Journal of Clinical Monitoring and Computing (2019) 33:481–491
https://doi.org/10.1007/s10877-018-0181-9

ORIGINAL RESEARCH

# A motor evoked potential trending system may discriminate outcome: retrospective application with three cases

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Received: 9 February 2018 / Accepted: 10 July 2018 / Published online: 13 July 2018


**Abstract**
This report presents a method for tracking Motor Evoked Potential (MEP) amplitudes over the course of a case using a moving least squares linear regression (LSMAs). During a case, newly obtained MEP amplitudes are compared to those predicted by a just previous linear regression (least squares moving average or LSMA). When detected by this comparison, a set criterion amplitude loss will then trigger linear regression of ensuing MEP amplitudes on an expanding step function which tracks the persistence of the amplitude loss for the remainder of the case. Three cases are presented. One in which the patient woke up with a newly acquired weakness in the left tibialis anterior and another in which MEP amplitudes were suddenly lost from the right foot, but after intervention, they were restored again. In a third case the patient again woke up with a new post-operative deficit, but MEP trial sampling had been more limited and variable than in the first two cases. When the linear trending method was applied to the affected myotome in the first case, the expanding step function regression was triggered after the moment of MEP loss and remained at a high level until the end of case. In the second case, the expanding step function regression was also triggered in the relevant myotome at the time of the reported MEP change, but diminished by end of case. In the third case the tracking method again successfully triggered a predictive R-Square despite the limited number of pre-event trials. The R-Square value of the expanding step function regression appears to have discriminative capability with regard to new post-op deficit. Given the importance of the intra-operative MEP for monitoring motor functioning and the high degree of variability that can affect it, the development of new quantitative, statistical methods to detect real from apparent MEP change will be necessary.

**Keywords** Intraoperative MEP trending · Variability · Least squares regression

## 1 Introduction

The transcranial motor evoked potential (tcMEP or MEP) is presently the only way to monitor anterior spinal cord function while the patient remains under general anesthesia. The MEP is however afflicted by a high degree of variability relative to other intraoperative monitoring modalities such as the somatosensory evoked potential [16, p. 118, 7.7.6]. Some of the sources of this variability have been identified such as anesthetic depth [3], time under anesthesia [10], type of anesthesia [1, 2, 9, 12], interaction of anesthesia and age [6], temperature [15], hemorrhage [7] and the interaction of anesthesia and hemorrhage [8]. Even so, much of the variability of the MEP remains unaccounted for. All of the above mentioned factors can vary during the course of a single spinal surgery, thus the MEP trajectory during a case can have more than one change in direction. It is against this complicated history that each new change must be compared in order to decide if there has been an iatrogenic event or not.

## 2 A system for trending intra-operative MEPs

The MEP amplitudes obtained during a case, along with the times at which they occurred, constitute a series of data pairs. The MEP amplitudes can be peak-to-peak, area under the curve, or any other type of amplitude

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measurement. These data pairs can be plotted in a two dimensional *x*- and *y*-Cartesian space commonly known as a *scatterplot*. Such a scatterplot can depict the entire history of the MEPs recorded from a single myotome during a case. A common way to assess the trajectory of data pairs in an *x*–*y* space is least squares linear regression (or LSM for least squares model). LSM is the best fit for a straight line through a data cloud. This line will have a slope which is the *regression coefficient* and an intercept with the *y*-axis which is the *y-intercept*. In the case where the slope equals zero (i.e. the trajectory is flat), the regression intercept and the average of all the *y*-values (MEP amplitudes in this application) will be identical. In the case where the slope is positive (i.e. the trajectory is increasing) or negative (i.e. the trajectory is decreasing) the regression intercept and the average *y*-value will differ. For each actual *x*-*y* data pair LSM also produces a corresponding *fitted* *y*-value. The fitted y-value is the y-value that lies on the straight regression line at a particular *x*-value. This may be different from the actually obtained y-value which may be at some distance in the vertical direction away from the straight regression line. The sum of the absolute differences between the fitted *y*-values and the actual or obtained *y*-values constitutes what is known as the *standard error of the model* or *SEM*. The SEM provides a measure of how well the straight line describes the data cloud, the smaller the SEM the better. Again in the case where the slope is zero, the SEM will be identical to the standard deviation around the average *y*-value.

A single linear regression including all available *x*–*y* data pairs would accurately describe the MEP trajectory if there was a single trend. However, as pointed out in the first paragraph, the MEP trajectory could vary across the case. In the world of financial analyses, there is a type of a *moving* linear regression known as the LSMA or least squares moving average [11, Chap. 11]. Here the term "average" is a misnomer since the LSMA is actually a moving regression, not a moving average. But it was introduced as an alternative to moving averages, so apparently the term "average" stuck. The idea of the LSMA is that instead of applying a single regression to the entire set of all available *N* data points in the *x*-*y* plane, a regression across a smaller number ($n < N$) of data points is used. The regression is applied to the first *n* data points, it is then advanced one data point and applied to the next *n* data points, and so on until all *N* data points have been used up. This will result in a total of $N - n + 1$ linear regressions, each with its' own estimated slope, standard error and *y*-intercept. In contrast to the moving average which produces only one statistical estimate (the average) each time it is computed, the LSMA produces *n* fitted points each time it is computed. Each fitted point is the central tendency estimate of what the true *y*-value (i.e., the *y*-value free of random noise) is at each associated *x*-value [4, Chap. 5].

The percent MEP amplitude decrease that is supposed to trigger an IONM alert has been variously proposed to be anywhere from 50 to 80% [5, 13, 14]. These percent amplitude losses involve comparison of the most recently obtained MEP amplitude with that of the just previous one, or an average of a number of just previously obtained amplitudes, or a computed baseline (usually the average of a small number pre-intubation, pre-positioning trials or pre-incision). All of these methods ignore the fact of pre-existing trend. Does the same percent amplitude loss carry the same alarm impact if the *n* previous trials had been a series of steadily increasing amplitude MEPs versus having a series of nearly identical amplitudes? One would guess that the former case would induce an even greater alarm since the expectation for the most recent trial should have been a *larger* amplitude then the just previous one. Likewise in the case of anesthetic fade, the next expected amplitude would be smaller than the just previous one. But what degree of amplitude loss would indicate continuation of anesthetic fade versus a new iatrogenic effect? Here is where a regression coefficient offers something a moving average cannot. The regression coefficient can be used to extrapolate what the next MEP amplitude should be. This is done by taking the last fitted data point as y-intercept and adding to it the product of the most recent regression coefficient and the time elapsed from the most recent trial back to the just previous one. This is the statistical estimate of what the present amplitude should be given the information available from the *n* preceding amplitudes. We shall refer to this extrapolated data point as the *predicted* point.

$$\text{Predicted}\,(t_N) = [\text{Fitted}(t_{N-1}) + (\text{Coefficient}_{N-n-2} \times (t_N - t_{N-1}))] \quad (1)$$

The most recent trial is trial N and we are at $t_N$ minutes into the case. We wish to obtain the predicted amplitude at time $t_N$. We take as our reference the last fitted data point at time $t_{N-1}$.

We add to this reference the difference in time since the last trial ($t_N - t_{N-1}$) multiplied by the regression coefficient from the *just previous* LSMA, that is $C_{N-n-2}$ not $C_{N-n-1}$. This is because if the most recently obtained trial constitutes a break from the pre-existing trend, we do not want it to contribute to the estimation of that trend. In addition to this estimate, the *N-n-2th* LSMA will provide a confidence interval above and below the projected estimate indicating what degree of spread might be expected given the variability of the *n* preceding amplitudes.

Compressive injuries to the spinal cord and nerve roots often appear as sudden MEP amplitude loss, in contrast to processes such as anesthetic fade wherein the amplitude loss is more gradual. A sudden change in a data series can be modeled by a *step function* which is a series of 0 s followed by a series of 1 s, the 0 s changing to 1 s at the point in time

when the sudden change takes place. Figure 1 shows a hypothetical scattergram for a case in which there is a sudden *y*- amplitude loss at *x*-time 12. The dashed line is the fitted linear regression of the *y* values on the *x* values. The dashed line is the fitted regression of the *y* values on a series of 0 s prior to *x* value 12 and a series of 1 s starting at *x* value 12. As opposed to linear regression, we will call this latter type of regression a *step function* regression. Regression models have associated with them a value called the *R Square* or $R^2$ which is measure of how well the regression model describes the data. The $R^2$ is the ratio of the sum of squares for the regression of *y* on *x* ($SS_{yx}$) over the sum of squares for *y* total ($SS_y$). In the following equation $\bar{y}$ is the mean of the individual $y_n$ values and $f_n$ are the above described fitted regression values.

$$R^2 = SS_{yx}/SS_y = Sum_{over\,n}\left(f_n - \bar{y}\right)^2 / Sum_{over\,n}\left(y_n - \bar{y}\right)^2 \quad (2)$$

As can be seen, when the fitted values are identical to the actual data values ($f_n = y_n$) the above expression becomes unity, meaning that regression fit is perfect (rarely the case). $R^2$ is expressed in terms of percent and can vary from 0 to 100%. An $R^2$ of 100% indicates the model completely describes the data. The linear regression over time depicted in Fig. 1 produces an $R^2$ of 75, which means a steady downward linear trend describes 75% of the total variance in the *y* values. The $R^2$ associated with the step function regression is 100% indicating that it completely describes the simulated data.

Using the predicted data points extrapolated from LSMAs and the $R^2$ derived from step function regression, a system for trending the MEP trajectory during a case and tracking any significant amplitude loss can be developed. An alarm is triggered by a set percent amplitude loss when the most recent obtained MEP amplitude is compared to the projected amplitude predicted by the most recent LSMA. Once an alarm is triggered on a given trial, a step function is applied at that time point with 0 values preceding it and a value of 1 for the most recent trial and all later trials. As each new trial is obtained, regression of MEP amplitudes on this growing

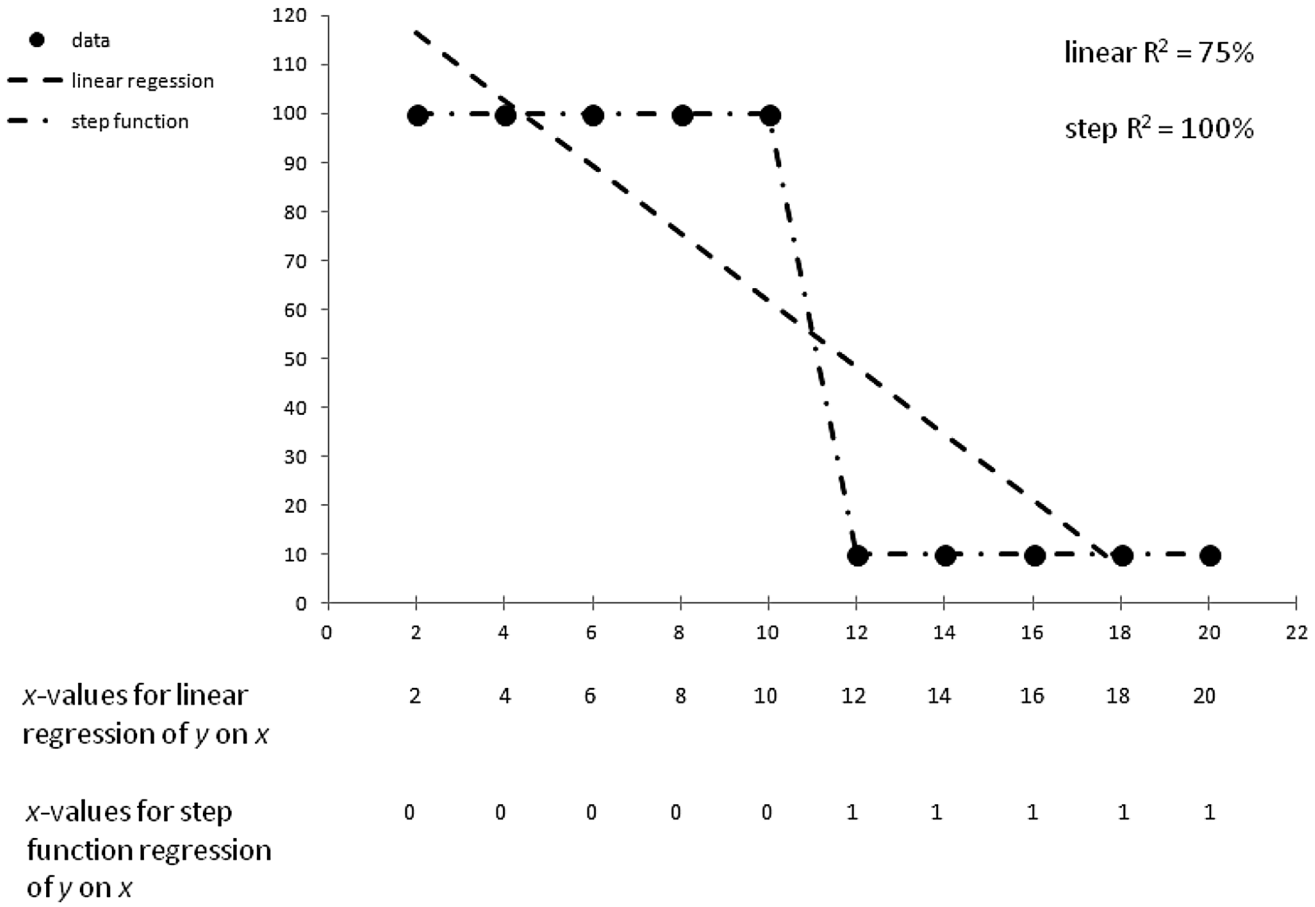



**Fig. 1** Cartesian scatterplot of linear and step function regressions on simulated data, *y*-values (large dots) are 100 up to $x = 10$ and are all 10 thereafter. Step function regression (dashes and dots) describes the data perfectly while linear regression on *x* (dashes) does not. This is reflected their respective $R^2$ values of 100 and 75%

step function will provide an $R^2$ whose percent value will reflect the magnitude of the amplitude loss for the rest of the case. If the amplitude loss was only transitory or the causes of the amplitude loss are alleviated, the $R^2$ will diminish as new trials are gathered. If the amplitude loss is persistent, the $R^2$ will remain at a steady level.

What follows is the retrospective application of the above described trending system to three actual cases. In the first case there was sudden MEP loss and the patient woke up with a newly acquired post-operative deficit. In the second there was also sudden MEP amplitude loss, but after surgical intervention the MEP amplitudes were restored and the patient woke up without new deficit. In the third case the patient again woke up with a new deficit. However, in contrast to the first case there were fewer trials obtained prior to the amplitude change and these were characterized by greater relative variability. Twelve point running LSMAs were used for all three cases to obtain predicted amplitudes according to Eq. 1. In order to trigger step function regression, a newly obtained MEP amplitude had to be (a) 65% less than the amplitude predicted by the just previous LSMA, and (b) below the 85% confidence interval associated with the just previous LSMA. If both these criteria were met on a single trial, a step function is created with 0 s associated with all trial times prior to the trigger and 1 s at all trial times after the trigger. The regression of trial amplitudes is re-computed as each new post-trigger trial is added on and with each re-computation and a new $R^2$ is obtained. The plot of these $R^2$s over time is what we refer to as the running $R^2$.

## 3 Case study 01: background

A 55 year old female diagnosed with fixed sagittal imbalance (i.e. flat-back syndrome) underwent a T10-pelvis instrumentation and fusion, as well as a pedicle subtraction osteotomy (PSO) at L4 to correct the lumbar deformity. TcMEPs were elicited by a Cadwell Elite TCS-4 Transcranial Stimulator. Stimuli were 8–9 single pulse trains with an interstimulus interval (ISI) of 2.0 ms. Starting voltage was 325 V. Anesthetic regimen included Desflurane at 1.5%, as well as 75–100 mcg/kg/min of propofol. Both pedicle screw instrumentation, as well as the osteotomy portion of the procedure, went uneventful. However, while "closing down" the osteotomy to correct the deformity around 220 min into the case, there was an 80% reduction in the amplitude of the TcMEP response in the left anterior tibialis. The surgeon was informed of these acute changes. Based upon this information, the surgeon removed the correction (i.e. opened the osteotomy) and found a disc fragment compressing the L4 nerve root. Despite an aggressive decompression of L4, the anterior tibialis never improved from its initial loss of 80%. Post operatively, the patient was found to be weaker, having 4/5 strength in left dorsiflexion.

## 4 Case study 01: application of the trending system

Figure 2 presents the first three baseline MEP waveforms and the last three from the left anterior tibialis during this case. The amplitude loss between start and end of case is obvious. Figure 3 presents the scatterplot of peak-to-peak MEP amplitudes from the left anterior tibialis over minutes. Given the dual trigger parameters described above, an automatic regression of the raw MEP amplitudes upon a growing step function was initiated at 220 min. The step function consisted of a value of 0 for all trials preceding 220 min and a value of 1 for all trials after that. As each new trial was obtained, a new step function regression was calculated and the running $R^2$ values over time are shown in the bottom panel of Fig. 3. Each new $R^2$ value is plotted at the time point of the newly obtained MEP trial that it was computed with. The statistics for the final step function regression performed when monitoring was stopped just before 400 min are presented in a small table in the middle of the figure. As can be seen, the $R^2$ increases rapidly at 220 min and remains elevated above 80% until the end of the case. The intercept for the final step function regression appears to correspond to the mean amplitude prior to the event at 220 min, while the coefficient for the step function regression corresponds to the persisting amplitude loss in microvolts after 220 min.

## 5 Case study 02: background

A 72 year old male diagnosed with a junctional kyphosis at T12, underwent a T3-pelvis instrumentation/fusion, as well as a vertebral body resection at T12. Intraoperative monitoring modalities included transcranial motor evoked potentials (TcMEPs). TcMEPs were elicited by a Cadwell Elite TCS-4 Transcranial Stimulator. Stimuli were 8–9 single, pulse trains with an interstimulus interval (ISI) between 2.0 and 2.5 ms. Anesthetic regimen included desflurane at 1.5%, propofol between 75 and 100 mcg/kg/min, as well as 3 mcg/kg/min of ketamine. While performing the vertebral column resection at T12 at around 335 min into the case, the surgeon fractured the right pedicle of the T12 vertebrae with a mallet, causing bone fragments to fall into the spinal canal and compress the spinal cord. There was a complete loss (100%) in the amplitude of the TcMEP response from the right foot. The surgeon was notified of this acute electrophysiological change. Acting upon this information, the surgeon immediately decompressed the spinal cord of bone fragments from the residual pedicle. Over the next hour, the

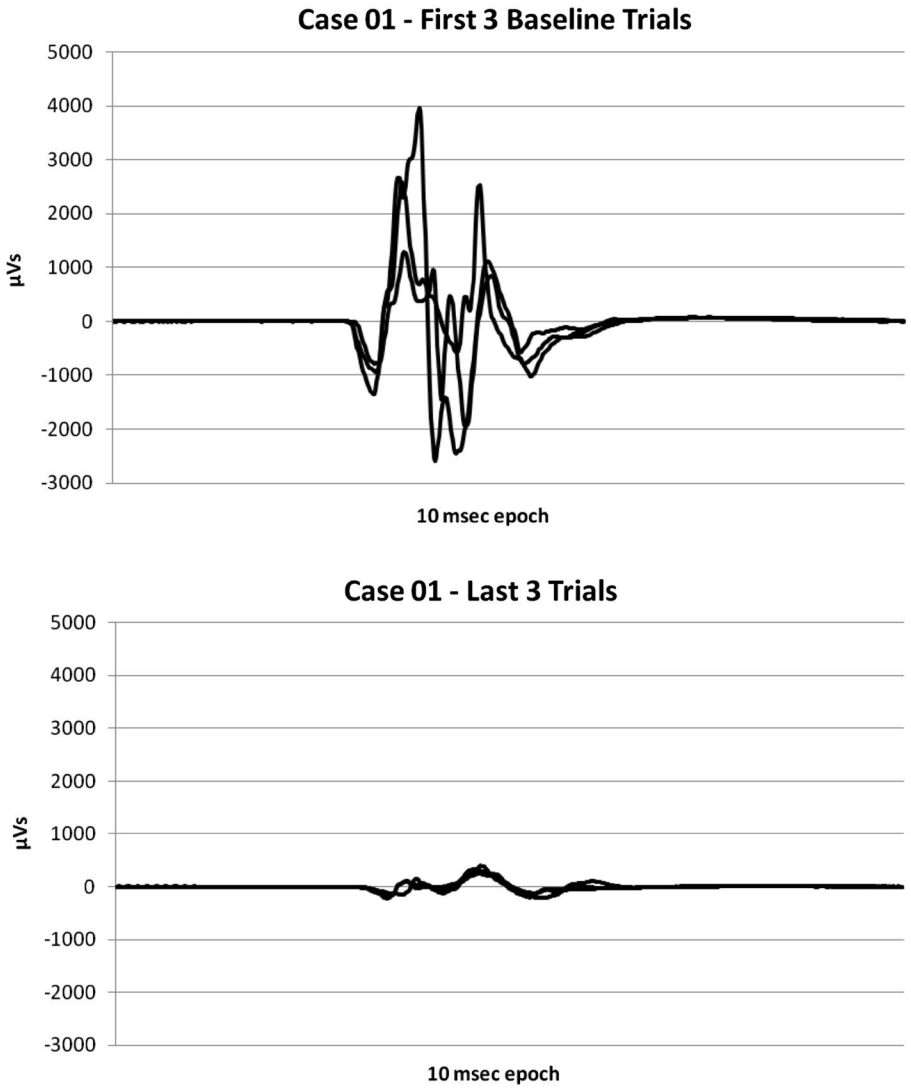
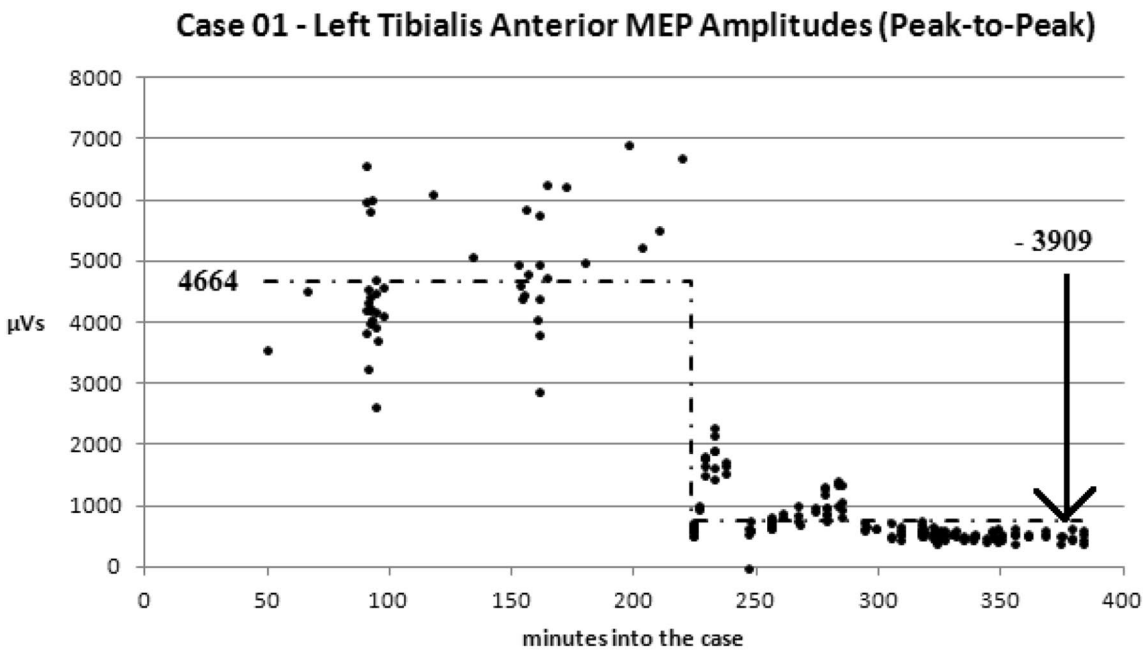



**Fig. 2** Left anterior tibialis MEP waveforms from Case 01

motors in the right foot progressively recovered to baseline values. After decompression of the residual pedicle from the canal and spinal cord, the VCR was completed with no further issues. Post operatively, the patient was found to be neurologically intact.

## 6 Case study 02: application of the trending system

Figure 4 presents the first three baseline MEP waveforms and the final three waveforms from the right foot during this case. Visual inspection suggests no great difference between the two waveform sets. Figure 5 presents the scatterplot of peak-to-peak MEP amplitudes from case 02 at the right foot (top panel), along with the final step function regression statistics (middle table) and plot of the running $R^2$ (bottom panel). Using the dual criterion alert trigger (60% amplitude loss *and* falling outside the lower 85% confidence limit) automatic regression of MEP amplitude upon a step function at 335 min was triggered. The associated running $R^2$ immediately shot up to near 100% but then declined to under 20% by end of case. As in case 01, the final step function regression intercept matches in microvolts the mean amplitude prior to the event at 335 min. However, the step function regression coefficient now describes the mean difference between baseline and all post-335 min amplitudes rather than baseline and the final amplitudes. This is because the post-335 min amplitudes *do not* approximate the final part of a step function (i.e. they have recovered to baseline levels by end of case) and thus the associated running $R^2$ is relatively small at 10% by the end of the case.




| *Regression Statistics* | |
|---|---|
| | *Coefficients* |
| Intercept | 4664 |
| Step Function | -3909 |

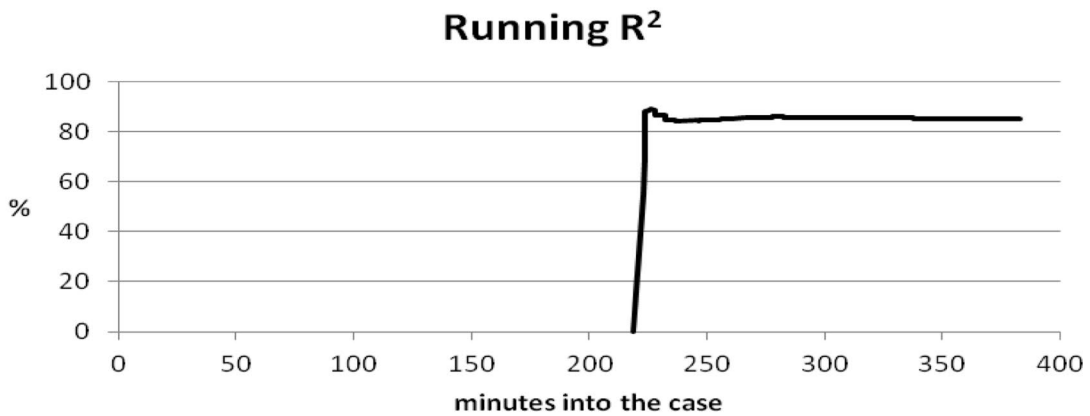



**Fig. 3** MEP peak-to-peak scatterplot, step function regression statistics and plot of the running $R^2$ for Case 01

## 7 Case study 03: background

This case involved a 57 year old man, who was undergoing an L5-S1 anterior lumbar interbody fusion (ALIF), followed by a posterior T10-pelvis fusion with possible Smith-Peterson Osteotomies (SPOs), for lumbar fixed-sagittal imbalance deformity. TcMEPs were elicited by a Cadwell Elite TCS4 Transcranial Stimulator. Stimuli were 9 pulse single trains with a 2.5 ms ISI. Starting voltage was 420 V. Baselines were recorded, but the multimyotomal TcMEPs were marginally reliable in amplitude and replicability due to 3.2% desflurane and 100 mcg/kg/min of propofol (upper panel in Fig. 6), necessitating a change in anesthetic management to TIVA. The patient was pharmacologically-paralyzed with 30 mg of rocuronium for the anterior exposure, preventing further monitoring with TcMEPs. During this time, desflurane was terminated, and ketamine was started at an infusion rate of 3 mcg/kg/min. Propofol remained at 100 mcg/kg/min. The anterior aspect of the procedure went uneventful with a lordotic cage being inserted into the L5-S1

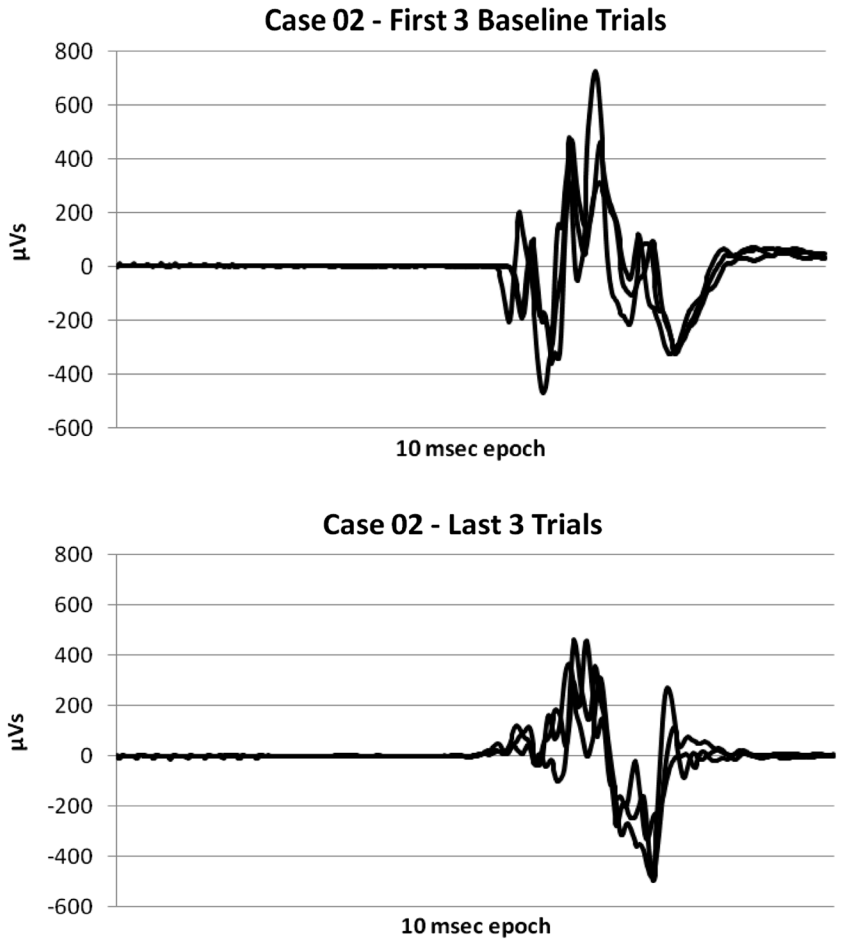



**Fig. 4** Right foot MEP waveforms from Case 02

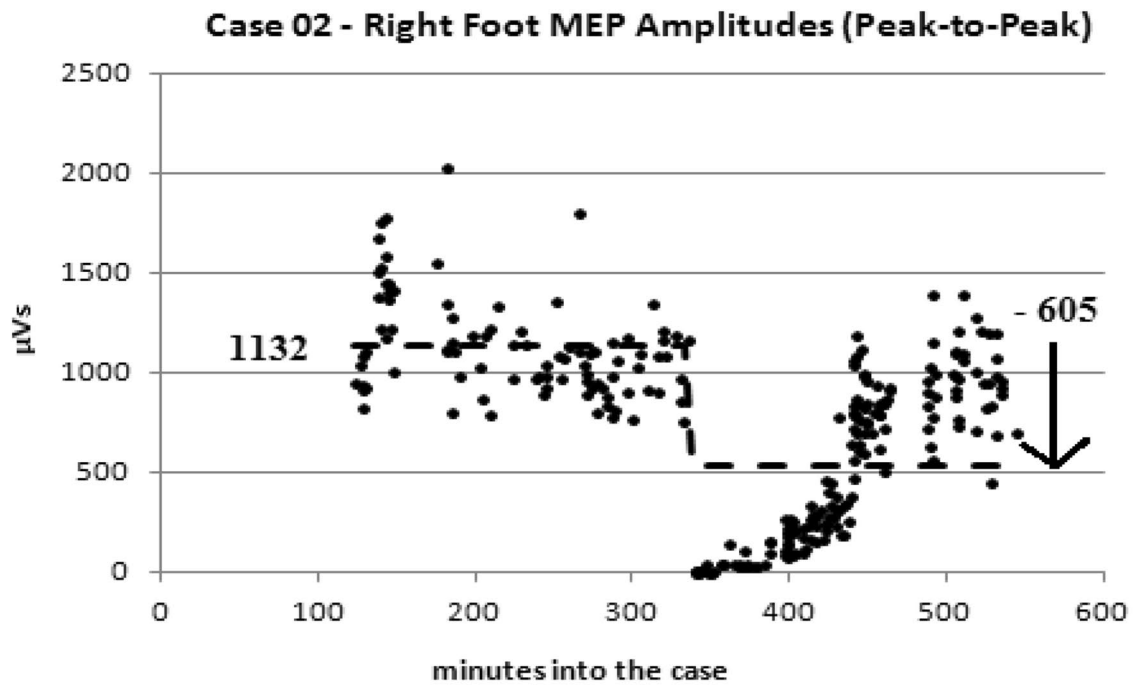
space. TcMEPs were highly robust and replicable during cage placement and during anterior closure. However, after moving the patient prone for the posterior portion of the surgery, the amplitude of the EHL appeared to have decreased. The surgeon investigated the L5 foramen and discovered that it was highly stenotic and concluded the lordotic cage was possibly contributing the new stenosis. Despite extensive decompression, the EHL TcMEPs remained down from original baseline values for the remainder of the operation (lower panel in Fig. 6). Postoperatively, the patient was 2/5 in motor strength in dorsiflexion.

## 8 Case study 03: application of the trending system

The top panel of Fig. 7 presents the scatterplot of MEP amplitudes from right extensor hallucis longus during this case. The group of trials prior to 50 min are the initial baseline. At roughly 100 µV peak-to-peak amplitude these are not very large. The effect of the switch to TIVA can be seen in the trials just after 100 min. There appears to be a boost in amplitude at this time, but the trials are still variable ranging from 150 to 400 microvolts. The post-turn MEP trials can be seen just after 200 min. At around 50–75 microvolts peak-to-peak amplitude they are considerably smaller than the group of trials just after 100 min but not that different from the initial baseline trials prior to 50 min. The loss in amplitude at 200 min triggered the application of a step function regression according to the algorithms dual criterion (> 65% amplitude loss and < 85% lower confidence interval). The running $R^2$ generated by the step function regression applied immediately after 200 min remained elevated up to 70% by end of case. The regression statistics show that this was an approximately 147 microvolt amplitude loss from an overall baseline amplitude of about 160 microvolts. Thus despite a relatively small number of pre-event trials with high variability, the algorithm successfully triggered an enduring $R^2$ consistent with the patients new post-operative deficit.

## 9 Discussion

It appears that the running step function $R^2$ at end of case successfully discriminated outcome in this small sample of cases (post-operative deficit, yes or no). Although the




| *Regression Statistics* | |
|---|---|
| | *Coefficients* |
| Intercept | 1132 |
| Step Function | -605 |

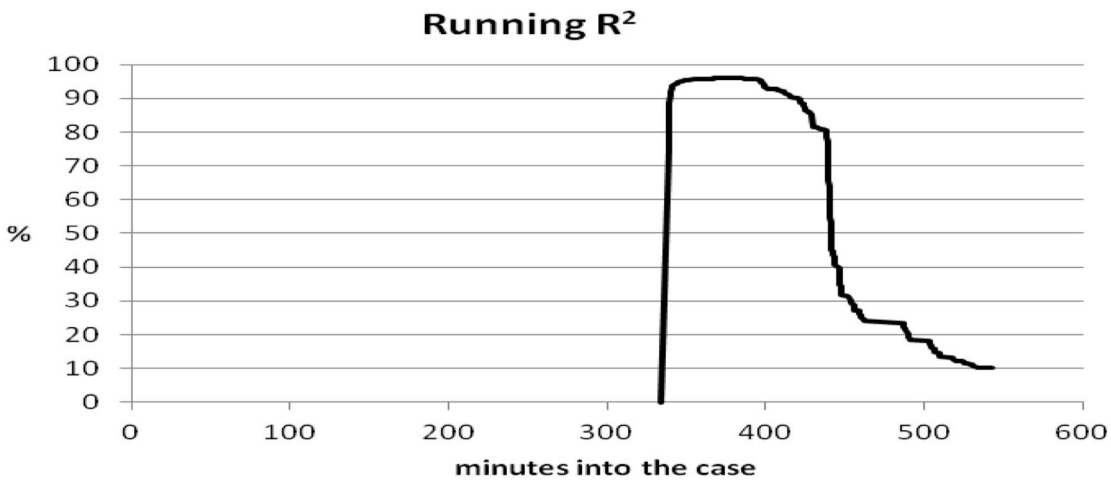



**Fig. 5** MEP peak-to-peak scatterplot, step function regression statistics and plot of the running $R^2$ for Case 02

trending system was applied retrospectively, the comparison of each newly obtained amplitude with the amplitude predicted by the 12-point running LSMA mimics the same situation that would occur as successive trials are gathered in real-time intra-operative monitoring. When the dual criteria of percent amplitude loss and occurrence of an amplitude value below the 85% lower confidence interval are met, an alert can be automatically created. The latter criterion (less than the 85% confidence interval) is very important. A large percent amplitude drop may be registered, but if it is not below a set confidence interval, this drop may be just an expected aspect of the existing variability. If the lower confidence interval reaches zero (or even negative values, which is statistically possible) it means that the monitoring

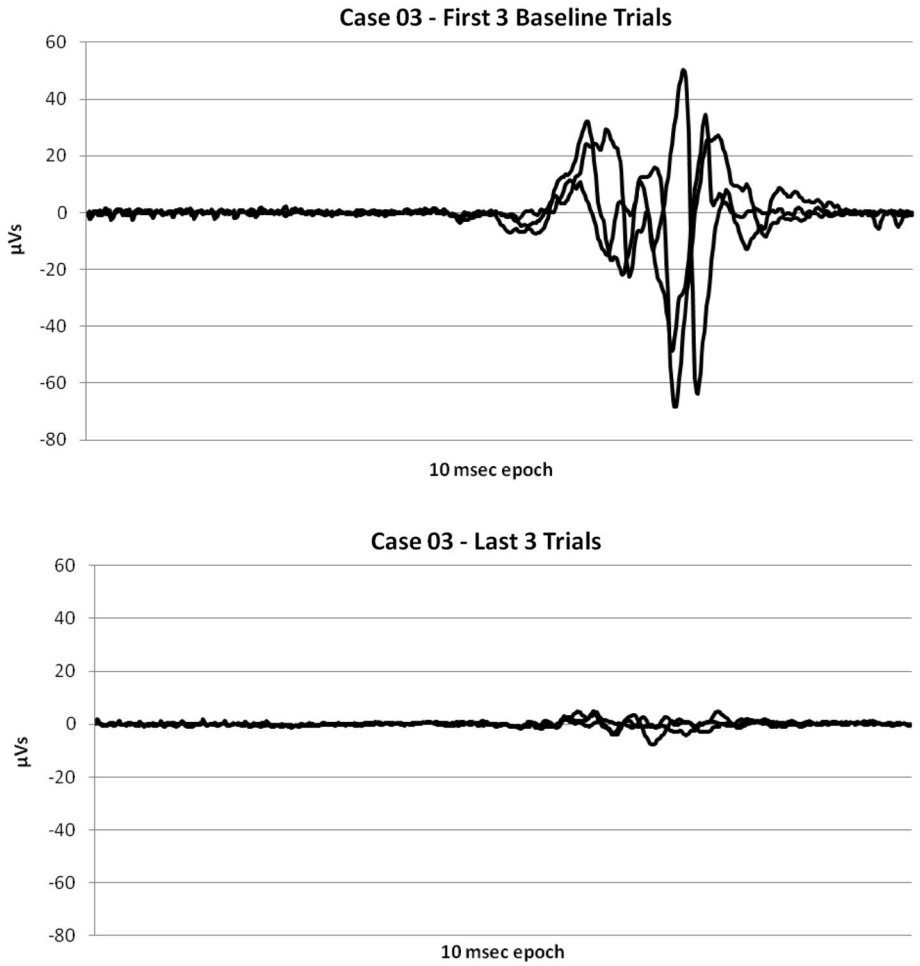
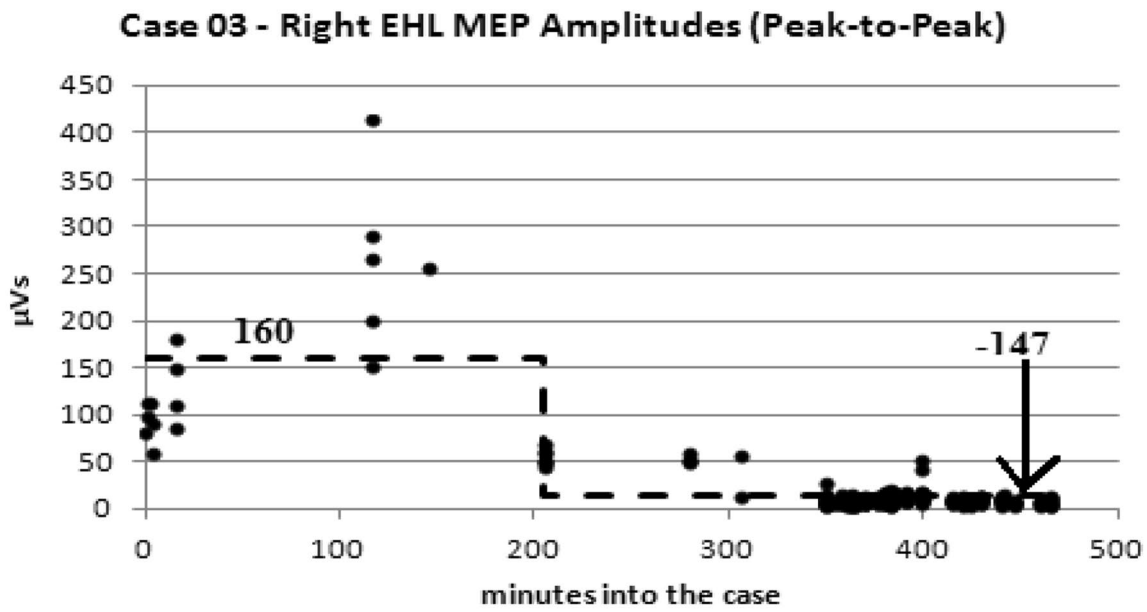



**Fig. 6** Right extensor hallucis longus waveforms from Case 03

modality is seriously compromised since zero amplitude MEPs may now be expected as a matter of course. An important application of the proposed trending system could be to track the lower confidence interval itself. If it touches floor, the surgical team should be informed that anesthesia, hemodynamics or other factors need to be changed because the monitoring modality involved can no longer be counted on.

We propose that both immediate trend *and* variability must be taken into account if it is to be determined that the MEP has *changed*. At any point in a case MEPs may have been increasing, decreasing or remaining the same. Change must be defined as a significant break from those trends. Change must also be defined as *larger* than the pre-existing variability. In order for change to be assessed as larger than pre-existing variability, pre-existing variability has to be *measured*. Linear least squares regression is eminently suitable for these tasks since it provides in one package the direction of trend (the regression coefficient), the spread about that trend (the standard error of the model, or even better the confidence interval derived from the standard error of the model since the gaps between sampling intervals will affect the size of the confidence interval) and how large change is when compared to the total variation (that is provided by the $R^2$). Using the method of successive LSMAs, it can be statistically estimated where the data are trending at any given point in the case. The confidence band associated with an LSMA gives a range in which the next MEP amplitude is expected to appear, assuming continuation of the trend modeled by the last LSMA. If the next MEP trial appears outside this range, this constitutes a "break" in the trend, which may be iatrogenic. The use of the running $R^2$ to determine whether a sudden change is persisting or not, will help to distinguish a real event from the random and wild fluctuations that can sometimes affect the MEP [16, p. 118, 7.7.6]. The preliminary results of the application of the trending system to these three cases suggest that the end-of-case $R^2$ could possibly function as an outcome predictor, higher values indicating probable post-operative deficit, lower values indicating that whatever event triggered it has been ameliorated.

There is no fixed optimal number of points for the LSMAs in this system yet. That will depend on the frequency of MEP sampling permitted by the surgeon and the variability of the




| Regression Statistics | |
|---|---|
| | *Coefficients* |
| Intercept | 160 |
| Step Function | -147 |

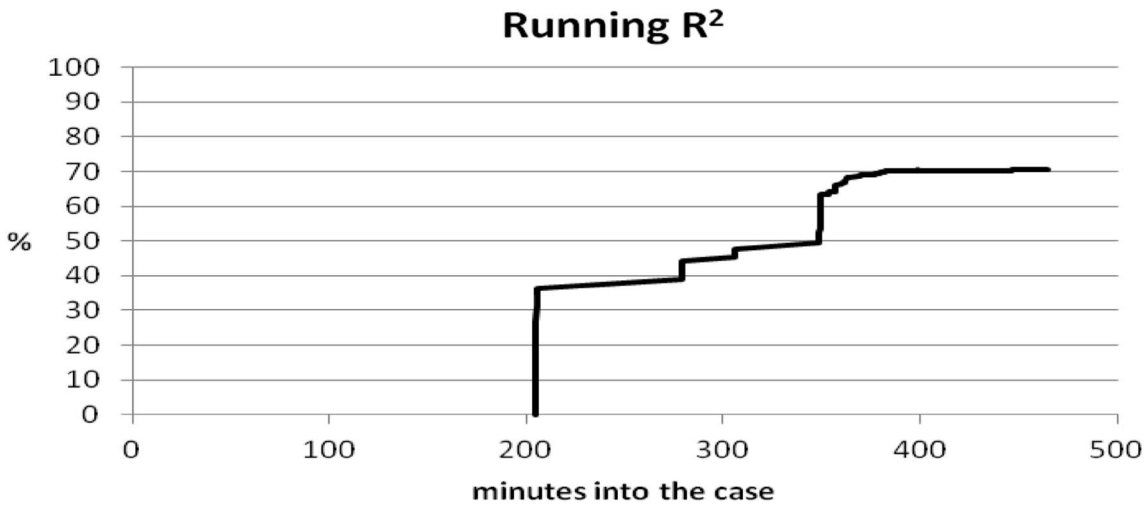



**Fig. 7** MEP peak-to-peak scatterplot, step function regression statistics and plot of the running $R^2$ for Case 03

MEP amplitudes for a particular case. The rule-of-thumb in statistics is that the more points there are, the more accurate will be the estimate. However, the point of this paper is that the trend in MEPs may change during a case. If there are so many points in the LSMAs that they encompass time periods greater than the changes that occur within them, then these changes will be obscured. The optimal number of points will be those long enough to produce statistically stable LSMAs but short enough to catch brief but important trends. The optimal number of points is best chosen by visually inspecting the amplitude-by-time scatterplots, and then deciding what might be the best fit.

We wish to state that the proposed tracking system does not constitute a replacement for the monitoring specialist in

the room. We propose that such tracking systems function as adjuncts to the specialist's decision making, to alleviate some of the uncertainty inherent in the variability of the modalities employed and the weighty consequences of the specialist's decisions. True, an algorithm does not become tired or make mistakes due to fatigue. However, an algorithm can only deal with what it has been programmed to deal with. Thus in order to eliminate the specialist in the room, the algorithm's programmer must anticipate every possible event that can happen during spinal surgery. It has been our experience that the unexpected can happen during spinal surgery, and when it does, the specialist in the room will still be necessary.

## Compliance with ethical standards

**Conflict of interest** The authors have no conflict of interest with regards to this study. The data reported are retrospective data. Patient treatment was not altered or affected in any way by gathering this data. No patient or medical provider identities are revealed in the submitted article.

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