

Available online at www.sciencedirect.com



Vision Research 43 (2003) 2357-2362

Vision Research

www.elsevier.com/locate/visres

# Effects of tenotomy surgery on congenital nystagmus waveforms in adult patients. Part II. Dynamical systems analysis

Kenichiro Miura, Richard W. Hertle, Edmond J. FitzGibbon, Lance M. Optican \*

Laboratory of Sensorimotor Research, National Eye Institute, National Institutes of Health, Bldg. 49, Rm. 2A50, Bethesda, MD 20892, USA Received 23 September 2002; received in revised form 31 March 2003

## Abstract

Congenital nystagmus (CN) is an aperiodic oscillatory eye movement disorder of unknown etiology. We examined the effect of horizontal rectus tenotomy with simple re-attachment on the dimensionality of the dynamical mechanism underlying CN. The correlation dimensions (CDs) were calculated from eight patients who had tenotomy surgery. We found no significant differences in the CDs that could be associated with the surgery. The change in dimensionality was less than 5% on average. The results suggest that the tenotomy has no effect, or only a quite small effect, on the underlying mechanism of the CN beats. © 2003 Elsevier Ltd. All rights reserved.

Keywords: Eye movement disorder; Congenital nystagmus; Tenotomy; Non-linear dynamics; Correlation dimension

## 1. Introduction

Congenital nystagmus (CN) is an aperiodic oscillatory eye movement disorder of unknown etiology. Patients with CN superimpose purposeful eye movements on top of those oscillations. Recently, Dell'Osso (1998) has proposed a new potential surgical therapy for CN, i.e. simply tenotomizing the four horizontal recti and reattaching them at their original insertions. The effect of this new surgical treatment on human patients with CN is now being studied. A preliminary report of subjective measures of the effects of surgery, such as visual acuity and the extended nystagmus acuity function (NAFX, Jacobs & Dell'Osso, 1998), has already appeared (Dell'Osso et al., 2000). Our two papers present an objective analysis of the effects of tenotomy surgery on the motor system that generates the CN waveform.

The results described in the companion paper have suggested that the waveforms of CN described in terms of the wavelet power spectrum did not change after the tenotomy surgery in adult patients (Miura, Hertle, FitzGibbon, & Optican, 2003). The wavelet spectral analysis helps to find changes in waveform characteristics, such as amplitude, frequency, and shape. However, the implications from that analysis do not go beyond phenomenological descriptions. In addition to the phenomenology of the effect of tenotomy surgery, we are also interested in whether the tenotomy surgery affects the underlying dynamical mechanism of the CN pattern generator, for example, by interrupting a proprioceptive feedback pathway. However, the wavelet spectral analysis is insufficient to address this issue completely. This paper concentrates on that point. As in the first paper, the lack of a definitive model of the CN generator leads us to adopt an analytical method that does not depend upon a specific model.

Non-linear time series analyses based on dynamical systems theory (dynamical systems analysis) allow us to directly examine the underlying mechanism that generates the observed time series. The dynamical systems analysis examines the characteristics of the dynamical system in state space. The state space is a vector space whose axes are formed by the state variables of a dynamical system. State variables are the variables that hold the past history of the system. For example, there are three state variables for eye rotations about a single axis: orientation, angular velocity, and angular acceleration. If you know these three variables at any point in time, you can predict where the system will be in the future. The state variables change their values as the dynamical system evolves in time, tracing out a trajectory in the state space. An attractor is the term used to

<sup>&</sup>lt;sup>\*</sup>Corresponding author. Tel.: +1-301-496-9375; fax: +1-301-402-0511.

E-mail address: LanceOptician@NIH.GOV (L.M. Optican).

<sup>0042-6989/\$ -</sup> see front matter @ 2003 Elsevier Ltd. All rights reserved. doi:10.1016/S0042-6989(03)00410-3

denote an invariant subset of state space to which the trajectories eventually converge. If the attractor of a system is known, many characteristics of that system, such as its dimensionality, can be determined. There is a practical method (*the method of delay*) to create a replica of the attractor (*reconstructed attractor*) from a time series that preserves the topological properties, (e.g. dimensionality) of the original one. Therefore, even without knowledge about the original system, we can examine the topological characteristics of the original attractor by examining the reconstructed one. Fig. 1 shows some examples of waveforms and their reconstructed attractors (three-dimensional views) obtained



Fig. 1. Examples of attractors (right column) reconstructed from time series (left column). (A) Sinusoidal waveform (dimension 1). (B) Sum of two harmonic waves (periodic oscillation, dimension 1). (C) Sum of two non-harmonic waves (aperiodic oscillation, dimension 2). (D) Sum of three non-harmonic waves (aperiodic oscillation, dimension 3). (E) Data from a patient with CN.

by using the method of delay. The *dimensionality* of an attractor represents how many parameters are needed to model the attractor in the state space. For example, the dimension is one for the cases shown in Fig. 1(A) and (B), in which the attractor occupies a curve, because the position of the state can be completely described by using one parameter (i.e. distance along the curve). The dimension is two for the case shown in Fig. 1(C), in which the attractor occupies a two-dimensional, toroidal, surface. The dimensionality of the attractor is related to the effective number of parameters in the mechanism that generates the time series.

CN waveforms also give rise to an attractor with the method of delay (Fig. 1(E)). (In this study, we assume only that the system which generates CN is deterministic, see below.) If a therapy changes the underlying mechanism of CN, it would cause a change in the attractor's characteristics. For example, suppose that the therapy simplifies the system generating CN by interrupting some of the effective signals in that system, e.g. proprioceptive feedback. Then, a reduced dimensionality would be observed after the therapy. Thus, measuring the dimensionality of the attractor should reveal whether the therapy had any effect on the underlying mechanism of CN (see also discussion). This is a particularly important test of potential CN therapies, because one suspected cause of CN is aberrant feedback from the periphery (Leigh & Zee, 1999; Optican & Zee, 1984). There are several previously used measures of the dimensionality of attractors (e.g. Kantz & Schreiber, 1997). Of them, correlation dimension (CD) is probably the most widely used, and is used here. The CD is a generalization of dimension to a non-integer, or fractal, dimension. This measure has been used in previous oculomotor research (Aasen, Kugiumtzis, & Nordahl, 1997; Shelhamer, 1992, 1997). Here, we examined whether there is a change in the dimensionality of the mechanism generating nystagmus beats that could be associated with tenotomy surgery.

# 2. Methods

The patients examined here, the procedure of the tenotomy surgery and the method of eye movement recordings were described in the companion paper. We calculated the CD from horizontal eye position segments (240 s long) that were recorded by using the paradigm in which the patients were encouraged to look straight ahead for about 4–10 min, using both eyes.

The first step for the computation of dimensionality is to form a reconstructed attractor by using the method of delay. A point of the reconstructed attractor at time t, y(t), is represented as  $y(t) = \{x(t), x(t+L), ..., x(t+(M-1)L)\}$ , where x(t) is measured eye position; M is the embedding dimension; L is the interval between components of each point x(t). For computational convenience, y(t) was created every 60 ms. Therefore, each reconstructed attractor consisted of about 4000 points.

The procedure to compute CD was based on the Grassberger–Procaccia method (Grassberger & Procaccia, 1983). The correlation integral C(r), which is the probability of the distance between a pair of points on the attractor being smaller than radius r was estimated by using Eq. (1):

$$C(r) = \frac{2}{(N - n_{\min})(N - n_{\min} - 1)} \times \sum_{i=1}^{N-n_{\min}} \sum_{j=n_{\min}}^{N} \Theta(r - ||y(i) - y(j)||),$$
(1)

where, N is the number of the points on the reconstructed attractor,  $\Theta(\cdot)$  is the Heaviside unit-step function;  $n_{\min}$  is the number (called the 'Theiler correction') which prevents the dimension estimates from being affected by the temporal correlation of a time series. We set  $n_{\min}$  to 5 for all the computations of the correlation integral, so that it covers about 300 ms. Note that preliminary investigation showed an  $n_{\min}$  corresponding to more than 150 ms had little affect on dimension estimates. Hence, this choice was quite safe. For deterministic systems, C(r) is expected to grow as  $r^d$  as  $r \to 0$ theoretically, where d is known as the CD. In practice, d is estimated from the scaling region, known as the interval of r where the slope  $d \log(C(r))/d \log(r)$  is flat, i.e. where C(r) exhibits scaling behavior. Here, the scaling region was determined as the interval of 1 log unit that is the nearest to r = 0, over which the standard deviation of the slope is <0.3 and the slope of the best fit line on  $d \log(C(r))/d \log(r)$  is <0.5. If there was no interval that satisfied these two conditions, the CD was not assigned. The mean value of the slope in this interval is the estimated dimension. To assist in the search for the scaling region, an upper limit in r was set in the same manner as that of Shelhamer (1997). The first peak in the histogram formed from the correlation integral was used to identify the upper limit of the scaling region, since this is the distance at which the computations began to run out of points on the reconstructed attractor.

As in the previous studies (Burioka, Cornelissen, Halberg, & Kaplan, 2001; Shelhamer, 1992, 1997), for each sequence, we estimated the dimension values from several reconstructed attractors with different M, whose embedding window size  $\tau_w (= (M - 1)L)$  was kept approximately constant. Typically, the dimension estimate for each eye position sequence was given by the average of CDs obtained from embeddings with three M's (M = 9, 10 and 11). If the CD for one of these three M's could not be obtained for a sequence, the dimension estimate for that sequence was given by the average of the remaining two. Otherwise, we did not assign the dimension estimate. Note that these three M's generally provided similar dimension values (less than 10% difference). That is a necessary condition to obtain valid dimension estimates. Generally, slope values were saturated at M of less than 9 (see Fig. 2 bottom). Therefore, this choice of M's from which the dimension was determined was not important. If no clear saturation of CD was seen as M increased, we did not assign the dimension value for this sequence. Here, we set  $\tau_w$  to 200 ms throughout all the dimension calculations (for this choice, see Section 4). Fig. 2 shows  $\log(C(r))$  as a function of log(r) (top), their slopes (middle) and dimension estimates for several embedding dimensions (bottom) computed from a segment 240 s long. In this example, the CD was estimated as 3.36. For most patients, the first 240 s segment was used to obtain the dimensionality for each recording session. For P5 and P7 who had about 10 min of recording in each session, CD was calculated from two successive segments (nonoverlapped) each 240 s long.



Fig. 2. Calculation of CD. *Top*: Correlation integrals calculated from reconstructed attractors with embedding dimension of 2–11. *Middle*: Slopes of the correlation integrals shown in the top panel. The vertical broken lines in these panels are the upper and lower bounds of the scaling region determined for the correlation integrals for embedding dimension of 10. *Bottom*: CD estimates for individual embedding dimensions.

# 3. Results

Fig. 3 compares eye movement sequences during 20 s starting 80 s after the beginning of the recording for five recording sessions (pre-surgery, 1, 6, 26 and 52 weeks after the surgery) of one patient (P3). This patient exhibited, in large part, jerk, dual jerk or pendular type waveforms whose direction sometimes alternated during this interval in the pre-surgery condition. Similar waveform types can be seen also in post-operative recording sessions. Thus, the nystagmus was still clearly evident even after the surgery for this patient. All eight patients we examined exhibited a nystagmus after the surgery which was hard to discriminate visually from pre-surgery nystagmus. Thus, it is not trivial to deter-

mine whether the dynamical system responsible for the generation of CN was modified by the surgery.

The aim of the present study is to examine this point. The dimensionality, which is examined here, reflects the number of effective parameters in a dynamical system, i.e. its complexity. Thus, measuring the dimensionality of the system should reveal whether the surgery had any effect on the underlying CN mechanism.

Fig. 4 shows CD estimates. For the patients who had three recording sessions before the surgery, the dimension values for pre-surgery of individual patients were obtained by averaging over the sessions. The pre-operative dimensionality of the CN of the patient, whose eye movement sequences are shown in Fig. 3, was about 3.6. The post-operative dimension estimates ranged from 3.3



Fig. 3. A comparison of horizontal eye movements of P3 from five recording sessions (pre-operation, and 1, 6, 26, and 52 wks post-operation). The eye movements over the interval of 20 s starting at 140 s after the beginning of the recordings are shown. Horizontal and vertical bars shown in left bottom of each panel indicates 1 s and 5°, respectively.



Fig. 4. CD estimates. For each patient, the dimension estimate of pre-surgery (black), 1 wk after (dark gray), 6 wks after (medium gray), 26 wks after (light gray) and 52 wks after (white) the surgery are shown from left to right. Error bars (too small to see in most cases) indicate 1 SD calculated from dimension estimates for three pre-surgery visits (P6–P10).

to 3.6. The maximum difference between pre- and postoperative dimensionality of this patient was about 8% of the pre-surgery values.

We examined whether there is a common effect of the surgery across all the patients. First, the difference in dimensionality among visits was examined using twoway ANOVA with the data of 6 patients (P2-3, P5-8) whose data were available for all the visits (pre-surgery, 1, 6, 26, 52 wks post-surgery). A statistical analysis showed no significant differences among experimental situations (p > 0.29). We also examined the difference in dimensionality between each visit after the surgery and the pre-surgery control using a paired *t*-test. Again, in both cases no significant difference between pre- and post-operative dimension was found (p > 0.06 for 1 wk)post (N = 8), p > 0.96 for 6 wks post (N = 7), p > 0.43for 26 wks post (N = 8), p > 0.40 for 52 wks post (N = 7)). The averages of percent change of post-operative from pre-operative dimensionality ((post-pre)/pre) across the patients were less than 5% for 1 wk, less than 1% for 6 wks, less than 5% for 26 wks and less than 4%for 52 wks after the tenotomy surgery.

#### 4. Discussion

In this study, we used a dimensionality measure to study the effect of the tenotomy surgery on the patient's eye movements. Previous quantitative examinations of the effect of a treatment for CN were based on amplitude, frequency and intensity of the nystagmus, time constant of the slow phase eye movements, the length of foveation time and NAF (and its variations) (Bosone, Reccia, Roberti, & Russo, 1989; Dell'Osso & Flynn, 1979; Mezawa, Ishikawa, & Ukai, 1990; Roberti, Russo, & Segrè, 1987; Sharma, Tandon, Kumar, & Anand, 2000; Sheth, Dell'Osso, Leigh, van Doren, & Peckham, 1995). In the companion paper, we used the wavelet power spectrum (Miura et al., 2003). These descriptions are useful clinically because they reflect the visual performance of patients and/or waveform shapes. In contrast, the dimensionality may not predict whether the patient's condition is improved. For example, if the CN waveform is scaled down in amplitude, the patient will have improved in a clinical sense. However, such a scaling will not change the dimensionality of the attractor. Even if a treatment reduced the dimensionality, any attractor or trajectory of a time series with a nonzero dimensionality still corresponds to an abnormal eye movement when the patient fixates a stationary target. (Here, we neglect the quite small eye movements during fixation of normal subjects.)

A dimensionality of 1 corresponds to a harmonic oscillation, one of 2 corresponds to an aperiodic amplitude-modulated oscillation etc. Thus, the reduction of dimensionality itself does not necessarily represent an improvement in visual performance of patients. However, the dimensionality measure can still be used to assess the effect of the treatment of CN on eye movements. If a therapy changes the underlying mechanism of CN, it will cause the state space attractor to change. Thus, measuring the dimensionality of the attractor should reveal whether the therapy had any effect on the underlying CN mechanism. This may give a clue to the etiology of CN that could not be obtained with the conventional measures described above.

Abadi, Broomhead, Clement, Whittle, and Worfolk (1997) introduced dynamical systems analysis to examine CN and showed that the dynamics around the fixed point of CN are low-dimensional and deterministic. Although their method could provide the dimensionality of CN, it is not necessarily suitable for the comparison in dimensionality among systems, such as pre- vs. postsystems, because their dimensionality measure is an integer number, i.e. it has low resolution. CD is more suitable for the comparison than the approach used by Abadi et al. because this quantity is a non-integer, or fractal, dimension. Therefore, in this study, we used CD as a measure of dimensionality of the system.

In practice, there are cases in which the choice of  $\tau_w$  is important to obtain the absolute dimension (Albano, Muench, Shwartz, Mees, & Rapp, 1988; Kugiumtzis, 1996). Despite this, which  $\tau_w$  is the optimal remains unsettled. Albano et al. (1988) demonstrated, using some mathematical models, that the use of too small or too large  $\tau_w$  resulted in no, or a small, scaling region with a smaller or larger dimension value than the actual one, respectively. They recommended the use of  $\tau_w$  of 1.0–4.0 times the autocorrelation time (the time required for the autocorrelation function to decrease to 1/e of its original value). Although the "good" range of  $\tau_w$  remains unclear, it is possible that a choice of  $\tau_w$  that is far from the recommended range may not reflect the complexity of the target signal.

Here, we used  $\tau_w$  of 200 ms to estimate CD. A wavelet analysis extracted the component that is closely correlated with the nystagmus beat structure from the original eye position signal (see companion paper). In most cases, the component could be obtained by the sum of wavelet details for scales of  $2^2-2^7$  ms (in some cases,  $2^2-2^8$  ms). The averages of autocorrelation times of this component over the patients were 53 ms for the sum of wavelet details over scales of  $2^2-2^7$  and 72 ms for that over scales of  $2^2-2^8$ , respectively.

Thus, our choice (200 ms) was in the recommended range (cf. above) for both values. Therefore, we believe that the dimension estimates obtained here reflect the complexity of the waveform generator that produces the nystagmus beat patterns, which is our primary concern. However, we do not discuss further the value of the dimension estimates themselves, because the absolute value of dimension is not of interest in this study. Here it is the change in dimension that is of interest, because the purpose of this study is to examine whether the surgery modified the underlying mechanism of CN beats.

If the surgery had really changed the system generating CN beats, there should have been changes in dimensionality measured by the CD. We tested this possibility here. Our results did not show any significant differences that were associated with the tenotomy surgery. The difference between pre- and post-operative dimensionality was less than 5% on average. This implies that there is no effect, or only a quite small effect, of the tenotomy surgery on the underlying mechanism that generates CN beats.

Recently, Dell'Osso, Hertle, Williams, and Jacob (1999) examined the effect of the same tenotomy as that in this study on an achiasmatic canine with CN. They concluded that the CN damped after the tenotomy. However, in their study, effects of the tenotomy were examined on only one canine. Although, we did see a decreased wavelet spectrum of the nystagmus for a few human patients in our study (see Fig. 5 in the companion paper), that decrease was not general across all the patients we examined. Therefore, we do not think that the finding in the canine study can be generalized to our patients. Our aim in this study is not to find effects in individual cases, but rather to examine whether there is a common mechanism by which the tenotomy surgery affects CN waveforms and the system generating them. If the tenotomy really affects the mechanism that generates CN, there would be common effects of this surgery on CN waveforms across all the patients who had the same surgical procedure. We concentrated on examining this point in this and the companion papers. Unfortunately, our two studies on human adult patients have consistently suggested that there is no, or only a quite small, common change in the CN waveform generator due to the tenotomy surgery. This finding casts doubt that proprioceptive feedback from the region of the tendon insertion is part of the motor mechanism generating CN.

#### References

- Aasen, T., Kugiumtzis, D., & Nordahl, H. G. (1997). Procedure for estimating the correlation dimension of optokinetic nystagmus signals. *Computers and Biological Research*, 30, 95–116.
- Abadi, R. V., Broomhead, D. S., Clement, R. A., Whittle, J. P., & Worfolk, R. (1997). Dynamical systems analysis: a new method of analysing congenital nystagmus waveforms. *Experimental Brain Research*, 117, 355–361.
- Albano, A. M., Muench, J., Shwartz, C., Mees, A. I., & Rapp, P. E. (1988). Singular-value decomposition and the Grassberger– Procaccia algorithm. *Physical Review A*, 38, 3017–3026.

- Bosone, G., Reccia, R., Roberti, G., & Russo, P. (1989). On the variations of the time constant of the slow phase eye movements produced by surgical therapy of congenital nystagmus: a preliminary report. *Ophthalmic Research*, 21, 345–351.
- Burioka, N., Cornelissen, G., Halberg, F., & Kaplan, D. T. (2001). Relationship between correlation dimension and indices of linear analysis in both respiratory movement and electroencephalogram. *Clinical Neurophysiology*, 112, 1147–1153.
- Dell'Osso, L. F. (1998). Extraocular muscle tenotomy, dissection, and suture: a hypothetical therapy for congenital nystagmus. *Journal of Pediatric Ophthalmology and Strabismus*, 35, 232–233.
- Dell'Osso, L. F., & Flynn, J. T. (1979). Congenital nystagmus surgery: A quantitative evaluation of the effects. *Archives of Ophthalmology*, *92*, 462–469.
- Dell'Osso, L. F., Hertle, R. W., Williams, R. W., & Jacob, J. B. (1999). A new surgery for congenital nystagmus: Effect of tenotomy on an achiasmatic canine and the role of extraocular proprioception. *Journal of AAPOS*, 3, 166–182.
- Dell'Osso, L. F., Hertle, R. W., FitzGibbon, E. J., Miles, F. A., Thompson, D., & Yang, D. (2000). Preliminary results of performing the tenotomy procedure on adults with congenital nystagmus (CN)—A gift from "man's best friend". In J. A. Sharpe (Ed.), *Neuro-Ophthalmology at the Beginning of the New Millennium* (pp. 101–105). Englewood: Medimond Medical Publications.
- Grassberger, P., & Procaccia, I. (1983). Measuring the strangeness of strange attractors. *Physica D*, 9, 189–208.
- Jacobs, J. B., & Dell'Osso, L. F. (1998). An expanded nystagmus acuity function. *Investigative Ophthalmology and Visual Science*, 39, S149.
- Kantz, H., & Schreiber, T. (1997). Nonlinear time series analysis. Cambridge University Press.
- Kugiumtzis, D. (1996). State space reconstruction parameters in the analysis of chaotic time series—the role of the time window length. *Physica D*, 95, 13–28.
- Leigh, R. J., & Zee, D. S. (1999). The neurology of eye movements (3rd ed.). Oxford: Oxford University Press.
- Mezawa, M., Ishikawa, S., & Ukai, K. (1990). Changes in waveform of congenital nystagmus associated with biofeedback treatment. *British Journal of Ophthalmology*, 74, 472–476.
- Miura, K., Hertle, R. W., FitzGibbon, E. J., & Optican, L. M. (2003). Tenotomy surgery does not change the pattern generator of congenital nystagmus waveforms in adult patients. I. Wavelet spectral analysis, in press.
- Optican, L. M., & Zee, D. S. (1984). A hypothetical explanation of congenital nystagmus. *Biological Cybernetics*, 50, 119–134.
- Roberti, G., Russo, P., & Segrè, G. (1987). Spectral analysis of electrooculograms in the quantitative evaluation of nystagmus surgery. *Medical and Biological Engineering and Computing*, 25, 573–576.
- Sharma, P., Tandon, R., Kumar, S., & Anand, S. (2000). Reduction of congenital nystagmus amplitude with auditory biofeedback. *Jour*nal of AAPOS, 4, 287–290.
- Shelhamer, M. (1992). Correlation dimension of optokinetic nystagmus as evidence of chaos in the oculomotor system. *IEEE Transactions on Biomedical Engineering*, 39, 1319–1321.
- Shelhamer, M. (1997). On the correlation dimension of optokinetic nystagmus eye movements: computational parameters, filtering, nonstationarity, and surrogate data. *Biological Cybernetics*, 76, 237–250.
- Sheth, N. V., Dell'Osso, L. F., Leigh, R. J., van Doren, C. L., & Peckham, H. P. (1995). The effects of afferent stimulation on congenital nystagmus foveation periods. *Vision Research*, 35, 2371– 2382.