Characterisation of congenital nystagmus waveforms in terms of periodic orbits

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Received 2 March 2001; received in revised form 3 December 2001

Abstract

Because the oscillatory eye movements of congenital nystagmus vary from cycle to cycle, there is no clear relationship between the waveform produced and the underlying abnormality of the ocular motor system. We consider the durations of successive cycles of nystagmus which could be (1) completely determined by the lengths of the previous cycles, (2) completely independent of the lengths of the previous cycles or (3) a mixture of the two. The behaviour of a deterministic system can be characterised in terms of a collection of (unstable) oscillations, referred to as periodic orbits, which make up the system. By using a recently developed technique for identifying periodic orbits in noisy data, we find evidence for periodic orbits in nystagmus waveforms, eliminating the possibility that each cycle is independent of the previous cycles. The technique also enables us to identify the waveforms which correspond to the deterministic behaviour of the ocular motor system. These waveforms pose a challenge to our understanding of the ocular motor system because none of the current extensions to models of the normal behaviour of the ocular motor system can explain the range of identified waveforms.

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Keywords: Nystagmus; Analysis; Fourier; Periodic orbits

1. Introduction

Congenital nystagmus is an involuntary oscillation of the eyes which develops at birth or shortly afterwards and persists through life. Clinically, the nystagmus has been described in terms of its peak-to-peak amplitude, frequency, mean velocity and waveform, but these measures do not directly relate to the aetiology of congenital nystagmus (Abadi & Dickinson, 1986; Yee, Wong, Baloh, & Honrubia, 1976). Because of the variability of congenital nystagmus waveforms, it is not yet even clear if the underlying mechanism is deterministic (Abadi, Broomhead, Clement, Whittle, & Worfolk, 1997; Reccia, Roberti, & Russo, 1990), although all the proposed explanations of congenital nystagmus have been based on deterministic models (Broomhead et al., 2000; Harris, 1995; Optican & Zee, 1984).

Consider the intervals between successive quick phases in a congenital nystagmus waveform. The variation of the length of these intervals could reflect the behaviour of a deterministic system behaving chaotically, a stochastic system or some combination of these two extreme cases, such as would arise if a deterministic system were contaminated by noise. Let the length of the nth interval be denoted by \( \tau_n \) and the length of the next interval by \( \tau_{n+1} \), then the behaviour of a deterministic system can be described by the map \( \tau_{n+1} = f[\tau_n, \tau_{n-1}, \ldots, \tau_{n-d+1}] \), where \( f \) in general is a nonlinear function and \( d \) is the number of previous intervals on which the next interval depends. At the other extreme, consider the behaviour of a stochastic system described by a map of the form \( \tau_n = \xi_n \), where \( \xi_n \) denotes selection of an interval length according to the probability distribution which defines \( \{\xi_n\} \) as an independent, identically

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distributed random process. So the behaviour of a deterministic system contaminated by noise can be described by the map $\tau_{n+1} = f[\tau_n, \tau_{n-1}, \ldots, \tau_{n-d+1}] + \alpha x_n$, where $x$ is a parameter giving the amplitude of the random term. A question which follows naturally from this description, is whether there is a deterministic component underlying the generation of the intervals between quick phases in congenital nystagmus? As the deterministic component will be directly related to the underlying mechanism of the ocular motor system, a further question is how do any deterministic components vary between waveforms?

Recent work in dynamical systems theory has shown that the behaviour of a deterministic system can be understood in terms of a limited number of fundamental cycles (Auerbach, Cvitanovic, Eckmann, Gunaratne, & Procaccia, 1987), and so identification of such cycles, generally, unstable, low-period periodic orbits, provides a method of characterising a deterministic system. A recently developed technique for finding periodic orbits in noisy experimental data involves transforming the data so that it is concentrated on the periodic orbits, which can then be easily identified by sharp peaks in a histogram of the transformed data (So et al., 1996, 1997). We successfully use this technique to identify the unstable periodic orbits in recordings of congenital nystagmus waveforms, and subsequently isolate the waveform shapes associated with the periodic orbits, which any deterministic model of congenital nystagmus must be capable of reproducing.

2. Methods

2.1. Subjects

Eye movement recordings were made from five adult subjects with idiopathic congenital nystagmus, who had conjugate and uniplanar eye movements. None of our subjects exhibited tropias, nor did they have any other ophthalmological disorders. Snellen acuity was measured at 6 m. Stereo-acuity was assessed with a TNO test. The values for each subject are given in Table 1. Informed consent was obtained according to the declaration of Helsinki.

2.2. Eye movement recording

The head was restrained with a head rest and supplementary cheek rests. Subjects were instructed to fixate a stationary point in the primary position. The fixation target subtended 1° and consisted of a small cross which was encompassed by a circle. Binocular horizontal eye movements were recorded with an IRIS 6500 (Skalar Medical, Delft, The Netherlands) infrared limbal tracker. The analogue output was filtered by a 100 Hz low-pass filter, digitised to 12-bit resolution, and then sampled at 5 ms intervals (equivalent to a sampling frequency of 200 Hz). The system was linear over a range of ±20° and had a resolution of 0.03 of a degree. Calibration was carried out by asking the subjects to follow a sinusoidally moving stimulus with an amplitude of ±5°. Data from one eye, selected at random, was used for analysis.

2.3. Spectral analysis

The procedure for estimating the power spectrum of the data was based on the recommendations of Press, Teukolsky, Vetterling, and Flannery (1992). We used segment lengths of 1024 data points, corresponding to a time interval of just over 5 s, which were overlapped by half the segment length. A Bartlett window, for which the weighting of a data point is a triangular function of time interval of just over 5 s, which were overlapped by half the segment length. A Bartlett window, for which the weighting of a data point is a triangular function of position in the window, was applied to the individual segments of data to avoid spurious high-frequency components due to inequality between the endpoints of the segment.

2.4. Periodic orbit theory

The periodic orbit approach originates with the assumption that the state of a deterministic system changes in accordance with a nonlinear function of the vector variable $x = (x_1, x_2, x_3, \ldots, x_d)$ which defines the state of the $d$-dimensional system. In the discrete case, the state of the system is considered at successive occasions $n = 0, 1, 2, 3, \ldots$ and the map $M$ from one state to the next is described by the difference equation:

$$x[n + 1] = M[x[n]]$$

Table 1: Clinical details of the subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age</th>
<th>Left VA</th>
<th>Right VA</th>
<th>Snellen acuity (seconds of arc)</th>
<th>Waveform</th>
<th>Length of recording (s)</th>
<th>Amplitude (deg)</th>
<th>Frequency (Hz) (Fourier)</th>
<th>Frequency (Hz) (periodic orbit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>26</td>
<td>6/12*</td>
<td>6/12</td>
<td>120</td>
<td>J</td>
<td>20</td>
<td>7.9</td>
<td>4.0</td>
<td>4.17</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>17</td>
<td>6/9*</td>
<td>6/9</td>
<td>60</td>
<td>Jef, DJ</td>
<td>30</td>
<td>4.0</td>
<td>3.32</td>
<td>3.17</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>51</td>
<td>6/12*</td>
<td>6/12</td>
<td>480</td>
<td>PPf*</td>
<td>50</td>
<td>5.5</td>
<td>3.13</td>
<td>2.99</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>18</td>
<td>6/9</td>
<td>6/9*</td>
<td>60</td>
<td>DJ</td>
<td>25</td>
<td>7.0</td>
<td>3.91</td>
<td>5.88</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>53</td>
<td>6/12*</td>
<td>6/12*</td>
<td>240</td>
<td>J</td>
<td>50</td>
<td>3.3</td>
<td>2.93</td>
<td>3.03</td>
</tr>
</tbody>
</table>

VA—visual acuity. The asterisk by a VA signifies that the data from this eye was analysed. J—jerk, Jef—jerk with extended foveation, DJ—dual jerk and PPf*—pseudopendular with foveating saccades.
We refer to a sequence of \( x[n] \) generated in this way as an orbit. An important technique of nonlinear dynamics is to analyse the behaviour of a system by treating the state variables as coordinates of a point in a state space, and then describing the geometrical properties of sets of points which are invariant under the map. In the simplest case, the behaviour of a system will settle down to a stable equilibrium, which will appear as a single point, or to behaviour which is periodic over \( p \) iterations of the map, which will appear as a set of \( p \) points in phase space. In addition to stable or periodic behaviour, such deterministic systems can also show chaotic behaviour, which appears as an invariant, generally fractal, set of points in a restricted region of phase space. Such a set is often referred to as a strange attractor (Ott, 1993).

Consider the case of a simple fixed point \( x^* \) such that \( M[x^*] = x^* \). The behaviour of the system close to this fixed point can be described by a Taylor series expansion of \( M[x] \) around \( x^* \):

\[
M[x[n]] = x^* + \nabla M[x[n] - x^*] + O((x[n] - x^*)^2)
\]

where \( \nabla M \) is the \( d \times d \) Jacobean matrix of first derivatives of \( M \) evaluated at \( x[n] \) and \( O \) is the error term that arises from taking only the linear terms of the series. Close to a fixed point, the behaviour of the system is approximately linear and the error term is negligible. It is shown by So et al. (1997) that one can use the numerical solution to this locally valid equation as a transformation which tends to move each data point closer to the fixed point. By simply rearranging the previous equation, we obtain an expression which moves \( x[n] \) to \( x^* \), for any \( x[n] \) sufficiently close to \( x^* \):

\[
x^* = [I - \nabla M]^{-1} \cdot [M[x[n]] - \nabla M[x[n]]]
\]

This is useful, because it is unlikely that data will actually contain many points close to \( x^* \) (in the noise-free case, the data would be constant if they contain \( x^* \)). Instead of using the Jacobean matrix directly to estimate the fixed point, it is found to be useful to add a further term to produce \( \nabla M^* \) an alternative estimate for \( \nabla M \):

\[
\nabla M^* = \nabla M + R[M[x[n]] - x[n]]
\]

where \( R \) is a \( d \times d \times d \) tensor of random numbers (So et al., 1997). The inclusion of this tensor is a refinement to the basic technique which removes any spurious fixed points associated with the transformation itself.

The state-space representation of the behaviour of a system can be reconstructed directly from a time series of experimental measurements taken from the system, using the method of delays. The method consists of taking \( m \) successive measurements and treating them as the coordinates of a vector in an \( m \)-dimensional space (Takens, 1981; Sauer, Yorke, & Casdagli, 1991). This construction can be shown, in general, to be equivalent to the construction of a transformation taking points in the state space into \( m \)-dimensional delay vectors. This transformation can be shown to be invertible (although generally this inverse is unknown) and differentiable (the inverse is also differentiable). In this sense the relationship between the state-space representation and the delay space representation is essentially a nonlinear change of coordinates. In the special case that we are studying local linear dynamics it can be shown that we should choose \( m = d \) (Ott, Sauer, & Yorke, 1994). In this case, we should find local linear dynamics governed by a matrix which is similar (in the mathematical sense) to the Jacobean \( \nabla M \). In particular, this matrix, constructed from the data, will have the same spectrum of eigenvalues as \( \nabla M \) and can be estimated by a least-squares process.

A previous investigation (Abadi et al., 1997) showed that during the foveation period of the waveform, the system behaves like a 3-dimensional linear system. For the present study, the dimension of the system was reduced by 1, essentially by constructing what is known as a Poincare map. This was done by thresholding the recorded waveforms and calculating the inter-threshold crossing intervals. We therefore used the version of the data transformation algorithm which is appropriate for 2-dimensional systems.

2.5. Testing against surrogate data

If the null hypothesis is taken to be that the data is generated by a random selection from a measured set of intervals, and the discriminator statistic is taken to be the number of intervals mapped onto a peak in the histogram, then the method of surrogate data can be used to statistically test the validity of the null hypothesis. In the simplest method of surrogate data, many different alternatives to the original data are generated by shuffling the order of the intervals. From this collection of data sets, an estimate of the distribution of the discrimination statistic is computed, which correctly tests the null hypothesis (Dolan, Witt, Spano, Neiman, & Moss, 1999).

Since the distribution of the discrimination statistic is not necessarily gaussian, the test of significance involved comparing the deviation at a peak in the transformed data from the average of the surrogate data, with the distribution of maximum deviations from the average in the surrogate data (So et al., 1997).

2.6. Waveforms associated with periodic orbits

When the system generating the nystagmus is behaving linearly, the transformation maps the intervals associated with successive nystagmus cycles onto the interval length of the periodic orbit. Therefore, the difference between the transformed interval length of a cycle and the interval length of the periodic orbit is a measure of how close in state space the cycle is to the...
periodic orbit. We have found examples of the waveforms associated with the periodic behaviour by selecting the cycles whose transformed interval lengths differ least from the interval lengths of the identified periodic orbits.

3. Results

Most subjects show a combination of different waveforms, and this was true of the five subjects used in this study. Examples of their eye movements in the primary gaze position are shown in Fig. 1. These examples were selected to show the context of the identified periodic orbits, and in consequence do not display the full range of waveforms of each subject. The waveforms were classified in accordance with the scheme introduced by Dell’Osso and Daroff (1975). The eye movement recordings from subjects 1 and 5 are examples of jerk waveforms, both with occasional changes of direction. Subject 2 shows a jerk with extended foveation waveform, again with instances of changes of direction, but also with instances of a dual jerk waveform. Subject 3 is an example of the pseudopendular with foveating saccades waveform. Subject 4 shows a dual jerk waveform.

Initial, quantitative characterisation of the different waveforms is typically given in terms of average frequency and amplitude of the waveforms. The most direct method of estimating the average frequency is by spectral analysis (Abadi & Worfolk, 1991; Reccia et al., 1990), and the normalised power spectra of the five subjects are shown in the left-most column of Fig. 2. For four of the subjects there is an isolated peak in the amplitude spectrum at the fundamental frequency of the oscillation. In subject 5 there is a noticeable peak at double the fundamental frequency. Although there is a peak at 4 Hz in the amplitude spectrum of subject 4, this is not an isolated peak.

The periodicities identified by transformation of the interval data are shown in the second column of Fig. 2. All the largest peaks were significant at the 2.5% level. The underlying periodicities recovered by the two techniques were in good agreement, except for the case of subject 4. Dual jerk waveforms consist of a mixture of jerk and pendular oscillations (Dell’Osso & Daroff, 1975), and in this case the frequencies of the jerk and the pendular oscillations are similar, and so one possibility is that the system is behaving quasiperiodically, with the two frequencies generating many peaks in the amplitude spectrum at integer multiples of their difference. In order to examine this possibility we examined the oscillations of the slow phase of subject 4 in isolation. In Fig. 3, the position traces for the slow phases have been superimposed to reveal similar changes in time. The corresponding velocity profiles are shown beneath the position traces, and the period of the slow phase cycles was estimated from the intervals between crossings of the 25° per second velocity level. The periodic orbit identified in subject 4 has a frequency of 6 Hz, whereas it appears from Fig. 3 that the slow phase cycles have a frequency of approximately 7.1 Hz, which supports the hypothesis that two independent oscillations are generating multiple peaks in the amplitude spectrum. To further investigate this hypothesis, we carried out the same examination of the data of subject 2, who also has a dual jerk waveform. In this case, the frequency of the periodic orbit is 3 Hz, but the estimated frequency of the slow phase oscillations is 10 Hz, so closely spaced peaks in the amplitude spectrum would not be predicted, and indeed, are not found in the data for this subject.

4. Discussion

Identification of the underlying period length in CN waveforms is related to the problem of estimating the average frequency of the waveform. The power spectrum of a CN waveform typically consists of two or three main peaks located at integer multiples of a fixed frequency. The lowest frequency has the largest amplitude, especially in the case of pendular nystagmus, and can be used to obtain an estimate of the average

![Fig. 1. Three second segments of the eye movement recordings from the five subjects examined in this study. The grey level of each cycle of the waveform has been set according to how closely the cycle maps onto the periodic orbit under the data transformation (see text for further details). Black corresponds to zero difference.](image-url)
frequency and amplitude of the CN (Abadi & Worfolk, 1991; Reccia et al., 1990). The shape of the power spectrum of the nystagmus waveforms, in which most of the energy is concentrated around a single frequency, is consistent with underlying periodic behaviour, rather than deterministic chaotic behaviour, which typically has a broad band spectrum (Tufillaro, Abbott, & Reilly, 1992). The data transformation technique for finding periodic orbits identifies period lengths which are similar to the those obtained from the peaks of the power spectra, but has the advantage that it can be used to identify passages in the data where the behaviour of the system most closely approximates to periodic behaviour.

We have found statistically significant evidence for periodic cycles within congenital nystagmus waveforms,
and this behaviour could arise from a deterministic system behaving chaotically, or from a periodic system with noise. In either case, the fixed point technique of So et al. (1996, 1997) is effective in recovering the underlying periodic orbits. To distinguish between the two possible mechanisms, would require a local linear analysis of the stability of the fixed point, as the chaotic mechanism will have a combination of a stable and an unstable direction, whilst the periodic mechanism will have both directions stable. Unfortunately, we have too few data points to fit such a model reliably, so we are unable to distinguish between the two possibilities with our data. Our data sets consist of several hundred intervals, whereas those for which linear models have been established typically consist of several thousand intervals. (Braun et al., 1997, 1999; Pei & Moss, 1996). However, several studies show that noise may play a crucial role in the calibration of the ocular motor system (Dean & Porrill, 1998; Harris & Wolpert, 1998), so that a periodic system with noise seems a more likely mechanism than a chaotic system. If the former is the case, then the most appropriate type of model for describing the relation between successive intervals will be a Markov process.

The finding that ocular motor system underlying congenital nystagmus has a deterministic component distinguishes it from vestibular and optokinetic nystagmus, which do not appear to be based on a deterministic mechanism. A model of optokinetic nystagmus, which used a random timing mechanism for the generation of fast phases, showed no difference from actual data on measures of predictability or recurrence (Shelhammer & Nabeel, 1997, Chap. 129). In the case of vestibular and optokinetic nystagmus, the eyes are moved to a new region of interest during the fast phase and matched to the image motion during the slow phase. The region of interest is presumably set by cortical processes which will have a large number of degrees of freedom.

Identification of the waveforms associated with periodic orbits within nystagmus recordings provides a challenge for models of the underlying ocular motor mechanism, which must be able to generate similar periodic orbits, if they are to be considered realistic. Several models have been produced which explain the different congenital nystagmus waveform shapes, but currently no model of the normal ocular motor system has been extended to produce a typical nystagmus time series. Optican and Zee (1984) proposed that in the normal eye movement system, the time constant of the neural integrator is lengthened by a positive eye position feedback loop and a negative eye velocity loop, and they hypothesized that in congenital nystagmus, the sign of the velocity feedback becomes reversed, leading to
instability in the system. Harris (1995) replicated congenital nystagmus waveforms by increasing the gain in a positive velocity feedforward pathway of a model of the normal smooth pursuit system. Broomhead et al. (2000) showed that an anomalous increase in the off response of burst cells results in the formation of congenital nystagmus waveforms.

The dual jerk waveforms of subjects 2 and 4 are problematical for these models. Currently, only the Optican and Zee model can explain them. In the Optican and Zee model, dual jerk waveforms appear through a combination of the effects of nonlinearities in the position and velocity feedback loops of the neural integrator, so that as soon as the slow phase velocity increases to a threshold level, the integrator/plant system becomes stable again, and eye velocity decreases again. However, as Optican and Zee themselves pointed out, an alternative explanation might be that the sinusoidal oscillations are due to delays in a feedback loop, in keeping with the superimposed waveforms of subject 4, which are shown in Fig. 3. Both short latency following (Miles, 1998) and the damped representation of eye position (Dassonville, Schlag, & Schlag-Rey, 1992) have a latency of around 80 ms and it may be that these signals have a longer latency in congenital nystagmus, which is often associated with a sensory deficit. These signals will need to be incorporated before a satisfactory model of congenital nystagmus is obtained. Recently it has been argued that an explanation of the mechanism of congenital nystagmus will only emerge within the context of a model which embraces all the oculomotor subsystems and their interactions, and not just a particular oculomotor subsystem, such as the saccade generator or the pursuit system (Dell’Osso & Jacobs, 2001).

We plan to apply the fixed point technique to the results of manipulating congenital nystagmus waveforms, by variation of gaze angle and feedback controlled target displacement, in order to delineate the waveforms changes that such a comprehensive model must be able to explain.

Analysis of congenital nystagmus in terms of periodic orbits has implications for control of the nystagmus waveform, since both periodic and chaotic systems can be controlled by making small perturbations to move the state of the system from close to one periodic orbit to another. Although the lack of evidence for chaotic behaviour rules out the use of chaos control techniques, the behaviour of a periodic system with noise can be stabilised by the use of periodic forcing. This technique for stabilising the nystagmus waveform could be investigated by repetitively displacing a stimulus with the same movement as that of the nystagmus cycle which most closely follows the period 1 orbit. The success of this approach could be measured in terms of changes in the length of the foveation period, since this is known to correlate with visual acuity.

Acknowledgements

We thank Mark Spano and Tom Carroll for pointing out the relevance of the technique of So et al. (1996, 1997) to our data.

References


