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A posturographic test to detect the impairment in postural steadiness after sedation and anesthesia

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Tiivistelmä – Referat – Abstract

Anesthetics and sedatives impair postural steadiness and may lead to falls. Since the drug offset and recovery rate is individual, the patient's steadiness and hence his/her safe discharge time is hard to predict. 103 patients with midazolam sedation and 92 patients anesthetized with propofol, were measured with a Nintendo® Wii balance board, before (PRE) and after (POST) endoscopy or colonoscopy. Out of four tested nonlinear algorithms, fuzzy sample entropy (FSE) separated the PRE and POST conditions of the midazolam group with the largest area under the receiver operating characteristic curve AUC, 0.85; FSE decreased with midazolam group from 0.22±0.04 to 0.16±0.04 (p<0.0001). In the propofol group FSE decreased from 0.21±0.04 to 0.19±0.04 with AUC=0.58 and p<0.001. As was expected, the impairment of steadiness was greater in the midazolam group than in the propofol group. Consequently the method can be used to test the impairment in postural steadiness due to midazolam. This study is a step towards developing a tester that indicates a safe patient discharge time after 'day surgery'.

Nukutus- ja rauhoittavat lääkkeet heikentävät tasapainoa ja saattavat aiheuttaa kaatumisia. Koska lääkkeistä toipuminen on yksilöllistä, potilaan tasapaino ja turvallinen kotiuttamisaika on vaikeaa arvioida. Mittasimme 103 midazolamilla rauhoitetun sekä 92 propofolilla nukutetun potilaan tasapainon Nintendo Wii Fit tasapainolaudalla, sekä ennen endoskopiaa tai kolonoskopiaa (PRE) että sen jälkeen (POST). Testasimme neljä epälineaarista algoritmia, joista FSE ('fuzzy sample entropy') erotti PRE ja POST tilanteen suurimmalla ROC-käyrän ('receiver operating characteristic') alle jäävällä pinta-alalla AUC, 0.85; FSE pieneni midazolam ryhmällä arvosta 0.22±0.04 arvoon 0.16±0.04 (p<0.0001). Propofol-ryhmällä vastaavat arvot olivat 0.21±0.04 ja 0.19±0.04, AUCn ollessa 0.58 (p<0.001). Tasapaino heikkeni odotetusti enemmän midazolam ryhmällä kuin propofol ryhmällä. Tämä tarkoittaa, että menetelmää voidaan käyttää midazolam-potilaiden tasapainon testaamiseen. Tämä tutkimus on askel lähemmäksi testeriä, jonka avulla voidaan määritellä turvallinen kotiuttamisaika päiväkirurgiapotilaille.

Avainsanat – Nyckelord – Keywords

Anesthesia, postural steadiness, midazolam, propofol, nonlinear sway measures

Säilytyspaikka – Förvaringställe – Where deposited

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Contents

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List of publications

I **Identifying a method to separate the postural steadiness before and after sedation: comparison of four nonlinear and three conventional measures.**
Aino Tietäväinen, Edward Hæggström, and Jeff E. Mandel
Medical Engineering and Physics (in review)

II **A simple method for detecting the effect of endoscopic sedation on postural steadiness.**
Jeff E Mandel, Aino Tietäväinen, Jose Otero, Edward Hæggström
Anesthesia & Analgesia (submitted)

Abbreviations and symbols

AP	Anterior-posterior
AUC	Area under the receiver operating curve
DFA	Detrended fluctuation analysis
c	Shape factor (FSE)
C_M	Correlation sum (D_2)
CI	Confidence interval
CNS	Central nervous system
COP	Center-of-pressure
d	(Divergence) distance (FSE, λ_{max})
D_2	Correlation dimension
E_i	$(F_{min,i}+ F_{max,i.})/2$, see section 2.3.1
EO	Eyes open
EC	Eyes closed
EMD	Empirical mode decomposition
f_{mean}	Mean frequency (Eq. 3)
$F_{min,i}$	Interpolated fit of local minima of a signal (EMD)
$F_{max,i}$	Interpolated fit of local maxima of a signal (EMD)
FSE	Fuzzy sample entropy
i,j,k,e	Dummy variables
IMF	Intrinsic mode functions
J	Lag (λ_{max} and D_2)
M	Embedding dimension (λ_{max} and D_2)
ML	Mediolateral
$M_{min,j}$	Local minima of a signal (EMD)
$M_{max,k}$	Local maxima of a signal (EMD)
m	Segment length (FSE)
N	Length of the signal
n	Polynomial order (DFA)
p	p-value from Wilcoxon signed rank test
PRE	Before the procedure
POST	After the procedure
r	Tolerance distance (FSE)
r_{D2}	Tolerance distance (D_2)
$Range$	Sway range (Eq. 1)
ROC	Receiver operating curve
x	COP signal
Δt	Sample interval
s	Segment length (DFA)
v_{mean}	Mean velocity (Eq. 2)
W	Cut-off parameter (DFA)
α	Scaling exponent (DFA)
λ_{max}	Largest Lyapunov exponent
μ	Smooth function (FSE)

1 Introduction

1.1 Motivation

Anesthetic drugs decrease postural steadiness and increase the risk of falls [1]. With some minor procedures ("day surgery"), such as endoscopy and colonoscopy, the residual effect of the drugs is the limiting factor for safe discharge. Since the drug offset rate –and hence the patient recovery– is individual, the state of steadiness after a procedure involving anesthetics is hard to predict.

From a managed health care perspective (cost-efficiency) hospitalization time should be minimized. Currently patients can be released after a certain time (e.g. 30 min) has passed from the procedure and when the patients' vital signs have returned to tolerable levels. The nurses in the recovery area subjectively assess whether the patient is fit for ambulation. A simple tester estimating the patient's fitness for ambulation would be a more objective measure of steadiness and could therefore perhaps decrease the risk of postoperative falls.

1.2 Aims

This thesis work aims to develop a simple tester to assess a patient's fitness for ambulation using posturographic balance measurements. We aim to:

1) identify an efficient (large area under the receiver operating characteristic curve, AUC, see section 2.4) method to detect the impairment in postural steadiness due to anesthetics (Study I),
2) determine whether the tester detects this impairment in patients that have been administered with two commonly used anesthetics, midazolam and propofol (Study II), and
3) present further evidence that the detected impairment in steadiness is due to the drugs and not caused by the procedure itself (Study II).

2 Theory

2.1 Postural steadiness

Maintaining balance is a nonlinear process in which the sensory organs (mainly visual, vestibular, and somatosensory) bring to the central nervous system (CNS) information about the body's orientation relative to the surrounding environment [2]. CNS integrates this information and commands the skeletal muscles to contract to maintain upright posture. In quiet, upright stance the objective is to keep the vertical projection of the body's center-of-mass within an area under the soles of the feet. Anything that affects the CNS or the skeletal muscles affects balance. Such things are in healthy individuals for example age, psychoactive substances, food intake and state of alertness [1-6].

Posturography measures a person's postural steadiness while he/she stands on a balance board [7]. The balance board records the net center-of-pressure (COP) trace along the mediolateral (ML) and anterior-posterior (AP) directions. Posturography is either *static*, where the person stands quietly in an upright stance on the board or *dynamic*, where the person, the board, or even an artificial horizon in front of the person is subjected to motion or disturbances [7].

Balance measurements may suffer from disturbances from external sources, for example voluntary or involuntary movements. Such disturbances may appear as nonstationarities [8] in the COP time series, making the signal mean and variance vary within the observation period. The COP signals have been found to be chaotic, which means that small external perturbations may cause large deviations in the system dynamic [9]. Chaotic signals are nonlinear and deterministic (i.e. causal, completely predictable) [9]. The opposite of a deterministic signal is a stochastic signal, where the signal cannot be predicted accurately due to its randomness. Signals generated by physiological processes exhibit inherent random noise [10]. All these attributes in the balance signal need to be addressed when analyzing the signal.

2.2 Anesthetics

Midazolam is a short acting benzodiazepine that is used for conscious sedation during minor procedures [11]. It is psychoactive drug that depresses the activity of the CNS. In addition to its sedative properties, midazolam's anterograde amnestic properties (i.e. the patient is unable to create new memories while under the influence of midazolam) relieve any unpleasant memories of the procedure [11]. It also reduces anxiety, and has hypnotic (sleep-inducing) and skeletal muscle relaxant properties [11].

Midazolam is suboptimal for producing and maintaining general anesthesia where the patient is unconscious, since a high dose is required which results in a slow recovery [11]. Propofol is a hypnotic agent that is commonly used when loss of consciousness is required [12]. It has similar subhypnotic properties as midazolam: sedative, amnestic, and anxiolytic [12].

Fentanyl is analgetic opioid (painkiller) that may be used with both midazolam and propofol [13]. Benadryl (diphenhydramine) is an antihistamine (allergy drug) [14] that can be used in addition to Fentanyl to augment sedation. Benadryl increases the body sway [14]. In this study we consider only patients who were administered either midazolam or propofol anesthetics possibly together with fentanyl or benadryl. The possible deteriorating effect induced by fentanyl or benadryl on posture is not considered separately from that of midazolam's or propofol's effect.

The context-sensitive half-time [15] is the time after the infusion has ended that is required for the plasma drug concentration to drop to 50% of its original concentration. The context-sensitive half-time is longer with midazolam than with propofol [15] and it increases with longer infusion time. Since the half-time can be used to estimate the offset of intravenous anesthetics [15], it may give some estimation of the expected patient recovery [16]. However, the decrement in drug concentration needed for recovery cannot be considered to be 50% [16]. Other drugs that patients have received may affect the recovery [16]. Moreover, individual differences in recovery are large and hence the recovery cannot be reliably estimated from the context-sensitive half-time alone [16]. However, literature has shown that both midazolam and propofol decrease postural

steadiness [1, 3, 4] and midazolam's impairing effect on steadiness seems to be more profound than the effect of propofol [4]. Propofol patients are also discharged sooner than midazolam patients [17]. Relying on findings in the literature [1, 3, 4] and on the estimated half-times for the two drugs, it may be expected that the propofol patients would show less impairment in postural steadiness after the procedure compared to midazolam patients.

2.3 Signal processing

2.3.1 EMD filter

Empirical mode decomposition (EMD) decomposes a signal into its elemental, polychromatic signals called intrinsic mode functions (IMF) [18, 19]. Each increasing order IMF has a decreasing mean frequency compared to the previous one. In biological signals such as the COP signal the first IMF contain mainly noise whereas the last one holds the signal's slow trend. When using the EMD method as a filter, the signal is recomposed using fewer IMFs than it originally contained, leaving out e.g. IMFs with the highest and lowest frequencies (bandpass filtering). The iterative EMD algorithm is:

1) Find all minima $M_{min,j}$ (i.e. local low points), where j=1,2,… and maxima $M_{max,k}$ (i.e. local high points), where k=1,2,… of the signal x_i, where i=1…N.
2) Interpolate between all $M_{min,j}$ using a cubic spline interpolation to get $F_{min,i}$ and between all $M_{max,k}$ to get $F_{max,i.}$
3) Let E_i=($F_{min,i}$+ $F_{max,i.}$)/2.
4) Denote x_i=x_i-E_i
5) Repeat 1)-4) until x_i remains nearly unchanged; this x_i is an IMF.
6) Subtract the IMF from the signal: x_i=x_i-IMF$_i$
7) Repeat 1)-6) until there is only one extremum left in x_i

The algorithm can be used with biological signals, since it was designed for nonlinear and nonstationary signals [19].

2.3.2 Conventional sway measures

COP traces are conventionally quantified by measures related to the signal's mean amplitude, velocity, frequency, or sway area [2]. In this study, we chose three commonly used sway measures, sway range (mm), mean velocity (mm/s), and mean frequency (Hz) [2] to quantify the effect of sedation and anesthetics on posture:

$$Range = \max(x) - \min(x), \tag{1}$$

$$v_{mean} = \frac{1}{N-1}\sum_{i=1}^{N-1}\frac{|x_{i+1} - x_i|}{\Delta t}, \tag{2}$$

$$f_{mean} = v_{mean} \cdot \left(\frac{2\pi}{N}\sum_{i=1}^{N}|x_i|\right)^{-1}, \tag{3}$$

where x is the COP signal, N is its length, and Δt the sampling period.

2.3.3 Nonlinear sway measures

We chose four commonly used nonlinear algorithms to quantify the drug induced impairment of postural steadiness. These algorithms are fuzzy sample entropy (FSE) [20] that quantifies the regularity or predictability of a signal; detrended fluctuation analysis (DFA) [21, 22] that quantifies the long-range correlation of the signal; the largest Lyapunov exponent (λ_{max}) [23] that quantifies the chaotic nature of the signal; and the correlation dimension (D_2) [24, 25] that gives an estimate of the number of the active control variables (i.e. degrees of freedom) of the underlying dynamics of the COP trace. These algorithms are detailed in Appendix A.

2.4 Statistics

The receiver operating characteristic (ROC) curve quantified by the area under the ROC-curve (AUC) can be used to estimate the merit of a test that separates two distributions [26] that may be non-Gaussian. This curve presents the fraction of correctly classified positive, or in our case, POST, cases (sensitivity) against the fraction of correctly classified negative, or in our case, PRE, cases (1-specificity). AUC=1 indicates a perfect test while AUC=0.5 indicates a random score. Confidence intervals (CI) for AUC can be acquired with bootstrapping [26].

A nonparametric Wilcoxon signed rank test [27] can be used to estimate whether two paired distributions are significantly different.

3 Methods

The measurements and setup were identical with the midazolam and propofol patients permitting us to compare the data. Study I identifies the method that detects the impairment in postural steadiness with high AUC after sedation with midazolam. Study II uses that optimal method, compares the tester's ability with both midazolam and propofol patients and gives further support that the measured effect is due to the drugs and not to the medical procedure itself.

3.1 Measurements

Both studies were exempt from having to obtain the patients' written consent by the Institutional Review Board of the University of Pennsylvania School of Medicine. The patients were instructed not to eat for 24 hours or to drink for 6 hours prior to the endoscopy or colonoscopy they were scheduled to undergo. The patients were measured with the Nintendo Wii balance board before the procedure in their waiting pod (PRE) and after the procedure in their recovery pod (POST) when they were deemed ready to be discharged. In both measurements the patients were instructed to stand on the board 60 s eyes open (EO) and then 60 s eyes closed (EC). They were instructed to relax, keep their hands at their sides, focus their eyes on a pattern of a curtain hanging in front of them (when EO) and refrain from speaking. A person stood next to the patients all times ready to support him in case he lost his balance. Patient data is presented in Table 1. The setup and the measurement are presented in Figures 1 and 2.

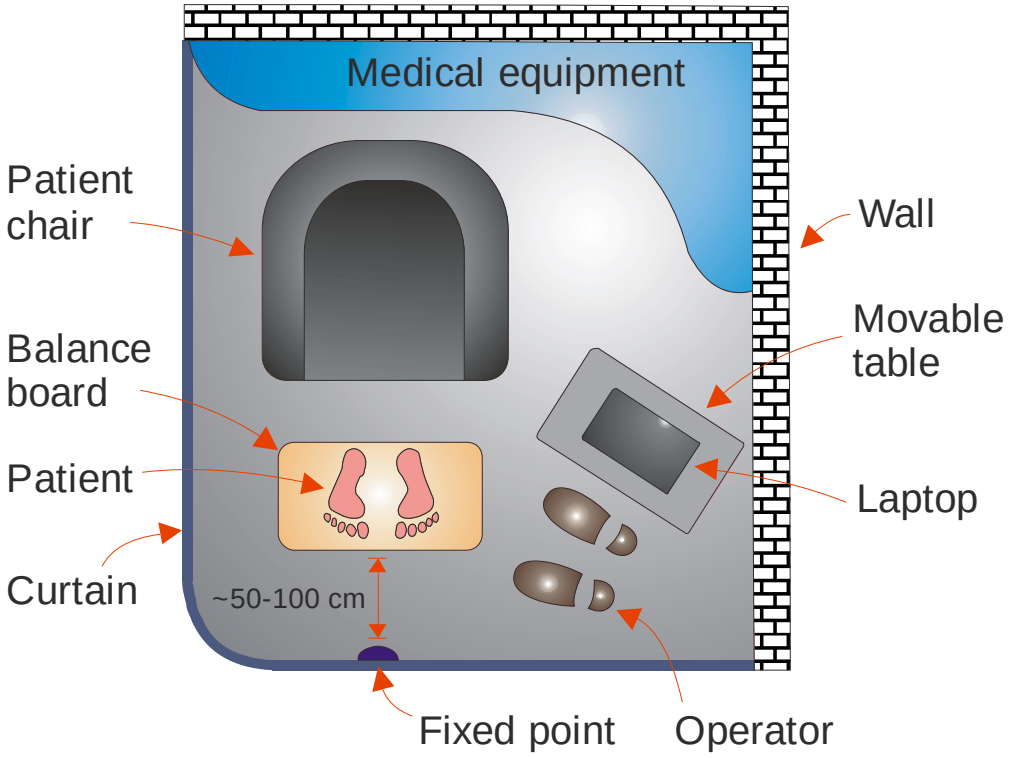

Fig. 1. Measurement setup. The measurements were conducted in the patient's waiting pod. The operator stood next to the patient during the measurement. The patient chose a pattern ("fixed point") in the curtain in front of him/her to focus eyesight.

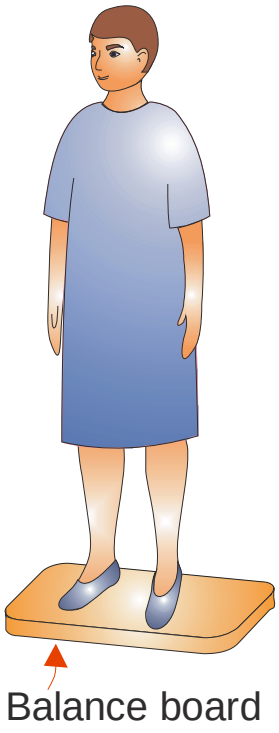

Fig. 2. The balance measurement. Patient stood on the balance board in a comfortable position, relaxed, hand at his/her side, and focusing eyesight on a pattern in the curtain ahead of him/her.

Table 1. Patient data, mean (SD) and the administered drugs.

	Midazolam	Propofol
Patients (males/females)	103 (42/61)	92 (41/51)
Age (years)	57 (12)	56 (15)
Height (cm)	169 (10)	169 (11)
Weight (cm)	83 (19)	82 (19)
Midazolam/kg (μg/kg)	63 (22)	-
Propofol/kg (mg/kg)	-	3.7 (2.0)
Benadryl/kg (mg/kg)	0.49 (0.18)[a]	-
Fentanyl/kg (μg/kg)	1.5 (0.5)	0.49 (0.43)

[a]mean (SD) of the 16 patients that received Benadryl

3.1.1 Equipment

The portable equipment consisted of a Nintendo® Wii Fit balance board [28] featuring 60 Hz sampling frequency and a PC computer that was connected to the balance board with a wireless Bluetooth® connection. The software was custom made and it was based on C# codes available in WiimoteLib open-source library [29].

3.2 Data analysis

Only the AP signal was considered, since the results from the ML signal were inferior compared to the AP signal, possibly due to not standardizing the stance. The AP signal was first standardized to zero-mean, and with nonlinear measures, to unit standard deviation. The signal was filtered with an EMD-based filter (section 2.3.1), recomposing the signal from IMFs 4 to 8. In study I the results from the unfiltered data are presented.

In study I we calculated all the nonlinear (FSE, DFA, λ_{max} and D_2) and conventional (*Range*, v_{mean} and f_{mean}) measures, presented in sections 2.3.2 and 2.3.3 for the midazolam data. We used 10 randomly chosen patient's data to optimize the parameters (*m*, *r* and *c* for FSE, *n* for DFA, and *M* and *J* for λ_{max} and D_2, Appendix A). We calculated all the nonlinear measures with different combinations of parameter values using the 10 patients' EO PRE and POST data and chose the combination that exhibited the largest AUC (Table 2). In study I we also tested the robustness of the nonlinear algorithms: we changed the parameter values by 500% and observed the resulting change in both AUC values and the sway measure (EO PRE and POST) values. The sway measure that exhibited the smallest

change in AUC was considered most robust. Since FSE separated the PRE and POST conditions with largest AUC in study I, we used this algorithm (only) in study II.

Table 2. The chosen parameter values in study I (all) and in study II (FSE).

Measure	Parameter	Chosen value
FSE	m	3
	r	0.1
	c	0.01
α	n	2
λ_{max}	M	10
	J	50
D_2	M	6
	J	5

3.3 Statistics

In study I we used ROC-curves (section 2.4) quantified by the AUC and the Wilcoxon signed rank test (section 2.4) to test the merit of the conventional and nonlinear sway measures with regards to separating the PRE and POST conditions. 95% CIs for AUCs were calculated using bootstrapping with 500 repetitions. We consider a p-value from the Wilcoxon's test less than 0.05 significant. In study II we used the same methods to compare the results between the midazolam and propofol patients.

4 Results

4.1 Study I

Both the conventional and nonlinear measures detected the impairment due to sedation. Fuzzy sample entropy (FSE) separated the PRE and POST condition in the midazolam group with the highest AUC (AUC=0.85, p<0.0001, m=3, r=0.1, c=0.001) using EO data and EMD filtering. FSE was also the most robust algorithm: changing the m, r and c parameters by 500% changed the AUC by no more than 2.4% (2.4%/500%=0.0048). EO data produced larger AUC compared to EC data and EMD filtering produced larger AUC compared to no filtering, except for the *Range* measure. Figure 1 presents the main results obtained with the FSE algorithm. Figure 2 presents the ROC-curves and AUC values of

all compared measures. Table 3 presents the main results for the EO condition using EMD filtering (except no filtering with *Range*).

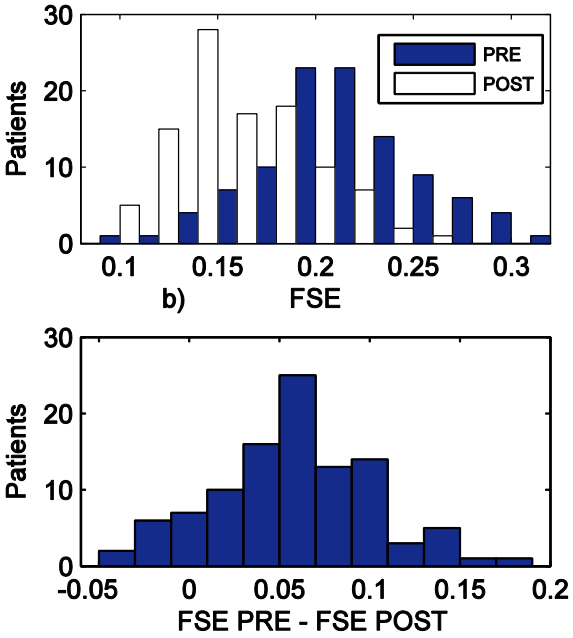

Figure 1. Main results of study I. a) The patients' FSE before ('PRE', blue bins) and after ('POST', white bins) the procedure. b) FSE PRE - FSE POST.

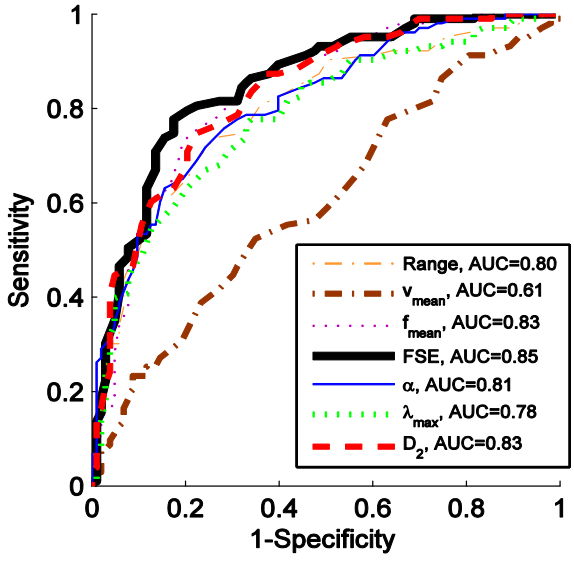

Figure 2. The ROC-curves and AUCs obtained with all the measures using the filtering and EO/EC condition that produced the largest AUC.

Table 3. Main results, mean (SD) of Study I with EMD filtering and EO condition, mean (SD) of the sway measures. With v_{mean} $p<0.05$ (PRE vrs. POST), with rest of the sway measures, $p<0.0001$.

		PRE	POST	AUC	95% CI
Range[a]	**(mm)**	32 (10)	49 (21)	0.80	0.74...0.85
v_{mean}	**(mm/s)**	7.4 (2.7)	8.6 (3.7)	0.61	0.54...0.67
f_{mean}	**(Hz)**	0.41 (0.10)	0.30 (0.07)	0.83	0.77...0.88
FSE		0.22 (0.04)	0.16 (0.04)	0.85	0.80...0.89
α		1.45 (0.16)	1.65 (0.16)	0.81	0.75...0.86
λ_{max}		0.33 (0.08)	0.24 (0.08)	0.78	0.72...0.83
D_2		1.55 (0.14)	1.39 (0.10)	0.83	0.78...0.87

[a]No filtering

4.2 Study II

The patients' gender, age, height, weight, or FSE scores of the PRE data were not significantly different between the midazolam and propofol groups. Both the midazolam and propofol groups exhibited a FSE significantly lower in the POST condition compared to the PRE condition ($p<0.001$). However, whereas with the midozolam group the AUC was 0.85 and 0.81 in EO and EC conditions, respectively, with the propofol group the same AUCs were only 0.58 and 0.59. Figure 3 presents the ROC curves of the midazolam and propofol groups, both with EO and EC conditions. Table 4 presents the main results (EMD filtering and EO condition) of Study II.

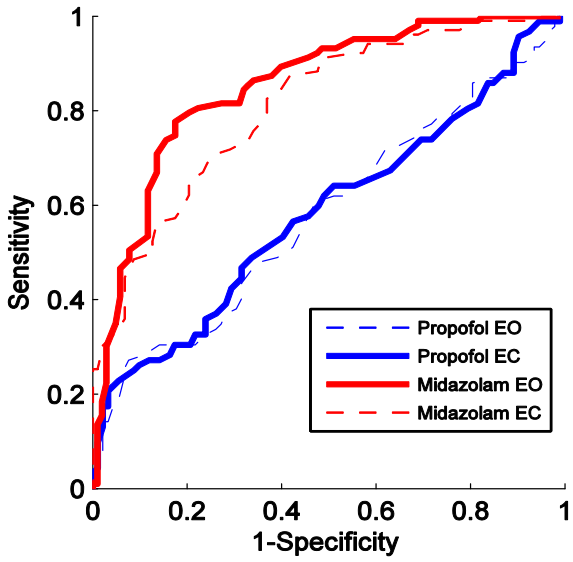

Figure 3. ROC-curves of the midazolam and propofol groups, with EO and EC conditions

Table 4. Main results, mean (SD) of Study II with EMD filtering and EO condition. With both midazolam and propofol groups $p<0.001$ (PRE vrs. POST).

	PRE	POST	AUC	95% CI
Midazolam	0.22 (0.04)	0.16 (0.04)	0.85	0.80...0.89
Propofol	0.21 (0.04)	0.20 (0.04)	0.58	0.46...0.63

5 Discussion

5.1 Study I

Both nonlinear and conventional sway measures detected the impairment in steadiness due to midazolam sedation. FSE was deemed the most efficacious method since it produced the largest AUC, 0.85 ($p<0.0001$). It was also the most robust method since its AUC changed only slightly while the input parameters were varied. The least efficacious (AUC=0.78) and also the least robust nonlinear method was λ_{max}. This was possibly due to two factors: first, λ_{max} requires a chaotic (nonlinear and deterministic) signal, and secondly we chose to use 10 randomly chosen patient's data to optimize the parameters, instead of using any of the commonly used methods [23, 25, 30]. However, the simple conventional sway measures *Range* and f_{mean} that require no input parameters also separated the PRE and POST conditions with high AUCs: 0.80 and 0.83. This means that we foresee future use of both the nonlinear and conventional sway measures.

5.2 Study II

Even though the POST FSE was significantly ($p<0.001$) lower compared to the PRE FSE in both the midazolam and propofol groups, the method separated the PRE and POST conditions only in the midazolam group: AUC was 0.85 with the midazolam group and 0.58 with the propofol group with EMD filtering and EO condition. This result was expected [4, 17]. However, since the anthropologic data and PRE FSE scores of the two groups were not significantly different and since the patients in both cases underwent different procedures (endoscopy or colonoscopy), the differences between the AUCs of the midazolam and propofol groups indicate that the impairment in postural steadiness is caused by the drugs and rather than by the procedure itself.

Nintendo Wii Fit balance board was sensitive and robust enough to be used in the clinical balance tests with midazolam patients. This means that a portable and affordable setup could be used along side with clinical force plates. Even though previous studies have been able to detect the impaired steadiness with dynamic posturography, we believe that portable, static setup is safer and easier in field-use. In fact, any movement of the balance board or suppression of the patient's senses leads to a more unstable subject. This may even lead to falls in the recovery area –the very thing that we try to prevent.

6 Conclusion

We showed that the portable and affordable Nintendo Wii Fit balance board –based setup together with EMD filtering and signal analysis using the FSE algorithm can detect the impairment of postural steadiness after sedation with midazolam. However, as was expected, the impairment in postural steadiness after general anesthesia with propofol was less evident and could not be reliably detected. The difference in tester efficiency between the drugs (with the same procedures and with patient populations that do not differ significantly in gender, age, height, weight, or PRE FSE scores) gives further proof that the impairment in postural steadiness is not caused by the procedures itself but rather by the drugs used. We consider the Wii Fit balance board to be a safe and field-usable alternative compared to dynamic posturography and conclude that the method has potential to serve as a screening tool to determine a safe discharge time for midazolam patients.

7 References

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Appendix A

This appendix presents the algorithms for the nonlinear measures.

A.1 Fuzzy sample entropy (FSE)

The FSE algorithm [20] compares all combinations of m-length sequences $X_i(m)=[x_i, x_{i+1},\ldots,x_{i+m-1}]$ and $X_j(m)=[x_j, x_{j+1},\ldots,x_{j+m-1}]$ $(i\neq j)$ of the signal, with i,j =1,2,..,N-m. The distance d between $X_i(m)$ and $X_j(m)$ is determined as $d(i,j)=\max_{0\leq k\leq m-1}|X_{j+k}-X_{i+k}|$. Next, a function $\mu(d(i,j),r,c)=\exp(-(d^{\ln(\ln 2^c)/\ln r})/c)$ is calculated, where the tolerance (distance) r, and the shape factor c determine the shape of the function μ. The smaller the distance d between $X_i(m)$ and $X_j(m)$, the larger the μ. Next, the following quantities are defined:

$$B_i^m(r)=\frac{1}{N-m-1}\sum_{j=1,\,j\neq i}^{N-m}\mu(d(i,j),r,c)\,, \tag{4}$$

$$B^m(r)=\frac{1}{N-m}\sum_{i=1}^{N-m}B_i^m(r)\,. \tag{5}$$

The procedure is repeated with m+1-length sequences (now $d(i,j)=\max_{0\leq k\leq m}|X_{j+k}-X_{i+k}|$) leading to $A^m{}_i(r)$ and $A^m(r)$:

$$A_i^m(r)=\frac{1}{N-m-1}\sum_{j=1,\,j\neq i}^{N-m}\mu(d(i,j),r,c)\,, \tag{6}$$

$$A^m(r)=\frac{1}{N-m}\sum_{i=1}^{N-m}A_i^m(r)\,. \tag{7}$$

The Fuzzy Sample Entropy is defined as:

$$FSE=-\ln\left(\frac{A^m(r)}{B^m(r)}\right). \tag{8}$$

A.2 Detrended fluctuation analysis (DFA)

In the DFA algorithm [21, 22] the signal x_i, where i=1…N, is first integrated and divided into non-overlapping segments of equal length, s. A polynomial of order n is fitted to each s-length segment, leading to fit f_i. Next, the square root of the average residuals of the segments is calculated:

$$F(s) = \sqrt{\frac{1}{N}\sum_{i=1}^{N}[x_i - f_i]^2} \tag{9}$$

$F(s)$ is plotted on a logarithmic scale against different s. The slope of the curve is the scaling exponent α. A larger value of α indicates a more persistent, 'smoother' signal.

A.3 Largest Lyapunov exponent (λ_{max})

The largest Lyapunov exponent algorithm [23] first presents the signal x_i in a state-phase presentation, X_i=[x_i, x_{i+J}, x_{i+2J},…,$x_{i+(M-1)J}$], where J is the lag, M the embedding dimension and X_i a point along a N-(M-1)J length trajectory. If initially close trajectories later diverge exponentially, λ_{max} is positive and the system is chaotic. The divergence is quantified using nearest neighbours, X_j; X_j is defined as the X_j which minimizes the Euclidean distance between X_j and X_j and which has a temporal separation greater than the mean period (here $1/f_{mean}$, see Eq. 3) of the signal [23]. The divergence at an instance i is:

$$d(i)_j = d(0)_j e^{\lambda_{\max}(i\Delta t)}, \tag{10}$$

where $d(0)_j$ is the initial distance between X_j and X_j. Hence, λ_{max} is estimated with a least-squares fit to the line $y(i)=1/\Delta t\langle \ln d(i)_j \rangle$, where $\langle\ \rangle$ is the average value over j neighbours [23].

A.4 Correlation dimension (D_2)

The correlation dimension algorithm [24, 25] starts with the same state-phase presentation as the λ_{max} algorithm. It then calculates the correlation sum C_M:

$$C_M(r_{D2}) = \frac{2}{(N-W+1)(N-W)} \sum_{i=1}^{N-W} \sum_{j=i+W}^{N} \Theta\left(r_{D2} - \left|X_i - X_j\right|\right), \quad (11)$$

where |.| indicate the Euclidean distance and W is a cut-off parameter that can be defined as a measure that depends on the signal properties [25]. In here, we decided to choose the same value as with λ_{max}: W is the mean period, $1/f_{mean}$ (Eq. 3). C_M behaves as a power law, $C_M(r) \propto r_{D2}$ for small values of r_{D2}. Hence D_2 is defined as the linear part of the slope of C_M against r_{D2} in logarithmic scale.