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Current Opinion in Systems Biology

On the concept of space in neuroscience

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Abstract

In this paper we study recording of neurons creating spatial information in the brain. To sets of spike trains we associate a topological space which captures the structure of the space in which the movement takes place. This space has an even richer structure depending on other than spatial stimuli. We describe a method to separate the various stimuli and conclude when they describe the structure of the space. We discuss what we should mean by neural space and its structure, and come up with some speculations for the future.

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Current Opinion in Systems Biology 2017, **1**:32–37

This review comes from a themed issue on **Future of systems biology**

Edited by **Arnold Levine**

For a complete overview see the Issue and the Editorial

Available online 10 December 2016

http://dx.doi.org/10.1016/j.coisb.2016.12.002

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Keywords

Neurons, spike trains, place cells, grid cells, persistent homology, dynamic Ising model, neural space, hyperstructure.

What is space? This is a fundamental philosophical and scientific question that crops up in many human intellectual activities. There does not seem to be a unique answer — it depends on the situation in question. Most of the time we think of space as whatever surrounds us — with or without objects. Are objects part of space? How do we perceive space?

Let us briefly look into some alternatives.

Mathematical space

Three dimensional space — our classical space surrounding us and which also may extend to higher dimensions, is closely connected to our notions of space. But in mathematics — geometry and topology — there are many abstract ramifications where also the notion of dimension has been given up. Modern mathematics uses a variety of very abstract notions of space.

Biological space

To various biological activities we may associate "spaces" in which these activities may be analyzed mathematically: genomic space, neural space, cognitive space, perceptive space and evolutionary space. The study of morphogenesis is closely related to geometric and topological spaces.

Neural space

Our intuition tells us that our perception of space is connected to the brain — certain areas and certain activities. In their pioneering work D. Hubel and T. Wiesel [12,13] demonstrated that visual information is encoded in the visual cortex of the brain.

But where in the brain is it being recorded where in three dimensional space we move and how is space itself being encoded in the brain? These questions led to fundamental discoveries by J. O'Keefe [16] and M.-B. Moser and E. Moser [10,15]. They recorded (approximately) single neuron firing patterns in certain brain areas in rats. O'Keefe discovered that in the hippocampus there were cells — called place cells — that fired at specific spots in space. The Mosers discovered cells in the entorhinal cortex — called grid cells — having firing patterns forming a hexagonal grid or lattice when the movement took place in a planar space.

From these experiments we know that the activity of place and grid cells has to do with our perception of space. Furthermore, head direction cells, border cells, etc. have also been discovered and found to play a role in spatial information in the brain.

The experiments produce firing patterns of neurons in the form of spike trains.

Therefore it is natural to form a space of spike trains produced by a suitable collection of neurons. Typically we will obtain a table of spike train data as in Figure 1.

The basic idea is the following. We consider a given collection of spike trains from a set of neurons. This is a finite set. Next we proceed to define a suitable "correlation distance" of spike trains. From this we want to associate topological spaces that can be analyzed by modern topological tools.

In recent years, a new mathematical method has been developed which is called *persistent homology*, see for example [8]. Let us illustrate the method by assuming that we are given a finite set of data with correlations. From this set of data we construct a filtered space and we compute the topological holes measured by homology theory. The invariant we end up with is called "barcodes", persistence diagrams or Betti-curves (see

Figure 1

time / neurons	$\cdots$ t $\cdots$
1	1
2	0
	1
	$\vdots$
	1
	1
$\vdots$	$\vdots$
	0
	0
	1
	$\vdots$
n	1

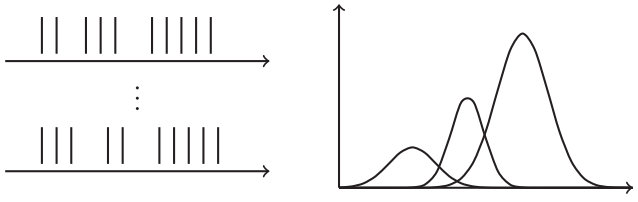
Spike train data.

Figure 2). The barcodes are basically intervals telling us when a "hole" in the space is being born and when it dies, depending on the correlation. We will in the following see how these barcodes capture the shape of the space in which the rat moves and other "cognitive" information used in spatial navigation. For details of this procedure see Appendix A.

The first work in this direction were done by Curto and Itskov [5], later refined in Guisti et al. [9], also interesting simulations are done by Dabaghian et al. [7]. In all these cases the underlying method is that of persistent homology discussing our first two highlight points.

However, it has turned out that neuroscientists have registered that the activity of place cells is being influenced also by more elaborate spatial stimuli like head direction and theta wave modulation. Are there other stimuli influencing place cells like olfactory and sensory stimuli, stress, hunger, cognitive factors, etc. – stimuli relevant for the perception of space and navigation? How can we possibly extract this from the observed data? This is exactly the question we address in the paper [4]. There we develop a method where we can infer away known stimuli from the data, and see if there is more structure left. How do we do this? We will now review the idea of [4].

Figure 2



From spike trains to Betti-curves.

The actual observed (or also simulated) data in the form of spike trains for a certain collection of neurons form a finite space with a correlation metric. To this we can apply persistent homology and obtain barcodes — a structured collection of intervals. Next we can use a generalized dynamic Ising Model from statistical mechanics to construct a model of the various stimuli to be used in simulations.

In this model the firing rates of the neurons at a given time are computed from a Hamiltonian function depending on the external stimuli of previous times. Let us call the external stimuli function for E.

Suppose given E and $E(\text{spatial})$ — the contribution from spatial data — then we compare the persistent homology of the two, and we see that when we infer away there may be still some structure left in the neural space to be accounted for.

Next we may try

$$E = E(\text{spatial}) + E(\text{Head direction})$$

but still there may still be more structure left to be accounted for. One may even add theta wave modulation

$$E = E(\text{spatial}) + E(\text{Head direction}) + E(\text{Theta})$$

and we continue until we have accounted for all known structure by proceeding as follows: take the produced data (observation or simulation), remove the known stimuli, produce new spike trains in the model, and compare with (scrambled) or random data. Since we know from [14] what the persistent homology ("Betti curve") of random complexes look like, we have a simple comparison test to decide whether the data are structured or random, see Appendix B and [4].

Let us summarize the key ideas of this new method:

(1) Start with real (or simulated) data. What are the external stimuli giving rise to the data?
(2) Assume that the external stimuli can be written as

$$E = E_1 + E_2 + \cdots + E_{n-1} + E_n$$

Suppose that $E_1, E_2, \ldots, E_n$ are then via our topological criterion compared with random structure.

(3) If we end up with random structure, we conclude that $E_1, E_2, \ldots, E_n$ have accounted for all the data. There is no more structure left, no more to learn.
(4) If after inferring away $E_1, E_2, \ldots, E_n$ using the model, we are still left with non-trivial persistent homology (non-random), then there must be one or more additional stimuli E_{n+1} causing this deviation.

(5) This is then being reported to the experimental neuroscientists as an indication of doing a new experiment identifying the biological content of E_{n+1}.
(6) We may have to iterate this process several times using the model before reaching randomness — meaning no more structure to be accounted for, hence completely accounting for the data.

This procedure outlines a program to be carried out on real data, and this work has already started, but not yet finished. Simulations indicate, and it seems likely, that the analysis of real data will show that *neural space* as represented by spike trains of place (and similar) cells is much more complex than ordinary geometric three dimensional space.

Our main point is that the present method is very well suited to discover the factors and stimuli involved in our concept of space.

The method described here is quite general and may not only be applied to other spatial cell types, but also to other biological and non-biological situations. Simulations may be found in [4], but the structure of the neural space of spike trains for real data of place cells still remains to be worked out, work in progress. In Appendix A we will describe this general and useful procedure in a more detailed algorithmic way. The method may also be used in studying the activity of brain areas in the form of fMRI data instead of single neuron data.

What about grid cells and the corresponding neural space of spike trains? As far as we know this has not yet been studied. Each grid cell fires in a hexagonal pattern which by symmetry is determined by its fundamental domain which by natural boundary identifications gives us a torus. Hence, Curto has in [6] suggested that a torus is the natural space associated to a grid cell. Analyzing grid cell data with our method remains to be done.

The future

What is a good notion of neural space? How is space perceived by the brain? We have used the term neural space tentatively for the set of spike trains with a correlation "distance", but this may not even be a finite metric space and we have described a procedure of how to associate a proper space to the set of spike trains.

To a given coherent collection of neurons $\mathcal{C}$ — like place cells and grid cells — it is reasonable to suggest that the naturally associated "neural space" is "the space of spike trains" that we have introduced. This space seems to contain more information than the three dimensional surrounding space. Other stimuli also relevant for the description of space and navigation in it are also being captured, and our method describes how to separate them. Furthermore we can test whether we have accounted for all relevant stimuli or whether there are more to be discovered. That is the message to the experimentalists.

Formally, $\mathcal{C} \to \text{Spike}\ (\mathcal{C}) = N(\mathcal{C})$ — "neural space of $\mathcal{C}$".

If experiments have proved that the collection $\mathcal{C}$ is involved in spatial information, one would expect that the structure of $N(\mathcal{C})$ would to give information about how space is perceived in the brain through relevant stimuli.

From existing information it may be tempting to speculate whether there are basically two cell types in the brain involved in spatial perception, extending place and grid cells.

Space cells (like grid cells, border cells,…) would be cells basically recording the intrinsic geometric and topological structure and properties of the surrounding space. We denote the family of space cells by $\mathcal{S}$.

Property cells (like place cells, speed cells, head direction cells,…) recording properties like place and coordinates in space, speed, head direction, etc. needed for navigation in space We denote the family of property cells by $\mathcal{P}$.

Let $(\mathcal{S}, \mathcal{P})$ denote the full family of space related cells.

We suggest the following definition:
Neural space $= N(\mathcal{S}, \mathcal{P})$.

As we have seen this is a richer space than the three dimensional space. Its structure may be studied by the method we have introduced here. Ideally one would like to have simultaneous recordings of $\mathcal{S}$ and $\mathcal{P}$ cells, but this seems to represent an experimental challenge. Is $N(\mathcal{S}, \mathcal{P}) = N(\mathcal{S}) \times N(\mathcal{P})$? Probably just locally. We assume the existence of a "projection" map: $N(\mathcal{S}, \mathcal{P}) \to N(\mathcal{S})$.The inverse image a point in $N(\mathcal{S})$ would be a "property" stalk in the sheaf language mentioned below.

Further challenges from our point of view would be:

Are the cell families $\mathcal{S}$ and $\mathcal{P}$ multitiered? A refined version of our method may be able to stratify the families into tiers, provided suitable data are given including simultaneous cell recordings of a collection of neurons. This would be similar to a type of Hebbian assemblies [11] organized into tiers. We suggest that the more precise structure here is that of an extended hierarchy that we call a hyperstructure, see Appendix C and references [1–3]. If such a structure exists, one should

expect such a multitiered structure of the neural space $N(\mathcal{S},\mathcal{P})$ as well leading to the next question.

Is neural space multitiered and is this how space is perceived in the brain? Why should we expect multiple tiers? Let us suggest one type of argument. Our surrounding space is not empty, it is filled up with simple and complex geometric objects. In describing real space we need a structure to describe objects, collections of objects, collections of collections etc. This kind of binding or gluing structure is offered through a hyperstructure in a sophisticated way.

The point is that if our surrounding space is multitiered, it seems reasonable $\mathcal{S}$ and be $\mathcal{P}$ will be as well in the sense that there will be $\mathcal{S}$ and $\mathcal{P}$ cells operating at each level. Can one detect object cells, object of objects cells, etc., not a cell for each object, but a family for each tier?

Are there level or tier cells? A challenge is to set up an experiment to decide this using the method described here. How does the brain process local data to form global structures? How do we get from spike trains to behavior? A daunting task! This is essentially the neural binding problem, that we addressed in [1]. It seems plausible that in gluing or integrating local information to global, levels or tiers are needed. Furthermore, in Appendix C we point out that there is a mathematical theory doing this, namely sheaf theory extended to multitiered structures. How is this helpful?

In local pieces (open sets) of $N(\mathcal{S})$ $\mathcal{P}$ cells assign properties by a map $N(\mathcal{S})\to N(\mathcal{S},\mathcal{P})$, this is called a presheaf (or a local section of the "projection"). When these data can be glued to global properties we call the assignment a sheaf, and there are precise conditions for this to happen. Not all presheaves are sheaves, meaning that we cannot always go from local information to global. This is meant to formalize in a computational way the fact that when we navigate in space we use properties of many stimuli: olfactory, tactile, visual, etc. and integrate them.

Could it be that the lack of ability to form global spatial information is connected with diseases like Alzheimer? If so, it should follow from calculating the sheaf obstruction from the neural space.

Conclusion

Our main point in this paper is to review the concept of space in neuroscience and describe a method to find out what influences neural space and its structural nature. We present some suggestions regarding the structure of "neural space" and what it may be made of. More experimental data will be needed to figure out the full structure of the general "neural" space — only time will tell what it looks like.

Acknowledgements

I would like to thank my collaborators M.B. Botnan, G. Spreemann and B. Dunn for discussions of the method described here. Furthermore, I would like to thank M. Thaule for his generous help in preparing this manuscript.

Appendix A. The general method

The method used in [4] can schematically be described stepwise as follows, almost like an algorithm.

(1) A finite set of Data (D) of some kind is given equipped with a correlation structure (D,c) where c is defined $c : D\times D\to[0,1]$.
(2) From the Data set to a graph. Let ε be given, then we form a graph as follows: the vertices are the elements of D, if $c(d,d')<\varepsilon$ we assign an edge between d and d'. We denote the graph $G_\varepsilon(D,c)$. Often we take $1-c$ as "geometric distance".
(3) From a graph to a space, see Figure 3. We extend the graph with cliques as in the figure and get what is called a simplicial complex — the clique or flag complex associated to the graph:

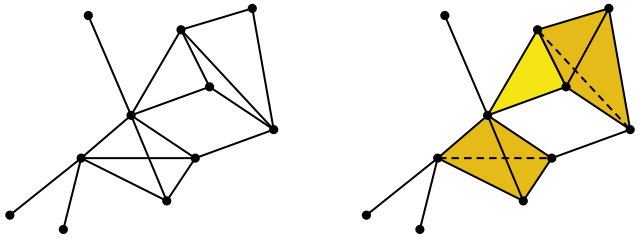
$$G_\varepsilon(D,c)\to\mathcal{S}G_\varepsilon(D,c).$$

(4) Filtered space. By varying ε we now get a chain or filtration:

$$\mathcal{S}G_{\varepsilon_0}(D,c)\subset\mathcal{S}G_{\varepsilon_1}(D,c)\subset\cdots\subset\mathcal{S}G_{\varepsilon_n}(D,c)\;=\;\mathcal{S}G_1(D,c).$$

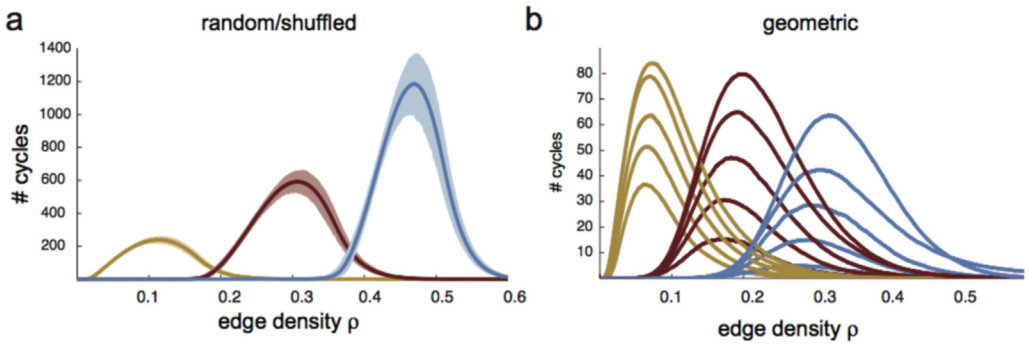
(5) Persistent homology. Taking the homology groups of the spaces in such filtrations gives exactly what is called persistent homology from which we can obtain Betti curves, see Figure 4, [4,9] and Appendix B for more details.
(6) D may depend on various factors, let us call them stimuli $\mathcal{S}_1,\mathcal{S}_2,\ldots,\mathcal{S}_r$. We assume an underlying dynamic model.
(7) We measure the degree of structure in the data by their Betti curves (or alternatively Barcodes or Persistence diagrams).
(8) No structure, then the Betti curves will have the very characteristic form as for random complexes. See Appendix B.
(9) Comparison. Use the method to compare $D(\mathcal{S}_1,\ldots,\mathcal{S}_k)$ and $D(\mathcal{S}_1,\ldots,\mathcal{S}_{k-1})$ to see the degree of structure that $\mathcal{S}_k$ contributes. Clearly structure here means topological structure.

Figure 3



The clique complex of a graph.

Figure 4



Structure (geometric) versus no structure (random).
This figure is collected from [9].

(10) The method described here is very general and may be used in other areas of systems biology and science in general for the analysis of finite data.

Appendix B. Betti curves and random complexes

Persistent homology gives us for each dimension and correlation value, the Betti number, representing the number of holes in the given dimension. Hence, we get a curve describing how the number of holes vary with the correlation, see Figures 2 and 4.

However, if the correlation complex (space) is random, having no structure, it is known from [14] that the Betti curves have a specific shape, see Figure 4.

From a data set we produce its Betti curves and we compare them with the sets for random data. In [4] we give comparison criteria, for example if the quotients of the peak Betti numbers are close to one, we take it as an indication that the complex coming from the data is random and has no structure. The criteria may be refined.

Appendix C. A mathematical speculation

The intuition with respect to our surrounding space would be that the spike trains of space cells give an intrinsic description of the space in question — like a planar region described by a hexagonal lattice or grid or the boundary of a domain, and property cells describe the properties of regions in space including coordinates, head direction, olfactory information, etc.

However, our surrounding space is not empty. It consists of lots of structured objects which after all are structured pieces of space: small planar areas, balls, tori, surfaces, … all put together. But objects may be simple and complex. We need a kind binding (gluing) structure to describe objects, objects of objects and higher collections of objects. This is captured by the notion of a hyperstructure, see [1,2].

Basically a hyperstructure is a structure on a set of basic objects with binding mechanisms forming collections, collections of collections etc. and in such a way that the properties of collections at one level are vital in their binding to form a next level object.

It may therefore be reasonable to assume that the space cells record a hyperstructured geometric collection of our surrounding three dimensional space. Let us denote the hyperstructure by

$$\mathcal{H} = (B_0, B_1, \ldots, B_n).$$

Here the B_i's represent the tiers of objects. We will think of the hyperstructure (hierarchy) of space cells as an extended version of Hebb assemblies in such a way that there are space cells registering objects (B_0), objects of objects (B_1), etc., but not a neuron for each object, etc., just families for each tier recording the appropriate B_i. Grid cells and border cells would be cells registering the B_0 tier.

This suggests two hyperstructures: of neurons and of space objects:

$$\mathcal{H}(\text{neural}) = \{\text{tiers of organized collections of neurons}\}$$

and

$$\mathcal{H}(\text{space}) = \{\text{tiers of organized collections of geometric objects in space}\}.$$

In the brain $\mathcal{H}(\text{space})$ is being created by $\mathcal{H}(\text{neural})$ in such a way that we have

$$\mathcal{H}(\text{space}) \supset \mathcal{H}(\text{neural})$$

as an indexing mechanism in the same way that grid cells give rise to a lattice.

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