Published in final edited form as:

J Neural Transm Suppl. 2009 ; (73): 121–128.

Chaotic versus stochastic dynamics: A critical look at the evidence for nonlinear sequence dependent structure in dopamine neurons

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Summary

The firing pattern of midbrain dopamine neurons is thought to have important behavioral consequences. Although these neurons fire regularly *in vitro* when deprived of their afferent inputs, they usually fire irregularly *in vivo*. It is not known whether the irregularity is functionally important, and whether it derives from intrinsic properties of dopamine neurons or network interactions. It is also not known whether the irregular firing pattern is fundamentally stochastic or deterministic in nature. Distinguishing between deterministic nonlinear structure associated with chaos and other sources of structure including correlated noise is an inherently nontrivial problem. Here we explain the geometric tools provided by the field of nonlinear dynamics and their application to the analysis of interspike interval (ISI) data from midbrain dopamine neurons. One study failed to find strong evidence of nonlinear determinism but others have identified such structure and correlated it with network interactions.

Keywords

Nonlinear dynamics; chaos; forecasting; correlation dimension

Introduction

Chaos (Strogatz 2000) is a mathematical term denoting activity patterns that appear to fluctuate randomly, and that arise from a sensitive dependence on initial conditions in a completely deterministic system, meaning that there is no noise or probabilistic component to the describing equations. Interest in chaotic firing patterns in dopamine neurons stems from a theory (King et al., 1984) that the equations that describe a model of the firing rate of dopamine neurons in the intact basal ganglia can enter chaotic regimes based upon the synthesis, effectiveness, and availability of dopamine at postsynaptic sites in the striatum. The major influences on the firing rate in this model were the level of external depolarizing input, the short inhibitory feedback loop mediated by local release of dopamine within the nigra acting at rate-modulating autoreceptors, and the long feedback loop mediated by feedback GABAergic inhibition from the striatum. A major nonlinearity was introduced into the system via the U-shaped dependency of dopamine synthesis in striatal terminals upon

impulse-dependent dopamine release, such that either decreases or increases in the firing rate could increase synthesis. The complexity of the system was increased by a long (20–30 minute) delay between changes in dopamine firing rate and changes in dopamine synthesis in the presynaptic terminals in the striatum. Chaotic dopamine neurodynamics (King et al 1984) were postulated to be responsible for the reported fluctuations in mood, attention, and activity in patients with schizophrenia, including delusions (Shaner 1999) as well as for the “On-Off” phenomenon in Parkinson’s disease.

In the King model, chaos was postulated to arise substantially from network influences on the firing rate of dopamine neurons, not from the intrinsic currents in dopamine neurons themselves, and was postulated to be detrimental to the contingent reinforcement attributed to dopamine signaling. However, dopamine neurons are capable of intrinsic pacemaking (Fujimura and Matsuda 1989; Grace and Onn 1989; Harris et al 1989; Kang and Kitai 1993; Yung et al. 1991) and are also capable of bursting in the presence of synaptic input *in vivo* (Grace and Bunney 1984b; Freeman et al. 1985) or pharmacological manipulations *in vitro* (Johnson et al. 1992; Ping and Shepard 1996). Single neurons that can exhibit both bursting and pacemaking are also capable of generating chaotic firing patterns without network involvement (Canavier et al 1990, Canavier et al 1993). Furthermore, it has been suggested that rather than being detrimental to certain computations, complex system dynamics on the edge of chaos may actually enhance them (Bertschinger and Natschlager 2004). Distinguishing between chaos and stochastic dynamics in electrophysiological data is difficult for two reasons. The first is that real time series are always contaminated by noise, hence there is an inevitable stochastic contribution. Second, in an electrophysiological context, information transmitted to downstream regions in general does not consist of a continuous times series, but rather of series of inter-event intervals called inter-spike intervals (ISIs) between action potentials.

Dopamine neurons *in vivo* can fire in a single spike mode or a bursting mode (Grace and Bunney 1984ab), but *in vitro* generally fire in a regular pacemaker-like pattern (Fig. 1A1). The application of the small conductance (SK) potassium channel blocker apamin to dopamine neurons in a slice preparation (Fig. 1A2) can cause them to fire less regularly (Ping and Shepard 1996), approximating the firing pattern *in vivo* more closely (Fig. 1B). Here we will examine the evidence for nonlinear sequence dependence of these intervals of dopamine neurons both in relative isolation and within a network context.

Methodological Approaches and Considerations

Dynamical Systems and Attractor Reconstruction

A dynamical system (Strogatz 2000) is one that changes in time. A deterministic dynamic system is completely specified by a set of state variables. Membrane potential is an example of a state variable for a neuron, but there are others that can be more difficult to observe, such as ionic concentrations or fractional activation or inactivation of ion channels. Each variable has an associated equation for the rate of change of that variable; the rate of change is measurable as the slope of a plot of the variable versus time. By definition, the rate of change of a variable can only depend on its own state and that of the other state variables. In all deterministic dynamical systems, the entire future time course of a solution can be

completely and uniquely determined by specifying a value for each of the state variables; these values are termed the initial conditions. In a linear system, the rate of change can only depend on the sum of the state variables, each scaled by a constant. The solution trajectories for each state variable are limited to some combination of exponentials with possibly complex exponents, such that the solutions either decay to a fixed point at the origin, blow up to infinity, or produce oscillations like sine waves. In a nonlinear system, the form of the dependencies of the rates of change of the state variables on other state variables is not constrained, and the possible solutions are therefore much richer. These solutions include a chaotic attractor in the state space in which the time course of the future trajectories on nearby points locally diverge exponentially from each other. However, the trajectories do not leave the attractor surface, which results in a complex fractal structure for the attractor and a sensitive dependence of the solution trajectories on initial conditions, which are the hallmarks of chaos. The fact that nearby initial conditions result in future time courses that are very different limits the predictability of the system. After the specification of initial conditions, the time window over which a prediction can be made that is better than simply using the mean value of the time series as a prediction is called the short term prediction horizon. In a chaotic system, the accuracy of the best possible prediction falls off exponentially in time. This follows because the state of a system can only be known with finite precision, and even slightly different initial conditions produce very different solutions after enough time elapses.

A time series is a series of observations of a state variable of the system. Given a stationary time series that is sufficiently long and sufficiently noise-free, an analog of the geometric attractor on which the dynamics in the full state space of the original system reside can be reconstructed (Packard et al 1980) in a state space formed entirely from observations of a single variable by creating points in a new state space in which the first coordinate is the observation itself and the remaining coordinates are delayed versions of an observation in the time series. The delay is called the lag, and the number of points is the embedding dimension. The lag is usually determined by the first zero of the autocorrelation function or of the mutual information (Kantz and Schreiber 1990). Each successive coordinate is the observation one additional time lag into the past. The embedding dimension is determined by trial and error, such that increasing it by one does not significantly affect the results. In other words, points that are nearby at a low value of the embedding dimension may no longer be neighbors as the embedding dimension is increased, which indicates that the estimate of the embedding dimension was initially too low. If the embedding dimension is increased beyond the optimum, the quality of the attractor (and the resulting nonlinear forecasting, see below) also degrades in a noisy environment (Yunfan et al 1998).

Correlation dimension

Given a reconstructed attractor, the correlation sum is the number of points that fall within a certain radius of each point, summed over all points and divided by the possible number of pairs of points. The slope of the logarithm of the sum as a function of the logarithm of the radius gives an estimate of the correlation dimension. If a three dimensional object, for example, is sampled at scales that are small relative to the object such that the balls of radius r generally fall within the object, the correlation sum should be proportional to the volume at

a given radius. Since the volume is proportional to r^3 , the logarithm of the sum should scale as $3 \log r$, hence the estimate of dimension should be approximately 3, which conforms to our intuition. The slope will be invariant only in a certain range of length scales, because very large scales sample regions that are not confined to the attractor, and very small scales may be smaller than the resolution between points and also sample the inherent measurement noise. For a chaotic attractor, the dimension will be fractal rather than integral, but may be low dimensional despite the apparent complexity. On the other hand, purely stochastic, or noisy, system will be infinite dimensional. One caveat is that the correlation dimension is best suited to quantify self similarity, or fractal dimension, when self similarity is known to be presented, and is much less suited to the task of establishing the low-dimensionality of a data set (Kantz and Schreiber 1999). This measure is very sensitive to nonstationarity in the data and to insufficient sampling. Another weakness is that points that are nearby in time are also nearby in the state space, but not as a result of geometrical structure but simply due to temporal contiguity, thus these points must be excluded from the correlation sum (Theiler 1986). This is frequently not done in practice, casting doubt upon the validity of some published results. In addition, the range of values of r for which the slope of the correlation sum as a function of the radius is constant should be invariant across a range of embedding dimensions above a minimum dimension in order to make a convincing case that the estimate is reasonable (Kantz and Schreiber 1999). The presence of noise can destroy the stable plateau of the scaling region in which the slope is invariant (Yunfan et al 1998). Furthermore, filtered noise can be incorrectly identified as low-dimensional based on the correlation dimension (Osborne and Provenzale 1989; Rapp 1993; Rapp et al 1993). Therefore additional methods are required to establish the presence of chaos or low dimensional nonlinear structure.

Nonlinear forecasting

A geometric attractor which has been reconstructed as described above can also be used to exploit the nonlinear dynamics inherent in the time series in order to forecast the evolution of the time series at each point into the future (Farmer and Sidorowich 1979). The data can be divided in two, such that part of the data is used to construct the attractor, and the other part is used to test the accuracy of the forecasting method. At a minimum, the point to be predicted and points that are close in time to it should be excluded from the prediction. The data that was not used to construct the attractor is also used to construct points with coordinates determined by the time lag and embedding dimension. For each point in the test set, the nearest neighbors on the reconstructed attractor are identified, and the weighted average of each point in their known future trajectories is used to estimate the future trajectories of the test points. Then the correlation coefficient between the actual and predicted future observation is used to quantify the accuracy of the prediction. In the studies described in this chapter that generated forecasts using the ISI series directly, an embedding dimension of 4 and a time lag of 1 was used in all cases unless otherwise noted.

ISI series versus a time series

An ISI series is not strictly a time series. ISI series from dopamine neurons are generated using a threshold crossing model, the ISIs are the intervals between the times that the membrane potential crosses a threshold in membrane potential from below. The time

intervals between threshold crossings are not sufficient to reconstruct the full attractor, but may be sufficient to reconstruct a rough analogy to a Poincare section with a dimension one less than the original attractor (Castro and Sauer 1997; Hegger and Kantz 1997). The application of attractor reconstruction methods which were developed for time series to ISI data, is only valid when the ISIs are shorter than the short-term prediction horizon (Racicot and Longtin 1997) and when the threshold used to generate the interspike interval times captures the relevant time scales of the underlying dynamics (but see Kaplan et al 1996 for a case when subthreshold dynamics were essential). This caveat also applies to the use of the correlation dimension and nonlinear forecasting methods that are based on attractor reconstruction. Several studies that address the feasibility of attractor reconstruction from an ISI series did not address the threshold crossing mechanism for generating ISIs, but rather attempted to reconstruct an input signal to an integrate and fire model (Sauer 1994 and 1997), which is a distinct problem.

Lovejoy et al 2001 and Canavier et al 2004 generated an approximate time series called a spike density function (SDF) from the ISI sequence by superimposing a Gaussian window at each spike time (see Fig. 2A). The purpose of this manipulation was to obtain a time series in order to determine whether its predictability fell off exponentially as would be expected of a chaotic time series. This exponential falloff would not be expected to be observable in an ISI series unless all ISIs were of similar length such that the ISI number index is a reliable measure of time. Figure 2 uses a noiseless model system (Plant and Kim 1976) to illustrate the approximate time series recovered from the spike train, seen as a comb plot on the y-axis, for a repetitively spiking pacemaker regime (Fig. 2A1) and a known chaotic regime (Fig 2B1). The top trace illustrates the mechanics of attractor reconstruction for the pacemaker. The time sequence of the points labeled x1, x2 and x3 is shown in Fig. 2A1 and the corresponding point on the simple geometric attractor corresponding to repetitive periodic activity is shown in Fig 2A2. The more complex waveform for simulated chaos is shown in Fig. 2B1 and the correspondingly more complex attractor is shown in Fig. 2B2.

Surrogate Data

The key to determining whether a time series or ISI sequence contains dynamic nonlinear structure is to isolate the amount of predictability that is due to nonlinear dynamics, and not to linear structure (autocorrelations) or static nonlinearities. This is accomplished by manipulating the original data to produce surrogate data sets that preserve the linear structure as well as any static nonlinearities, but destroy any nonlinear dynamical structure. The null hypothesis is that the time series (or ISI series) was produced by linear system with additive noise, and that the amplitude was then scaled nonlinearly to produce the observed time (or ISI) series. This nonlinearity is called static because it is not dependent on the temporal history, but only on the instantaneous value of the underlying linear system. These surrogates are known as Gaussian surrogates (Theiler et al 1992) and are produced as follows. First a set of Gaussian deviates are generated, and arranged in the same rank order as the original data series. Then the Fourier transform is applied to the rank ordered Gaussian deviates. The phase of the transform is randomized, then the inverse transform of the phase-randomized transform is computed. The original data is then shuffled so that its rank order corresponds to that of the inverse transform of the phase randomized Gaussian

deviates. This preserves the underlying linear autocorrelation structure of the data as well as any static nonlinearities, but destroys any sequence dependent information. Any statistical analysis of whether predictability is due to nonlinear dynamical structure must arise from comparison of the predictability of the actual data compared to surrogate data that controls for predictability due to other sources, such as nonlinear structure.

The surrogate data can be used to estimate a z-score (Thieler et al 1992) $(Q - \mu)/\sigma$ for an observable (Q) by using the mean (μ) and standard deviation (σ) of the surrogates, which can be used to find p values under an assumption of Gaussian distribution, or more rigorously, using a nonparametric method to determine the distribution of the statistic nonlinearity in the surrogate data. There are potential problems with this type of surrogate data, such as end effects (Schreiber and Schmitz 2000) and mismatches between discrete frequencies in a Fourier series and the fundamental frequencies of nearly periodic time series (Stam et al 1998). Another type of surrogate data that preserves both linear and static nonlinear structure is simply to reverse the order of the time series or sequence (Stam et al 1998) but this one manipulation is not sufficient to generate sufficient surrogates to use the statistical method described above.

Survey of Literature Results

Nonbursting dopamine neurons

In order to determine whether dopamine neurons were intrinsically capable of generating chaotic firing patterns, Lovejoy et al 2001 examined ISI data from substantia nigra pars compacta dopamine neurons both in a slice preparation treated with the small conductance (SK) potassium channel blocker apamin and from irregularly firing neurons recorded extracellularly *in vivo* in anesthetized rats. The hypothesis underlying this work was that the irregular firing pattern observed *in vivo* results from modulation of the SK current in the intact animal, and this firing pattern could best be mimicked *in vitro* by reducing the level of SK conductance (see Fig. 1). Note that the distributions of the ISIs *in vitro* in the presence of 300 nM apamin (Fig. 1B1) and in irregularly firing neurons recorded *in vivo* (Fig. 1B2) are reasonably similar. Since the focus was on irregular firing and not on bursting, only records that contained fewer than six bursts of three or more spikes (burst defined as in Grace 1984b) in a total of 1000 ISIs and fewer than 2% doublets were examined. Lovejoy et al (2001) generated a time series from the ISI data as described above and made iterative forecasts by predicting the time course starting from each observation in the half of the data set not used to generate the attractor for as far into the future as the data allowed. The prediction error increased exponentially in time as expected for a chaotic time series. However, these results were not compared to surrogate data generated from the original ISI series. Canavier et al (2004) made such a comparison using surrogates created from randomly shuffled ISIs, which destroys all temporal structure, not just the dynamic nonlinear structure as in the Gaussian scaled surrogates described earlier. We found that the prediction error did indeed scale exponentially in time for the original data, as evidence by an initial straight line on a semi-log plot of prediction error for both the *in vitro* (Fig 3A, open squares) and *in vivo* data (Fig 3B, open squares). The prediction error was quantified in bits (Wales 1991) as $\log_2[1-\rho]$ bits, where ρ is the Pearson's correlation coefficient between

the predicted and actual SDF. However, so did the prediction error for the randomly shuffled intervals in which all temporal sequence structure was removed. Therefore the apparent exponential scaling was an artifact of the creation of the SDF using a Gaussian window, which introduced spurious predictability into the time series, combined with the ISI distributions of the irregularly firing dopamine neurons (Fig 1B). The distribution of the ISIs apparently limits the falloff in predictability compared to that of Poisson-distributed intervals, which do not produce SDFs that exhibit exponential falloff (Lovejoy et al 2001). The SDF method was robustly able to detect chaos (Canavier et al. 2004) in a model known to be in a chaotic regime, so its inability to detect chaos in the experimental data may simply mean that the data is too noisy or that ISIs do not allow for adequate sampling of the system dynamics.

All other studies on nonlinear forecasting in dopamine neurons forecast directly from the ISI series without creating the SDF, and forecast only one ISI into the future. Since the SDF method did not give conclusive evidence of chaotic structure, predictions using this methodology and the random Gaussian surrogates described above were then applied. The null hypothesis that the data were produced by a linear process with additive Gaussian noise and a static nonlinearity was rejected for four of five neurons *in vitro* and two of nine neurons *in vivo*. The Spearman rank correlation coefficients (r_s) between the predictions and the actual ISIs were 0.386 ($p < 0.0001$), 0.381 ($p < 0.005$), 0.311 ($p < 0.015$) and 0.255 ($p < 0.0003$) for the *in vitro* records that differed significantly from the Gaussian scaled surrogates, and 0.13 ($p < 0.005$) and 0.16 ($p < 0.0001$) for the *in vivo* records. The use of time-reversed records produced mixed results, producing correlation coefficients similar to the original data for the *in vitro* records, but values in the range of the surrogates for the *in vivo* records. Overall, the evidence from this study for nonlinear sequence dependent structure was not compelling.

Bursting dopamine neurons: Basal nonlinear sequence dependence and the effect of forebrain hemisection

Hoffman et al (1995) recorded ISIs from substantia nigra pars compacta dopamine neurons in unanesthetized rats in low *cerveau isole* preparations in order to detect basal nonlinear sequence dependent predictability. The basic questions addressed by this study and the subsequent one described below were as follows. Does the nonlinear structure of DA neuron ISIs arise primarily from burst associated properties of the neuron itself or from the temporal organization of its synaptic inputs? In contrast to Canavier et al., (2004) which excluded neurons that exhibited too many bursts, Hoffman et al., (1995), excluded data with too few bursts, as the records examined were required to have more than ten bursts in 2100 or 2400 ISIs. They obtained a r_s of 0.25 ± 0.09 for fifteen cells, and ten differed significantly from their Gaussian-scaled surrogates ($p < 0.0005$). However, the specific cells identified as being significantly different were not entirely consistent when results from embedding dimensions of 4 and 7 were compared. The correlation dimension identified the dimension of 9 of 15 cells as being significantly different from their controls, but there was no correlation between the z-scores obtained for nonlinear forecasting and correlational dimension, which casts doubt on the correlational results because forecasting is the more robust measure (Yunfan et al 1998). The authors referred to the correlation dimension as correlational

complexity instead of dimension, and noted that in their study, this quantity was highly sensitive to embedding dimension. This sensitivity also decreases confidence in the meaning of this measure (see *Correlation Dimension*, above) in the context of nonlinear dynamics. Bursting did not differ significantly between the surrogates and the actual data, which indicates that bursting alone is not the primary source of nonlinear structure in the data.

Hoffman et al. (2001) followed up with a study of anesthetized rats with and without basal forebrain hemisection. The underlying hypothesis was that the decrease in the coefficient of variation (CV) observed in dopamine neurons in a slice preparation compared to in an intact animal (Shepard and Bunney 1988) results at least partially from network interactions with the forebrain. The hemisection caused a significant reduction in CV as well as a significant reduction in predictability, although the former did not account for the latter statistically. The mean r_s for the unlesioned animals was 0.313 ± 0.076 , which is comparable to the results obtained in their original study, whereas the mean for the hemisected animals was 0.184 ± 0.105 ($p < 0.002$). Gaussian surrogates were not used to determine if the decrease in predictability derived primarily from linear or nonlinear sources, but based on the reported values for control and surrogates in other studies (Di Mascio et al 1999ab), it is likely that the degradation in predictability is due to loss of nonlinear structure. Again, no correlation between burst firing and predictability was found.

Effects of Aging and of Serotonin Denervation

Di Mascio et al. (1999a) applied analytical methods identical to those of Hoffman et al. (1995) to sequences of 2000 ISIs recorded from ventral tegmental dopamine neurons in anesthetized rats. They compared young, adult, and aged rats. The mean r_s for the twelve records from young rats was 0.22 ± 0.10 , which was significantly different from the mean of 0.11 ± 0.08 obtained for their Gaussian-scaled surrogates ($p < 0.0001$). For the 20 cells from adult rats the mean r_s was 0.18 ± 0.09 , which was also significantly different from the mean of 0.11 ± 0.06 observed for the surrogates ($p < 0.0001$). On the other hand, the mean r_s of the records from the aged rats was only 0.11 ± 0.09 , which was comparable to that of the Gaussian scaled surrogate data, which was 0.09 ± 0.05 ($p < 0.18$). Therefore the young and adult rats showed strong evidence of nonlinear sequence structure that was lacking in the aged rats. No consistent, significant differences were found in measures of bursting activity across the three groups, so differences in bursting could not account for differences in predictability.

Di Mascio et al. (1999b) also investigated, using similar methods, the effects of serotonin denervation mediated by whole brain 5,7-dihydroxytryptamine (5,7-DHT) lesions on ventral tegmental area dopamine neurons in anesthetized rats. Twelve control records had an r_s of 0.26 ± 0.08 , whereas that of the Gaussian-scaled surrogates was 0.16 ± 0.07 ($p < 0.00003$). The 5,7-DHT lesioned group had an r_s of 0.19 ± 0.09 , which did not differ significantly from their Gaussian-scaled surrogates 0.16 ± 0.05 ($p < 0.15$). This group also found no significant correlation between bursting and predictability.

Conclusions

The determination of nonlinear structure in noisy ISI data is nontrivial and fraught with pitfalls. Nonetheless, judicious use of controls such as Gaussian surrogate data increases confidence that actual nonlinear sequence structure is being measured. The decrease in predictability observed after forebrain hemisection (Hoffman et al 2001) or serotonin denervation (Di Mascio et al 1999b) supports the hypothesis that network interactions rather than intrinsic dynamics are largely responsible for nonlinear sequence dependent predictability in midbrain dopamine neurons. Somewhat surprisingly, no evidence has been found linking the prevalence of bursting to the amount of nonlinear structure, despite the widespread agreement that bursting is a salient network phenomenon. Furthermore, in contrast to the idea that chaotic complexity is detrimental to system performance, the decrease in nonlinear sequence structure with age (Di Mascio et al 1999a), serotonin denervation (Di Mascio 1999b), and forebrain hemisection (Hoffman et al 2001) supports the idea that complexity in the sequence structures of ISI series in midbrain dopamine neurons enhances rather than degrades system functionality, as aged, lesioned, and hemisectioned animals are likely to be less functional than their non-aged or intact counterparts.

Acknowledgments

The authors acknowledge support from National Institute of Neurological Disorders and Stroke grant number NS061097.

References

- Bertschinger N, Natschlager T. Real-Time Computation at the Edge of Chaos in Recurrent Neural Networks Neural Computation. 2004; 16:1413–1436.
- Canavier CC, Clark JW, Byrne JH. Routes to chaos in a model of a bursting neuron. Biophys J. 1990; 57:1245–125. [PubMed: 1697484]
- Canavier CC, Clark JW, Baxter DA, Byrne JH. Nonlinear dynamics in a model neuron provide a novel mechanism for transient synaptic inputs to produce long-term alterations of postsynaptic activity. J Neurophysiol. 1993; 69:2252–2257. [PubMed: 8350142]
- Canavier CC, Perla SR, Shepard PD. Scaling of prediction error does not confirm chaotic dynamics underlying irregular firing using interspike intervals from midbrain dopamine neurons. Neuroscience. 2004; 129:491–502. [PubMed: 15501606]
- Castro R, Sauer T. Correlation dimension of attractors through interspike intervals. Physical Review E. 1997; 55:287–290.
- Di Mascio M, Di Giovanni G, Di Matteo V, Esposito E. Reduced chaos of interspike interval of midbrain dopaminergic neurons in aged rats. Neuroscience. 1999a; 89:1003–1008. [PubMed: 10362290]
- Di Mascio M, Di Giovanni G, Di Matteo V, Esposito E. Decreased chaos of midbrain dopaminergic neurons after serotonin denervation. Neuroscience. 1999b; 92:237–243. [PubMed: 10392846]
- Farmer JD, Sidorowich JJ. Predicting chaotic time series. Phys Rev Lett. 1979; 59:845–848. [PubMed: 10035887]
- Freeman AS, Meltzer LT, Bunney BS. Firing properties of substantia nigra dopaminergic neurons in freely moving rats. Life Sci. 1985; 36:1983–1994. [PubMed: 3990520]
- Fujimura K, Matsuda Y. Autogenous oscillatory potentials in neurons of the guinea pig substantia nigra pars compacta *in vitro*. Neurosci Lett. 1989; 104:53–57. [PubMed: 2812536]

- Grace AA, Bunney BS. The control of firing pattern in the nigral dopamine neurons: Single spike firing. *J Neurosci*. 1984a; 4:2866–2876. [PubMed: 6150070]
- Grace AA, Bunney BS. The control of firing pattern in the nigral dopamine neurons: Burst firing. *J Neurosci*. 1984b; 4:2877–2890. [PubMed: 6150071]
- Grace AA, Onn S-P. Morphology and electrophysiological properties of immunocytochemically identified rat dopamine neurons recorded *in vitro*. *Journal of Neuroscience*. 1989; 9:3463–3481. [PubMed: 2795134]
- Harris NC, Webb C, Greenfield S. A possible pacemaker mechanism in pars compacta neurons of the guinea-pig substantia nigra revealed by various ion channel blocking agents. *Neuroscience*. 1989; 31:355–362. [PubMed: 2552348]
- Hegger R, Kantz H. Embedding sequences of time intervals. *Europhysics Letters*. 1997; 38:267–272.
- Hoffman RE, Shi W-X, Bunney BS. Nonlinear sequence-dependent structure of nigral dopamine neuron interspike interval firing patterns. *Biophysical J*. 1995; 69:128–137.
- Hoffman RE, Shi W-X, Bunney BS. Anatomic basis of sequence-dependent predictability exhibited by nigral dopamine neuron firing patterns. *Synapse*. 2001; 39:133–138. [PubMed: 11180500]
- Johnson SW, Seutin V, North RA. Burst-firing in dopamine neurons induced by N-methyl-D-aspartate: Role of electrogenic sodium pump. *Science*. 1992; 258:665–667. [PubMed: 1329209]
- Kang Y, Kitai ST. Calcium spike underlying rhythmic firing in dopaminergic neurons of the rat substantia nigra. *Neurosci Res*. 1993; 18:195–207. [PubMed: 7907413]
- Kantz, H.; Schreiber, T. *Nonlinear time series analysis*. Cambridge University Press; Cambridge: 1999.
- Kaplan DT, Clay JR, Manning T, Glass L, Guevara MR, Shrier A. Subthreshold dynamics in periodically stimulated squid giant axons. *Physical Review Letters*. 1996; 76:4074–4077. [PubMed: 10061185]
- King R, Barchas JD, Huberman BA. Chaotic behavior in dopamine neurodynamics. *Proc Nat Acad Sci USA*. 1984; 81:1244–1247. [PubMed: 6583705]
- Lovejoy LP, Shepard PD, Canavier CC. Apamin-induced irregular firing *in vitro* and irregular single-spike firing observed *in vivo* in dopamine neurons is chaotic. *Neuroscience*. 2001; 104:828–840.
- Osborne AR, Provenzale A. Finite correlation dimension for stochastic systems with power-law spectra. *Physica D*. 1989; 35:357–381.
- Packard N, Crutchfield J, Farmer JD, Shaw R. Geometry from a time series. *Phys Rev Lett*. 1980; 45:712–716.
- Ping HX, Shepard PD. Apamin-sensitive Ca^{2+} -activated K^+ channels regulate pacemaker activity in nigral dopamine neurons. *NeuroReport*. 1996; 7:809–814. [PubMed: 8733751]
- Plant RE, Kim M. Mathematical description of a bursting pacemaker neuron by modification of the Hodgkin-Huxley equations. *Biophys J*. 1976; 16:227–244. [PubMed: 1252578]
- Racicot DM, Longtin A. Interspike interval attractors from chaotically driven model neurons. *Physica D*. 1997; 104:184–204.
- Rapp PE. Chaos in the neurosciences: cautionary tales from the frontier. *Biologist*. 1993; 40:89–94.
- Rapp PE, Albano AM, Scmah TI, Farwall LA. Filtered noise can mimic low-dimensional chaotic attractors. *Phys Rev E*. 1993; 46:2289–2297.
- Sauer T. Reconstruction of dynamical systems from interspike intervals. *Physical Review Letters*. 1994; 72:3811–3814. [PubMed: 10056303]
- Sauer T. Reconstruction of integrate and fire dynamics. *Fields Institute Communications*. 1997; 11:63–75.
- Schreiber T, Schmitz A. Surrogate time series. *Physica D*. 2000; 142:346–382.
- Shaner A. Delusions, superstitious conditioning and chaotic dopamine neurodynamics. *Medical Hypotheses*. 1999; 52:119–123. [PubMed: 10340292]
- Shepard PD, Bunney BS. Effects of apamin on the discharge properties of putative dopamine-containing neurons *in vitro*. *Brain Res*. 1988; 463:380–384. [PubMed: 3196925]
- Stam CJ, Pijn JPM, Pritchard WS. Reliable detection of nonlinearity in experimental time series with strong periodic components. *Physica D*. 1998; 112:361–380.

- Strogatz, SH. Nonlinear Dynamics and Chaos: With Applications to Physics, Biology, Chemistry and Engineering. Westview Press; Cambridge: 2000.
- Theiler J. Spurious dimension from correlation algorithms applied to limited time series data. Phys Rev A. 1986; 34:2427–2432. [PubMed: 9897530]
- Thieler J, Eubank S, Longtin A, Galdrikian B, Farmer JD. Testing for nonlinearity in time series: the method of surrogate data. Physica D. 1992; 58:77–94.
- Wales DJ. Calculating the rate of loss of information from chaotic time series by forecasting. Nature. 1991; 350:485–488.
- Yunfan G, Jianxue X, WEi R, Sanjue H, Fuzhou W. Determining the degree of chaos from analysis of ISI time series in the nervous system: a comparison between correlation dimension and nonlinear forecasting methods. Biological Cybernetics. 1998; 78:159–165. [PubMed: 9525040]
- Yung WH, Hausser MA, Jack JJB. Intrinsic membrane properties of dopaminergic and nondopaminergic neurones of the guinea-pig substantia nigra pars compacta in vitro. J Physiol (Lond). 1991; 426:643–667. [PubMed: 2061849]

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Figure 1.

Irregular firing *in vivo* can be approximated *in vitro* by bath application of apamin. A. Intracellular membrane potential recordings from substantia nigra dopamine neurons in a slice preparation. A1. Control. A2. Bath application of 300 nM apamin induces irregular firing. B. ISI histograms. B1. Distribution of interspike intervals in an apamin treated neuron *in vitro*. B2. Distribution of interspike intervals in an irregularly-firing dopamine neuron recorded extracellularly *in vivo*. Adapted from Canavier et al. 2004.

Figure 2.

Time series (SDF) generation from an ISI Sequence and attractor reconstruction from a time series. A. Model pacemaker neuron. The spike times are shown as a comb plot on the x-axis in A1. The solid curve in A1 is the spike density function (SDF) created by superimposing a Gaussian window at each spike time. The three points (x_1, x_2, x_3) in A1 are separated by a time lag, and are used as the coordinates to create the labeled point on the limit cycle attractor in A2. B. Model chaotic neuron. The same procedure was used to create the more complex waveform for the spike train shown in A1, and the coordinates each point in the attractor in B2 was created from a set of time lagged points in B1 as in the example shown in A. Adapted from Lovejoy et al 2001.

Figure 3.

Application of nonlinear forecasting to SDF generated from ISIs. The rate of loss of predictability in bits is given on the y-axis as a function of the prediction time for both the original data and randomly shuffled surrogates. A straight line on a semilog plot indicates exponential decay of predictability. Although exponential decay of predictability is a hallmark of chaos, in this case it is spurious because the dotted lines were produced from randomly shuffled ISI series with no temporal structure. A. Predictions from original and shuffles from neurons *in vitro* treated with apamin. B. Predictions from neurons *in vivo*. Adapted from Canavier et al. 2004.