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A Novel Approach to Measure Variability in the Anterior Cruciate Ligament Deficient Knee During Walking: The Use of the Approximate Entropy in Orthopaedics

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A novel approach to measure variability in the anterior cruciate ligament deficient knee during walking: the use of the Approximate Entropy in orthopaedics

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ABSTRACT

Objective: The evaluation of variability of biological rhythmic activities through measures such as Approximate Entropy (ApEn) has provided important information regarding pathology in disciplines such as cardiology and neurology. This research lead to the "loss of complexity hypothesis" where decreased variability is associated with loss of healthy flexibility rendering the system more rigid and unable to adapt to stresses. ApEn as a measure of variability and complexity, correlates well with pathology while, in some cases, it is predictive of subsequent clinical changes. The study of human gait could benefit from the application of ApEn since it is also a rhythmical oscillation. Our aim was to assess the variability of the ACL deficient knee, since ACL rupture is a common musculoskeletal injury and is accompanied by altered gait patterns and future pathology in the joint. We hypothesized that the ACL deficient knee will exhibit more regular and less variable walking patterns than the contralateral intact knee.

Methods: Ten subjects with unilateral deficiency walked on a treadmill at their self-selected speed, 20% faster, and 20% slower, while kinematics were collected (50Hz) from 80 consecutive strides for each condition. The ApEn of the resulted knee joint flexion-extension time series was calculated.

Results: Significantly smaller ApEn values were found in the ACL deficient knee when compared with the contralateral intact ($F=5.57$, $p=0.022$), for all speeds. ApEn values significantly increased ($F=5.79$, $p=0.005$) with increases in walking speed.

Conclusions: The altered properties of the ACL deficient knee, which exhibits more regular and less variable patterns than the contralateral intact knee, may decrease the adaptability of the system rendering it less able to adjust to perturbations. This could

explain the increased future pathology found in the deficient knee. ApEn can be an important tool in assessing pathology and therapeutic interventions in orthopaedics.

Key words: Anterior Cruciate Ligament deficiency, Approximate Entropy, regularity, complexity, walking

INTRODUCTION

The study of variability in biological rhythmic activity (i.e. heart beat) has provided with extremely useful insights for the understanding of pathology. Specifically, numerous studies in diverse medical areas have shown that a decreased amount of variability is related with pathology. These investigations include medical domains such as heart rate control, sudden cardiac death syndrome, and epileptic seizures [Goldberger et al 1988, Babloyantz and Destexte 1986, Kaplan et al 1991]. Furthermore, a hypothesis has been proposed, where variability is described as "healthy flexibility" [Pool 1989, Goldberger et al 2002]. These investigations indicate that variations in the behaviour of the biological system may be necessary to provide flexible adaptations to everyday stresses placed on the human body. Alternatively, a lack of "healthy flexibility" is associated with rigidity and inability to adapt to stresses. This hypothesis is called the "loss of complexity hypothesis". Based on this hypothesis, it is possible that injury or pathology can result in a loss of healthy flexibility or complexity which may not be regained despite therapeutic intervention.

Another biological rhythm that can benefit from this approach is human gait. Similarly to the beating of the heart, human gait is also a rhythmical oscillation. The legs continuously oscillate backward and forward generating progression and movement. However, these movements are not the same every time and it has been shown that variability exists in human gait from one stride to another, the so called stride-to-stride variability [Hausdorff et al 1995]. Examination of this variability could provide with similar insights to pathology of the neuromusculoskeletal system as it was done with the cardiovascular system. Actually, such an approach has already been used in neurology

and in geriatrics for the examination of the effects of diabetic neuropathy, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis and aging on gait patterns [Dingwell and Cusumano 2000, Hausdorff et al, 2000, Buzzi et al 2003]. However, limited efforts [Stergiou et al 2004] have been made to utilize the evaluation of stride-to-stride variability in orthopaedics, even though such information can be important to evaluate success in surgery (i.e. ligament reconstruction, joint arthroplasty) or the effect of a specific musculoskeletal pathology. An example of such pathology can be the rupture of a ligament that connects the segments of the lower extremities and allows the natural walking oscillations to occur.

Anterior cruciate ligament (ACL) rupture is such a pathology and a common injury of the knee joint [Griffin et al 2000] that occurs during both contact and non-contact activities. Furthermore, ACL deficiency has been related to increased likelihood for developing future pathology at the knee joint [Murrell et al 2001]. ACL deficient patients exhibit excessive tibial rotation and anterior tibial translation [Lysholm M and Messner K, Georgoulis et al 2003]. Several studies have also shown alterations of walking patterns with ACL deficiency [Wexler et al 1998, Georgoulis et al 2003]. We propose to examine how variability during walking is affected by ACL deficiency. Specifically, our aim is to examine the variability that exists in the flexion and extension of the knee joint during walking when the ACL is ruptured. To elicit larger changes in variability, we also used different walking speeds. We hypothesized that "the loss of complexity" hypothesis will be true even in an orthopaedic problem such as ACL deficiency. Thus, the ACL deficient knee will exhibit a decrease in variability when compared with the intact contralateral knee in all speeds examined.

To accomplish our aim, we have set out to examine variability using Approximate Entropy (ApEn) [Stergiou et al 2004, Pincus SM and Goldberger AL, 1994]. ApEn has been widely used in pathological conditions and it has been found that sickness and aging correlate well with ApEn values [Vaillancourt and Newell 2000, Bhattacharya J 2000, Pincus and Viscarello 1992, van den Berg et al 1998, Kaplan et al 1991, Ryan et al 1994]. Specifically, in neurology it has been shown that both resting and postural tremor exhibit smaller ApEn values in patients with Parkinson's disease than in controls [Vaillancourt and Newell 2000] while epilepsy has been related to decreased electroencephalographic ApEn values [Bhattacharya J 2000]. The study by Pincus and Viscarello [Pincus and Viscarello 1992] demonstrated that decreased fetal heart rate values correspond to increased likelihood of acidosis. In endocrinology, it has been demonstrated that patients with acromegaly have altered ApEn values in growth hormone when compared to controls and that normalization is achieved after pituitary surgery [van den Berg et al 1998]. In addition it has been demonstrated that healthy elderly individuals exhibit decreased blood pressure and heart rate ApEn values when compared to healthy young adults and that women have higher heart rate ApEn than men [Kaplan et al 1991, Ryan et al 1994]. In anesthesiology, decreased electroencephalographic ApEn values were found with increasing desflurane concentrations [Bruhn J et al 2000]. It is also remarkable that ApEn changes have been seen to be predictive of subsequent clinical changes [Vikman et al 1999]. Specifically, in cardiology ApEn has been shown to be predictive of atrial fibrillation [Vikman et al 1999]. ApEn has been also used to assess postural sway and its evolution with age, as well as the development of independent sitting [Newell 1997,

Harbourne and Stergiou 2003]. But, to our knowledge, despite its increasing use in various medical fields, ApEn has not been used in orthopaedics.

METHODS AND MATERIALS

Subjects: Ten subjects (8 males, 2 females; mean age 34.7±11.1 yr, mean mass 77.3±16.7 kg, mean height 1.73±0.9 m,) that were diagnosed with complete ACL rupture using MRI scans volunteered for the ACL deficient group. In seven cases the diagnosis was later confirmed with knee arthroscopy. The mean time from injury to test was 19.9 months. Clinically, the level of deficiency was evaluated with physical examination using the Lysholm scores (68±13) and static measurement of tibial translation using KT-1000 (side-to-side differences more than 3.5 mm). The patients' level of activity was assessed with Tegner scores (mean values before and after the ACL rupture: 6.5 and 4 respectively). All subjects signed an informed consent according to the University Institutional Review Board. Permission was also obtained by the patients' physicians.

Protocol: The subjects walked on a motorized treadmill (SportsArt 6005; SportsArt America; Woodinville, WA), while a 6-camera optoelectronic system (Peak Performance Technologies; Inc.; Englewood; CO) captured the movements of fifteen reflective markers placed on selected bony landmarks of the lower limbs and the pelvis using the model described by Davis [Davis et al 1991]. The reflective markers were placed on the skin surface of both anterior superior iliac spines, mid-femurs, lateral femoral epicondyles, mid-tibias, lateral malleoli, outsoles of the shoes approximately at the second metatarsal heads, heels and the sacrum. All markers were positioned on the participating subjects by the same examiner. Using anthropometric measurements and the position of the reflective markers, we calculated the three-dimensional knee joint angular displacement using the algorithms described by Davis [Davis et al 1991]. In the present study, we only analyzed the sagittal knee angular displacement (flexion/extension) of the

knee. We chose to examine only this data, because data from the other two planes (frontal and transverse), when collected via skin markers, has been associated with increased amount of error [Cappozzo et al 1996]. Increased amount of measurement error in the data can mask the true nature of stride-to-stride variability and can possibly lead to incorrect conclusions [Rapp 1994]. We also collected three-dimensional data instead of two-dimensional to minimize measurement error due to perspective error [Areblad et al 1990].

All subjects were given ample time to warm up and familiarize with walking on the motorized treadmill at their self-selected pace which represented their most comfortable and natural walking speed. The familiarization period was six minutes which is considered sufficient for the achievement of reliable measurements [Matsas et al 1999] .Based on this pace, two new speeds were determined for each subject: one faster (20% larger) and one slower (20% smaller). The selection of this percentage was based on the following. The literature has shown that the average preferred walking speed for young healthy adults is $1.4ms^{-1}$ [Laurent and Pailhous 1986, Murray et al 1966]. The transition from walking to running usually occurs at $2.1ms^{-1}$ [Diedrich and Warren 1995]. Therefore, by increasing the walking speed by 20%, we avoided such a transition. Furthermore, such increments of speeds have been shown to affect biomechanical parameters [Voloshin, Stergiou et al 1999]. For every speed, data were collected continuously for two minutes at 50 Hz. The collected data represented at least 80 continuous walking strides. Lastly, the mean comfortable self-selected speed used by the subjects in the present study was $0.77\pm0.16ms^{-1}$.

Data Analysis: The unfiltered time series of the knee flexion/extension were analysed using the ApEn measure. Each time series consisted of 5750 data points, which is considered sufficient for this type of analysis [Pincus and Goldberger, 1994]. The number of input data points for ApEn computations is typically between 100 and 5000. The data were analyzed unfiltered so as to get a more accurate representation of the variations within the system [Mees and Judd 1993]. Furthermore, it was assumed that since the same instrumentation was used for all subjects, the level of measurement noise would be consistent for all subjects and that any differences could be attributed to changes within the system itself [Rapp PE, Stergiou et al chapter 2004]. Therefore, filtering the data may have eliminated important information and provided a skewed view of the system's behaviour.

ApEn can quantify the regularity or predictability of a time series [Pincus and Goldberger 1994,]. Specifically, ApEn measures the logarithmic probability that a series of data points a certain distance apart will exhibit similar relative characteristics on the next incremental comparison within the state space [Pincus and Goldberger 1994,]. Time series with a greater likelihood of remaining the same distance apart upon comparison will result in lower ApEn values, while data points that exhibit large differences in distances between data points will result in higher values. The ApEn mathematical definition is described in great detail in Pincus [Pincus and Goldberger 1994] and Pincus and Kalman [Pincus and Kalman 1997]. Here, we will present a compound version of this definition, as it has been adapted from these publications. Thus, to define ApEn [better identified as ApEn*(m, r, N)*]:

1) we start with our *N* input data points *u(1), u(2), …, u(N)* and we also incorporate two input parameters, *m* and *r*. The input parameter *m* is the length of compared runs, and *r* is a tolerance.

2) we form vector sequences *x(1)* through *x(N – m – 1)* from the *{u(i)}*, defined by *x(i) = [u(i), …, u(i + m – 1)]*. These vectors are basically *m* consecutive *u* values, beginning with the *i-th* point.

3) we define the distance *d[x(i),x(j)]* between vectors *x(i)* and *x(j)* as the largest difference in their respective scalar components.

4) we use the vector sequences *x(1)* through *x(N – m – 1)* to create (for each $i \neq N - m + 1$)

$C_i^m(r)$ = (number of x(j) such that d[x(i),x(j)] # *r*) / (N – *m* + 1) Equation 1.

The $C_i^m(r)$ values measure (within the tolerance *r*) the regularity of patterns similar to a given pattern of window length *m*.

5) we define $\Phi^m(r)$ as the average value of $\ln C_i^m(r)$, where ln is the natural logarithm. Lastly, we define Approximate Entropy as

$$\text{ApEn}(m,r,N) = \Phi^m(r) - \Phi^{m+1}(r) \qquad \text{Equation 2.}$$

Using ApEn we basically calculate the logarithmic probability that runs of patterns that are close (e.g., within tolerance *r*) for *m* observations remain close (with the same tolerance) on the next incremental comparisons. In all human movement studies that have used ApEn [Vaillancourt and Newell 2000, Newell 1997, Stergiou 2004], a value of two was used for *m*, while the values of r were between 0.20 and 0.25. Thus, we elected to use an *m* value equal with 2 and an *r* value equal with 0.2. ApEn was computed

for all time series from all subjects and for all speed conditions using these algorithms implemented in Matlab (The MathWorks, Inc., MA, Version 6.1).

ApEn values typically range from zero to two. Values closer to zero are consistent with greater periodicity. Conversely, values nearing two represent greater irregularity [Pincus and Goldberger 1994]. To illustrate this point we included in Figure 1 some know time series. Using these known time series, we estimated the ApEn values to be 0.000 for the periodic data (the sine wave), 0.4496 for data that have known deterministic/chaotic order (Lorenz attractor), and 1.996 for random data (white noise). It is evident from these values that the higher the complexity, the larger the value of the ApEn.

INSERT FIGURE 1 ABOUT HERE

Statistical Analysis: A two by three (side by speed) analysis of variance, repeated on both factors, was performed on the ApEn group means. This comparison allowed the identification of the effect of the speed protocol, the differences between the two sides (the ACL deficient and the intact contralateral knee) and the interaction between these two factors. Post-hoc analysis using paired t-tests was employed when appropriate. The a-level was set at 0.05.

RESULTS

Significant differences were found between the ACL deficient and the contralateral intact knee ($F=5.57$, $p=0.022$). Specifically, we found that the ACL deficient knee exhibits smaller ApEn values than the contralateral intact knee for all speeds examined (Figure 2). Furthermore, significant differences were found for the ApEn values among the three speeds ($F=5.79$, $p=0.005$). This result is illustrated in Figure 2, where ApEn values increased with increases the walking speed. The post-hoc analysis revealed that significant differences existed in all comparisons between the speed conditions. No significant interaction was found between the two factors ($F=0.339$, $p=0.714$).

INSERT FIGURE 2 ABOUT HERE

Representative data are presented in Figure 3. In this graph, we can clearly observe the periodic nature of human locomotion as reflected in the knee flexion/extension time series. This is why the ApEn values in the present study are quite small (between 0.1 and 0.4). As mentioned above and shown in Figure 1, periodic time series has small ApEn values. Furthermore, it is important to mention that significant differences do exist between the data presented in Figure 3A and 3B as it was shown above by our statistical analysis. This clearly shows the tremendous value of the variability analysis performed in the present study because it is impossible to discern with the naked eye differences between conditions in Figure 3. This is similar with cardiology where seemingly similar ECG outputs have subtle variability differences that could be important for the diagnosis of pathology [Pincus and Viscarello 1992, Ryan et al 1994].

INSERT FIGURE 3 ABOUT HERE

DISCUSSION

The goal of this study was to examine how variability during walking is affected by ACL deficiency. Specifically, we wanted to evaluate the variability that exists in the flexion and extension of the knee joint during walking when the ACL is absent. We incorporated a speed protocol to elicit larger changes in variability. Our hypothesis was in line with "the loss of complexity" hypothesis that was generated in other medical disciplines (i.e. cardiology). We speculated that it will be true even in an orthopaedic problem such as ACL deficiency. Thus, we hypothesized that the ACL deficient knee will exhibit a decrease in variability when compared with the intact contralateral knee in all speeds examined. To achieve our goal we used the Approximate Entropy (ApEn) measure. This variable has been used widely in other medical domains such as endocrinology, cardiology, and neurology to explore variability. To our knowledge it has never been used in orthopaedics to explore changes in the musculoskeletal system such as ACL deficiency.

The usage of ApEn makes perfect sense if we consider that it evaluates the entire data sequence generated. In other words every data point in the time series is examined. Such an evaluation is impossible with common linear tools like the standard deviation. Linear tools only provide a measure of the amount of variability that is present in the gait pattern and may mask the true structure of motor variability. Masking occurs when strides are averaged to generate a "mean" picture of the subject's gait. This averaging procedure may lose the temporal variations of the gait pattern. Additionally, the statistical processing of linear measures requires random and independent variations between subsequent strides. This is not true since it has been shown that stride-to-stride variability

is not due to measurement noise [Hausdorff et al. 1995, Dingwell and Cusumano 2000]. On the contrary, it has been shown that each system is characterized with inherent variability that results from the underlying mechanisms of the system [Hausdorff et al. 1995, Dingwell and Cusumano 2000, Goldberger et al 2002]. This variability has deterministic nature or in other words it has order. Furthermore, several researchers have found that it can play a critical role in pattern formation and perception and provides the system with great complexity and the ability to accommodate to possible perturbations it may experience [Goldberger et al 2002, Pool 1989]. Aging and pathological conditions have been related with a deterioration of this variability, which has been associated with reduced complexity and narrowed functional responsiveness [Goldberger et al 2002, Pool 1989].

Our ApEn results (in both knees and in all speeds) are closer to the ApEn value of the periodic time series (Figure 1). This is probably due to the cyclic repetitive nature of human gait as it was illustrated in Figure 3. However, differences between the deficient and the intact knee as well as differences among the three speeds were identified. Specifically, the ACL deficient knee exhibited smaller ApEn values than the contralateral intact knee in all walking speeds, which signifies that the ACL deficient knee moves along more regular and less variable patterns than the contralateral intact knee. This finding supported the “loss of complexity hypothesis” which stated that disease results in increased regularity and loss of complexity. Indeed, such transitions to more regular and less variable patterns were observed in various pathologic conditions, including sudden cardiac death, epilepsy, Parkinson’s disease, cardiac arrhythmias and acodosis in fetuses.

[Vaillancourt and Newell, Bhattacharya J 2000, Pincus and Viscarello 1992, Vikman 1999, Goldberger 1988, Babloyantz and Destexte 1986].

In human gait it has been demonstrated that loss of complexity does exist [Hausdorff et al, 2000, Hausdorff et al 1999]. Actually, it seems that complexity in gait patterns seems to evolve during childhood and degrade both with physiologic aging and with certain degenerative neurological diseases (i.e. amyotrophic lateral sclerosis). In our study, complexity was assessed through ApEn and it was shown that ACL deficiency leads to greater regularity. This loss of complexity could explain the differences in regularity between the ACL deficient knee and the intact knee. It has been demonstrated that the ACL apart from having mechanical properties, incorporates mechanoreceptors [Schultz et al 1984] and therefore, its loss is associated with a loss of afferent proprioceptive input. Furthermore, ACL deficiency has been associated with changes in the central nervous system [Valeriani et al 1996]. These neural changes due the absence of the ACL are reflected in the loss of complexity in the system.

As proposed by the loss of complexity hypothesis the decreased complexity correlates well with narrowed functional responsiveness of the system. Therefore, we propose that the loss of the ACL could render the knee less able to adjust to the unpredictable and ever changing environmental demands. This results in a knee that is more susceptible to future injury and osteoarthritis. This proposition is actually supported by the increased amount of future pathology found in ACL deficient knees [Murrell 2001]. However, it needs to be rigorously in future studies.

Our results also showed that as walking speed increased walking patterns became more irregular. This could be due to the fact that faster walking requires the recruitment

of additional resources (i.e. muscles, motor units), which could probably result in increased possibility of error within the system and thus, increased randomness.

A possible limitation of the study is that our subjects walked on a motorized treadmill instead of overground. Dingwell et al. [Dingwell et al 2001] found that treadmill walking can possibly affect measures of variability when compared to overground walking. However, Matsas et al demonstrated that knee joint kinematics from familiarized treadmill walking can be generalized to overground walking [Matsas et al 2000] . Furthermore, the collection of a large number of continuous data required for the calculation of stride-to-stride variability enforces the walking measurements to be collected on a motorized treadmill. In the present study, we also selected to use a motorized treadmill because we wanted to ensure that the speed remains constant for each condition. It has been shown that walking overground does not warrant a constant speed for a long period of time (such as in the case with multiple footfalls) due to intermittency [Minetti 1985, Weinstein 2001]. It has also been found that speed can affect variability during walking [Diedrich and Warren 1995]. Therefore, in the present study we selected to use a motorized treadmill to eliminate any confounding effects of the walking speed within conditions.

In conclusion, our results showed that the ApEn measure could prove to be of great importance in orthopaedics providing the clinician with a mean of dynamical assessment of the effect of the pathology on movement and of the results of various therapeutic interventions. We have shown that the “loss of complexity” hypothesis may be more universal than their proponents suggested. Pathologies of biorhythms are similar no matter if you deal with the cardiovascular, the nervous, or the musculoskeletal system.

Our future work will focus in the usage of ApEn to identify surgical efficiency of ACL reconstruction with various techniques.

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Glossary

Approximate Entropy: A non-linear measure that quantifies the regularity (predictability) of a time series. The smaller the ApEn the more regular and predictable the system is. ApEn values range from zero to two. A zero value corresponds to a periodic behavior, while a value of two describes a completely random time series.

Chaotic: A system is chaotic when its behavior is aperiodic, seemingly random and unpredictable but contains order and is deterministic in nature, like the Lorenz attractor illustrated in Figure 1.

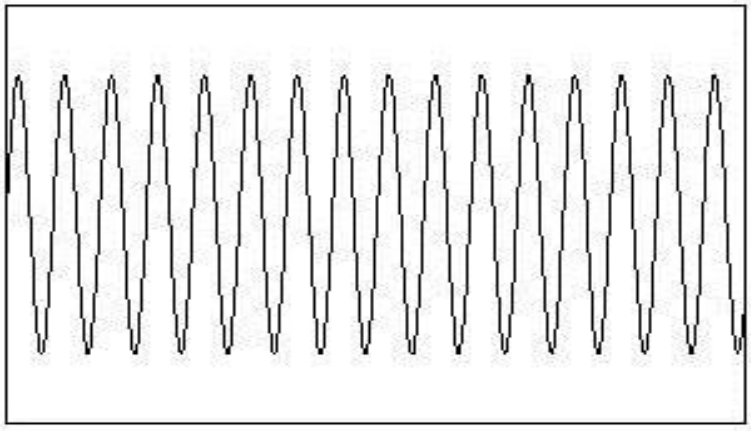
Deterministic: A system is deterministic when its behavior arises from known equations and is dependent on initial conditions.

Periodic: A system is periodic when its behavior is repeatable (in an exact way) over a given time interval, like the sine wave illustrated in Figure 1.

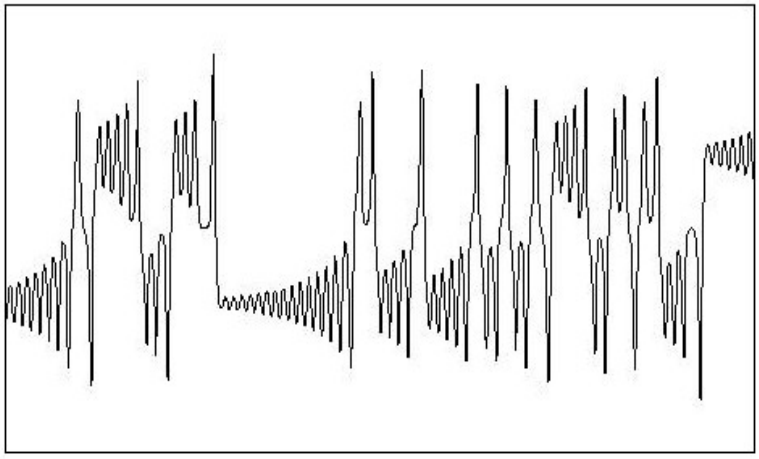
Random: A system is random when its behavior never repeats itself, is unpredictable and contains no order like white noise which is illustrated in Figure 1.

Stride-to-stride variability: the variations observed among subsequent strides.

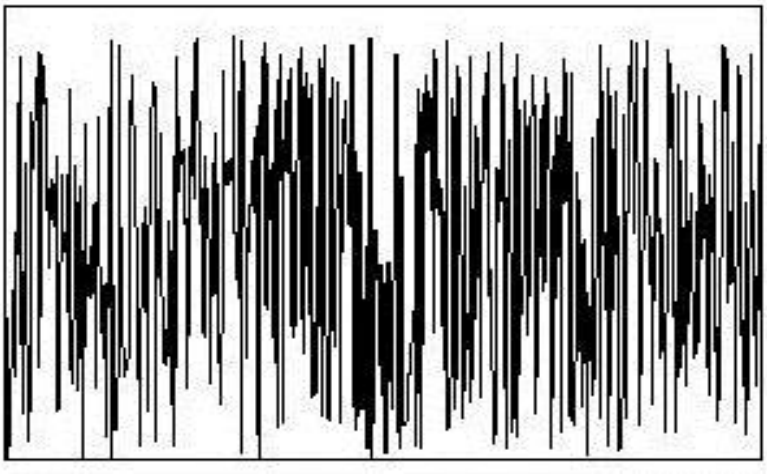
Figure 1



A



B



C

Figure 2

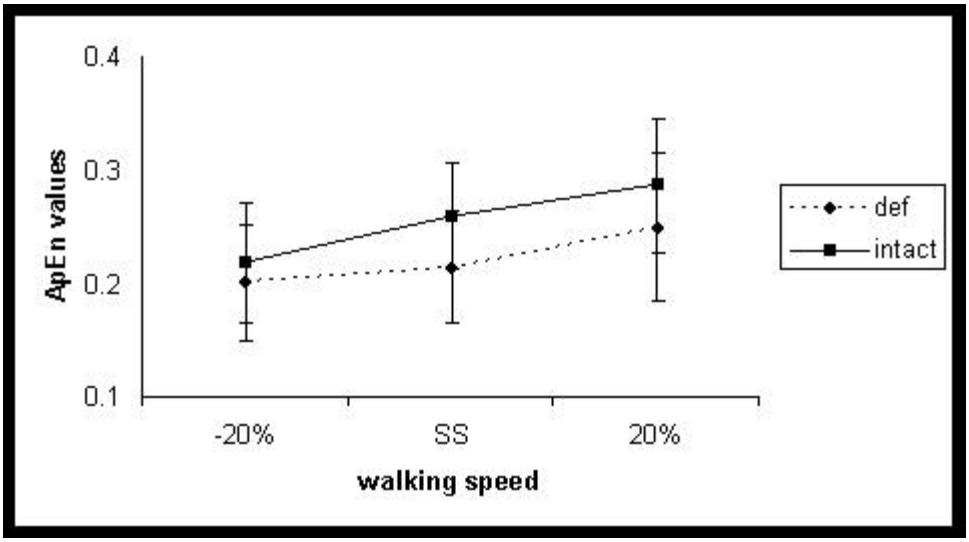
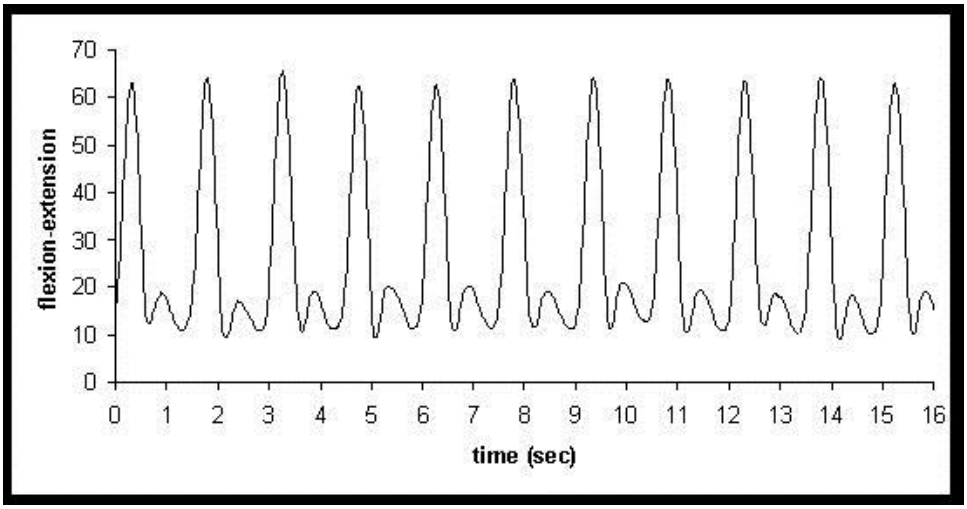
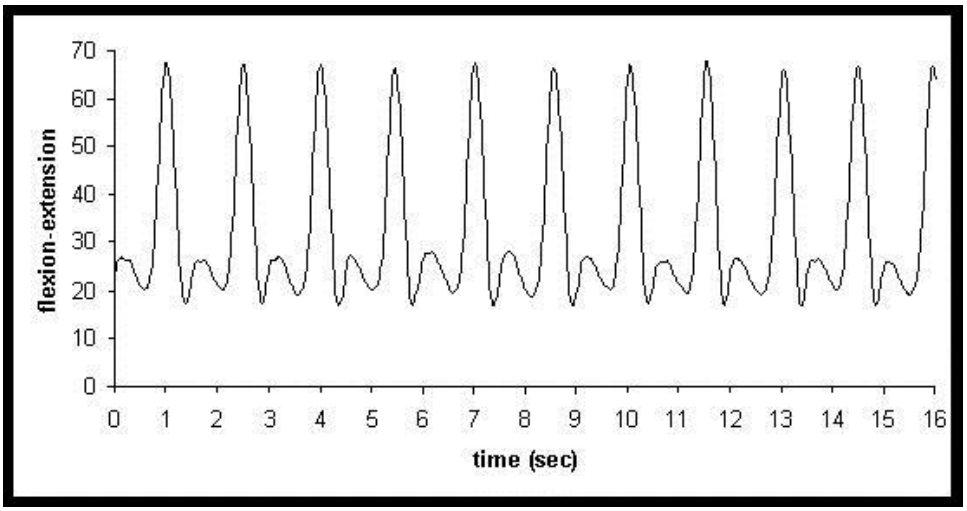


Figure 3


flexion-extension
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
time (sec)

A


flexion-extension
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
time (sec)

B

Legends

Figure 1

A. The time series from a simple periodic function sin(t/10). Periodic behavior always repeats itself and is highly predictable.

B. A time series from a known chaotic system (the Lorenz attractor).

C. A time series from random numbers with a Gaussian noise centered on zero and a standard deviation of 1.0.

Figure 2

Graphical representation of the means of the ApEn values and their standard deviations for both the ACL deficient and the intact contralateral knee in all conditions.

Figure 3

Representative flexion-extension time series from (A) ACL deficient knee and (B) the contralateral intact knee. It is evident that the subtle differences detected with the use of ApEn between these two conditions can not be discerned with the naked eye.