PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES

Nonlinear Forecasting of Non-Uniform Chaotic Attractors in an Enzyme Reaction [and Discussion]

L. F. Olsen, K. R. Valeur, T. Geest, C. W. Tidd, W. M. Schaffer and D. Lloyd

Phil. Trans. R. Soc. Lond. A 1994 **348**, 421-430
doi: 10.1098/rsta.1994.0101

Nonlinear forecasting of non-uniform chaotic attractors in an enzyme reaction†

By L. F. Olsen[1], K. R. Valeur[1], T. Geest[1], C. W. Tidd[2] and W. M. Schaffer[2]

[1]*Physical Biochemistry Group, Institute of Biochemistry, Odense University, Campusvej 55, DK-5230 Odense M, Denmark*

[2]*Department of Ecology and Evolutionary Biology, The University of Arizona, Tucson, Arizona 85721, U.S.A.*

Nonlinear forecasting was used to predict the time evolution of fluctuating concentrations of dissolved oxygen in the peroxidase–oxidase reaction. This reaction entails the oxidation of NADH with molecular oxygen as the electron acceptor. Depending upon the experimental conditions, either regular or highly irregular oscillations obtain. Previous work suggests that the latter fluctuations are almost certainly chaotic. In either case, the dynamics contain multiple timescales, which fact results in an uneven distribution of points in the phase space. Such 'non-uniformity,' as it is called, is a rock on which conventional methods for analysing chaotic time series often founder. The results of the present study are as follows. 1. Short-term forecasting with local linear predictors yields results that are consistent with a hypothesis of low-dimensional chaos. 2. Most of the evidence for nonlinear determinism disappears upon the addition of small amounts of observational error. 3. It is essentially impossible to make predictions over time intervals longer than the average period of oscillation for time series subject to continuous and frequent sampling. 4. Far more effective forecasting is possible for points on Poincaré sections. 5. An alternative means for improving forecasting efficacy using the continuous data is to include a second variable (NADH concentration) in the analysis. Since non-uniformity is common in biological time series, we conclude that the application of nonlinear forecasting to univariate time series requires care both in implementation and interpretation.

1. Introduction

In the past decade, numerous methods have been proposed to distinguish low-dimensional chaos from the output of stochastic processes. Of these, two of the most widely utilized entail estimating the system's fractal dimension (Grassberger & Procaccia 1983) and its maximum Lyapunov exponent (Wolf *et al.* 1985). Specifically, non-integer dimensions and positive exponents, so-called 'fingerprints' of chaos, have been taken as evidence of nonlinear determinism (Abraham *et al.* 1989; Tsonis 1992). In part, the popularity of this approach reflects the

† This paper was produced from the authors' disk by using the TEX typesetting system.

Phil. Trans. R. Soc. Lond. A (1994) **348**, 421–430
Printed in Great Britain

fact that dimension and Lyapunov exponents feature prominently in the theory of chaotic dynamical systems. Moreover, the algorithms in question are easily implemented on the computer. Unfortunately, there is a growing body of evidence (Osborne & Provenzale 1989; Ruelle 1990; Ellner 1991) to suggest that these and other methods designed to estimate dynamical invariants can be 'fooled' by stochastic time series in which there is demonstrably no chaotic behaviour at all.

One approach to resolving this dilemma is the 'method of surrogate data' whereby analyses of experimental data are compared with corresponding calculations carried out on stochastic data sets reproducing the linear properties of the original (Theiler *et al.* 1992). An alternative methodology, and the subject of the present report, is due to Casdagli (1992). Here, techniques from nonlinear forecasting (see below) are utilized to evaluate stochastic alternatives to nonlinear determinism. Rejection of the null hypotheses is taken as evidence favouring, though not necessarily proving, that the data are, in fact, chaotic.

Nonlinear forecasting (Farmer & Sidorowich 1987) is based on the observation that even for chaotic systems, nearby points in the phase space travel together over the short term and, in some instances, for extended time periods. Accordingly, it is possible to approximate the 'rules' by which a chaotic system evolves, even though one has no idea as to the actual equations governing the motion. Sugihara & May (1990) were among the first to apply nonlinear forecasting to biological time series. They argued that chaotic data exhibit a characteristic 'prediction profile', a consequence of sensitivity to initial conditions (Ruelle 1979), whereby the initial decline in predictability follows a negative exponential (see also, Farmer & Sidorowich 1987; Wales 1991). This pattern, they maintained was relatively insensitive to short data sets and noise, and could be used to distinguish chaos from regular dynamics in the presence of observational error.

In fact, certain types of stochastic behaviour (Lefebvre et al, 1993) exhibit similar declines in predictability. However, the scaling behaviour of predictive power with prediction time of such data is different from that of chaotic data (Sugihara & May 1990; Tsonis & Elsner 1992). Additionally, Casdagli (1992) has proposed a variant on the basic method which he suggests can be used to distinguish low-dimensional chaos from stochastic dynamics. Essentially, one uses local linear maps, induced from the reconstructed flow, to forecast the time evolution of the system. By varying what is meant by 'local', one can determine whether the dynamics are more in accordance with chaos or stochastic autoregression. That is, for a chaotic system, increasing the size of the neighbourhoods for which the linear maps are computed should lead to declining predictability, i.e. the nonlinear nature of the flow means that linear approximations to the vector field change over the phase space. Conversely, for linear stochastic systems, the rules of motion do not change over the phase space. In this case, increasing neighbourhood size results in more points being used to induce the maps. Hence, the error resulting from finite data sets will be reduced and forecasting efficacy will improve or remain constant.

Most of the algorithms used to estimate fractal dimensions and the like were developed and tested using data from dynamical systems in which points are more or less evenly distributed in the phase space. However, in biology, we often encounter highly unequal distributions. Following Nicolis *et al.* (1983), we shall refer to systems exhibiting such distributions as 'non-uniform'. Biological examples of non-uniform dynamics include the irruptive behaviour of ecological

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES

populations including insects and small mammals (May 1978), fluctuations in incidence rates of childhood diseases (Schaffer *et al.* 1988; Tidd *et al.* 1993), cardiac activity as indexed by the electrocardiogram (Babloyantz & Destexhe 1988), and the relaxation oscillators observed in certain enzyme-catalysed reactions (Geest *et al.* 1993). Even in the absence of noise, non-uniformity can play havoc with nonlinear methods. For example, in the case of irruptive time series, the standard techniques underestimate both the fractal dimension and the maximum Lyapunov exponent (Schaffer *et al.* 1988; Tidd *et al.* 1993). Conversely, when applied to relaxation oscillators, these methods underestimate the dimension and overestimate the exponent (Geest *et al.* 1993).

Nonlinear forecasting schemes also have problems with non-uniform dynamics. In particular, predictability is often much lower than one would anticipate from other estimates of the system's sensitivity to initial conditions (Tidd *et al.* 1993; Geest *et al.* 1993). Nonetheless nonlinear forecasting can provide useful information about non-uniform time series which cannot be obtained from attempts to estimate fractal dimensions and Lyapunov characteristic exponents. For example, forecasting may help to discriminate between different deterministic or stochastic models of the data (Tidd *et al.* 1993; Geest *et al.* 1993).

In the present paper, we use nonlinear forecasting to study non-uniform data from a biochemical system, the peroxidase–oxidase reaction. The results support previously reported evidence (Olsen & Degn 1977; Olsen 1983; Geest *et al.* 1992, 1993) for low-dimensional chaos in this system. However, if the experimental data are perturbed by the addition of even small amounts of noise, much of the evidence for nonlinear determinism disappears. A further consequence of non-uniformity in the experimental data is that predictions based on embedded time series of O_2 concentration are essentially impossible for prediction times longer than an average period of oscillation. Predictions over longer timescales can be achieved if a second measured variable is used as a reference variable or if predictions are made using return maps rather than continuous time series.

2. The experimental system

The peroxidase–oxidase (PO) reaction is the oxidation of reduced nicotinamide adenine dinucleotide (NADH) with molecular oxygen as the electron acceptor:

$$O_2 + 2NADH + 2H + 2H_2O + 2NAD^+.$$

When the reaction takes place at low pH with continuous supplies of both NADH and O_2, and in the presence of 2,4-dichlorophenol and methylene blue, the concentrations of O_2 and NADH oscillate (Nakamura *et al.* 1969; Olsen & Degn, 1978). In addition to periodic behaviour, both quasi-periodicity (Samples *et al.* 1992; Hauck & Schneider 1993) and chaos (Olsen & Degn 1977; Geest *et al.* 1992, 1993; Rys & Wang 1992; Förster *et al.*

1994; Hauck & Schneider 1994) have been observed. In addition, there is experimental evidence for a period doubling route to chaos followed by stable period-3 oscillations as the concentration of dichlorophenol is increased (Geest *et al.* 1992; Steinmetz *et al.* 1993; Hauck & Schneider 1994). Since the evidence for chaos in this system is unequivocal, the data constitute an ideal test case for determining the efficacy and reliability of published methods for detecting nonlinearity and

chaos in experimental time series. An additional advantage of the PO system is that the experimental results are largely reproducible by a simple mathematical model consisting of four nonlinear differential equations (Olsen 1983).

3. Materials and methods

Horseradish peroxidase (RZ 3.0) and NADH were purchased from Boehringer, Mannheim. 2,4-dichlorophenol and methylene blue (analytical grade) were obtained from Merck.

Experiments were conducted in a 20×20 mm quartz cuvette fitted with a stirrer. The cuvette was mounted in an Aminco DW 2000 dual wavelength spectrophotometer or in a Shimadzu UV-1201 single beam spectrophotometer. NADH was measured as the absorbance change at 360 nm or as the difference in absorbance at 360 nm and 380 nm. The oxygen concentration was measured with a Clark electrode inserted into the side of the cuvette. The data from the spectrophotometer and the oxygen electrode were both sampled at 1 s intervals by a personal computer through an interface board and stored on disk for later analyses. There were two experimental protocols.

Protocol I is described by Geest *et al.* (1992, 1993). Here, a 0.08–0.2 M solution of NADH is pumped at a rate of 20–40 l h^{-1} into a 7 ml reaction mixture containing 0.1 M sodium acetate, pH 5.1, 30–40 μM 2,4-dichlorophenol, 0.1 μM methylene blue and 0.5–1.0 M peroxidase. The oxygen was transported into the reaction mixture by diffusion from a gas head space above the liquid containing a mixture of oxygen and nitrogen with an O_2 content of 1.42% (v/v). The oxygen transfer constant was 0.0037 s^{-1}.

Protocol II involves a continuous flow stirred tank reactor (CSTR) with an effective liquid volume of 6.9 ml. The flow rate was controlled by a Harvard Apparatus model 22 syringe pump. Reactants were fed into the CSTR as two solutions in gastight syringes (Hamilton). One syringe contained 0.2 M sodium acetate, pH 5.1, 0.5 μM peroxidase, 0.2 μM methylene blue and 100 μM 2,4-dichlorophenol and the other contained 0.4 mM NADH in distilled water. The solutions were equilibrated with pure nitrogen before use. The dilution rate for the inflow of reactants was held constant at 4.4×10^{-4} s^{-1}. In these experiments the oxygen content of the gas phase was 0.63% (v/v) and the oxygen transfer constant was 0.0048 s^{-1}. The temperature was 28 °C in all experiments.

Four apparently chaotic experimental time series (O_2 and NADH concentrations) were the subjects of analysis. Of the four data-sets, three were obtained via Protocol I described above, while the fourth was obtained via Protocol II. In each case, the data were subdivided and the ability of the first part, the 'atlas', to predict the time evolution of the second assessed. Predictions were generated by zeroth, first and second order local predictors following the approach of Farmer & Sidorowich 1987 (see also Schaffer & Tidd 1990). Predictability was indexed by the square of the standard correlation coefficient of predicted against observed concentrations and also by the normalized root mean square error.

4. Results

In figure 1, we give an example of chaotic fluctuations of $[O_2]$ in the experimental system. Here we display a representative time series, a reconstructed (Takens 1981) phase portrait, and a return map. We emphasize that qualitatively sim-

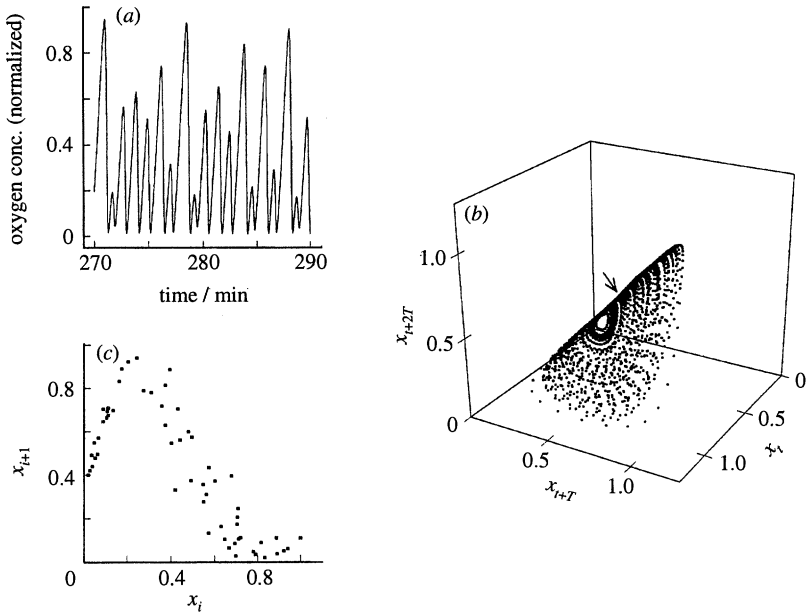

Figure 1. Chaotic dynamics in the peroxidase–oxidase reaction. (*a*) Time series of oxygen, (*b*) three-dimensional phase plot of the reconstructed time series using a delay of 6 s, and (*c*) return map constructed from a Poincaré section. The experiment was made using method I described in § 3. The experimental conditions were: 0.7 M peroxidase, 0.1 μM methylene blue and 35.7 μM dichlorophenol; 0.2 M NADH was infused at a rate of 22.5 l h^{-1}. Other conditions as described in § 3.

ilar dynamics were observed for both experimental protocols. In figure 1*b* we have plotted the phase portrait as points to emphasize the non-uniformity of the data. More than two thirds of the points are concentrated in the narrow bundle indicated by the arrow.

One approach to identifying nonlinearity in experimental time series involves nonlinear forecasting via local linear predictors (Casdagli 1992). Here, the data are embedded in an m-dimensional space by application of Takens's method of delays. For each embedding dimension, m, one varies the number, k, of neighbouring (in the phase space) atlas points used to forecast the time evolution of the target point in question. For each k, we calculate the normalized root-mean-square error, $E_m(k)$, averaged over all the target points and looks for the k-value, $k_{\min}$, which gives the lowest $E_m(k)$. Casdagli argues that if $k_{\min}$ is small, then the data are best described by a deterministic, nonlinear model. Conversely, intermediate values of $k_{\min}$ suggest that the best descriptor of the data is nonlinear stochastic models, while high values of $k_{\min}$ correspond to linear stochastic models.

Figure 2*a* shows a plot of $E_m(k)$ against k for various embedding dimensions. Overall, predictability declines as the number of points (and hence the size of the neighbourhood) used to generate the predictions increases. According to Casdagli, this suggests that the data are best described by a deterministic, nonlinear model. Further evidence for this conclusion is presented in figure 2*b*. Here we plot $E_m(k)$ for a set of 'surrogate data' which reproduce its power spectrum but with the phases randomized. As discussed by Theiler *et al.* (1992), the surrogate data are equivalent to output from a linear stochastic process. In this case, forecasting

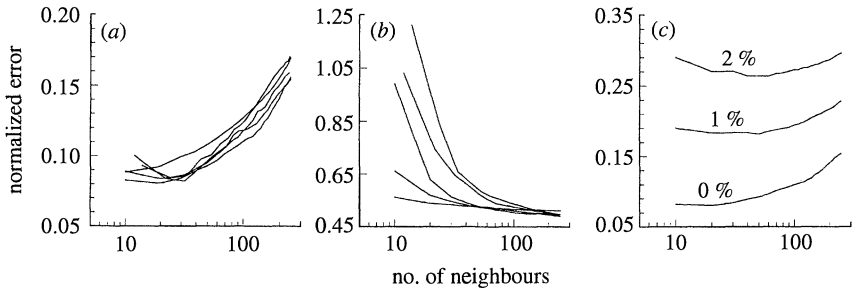

Figure 2. Forecasting errors for measurements of oxygen from the PO reaction and corresponding surrogate data generated by randomizing the phases of the discrete Fourier transform of the original data and inverting the randomized spectrum. (*a*) Original data; (*b*) surrogate data; (*c*) original data with 0, 1, and 2% observational noise. 3780 data were embedded in dimensions 2 to 6 (in (*c*) the embedding dimension was 3) using a delay of 6 s. The first 3000 points were used to predict the remaining 780 points. A local linear prediction scheme was used and the number of nearest neighbours was varied. Prediction time was 6 s. Experimental conditions as in figure 1.

efficacy declines as we increase the number of points used to induce predictions. This, of course, is what Casdagli tells us should happen, and it indicates in a dramatic way that the experimental time series contains functionally important nonlinearities. In short, application of Casdagli's method provides yet another bit of evidence supporting a chaotic interpretation of irregular fluctuations in the reaction.

Sadly, the efficacy of this approach turns out to be sensitive to the level of observational error which in many systems is far greater than that encountered in the case of the PO reaction. Specifically, if we corrupt the experimental data with small (1–2%) amounts of noise, $k_{\min}$ is shifted toward higher values or vanishes completely (figure 2*c*). At 2% noise predictability is lost to the extent that, according to Casdagli, one can only conclude that the time series is nonlinear, but not that it is low-dimensional, i.e. chaotic. In other words, a small increase in observational error can weaken or entirely eliminate the evidence for low-dimensional chaos as indicated by the present technique. Elsewhere, we argue that this sensitivity is a consequence of the data's non-uniform character.

Because of sensitivity to initial conditions, it is expected (Farmer & Sidorowich 1987; Sugihara & May 1990; Wales 1991; Tsonis & Elsner 1992) that predictability for chaotic data should decline with increasing length of the prediction interval. Moreover, there exist scaling statistics which, at least in principle, relate predictability profiles to the rate at which neighbouring trajectories diverge in the phase space. For our data we observe such a decline in prediction efficacy with increasing length of the prediction interval. However, if we compare the prediction profiles obtained for the continuous data and for the maps respectively, we find that the predictive power of the map is far greater than that of the continuously sampled time series. Additionally, the scaling statistics of the two profiles (data not shown) are different, to the point that the profile for the continuously sampled data is inconsistent with an interpretation of low-dimensional chaos (Wales 1991; Tsonis & Elsner 1992).

Why are return maps more predictable than the continuous data? To answer this question we made a number of forecasts of points from different regions of the reconstructed attractor. Two such forecasts are shown in figure 3. Here we com-

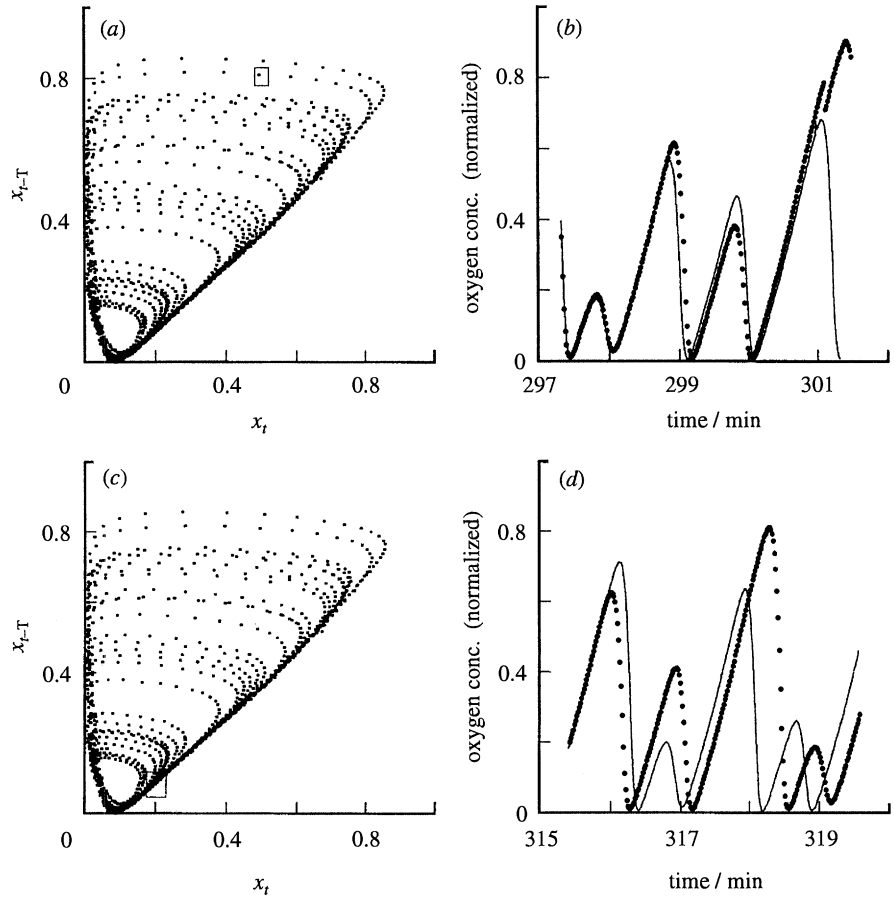

Figure 3. Nonlinear forecasting of different regions of the reconstructed phase plot. In (*a*) and (*c*) the boxes indicate the points to be predicted. In (*b*) and (*d*) the predicted (filled circles) and observed values (solid lines) are shown for a prediction time of 240 s. The data were embedded in three dimensions using a delay of 10 s. The first 2000 points were used to predict the remaining 1780 points. A zero-order prediction scheme was used. Experimental conditions as in figure 1.

pare the predictability of a point on the Poincaré section used to construct the return map with that of a second point in the compressed region of the attractor. In the latter case predicted and observed values diverge rapidly. Conversely trajectories based at points on the section are much more predictable. This suggests that the limited predictive power of the continuous data is due to the preponderance of points in the compressed region, which has low predictability, and hence to the non-uniformity.

Similar results (not shown) were obtained using data produced by a mathematical model (Olsen 1983) of the PO reaction, i.e. the predictive power of points in the compressed region of the attractor is essentially zero for values of T_p in excess of the average period of oscillation. Why is this compressed region so unpredictable? To understand this we studied Poincaré sections of this region for the model data. We found that these sections evidence a complex mixing of trajectories with the consequence that nearby points on the section do not necessarily

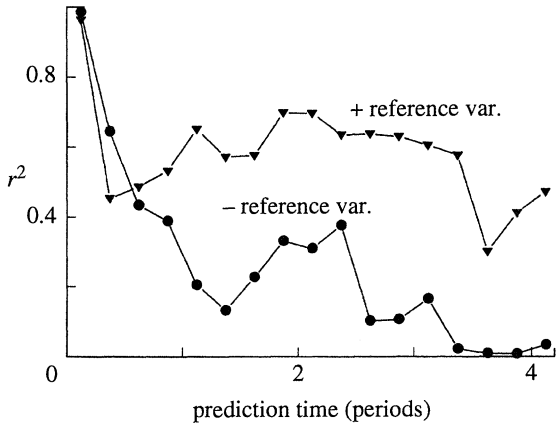

Figure 4. Prediction profile for continuous oxygen data and continuous oxygen plus NADH data. Prediction time is normalized to the average period of oscillation which was 200 s. The data-set contained 10000 measurements of oxygen and NADH. First the oxygen data were embedded in three dimensions using an embedding delay of 20 s. The first 7000 points were used to predict the remaining 3000 points and the squared correlation coefficient was plotted against prediction time. Next the oxygen data were embedded in two dimensions and the NADH data were used as the third variable. Again the first 7000 points were used to predict the last 3000 points and the squared correlation coefficient was plotted against prediction time. The experiment was made using Method II described in § 3.

correspond to nearby trajectories in state space at a later time. Obviously, what is needed is a way of 'unfolding' these regions such that points which are initially close together do not wind up too far apart. In principle, one can do this by increasing the embedding dimension. However, for experimental systems subject to dynamical and observational noise, this introduces yet another source of error, i.e. the 'dimensions' are lagged values of the observed variable and the longer the lag the greater the error. Alternatively, one can include a second variable in the analysis. Figure 4 illustrates the results of supplementing the $[O_2]$ time series with simultaneous determinations of [NADH], i.e. the oxygen data were embedded in two dimensions and the NADH data used as a third variable. As one might hope, long term predictive power is greatly enhanced by the inclusion of this extra variable.

5. Discussion

The foregoing analysis may be viewed as an exercise in the study of non-uniform data. Having investigated the effects of noise on the prediction statistics for such data, we conclude that evidence for nonlinear determinism is easily obscured by small amounts of measurement error. Moreover, prediction profiles of non-uniform data reveal a scaling behaviour inconsistent with the hypothesis of low-dimensional chaos, i.e. predictability declines too rapidly. In short, nonlinear forecasting applied to non-uniform chaotic data can easily lead to the wrong conclusion, i.e. that the time series evidence stochasticity as opposed to chaos. As noted above, non-uniform data in biological systems are a commonplace and are often contaminated with far more noise than the PO data which are obtained in a carefully controlled laboratory situation. A much studied example of non-uniform biological data are monthly notifications of measles in large First World

cities. Following the application of nonlinear forecasting to such time series, Ellner (1992) and Casdagli (1992) concluded that the evidence for low-dimensional chaos in the data is at best ambiguous. Ellner, in particular, pointed to the fact that log transforming the data resulted in an increase in long term predictive power from which he concluded that the shape of the prediction profile is indecisive. In fact, for irruptive time series, the effect of such a transformation is to reduce the degree of non-uniformity, which is also the effect of restricting one's analysis to return maps computed from Poincaré sections of the sort shown in figure 1. Accordingly, we would argue that Ellner's results are consistent with the thrust of the present paper which is that non-uniformity is a source of Type II error whereby one incorrectly accepts the null hypothesis of stochastic dynamics. For the particular case of measles, this point of view is further supported by the results reported by Tidd *et al.* (1993).

This work was supported by grants from the Danish Natural Science Research Council to LFO and from National Institutes of Health to W.M.S. We thank Bruce Kendall for stimulating discussions.

References

Abraham, N. B., Albano, A. M., Passamante, A. & Rapp, P. E. (eds) 1989 *Measures of complexity and chaos.* NATO ASI Series B, vol. 208. New York: Plenum Press.

Babloyantz, A. & Destexhe, A. 1988 Is the normal heart a periodic oscillator? *Biol. Cybern.* **58**, 203–211.

Casdagli, M. 1992 Chaos and deterministic versus stochastic nonlinear modelling. *Jl R. statist. Soc.* B **54**, 303–328.

Ellner, S. 1991 Detecting low-dimensional chaos in population dynamics data: a critical review. In *Chaos and insect ecology* (ed. J. A. Logan & F. P. Hain), pp. 63–90. Blacksburg, Virginia: University Press of Virginia.

Farmer, J. D. & Sidorowich, J. J. 1987 Predicting chaotic time series. *Phys. Rev. Lett.* **59**, 845–848.

Förster, A., Hauck, T. & Schneider, F. W. 1994 Chaotic resonance of a focus and entrainment of a limit cycle in a periodically driven peroxidase–oxidase reaction in a CSTR. *J. phys. Chem.* **98**, 184–189.

Geest, T., Steinmetz, C. G., Larter, R. & Olsen, L. F. 1992 Period-doubling bifurcations and chaos in an enzyme reaction. *J. phys. Chem.* **96**, 5678–5680.

Geest, T., Olsen, L. F., Steinmetz, C. G., Larter, R. & Schaffer, W. M. 1993 Nonlinear analyses of periodic and chaotic time series from the peroxidase–oxidase reaction. *J. phys. Chem.* **97**, 8431–8441.

Grassberger, P. & Procaccia, I. 1983. Measuring the strangeness of strange attractors. *Physica* D **9**, 189–208.

Hauck, T. & Schneider, F. W. 1993 Mixed-mode and quasi-periodic oscillations in the peroxidase–oxidase reaction. *J. phys. Chem.* **97**, 391–397.

Hauck, T. & Schneider, F. W. 1994 Chaos in a Farey sequence through period doubling in the peroxidase–oxidase reaction. *J. phys. Chem.* **98**, 2072–2077.

Lefebvre, J. H., Goodings, D. A., Kamath, M. V. & Fallen, E. L. 1993 Predictability of normal heart rhythms and deterministic chaos. *Chaos* **3**, 267–276.

May, R. M. 1978 Fluctuations in abundance of tropical insects. *Nature, Lond.* **278**, 505–507.

Nakamura, S., Yokota, K. & Yamazaki, I. 1969 Sustained oscillations in a lactoperoxidase, NADH and O_2 system. *Nature, Lond.* **222**, 794.

Nicolis, J. S., Meyer-Kress, G. & Haubs, G. 1983 Non-uniform chaotic dynamics with implications to information processing. *Z. Naturf.* A **38**, 1157–1169.

Olsen, L. F. 1983 An enzyme reaction with a strange attractor. *Phys. Lett.* A **94**, 454–457.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES

Olsen, L. F. & Degn, H. 1977 Chaos in an enzyme reaction. *Nature, Lond.* **267**, 177–178.

Olsen, L. F. & Degn, H. 1978 Oscillatory kinetics of the peroxidase–oxidase reaction in an open system. Experimental and theoretical studies. *Biochim. Biophys. Acta* **523**, 321–334.

Osborne, A. R & Provenzale, A. 1989 Finite correlation dimension for stochastic systems with power law spectra. *Physica* D **35**, 357–381.

Ruelle, D. 1979 Sensitive dependence on initial condition and turbulent behaviour of dynamical systems. *Ann. N.Y. Acad. Sci.* **316**, 408–416.

Ruelle, D. 1990 Deterministic chaos: the science and the fiction. *Proc. R. Soc. Lond.* A **427**, 241–248.

Rys, P. & Wang, J. 1992 Hydrogen/deuterium isotope effects in the oscillating peroxidase–oxidase reaction. *Biochem. Biophys. Res. Commun.* **186**, 612–616.

Samples, M. S., Hung, Y.-F. & Ross, J. 1992 Further experimental studies of the horseradish peroxidase–oxidase reaction. *J. phys. Chem.* **96**, 7338–7342.

Schaffer, W. M., Olsen, L. F., Truty, G. L., Fulmer, S. L. & Graser, D. J. 1988 Periodic and chaotic dynamics in childhood infections. In *From chemical to biological organization* (ed. M. Markus, S. C. Müller & G. Nicolis), pp. 331–347. Berlin: Springer-Verlag.

Schaffer, W. M. & Tidd, C. W. 1990 *NLF: nonlinear forecasting for chaotic dynamical systems.* Tucson, Arizona: Dynamical Systems, Inc.

Steinmetz, C. G., Geest, T. & Larter, R. 1993 Universality in the peroxidase–oxidase reaction: period doublings, chaos, period three, and unstable limit cycles. *J. phys. Chem.* **97**, 5649–5653.

Sugihara, G., Grenfell, B. & May, R. M. 1990 Distinguishing error from chaos in ecological time series. *Phil. Trans. R. Soc. Lond.* B **330**, 235–251.

Sugihara, G. & May, R. M. 1990 Nonlinear forecasting as a way of distinguishing chaos from measurement error in time series. *Nature, Lond.* **344**, 734–741.

Takens, F. 1981 Detecting strange attractors in turbulence. In *Dynamical systems and turbulence* (ed. D. Rand & L. S. Young), pp. 366–381. Berlin: Springer-Verlag.

Theiler, J, Galdrikian, B., Longtin, A., Eubank, S. & Farmer, J. D. 1992 Using surrogate data to detect nonlinearity in time series. In *Nonlinear modelling and forecasting* (ed. M. Casdagli & S. Eubank), pp. 163–188. Redwood City, California: Addison-Wesley.

Tidd, C. W., Olsen, L. F. & Schaffer, W. M. 1993 The case for chaos in childhood epidemics. II. Predicting historical epidemics from mathematical models. *Proc. R. Soc. Lond.* B **254**, 257–273.

Tsonis, A. A. 1992 *Chaos: from theory to applications.* New York: Plenum Press.

Tsonis, A. A. & Elsner, J. B. 1992 Nonlinear prediction as a way of distinguishing chaos from random fractal sequences. *Nature, Lond.* **358**, 217–220.

Wales, D. J. 1991 Calculating the rate of loss of information from chaotic time series by forecasting. *Nature, Lond.* **350**, 485–488.

Wolf, A., Swift, J. B., Swinney, H. L. & Vastano, J. A. 1985 Determining Lyapunov exponents from a time series. *Physica* D **16**, 285–317.

Discussion

D. Lloyd (*Microbiology Group, UWCC, Cardiff, U.K.*). Are there any 'dead spots' in the continuously stirred reactor? Is the system spatially homogeneous? For instance, what happens if you change the stirring rate?

L. F. Olsen. If we change the stirring rate we also change the surface area of the liquid. This results in a change in the oxygen supply rate and hence a change in dynamics irrespective of whether the system is spatially homogeneous or not.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES