The emergence of coherent activity in living neuronal networks

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How collective, spontaneous activity emerges in neuronal networks is a fundamental problem both in neuroscience and in statistical physics. It is the ultimate paradigm of complex emergent behavior. Unraveling the mechanisms behind the emergence of spontaneous activity is key to understand more complex phenomena like brain rythms, retinal waves, epileptic seizures and synchronization and communication of distant brain areas[1].

In recent years, the study of well controlled in vitro neuronal cultures as simple model systems of neuronal tissues has emerged as a fruitful complementary approach. The fact that relatively simple neuronal cultures already exhibit rich patterns of activity makes them particularly appealing in the search of general physical organization principles behind collective behavior of neurons.

When neurons are left to grow freely *in vitro*, they create their own network of connections and spontaneouslly reach a coherent state of collective firing in a pattern of nearly periodic giant bursts[2,3] (Fig 1). By combining high-resolution calcium fluoresence imaging with modelling *in silico*, we show that this behavior is controlled by the propagation of waves that nucleate randomly within a set of points that is specific to each culture. Stochastic nucleation is made consistent with highly periodic bursting by the phenomenon of *noise focusing*, a form of implosive avalanche dynamics in integrate-and-fire networks that provides an ultra-fast nucleation mechanism. The resulting scenario challenges previous understanding of spontaenous activity of neuronal cultures while providing a quantitative explanation of the early stages of network self-organization as a noise-driven phenomenon.

Experimentally we studied the initiation and propagation of spontaneous activity in primary cultures of rat cortical neurons. We used high-speed calcium fluorescence imaging to resolve the sequence of neuronal activiation with high spatial (μm) and temporal ($5ms$) resultion. We were able to resolve the temporal sequence of ignition of each neuron and identify those that initiated the activity. The analysis showed that activity starts in a confined group of neurons and later propagates steadily through all the culture. The analysis also showed that prefered ignition zones exist in the culture. We were also able to resolve the statistics of the probability of nucleation in different sites of the culture.

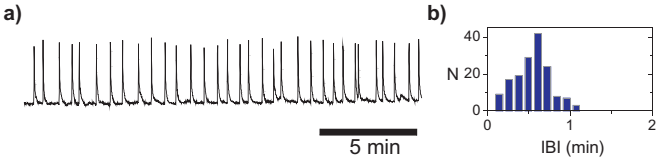

FIG. 1. **a)** Temporal evolution of global bursting activity through calcium imaging (fluorescence intensity in a.u.). **b)** Histogram of the interburst interval (time between two consecutive global bursting events).

Through *in silico* modeling we were able to identify the key factors behind the emergence of spontaneous activity in neuronal cultures. A new mechanism of directed noise amplification which we call *noise focusing* is responsible for the observed behavior. The observed spontaneous activity is a result of a cyclic sequence of: (i) an implosive phase (noise focusing); (ii) an explosive phase (activity propagation); and (iii) a silent phase of network recovery. The bursts appear nearly periodic because steps (i) and (ii) are much faster than (iii). The fast nucleation (i) however, is a nontrivial step that challenges simple statistical analysis, and tracks down novel insights into the interplay between topology and dynamics in directed networks.

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[1] A. G. Blankenship and M. B. Feller, Nat. Rev. Neurosci. **11**, 18-29 (2010).
[2] J. P. Eckmann , O. Feinerman, L. Gruendlinger, E. Moses, J. Soriano and T. Tlusty, Phys. Rep., **449**, 54 (2007).
[3] J. Soriano, M. Rodríguez Martínez, T. Tlusty and E. Moses, Proc. Natl. Acad. Sci. USA, **105**, 13758 (2009).