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Function follows dynamics, not (only) structure: from neural cultures to flexible information routing in the brain

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Abstract—Structural connectivity, describing actual synaptic connections, contribute to shape spontaneous or induced neural activity generated by neural circuits, both *in vitro* and *in vivo*. However, the resulting dynamics is not fully constrained by structural connectivity and different activity patterns can be generated by a same network, depending on its dynamical state. Beyond structural connectivity, actual influences between neurons in a circuit are described by directed functional connectivity, assessed by means of causal analysis. Thus, structural networks with a rich repertoire of possible dynamics give rise to a multiplicity of functional networks. We illustrate here, resorting to simulations of large networks of spiking neurons, two examples of state-dependent functional connectivity. First we consider a model of a culture of dissociated neurons *in vitro*, undergoing spontaneous switching between bursting and non-bursting states. Second, we consider how multistability between alternative oscillatory coherence modes in mesoscale cortical circuits might underlie flexible functional reconfiguration and information routing.

1. Introduction

Flexible transmission of information is a core feature of biological systems. For instance, the firing activity of neurons conveys information about the external world or internal brain states. Arguably, the correct timing of the exchanged signals is crucial for a correct relay of information through complex networks. A natural device to achieve such temporal coordination might be self-organized synchronization. Oscillatory synchronization, in particular, has been observed in interaction networks arising in very diverse domains. In particular, consistent experimental evidence as been cumulated for the role played in perception and cognition by oscillatory coherence in neural circuits at multiple scales [1, 2]. Notably, according to the “communication-through-coherence” hypothesis [3], information exchange between two neuronal populations is enhanced when the oscillations of their coherent activity is suitably phase-locked with a suitable phase-relation. Therefore the efficiency and the directionality of informa-

tion transmission between neuronal populations is affected by changes in their synchronization pattern, as also advocated by modeling studies [4, 5]. Furthermore synchronization in networks of spiking neurons can arise in many forms, ranging from sparsely synchronized periodic oscillations [6], to low-dimensional chaotic rhythms [7, 8] to temporally-irregular avalanche-like bursting [9].

The circuits of the brain must enact a sweeping amount of functions. How can a flexible control of local computations or global “brain states” be achieved despite the fact that anatomic interconnections are essentially fixed on fast timescales relevant for perception or behavior? In systems neuroscience, a distinction is made between structural and directed functional connectivities [10]. Structural connectivity describes actual synaptic connections. On the other hand, directed functional connectivity is estimated from time-series of simultaneous neural recordings using causal analysis [11], to quantify, beyond correlation, directed influences between brain areas. Here, we revisit recent modeling work [5, 12] showing that even simple structural circuits can give rise to a multitude of “effective circuits”.

We simulate large networks of spiking neurons representing systems at different scales, i.e. synchronously bursting cultures of dissociated neurons [12] and mesoscopic motifs involving brain areas undergoing a coherent oscillatory activity [5]. For both these systems, estimating directed functional connectivity from synthetic activity time-series, we establish that different dynamical states of a network with fixed structural connectivity are associated to functional connectivities with qualitatively different topologies. Finally, we conclude with some free thoughts on the link between structure and function, which is mediated non-trivially by emergent complex dynamics.

2. Functional interactions in bursting cultures

Analysis of neuronal cultures *in vitro* is emerging as a versatile paradigm [13] in the quest for uncovering neuronal connectivity [14] and its interplay with dynamics. Using calcium imaging techniques, the activity of order 10^2 – 10^3 cells in *in vitro* can be simultaneously monitored,

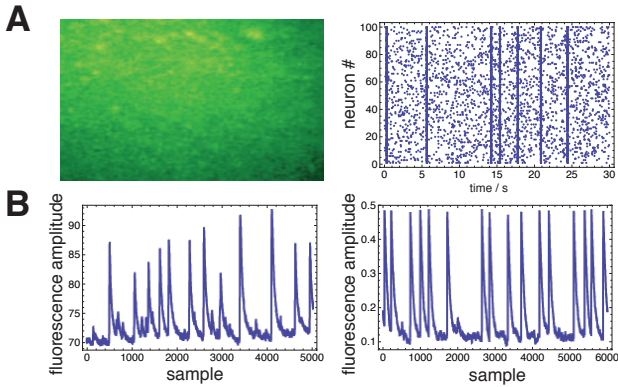


Figure 1: *Bursting neuronal cultures in vivo and in silico.* A: a frame of a calcium imaging movie of the dynamics of a real culture is compared with the raster plot of a simulated network of integrate-and-fire neurons. B: examples of real (left) and synthetic (right) time-series of average calcium fluorescence. Highly synchronous network bursts are manifested by fluorescence peaks, in both experiment and simulations. For details of simulations see [12].

even if with a time-resolution of few tenths of a ms, i.e. slower than the cell’s firing by an order of magnitude. We have introduced in [12] an algorithm for the reconstruction of the connectivity of cultured networks based on calcium fluorescence time-series. Our method is based on Transfer Entropy (TE)[15], an information-theory based generalization of Granger Causality [11]. An important advantage of our approach is its model-free nature, not assuming specific models of neuronal activity or network connectivity and not being constrained to linear interactions between nodes.

To benchmark our reconstruction algorithm we have introduced an *in silico* model of *in vitro* cultures, designed to reproduce the occurrence of temporally irregular switching between states of weak-rate asynchronous activity and states of highly synchronous activity, commonly denoted as “network bursts” [14]. All the details, including simulation parameters, can be found in [12]. Here we briefly mention that we simulated the spontaneous spiking dynamics of networks of excitatory integrate-and-fire neurons, matching typical experimental conditions. Network bursts occur in our model thanks to the introduction of limited neurotransmitter resources [16]. Realistic bursting rates and distributions could be obtained for very diverse structural topologies, notably with arbitrary clustering levels [12]. Synthetic calcium fluorescence time series were then produced based on this spiking dynamics. Figure 1 shows a comparison between real and simulated calcium fluorescence signals. Network bursts are evident in both real and synthetic traces.

We extract then directed functional connectivity based on time-series x_n and y_n of (high-passed) simulated calcium fluorescence, evaluating a generalized TE for every pair of

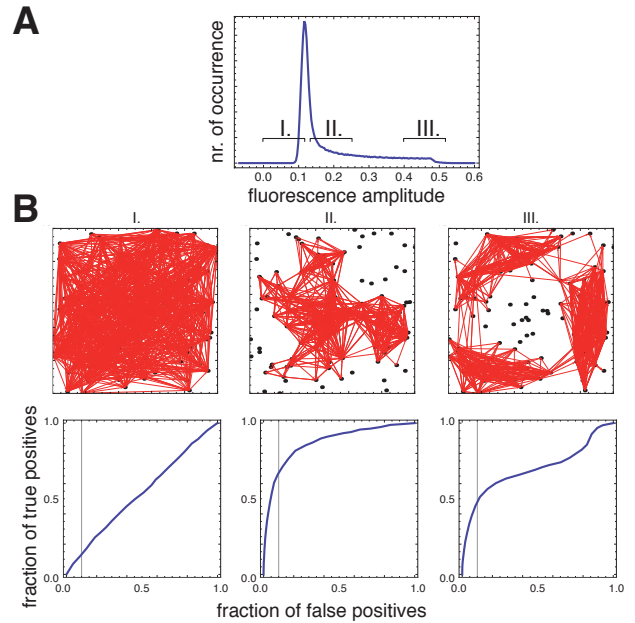


Figure 2: *State-dependency of functional connectivity in simulated cultures.* A: the distribution of mean fluorescence levels g_n presents an initial gaussian rise, followed by a transition region and then by a (initially power-law) tail. B: directed functional connectivity networks retrieved in different dynamical regimes by Transfer Entropy. Also shown are ROC curves for network reconstruction from different dynamical regimes, describing quality of overlap between functional networks and the underlying structural connectivity. A vertical line denotes the position on the ROC curve corresponding to the depicted networks. The considered regimes are: I. Noise-dominated weak rate regime. II. Inter-bursts regime with intermediate firing rate. III. Fully developed bursts regime. See [12] for details.

nodes X and Y :

$$\text{TE}_{Y \rightarrow X}^*(\tilde{g}) = \sum P(x_{n+1}, x_n, y_{n+1}, y_n | \tilde{g}_* < g_{n+1} < \tilde{g}^*) \cdot \log \frac{P(x_{n+1}|x_n, y_{n+1}, y_n | \tilde{g}_* < g_{n+1} < \tilde{g}^*)}{P(x_{n+1} | x_n, \tilde{g}_* < g_{n+1} < \tilde{g}^*)} \quad (1)$$

Our generalized TE differs from its basic formulation in [15] under two main aspects. The first is *instantaneous feedback*, i.e. the appearance of y_{n+1} in equation (1), accounting for possible causal interactions faster than the poor sampling resolution. The second is *conditioning on mean field*, restricted to a range $\tilde{g}_* < g_{n+1} < \tilde{g}^*$, where g_n is the average network fluorescence. Setting a specific range $[\tilde{g}_*, \tilde{g}^*]$ corresponds to a crude way to select a specific dynamical regime. For instance, asynchronous inter-burst periods or synchronous bursting epochs are associated to different mean fluorescence ranges (Figure 2A).

Functional networks associated to different dynamical regimes are obtained by including into the network all

the edges whose generalized TE score is above a certain threshold specified a priori. For synthetic data the overlap between the reconstructed functional network and the known ground-truth structural connectivity can be evaluated for different choices of the threshold, and results of this comparison can be summarized by receiver-operating-characteristic (ROC) curves, for different dynamical regimes. As shown in Figure 2B, functional topologies in inter-burst and in bursting regimes are very different and can be quite different from structural topology.

When considering very low fluorescence level, what we see is essentially noise (Figure 2B, regime I). Correspondingly, links are entered into the reconstructed functional network practically at random, as indicated by a diagonal ROC curve. We consider then intermediate fluorescence levels, associated to an activity significantly above baseline, but not yet elevated as in fully developed bursts. In this inter-bursts regime (Figure 2B, regime II), the retrieved functional network is strongly correlated with the underlying structure, since detected causality reflect primarily the direct influence of pre-synaptic neurons on post-synaptic targets. When bursts are fully developed (Figure 2B, regime III), the network is a critically excitable state, where the firing of a single neuron can trigger an avalanche of firing extending even to neurons not structurally connected to it. In this regime, therefore the retrieved functional network reflects communities of tightly synchronous firing, rather than structural topology. The ROC curve indicates thus a poorer quality structural reconstruction, even if the localization and the extension of synchronous communities continue to be shaped, roughly, by structure (as denoted by a better-than-random ROC curve).

3. Functional interactions in oscillating motifs

Moving then to a larger scale, we simulate structural motifs involving a small number of coupled brain areas. A local area is modeled as a random network of thousands of excitatory and inhibitory spiking neurons. In addition to diluted inhibition and excitation within each area, long-range excitation between areas is also introduced. Details of the model are given in [5], but parameters are selected in such a way that isolated areas undergo a collective oscillation at a frequency of $\sim 40 - 60$ Hz. When connected into a motif, with identical probability of long-range connections in all directions, these locally-generated oscillations engage into phase-locked states. For increasing coupling strengths, these synchronous oscillations can become chaotic leading to perturbation of precise phase-locking. Note that despite the regularity of collective activity, as tracked for instance by average membrane potential (as a proxy for “Local Field Potential”, or “LFP”), individual neurons continue to fire very irregularly (see Figure 3A–C). In such sparsely synchronized states, individual spike trains can be very entropic, i.e. convey potentially large amount of information, even when the ongoing oscillation is periodic.

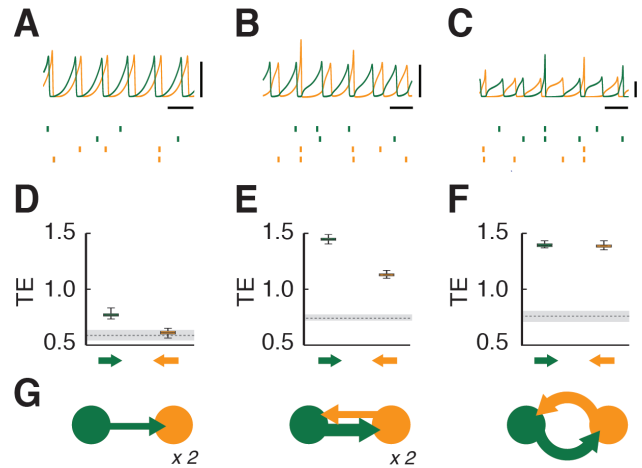


Figure 3: *State-dependency of functional connectivity in simple motifs of interacting populations.* Shown here are dynamical states and resulting directed functional connectivities of a motif of $N = 2$ brain areas structurally connected in a symmetric way. A–C: simulated “LFPs” and spike trains of the two populations for three different strengths of the symmetric inter-areal coupling, leading to more or less regular phase-locked states. D–E: Transfer entropies for the two possible directions of functional interaction, associated to the dynamic states in panels A–C. A grey band indicates threshold for statistical significance of a causal interaction. G: graphic depiction of the functional interactions between the two areas, as captured by Transfer Entropy, in the states that can then be described of effective entrainment (A), leaky effective entrainment (B) and mutual entrainment (C). A multiplier factor indicate multistability between motifs with same topology but different direction. For more details on spiking simulations see [5].

In a broad range of conditions (notably, when local inhibition is strong [7]), populations lock in out-of-phase configurations, in which some areas lead in phase over the others. The symmetry of such phase-locked states is weaker than the structural motif full symmetry. Due to this spontaneous symmetry breaking, anisotropy of functional interactions can then emerge, as revealed by ordinary Transfer Entropy [15] between “LFP” time-series (cfr. Figure 3D–F) or mutual information between spike trains (cfr. [5]).

TE analyses can be summarized in graphical form by drawing the possible “functional motifs” that a given structural motif can generate. In Figure 3G arrows of increasing thickness indicate statistically significant causal interactions of increasing strength. Thus, the net information transfer over a $N = 2$ fully symmetric structural topology can be unidirectional (Figure 3A and D) or bidirectional anisotropic (Figure 3B and E) or balanced (Figure 3C and F), depending on the coupling strength. Furthermore, multistability between motifs with different dominant directionality exists whenever the symmetry of the functional

motif is broken, in such a way that rewiring of directed functional connectivity can be achieved just through suitable transient perturbations to the ongoing oscillations [5].

4. Discussion

The architect Louis Sullivan first popularized a tag line stating that “form follows function”. The two examples just reviewed certainly disclose that “function doesn’t follow structure (trivially)”: functional connectivity can for instance display a clustered community structure (Figure 2) or be strongly anisotropic (Figure 3) even when structural connectivity is homogeneous or symmetric. These examples also showed that “function follows dynamics”, since the properties of the dynamical states supported by a given structure determine the resulting functional connectivities.

Still and all, functional connectivity patterns of whole-brain activity are known to be strongly determined by structure [17]. Note that, in our examples, structure was fixed a priori, but, in nature (or in the dish) networks are shaped by spontaneous growth and eventually, on longer time-scales, evolution. Which is then the optimization goal that self-organized design tries to achieve? We don’t know the answer, but if, as sometimes speculated [18], brain structural topology had developed such to lead to rich repertoires of possible dynamics, it might well be that Louis Sullivan’s motto applies as well to the description of living neural circuits at multiple scales, even if only through an indirect detour involving nonlinear dynamics.

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References

- [1] R. Eckhorn et al, “Coherent oscillations: a mechanism of feature linking in the visual cortex? Multiple electrode and correlation analyses in the cat”, *Biol Cybern*, vol. 60, pp. 121–130, 1988.
- [2] F. Varela, J. P. Lachaux, E. Rodriguez, & J. Martinerie, “The brainweb: phase synchronization and large-scale integration”, *Nat Rev Neurosci* vol. 2, pp. 229–239, 2001.
- [3] P. Fries, “A mechanism for cognitive dynamics: neuronal communication through neuronal coherence”, *Trends Cogn Sci* vol. 9, pp. 474–480, 2005.
- [4] A. Buehlmann & G. Deco, “Optimal information transfer in the cortex through synchronization”, *PLoS Comp Biol* vol. 6, e100934, 2010.
- [5] D. Battaglia, A. Witt, F. Wolf & T. Geisel, “Dynamic effective connectivity of inter-areal brain circuits”, *PLoS Comp Biol* vol. 8, e1002438, 2012.
- [6] N. Brunel, & X. J. Wang, “What determines the frequency of fast network oscillations with irregular neural discharges?”, *J Neurophysiol*, vol. 90, pp. 415–430, 2003.
- [7] D. Battaglia, N. Brunel, & D. Hansel, “Temporal decorrelation of collective oscillations in neural networks with local inhibition and long-range excitation”, *Phys Rev Lett*, vol. 99, p. 238106, 2007.
- [8] D. Battaglia, & D. Hansel, “Synchronous chaos and broad band gamma rhythm in a minimal multi-layer model of primary visual cortex”, *PLoS Comput Biol*, vol. 7, e1002176, 2011.
- [9] A. Levina, J. M. Herrmann, & T. Geisel, “Dynamical synapses causing self-organized criticality in neural networks”, *Nat Phys* vol. 3, pp. 857–860, 2007.
- [10] K. J. Friston, “Functional and effective connectivity: a review”, *Brain Connectivity* vol. 1, pp. 13–36, 2011.
- [11] B. Gourévitch, R. L. Bouquin-Jeannès & G. Faucon, “Linear and nonlinear causality between signals: methods, examples and neurophysiological applications”, *Biol Cybern*. vol. 95, pp. 349–369, 2006.
- [12] O. Stetter, D. Battaglia, J. Soriano, & T. Geisel, “Model-free reconstruction of excitatory neuronal connectivity from calcium imaging signals”, *PLoS Comput Biol*, in press; preprint: arXiv:1201.0732.
- [13] J. P. Eckmann et al., “The physics of living neural networks”, *Physics Reports* vol. 449, pp. 54–76, 2007.
- [14] J. Soriano, M. R. Martinez, T. Tlustý & E. Moses, “Development of input connections in neural cultures”, *Proc Natl Acad Sci U S A*, vol. 105, pp. 13758–13763, 2008.
- [15] T. Schreiber, “Measuring information transfer”, *Phys. Rev. Lett.*, vol. 85, pp. 461–464, 2000.
- [16] M. Tsodyks, A. Uziel & H. Markram, “Synchrony generation in recurrent networks with frequency-dependent synapses”, *J Neurosci* vol. 20, pp. 1–5, 2000.
- [17] C. J. Honey, R. Kötter, M. Breakspear, & O. Sporns, “Network structure of cerebral cortex shapes functional connectivity on multiple time scales”, *Proc Natl Acad Sci USA*, vol. 104, pp. 10240–10245, 2007.
- [18] G. Deco, V. K. Jirsa VK & R. McIntosh, “Emerging concepts for the dynamical organization of resting-state activity in the brain”, *Nat Rev Neurosci* vol. 12, pp. 43–56, 2011.