Population Analysis of Kalman-Filtered Permutation Entropy of the Electroencephalogram

Erik Olofsen
Department of Anesthesiology, Leiden University Medical Center, The Netherlands
email: e.olofsen@lumc.nl

Objectives

General anesthetics produce dose-dependent effects on the electroencephalogram (EEG), causing an increase in power combined with a decrease in average EEG frequency. [1] A novel EEG-derived parameter is the permutation entropy (PE) of the EEG. [2] Important advantages are its robustness under eye blinks, and its ease of computation. The permutation entropy quantifies the probability distribution of motifs present in the signal. Because of the ordinal (counting) nature of the PE, it is dominated by the presence of high EEG frequencies, even if they have quite small amplitudes.

Anesthetic concentration-effect data fits often show systematic misfits, due to correlated residuals, which could lead to biased standard errors of parameter estimates and false conclusions from statistical tests. Kalman filters may be constructed to separate measurement and process noise. [3]

Study objectives were:

- To construct a pharmacokinetic-pharmacodynamic (PK-PD) model, including a Kalman filter, to analyze isoflurane concentration-permutation entropy data;
- To gain more insight into the effects of the incorporation of a Kalman filter, by fitting models with and without a Kalman filter to simulated data;
- To study whether observed gender differences in parameters values from a two-stage analysis had statistical significance.

Methods

Calculation of Permutation Entropy

The following figure illustrates the calculation of the permutation entropy (using Shannon's uncertainty formula):

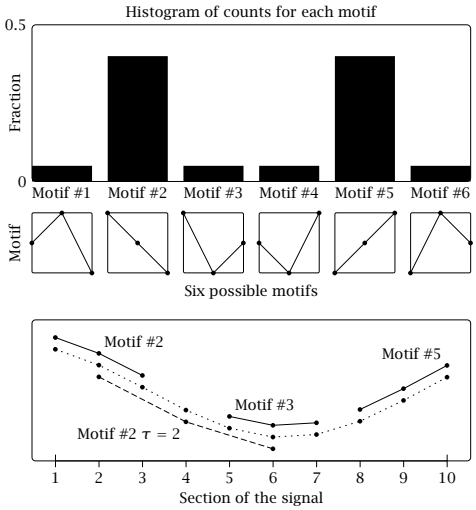

Figure 1: Lower panel: extraction of ordinal patterns from the EEG signal. As the algorithm moves sequentially through the EEG signal, the sections ("motifs" consisting of three data points' length) are classified as one of the six possible patterns, depicted in the middle panel. Upper panel: histogram of the occurrence of each motif in the signal. The dashed-line motif demonstrates the operation of the $\tau = 2$ lag.

Pharmacodynamic Model

The data from 14 patients (7M/7F) were analyzed with a pharmacodynamic model [1] consisting of a hypothetical effect compartment and a sigmoid Emax model with output $E(t)$.

Methods (continued)

The Extended Kalman Filter

The Extended Kalman filter is a method to track the state of a (linearized) nonlinear system in the presence of measurement and system noise. [3] The system state x and a function $g(x)$ need to be defined which describes how it evolves in time, how it is affected by an input, and how it propagates to the output. Two versions were constructed:

- Version A assumes that colored noise is present on the model output, albeit limited by $E_{max} \leq 1$ and $E_{min} \geq 0$. With

$$y(t) = \log\left(\frac{1 - E(t)}{E(t)}\right), \tag{1}$$

where $E(t)$ is the output of the sigmoid-Emax model, and

$$dx = g(x)dt + \nu = -\frac{x(t)}{\tau}\,dt + \nu, \tag{2}$$

where x is the state of the system, ν is system noise, and τ is a time constant, the output is given by

$$E'(t) = \frac{1}{1 + \exp(x + y)} + \epsilon. \tag{3}$$

So $E'(t)$ resembles the original $E(t)$, but contains colored noise, and lies in interval (0,1) (if $\epsilon = 0$).

- Version B assumes that noise enters the system at the input. Because the noise term ν has to be normally distributed, it was added to the logarithm of concentration, and then

$$dx = \frac{1}{\tau}\left(y \cdot \log\left(\frac{C_{ET}(t) + C_{ET,0}}{C_{50}}\right) - x\right)\,dt + \nu \tag{4}$$

and the output is given by

$$E'(t) = E_{min} + \frac{1 - E_{min}}{1 + \exp(x)} + \epsilon, \tag{5}$$

where $C_{ET,0}$ a parameter that yields finite values of the logarithm and replaces E_{max}.

Simulations

The model incorporating Kalman filter version B was used to generate 1000 sets of artificial data of 100 individuals. These data were fitted by the same model to check that the parameter estimation is consistent, and by the model without Kalman filter.

Results

The population analysis of the permutation entropy data without Kalman filter resulted in an estimate of $y \approx 6.8$ and interindividual variance of ≈ 2.3. With Kalman filter A these increased to ≈ 22 and 10, respectively. This means that PE as a measure effectively reduces to an on/off indicator. The following table presents the results employing Kalman filter B:

Par.	Est.	SE	ω^2	SE
$t_{\frac{1}{2},k_{e0}}$	3.50	0.25	-	-
y	2.60	0.68	0.036	0.020
C_{50}	0.64	0.20	0.021	0.011
$C_{ET,0}$	0.28	0.16	-	-
E_{min}	0.699	0.008	0.017	0.007

y and its interindividual variance decreased to useful values. Figure 2 shows that PE is still sensitive to higher isoflurane concentrations (dark green line) instead of being saturated (dark red line). High-frequency EEG and/or EMG activity that elevated the PE seems to be filtered out. Earlier observed gender differences in $t_{\frac{1}{2},k_{e0}}$ disappeared.

Results (continued)

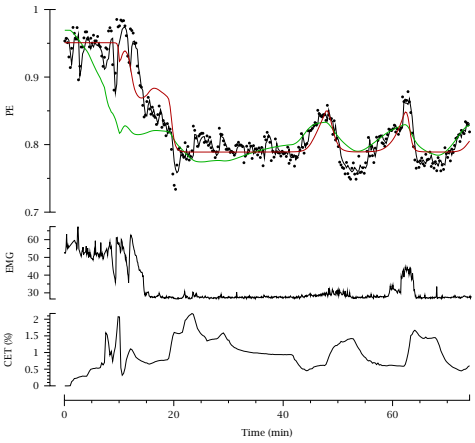

Figure 2: PE data fits without Kalman filter (red line) and with Kalman filter B (green line).

The simulation study showed that all parameters (and SEs) are well estimable (*cf.* previous table):

Par.	Est.	SD	med.(SE)	ω^2	SD	med.(SE)
$t_{\frac{1}{2},k_{e0}}$	3.46	0.091	0.093	-	-	-
y	2.49	0.18	0.18	0.0328	0.0066	0.0064
C_{50}	0.622	0.051	0.051	0.0218	0.0050	0.0050
$C_{ET,0}$	0.270	0.039	0.040	-	-	-
E_{min}	0.699	0.003	0.003	0.0164	0.0025	0.0024

Interindividual variability was overestimated when the data were fitted with a model without Kalman filter:

Par.	Est.	SD	med.(SE)	ω^2	SD	med.(SE)
$t_{\frac{1}{2},k_{e0}}$	3.71	0.23	0.22	0.288	0.068	0.055
y	2.67	0.22	0.21	0.63	0.15	0.13
C_{50}	0.531	0.019	0.017	0.082	0.021	0.018
E_{max}	0.961	0.002	0.002	0.296	0.044	0.043
E_{min}	0.697	0.006	0.006	0.056	0.014	0.012

Conclusions

- While the PE is insensitive to eye blinks, it is sensitive to high frequency components present in the EEG just before loss of consciousness. This results in a steep concentration-effect relationship. Analysis of EEG data with a Kalman filter accentuated or filtered out this phenomenon, depending on the postulated location of process noise.
- It should be noted that this artifact filtering is only possible if the anesthetic concentration is known.
- The model parameters, and hence the permutation entropies at different levels of anesthetic concentration, were not dependent on the gender of the patients.
- Process noise may substitute for model inadequacies, in this case an EEG effect which was (in the model) not related to anesthetic concentration. The confounding effect may need to be scaled, due to nonlinearities, to the level of the real process noise.
- Without Kalman filtering, interindividual variability may be biased upward by intra-individual process noise.

References

[1] E Olofsen and A Dahan. The dynamic relationship between end-tidal sevoflurane and isoflurane concentrations and bispectral index and spectral edge frequency of the electroencephalogram. *Anesthesiology*, 90:1345–53, 1999.

[2] E Olofsen, J W Sleigh, and A Dahan. Permutation entropy of the electroencephalogram: a measure of anaesthetic drug effect. *Br J Anaesth*, 101:810–821, 2008.

[3] C W Tornøe, R V Overgaard, H Agersø, H A Nielsen, H Madsen, and E N Jonsson. Stochastic differential equations in nonmem: Implementation, application, and comparison with ordinary differential equations. *Pharm Res*, 22:1247–58, 2005.