply generating the data as a stochastic temporal series after spectral transformation:

$$Y(t) = u(t),$$

where

$$u(t) = \sum \alpha_j \delta(t_i - t_0),$$

and the statistical series is defined as

$$y(t) = \sum \sum \beta_k f_k(t_i - t_0) + \varepsilon(t),$$

$Y(t)$ is the signal value at moment t and is established as an accumulated function in the period of time $(t_i - t_0)$ pondered by the linear parameter α_j, (ii) the second generation of simulators is the result of the convolution of the temporal series with the hemodynamic response function (HRF), generally based on the gamma distribution, as follows:

$$Y(t) = u(t) \otimes h(\tau) = \int u(t - \tau) h(\tau) d\tau,$$

where

$$h(\tau) = \sum \beta_k f_k(\tau),$$

and it implies incorporating the stimulus effect to the time effect, thus convoluting both functions, and finally and most recent, (iii) third generation, which implies the incorporation of the dynamic components into the data generation procedure. This way, the origin function can be described in this case as: $Y = \varphi(B, D, P, A, E)$. Each matrix involves a different effect for the simulation of *Y*, where *Y* has been defined as a $3D + t$ matrix of a size matching the temporal series necessary for fMRI. In this case, *B* is the constant reflecting the brain's anatomy, *D* assumes the slow functioning of the baseline, *P* implies the representations caused by noise, *A* represents the fluctuations of the hemodynamic function (at this point we recover the characteristics of the second time of simulation), and *E* is the random measurement error typical of statistical models. Evidently, φ is assumed as any linear or non-linear function. In fact, components can be included in the proposed model that includes effects to estimate. The specific conception of this simpler proposal is defined as a linear model of the type $Y = X_B\beta_B + X_D\beta_D + X_P\beta_P + X_A\beta_A + E$. In this case, we assume *E* as a Gaussian distribution $N(0, \sigma^2)$.

However, despite the fact that in recent years there has been an increase of studies using simulations; they have not been systematically reviewed.

Accordingly, it remains unclear what the usual procedure is for signal simulation, in which cases it is applied, what limitations it presents and, most interestingly, what its limits are in recognising the stochastic behavior of the simulated signal.

Consequently, the aim of this paper is to conduct a review of the simulation studies carried out so far to study brain connectivity – functional or effective – with fMRI data. In essence, the objective is to establish how the simulations were generated in order to discover whether the same basic patterns exist in the simulations and, therefore, whether it is possible to compare the goodness and efficiency of the different types of analytic strategies used to study brain connectivity with fMRI data in computational neuroscience studies, unlike Welvaert and Rosseel [173] we focused only in simulation for the study of brain connectivity. We focus on describing the state of the art regarding simulations in fMRI studies and contributing to select the best statistical approach to signal studies. One single correlation matrix as an input for the connectivity study allows us to obtain different estimations depending on the technique employed. This effect, which is widely known in other fields of applied statistics, seems to be overlooked in this field as there is no clear stable analysis pattern and there is ample diversity of techniques and resources. To prevent this variability, it is important to study the statistical properties of those techniques in relation to the signal data analysed and, to do so, we need to know the properties of the possible simulators.

Method

Search of studies

The articles included in the present study were searched for in the Web of Science (WoS) and PubMed databases, as well as in other sources. To be included in the present study, the articles had to comply with the following criteria: they had to be original fMRI papers approaching the brain connectivity topic with simulation data published up to December 2015. The search for papers was conducted by means of a Boolean algorithm using the

following keywords: ‘fMRI’, ‘simulation’ and ‘brain connectivity’ or ‘fMRI’, ‘simulation’ and ‘functional connectivity’ or ‘fMRI’, ‘simulation’ and ‘effective connectivity’. The Boolean operator ‘and’ was used in order to connect these keywords. In addition, the keywords “brain connectivity”, “functional connectivity” and “effective connectivity” were written between double quotation marks in order to detect those papers containing both words jointly. The WoS and PubMed search was done independently by two researchers, and we obtained a 96.33% rate of agreement in the search done between them; all the papers found by the two researchers were considered in the study. Following these search criteria, we found a total of 83 records on WoS and a total of 62 records on PubMed in the first search (brain connectivity), 326 records on WoS and a total of 152 records on PubMed in the second search (functional connectivity), and 194 records on WoS and a total of 57 records on PubMed in the third search (effective connectivity). After removing the duplicates, a total of 649 records were screened plus 14 records from other sources. Out of the 663 total records, 471 were discarded because they were not actually simulation studies. The remaining 192 articles were fully reviewed, and 58 of them were discarded: 21 because they were not simulation studies, 30 because, in spite of them being simulation studies, the simulated data was in the paradigm of EEG, MEG or DTI data; and 7 because the authors of the paper presented a platform for full brain network simulations, but did not perform any simulation study. Eventually, 134 studies were included in the current study (identified with ∗ in the bibliography). Figure 1 presents a graph of the process that summarizes this search.

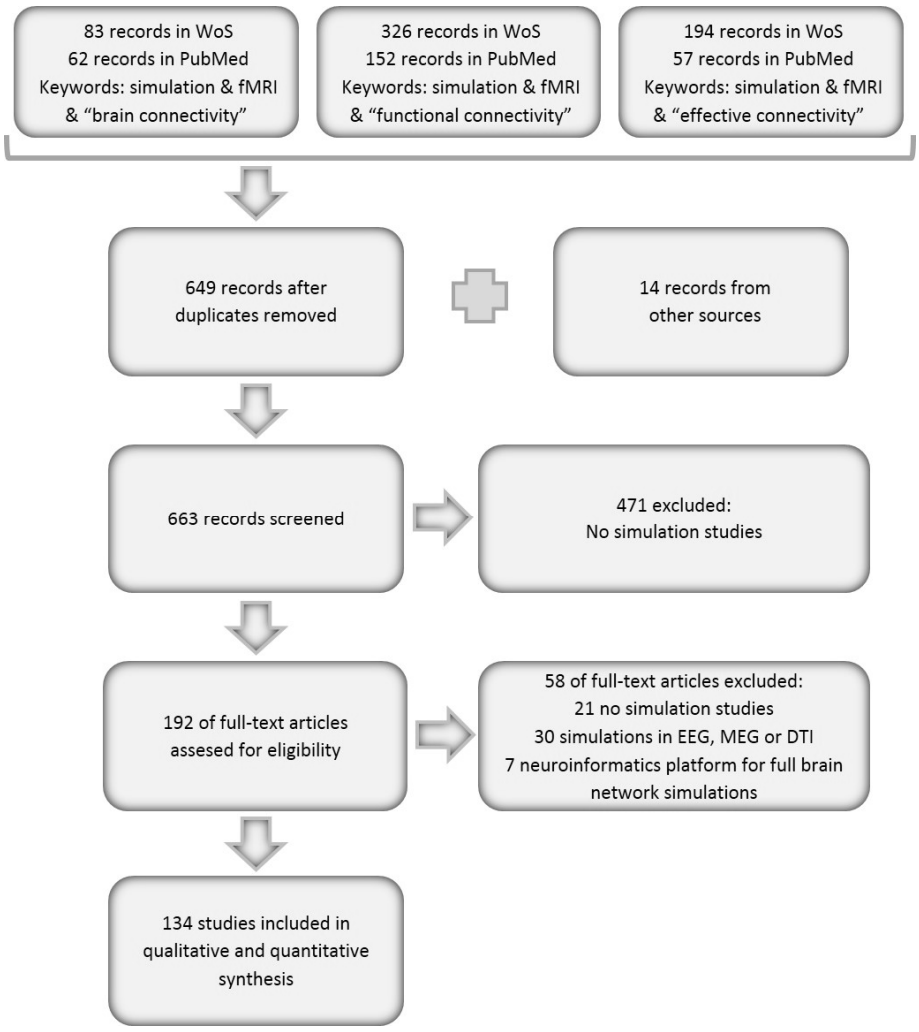


Figure 1. Flow chart describing the bibliographic search.

Coding of the variables

We applied a codification template to each of the selected papers in order to obtain the values of the different variables under study. For each paper, we registered the variables listed in Table 1. Some of them are context variables used to characterize the selected papers while the majority of the variables are related to different parameters for a simulation study in fMRI data.

Namely, methodological parameters comprise the following information: the type of fMRI data simulated (time series, time series convolved to generate BOLD signal, ROIs or network); toolboxes used to generate the simulation; the type of study under which the data was generated (blocks, event-related, or a resting state situation); the number of samples of individuals simulated; the kind of strategy that was used to analyse the simulated data; and finally, certain variables related to the probabilistic model used to simulate the data. We studied the following variables: the model used to generate the signal; the model used to generate white noise, in this context white noise is the noise that the authors added to the signal in order to generate variability in the data equivalent to the random measurement error; whether the authors used a seed (specific voxel or ROI) to generate the data; whether the authors included a mechanism such as spatial or temporal noise to correct the raw simulated data in order to obtain a more realistic fMRI scenario or to test the effect of different noise sources, this mechanism is a step more in the generation of the simulated data previously to analyse the synthetic data generated; and finally whether the authors report the script of the simulation generated. The goal of the studies is not considered a variable to analyse because all the studies generally have as a goal the accuracy study of an analytic strategy, whether graphical or numerical.

Regarding the type of simulated data, we distinguish those studies that only generated time series from those that generated time series convolved to HRF to simulate the BOLD signal (i.e. the convolution of a time series function and the gamma distribution) for each voxel, and from those that simulated ROI-based structures (regardless of the convolution with a hemodynamic response function). The BOLD signal in an fMRI study is collected as a time series, and in consequence simulate time series with temporal dependency is a correct way of simulate data in the context of a fMRI study. A fourth group of studies simulated the whole brain as a complex and dynamic network with brain regions as nodes and connectivity paths as edges, aiming to study the temporal changes in brain connectivity.

Table 1. List of variables according to their characteristics and codifications

Variables	Type
Year of publication (2001 to 2015)	Context
Document type	Context
Periodic publication	Context
Number of authors	Context
Language	Context
Type of data simulated (time series, time series convolved to generate BOLD signal, ROIs or network)	Methodological
Toolboxes used to generate the simulation	Methodological
Type of study (blocks, event-related, resting)	Methodological
Number of samples simulated	Methodological
Data analysis of the simulations	Methodological
Probabilistic model to simulate the data Signal model Noise model Seed simulations Mechanism to correct simulations Existence of the script	Methodological

Data analysis

All the analyses were conducted with the SPSS software, version 23, and involved the description of the different coded variables obtaining the frequencies and percentages of papers for each category of the variables analysed.

Results

In this section, we will present the descriptive statistics of the coding conducted in each paper. We structured the results into two subsections, one that characterizes the articles analysed, and another where we will present the description of those variables regarding the simulations conducted in the articles.

Characterization of the articles

In Table 2, we report the descriptive statistics about context variables. All the publications under study were written in English, and 132 out of the

134 documents were original research articles, except for two conference proceedings. Fifty-two papers (38.8%) were published in NeuroImage, followed by nine papers published in Brain Connectivity. It is important to point out that 19 papers were published in a different journal: Brain Research, Chaos, Clinical Neurophysiology, Current Opinion in Neurology, Computational and Mathematical Methods in Medicine, Computational Statistics & Data Analysis, Frontiers in Neuroinformatics, Frontiers in Systems Neuroscience, IEEE Transactions on Neural Networks, Journal of Computational Neuroscience, Journal of Magnetic Resonance Imaging, Journal of Physiology, Magnetic Resonance in Medicine, Medical Image Computing and Computer-Assisted Intervention, Methods of Information in Medicine, PeerJ, Physiological Measurement, Statistica Sinica and the proceedings of the 35th Annual International Conference of the IEEE EMBS.

Finally, in Figure 2, we present the number of publications by year. As we can see in this Figure, only 27 papers were published before 2010, and 93 (69.4%) have been published within the last 5 years.

Table 2. Description of context variables

Variables	Values	Frequency	(%)
Document type	Paper	132	(98.5%)
	Proceedings	2	(1.5%)
Periodic publication	NeuroImage	52	(38.8%)
	Brain Connectivity	9	(6.7%)
	Human Brain Mapping	8	(5.8%)
	IEEE Transactions on Biomedical Engineering	7	(5.2%)
	Magnetic Resonance Imaging	7	(5.2%)
	Journal of Neuroscience Methods	6	(4.5%)
	Frontiers in Neuroscience	5	(3.7%)
	IEEE Transactions on Medical Imaging	5	(3.7%)
	PLoS ONE	5	(3.7%)
	PLoS Computational Biology	3	(2.2%)
	Brain Topography	2	(1.5%)
	Frontiers in Computational Neuroscience	2	(1.5%)
	Frontiers in Human Neuroscience	2	(1.5%)
	Journal of Neuroscience	2	(1.5%)
	Others	19	(14.2%)

Number of authors	1	2	(1.5%)
	2	22	(16.4%)
	3	27	(20.1%)
	4	34	(25.4%)
	5	23	(17.2%)
	6	16	(11.9%)
	7	6	(4.5%)
	8	2	(1.5%)
	9	1	(0.7%)
	11	1	(0.7%)

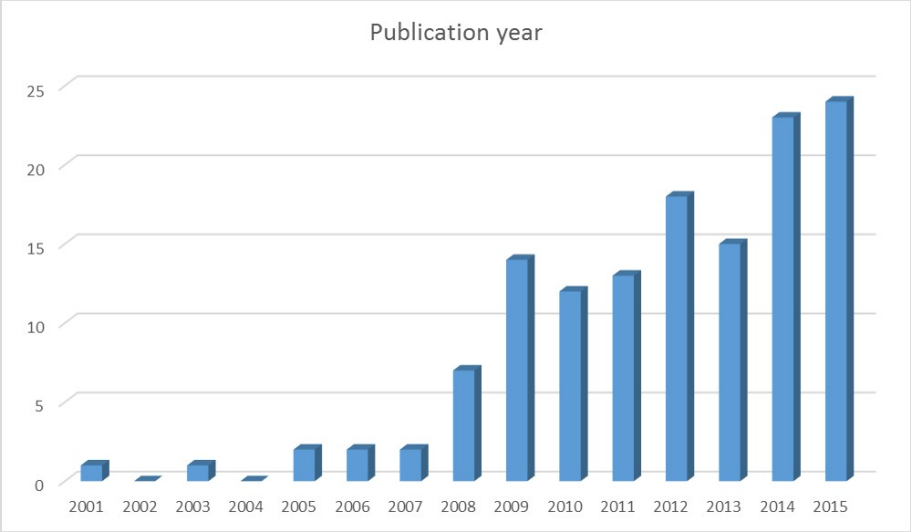


Figure 2. Bar chart of the number of publications per year.

Simulations description

In Table 3, we present the description of the methodological variables related to the simulation study. A total of 28 works simulated total brain network and a total of 74 works simulated regions of interest (ROIs) directly. The number of regions simulated varied greatly, from 2 to 998, while in some works, different numbers of ROIs are simulated depending on the different simulation scenarios used. We consider it important to point out that

in 97 of the papers analysed there is no information regarding the toolboxes used to generate the simulations, possibly because they designed their own simulation programme.

Twenty-nine works simulated data under block study, six under an event-related study, 45 under a resting-state situation – in order to study the Default Mode Network (DMN) in some cases –, two a mixing between a resting state situation and a block design, and in 52 (38.8%) papers this information was not specified (Table 3).

The information about the number of simulated samples appears in 93 of all the works reviewed (Table 3). Most of them simulate over 20 samples (38.8%), reaching 500 samples or more in some cases, but in some cases the authors generated a single sample of individuals (26). At this point we consider it important to remark that, in some papers, for each subject simulated, the authors simulated different time series and, in those cases, the number of time series simulated ranged between 50 and 5,000.

The data analyses of the simulations were based on general linear models in 70 out of the 134 works, using models such as dynamic causal models (DCM), autoregressive vectors (VAR) or Granger causality model (GCM). In 23 papers the data analyses comprised the efficiency study of a proposed algorithm with measures that could be either descriptive or both descriptive and inferential. We consider it important to mention that in the latter case, the data analysis of the simulated data was not specified in four of the studies (Table 3).

As for the probabilistic model used to generate the simulated data, we have divided this information into five subsections: the model used to generate the raw signal; what model they used to add white noise to the signal; whether they used a seed to conduct the simulations; whether the authors used a mechanism to correct the simulated data adding for example: spatial noise, temporal noise or frequency dispersion and whether the authors added the script used to generate the simulations to the paper (Table 3). Regarding the model used to generate the signal and the white noise, the most remarkable aspect in both cases is that this information is absent from

some papers, more specifically in 17 works for the signal model and in 36 works for the white noise model. The most widely used model in the case of signal is the autoregressive vectors (47), followed by time series convolved with hemodynamic response function (in general generated by the gamma distribution) (39), time series plus the balloon-Windkessel model (13), Gaussian (11), sinusoid wave (3), uniform distribution (3) and finally one paper derived the simulation from real data. In 81 papers the model used to add white noise to the signal was the Gaussian. Only in eleven papers were seeds used to generate the simulations. In these cases, when we speak about the use of seeds to generate the simulations, we mean to fix a voxel or a ROI to generate the simulation. Seventy-two papers used a mechanism to correct the simulated data, for example spatial noise, temporal noise or frequency dispersion. This information does not appear in 27 of the 134 papers analysed, where we must assume that the authors did not apply any corrections to the simulated data. Of the seventy-two papers that the authors used a mechanism to correct the raw simulated data, in twenty no information appears to known how they apply the correction, in seventeen they apply some mechanism related to add some artefact to the signal similar to head motion, for example deterministic noise, random signal spike, thermal white noise, and finally in thirty-five papers the authors used some mechanism to add physiological noise to raw signal like cardiac rate or respiratory movement, the strategy used to add this type of noise is modification of the Hz (14 papers), autoregressive models (10 papers), normal distribution (10 papers) or general linear model (1 paper), and finally 129 of the papers did not add the script of the simulation generated (Table 3).

Table 3. Description of methodological variables

Variables	Values	Frequency	(%)
Type of data simulated	Time series	22	(16.4%)
	Time series convolved to generate BOLD signal	10	(7.5%)
	ROIs	74	(55.2%)
	Network model (whole brain)	28	(20.9%)
Toolboxes used to generate simulations	AFNI	2	(1.5%)
	Connectionist platform	1	(0.7%)
	FMRIB	1	(0.7%)
	FSL: DTT	1	(0.7%)
	Home made	3	(2.2%)
	MATLAB (for example Math Works, SimTB)	12	(10.5%)
	NetSIM	1	(0.7%)
	SPM	6	(4.5%)
	SPM: DCM	8	(6.0%)
	No information	97	(72.4%)
Type of study	Blocks	29	(21.6%)
	Event-related	6	(4.5%)
	Resting state	45	(33.6%)
	Resting state and blocks	2	(1.5%)
	Not defined	52	(38.8%)
Number of samples simulated	1	26	(19.4%)
	Between 2 and 10	7	(5.2%)
	Between 11 and 20	8	(6.0%)
	More than 20	52	(38.8%)
	No information	41	(30.6%)
Data analysis of the simulations	Algorithm efficacy (descriptive or inferential measures)	23	(17.2%)
	Correlation study	23	(17.2%)
	General linear model (DCM, VAR, MAR, GCM, etc.)	70	(52.2%)
	Graphic	14	(10.4%)
	Not defined	4	(3.0%)

Probabilistic model to simulate the data			
Signal model	Autoregressive vectors (time series)	47	(35.1%)
	Derived from real data	1	(0.7%)
	Gaussian	11	(8.2%)
	Sinusoid wave	3	(2.2%)
	Time series convolved with HDF (Gamma distribution)	39	(29.1%)
	Time series plus balloon-Windkessel model	13	(9.7%)
	Uniform	3	(2.2%)
	Not specified	17	(12.7%)
Noise model	Gaussian	81	(60.4%)
	Rice noise	4	(3.0%)
	White noise	11	(8.2%)
	Noiseless	2	(1.5%)
	Not specified	36	(26.9%)
Seed simulations	Yes	11	(8.2%)
	No	123	(91.8%)
Mechanism to correct simulations	Yes	72	(53.7%)
	No	35	(26.1%)
	No information	27	(20.2%)
Existence of Script	Yes	5	(3.7%)
	No	129	(96.3%)

Discussion

In this paper, we have shown a systematic analysis of works included in the Web of Science and PubMed regarding simulation studies on brain connectivity for fMRI studies, works that studied functional or effective connectivity. The results obtained show a rather erratic behavior in the use of fMRI signal simulators in the sense that there is no recognisable, systematic pattern as to how to approach signal simulations in the case of fMRI data.

Regardless of the general descriptions in Table 3, we think that it is important to point out, as a first observation, that most of the papers reviewed do not provide sufficient information about the simulation procedures in order to know in detail the basis and tools of the approach at hand. This is not only a characteristic of simulation fMRI studies. Carp [20] point out the

lack of methodological information in fMRI studies, and consequently the difficulty to replicate the research. For example, in 17 works the information about how the signal was simulated was not provided, 36 works did not specify the white noise model used, 52 works did not specify the design under which the simulation data had been generated and 129 works did not add the script used to generate the simulation. Thirty-nine studies convolved the time series generated with hemodynamic response function, usually with the gamma function – one of those recommended to generate fMRI data (Erhardt et al. [49]; Welvaert and Rosseel [173]). Eleven of the papers used the Gaussian model. This probabilistic model, however, is not appropriate to generate an fMRI signal because the BOLD signal does not follow a normal distribution (Boubela et al. [13]). On the other hand, some of the authors used an autoregressive function to generate the signal, this could be appropriate because in fMRI the data have serial dependencies. Welvaert and Rosseel [173] recommend simulating fMRI data by following a gamma function or the use of the balloon model proposed by Buxton et al. [18] in order to generate the dynamics of brain activity, used in thirteen of the papers analysed. Complementary to this, the simulation based on the balloon model assumes a model that assumes the capillary volume fixed but the venous volume can change (same as a balloon) with a pressure/volume response curve that may vary. Keeping in mind that this type of simulation appears to be the best fit for the characteristics of fMRI signal, it would seem logical to use it more frequently. Regarding the papers that provide information on the simulation of white noise, in most of them the model used was the Gaussian, the simplest model recommended to add noise to the fMRI signal (Smith et al. [154]; Welvaert and Rosseel [173]).

In any case, despite the difficulty to reproduce the simulations generated in the papers analysed because of the loss of information, 72.4% of the analysed papers do not have information about the toolboxes used to generate the simulations, the works analysed generally meet the objective that the authors had proposed, which is, in general, the adequacy of an analytical strategy, graphical or numerical. Another aspect to highlight is evolution, as the strategies used to generate the simulations. In the early

years researchers simulated only temporal series, while later they convolved these series with the hemodynamic response function to emulate the BOLD signal in the simulated data; and in recent years researchers have been trying to emulate the brain's dynamics using, for example, the aforementioned more complex approach based on the balloon model. It is encouraging to think that, if in the last 15 years, there has been such an evolution, in the near coming years the simulations will be closer to a perfect replication of brain activity working with numerous data points.

As a conclusion we think that the journals could be more accurate as regards the review of simulation studies for the study of brain connectivity in fMRI data, as the papers published so far do not provide sufficient information to replicate the simulation. This is a problem because it reduces the possibility to generate more knowledge in the same line as other authors. Probably the future of the simulations in this field would be related to the use of certain simulation routines created for R software – such as the neuRosim package (Welvaert et al. [172]), that generates pre-processed fMRI data and could include different noise sources (temporal, spatial, physiological, etc.) or likewise, the use of other MATLAB-based toolboxes such as simTB (Erhardt et al. [49]), or The Virtual Brain (TVB) (Ritter et al. [131]; Sanz Leon et al. [142] or Woodman et al. [175]), which is a platform for full brain network simulation.

Simulation studies in the field of fMRI data should be more commonly used because there are many procedures about which we do not know whether they operate efficiently, (e.g. the smoothness process in the pre-processing BOLD signal). The necessity to conduct simulation studies is even more important when we try to analyse effective connectivity because the statistical models used so far, such as the structural equation models (SEM) and their variants, the dynamical causal models (DCM), or the Granger causality models (GCM), have some limitations. For example, one of their most important limitations is that the number of ROIs that can be modelled at the moment is small due to its high computational demands. One further limitation is the serial dependence of the series to analyse, given that some current analysis strategies do not properly take this aspect into account.

We consider it important to remark that, in recent years, the model to conduct simulation studies with an fMRI signal has shifted to the so-called third-generation simulation models. These models generate the brain network activation as a complex dynamic system with inhibitory and excitatory groups of neurons. Some of these generation data follow the balloon-Windkessel model. These models are different from the statistical simulation models based on a sampling distribution of a voxel, or a group of voxels, with different activation as a simple time series, or as a time series convolved to the hemodynamic response function to generate the BOLD signal. Some of the papers studied in this review are examples of simulation works based on the third-generation models, for example Deco and Jirsa [37], Deco et al. [39] or Senden et al. [148], which are a promising perspective in this area as they attempt to model brain activity as the functioning of a complex and dynamic network.

Conclusions

In summary, our systematic review allows us to conclude that, firstly, there exist two different types of simulation studies: dynamic and statistical simulations. In dynamic simulations the authors try to generate the dynamics of the brain activity, while in statistical simulations the authors are, in general, more focused on the time series simulated, but in some cases, they adapt this time series to a hemodynamic function.

Secondly, there is no standard mechanism to simulate data in fMRI studies. As a consequence, we consider it important to unify simulation studies in this area in order to make research more easily reproducible and comparable. This unification should include appropriate reports of the simulation parameters and the simulation algorithm. This unification would lead to certain guidelines in the line of the work by Poldrack et al. [123], which presents certain guidelines to report fMRI studies. So, briefly, in our opinion, it might be interesting that all simulation studies in this area should provide the following information:

- An appendix or a web page or a link to the paper with the simulation script and the characteristics of the parameters of simulation. And also report the toolboxes used to simulate the data.
- Clear identification of the simulation baseline values, sample generation systems and number of simulations done.
- The possibility to determine a reference standard template that allows us to assess the goodness of the simulation. Simulating a brain volume is not the same as simulating a quantitative variable, and maybe the future of simulation in this area is the third-generation simulation, which considers the brain as a complex, dynamic system model. Anyway, the authors must to report in the method section if they are doing a statistical simulation or a dynamic simulation.

Finally, the data and the contributions of this work allow us to elaborate a set of initial recommendations about the simulation procedures to do in fMRI designs. We believe that there exist three fundamental elements that must guarantee: (i) a correct definition of the probability model that incorporates the signal/noise ratio in order to make a true replication of the record conditions with real data; (ii) identify bias corrections that are derived of the lack of a real neuroanatomic model, and so, the simulations must correspond to plausible anatomic processes and substrates, and (iii) the simulated values must correspond to recognisable methodological substrates that could be analysed using the described conventional techniques; because if the simulation processes are used in resting state designs, for example, the signal behaviour is clearly different than if we used an event-related design or a box-car design. These three simple recommendations have a structural character, and jointly with the other recommendations done previously, should allow facilitate replications that at the moment are practically impossible to do in simulated fMRI data. Probably, the main conclusion of this paper is related to the necessity to elaborate consensus guidelines standards to make and report fMRI simulation studies, done by teamwork of experts in this field (task force).

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