Nonlinear Local Electrovascular Coupling. II: From Data to Neuronal Masses

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Abstract: In the companion article a local electrovascular coupling (LEVC) model was proposed to explain the continuous dynamics of electrical and vascular states within a cortical unit. These states produce certain mesoscopic reflections whose discrete time series can be reconstructed from electroencephalography (EEG) and functional magnetic resonance imaging (fMRI). In this article we develop a recursive optimization algorithm based on the local linearization (LL) filter and an innovation method to make statistical inferences about the LEVC model from both EEG and fMRI data, i.e., to estimate the unobserved states and the unknown parameters of the model. For a better understanding, the LL filter is described from a Bayesian point of view, providing the particulars for the case of hybrid data (e.g., EEG and fMRI), which could be sampled at different rates. The dynamics of the exogenous synaptic inputs going into the cortical unit are also estimated by introducing a set of Gaussian radial basis functions. In order to study the dynamics of the electrical and vascular states in the striate cortex of humans as well as their local interrelationships, we applied this algorithm to EEG and fMRI recordings obtained concurrently from two subjects while passively observing a radial checkerboard with a white/black pattern reversal. The EEG and fMRI data from the first subject was used to estimate the electrical/vascular states and parameters of the LEVC model in V1 for a 4.0 Hz reversion frequency. We used the EEG data from the second subject to investigate the changes in the dynamics of the electrical states when the frequency of reversion is varied from 0.5–4.0 Hz. Then we made use of the estimated electrical states to predict the effects on the vasculature that such variations produce. *Hum Brain Mapp* 28: 335–354, 2007. © 2006 Wiley-Liss, Inc.

Key words: fusing EEG and fMRI data; state space models; statistical inferences

INTRODUCTION

A common aspect in several previous forward/generative models of electroencephalography (EEG) [e.g., David and Friston, 2003; Jirsa and Haken, 1996; Lopes da Silva et al., 1976; Robinson et al., 2001; Stam et al., 1999; Wilson and Cowan, 1972; Zetterberg et al., 1978] and also of functional magnetic resonance imaging (fMRI) [e.g., Almeida and Stetter, 2002; Aubert and Costalat, 2002; Deco et al., 2004; Friston et al., 2000, 2003; Husain et al., 2004; Tagamets and Horwitz, 1998; Zheng et al., 2002] is that they can be formulated as a continuous dynamic system describing the temporal course of certain states with specific physiological meanings. Synthetic EEG and fMRI data can be obtained from these models by discretely sampling combinations of these states (i.e., often explicitly represented by an observation equation) additionally polluted by measurement errors. In most of cases, such combinations are linear, but in some nonlinearities are

Contract grant sponsors: JST/RISTEX; R&D promotion scheme for regional proposals promoted by TAO; the 21st Century Center of Excellence (COE) Program (Ministry of Education, Culture, Sports, Science and Technology) "A Strategic Research and Education Center for an Integrated Approach to Language, Brain and Cognition"; Management Expenses Grants of Tohoku University.

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Received for publication 16 November 2005; Accepted 9 March 2006

DOI: 10.1002/hbm.20278

Published online 24 August 2006 in Wiley InterScience (www.interscience.wiley.com).

required at the observation level. An example of this is when we try to relate the vascular states in the balloon model to the blood oxygenation level-dependent (BOLD) signal [Buxton et al., 1998].

These states tend to be mesoscopic in character: for example, the electric membrane potentials of large-scale neuronal populations and the cerebral blood volume in brain regions containing a large number of expandable postcapillary venules. Additionally, they describe physical magnitudes that are directly or indirectly related to diffusion phenomena: e.g., ionic flows through the cellular membrane, neurotransmitter migrations inside the synaptic cleft, and oxy and deoxy hemoglobin flows within the capillary bed. Hence, the dynamics of these states should include population and diffusive random effects, which, to a large extent, explains why several of the above-mentioned models were extended with further stochastic driven forces (e.g., Wiener processes) of intrinsic biophysical origin. In particular, Valdés et al. [1999] and Riera et al. [2004a] presented stochastic versions of the neuronal population model for the alpha rhythm [Zetterberg et al., 1978] and of the modified balloon approach [Friston et al., 2000], respectively.

Therefore, the most up-to-date acknowledged forward/generative models of EEG and fMRI could be, in principle, formulated in the context of the continuous-discrete *state space theory*. A continuous-discrete state space model is, by definition, a two-part model: a *continuous diffusion process* representing the dynamics of the states (i.e., usually described by a set of stochastic differential equations, SDE) and a *discrete equation* relating these states to a number of observations. The state space formalism provides a useful framework to fit existing models to actual data, known as “statistical inferences,” which is of central importance when evaluating the competence of a particular model. In order to make statistical inferences for state space models from discrete data, two major problems need to be solved: 1) estimating the unobservable states (given that the parameters of the model are known), and 2) estimating the parameters of the model themselves. These two inference problems are closely related, and in many practical cases it is necessary to solve both at the same time [e.g., in neuroscience: Valdés et al., 1999; Riera et al., 2004a; in finance: Ghysels et al., 1996; Ozaki et al., 2001; in epidemiology: Pedrosa et al., 2003]. See also Ozaki et al. [2004] for a more detailed revision.

The basis for the solution to inference problem (1) was established by Kalman [1960, 1963; see also Kalman and Bucy, 1961], who provided a recursive and computationally efficient method to solve the filtering and prediction problems. Unfortunately, Kalman’s method is only applicable to linear/autonomous state space models with additive Wiener processes. In the last 40 years, a large variety of recursive nonlinear filters have been considered [Daum, 1986; Lainiotis, 1974; Liang, 1983; Ozaki, 1993; Schwartz and Stear, 1968, etc.], e.g., the extended Kalman, Gaussian, and local linearization (LL) filters. There is a considerable amount of evidence suggesting that the LL filter is the most computationally

stable and efficient of them [Ozaki, 1993; Ozaki et al., 2000].

Because of the lack of theoretical results related to the solution of inference problem (2), the subject continues to receive considerable attention. Essentially, there have been four methods developed to date [see Jimenez et al., 2006, for an updated review]: the maximum likelihood [Schweppe, 1965], the innovation [Ozaki, 1994], the prediction error recursions [Jazwinski, 1970], and the quasi-likelihood [Nolsoe, 2000] methods. The use of the maximum likelihood method is restricted to linear state space models with additive noise. In such simple cases, the conditional probabilistic distribution function (pdf) used to compute the likelihood function is Gaussian; hence, the Kalman filter is used to accurately evaluate its conditional mean and variance. The innovation estimators are obtained from maximizing the likelihood function associated with the discrete innovations process [Kailath, 1974], assuming that if the model is reliable it should be a pure white noise process. Ozaki [1994] suggested the use of the LL filter to evaluate the first two conditional moments of an approximated Gaussian pdf. In the least-square method based on the prediction errors, the parameters are estimated ad hoc by applying a recursive filter to the extended state space model resulting from the addition of a new state for each unknown parameter. The quasi-likelihood estimators are obtained by solving the nonlinear equation defined by the optimal estimating function. Among them, the innovation method based on the LL filter is the most suitable for solving inference problem (2) because: i) it can be applied to nonlinear and nonautonomous state space models (also with nonclassical random effects); ii) the solution to inference problem (1) can be obtained in a straightforward manner; iii) the computational cost is low; and iv) the distribution of fitting-innovations can be used to evaluate the quality of the estimates.

In the companion article we proposed a canonical neuronal mass model to explain the dynamics of intrinsic electrical states in a cortical unit. These electrical states subsequently induce changes in the dynamics of the vasculature. The vascular states were modeled by an extended balloon approach. The combination of these two models (i.e., the local electrovascular coupling, LEVC, model) constitutes the drift component of a dynamic system, which is nonautonomous due to the time varying synaptic inputs I_1^+ , I_2^+ , and I_3^+ . Besides the drift, Riera et al. [2006] proposed a multidimensional stochastic force, which additively perturbs the dynamics of the states. The states and certain EEG/fMRI mesostates relate by linear/nonlinear observation equations. This state space model constitutes an effort to bring together electrovascular physiological processes and EEG/fMRI data, creating perspectives for a feasible data fusion in the context of the time series analysis. The fusion of EEG and fMRI data is currently the focus of attention of neuroimagers, which clearly shows the high expectations held with regard to the development of concurrent EEG and fMRI recording systems [Goldman et al., 2000; Salek-Haddadi et al., 2003]. However, for technological and biophysical reasons the

sampling rates of EEG and fMRI signals are usually different, implying that they are not observed at the same time instants. For example, EEG signals can be recorded at frequencies higher than 200 Hz, while the maximal time resolution for fMRI signals is around 1 Hz. Hence, a new challenge is added to the already colossal inference problems mentioned above: *How can we make statistical inferences about a state space model if the observations are hybrid, with missing values that are heterogeneous in nature?*

In this article the innovation method based on the LL filter is adapted to deal with that class of inference problems that result in a recursive optimization algorithm. With that proposal, the synaptic inputs I_1^+ , I_2^+ , and I_3^+ to the cortical unit are modeled as a linear combination of Gaussian radial basis functions, providing a plausible way to determine their respective time courses. The amplitudes of these quasi-regularly spaced Gaussians, of around 15.6 ms in width, are set as additional parameters to be estimated from the data. Because most of the parameters of the model have a direct physiological interpretation, their values are constrained to vary within certain ranges. Therefore, fitting the amplitudes of these Gaussians is essential to tailor our model to actual data. However, we estimate those parameters with no straight physiological interpretation. We normalize the log-likelihood function of the innovations process and the parameters to provide a much better convergence in the recursive optimization algorithm [Gill et al., 1981]. We investigate the bias in estimating the parameters from 500 simulations, a key measure when studying the identifiability of the state space model.

In particular, we used this algorithm to make statistical inferences about the LEVC model from actual EEG and fMRI recordings obtained concurrently from two healthy subjects during a visual experiment (a radial checkerboard with a white/black pattern reversal). We estimated the electrical/vascular states and the parameters of the model at once using EEG and fMRI mesostates obtained from the first subject (reversing frequency of 4.0 Hz). The EEG mesostates obtained from the second subject were used to make statistical inferences about the canonical neuronal mass (reversing frequencies: 0.5, 1.0, 2.0, and 4.0 Hz). From the estimated electrical states, the fMRI mesostates corresponding to each frequency were predicted and compared with those obtained from fitting the respective hemodynamic response functions (HRF) nonlinearly to the data [Friston, 2002] via the statistical parametric mapping toolbox SPM2 (Wellcome Department of Imaging Neuroscience, UCL). The null hypothesis that the fitting-innovations have a Gaussian distribution is used in both analyses as an indicator of the goodness-of-fit. For this purpose, the Kolmogorov–Smirnov test is directly applied [Chakravarti et al., 1967].

The remainder of this article is organized as follows. In Materials and Methods the LL filter and the innovation method are explained using a Bayesian context. The experimental design and data preprocessing are also detailed. In the first section of the Results and Discussion we inspect the identifiability of the state space model. In the second section

the LEVC model is fitted to concurrent EEG/fMRI data obtained from the first subject. The EEG data obtained from the second subject is used in the third section to make statistical inferences about the canonical neuronal mass, and subsequently, to predict the reaction of the vasculature. In the Future Implications section we highlight the future physical and physiological implications of this work.

MATERIALS AND METHODS

LL Filter and the Innovation Method

A continuous-discrete state space model with an *additive* multidimensional Wiener process $Gd\tilde{w}$ is defined by combining the continuous SDE:

$$d\tilde{x} = \tilde{f}(t, \tilde{x}; \boldsymbol{\theta})dt + Gd\tilde{w} \quad (1a)$$

and the discrete observation equation:

$$\tilde{z}_{s_k} = \tilde{h}_{s_k}^{\Phi}(\tilde{x}(s_k)) + \tilde{e}_{s_k} \quad \{s_k; k = 1, \dots, N\} \quad (1b)$$

The measurement errors $\tilde{e}_{s_k}$ are assumed to be i.i.d. (i.e., $\tilde{e}_{s_k} \sim N(\tilde{0}, \boldsymbol{\Omega}_{s_k})$). The function $\tilde{f}(\cdot, \cdot; \boldsymbol{\theta})$ constitutes the nonautonomous drift component with parameters $\boldsymbol{\theta}$. The observations $\tilde{z}_{s_k}$ can be hybrid in general with heterogeneous missing values; hence, the function $\tilde{h}_{s_k}^{\Phi}(\cdot)$ (with observational parameters Φ) and the variance–covariance matrix $\boldsymbol{\Omega}_{s_k}$ must be defined for each time instant s_k . The set $\boldsymbol{\vartheta} = (\boldsymbol{\theta}, \Phi, G, \boldsymbol{\Omega}_{s_k})$ summarizes the whole parameters of the state space model (1). The particulars of Eqs. 1a,b for the LEVC model are given in Appendix A.

LL filter

From a Bayesian point of view [Jazwinski, 1970], to solve inference problem (1) for the state space model (Eq. 1), i.e., to estimate $\tilde{x}(t)$ given $\boldsymbol{\vartheta}$ is known, the evolution in time of the conditional pdf $p(t, \tilde{x}(t)/Z_{s_k})$ must be determined. The set $Z_{s_k} = \{\tilde{z}_{s_1}, \dots, \tilde{z}_{s_k}\}$ comprises the observations previous to time instant t . This conditional pdf is in general non-Gaussian, with the exception of only a few simple state space models. It conveys the amount of certainty about the knowledge of the value of $\tilde{x}(t)$ from the data. Equations that describe the evolution in time of $p(t, \tilde{x}(t)/Z_{s_k})$ and, in particular, the first two conditional moments of $\tilde{x}(t)$ are well known [Jazwinski, 1970]. However, these equations usually do not have explicit solutions and approximations are required.

The more known of these approximations are the so-called recursive filters, which assume the $p(t, \tilde{x}(t)/Z_{s_k})$ Gaussian to provide a feasible estimate for the time-varying conditional mean $\tilde{x}_{t/s_k}$ and variance $\mathbf{P}_{t/s_k}$:

$$\begin{aligned} \tilde{x}_{t/s_k} &= \int p(t, \tilde{x}(t)/Z_{s_k})\tilde{x}(t)d\tilde{x}(t) \\ \mathbf{P}_{t/s_k} &= \int p(t, \tilde{x}(t)/Z_{s_k})(\tilde{x}(t) - \tilde{x}_{t/s_k})(\tilde{x}(t) - \tilde{x}_{t/s_k})^T d\tilde{x}(t) \end{aligned}$$

Figure 1.

Diagram of the main algorithm in the LL filter. This algorithm is comprised of sequential filtering and prediction steps. For convenience, it has been set $s_0 = t_0$. The MATLAB function $[t, \tilde{x}, \mathbf{P}] = \text{Assigner}(t', \tilde{x}', \mathbf{P}')$ assigns values; i.e., $t \leftarrow t'$, $\tilde{x} \leftarrow \tilde{x}'$ and $\mathbf{P} \leftarrow \mathbf{P}'$.

If $t = s_k$, $\tilde{x}_{s_k/s_k}$ and $\mathbf{P}_{s_k/s_k}$ are called filter and filter variance, respectively. For $t > s_k$, $\tilde{x}_{t/s_k}$ and $\mathbf{P}_{t/s_k}$ are the corresponding predictor and predictor variance. The superscript "T" denotes the transpose of a vector (matrix).

In a recursive filtering based on Kalman's ideas, $\tilde{x}_{t/s_k}$ and $\mathbf{P}_{t/s_k}$ are updated from information contained in both the data Z_{s_k} (i.e., the **Filtering** _{s_k}) and the state space model (i.e., the **Prediction** _{s_k}) while time t propagates forward. At the

start, the prediction step is performed to estimate $\tilde{x}_{s_1/s_0}$ and $\mathbf{P}_{s_1/s_0}$ at the time instant of the first observation s_1 from the initial conditions $\tilde{x}_{0/0}$ and $\mathbf{P}_{0/0}$ at time instant t_0 , which is followed by N (i.e., number of observations) iterations from s_1 to s_N (Fig. 1). In the k -th iteration, the filtering step is applied initially to rectify the predicted values $\tilde{x}_{s_k/s_{k-1}}$ and $\mathbf{P}_{s_k/s_{k-1}}$ at time instant s_k by using the data $\tilde{z}_{s_k}$ and after that, the prediction step is used to approximate the evolution of $\tilde{x}_{t/s_k}$ and $\mathbf{P}_{t/s_k}$ within the interval with missing data defined by s_k and the time instant of the consecutive observation s_{k+1} . For convenience, the filtering step is always defined in terms of the innovations process (i.e., $\tilde{v}_{s_k}$ for the k -th iteration, the variance of which is Σ_{s_k}). Figure 2 shows detailed diagrams of the filtering (left) and prediction (right) steps for the k -th iteration.

The LL filter was initially developed by Ozaki [1993], and latter extended [Jimenez and Ozaki, 2003; Ozaki and Iino, 2001] to cope with the estimation problems of state space models with at least one of the following characteristics: 1) nonlinear or nonautonomous terms and 2) random effects with noise structures more complex than additive Wiener processes. It is distinguished from other iterative filters by the fact that functions $\tilde{f}(\cdot, \cdot; \boldsymbol{\theta})$ and $\tilde{h}^\Phi(\cdot)$ are linearized inside each interval $[t, t + \Delta_k]$ and at $\tilde{x}(s_k)$, respectively. The optimum step size Δ_k must be selected for each iteration. In this work we used the LL filter to estimate $\tilde{x}(t)$ in a state space model like Eq. 1 from hybrid data that were recorded with different sampling rates. The particularities of the MATLAB (Natick, MA) functions **Innovation**®, **Filter**® and **Predictor**® _{Δ_k} for the LL filter are presented in Appendix B.

Figure 2.

Detailed diagrams of filtering and prediction steps. The MATLAB functions involved in the LL filter are defined in Appendix B.

Innovation method

As mentioned above, the innovation method provides a solution to inference problem (2), i.e., estimating the parameters of the model ϑ . Considering that the innovations process $\tilde{v}_{s_k}$ associated with a reliable state space model is approximately a Gaussian independent random vector for $\lambda = \max_k\{s_{k+1} - s_k\}$ small enough, the innovation estimator $\hat{\vartheta}$ can be obtained by maximizing the log-likelihood function $l_Z(\vartheta)$ defined from $\tilde{v}_{s_k}$ given data $Z = \{\tilde{z}_{s_k}, k = 1, \dots, N\}$. That is the optimization problem $\hat{\vartheta} = \arg\{\min_{\vartheta}\{-l_Z(\vartheta)\}\}$ [Jimenez and Ozaki, 2006; Ozaki, 1994], where $l_Z(\vartheta)$ is evaluated by propagating the LL filter:

$$l_Z(\vartheta) = -N \ln(2\pi) - \sum_{k=1}^N (\ln|\Sigma_{s_k}| + \tilde{v}_{s_k}^T \Sigma_{s_k}^{-1} \tilde{v}_{s_k}) \quad (2)$$

Once the parameters have been estimated, the fitting conditional mean $\hat{x}_{t/s_k}$ and variance $\hat{P}_{t/s_k}$ in the interval $t_0 \leq t \leq T$ are evaluated by propagating the LL filter with the estimated parameters $\hat{\vartheta}$. Therefore, inference problems (1) and (2) for the state space model (Eq. 1) are solved in one fell swoop.

The log-likelihood function $l_Z(\vartheta)$ depends on the initial values of the conditional mean $\hat{x}_{0/0}$ and variance $P_{0/0}$, which in general must be also inferred from data. However, in particular for the experimental data used here, it is assumed that $\hat{x}_{0/0} = \hat{x}_0$ [see Riera et al., 2006] and $P_{0/0} = 0$, since the cortical unit is in a resting condition at the initial time t_0 .

Two factors undermine the reliability of the state space model (Eq. 1) to represent a set of data: the state space model is not valid, or it is, but at least one of its parameters is wrong. In the latter case, the recursive optimization algorithm presented above (Fig. 3) will permit us to find the correct parameters, and the resulting fitting-innovations $\hat{v}_{s_k}$ will be a Gaussian independent random process. The fitting-innovations are the prediction errors remaining after the estimation. The Kolmogorov-Smirnov test [Chakravarti et al., 1967] could be used to decide if the fitting-innovations have a Gaussian pdf with a zero mean and a constant variance over time, which is equivalent to evaluating the quality of the estimates. Note that the test also allows us to decide if the covariance between two observations (they could be of different modalities) is zero.

The Kolmogorov-Smirnov test is based on the empirical pdf. The main advantage is that it is an exact test; i.e., it does not depend on the underlying cumulative pdf being tested (e.g., the chi-square goodness-of-fit test depends on an adequate sample size for the approximations to be valid). However, in order to use this test the pdf must be fully specified. An additional limitation is that the test tends to be more sensitive near the center of the distribution than at the tails.

Concurrent EEG and fMRI Experiments

Two healthy subjects participated in this experiment. The experiment was carried out at Tohoku University; hence, the

Figure 3.

The recursive optimization algorithm. Formula (2) defines the MATLAB function $l_Z(\vartheta) = \text{Log-Likelihood}(\vartheta, Z)$. ϑ_0 represents the initial parameters.

informed consent of both subjects was required in accordance with its Institutional Review Board.

Visual paradigm

A single trial of this visual experiment consisted of radial checkerboard (10 rings at 10° eccentricity, checker angle: 10°) stimulation with a white/black pattern reversal at 0.5, 1.0, 2.0, or 4.0 Hz displayed over 4 s. The average luminance during the stimulation interval was maintained around 13.5 cd/m². The stimulation interval was followed by a poststimulus interval of 21 s, during which a gray screen of equal average luminance was presented. The subjects were instructed to fixate on a central small white circle (visual angle 0.3°) presented continuously throughout the experiment.

MRI acquisition. T2-weighted, gradient-echo, echo-planar imaging (EPI) (echo time 40 ms, flip angle 85°, field of view 192 mm and bandwidth 2,170 Hz) were obtained using a 1.5-T MRI scanner with a circular head coil (Siemens Magnetom Symphony, Erlangen, Germany). The interscan intervals and voxel sizes were different for each subject; hence, they will be specified in second and third sections of the Results and Discussion, respectively. The T1 structural images were obtained for each subject with a spoiled grass gradient sequence (176 sagittal slices, 1.0 mm thickness with no skip, repeat time 2,000 ms, echo time 4 ms, flip angle 15°). The images were reconstructed as a 176 × 256 × 256 matrix with a 1.0 × 1.0 × 1.0 mm³ spatial resolution.

EEG acquisition. EEG was recorded inside the 1.5-T MRI scanner with a commercially available MR-compatible 64-

channel BrainAmp system (Brain Products, Munich, Germany), sampled at 5 kHz with a bandpass filter of 0.5–125 Hz. The electrodes were positioned on the scalp following the international 10/10 system using the BrainCap-MR 64 channel-Melquest. The reference was attached to the subjects' left earlobe. The impedances of all channels were maintained below 5 k Ω . The positions of the electrodes and a few external landmarks were determined using a 3D positions indicator system (Isotrack II, Polhemus Product, Colchester, VT). The coordinates of the electrodes and external landmarks for each subject were corrected in order to match them to the respective individual T1 structural image.

MRI data analysis. The fMRI scans were preprocessed (i.e., realignment, slice timing adjustment, coregistration, spatial normalization, and spatial smoothing with 6-mm isotropic full width at half maximum, FWHM, Gaussian kernel) using SPM2. The BOLD signal in each trial was modeled as a boxcar function of 4 s duration convolved with a canonical HRF. The time and dispersion derivatives of the HRF were also included in the linear regression model (i.e., three regressors). The statistical model included global, low-frequency/motion-related confounds, and residual serial correlations [Penny et al., 2003].

Either cognitive subtraction or conjunction analyses were used to localize the striate cortex V1 and also to determine its functional extension. A global BOLD effect at V1 was characterized in terms of the first principal component of the adjusted data (removing the nonlinear drift and the effects of confounds) from voxels within two spherical volumes of about 6 mm in radius, each centered on the maximum of activation for each hemisphere. In this analysis, only the voxels surviving a threshold of $P = 0.001$ in the SPM2 analysis were considered. The final slow dynamic fMRI mesostates β_{s_k} were obtained from averaging the BOLD effect over the single trials.

EEG data analysis. The imaging and ballistocardiogram artifacts in the EEG recordings were removed using the *adaptive finite impulse response* [Wan et al., 2006a] and the *wavelet-based nonlinear noise reduction* [Wan et al., 2006b] methods, respectively (with an artifact rejection level of ± 50 μ V). In order to obtain a 3D reconstruction of the primary current density (PCD), a high-resolution grid ($4.0 \times 4.0 \times 4.0$ mm³) was defined on the T1 individual structural image. The positions of the grid and electrodes were normalized to the Talairach coordinate system using the affine transformations obtained from the SPM2 preprocessing. An isotropic and piecewise homogeneous volume conductor model of the head was assumed, which included three compartments (i.e., the brain, the skull, and the scalp). The surfaces limiting these compartments were extracted from the T1 individual structural images and were later tessellated [see Riera et al., 2005, for further details]. The electric lead field was calculated by applying a boundary element method (BrainStorm MATLAB Toolbox). At each grid point the orientation of the PCD $\vec{\mu}$ was fixed and only its amplitude was allowed to vary with

time. These orientations and time-varying amplitudes were estimated from artifact-free EEG recordings using the *nonlinear beamformer technique* with linearly constrained minimum variance [Robinson and Vrba, 1999; Singh et al., 2003; Van Veen et al., 1997] considering the spatial restrictions provided by the fMRI activation tests. The global PCD effect in V1 was calculated by pooling the reconstructed amplitudes of the PCD within the spherical volumes defined in the fMRI data analysis. Finally, the fast dynamic EEG mesostates α_{s_k} were obtained from averaging the PCD effect over the single trials.

RESULTS AND DISCUSSION

Identifiability of the State Space Model

Several criteria were considered in order to select the parameters of set ϑ to be estimated from the EEG/fMRI data. We acknowledge that most of the parameters of the model were established from a rigorous biophysics model, which makes them very narrow in range. Therefore, we estimated only the more ambiguous parameters (see Table IA). We believe that it was of more interest to determine the relative synaptic/energetic contributions of the excitation and the inhibition than to estimate factors α_k and χ_k ($k = \{PC, IN\}$) themselves. For that reason, the parameters θ_{13} and θ_{17} , describing the excitation, were fixed and their respective versions θ_{14} and θ_{19} for the inhibition were estimated from the data.

Additionally, the canonical neuronal mass model comprises a nonlinear voltage–ampere relationship that probably filters any noise contribution to the data of several of the electrical states. Therefore, only the variance g_8 of the most directly contributing electrical state (i.e., the electric potential Φ related to the extracellular electric current) was estimated. In the balloon approach, the content of deoxy hemoglobin q is thought to be a vascular state with higher fluctuations in terms of population and diffusive random effects; hence, only the variance g_{15} was estimated. Table IB summarizes the values used here for the multidimensional Wiener processes. The variance σ_β^2 should be fitted ad hoc to the fMRI mesostates β_{s_k} . The observation equation for EEG mesostates α_{s_k} is linear; hence, the variances σ_α^2 and g_8 are indistinguishable. For that reason, we will impose $\sigma_\alpha^2 = 5 \times 10^{-6}$.

A simulation study was carried out in order to study the viability of the model estimation. With this proposal, a set of 500 trials of the continuous states $\tilde{x}(t)$ and the discrete observations $\tilde{z}_{s_k}$ of the space state model (Eq. 1) was generated. In each trial, 25,000 values of $\tilde{x}(t)$ were computed by applying the LL scheme [Jimenez et al., 1999; Jimenez, 2002] to the SDE (Eq. 1a), with an integration step of 0.001 s. The states $\tilde{x}(t)$ were conveniently sampled according to the Eq. 1b to generate 2,500 α_{s_k} and 25 β_{s_k} mesostates. Hence, the sampling rates were 0.01 s and 1 s for the EEG and fMRI mesostates, respectively. The optimum step size used in the LL filter was fixed for all iterations at $\Delta_k = 0.002$ s. For each simulated trajectory of the mesostates the estimable parameters in ϑ

TABLE I. A. The parameters θ : actual values, relationships with the LEVC model and dimensions. The ambiguous parameters have to be estimated from data. B. The strengths (or variances) of the additive Wiener processes.

A. Parameters θ												
Electrical							Vascular					
Parameter		Actual value					Parameter		Actual value			
$\theta_1 = -1/\tau_m$		-33.3 s^{-1}					$\theta_{15} = -2\delta\omega_0$		$-2\pi \text{ (12.8 Hz)}$			
$\theta_2 = R_m^0/\tau_m$		$136 \text{ G } \Omega \text{ s}^{-1}$					$\theta_{16} = -\omega_0^2$		-2527 s^{-2}			
$\theta_3 = \gamma_{PC}$		6 mV^{-1}					$\theta_{17} = \omega_0^2 A_{PC} \rho_{PC}$		2527 s^{-2}			
$\theta_4 = \gamma_{PC} V_0^{PC}$		3.6					$\theta_{18} = (C_m)^2/\omega_{PC}$		$0.001 \text{ V}^{-2} \text{ s}^2$			
$\theta_5 = \gamma_{IN}$		5 mV^{-1}					$\theta_{19} = \omega_0^2 A_{IN} \rho_{IN}$		To be estimated s^{-2}			
$\theta_6 = \gamma_{IN} V_0^{IN}$		3.5					$\theta_{20} = (C_m^0)^2/\omega_{IN}$		$0.001 \text{ V}^{-2} \text{ s}^2$			
$\theta_7 = -R_m/(R_i^1 + R_e^1)$		-5.76					$\theta_{21} = u_0$		0			
$\theta_8 = -R_m/(R_i^2 + R_e^2)$		-0.58					$\theta_{22} = 1/\tau_s$		To be estimated s^{-1}			
$\theta_9 = R_e^2/(R_i^2 + R_e^2)$		0.54					$\theta_{23} = 1/\tau_f$		To be estimated s^{-1}			
$\theta_{10} = R_m/\tau_m$		$95.7 \text{ G } \Omega \text{ s}^{-1}$					$\theta_{24} = 1/\tau_0$		To be estimated s^{-1}			
$\theta_{11} = R_m/R_m^1$		12.93					$\theta_{25} = \alpha$		To be estimated			
$\theta_{12} = R_m/R_m^2$		4.3					$\theta_{26} = 1 - E_0$		To be estimated			
$\theta_{13} = \alpha_{PC}$		0.4 pA										
$\theta_{14} = \alpha_{IN}$		To be estimated pA										
B. Additive Wiener processes g_i $\{i = 1, \dots, 15\}$												
g_1	g_2	g_3	g_4	g_5	g_6	g_7	g_8	g_{10}	g_{11}	g_{12}	g_{13}	g_{14}
0.8	0.8	0.8	0	0.8	0.8	0.8	0	0.009	0	0.009	0	0
g_8 and g_{15} (To be estimated)												

were calculated using the innovation method (see LL Filter and the Innovation Method). The optimization problem involved in the innovation method was solved using the MATLAB function “*fmincon*,” with tolerances 10^{-8} , 10^{-10} , and 10^{-8} for the parameter lower/upper bounds, ϑ and $l_Z(\vartheta)$, respectively. These tolerances define a criterion for convergence in the optimization problem. The parameter lower/upper bounds were fixed according to their biophysical ranges. Random values of the initial parameters ϑ_0 , sampled from a uniform distribution, were used to initialize the recursive optimization algorithm for each trial.

Table II presents the mean value of estimated parameters $\hat{\vartheta}$ and the 95% confidence interval. Figure 4 shows the histograms of these estimated parameters as well as the range of initial values ϑ_0 (black bars). Note that the bias in the estimation is negligible for all the estimated parameters, while, with the exception of parameters A_i^3 and g_{15} , the histograms of the estimates are unimodal with approximate Gaussian distributions. These results indicate that several parameters of the LEVC model can be identified from the EEG and fMRI data with high precision, while others, like A_i^3 and g_{15} , can only be approximately estimated.

Fitting the LEVC Model to Concurrent EEG/fMRI Data

In this section the state space model (Eq. 1) is fitted to concurrent EEG and fMRI mesostates calculated for the first subject, a healthy 44-year-old male. The radial checkerboard (see Concurrent EEG and fMRI Experiments) reverses the

white/black patterns at 4.0 Hz. The whole experimental session consisted of 30 sequential single trials. In each scanning, eight horizontal slides covering the whole brain were obtained with the scanner’s parameters: an interscan interval of 1,000 ms, a voxel size of $3 \times 3 \text{ mm}^2$ in-plane, and a thickness of 10 mm with a 5-mm gap.

We performed the on-off (i.e., stimulating and resting conditions) contrasts SPM2 t-Test for a cognitive subtraction analysis (Fig. 5A, with $P < 0.001$, uncorrected). The maximum of activation in each hemisphere is thought to lie within the V1 region of this subject. In Figure 5B the spher-

TABLE II. Estimated values of parameters from simulated trials

Parameters	Estimates	Actual values	Range
A_i^1 (pA)	0.798 ± 0.13	0.8	[0.5, 1.1]
A_i^2 (pA)	0.403 ± 0.07	0.4	[0.1, 0.7]
A_i^3 (pA)	1.056 ± 0.919	1.0	[0.7, 1.3]
θ_{14} (pA)	0.296 ± 0.056	0.3	[0, 0.6]
g_8 (mV)	0.503 ± 0.065	0.475	[0.17, 0.77]
$\theta_{19} \times 10^{-3}$ (s^{-2})	2.141 ± 0.3	2.021	[1.722, 2.321]
θ_{22} (s^{-1})	0.253 ± 0.023	0.258	[0.16, 0.36]
θ_{23} (s^{-1})	0.136 ± 0.012	0.141	[0.04, 0.24]
θ_{24} (s^{-1})	0.38 ± 0.02	0.382	[0.232, 0.532]
θ_{25}	0.525 ± 0.014	0.53	[0.33, 0.73]
θ_{26}	0.463 ± 0.016	0.46	[0.26, 0.66]
$g_{15} \times 10^3$	0.487 ± 0.196	0.45	[0.3, 0.6]

The estimates are given with a 95% confidence interval. The actual values and the range of initial values ϑ_0 are also shown.

Figure 4.

The histograms of the estimated parameters. A total of 500 trials were used to obtain these histograms. In each panel the vertical line and the black bar on the top represent the true value of the parameter and the range of initial values ϑ_0 , respectively. Black arrows indicate when the estimated parameter reached the lower or upper bound.

ical volumes used to represent the functional extension of V1 in both hemispheres are rendered. The orientations (C) and time-varying amplitudes (D) estimated from the EEG data, taking into account the spatial restrictions provided by the fMRI data (SPM2 t-Test), are also shown in Figure 5. These magnitudes were visualized only for grid points inside the spherical volumes. We present the orthogonal planes so that readers get a better idea how the PCD is distributed inside V1 (Fig. 5E).

The fast α_{sk} and slow β_{sk} mesostates associated with the PCD and BOLD global dynamics in V1 are shown in Figure 6. The EEG mesostates α_{sk} change very quickly and follow the pace-frequency during the interval of stimulation (black bar, top left). However, as expected, these changes induce a delayed and long-lasting effect in the vasculature, represented by the fMRI mesostates β_{sk} .

In Figure 7 (upper panel), the detailed time course of the EEG mesostates α_{sk} within the interval of stimulation (black bar, bottom) is shown. Any abrupt change in the visual field content, henceforth referred to as a single event, will trigger a neuronal response in V1. The timing of single events are indicated in this panel by small gray triangles. An extra event is included in order to account for the offset neuronal response, which is essentially related to a bouncing effect that appears after stimulation ceases (a vertical gray line shows the beginning of this event). All these neuronal responses will depend on the particular phase of V1 when the event occurs. We can classify at least three main phases (see gray bars a, b, and c shown on the top): a) the initial phase, distinguished by the fact that the event alters a V1 that has

been previously in a resting state; b) the following steady-state phase, which is characterized by an adaptation of V1 to the regular sequence of events; and c) the final phase that corresponds to the above-mentioned bouncing effect. However, with the exception of the bouncing phase, the normalized waveforms of the neuronal responses have certain aspects in common, no matter when the event occurs. Note that these waveforms are comprised of at least four distinguishable components (C_1 , C_2 , C_3 , and C_4). These components appear clearly after averaging the normalized waveforms corresponding to all single events within the stimulation interval (i.e., excluding the last phase), thus eliminating any contribution non-locked to the events (Fig. 7, lower panel). Quite interesting is the fact that these waveforms are remarkably similar to those of the event-related potentials recorded by intracranial subdural electrodes (mastoid reference) implanted in the pericalcarine cortex of epileptic subjects [Huettel et al., 2004] (the visual experiment consisted of a single high-contrast black/white radial checkerboard that remained static over different durations). In fact, four components with comparable latencies and a further equivalent offset response were reported in that study [figs. 3 and 4 in Huettel et al., 2004]. However, the polarities of these components and of the offset response depend on the location of the electrode, with polarities reversals in consecutive electrodes. This finding may be related to the fact that the electrodes bracketed the PCD. In contrast, in our case the EEG mesostates α_{sk} in Figure 7 do represent the amplitudes of the PCD, which is thought to be oriented normal to the cortical surface.

Figure 5.

A: The maximums of the contrasts SPM2 t-Test used to localize V1. **B:** The spherical volumes delimiting V1. **C:** The PCD orientations inside V1. **D:** The time-varying amplitudes of these PCDs (they have similarities). **E:** Orthogonal planes of the PCD orientations. All these 3D views overlap the T1 structural image.

Figure 6.

The time course of mesostates α_{s_k} and β_{s_k} are shown in the upper and bottom panels, respectively. The black box represents the stimulation interval. For illustrative purpose, we connected the real observations (i.e., dots for EEG and encircled crosses for fMRI) by continuous lines.

Figure 7.

The upper panel shows the detailed time course of mesostates α_{s_k} during the stimulation interval (black box). The gray bars on the top represent the time windows for phases a, b, and c. The small gray triangles are used to label the beginning of each single event within the stimulation interval and a vertical gray line is used to label the initialization of an equivalent event in the bouncing phase c. The middle panel shows the sequence of Gaussians radial basis functions used to describe the dynamics of the synaptic inputs. Three Gaussians representing I_1^+ , I_2^+ , and I_3^+ (with delays 140, 205, and 100 ms with regard to the beginning of the event, respectively) were used for each single event. The Gaussians in phase a were set up 10 ms earlier. The bottom panel shows the average of normalized waveforms over all single events within the stimulation interval (i.e., excluding the event in phase c). Arrows mark the maximum values of components C_1 , C_2 , C_3 , and C_4 . The positions and widths of these Gaussians were adjusted by simple inspection of the innovation process and also considering the characteristics of components C_1 , C_2 , and C_3 .

The nature of these components cannot be understood without characterizing V1 in terms of its circuitry and microarchitecture. The model of V1 in monkeys and mice (Fig. 8), the properties of which are summarized below, provides a useful approach to comprehend early visual processing in humans.

1. The lateral geniculate nucleus (LGN) projects most of its axons onto sublayer IV-C (although a few axons also reach layer VI), which in effect constitutes the input to the cortex of the afferent thalamocortical (TC) pathway [Callaway, 1998]. In sublayer IV-C, a single TC axon connection is 4.8 times more effective than the intracortical connection between any two cortical neurons from the same layer [Gil et al., 1999].
2. The TC pathway consists of two convergent tracts: one excitatory via small spiny stellate (SS) cells (which are electrotonically very compact; Segev et al. [1995]) and a

Figure 8.

The model of V1 in monkeys and mice. In V1, the classical layer IV is divided into different sublayers (A, B, C [α and β]). The TC pathway is comprised of two different tracks: inhibitory and excitatory. They both reach the neocortex at the level of sublayer IV-C. The inhibitory track impinges directly the feedforward GABAergic INs, whereas the excitatory track influences the layer V PC via SS by direct and/or indirect paths (shown by dashed red lines). The indirect path between SS and layer V PC is thought to have a relay site at the supragranular layers (from II to IV-B). The layer V PCs (so named because their somas are mainly on this layer) cover the entire cortex with dendrites distributed along all layers. The apical tuft (layer I) and basal (layer V) dendrites are of particular interest because they are directly implicated in the LEVC model. The feedback GABAergic INs are also shown in this scheme. The excitatory and inhibitory interactions between neurons are represented by the red and blue connecting curves, respectively. The possible sites of origin of components C_1 , C_2 , C_3 , and C_4 are also indicated.

further inhibitory via feedforward (or transmission) GABAergic interneurons (INs) [Gil and Amitai, 1996].

3. TC axons reaching sublayer IV-C are also expected to impinge on the midapical (oblique) dendrites of the layer V pyramidal cells (PCs). Although SS cells in sublayer IV-C project axons to layer V *directly*, their denser axonal projections target supragranular layers (i.e., from II to IV-B; Lund [1987], Callaway and Wiser [1996]). Neurons in these superficial layers then project dense axons to layer V [Blasdel et al., 1985; Callaway and Wiser, 1996]. This may represent an *indirect* way that the excitatory track of the TC pathway invade layer V PCs. Note that the vast majority of excitatory corticocortical synapses in layer V are made with other PCs. The nonprojecting PCs in layer V are thought to target superficial layers, which may underpin an excitatory feedback mechanism [Briggs and Callaway, 2005].
4. The layer V PCs are the biggest in the neocortex and their long horizontal axons make contact with infragranular layers [Hallman et al., 1988]. These local axonal arbors are assumed to be involved in some sort of mechanism producing a delayed feedback inhibitory effect (via feedback GABAergic INs) on the layer V

PCs, which evidently could serve to balance the predominance of the excitatory drive while creating high temporal precision.

5. The thalamus-evoked inhibition has a very short latency. The GABAergic IN track of the TC pathway has a lower threshold to induce a feedforward inhibition than the intracortical circuit. TC stimulation induces an inhibitory response at intensities equal to or less than those required for evoking an excitatory response [Gil and Amitai, 1996].
6. The sublayer IV-C of the visual cortex is additionally divided into two, IV-C α and IV-C β . From this subdivision, the TC pathway can be differentiated into magno (M) and parvo (P) routes depending on where in sublayer IV-C the LGN project their axons (i.e., C α and C β are the targets of M and P routes, respectively). It is well known that these pathways are involved in the recognition of low but rapid spatial movements and luminance contrast (M) as well as shapes with very high spatial resolution and color (P). In a recent article, Tucker and Katz [2003] explored the spatial and temporal distribution of excitation and inhibition of a horizontal network in V1 at layer II/III, a target of the complementary Konio (K) route of the TC pathway. This latter route is thought to play an important role in saccadic suppression [Callaway, 1998].

Based on these properties of V1 and according to the characteristics of the stimulus used, we hypothesize that the TC pathway produces components C_1 and C_2 . In particular, the component C_1 might correspond to a prompt influence of the inhibitory track of this pathway on the layer V PC and the delayed/reversed component C_2 may be associated with a direct and/or indirect influence of the excitatory track on this type of cell. The component C_3 could have originated by the input at the apical tuft, which is presumed to have one or several of the following origins: the commissural axons, the extrastriate cortex, and the excitatory feedback loops via nonprojecting PCs in layer V. Finally, we speculated that component C_4 is associated with a delayed inhibitory effect due to the feedback GABAergic INs. These hypotheses are compatible with the time course of the EEG mesostates α_{s_k} if the PCD (i.e., $\bar{\mu}$) are oriented from surface to deeper layers, a fact difficult to demonstrate but that seems to be satisfied from Figure 5C,E.

In accordance with our hypotheses, three Gaussians of around 15.6 ms in width were allocated in each single event, describing the synaptic inputs I_1^+ , I_2^+ , and I_3^+ respectively (see Fig. 7, middle panel). The centers of these Gaussians were set up according to the latencies of components C_2 , C_3 , and C_1 , respectively.

From now on, we present the results obtained after fitting the state space model (Eq. 1) to mesostates α_{s_k} and β_{s_k} . In Figure 9, the upper panels show the overlapping of actual EEG mesostates α_{s_k} (encircled crosses) and their continuous estimator $\hat{\alpha}_t$ (line), the latter is obtained from evaluating the observation equations (Eq. 1b) at the fitting conditional mean $\hat{\hat{x}}_{t/s_k}$. The filtering and prediction steps of the LL filter

Figure 9.

The upper panels show the actual discrete mesostates α_{s_k} (encircled crosses) and their continuous estimator $\hat{\alpha}_t$ (line). On the top of these panels the dynamics for the first single event are shown in detail. The filtering and prediction steps are symbolically represented (black and gray arrows, respectively). Note that during the prediction step $\hat{\alpha}_t$ continuously deviates from the genuine trajectory, but this effect is subsequently corrected using the data in the filtering step. The fitting-innovations $\hat{v}_{s_k}^\alpha$ and their histogram

are plotted in the middle and bottom panels, respectively. The panels on the left side are obtained from the application of the LL filter to the data using the initial parameters ϑ_0 , and those on the right side are obtained in the same way but using the innovation estimators $\hat{\vartheta}$. Note that the filtering-jumps, which affect the Gaussianity in the fitting-innovations, disappear after estimating the parameters.

become visible after enlarging the first single event (top). The corresponding fitting-innovations $\hat{v}_{s_k}^\alpha$ of EEG mesostates α_{s_k} and its histogram are shown in the middle and bottom panels, respectively. Figure 10 shows equivalent panels for the fMRI mesostates β_{s_k} . In both figures the panels correspond to applying the LL filter using the initial parameters

ϑ_0 (on the left) and the innovation estimator $\hat{\vartheta}$ (on the right). It can be noted that the Kolmogorov–Smirnov test of Gaussianity was accepted for the histogram of the fitting-innovations $\hat{v}_{s_k}^\alpha$ after estimating parameters $\hat{\vartheta}$. Unfortunately, due to there being only a few fMRI observations available, the test of Gaussianity was not accepted for the histogram of the

Figure 10.

The same panels as in Figure 9, but in this case for the mesostates β_{s_k} .

Figure 11.

The time courses of the fitting conditional mean $\hat{x}_{t/s_k}$ for both electrical (for the first 4 s, left) and vascular (for the whole 25 s, right) states. The time courses of states r and u are expanded for the first 4 s (top right panels). The estimated amplitudes of the Gaussians radial basis functions are shown in the bottom left panel. For each single event, three amplitudes are provided: I_1^+ in light gray, I_2^+ in dark gray, and I_3^+ in black. The arrow marks the event in the bouncing phase.

fitting-innovations $\hat{\theta}_{s_k}^\beta$ even after estimating parameters $\hat{\theta}$. These figures allow us to evaluate the goodness-of-fit of the LEVC model to the concurrent EEG and fMRI data.

Figure 11 presents the time courses of the fitting conditional means $\hat{x}_{t/s_k}$ corresponding to the electrical (for the first 4 s, left) and vascular (for the whole 25 s, right) states, which resemble the expected dynamics of the LEVC model (comparable with the simulations of $\tilde{x}$; figs. 4 and 7 in Riera et al. [2006]). The time courses of states r and u are expanded for the first 4 s (top-right). In the bottom-left panel, one of our most interesting results is presented: the amplitudes of the Gaussians representing the synaptic inputs I_k^+ (with $k = 1, 2, 3$). A total of 17 amplitudes for each synaptic input were estimated over the three different phases. In particular, the amplitudes of synaptic inputs I_1^+ and I_2^+ reach the largest values for the isolated event in phase a; in this phase the four components are 10 ms earlier. The amplitudes of the synaptic inputs seem to be modulated during the steady-state condition (i.e., phase b), which could give a foundation to the resonance phenomena reported recently in the visual cortex during flicker stimulation [Herrmann, 2001]. Conversely, the synaptic input I_3^+ maintains a constant amplitude in phases a and b. In phase c, the influence from the excitatory track

of the TC pathway ceases to exist and only a bouncing effect, which we believe is inhibitory in character, remains. This effect was explained by an increased influence of the inhibitory track of the TC pathway (i.e., I_3^+ , see arrow in Fig. 11, bottom left panel). However, the authors recognize that the same effect could be explained either by the inhibitory feedback via GABAergic INs or by the existence of the above-mentioned excitatory feedback mechanism.

The estimated values of the parameters are shown in Table III. In this case, the ad hoc variance for fMRI mesostates β_{s_k} was $\sigma_\beta^2 = 1.0 \times 10^{-7}$.

Predicting the Vascular Reaction from the EEG Signals

Can we predict the vascular reaction from the EEG signals? To answer this question, in this section we use the EEG mesostates α_{s_k} calculated from the second subject for a radial checkerboard (see Concurrent EEG and fMRI Experiments) reversing black/white patterns at frequencies 0.5, 1.0, 2.0, and 4.0 Hz. The subject was a healthy 39-year-old male. The whole experimental session consisted of 10 sequential single trials for each frequency. In each scanning, 20 horizontal

TABLE III. Estimated values of parameters from concurrent EEG and fMRI data

Parameters	θ_{14} pA	g_8 mV	θ_{19} s ⁻²	θ_{22} s ⁻¹	θ_{23} s ⁻¹	θ_{24} s ⁻¹	θ_{25}	θ_{26}	g_{15}
Estimates	1.18	1.35	1.59×10^3	0.29	0.16	0.38	0.48	0.43	9×10^{-3}

Figure 12.

The upper panels show α_{s_k} (black dots) and $\hat{\alpha}_t$ (line), the latter calculated using the innovation estimators $\hat{v}$. Below these panels, $\hat{v}_{s_k}^\alpha$, the amplitudes of the Gaussians radial basis functions and the histograms of $\hat{v}_{s_k}^\alpha$ are plotted, respectively. The estimated values of θ_{14} and g_8 are shown on the bottom right. The frequencies used were (A) 0.5 Hz, (B) 1.0 Hz, (C) 2.0 Hz, and (D) 4.0 Hz.

slides covering the whole brain were obtained with the scanner's parameters: an interscan interval of 2,500 ms, a voxel size of $3 \times 3 \times 6.6\text{mm}^3$ with a 0.6-mm gap.

First we estimated the electrical states and parameters of the model corresponding to the canonical neuronal mass from the EEG mesostates. Then, in a second step, these electrical states were used in the LEVC model to predict the fMRI mesostates β_{s_k} for each frequency. The predicted fMRI mesostates were compared with those obtained after fitting the modified balloon approach to the raw fMRI data (via the SPM2 MATLAB code for nonlinear estimation of the HRF; Friston [2002]), which we named "actual" fMRI mesostates.

Wan et al. [2006c] designed such a visual paradigm to demonstrate a linear relationship in V1 between the power of the PCD and the synaptic efficacy in the modified balloon approach from concurrent EEG and fMRI recordings (using five healthy subjects). In this section, for convenience we revisit some of their results:

- We used an SPM2 f-Test (all frequencies) to perform a conjunction analysis [Price et al., 1997]. A maximum of activation was located around V1 in both hemispheres (see the results of the SPM2 f-Test for this particular subject in Wan et al., [2006c], Fig. 1).
- The nonlinear HRF was estimated using two-sided regions of interest, each centered in the maximum of the corresponding hemisphere with a radius of 6 mm. To do so, we modeled the input $u(t)$ in the modified balloon approach as a boxcar function of 4s in duration. The parameters in the modified balloon approach were estimated using an EM implementation of a Gauss-Newton search method for the maximum of the conditional or posterior pdf with priors [Friston, 2002]. The estimated values of these parameters were as follows: signal decay $\tau_s = 1.47s$, autoregulation $\tau_f = 2.50s$, transit time $\tau_0 = 1.01s$, stiffness

$\alpha = 0.32$, and resting oxygen extraction fraction $E_0 = 0.34$. The synaptic efficacies ϵ were 0.36, 0.56, 0.54, and 0.68 (all with a confidence interval of ± 0.1) for the stimulation frequencies 0.5, 1.0, 2.0, and 4.0 Hz, respectively.

The results from making statistical inferences about the canonical neuronal mass (i.e., both electrical states and parameters of the model) for all frequencies are presented in Figure 12. The test of Gaussianity was always accepted. Note that parameter θ_{14} augments considerably (exception: the optimization algorithm reached its lower bound in the case of 1.0 Hz) with an increase in the reversion frequency, which could indicate a reinforcement of internal inhibitions in V1. The actual and predicted fMRI mesostates β_{s_k} are shown in Figure 13. The actual β_{s_k} were obtained for each frequency using the corresponding synaptic efficacy ϵ and a boxcar model of $u(t)$ in the modified balloon approach. The predicted β_{s_k} were obtained using the estimated electrical states and also the parameter θ_{14} in the LEVC model. In both cases, 1) we used the values of parameters τ_s , τ_f , τ_0 , α , and E_0 estimated by using the SPM2 MATLAB code, and 2) neither measurement errors nor random effects were included. Here we would like to clarify that the complexity of the dynamics of the input $u(t)$, perhaps produced by the existence of phases a, b, and c, was not considered when estimating the vascular parameters. A method to estimate the dynamics of this input accurately from actual fMRI data was proposed in Riera et al. [2004a].

The normalized waveforms of actual and predicted β_{s_k} are very similar (see Fig. 13, left). If we look at the amplitude vs. frequency relationships for both actual and predicted β_{s_k} , it can be noted that the tendencies with which their amplitudes increase are equivalent. In this frequency range the amplitude of the fMRI mesostates increase almost linearly, with comparable slopes for both actual and predicted fMRI

Figure 13.

Right: the normalized waveforms of actual (continuous line) and predicted (encircled crosses) mesostates β_k for each frequency. Left: the amplitude vs. frequency relationships for both actual and predicted mesostates. The amplitudes correlate linearly with the frequency, with comparable slopes but shifted intercepts.

mesostates. However, their intercepts (at zero) are shifted in a factor of around 8×10^{-3} (Fig. 13, right).

FUTURE IMPLICATIONS

In this article we have formulated the LEVC model into the *state space* formalism, which permitted us to make statistical inferences about its states and parameters from EEG and fMRI data. To achieve that purpose, the LL filter and the innovation method were lightly modified in order to apply them to hybrid data with heterogeneous missing values, resulting in a recursive optimization algorithm. EEG and fMRI data obtained from two healthy subjects during a classical visual paradigm were used in this study. The EEG and fMRI data from one subject was used to identify the whole LEVC model in V1 (i.e., states and parameters of the model), while we employed EEG data from a second subject to predict the vascular dynamics of V1 from a previous identification of the electrical states and parameters of the underlying canonical neuronal mass. The main results were interpreted in a physiological context, and they were discussed with the help of comparative models of V1 in monkeys and mice. This work has several future implications, as detailed below.

Physics Implications

Postsynaptic potentials may be a sound indicator of the neuronal activity in a population of neurons. However, the geometrical and electrotonic characteristics of the neurons producing these postsynaptic potentials, as well as the locations where they originated inside each neuron, are relevant particulars when interpreting neuronal activity. For example, a large amount of these postsynaptic potentials arriving at the dendrite trees can be annulled or reinforced by com-

plex spatiotemporal electrotonic integrators, thus producing trains of action potentials depending on their phases, synchronisms, and arrival locations. Until now, we have erroneously identified neuronal activity with the PCD obtained from EEG data after solving an ill-posed inverse problem, which has attracted the attention of physicists, mathematicians, and biologists for more than 40 years. By far, the most important implication of this work is that even in an ideal situation in which we are able to determine the spatial configurations of the PCD uniquely in the whole brain without the need for much computational effort, a second inverse problem also ill-posed in nature will come to light. In this article we formulated this inverse problem as the determination of the electrical states (i.e., the membrane potentials) in a neuronal mass from the reflections they produce in the neuropil (i.e., the extracellular electric currents). We have made a first move in order to solve this latter inverse problem by introducing a canonical neuronal mass model, which permitted us to make use of several mathematical tools already developed in the context of time series analysis. We would like to emphasize the fact that a unique characterization of the inputs I_1^+ , I_2^+ , and I^- reaching the layer V PC is impossible; hence, we have to use a priori suitable physiological constraints to exclude the meaningless dynamics of these inputs.

In addition, the brain vasculature acts as a lowpass filter to the temporal dynamics of the most common electrophysiological indexes of neuronal activity. In spite of its excellent spatial resolution to determine brain areas with increased oxygen consumption or vascular reaction, from BOLD signals we cannot distinguish the energy budget allocated for the inhibitions and excitations, which constitutes a vulnerable point in fMRI studies. In this sense, the combination of electrophysiological (e.g., EEG) and vascular/metabolic

(fMRI) measurements with forward/generative models like the one presented here will offer promising means to reconstruct not only the actual neuronal activity but also the fuel consumed by neuronal masses to generate it.

In our opinion, neuroimagers must be more conservative when discussing their results, and they should limit themselves to clearly stating what has actually been observed with the technique utilized. Phrases like “neuronal activity” must not be misused in the context of EEG and fMRI analysis. Additionally, we strongly recommend the use of models that take account of spatial and temporal constraints to determine both the location and the dynamics of the PCD [Yamashita et al., 2004] and BOLD [Riera et al., 2004b] signal in a unified approach [see, for example, Riera et al., 2005].

Physiological Implications

The analysis of the effective connectivity among neuronal masses has been the focus of attention of neuroscientists over the last decade. This work impacts heavily on this issue. Our results suggest that any causal relationship between remote brain areas must be studied considering the specificities (i.e., anatomical and physiological properties) of these areas, and that the use of general methodologies might lead to incorrect results. For instance, in the neocortex the nature of a connection could be of different types, as discussed in Part I of these two companion articles (i.e., excitatory at the basal/apical dendrites trees of the layer V PCs, inhibitory at GABAergic INs, etc.). Therefore, connectionist models between brain areas must be particularized in accordance with each experimental design.

Several detailed models have been proposed to account for the neuronal computation in the neocortex [see, for example, Traub et al., 2005]. However, these models must be simplified in order to use them to better understand EEG and fMRI data. We developed a simple canonical neuronal mass model for a cortical unit and applied it to study the basic processing inside V1. We introduced a priori information about the synaptic inputs (e.g., widths and latencies) based on specific mechanisms related to V1 for the particular experimental paradigm used. If, rather than a flashing radial checkerboard, the visual stimuli consists of color or moving patterns, these synaptic inputs must be reconsidered. The same is true if we were to apply this model to data obtained from an experimental paradigm that includes activation of other brain areas (e.g., auditory, motor, and sensorial cortices). What is more, in a situation of multiple stimuli these synaptic inputs must be estimated taking into account the interactions among different brain areas.

Nitric oxide has been recognized as a chief mediator between the electrical and vascular systems in the brain. It is believed to be an ideal molecule for this coupling due to the following: 1) it is locally produced by neurons/astrocytes during brain activation; 2) it is a potent vasodilator; 3) it is diffusible; and 4) it has a short life. For these reasons, we have modeled the dynamics of nitric oxide within a cortical unit and considered it a putative facilitator of the arterioles/capillaries response. However, our model is applicable if

any other vasoactive substances are later confirmed to also mediate this coupling (e.g., peptides/hormones [VIP, NPY, SOM], prostanoids [PG, PGL₂, TXA₂], acids [EET, 20-HETE], neurotransmitters [ACh, 5-HT, NA, GABA], others [adenosine, K⁺, H⁺, CO₂]). A detailed model of this coupling in the cerebellum of rats has been recently fitted to data recorded from microelectrodes and laser-doppler flowmetry [Rasmussen, 2004].

ACKNOWLEDGMENT

The authors thank Dr. Eduardo Aubert from the Cuban Neuroscience Center, Havana, for kindly generating the 3D illustrations.

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APPENDIX A

State Space Representation of the LEVC Model

Continuous SDE

The drift component $\tilde{f}(\tilde{x}, t; \theta)$:

$$f_1(\tilde{x}, t; \theta) = \theta_1 x_1(t) + \theta_2 I_3^+(t, \theta_3^A) \quad (\text{I-1})$$

$$f_2(\tilde{x}, t; \theta) = \theta_1 x_2(t) + \theta_2 \theta_{13} f(x_3(t), \theta_3, \theta_4) \quad (\text{I-2})$$

$$\begin{aligned} f_3(\tilde{x}, t; \theta) = & \theta_1 \left(1 - \theta_7 - \theta_8 - \frac{\theta_7}{\theta_{11}} - \frac{\theta_8}{\theta_{12}} \right) x_3(t) + \frac{\theta_1 \theta_7 \theta_8}{\theta_{11} \theta_{12}} x_4(t) \\ & + \theta_1 \theta_7 x_5(t) + \theta_1 \theta_8 x_6(t) - \theta_1 \left(\frac{\theta_7}{\theta_{11}} + \frac{\theta_8}{\theta_{12}} \right) x_7(t) \\ & - \theta_{10} \theta_{14} (f(x_1(t), \theta_5, \theta_6) + f(x_2(t), \theta_5, \theta_6)) \quad (\text{I-3}) \end{aligned}$$

$$\begin{aligned} f_4(\tilde{x}, t; \theta) = & \theta_1 x_4(t) - \theta_1 (1 + \theta_{11} + \theta_{12}) x_3(t) + \theta_1 \theta_{11} x_5(t) \\ & + \theta_1 \theta_{12} x_6(t) - \theta_1 x_7(t) \quad (\text{I-4}) \end{aligned}$$

$$f_5(\tilde{x}, t; \theta) = \theta_1 x_5(t) + \theta_{10} I_1^+(t, \theta_1^A) \quad (\text{I-5})$$

$$f_6(\tilde{x}, t; \theta) = \theta_1 x_6(t) + \theta_{10} I_2^+(t, \theta_2^A) \quad (\text{I-6})$$

$$\begin{aligned} f_7(\tilde{x}, t; \theta) = & \theta_1 x_7(t) \\ & + \theta_{10} \theta_{14} (f(x_1(t), \theta_5, \theta_6) + f(x_2(t), \theta_5, \theta_6)) \quad (\text{I-7}) \end{aligned}$$

$$\begin{aligned} f_8(\tilde{x}, t; \theta) = & \theta_1 \left(1 - \theta_7 - \theta_8 - \frac{\theta_7}{\theta_{11}} - \frac{\theta_8}{\theta_{12}} \right) x_8(t) + \frac{\theta_1 \theta_7 \theta_8}{\theta_{11} \theta_{12}} x_9(t) \\ & - \theta_1 \theta_7 \theta_9 x_5(t) + \theta_1 \theta_7 \theta_9 \left(1 + \frac{1}{\theta_{11}} \right) x_6(t) + \theta_9 \theta_{10} \theta_{14} \\ & \times (f(x_1(t), \theta_5, \theta_6) + f(x_2(t), \theta_5, \theta_6)) + \frac{\theta_9 \theta_{10}}{\theta_{12}} I_2^+(t, \theta_2^A) \\ & + \frac{\theta_1 \theta_7 \theta_9}{\theta_{11}} x_7(t) \quad (\text{I-8}) \end{aligned}$$

$$f_9(\tilde{x}, t; \theta) = \theta_1 x_9(t) - \theta_1 (1 + \theta_{11} + \theta_{12}) x_8(t) \quad (\text{I-9})$$

$$\begin{aligned} f_{10}(\tilde{x}, t; \theta) = & \theta_{15} x_{10}(t) + \theta_{16} x_{11}(t) + \theta_{17} g(f_3(\tilde{x}(t), t; \theta), \theta_{18}) \\ & + \theta_{19} (g(f_1(\tilde{x}(t), t; \theta), \theta_{20}) + g(f_2(\tilde{x}(t), t; \theta), \theta_{20})) \quad (\text{I-10}) \end{aligned}$$

$$f_{11}(\tilde{x}, t; \theta) = x_{10}(t) \quad (\text{I-11})$$

$$\begin{aligned} f_{12}(\tilde{x}, t; \theta) = & (x_{11}(t) - \theta_{21}) - \theta_{22} x_{12}(t) \\ & - \theta_{23} (x_{13}(t) - 1) \quad (\text{I-12}) \end{aligned}$$

$$f_{13}(\tilde{x}, t; \theta) = x_{12}(t) \quad (\text{I-13})$$

$$f_{14}(\tilde{x}, t; \theta) = \theta_{24} x_{13}(t) - \theta_{24} (x_{14}(t))^{1/\theta_{25}} \quad (\text{I-14})$$

$$\begin{aligned} f_{15}(\tilde{x}, t; \theta) = & \frac{\theta_{24}}{(1 - \theta_{26})} (1 - \theta_{26}^{1/x_{13}(t)}) x_{13}(t) - \theta_{24} x_{15}(t) \\ & \times (x_{14}(t))^{(1 - \theta_{25})/\theta_{25}} \quad (\text{I-15}) \end{aligned}$$

With $f(x, \theta, \theta') = (1 + 0.03e^{-\theta x + \theta'})^{-33.3}$ and

$$g(x, \theta) = 1 - \exp(-\theta x^2).$$

The vector

$$\tilde{\mathbf{x}} = \left\{ \begin{array}{cccccccccccccccc} x_1 & x_2 & x_3 & x_4 & x_5 & x_6 & x_7 & x_8 & x_9 & x_{10} & x_{11} & x_{12} & x_{13} & x_{14} & x_{15} \\ V_{IN}^T & V_{IN}^E & V_{PC} & \mathbf{\Omega} & v_1 & v_2 & v_- & \mathbf{\Phi} & \mathbf{\Theta} & r & u & s & f & v & q \end{array} \right\}$$

contains the state variables of the LEVC model. The parameters $\mathbf{\theta}^M = \{\theta_k, k = 1, \dots, 26\}$ are defined to warrant an identifiable state space model. Most of them do not have a direct physiological interpretation, but they relate simply to the original parameters of the LEVC model (see table).

A parametric representation of the nonautonomous synaptic inputs I_k^+ is reached by introducing Gaussian radial basis functions $\beta_l(t) = \exp(-|t - t_l|^2/2\sigma^2)$ of around $\sigma = 15.6$ ms in width and quasi-regularly spaced along time.

$$I_k^+(t, \mathbf{\theta}_k^A) = \sum_l A_l^k \beta_l(t) \quad k = \{1, 2, 3\}$$

The coefficients $\mathbf{\theta}_k^A = \{A_l^k; l = 1, \dots\}$ also constitute parameters of the state space model. We define the set of parameters in the drift components as $\mathbf{\theta} = \{\mathbf{\theta}^M, \mathbf{\theta}_k^A; k = 1, 2, 3\}$.

The additive Wiener processes are assumed independent $\mathbf{G} = \text{diag}(g_i)$, where the magnitudes g_i $\{i = 1, \dots, 15\}$ represent their strengths (or variances).

Hybrid observations recorded with different sampling rates

The EEG and fMRI mesostates are equivalent to the observations in our state space model. As a consequence, these mesostates are directly obtained from hybrid data (i.e., EEG and fMRI); their time series could have missing values, which are heterogeneous in nature (Fig. I-1). Therefore, the

function $\tilde{h}_{s_k}^\Phi(\tilde{\mathbf{x}}(s_k))$ and the variance-covariance matrix $\mathbf{\Omega}_{s_k}$ would have different dimension “ d ” at each s_k . They must be evaluated as specified in the table below.

Data		$\tilde{h}_{s_k}^\Phi(\tilde{\mathbf{x}})$	$\mathbf{\Omega}_{s_k}$
Single ($d = 1$)	Electrical	$h_\alpha^\Phi(\tilde{\mathbf{x}}(s_k))$	σ_α^2
	Vascular	$h_\beta^\Phi(\tilde{\mathbf{x}}(s_k))$	σ_β^2
Simultaneous ($d = 2$)		$\begin{pmatrix} h_\alpha^\Phi(\tilde{\mathbf{x}}(s_k)) \\ h_\beta^\Phi(\tilde{\mathbf{x}}(s_k)) \end{pmatrix}$	$\begin{pmatrix} \sigma_\alpha^2 & 0 \\ 0 & \sigma_\beta^2 \end{pmatrix}$

The functions $h_\alpha^\Phi(\cdot)$ and $h_\beta^\Phi(\cdot)$ were discussed in Riera et al. [2006].

$$h_\alpha^\Phi(\tilde{\mathbf{x}}(s_k)) = \mathbf{X}_8(s_k)$$

$$h_\beta^\Phi(\tilde{\mathbf{x}}(s_k)) = 0.02 \left[7(1 - \theta_{26})(1 - x_{15}(s_k)) + 2 \left(1 - \frac{x_{15}(s_k)}{x_{14}(s_k)} \right) + (1.8 - 2\theta_{26})(1 - x_{14}(s_k)) \right]$$

Note that for the LEVC model $\mathbf{\Phi} \subset \mathbf{\theta}$.

APPENDIX B

MATLAB Functions for the LL Filter

In the filtering step, which is applied at time instant s_k , the a posteriori conditional pdf $p(\tilde{\mathbf{x}}(s_k)/\{Z_{s_{k-1}}, \tilde{z}_k\})$ is directly ob-

Figure I-1.

EEG and fMRI hybrid data with heterogeneous missing values. The EEG and fMRI signals are sampled within the time window $[t_0, T]$ at instants defined by black and gray bars, respectively. The arrows show time instants when simultaneous EEG and fMRI observations occur. The optimum step size Δ_k to predict the conditional mean and variance of $\tilde{\mathbf{x}}(t)$ in the k -th iteration of the LL filter is also illustrated (bottom).

Parameter transformations

Electrical	Vascular
$\tau_m = -1/\theta_1$	$\delta = -\theta_{15}/(2\sqrt{-\theta_{16}})$
$R_m^0 = -\theta_2/\theta_1$	$\omega_0 = \sqrt{-\theta_{16}}$
$\gamma_{PC} = \theta_3$	$A\chi_{PC}\rho_{PC} = -\theta_{17}/\theta_{16}$
$V_0^{PC} = \theta_4/\theta_3$	$\omega_{PC} = (C_m)^2/\theta_{18}$
$\gamma_{IN} = \theta_5$	$A\chi_{IN}\rho_{IN} = -\theta_{19}/\theta_{16}$
$V_0^{IN} = \theta_6/\theta_5$	$\omega_{IN} = (C_m^0)^2/\theta_{20}$
$(R_i^1 + R_e^1) = \theta_{10}/(\theta_1\theta_7)$	$u_0 = \theta_{21}$
$R_i^2 = \theta_{10}(1 - \theta_9)/(\theta_1\theta_8)$	$\tau_s = 1/\theta_{22}$
$R_e^2 = \theta_9\theta_{10}/(\theta_1\theta_8)$	$\tau_f = 1/\theta_{23}$
$R_m = -\theta_{10}/\theta_1$	$\tau_0 = 1/\theta_{24}$
$R_m^1 = -\theta_{10}/(\theta_1\theta_{11})$	$\alpha = \theta_{25}$
$R_m^2 = -\theta_{10}/(\theta_1\theta_{12})$	$E_0 = 1 - \theta_{26}$
$\alpha_{PC} = \theta_{13}$	
$\alpha_{IN} = \theta_{14}$	

tained using Bayes' theorem. In this step, new data $\tilde{z}_k$ is included.

$$p(\tilde{x}(s_k) / \{Z_{s_{k-1}}, \tilde{z}_k\}) = \frac{p(\tilde{z}_k / \tilde{x}(s_k), Z_{s_{k-1}}) p(\tilde{x}(s_k) / Z_{s_{k-1}})}{p(\tilde{z}_k)}$$

The more nonlinear function $\tilde{h}_{s_k}^\Phi(\cdot)$ is at $\tilde{x}(s_k)$, the more remote this a posteriori pdf is from Gaussianity [Tarantola, 2005]. The weakest case of nonlinearity arises when this function is linearized around the predictor $\tilde{x}_{s_k/s_{k-1}}$ (Fig. II-1, left).

$$\tilde{z}_{s_k} = \tilde{h}_{s_k}^\Phi(\tilde{x}_{s_k/s_{k-1}}) + \mathbf{C}_{s_k}^\Phi(\tilde{x}(s_k) - \tilde{x}_{s_k/s_{k-1}}) + \tilde{e}_{s_k}$$

The matrix $\mathbf{C}_{s_k}^\Phi$ is the Jacobian of function $\tilde{h}_{s_k}^\Phi(\cdot)$ evaluated at $\tilde{x}_{s_k/s_{k-1}}$.

The innovations process $\tilde{v}_{s_k}$ is defined as the residual between the actual observation $\tilde{z}_{s_k}$ and its predicted value $\tilde{h}_{s_k}^\Phi(\tilde{x}_{s_k/s_{k-1}})$ (Fig. II-1, left); hence, it can be used to test the authenticity of the state space model to explain the data.

$$\tilde{v}_{s_k} = \tilde{z}_{s_k} - \tilde{h}_{s_k}^\Phi(\tilde{x}_{s_k/s_{k-1}}) \quad (\text{II-1a})$$

$$\Sigma_{s_k} = \mathbf{C}_{s_k}^{\Phi T} \mathbf{P}_{s_k/s_{k-1}} \mathbf{C}_{s_k}^\Phi + \Omega_{s_k} \quad (\text{II-1b})$$

Equations II-1 define the MATLAB function $[\tilde{v}_{s_k}, \Sigma_{s_k}] = \text{Innovation}^{\Phi}(\tilde{x}_{s_k/s_{k-1}}, \mathbf{P}_{s_k/s_{k-1}}, \tilde{z}_{s_k})$.

The filter $\tilde{x}_{s_k/s_k}$ and filter variance $\mathbf{P}_{s_k/s_k}$ are the resulting mean and variance of the a posteriori conditional pdf after linearization. By assuming the a priori conditional pdf $p(\tilde{x}(s_k) / Z_{s_{k-1}}) \sim N(\tilde{x}_{s_k/s_{k-1}}, \mathbf{P}_{s_k/s_{k-1}})$, it can be proved that the a posteriori conditional pdf satisfies $p(\tilde{x}(s_k) / \{Z_{s_{k-1}}, \tilde{z}_k\}) \sim N(\tilde{x}_{s_k/s_k}, \mathbf{P}_{s_k/s_k})$ [Tarantola, 2005], with:

$$\tilde{x}_{s_k/s_k} = \tilde{x}_{s_k/s_{k-1}} + \mathbf{C}_{s_k}^{\Phi+} \tilde{v}_{s_k} \quad (\text{II-2a})$$

$$\mathbf{P}_{s_k/s_k} = \mathbf{P}_{s_k/s_{k-1}} - \mathbf{C}_{s_k}^{\Phi+} \mathbf{C}_{s_k}^\Phi \mathbf{P}_{s_k/s_{k-1}} \quad (\text{II-2b})$$

The matrix $\mathbf{C}_{s_k}^{\Phi+} = (\mathbf{C}_{s_k}^{\Phi T} \Omega_{s_k}^{-1} \mathbf{C}_{s_k}^\Phi + \mathbf{P}_{s_k/s_{k-1}}^{-1})^{-1} \mathbf{C}_{s_k}^{\Phi T} \Omega_{s_k}^{-1}$ represents a pseudo-inverse of $\mathbf{C}_{s_k}^\Phi$ in the probabilistic metric of the predictor variance $\mathbf{P}_{s_k/s_{k-1}}$ and the variance-covariance matrix Ω_{s_k} of the measurement errors, and it is called, in the filtering context, the filter gain.

Equations II-2 define the MATLAB function $[\tilde{x}_{s_k/s_k}, \mathbf{P}_{s_k/s_k}] = \text{Filter}^{\Phi}(\tilde{x}_{s_k/s_{k-1}}, \mathbf{P}_{s_k/s_{k-1}}, \tilde{v}_{s_k})$.

An interesting point is that the LL filter's estimate of Σ_{s_k} (II-1b) may indicate some small component of the actual variance of the residuals, when in fact it is relatively large. This becomes clear when one examines the expression used to update $\mathbf{P}_{s_k/s_k}$ at the filtering step (II-2b), which does not depend on any information of the residuals at s_k .

Unlike in the filtering step, no new data is provided in the prediction step; therefore, the state space model (in particular the SDE (1a)) should be considered reliable to predict $\tilde{x}_{t/s_k}$ and $\mathbf{P}_{t/s_k}$ for $t \in (s_k, s_{k+1}]$ (Fig. II-1, right). An internal cycle with optimum step size Δ_k is defined in this interval to

Figure II-1.

The illustration of the filtering and prediction steps in the LL filter. The filtering step is exemplified assuming a single observation, although generalizing in case of simultaneous observations is trivial.

sequentially update the predictor and the predictor variance at time instant $t + \Delta_k$ from their values at time instant t . The outputs of the filtering step $\tilde{x}_{s_k/s_k}$ and $\mathbf{P}_{s_k/s_k}$ previously calculated, are used as the respective initial values in this cycle. In general, Δ_k could be different for each iteration. Note also that the predictor $\tilde{x}_{s_k/s_{k-1}}$ and predictor variance $\mathbf{P}_{s_k/s_{k-1}}$ used before in the filtering step, are obtained from $\tilde{x}_{s_{k-1}/s_{k-1}}$ and $\mathbf{P}_{s_{k-1}/s_{k-1}}$ in the last prediction cycle of the preceding iteration.

The marginal pdf (conditioned also to data Z_{s_k}) $p(\tilde{x}(t + \Delta_k) / Z_{s_k})$ is obtained by integrating the conditional joint pdf $p(\tilde{x}(t), \tilde{x}(t + \Delta_k) / Z_{s_k})$ for all possible events in $\tilde{x}(t)$. The conditional joint pdf can be rewritten by means of Bayes' theorem; hence,

$$p(\tilde{x}(t + \Delta_k) / Z_{s_k}) = \int p(\tilde{x}(t + \Delta_k) / \tilde{x}(t), Z_{s_k}) p(\tilde{x}(t) / Z_{s_k}) d\tilde{x}(t).$$

The marginal pdf is non-Gaussian for state space models with SDE satisfying characteristics (1) and (2) mentioned in Materials and Methods (LL filter). The most remarkable attribute of the LL filter is the linearization of the function $\tilde{f}(\cdot, \cdot; \theta)$ inside each interval $[t, t + \Delta_k]$ around the values of the predictor $\tilde{x}_{t/s_k}$ at time instant t .

$$d\tilde{x} = (\mathbf{A}_t^0 \tilde{x} + \tilde{a}_t^0(s, \Delta_k)) ds + \mathbf{G} d\tilde{w}$$

The initial condition is $\tilde{x}(t) = \tilde{x}_{t/s_k}$. The conditional pdf $p(\tilde{x}(t + \Delta_k) / \tilde{x}(t), Z_{s_k})$ is then approximately Gaussian; hence, assuming $p(\tilde{x}(t) / Z_{s_k}) \sim N(\tilde{x}_{t/s_k}, \mathbf{P}_{t/s_k})$, it can be proved that $p(\tilde{x}(t + \Delta_k) / Z_{s_k}) \sim N(\tilde{x}_{t+\Delta_k/s_k}, \mathbf{P}_{t+\Delta_k/s_k})$, and so the expressions (II-3) can be derived (see Jimenez and Ozaki 2003).

$$\tilde{x}_{t+\Delta_k/s_k} = \tilde{x}_{t/s_k} + \int_0^{\Delta_k} \exp(\mathbf{A}_t^0(\Delta_k - s)) [\mathbf{A}_t^0 \tilde{x}_{t/s_k} + \tilde{a}_t^0(s + t, \Delta_k)] ds \quad (\text{II-3a})$$

$$\mathbf{P}_{t+\Delta_k/s_k} = \exp(\mathbf{A}_t^0 \Delta_k) \mathbf{P}_{t/s_k} \exp(\mathbf{A}_t^0 \Delta_k)^T + \int_0^{\Delta_k} \exp(\mathbf{A}_t^0 s) \mathbf{G} \mathbf{G}^T \exp(\mathbf{A}_t^0 s)^T ds \quad (\text{II-3b})$$

The matrix $\mathbf{A}_t^0$ is the Jacobian of function $\tilde{f}(\cdot, \cdot; \boldsymbol{\theta})$ at $\tilde{x}_{t/s_k}$ and time instant t . The definition of vector $\tilde{a}_t^0(\cdot, \Delta_k)$ depends on the type of expansion used to approximate $\tilde{f}(\cdot, \cdot; \boldsymbol{\theta})$. *Taylor*

$$\tilde{a}_t^0(u, \Delta_k) = \tilde{f}(t, \tilde{x}_{t/s_k}; \boldsymbol{\theta}) - \mathbf{A}_t^0 \tilde{x}_{t/s_k} + \frac{\partial \tilde{f}(t, \tilde{x}_{t/s_k}; \boldsymbol{\theta})}{\partial t} (u - t)$$

Ito-Taylor

$$\tilde{a}_t^0(u, \Delta_k) = \tilde{f}(t, \tilde{x}_{t/s_k}; \boldsymbol{\theta}) - \mathbf{A}_t^0 \tilde{x}_{t/s_k} + \left\{ \frac{\partial \tilde{f}(t, \tilde{x}_{t/s_k}; \boldsymbol{\theta})}{\partial t} + \frac{1}{2} \sum_{ij} [\mathbf{G} \mathbf{G}^T]_{ij} \frac{\partial^2 \tilde{f}(t, \tilde{x}_{t/s_k}; \boldsymbol{\theta})}{\partial x_i \partial x_j} \right\} (u - t)$$

Equations II-3 define the MATLAB function $[\tilde{x}_{t+\Delta_k/s_k}, \mathbf{P}_{t+\Delta_k/s_k}] = \text{Predictor}_{\Delta_k}^0(t, \tilde{x}_{t/s_k}, \mathbf{P}_{t/s_k})$.

To evaluate numerically the integrals in II-3, theorem 1 in Van Loan [1978] must be used.

For the optimal performance of the LL filter, both linearizations proposed above should provide a good approximation of the state space model. In the particular case of linear/autonomous state space models with additive Wiener processes, the formulae for calculating the filter and filter variance in the LL filter reduce to those proposed in the original Kalman filter, and the cycle in the prediction step disappears. For this case, the predictor and predictor variance can be exactly evaluated using closed formulae. This is the simplest case of a state space model, and the only one for which the conditional pdf is Gaussian along the filter propagation. The LL filter has been explained in this appendix only for state space models with additive Wiener processes. Even so, the LL filter can also be applied to state space models with nonclassical random effects (see, for example: Ozaki and Iino [2001] for Poisson point processes, Jimenez and Ozaki [2003] for weighted sum of multiplicative Wiener processes).