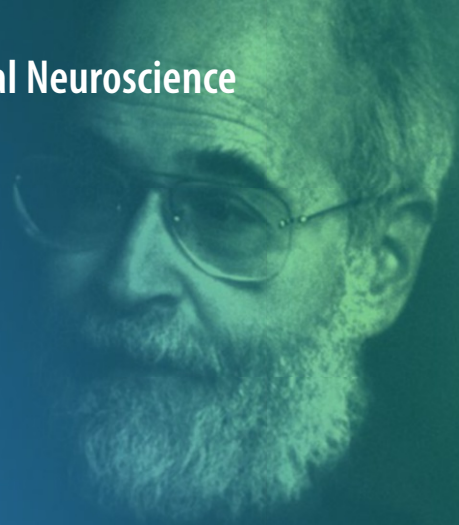


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Editors



Introducing Computation to Neuroscience

Selected Papers of George Gerstein

Chapter 7

Dynamics of Neuronal Interactions



Interactions Between Neurons and with George Gerstein

Ad Aertsen

I first met George Gerstein in the early summer of 1981 when George visited Peter Johannesma, my PhD supervisor at the University of Nijmegen. George and Peter were old friends from the times they both worked on random walk models of single-neuron spiking activities. I used the occasion to proudly present George a copy of my PhD thesis that I had just submitted to the Physics Department a week earlier. Also, I collected all my courage to ask him if he could imagine me doing a postdoc in his lab at UPenn. George's immediate response to my question was typically George, as I would learn later on. Yes, he would be willing to give this a thought, but not before I had not visited his lab plus at least three other labs and tested the waters at each of these.

Thus, later that year, after the defense of my thesis and a vacation with my family following it, I organized my first trip to the USA, to visit George's lab in Philadelphia, plus several other labs at the East and West Coasts. Needless to say that also after these several lab visits, I stuck to my original plan to do my postdoc with George. Since George was kind enough to live with that prospect, we sat down and drafted a plan for my project, both regarding its science and for obtaining funding for it. As it turned out, the first was the easiest, the second quite a bit harder.

The reason I wanted to do my postdoc with George and learn from his expertise with multiple-neuron recordings and their analysis resided in a disappointing finding in my PhD thesis work. There I had studied the stimulus-response relations of neurons in the auditory systems of cats and frogs. Using cross-correlation analysis

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along the Wiener–Volterra framework on nonlinear systems theory, we measured and compared the spectro-temporal receptive fields (STRF) of neurons for different types of acoustic stimuli, including Gaussian white noise, randomized sequences of tones, and a variety of natural sounds (Aertsen and Johannesma, 1981a). Much to our chagrin, however, and in spite of applying the most sophisticated corrections for nonlinearities we could think of at the time, we found that many of the neurons’ receptive fields, especially those of neurons in more central areas, were not stimulus-invariant. That is, receptive fields of neurons determined with one stimulus type, say tones, did not allow us to make meaningful predictions regarding these neurons’ receptive fields determined with another stimulus type, say natural sounds (Aertsen and Johannesma 1981b). After thinking about this negative result for a long time, I had come to the conclusion that we had reached the boundaries of meaningful single-neuron studies. Instead, we needed to study multiple neurons at a time and try to incorporate the presumably nonlinear, stimulus-dependent interactions between these neurons to understand and interpret their receptive field properties under varying stimulus conditions. Having read George’s papers on neuronal interactions and multiple-neuron studies, it was obvious to me that I should turn to his expertise, if I ever wanted to make relevant progress on this ambitious research goal—one that would, in fact, occupy me for the rest of my scientific life.

Having settled the science part, it was time to find funding for enabling me to do this postdoctoral project, that is, to raise enough funding to pay for my salary to help me sustain my small family (my partner Mieke and our daughter Woosje) during this expedition. I soon had to find out, though, that Dutch funding agencies at the time had a peculiar condition for funding a postdoctoral project abroad: funding was only provided to candidates who could provide convincing evidence of a position in Dutch academia after returning from the postdoc. As I could not deliver any such evidence and EU funding did not exist yet at the time, I had to turn to George for help. And, very kindly, George helped me by paying my salary from a newly acquired research grant and by paying for my travel to the USA by inviting me as a speaker to a conference he organized, together with Don Perkel, at Stanford University. In retrospect, I suspect that the unfriendly conditions of the Dutch funding agencies contributed to the fact that, after my postdoc, I never considered returning to the Netherlands.

Having science and funding assured, we now only needed to get my family and me to the USA. Here, a new interesting problem presented itself. Since Mieke and I were not married at the time, my postdoc J1-visum did not allow her and our daughter to come and live with me in the USA. Once again, George helped out: via a befriended Professor of Cultural Anthropology at Haverford College, Mieke magically obtained a J1-visum for an Anthropology research project there. This was one of my first encounters with “fake news” from the USA, but one that helped us tremendously—all in the spirit of George’s motto: “Up the opposition!” When I then inquired, whether we would need any documents to bring our daughter’s cat, George replied that it would be helpful if we could document that our cat did not have any obvious communist inclinations.

Once I arrived in Philadelphia in May 1983, I was given a desk in one of George's lab offices in the Richards Building at Hamilton Walk. I learned that this building was a National Historic Landmark in American architecture, designed by the famous architect Louis Kahn. To be honest, I never perceived it as a landmark. To me, it felt more like a run-down, over-crowded, derelict research building, close to its collapse. But here, I also learned from my fellow students an interesting US technique to control the office temperature: by carefully adjusting and upregulating both the heating and the air conditioning, any desirable temperature could be reached and maintained, irrespective of outdoor conditions—and irrespective of energy demands. Luckily enough, I did not spend too much time in this office and, instead, spent most of my time in George's lab, down in the basement. Here, George had his experimental setup and also his computers. In fact, when I arrived, George had just bought a new big computer from his latest research grant. The first thing he did was to open it up, complain about its terrible design, and start to rewire it from scratch. This took him several weeks, until he was satisfied with its performance. The computer, afterward, never looked the same and remained in a somewhat “opened” condition—but it worked.

During my postdoc with George, I mainly worked on two projects with him. The first was a reasonably straightforward study on the differential sensitivity of cross-correlation analysis of two-neuron spike train recordings for excitatory vs. inhibitory interactions among the recorded neurons in the low firing rate regime, typical for the neocortex (Aertsen and Gerstein 1985). Here, we learned that from analyzing such recordings, excitatory interactions should be much easier to detect than inhibitory ones, determined by the low firing rate regime (in a high firing rate regime, it should be the other way around)—a finding that was supported and also later corroborated by many physiological experiments. In the second project, we followed up on an earlier study by George, together with Judy Dayhoff and Don Perkel, in which they had developed a new method of analyzing spike time correlations between any number N of simultaneously recorded neurons (Gerstein et al. 1985a). In this method, called “gravitational clustering,” they had mapped the problem of finding temporal correlations among the spike times of N neurons into the spatial problem of finding clustering among hypothetical charged particles in an N space, with the time course of the particles' charges being determined by the corresponding neurons' spike time recordings. My contribution to this second project consisted of two parts (Gerstein and Aertsen 1985). First, I played around with different temporal rules of charge assignment, trying to figure out, if such rules could help teasing apart the signatures of different topologies of interactions among the neurons, such as direct connections, shared inputs, and other types of network motifs. Second, in an attempt to go beyond pair-distance analyses, I tried visualizing the particles' trajectories in the N space by studying different (nonlinear) projections onto an appropriately chosen (possibly moving) plane, such that visual inspection of the resulting movies (Fig. 7.1) could possibly help us discerning different patterns of interactions among the neurons. For a more in-depth discussion of the gravitational clustering method, I refer to the chapters in this book by Stuart Baker (Chap. 13, this volume), who later improved the gravitational clustering method and made it

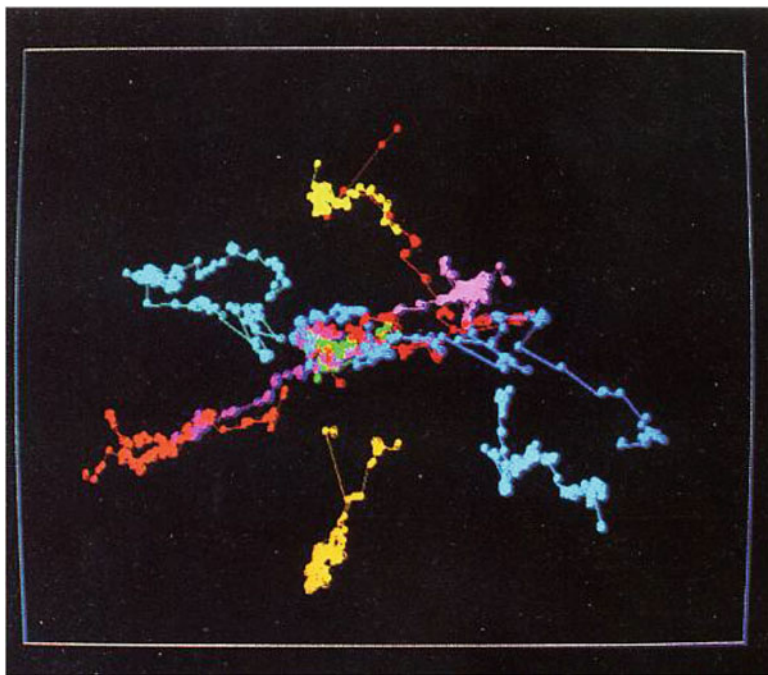


Fig. 7.1 2D projection of the trajectories of 10 particles, representing the spiking activities of 10 simultaneously recorded neurons. The closer the particles at the end of “gravitational clustering,” the more correlated the spiking activities of the corresponding neurons

computationally more efficient, and by Bruce Lindsey (Chap. 5, this volume), who applied the method to his recordings from respiratory networks in the cat brain stem.

After finishing my postdoc with George in August 1984, I returned to Europe, to start my own group in the lab of Valentino Braitenberg at the Max Planck Institute in Tübingen. Here, among other things, I continued to work on the gravitational clustering approach, trying to apply it to multiple-unit recordings from monkey visual cortex, made by Jürgen Krüger in Freiburg and, together with Tobias Bonhoeffer, my first PhD student in Germany, studying the clustering dynamics by trying to normalize the correlation dynamics for stimulus-induced spike rate variations of the neurons recorded from. In the course of this study, we found that the math of the gravitational clustering rules could be relatively simply mapped onto the evolution of a neuronal network connectivity matrix, subject to a Hebbian plasticity rule. The results of this study, both the theoretical findings and the results from analyzing the monkey recordings, we published in the *Proceedings Book of a beautiful conference in Naples and Amalfi* (Aertsen et al. 1987), organized by Eduardo Caianiello (according to Valentino, his co-organizer, financed by whitewashed Mafia funds). We also discovered that publishing our results this way helped to ensure that nobody ever noticed our insightful findings.

Meanwhile, the confounding effects of stimulus- and behavior-induced nonstationarities of neuronal firing rates on correlation-based measures of their interactions kept bothering me. It was obvious that these interactions were dynamic, but how to separate the interaction dynamics from the individual neurons' firing rate dynamics? I tried several things but did not really make much progress. Then, in the autumn of 1986, George Gerstein joined us in Tübingen, for a sabbatical year in Valentino's lab—and we decided to make this a main issue. Building on his earlier work with Don Perkel, on drawing two-dimensional raster displays of the joint spiking of pairs of neurons (Gerstein and Perkel 1969, 1972), we developed a technique to quantify such joint spiking diagrams and, more importantly, to normalize the observed “raw” correlations for any underlying stimulus- and/or behavior-induced modulations of the neurons' firing rates (Aertsen et al. 1989). The result we called the Joint-PST (Fig. 7.2), a 2D histogram, also in reference to the PST (the Peri-Stimulus Time histogram), developed many years earlier by George and Nelson Kiang to capture the single-neuron spiking dynamics in response to a sensory stimulus (Gerstein and Kiang 1960). To evaluate the significance of features in the JPST histogram, we used a measure called “surprise.” This was originally introduced into neuroscience by Charles Legédy and further developed by my Tübingen colleague Günther Palm.

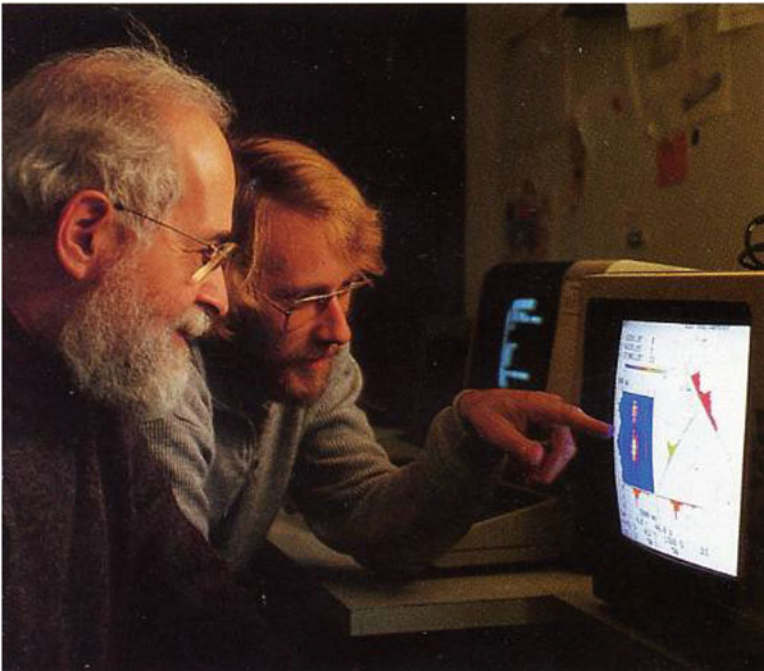


Fig. 7.2 George Gerstein (l.) and Ad Aertsen, inspecting early results of Joint-PST analysis of spike trains from two simultaneously recorded neurons. Picture taken early 1987, during the sabbatical year of George at the MPI for Biological Cybernetics in Tübingen

In fact, during George's sabbatical in Tübingen, the three of us together wrote a paper on how to measure the statistical significance of spike correlations (Palm et al. (1988); for further details I refer to Günther's Chapter in this book). Finally, to make sure that George also had some hardware to play with in Tübingen, Andreas Kreiter set out to build a real-time single-board spike sorter, in his Diploma thesis project under George's and my supervision (Kreiter et al. 1989).

We applied the Joint-PST in a number of studies, first on recordings from simulated networks to calibrate its performance, and then on various sets of experimental data from in vivo spike train recordings. However, it took me until 1991, during a sabbatical year in the labs of Eilon Vaadia and Moshe Abeles at the Hebrew University in Jerusalem, to make a convincing case for truly dynamical, stimulus- and behavior-dependent neuronal interactions in the brain of an awake, behaving monkey (Aertsen et al. 1991)—a result we were very excited about, but which took us several more years to get it decently published (Vaadia et al. 1995).

Also after this sabbatical year in Tübingen, George and I remained in close contact. Thus, he spent several extended research visits in my lab, first at the Weizmann Institute in Israel (a visit he combined with a longer stay in Moshe Abeles' lab at the Hebrew University, where they continued their search for repeating spike patterns, see Moshe's Chapter in this book), and later also at the University of Freiburg, after I moved there in 1996. Over the years, I was fortunate enough to be able to write several more papers and book chapters with George (Aertsen et al. 1986; Aertsen and Gerstein 1991; Gerstein et al. 1985b, 1989). I remember each of them with fondness and as a privilege to be able to interact with an incredibly creative and rigorous mind. I am grateful for this—and I miss him.

References

- Aertsen AMHJ, Gerstein GL (1985) Evaluation of neuronal connectivity: Sensitivity of cross-correlation. *Brain Res* 340(2):341–354. [https://doi.org/10.1016/0006-8993\(85\)90931-X](https://doi.org/10.1016/0006-8993(85)90931-X)
- Aertsen AMHJ, Gerstein GL (1991) Dynamic aspects of neuronal cooperativity: Fast stimulus-locked modulations of 'effective connectivity'. In: Krüger J (ed) *Neuronal cooperativity*. Springer series in synergetics, vol 49, pp 52–67. https://doi.org/10.1007/978-3-642-84301-3_4
- Aertsen AMHJ, Johannesma PIM (1981a) The spectro-temporal receptive field: A functional characteristic of auditory neurons. *Biol Cybern* 42(2):133–143. <https://doi.org/10.1007/BF00336731>
- Aertsen AMHJ, Johannesma PIM (1981b) A comparison of the spectro-temporal sensitivity of auditory neurons to tonal and natural stimuli. *Biol Cybern* 42(2):145–156. <https://doi.org/10.1007/BF00336732>
- Aertsen A, Gerstein GL, Johannesma P (1986) From neuron to assembly: Neuronal organization and stimulus representation. In: Palm G, Aertsen A (eds) *Brain theory*. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-642-70911-1_3
- Aertsen A, Bonhoeffer T, Krüger J (1987) Coherent activity in neuronal populations: Analysis and interpretation. In: Caianiello ER (ed) *Physics of cognitive processes*, vol 42. World Scientific Press, Singapore, pp 1–34
- Aertsen AM, Gerstein GL, Habib MK, Palm G (1989) Dynamics of neuronal firing correlation: modulation of "effective connectivity". *J Neurophysiol* 61(5):900–917. <https://doi.org/10.1152/jn.1989.61.5.900>

- Aertsen A, Vaadia E, Abeles M, Ahissar E, Bergman H, Karmon B, Lavner Y, Margalit E, Nelken I, Rotter S (1991) Neural interactions in the frontal cortex of a behaving monkey: Signs of dependence on stimulus context and behavioral state. *J Hirnforsch* 32(6):735–743
- Gerstein GL, Aertsen AM (1985) Representation of cooperative firing among simultaneously recorded neurons. *J Neurophysiol* 54(6):1513–1528. <https://doi.org/10.1152/jn.1985.54.6.1513>
- Gerstein GL, Kiang NS (1960) An approach to the quantitative analysis of electrophysiological data from single neurons. *Biophys J* 1(1):15–28. [https://doi.org/10.1016/s0006-3495\(60\)86872-5](https://doi.org/10.1016/s0006-3495(60)86872-5)
- Gerstein GL, Perkel DH (1969) Simultaneously recorded trains of action potentials: Analysis and functional interpretation. *Science* 164(3881):828. <https://doi.org/10.1126/science.164.3881.828>**
- Gerstein GL, Perkel DH (1972) Mutual temporal relationships among neuronal spike trains: Statistical techniques for display and analysis. *Biophys J* 12(5):453–473. [https://doi.org/10.1016/S0006-3495\(72\)86097-1](https://doi.org/10.1016/S0006-3495(72)86097-1)**
- Gerstein GL, Perkel H, Dayhoff E (1985a) Cooperative firing activity in simultaneously recorded populations of neurons: Detection and measurement. *J Neurosci* 5(4):881–889. <https://doi.org/10.1523/JNEUROSCI.05-04-00881.1985>
- Gerstein GL, Aertsen A, Bloom M, Espinosa I, Evanczuk S, Turner M (1985b) Multi-neuron experiments: Observation of state in neural nets. In: Haken H (ed) *Complex systems - Operational approaches*. Springer, Berlin, Heidelberg, pp 58–70
- Gerstein GL, Bedenbaugh P, Aertsen AMHJ (1989) Neuronal assemblies. *IEEE Trans Biomed Eng* 36(1):4–14. <https://doi.org/10.1109/10.16444>**
- Kreiter AK, Aertsen AMHJ, Gerstein GL (1989) A low-cost single-board solution for real-time, unsupervised waveform classification of multineuron recordings. *J Neurosci Methods* 30(1):59–69. [https://doi.org/10.1016/0165-0270\(89\)90075-7](https://doi.org/10.1016/0165-0270(89)90075-7)
- Palm G, Aertsen AMHJ, Gerstein GL (1988) On the significance of correlations among neuronal spike trains. *Biol Cybern* 59(1):1–11. <https://doi.org/10.1007/BF00336885>
- Vaadia E, Haalman I, Abeles M, Bergman H, Prut Y, Slovin H, Aertsen A (1995) Dynamics of neuronal interactions in monkey cortex in relation to behavioural events. *Nature* 373:515–518. <https://doi.org/10.1038/373515a0>