Unstable periodic orbits (UPOs) analysis has now become an established tool for detecting determinism in biological systems. If the system is truly deterministic, accurate UPO characteristics can be further used for application of control or anti control strategies with potential medical application. However, accurate biological time series analysis for UPOs critically depend on the length of the data set, strength of the noise, type of geometry, nonstationarity etc. In this work we show that it is possible to establish determinism through UPO analysis in presence of all these factors. However, the inaccuracy in the measured UPO parameters and non-stationarity nature of biological systems mean only adaptive control strategies are useful for successful chaos control in such systems. At the same time, comparable success of adaptive control strategies on a stochastic neural network model of epileptic slices demand more stringent criteria for linking adaptive control success with determinism.

I. INTRODUCTION

Chaos control—a method for maintaining periodic dynamics in chaotic systems—has received considerable attention following successful experimental demonstration in physical, chemical and biological systems [1]. Applications of chaos control techniques [2, 3] in neural dynamics, mainly due to its possible medical applications in the treatment of epilepsy [4], have also been explored for some time. A number of anti-control of chaos methods have also been developed for this purpose [4-9]. Establishing the occurrence of deterministic chaos in epilepsy is of fundamental importance. Along with the possibility of understanding the underlying neuronal dynamics [10-13] it also opens the possibility of short term prediction and control that has potential medical applications.

The first experimental demonstration of chaos control in epilepsy on spontaneously bursting epileptic hippocampal slices by Schiff et al. [4] has triggered most of the research activity in this direction. In this experiment, occurrence of recurrent unstable periodic orbits (UPOs) like trajectories and apparent success of chaos control based on these trajectories were interpreted as evidence for chaotic dynamics. This was immediately challenged with application of the same method with comparable success on a noise driven non-chaotic FitzHugh-Nagumo neuronal model [13]. To resolve this, new surrogate time series analysis techniques were developed [15-17] for both searching the UPOs in a time series and for assigning statistical significance to them. Application of this method on the inter burst interval (IBI) data sets from brain slices [8] and on human epileptic electroencephalogram (EEG) for statistically significant UPOs reported clear evidence of determinism [18]. However, a rigorous simulation of the chaos control experiment on a stochastic neural network model for epileptic brain slices could also successfully reproduce most of the observations reported in the experimental study by Schiff et al. [19]. The surrogate methods for statistically significant UPOs, when applied to stochastic burst intervals obtained from this computer model, also produced results comparable to those reported earlier [16, 18]. Due to these conflicting results, the issue of unambiguously establishing deterministic chaos in epilepsy based on statistically significant UPOs remained inconclusive.

The chaos control experiment on epileptic hippocampal slices has been subsequently repeated by Slutzky et al. [21-23] adopting more stringent UPOs detection method [9] along with a more robust adaptive chaos control technique [24].
Successful chaos control, as well as statistically significant UPO analysis of the time series from this experiment claim to re-establish the original conclusions of low dimensional deterministic chaos in epileptic brain slices. Various other methods have been developed to distinguish between deterministic chaos and noise \cite{25,29} and applied to EEG data to detect seizure \cite{25}. These positive and promising results, however, have not lead to any real application so far. This is because strong skepticism continues to persist on the two main issues:

- whether the apparent UPOs in epileptic EEG truly originate from an underlying deterministic dynamics that can be reconstructed or used, and
- whether the apparent success of any control strategy using the reconstructed dynamics can be conclusively interpreted as due to the deterministic nature of the underlying dynamics.

The difficulties in providing a clear and convincing answer to these two issues in the context of epilepsy are numerous. The underlying dynamics of an epileptic brain slice is unknown and high-dimensional, even the smallest of brain slices contain tens of thousands of neurons, whereas the applied tools of non-linear dynamics and deterministic chaos were only proven on low dimensional known chaotic systems.

The chaos control experiments are based on UPOs extracted from short inter burst intervals (IBIs). The apparent geometry visible in the return maps of truly chaotic systems is absent in the return maps of the epileptic IBIs in all the reported works. Interspike time intervals from rat facial cold receptor for which statistical significant UPOs are established show return map geometry consistent with UPO trajectories \cite{30}. However, no such geometry is visible for interburst intervals data from epileptic hippocampal slices \cite{4,23}. Traditional surrogate analysis to assess statistical significance of UPOs in such return maps have provided mixed results \cite{17,19}. New surrogate method that preserves the attractor shape in the shuffled surrogates have been found to be more suitable in such time series analysis for UPO detection \cite{30}. Even if the apparent recurrent UPO like trajectories truly originate from an underlying deterministic dynamics, how reliable are the fixed point, stable and unstable manifolds derived from this small number of short sequences from these noisy return maps with no apparent geometry? The lack of geometry could also be due to noise and it is claimed that presence of chaos can still be concluded if the observed UPOs are recurrent and statistically significant. However, recurrent UPOs with similar statistical significance have been reported from IBIs from stochastic neuron models as well \cite{14}. Analysis of biological time series and EEG data for seizure like activity and its suppression have been done using tools other than UPO analysis also \cite{2,9,25}.

A clear distinction based on the underlying dynamics must exist between the periodic dynamics of a system under chaos control and one induced by periodic pacing or demand pacing. The response of a brain slice to external stimulation is largely unknown and different from a physical systems. Further, frequent external stimulation can cause permanent change in the underlying dynamics or in the system parameters. This is evident from a recent experiment showing control of seizures through electrical stimuli \cite{51}. Therefore, it is necessary to show that the periodic dynamics under chaos control is not due to any kind of biological synchronization with the external stimuli.

Although the original chaos control experiment \cite{4} assumed recurrent UPOs around the same trajectory as signature of determinism and chaos control was based on equation of manifolds derived from multiple UPO trajectories in the return map of IBIs, subsequent surrogate analysis have concluded presence of statistically significant “non-stationarity or drifting” UPOs from rat hippocampal slices \cite{15,16}. To ensure successful chaos control, even around such drifting UPOs, adaptive chaos control techniques have been proposed \cite{32}. Adaptive chaos control using more stringent UPO detection technique have been proposed \cite{24} and applied successfully in a repeat chaos control experiment in epileptic hippocampal slices \cite{21}.

The experiment of Slutzky et al. \cite{21} provides valuable new insight and addresses some of these issues anew, but a number of questions still remain. In this paper, we attempt to answer some of these questions by computer simulation of this adaptive chaos control experiment on a stochastic neural network model for the epileptic brain slices. The general question of deterministic chaos in neural systems is a vast field of research and this work focuses only on the reliability of UPO based chaos control applications in epileptic brain slices and the conclusions drawn from them. In the concluding section we summarize the main unresolved questions that prevent us from unambiguously establishing that the bursting in epileptic brain slices is chaotic dynamics in presence of noise rather than stochastic in origin.

II. DETERMINISM FROM UPOS

According to the cyclic theory of Chaos, chaotic dynamics is built upon “skeleton” formed by UPOs \cite{33}. Due to ergodicity, the system visits these UPOs along stable manifold and departs away from it along unstable manifold. However, time series analysis methods that chose the detection of these statistically significant UPOs as a criterion for establishing deterministic chaos are more recent. A number of different techniques for search of UPOs in time series obtained from both low dimensional and high dimensional systems have been proposed \cite{4,15,24,34,37} and subsequently applied to time series from physiological and biological systems \cite{4,9,11,12,13,21,24,29,33,38}. Most of these methods adopt surrogate methods to establish the statistical significance of the detected UPOs.

In an earlier work \cite{20}, the topological recurrence method \cite{35} was found to unambiguously reject short stochastic time series as non-chaotic when other methods erroneously found statistically significant UPOs in them. All methods tend to accurately discriminate chaotic and non-chaotic time series when data sets were sufficiently large (datasets of size > 4096). However, results from shorter data sets were not
reliable. Among various UPO detection methods, the topological recurrence method is the simplest and used regularly in analyzing biological time series although length of biological time series are usually small. Therefore, a rigorous analysis of the reliability of this geometric method in the context of length of data set, level of noise, nature of geometry and nonstationarity is necessary because each of these affects the geometry of the return map and, therefore, likely to affect the results.

A. Characterizing UPOs

The topological recurrence method for detection of UPOs adopts three levels of filtering to encounter UPO trajectories from the return map of a dynamics [34, 35, 39].

- **Level 0**: Out of five sequential points, first three approach the identity line with increasing perpendicular distance and the last three depart from the identity line with increasing perpendicular distance.

- **Level 1**: Linear least square fit to the first three points must have a slope in the range $|\lambda_s| < 1$ identifying a stable manifold and linear least square fit to the last three points must have a slope in the range $-1 \geq \lambda_{us} > -\infty$ identifying an unstable manifold.

- **Level 2**: Distance of the fixed point (estimated from the intersection point of the two straight line fits in the previous step) from the identity line must be less than or equal to $\frac{1}{m}$ times the average perpendicular distance of the five data points from the identity line.

Although **Level 0** and **Level 1** are based on the defining geometric properties of the UPOs, the **Level 2** criterion was ad-hoc and has been used differently in different applications [38, 40]. The **Level 1** criterion in [35] only included the slope condition for “flip” saddles. If the linear fits in **Level 1** truly represent the stable and unstable manifolds, their intersection would lie on the identity line at the fixed point. In noisy data sets this condition may not be met exactly. Therefore, in **Level 2**, a relaxed criterion is adopted to discriminate candidate UPO trajectories from the spurious ones. We have generalized the **Level 2** criterion to arbitrary $m$, where as the original criterion [35] was defined for $m = 2$. Higher $m$ would demand the estimated fixed point (the intersection point) to be more closer to the identity line. Although this is expected to give more accurate UPO parameters, there will be lesser number of candidate UPO trajectories.

B. Statistical significance of UPOs

To determine whether the detected UPOs actually originate from deterministic and not from stochastic dynamics, surrogate analysis methods have been proposed [15, 30, 34, 35, 41]. In the topological recurrence method [35], the $K$ value

\[ K = \frac{(N - \bar{N}_s)}{\sigma_s}, \]  

defines the statistical significance of the observed UPOs. Here $N$ is the number of successful UPO encounters in the original data, $\bar{N}_s$ is the average number of successful UPO encounters in the surrogate data set, and $\sigma_s$ is the standard deviation of the number of observed UPOs in the surrogate data. $K > 3$ signifies a statistical confidence level of more than 99% in rejecting the null hypothesis that the data originated from a random process [35].

C. Results

We applied the topological recurrence method to estimate dynamical parameters by looking for candidate UPOs in the first return map of three known deterministic chaotic systems, each having a different geometry. We then compared the estimated UPO characteristics with the true values. Dependence on the effect of noise, length of data sets and nature of geometry on the estimation of dynamical parameters are studied in detail. For each data set, at each level of filtering, a number of candidate UPOs are obtained. For each of these trajectories, the three parameters characterizing the UPO trajectories ($\lambda_s$, $\lambda_{us}$, and the fixed point) are determined. Statistical fluctuations of the estimated dynamical parameters are analyzed by measuring the mode and the range (difference between maximum and minimum values). This is done for different levels of noise, different lengths of data sets, and different levels of filtering.

The three systems being studied are: Hénon map, Ikeda map and Rössler attractor. The dynamics of Hénon map is described by

\[ X_{n+1} = 1 + bY_n - aX_n^2, \]
\[ Y_{n+1} = X_n + \epsilon Z, \]

where $a=1.2$, $b=0.3$, and $\epsilon$ denotes strength of the dynamical noise. $Z$ is a uniform random variable in the range $[-1,1]$.

For these set of parameter values and $\epsilon = 0$, the true values characterizing the UPOs are: $\lambda_s = 0.178$, $\lambda_{us} = -1.69$, and fixed point at $X^* = 0.6667$ [39].

Hénon map has been analyzed earlier using only the **Level 0** topological recurrence method combined with a matrix fit algorithm [39]. The dynamical parameters were estimated and analyzed with or without noise. In this work we try to understand the deviation of estimated results from actual values in the presence of noise, its dependence on length of data sets as well as its dependence on the nature of the geometry. At each **Level**, a number of candidate UPO trajectories are observed and dynamical parameters are computed from linear fits to these trajectories. These results are summarized in Table 1.

In absence of noise, *mode* of the estimated dynamical parameters is nearly the same for different levels of filtering.
This has been observed earlier also [39]. In absence of noise, Level 0 is adequate for the purpose of establishing statistically significant UPO detection. Range of the estimated parameter values decreases as the filtering criteria is made more stringent, i.e., as one goes from Level 0 to Level 2. In presence of noise, the geometry of the return map also gets noisy. As expected, this leads to inaccurate estimate as well as increase in the values of range. The value of the mode for the stable manifold estimates for Level 0 and Level 1 filtering criteria deviates significantly from the mode of Level 2 estimated values, although the secondary peak is nearly the same as the mode of Level 2 estimate. This signifies occasional failure of Level 0 and Level 1 criteria in the presence of noise. Also, the mode of stable manifold estimates is nearly 40-50% more than the true value, while the deviations in the mode of unstable manifolds and fixed point estimates are less than 10%. We have added a further filter in Level 2, i.e., the value of m. The results presented in Fig. ?? are for m = 2 and those summarized in Table 1 are for m = 2, 5 and 10. Increasing m does not lead to significant improvement in the UPO parameters, but the number of candidate UPO trajectories decreases significantly. With increasing m, K-value remains nearly identical for small datasets and increases for large datasets with or without noise as shown in Fig. [3]

Surprisingly, while the variations in UPO parameter estimates increase with noise, no significant change is observed in the K-statistics shown in Fig. [3]. This means that the topological recurrence method is fairly robust in establishing determinism in the presence of moderate noise in data sets of moderate length (data size > 1024). For the same length data set, the number of candidate UPOs detected at each level decreases with increase in strength of noise. Unchanged K-statistics indicates that the number of candidate UPOs detected in the surrogate data sets also decreases.

To understand how the topological recurrence method depends on the type of geometry in the return map of the dynamical system, two other systems are also analyzed. The Ikeda map is described by

\[
\begin{align*}
t_n &= a - b/(1 + X_n^2 + Y_n^2), \\
X_{n+1} &= 1 - uX_n\cos(t_n) - uY_n\sin(t_n) + \epsilon z_1, \\
Y_{n+1} &= uX_n\sin(t_n) + uY_n\cos(t_n) + \epsilon z_2,
\end{align*}
\]

(3)

where \(a = 0.4, b = 6.0, u = 0.9\). For these set of parameter values, the fixed point is 1.0550, the slope of the stable manifold is 0.6634 and the slope of the unstable manifold is -1.221 [42]. \(\epsilon\) denotes strength of dynamical noise, \(z_1\) and \(z_2\) are uniform random variables in the range [-1, 1]. The data for \(X\) are analyzed for UPOs using topological recurrence criteria. In absence of noise, the mode of all the three estimated parameters improve significantly as the filtering criteria is made more stringent. However, stable manifold estimate deviates significantly from the actual value even for Level 2 filtering (mode is 0.070592 and range is 0.6930 for 50 datasets of length 4096). In absence of noise, out of 50 data sets of size 4096 each, only 35 give successful UPO candidates at Level 2, out of which 17 data sets give just one successful UPO candidate. In presence of noise, the fixed point estimate deviate from true value by 10% for Level 2 filtering (for \(\epsilon = 0.2\)). Unstable manifold estimates deviate by 20% for different levels of filtering with or without noise. With addition of noise, there is uniform increase in the range of all estimates indicating greater deviations from actual parameter values. When dynamical noise is introduced, 42 data sets give successful UPO candidate at Level 2 out of which 15 data sets have just one successful candidate UPO. This indicates that for this geometry, the system dynamics do not visit close to the fixed point frequently and the estimated parameters deviate significantly from true values because of this reason.

| Noise | Level | \(\lambda_u\) mode range | \(\lambda_u\) mode range | \(x^*\) mode range |
|-------|-------|-------------------------|-------------------------|----------------------|
| 0.0   | 0     | 0.2576 1.2572           | -1.7850 1.7006         | 0.6701 0.6752        |
|       | 1     | 0.2576 1.2572           | -1.7850 0.8289         | 0.6747 0.5906        |
|       | 2 (m=2) | 0.2548 1.2201         | -1.7950 0.8276         | 0.6724 0.4908        |
|       | 2 (m=5) | 0.2560 1.2189         | -1.7986 0.8206         | 0.6730 0.4893        |
|       | 2 (m=10) | 0.2550 1.2198        | -1.7974 0.7993         | 0.6736 0.4294        |
| 0.1   | 0     | -0.5533 1.4589         | -1.7798 12.089         | 0.6556 1.5305        |
|       | 1     | -0.5533 1.4589         | -1.7798 6.3346         | 0.6556 1.5305        |
|       | 2 (m=2) | 0.2271 1.4584         | -1.7998 6.3346         | 0.6591 0.5071        |
|       | 2 (m=5) | 0.2374 1.4336         | -1.800 3.6838          | 0.6618 0.5145        |
|       | 2 (m=10) | 0.2397 1.3819        | -1.7751 6.3288         | 0.6710 0.5024        |
| 0.2   | 0     | -0.5588 1.5661         | -1.7832 13.7858        | 0.6522 1.5507        |
|       | 1     | -0.5688 1.5097         | -1.7832 10.178         | 0.6521 1.5507        |
|       | 2 (m=2) | 0.2312 1.5097         | -1.7832 10.173         | 0.6544 0.5658        |
|       | 2 (m=5) | 0.2380 1.4797         | -1.8197 4.3313         | 0.6700 0.5263        |
|       | 2 (m=10) | 0.2490 1.4092        | -1.7850 8.5878         | 0.6755 0.5122        |

TABLE 1: Manifolds and fixed point estimate using topological recurrence criteria from 50 ensembles 4096 point dataset of Hénon map (Actual \(\lambda_u\), \(\lambda_u\), \(x^*\) are 0.178, -1.69 and 0.6667 respectively.)
FIG. 1: UPO analysis of Hénon map ($X_{n+1}$ vs. $X_n$) without noise using topological recurrence criterion. (a) Actual return map, (b) Level 0 filtered, (c) Level 1 filtered and (d) Level 2 filtered UPO trajectories respectively.

The Rössler attractor is a continuous time dynamical system described by

\[
\begin{align*}
\dot{x} &= -(y + z), \\
\dot{y} &= x + ay, \\
\dot{z} &= b + z(x - c) + \sqrt{2D}\xi(t),
\end{align*}
\]

where \(\xi(t)\) is gaussian white noise with zero mean and unit variance. \(D\) is the amplitude of dynamical noise. The values of the parameters are \(a = 0.2\), \(b = 0.2\), and \(c = 5.7\). From X=0 plane Poincaré section is obtained and the variable \(y\) is used for further analysis [39]. The actual fixed point, stable manifold and unstable manifold are \(-8.39, -2.34 \times 10^{-7}\) and \(-2.40\) respectively.

For this system, the topological recurrence criteria shows strong dependence on the geometry of the Poincaré section. In absence of noise, the mode of the estimates of \(\lambda_s\) vary with each level of filter \((-0.571\) with a range of \(0.9649\) for both Level 0 and Level 1, and \(-0.025129\) with a range of \(0.58709\) for Level 2). These estimates are significantly different from the actual values. It appears that the method fails because \(\lambda_s\) is close to zero. Unstable manifold estimates for Level 0 and Level 1 filtering are close to actual value (mode is \(-2.1133\) and range is nearly \(2.0\)), but deviates significantly from the actual value for Level 2 (mode is \(-1.1049\) with range \(0.6406\)). Fixed point estimates are fairly accurate for Level 2 filtering criteria (mode is \(-8.4314\) with range of \(0.94955\)). For this geometry, the estimates do not deteriorate much with introduction of noise, although the variability increases marginally. In absence of noise, out of 50 data sets of size 4096, 16 data sets give successful UPO candidates at Level 2 filtering, out of which 13 data sets have just one successful candidate UPO, the reason for large deviation in stable and unstable manifold. Similar results are obtained when dynamical noise is introduced in the system. Above observations show that geometrical structure greatly influences the frequency of UPO visit as well as the accuracy in the estimation of dynamical parameters. However, the statistical significance of the UPOs assessed at all levels of noise is above 95%. The topological recurrence method is robust in establishing all these systems to be deterministic even in the presence of moderate noise. Large values of \(m\) signifies close visit to UPOs. For Hénon map, UPO candidates satisfying conditions for higher \(m\) are easily obtained, while for Ikeda map and Rössler attractor, even UPO candidates satisfying \(m = 2\) criteria is not found frequently. This means that choice of \(m\) value to improve UPO detection will depend on the system under investigation.

In the above analysis, random shuffled surrogates were used. It has been pointed out that random surrogates that preserve the attractor shape are more appropriate [30]. From, the results of the surrogate analysis of Hénon map using surrogates that preserve attractor shape, it is observed that K-statistics for Level 0 is similar to that of shuffled surrogates for different strength of noise and length of data sets. No can-
candidate UPO was found for Level 1 and Level 2 for data sets of length less than 16384. For data set of length 16384 and \( m = 2 \), Level 1 and Level 2 statistical significance is > 99 \%. As noise is added, K-statistics value decreases for Level 1 and Level 2. Similar results are obtained for \( m = 5 \) and \( m = 10 \). As \( m \) is increased, K-value for Level 0 increases while it decreases for Level 1 and Level 2. We observe that for systems with deterministic geometry, the random surrogates that preserve attractor shape are less likely to have candidate UPOs, resulting in higher K-statistics. However, if the return map does not have any visible geometry, the attractor shape preserving surrogates do not improve statistical tests significantly.

These results suggest that the UPO parameter estimates are good when the system dynamics repeatedly visits very close to the UPOs. With increase in the length of data sets, number of visits as well as number of close encounters with UPOs increase yielding very good estimates of the fixed point and slopes of the stable and unstable manifolds. Close encounter with UPOs and accuracy of dynamical parameter estimation depends strongly on geometrical structure. The statistical significance of UPO detection is above 95\% for the diverse cases examined indicating this to be a general result. As noise level is increased, smearing of the UPO structure takes place and manifold estimates deteriorate, although statistical significance remains high. With small length of data sets and high level of noise, obtaining statistically significant result depends on the frequency of UPO visits, which in turn depends on the geometry of the return map. There is a decrease in number of successful encounters at each level. We also observe that the UPO parameters do not improve significantly by increasing \( m \). Increasing \( m \) is analogous to looking for close encounters to UPOs, which results in decrease in number of successful encounters. Even at low level of noise and for long data sets, the estimated UPO parameter values are not accurate enough for control applications. Another crucial observation is that the method works well for the dynamics where the third point of the candidate UPOs is actually close to the fixed point. The topological recurrence criteria assumes that this point belongs to both the stable and the unstable manifold.

\[ \text{FIG. 2: UPO analysis of Hénon map } (X_{n+1} \text{ vs. } X_n) \text{ with noise (} \epsilon = 0.2) \text{ using topological recurrence criterion. (a) Actual return map, (b) Level 0 filtered, (c) Level 1 filtered and (d) Level 2 filtered UPO trajectories respectively.} \]

D. Modified UPOs selection criterion using dynamical transformation method

The results and analysis presented in the previous section point to two major shortcomings of the topological recurrence criteria. The fixed point estimate as determined from the intersection of the linear fits to the approaching and receding set of points is inaccurate. The requirement that the fixed point need to be close to the identity line rather than a specific point on the identity line introduces additional error.

Instead of using least square fit, we adopt a method used by Dolan \[39\] to obtain estimates of fixed point and manifolds.
In the vicinity of UPO, system dynamics is approximated as
\[ X_{n+1} = AX_n + BX_{n-1} + C. \] (5)

The Level 0 criterion gives five consecutive points defining the UPO trajectory near the fixed point. Slopes of the manifolds and the fixed point of the detected UPOs were obtained by solving the three simultaneous linear equations obtained from the three triplets of the candidate UPO trajectory. This gives significantly improved result than the least square method of Level 1. Instead of the average distance from the identity line criterion in Level 2, we use a new criterion that uses the So et al. method of dynamical transformation that gives very good estimate of period 1 fixed point even in presence of noise. We redefine the Level 2 criterion as

\[ \text{Level 2: } \frac{|x_2^* - x_1^*|}{x_2^*} \leq \delta, \] (6)

where \( x_2^* \) is the fixed point estimate from dynamical transformation method, and \( x_1^* \) is the fixed point estimate from Level 1 using Eqn. 5. \( \delta \) is a measure of close encounter with UPOs.

The results from this hybrid method that combines the original topological recurrence criterion with the matrix fit algorithm and dynamical transformation method for the Hénon map are presented in Table 2. Adopting the matrix fit algorithm Eqn. 5 gives different values for the fixed point and the slopes of the manifolds than the original topological recurrence criterion. There is significant improvement in the accuracy of the UPO parameters compared to the results from the topological recurrence criterion summarized in Table 1.

Values of \( \delta \) used for Hénon map are 0.001, 0.005 and 0.005 for the noise values 0.00, 0.10 and 0.20 respectively. With or without noise, estimates approach the actual values as filtering is made more stringent. Estimates of stable manifolds deviate by 5% to 10% as noise varies from 0.0 to 0.2. The estimates of the unstable manifold deviate from 6% to 15% for the same noise variation. At Level 2, the fixed point estimates are accurate up to 0.5% for these noise values. For all the three parameter estimates, results for Level 0 and Level 1 are identical for noise level 0.0 and 0.1, while for noise 0.2, there is marginal variation only in the stable manifold estimate.

Values of \( \delta \) used for Rössler attractor are 0.001, 0.005 and 0.005 for the noise values 0.00, 0.10 and 0.20 respectively. Results for the stable manifold estimates at Level 2 are \(-0.01648, -0.02275, -0.01989\) for \( D = 0.0, 0.1, 0.2 \) respectively, showing large deviation from the true value. This is due to the small magnitude of the slope of the actual stable manifold. Results for the unstable manifold and fixed points, for different levels of filtering and strength of noises, are identical with accuracy up to 12% and 1% respectively. Results for Level 0 and Level 1 are identical for strength of noise varying from 0.0 to 0.2 for all the three parameter estimates.

For Ikeda map, value of \( \delta = 0.1 \) is used for three noise values 0.00, 0.10 and 0.20. For Level 2 filtering, fixed point estimates deviate up to 3% for different strengths of noise. Result for unstable manifold differs by 50% for noise 0.0 and 0.1, and by 70% for noise 0.2. Estimates of stable manifold differs by 50% for Level 2 filtering (for different strengths of noise). Results of Level 0 and Level 1 are not identical as is observed in case of Hénon map and Rössler attractor.

The results at Level 0 and Level 1 filter are not close to actual UPO parameters for the three systems studied. Otherwise, UPO parameters at the end of Level 2 of the hybrid method are very close to the actual values except for the Ikeda map. Comparing the results from the three systems analyzed in this work, we find that with matrix fit algorithm, only a very small fraction of the UPOs detected in Level 0 are rejected at the next level of filter Level 1. The Level 2 filter is more stringent and is the reason behind very accurate parameter estimation even in the presence of moderate noise. This hybrid method works better than the topological recurrence method. Better parameter estimation results from adoption of a more accurate fixed point in Level 2. Close encounter with UPOs can be adjusted depending on the geometrical structure. If \( \delta \) value is large, stable and unstable manifold estimate won’t be good but fixed point estimate will be good, which is primarily due to the inclusion of the dynamical transformation method.

### III. CHAOS CONTROL USING ADAPTIVE UPO TRACKING

Results of previous section suggest that unambiguous detection of UPOs is often possible in short and noisy biological time series through topological recurrence criteria. However, we also observe that estimation of quantitative parameters characterizing the UPOs deteriorate rapidly with addition of noise. In this context, it is important to reinterpret...
control strategies reported to be successful and carefully re-design such experiments in future. This is why the deterministic interpretation of the original chaos control experiment on epileptic brain slices was questioned earlier [13, 19].

The results and analysis presented in the previous section show the unreliability of the UPO parameters obtained from return maps with noisy geometry even when the data is from known deterministic dynamics. Return maps plotted from biological time series invariably lack any noticeable geometry [4, 21]. Although chaos control is an efficient tool for confining system dynamics to any of the periodic orbits by suitable intervention at appropriate times, reliable estimation of fixed point, slope of manifolds and nonstationarity pose tough challenge for good chaos control. To understand the apparent success of the repeat chaos control experiment on epileptic brain slices by Slutzky et al. [21, 23], it is necessary to first judge if the apparent success unambiguously originate from the underlying deterministic dynamics and made possible because of the adoption of more stringent detection and control strategies. We first examine the efficacy of the adaptive UPO tracking along with stable manifold perturbation (SMP) method that is used to obtain good control results for Hénon map (Eqn. 2) in a known deterministic system [24].

In the vicinity of UPOs, system dynamics can be approximated by Eqn. 5 which can be written as

\[
X_{n+1} = (\lambda_s + \lambda_u)X_n - \lambda_s\lambda_u X_{n-1} + X^\ast(1 + \lambda_s\lambda_u - \lambda_s - \lambda_u),
\]

where \(\lambda_s, \lambda_u\) and \(X^\ast\) are actual stable eigenvalue, unstable eigenvalue and fixed point respectively [24]. Chaos control by stable manifold perturbation (SMP) is done through

\[
X_{n+1} = \lambda_s(X_n - X^\ast) + X^\ast.
\]

UPO parameters estimated using the hybrid topological recurrence criterion is used for initiating SMP and then system dynamics is allowed to evolve naturally. If the trajectories stay within a control region, no further perturbation is applied. SMP is again applied when the system comes out of the control region. To do this, first natural triplets \((X_{n+1}, X_n, X_{n-1})\), where \(X_{n+1}\) correspond to natural dynamics, are obtained. Least square fit using singular value decomposition (SVD) is performed on a set of 10 natural triplets to obtain new estimates of stable manifold and fixed point [24]. SMP is again applied using revised estimated values. The process is continued till the control cannot be improved further.

In the absence of noise and nonstationarity, our UPO parameter estimates improve with each iteration and approach the actual values. With accurate UPO parameter estimates, the control lasts for significant duration without needing any external intervention as shown in Fig. 4. However, with the addition of noise, accuracy of the UPO parameter estimates deteriorates and adaptive tracking fails at regular intervals. With no noise, control application was needed on an average every 1-th iteration while with a small value of noise, control application was needed every 7th iteration on an average. This signifies the difficulty of adaptively controlling a known deterministic system even in the presence of very low level of dynamical noise that does not alter the geometry of the return map appreciably [13].

To re-examine the apparent success of the repeat chaos control experiment on epileptic brain slices using the stringent adaptive tracking method [22, 23], we repeat the procedure on a stochastic neural network model of epileptic brain slices [19, 20] with same strategy. For completeness, a brief description of this computer model for epileptic hippocampal slices [43] is presented below. The neural network consists of \(N\) McCulloch-Pitts (binary) neurons \(S_i \in \{0, 1\}\), each exci-

| Noise Level | \(\lambda_s\) Mode Range | \(\lambda_u\) Mode Range | \(x^\ast\) Mode Range |
|-------------|--------------------------|--------------------------|--------------------------|
| 0.0         | 0.1064 0.8919 -1.7929 0.8361 0.0647 0.3764 |
| 0.1         | 0.1428 7.6847 -1.7719 10.417 0.6593 0.4338 |
| 0.2         | 0.1432 12.766 -1.7008 20.417 0.6512 1.8558 |

TABLE II: Manifolds and fixed point estimate using modified Pei-Moss criterion from 50 ensembles 4096 point data set of Hénon map (Actual \(\lambda_s, \lambda_u, x^\ast\) are 0.178, -1.69 and 0.6667 respectively.)

![FIG. 4: Adaptive control of Hénon map (a) without noise, (b) with noise=0.005](image-url)
tatory, where 0 and 1 represent the low and high firing rates respectively. The inhibitory neurons are collectively modelled by a background inhibition that is proportional to the number of active excitatory neurons. The “local field” at the $ith$ neuron at time $t$ is given by

$$h_i(t) = \sum_{j=1}^{N} [J_{ij}S_j(t) - wS_j(t)] + \lambda(K_{ij}S_j(t-\tau) - wS_j(t-\tau)),$$

where $w$ is the relative strength of inhibition, $\lambda$ is the relative strength of the delayed signal, and $\tau$ is the time delay associated with the delayed signal. The four terms from left, fast global excitation, fast global inhibition, slow global excitation and slow global inhibition are essential [44] for a realistic modelling of neural oscillations in the hippocampus. The “time” $t$ is discrete, with each unit (referred to as one “pass”) corresponding to the updating of $N$ neurons. The neurons are updated one at a time in a random sequence, according to the rule: $S_i(t+1) = 1$ if $h_i(t) \geq 0$ and $S_i(t+1) = 0$ if $h_i(t) < 0$.

A fixed number $(q)$ of random low activity patterns (“memories”) $\{\xi_i^\mu\}$, $i = 1, 2, \ldots, N; \mu = 1, 2, \ldots, q$, are stored in the synaptic matrices $J_{ij}$ and $K_{ij}$ as $J_{ij} = \Theta(\sum_{\mu=1}^{q} \xi_i^\mu\xi_j^\mu)$ and $K_{ij} = \Theta(\sum_{\mu=1}^{q} \xi_i^{\mu+1}\xi_j^\mu)$ respectively. $\Theta(x) = 1(0)$ if $x > 0 (x \leq 0)$, $\xi_i^{\mu+1} = \xi_i$ and $J_{ii} = K_{ii} = 0$. Each memory contains $n$ “active” neurons chosen randomly and $n = \sum_{i=1}^{N} \xi_i^\mu << N$ ensures low average activity of the network in the absence of any external stimulus. Due to the properties of the synapses and with appropriate choice of other parameters (specifically, for $\lambda > 1$ and $w < 1$), the network exhibits a low-activity limit cycle in which all the $q$ memories are visited sequentially [43]. In this work, the chosen parameter values are: $N = 200$, $q = 20$, $n = 10$, $w = 0.6$, $\lambda = 2$, $\tau = 2$ passes.

The hippocampal brain slices used in the chaos control experiments were chemically kindled to generate epilepsy. This process is replicated in this computer model by reduced inhibition (equivalent to excitation) accompanied with hebbian learning [43]. The network was excited by choosing $w = 0.24$ for 50 initial passes during which new fast connections were created through a hebbian learning mechanism. Addition of these new connections generates spontaneous population bursting similar to the bistable dynamics of epileptic bursts and it has been established that in this computer model of epileptic brain slices, the underlying dynamics of these epileptic bursts are stochastic in nature [20].

Although this model with binary neurons and synapses may be inadequate for truly describing neurobiological dynamics of an hippocampal slice that depends crucially on the detailed biophysical properties of individual neurons, it incorporates a number of important neurobiological features of kindled brain slices. Networks of binary neurons can still qualitatively describe the collective dynamical behavior of biological networks. In the context of this paper, however, this model is ideally suited for simulating the control experiments on computer similar to the real experiments on brain slices. Further, the proven stochastic nature of the bursting dynamics makes it a suitable surrogate model on which UPOs detection and adaptive chaos control experiments should be reasonably difficult to reproduce with comparable success and qualitatively different from the real brain slices, if the bursting dynamics of the real biological systems were deterministic in nature. Typical bursting dynamics and the first return maps of inter burst intervals (IBIs) from the computer model are shown in Fig. 5 for completeness.

Fixed point of the dynamics is estimated from the first return map of the IBIs using dynamical transformation method of So et al. [15] and manifolds are estimated using modified UPO selection criterion. To apply control, fixed radius($R_F$) within which control has to be applied is fixed as well as the desired radius within which IBIs will be left unperturbed, called control radius($R_C$). Control is switched on when current IBI lies in $R_F$ and continued till the time it enters $R_C$ [21]. Once we get inter-burst interval(IBI) within $R_F$, time of next IBI is calculated using

$$T_{n+1} = \lambda_s(T_n - fp) + fp,$$

where $T_n$ is the time interval between $n^{th}$ and $(n-1)^{th}$ IBI, $\lambda_s$ is the slope of the stable manifold and $fp$ is the fixed point.
If a burst is obtained before or up to the estimated time of burst, time for the next burst is calculated and the process is continued. Otherwise inhibition ($\omega$) is reduced for next five passes to generate a stimulated burst [20].

It is found that as $R_C$ is decreased, more and more number of control stimuli has to be applied and variance of IBIs decreases Fig. 6. As $R_F$ is decreased, lesser number of control stimuli has to be applied and variance of IBIs increases. To get quality control, both $R_C$ and $R_F$ value have to be optimized taking into consideration variance of IBIs. Quality of control is improved by adaptive tracking of UPOs. We use 10 natural triplets to refine the value of fixed point and manifolds by least square fit method using singular value decomposition. Care is taken that, naturally terminated IBI must lie within a small radius ($R_{NT}$) from previous estimate of fixed point. To tackle the problem of fluctuations in the fixed point estimate, previous fixed point estimate is refined if and only if new estimate lies within a small radius from the previous fixed point called a process known as fixed point adjustment maximum (FAM) [21]. This process helps tackle the problem of nonstationarity. Control applications for different values of the control radii are shown in Fig. 7. It is observed that application of chaos control reduces the concentration of IBIs over and above the fixed point. The SMP control ensures external stimuli if the IBIs are above the fixed point because slope of the stable manifold is usually small. Therefore, lesser the concentration above fixed point, better is the quality of control. Control achieved was good but deteriorated once adaptive tracking was introduced as there is modification either to the stable eigenvalue or to the fixed point. Number of passes required to obtain desired number of IBIs decreases as control is applied.

As control radius ($R_C$) is increased, the fraction of IBIs above the fixed point decreases and the fraction of Stimulated IBIs increases. As the strength of inhibition is reduced, less number of IBIs are simulated keeping other parameters constant. Decreasing concentration of points over and above fixed point requires more and more number of control stimuli, indicating equivalence of chaos control and demand pacing. Result of our adaptive chaos control application on the stochastic neuron model of epileptic brain slice is shown in Fig. 2. Quality of control, effect of control radii on the variation of the variance and fraction of stimulated IBIs are found to be in very good agreement with the results of adaptive chaos control experiment performed on actual biological network [21]. This indicates that more stringent UPO detection or adaptive UPO control may not necessarily be the reason of successful chaos control in this experiment. This comparison also indicates that the true system and the stochastic neural network models can be discriminated through UPO analysis using topological recurrence criteria, but, the two systems cannot be discriminated on the basis of the chaos control although one is clearly a stochastic system.

IV. DISCUSSION AND CONCLUSION

Nonlinear dynamics tools have been immensely useful in both the understanding of biological systems and specific control applications in such systems. However, in biological systems, applications of nonlinear time series analysis tools for establishing determinism have not been straightforward. This work addresses two specific but important issues in this context - establishing determinism through detection of statistical significant UPO trajectories in the return map of interspike or interburst intervals, and extracting parameters of the underlying chaotic dynamics for applications of chaos control. Although the issues and the results presented in this work are relevant for biological systems in general, the current study has focussed on epileptic systems in particular.

Contrary to regular dynamical systems, biological time series are short, noisy, and nonstationary. We find that amongst all UPO detection methods, the topological recurrence method [33] is most reliable for analysis of biological time series for determinism. It detects, with reasonable success, statistically significant UPOs in different known dynamical systems with different geometry and in presence of moderate noise. It is also observed that as long as the added noise does not significantly alter the shape of the attractor in the return map, the method is found to be robust and applicable for datasizes exceeding 1000. However, the method was found to be not accurate in determining the fixed point of the detected UPO trajectory. This in turn affects the measurement of slopes of the stable and unstable manifolds. At the same time, a dynamical transformation method [15] is more accurate in determining the location of fixed point in the return map. We propose a new hybrid UPO detection method that combines topological recurrence method for UPO trajectory, dynamical transformation for the fixed points, and matrix fit algorithm for slope of the manifolds and this gives statistically significant UPO detection and much improved UPO parameters. For researchers analyzing biological time series, this can be a robust method for establishing determinism. This also establishes UPO detection as a viable tool for establishing determinism in moderate sized noisy biological time series, provided appropriate surrogate analysis is adopted for determining the statistical significance of the detected UPOs. Although the success of the method can be generalized to systems of different attractor shape and geometry, the statistical significance of UPOs depend on the geometry of the UPO trajectory and the frequency of visiting the trajectory.

The method does not, however, provide very accurate UPO...
parameters for chaos control strategies. Our results, obtained from known dynamical systems with noise, suggest that even minor inaccuracy in the UPO parameters makes the chaos control drift quickly, needing frequent external stimuli to keep the system near the targeted periodic orbit. The error is likely to become more serious if the system is nonstationary. If the UPOs drift because of nonstationarity, the UPO trajectories are to be repeatedly assessed from short windows. The existing methods are not reliable in determining UPO parameters from short data windows if noise is present. New adaptive methods have been proposed to overcome this. The repeat chaos control experiments conducted by Slutzky et al [21–23] reported to have achieved successful control by adopting stringent adaptive tracking and detection techniques. However, our analysis demands a more careful examination of the procedure and interpretation of the reported control results. Using a computer model of epileptic brain slices, the chaos control experiment is repeated using the same adaptive tracking method and produced comparable results. Since the epileptic bursts timings in the computer model is stochastic in nature, the comparable success casts doubt on the interpretation of the results of the experiments on real system. Since the original system also needed frequent stimulus, the application strategy is similar to demand pacing, although chaos control strategy that exploits underlying deterministic dynamics ought to be significantly different from demand pacing.

The results and analysis presented in this work may not be sufficient to conclude that determinism is positively absent in epileptic EEG. It simply means that for a sufficiently high dimensional and noisy biological system such as the epileptic brain slice, the underlying dynamics, even if possibly deterministic, is difficult to unfold with the currently available nonlinear dynamics tools. The underlying biological complexity and stochastic fluctuations make the task difficult. Nevertheless, non linear time series analysis has been seen useful in analysis of such systems. Finding more useful complexity measures as well as developing more stringent dynamical tools to unambiguously describe the dynamics of such biological system continue to remain a challenging task.

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