FROM BOLD-FMRI SIGNALS TO THE PREDICTION OF SUBJECTIVE PAIN PERCEPTION THROUGH A REGULARIZATION ALGORITHM

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ABSTRACT

Functional magnetic resonance imaging, in particular the BOLD-fMRI technique, plays a dominant role in human brain mapping studies, mostly because of its non-invasiveness and relatively high spatio-temporal resolution. The main goal of fMRI data analysis has been to reveal the distributed patterns of brain areas involved in specific functions, by applying a variety of statistical methods with model-based or data-driven approaches. In the last years, several studies have taken a different approach, where the direction of analysis is reversed in order to probe whether fMRI signals can be used to predict perceptual or cognitive states. In this study we test the feasibility of predicting the perceived pain intensity in healthy volunteers, based on fMRI signals collected during an experimental pain paradigm lasting several minutes. In particular, we introduce a methodological approach based on new regularization learning algorithms for regression problems.

1. INTRODUCTION

Several neuroimaging techniques are today available for the detection of the activity patterns which characterize human brain function. They measure the spatial distribution and/or the temporal course of physical entities which are strictly connected to neural activity. One of the most recently developed non-invasive techniques is functional Magnetic Resonance Imaging (fMRI) based on BOLD (Blood Oxygenation Level Dependent) contrast ([1]). Using properly weighted MR images, local changes in deoxyhaemoglobin concentration, originating from the vascular response to neuronal mass activity, can be revealed with such technique.

In fMRI, the acquisition of a sequence of cerebral 3D images during the execution of a particular motor, cognitive or sensory task, allows to construct the temporal course of the haemodynamic response, following neuronal activity, at the voxel level. The majority of fMRI data analysis methods are aimed at searching for functional localization, i.e., obtaining a spatial map of activated brain areas when performing a task. To this end, the conventional approach consists of convolving the vector representing the paradigm timing with an estimate of the haemodynamic impulse response function. The result is then used as a regressor of interest in a General Linear Model ([2]) or as a reference function to be correlated with the recorded signals.

However, in the last few years, a growing number of studies have taken a different approach, where the direction of analysis is reversed in order to probe whether the acquired fMRI signals can be used to predict perceptual or cognitive states. To this end, many different methods have been proposed (e.g. Support Vector Machines for Regression, Relevance Vector Regression) but so far no one can be considered the best methodology ([3, 4, 5]). A new set of techniques can be obtained by restating the machine learning problem as a linear inverse problem and, more precisely, by reviewing the aim of building a model close to the data, which is able to generalize as a problem of regularization of an ill-conditioned linear system ([6]). The effectiveness of these algorithms in learning tasks has been extensively tested on real and synthetic data, often improving the performance of the state-of-the-art results. Interestingly, the implementation of the above algorithms is reduced to few lines of code. In this paper we consider one of these techniques, the so called ν-method, and test its efficiency for the prediction of subjective pain perception of healthy volunteers. Analyzed data were BOLD-fMRI signals collected during an experimental pain paradigm lasting several minutes ([7]).

The plan of the paper is as follows: in Section 2 we recall the general formulation of the statistical learning problem and we define the algorithm we will use in the tests, while in Section 3 we introduce the fMRI experiment, describe some topics concerning the implementation and the choice of the parameters involved to build the model and finally discuss the results. Our conclusions are offered in Section 4.

2. THE ν-METHOD

Within the standard machine learning framework, a regression problem can be state as follows: given a compact subset X of $\mathbb{R}^m$, a real number $M > 0$, the interval $Y = [-M, M]$ and a training set of data $S = \{(\boldsymbol{x}_i, y_i) : i = 1, \ldots, n\} \subset X \times Y$, find a function $f : X \to Y$ that fits the elements of S and is able to provide a good prediction $y \in Y$ for a new example $\boldsymbol{x} \in X$. In general, this function will solve a minimization problem

$$\min_{f \in \mathscr{H}} \frac{1}{n} \sum_{i=1}^{n} V(\boldsymbol{x}_i, y_i, f(\boldsymbol{x}_i)) + \lambda \| f \|^2_{\mathscr{H}},$$

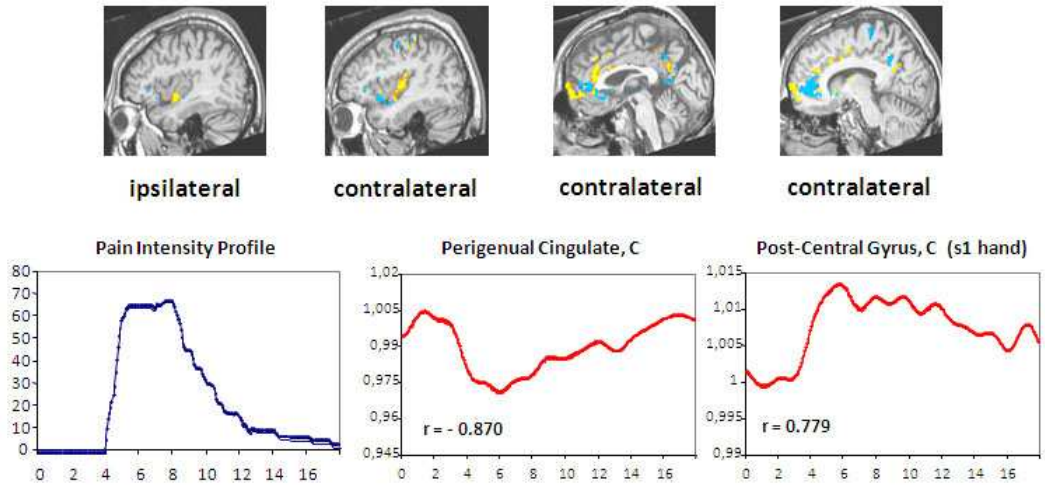

Figure 1: *Top*: clusters with signal time courses positively (yellow) or negatively (blue) correlated with the psychophysical curve for a representative subject. *Bottom*: psychophysical pain intensity and averaged signals from two representative ROIs.

where $V : X \times Y \times Y \to [0, +\infty)$ is a *loss function* which weights the errors made by f on the training set and $\mathscr{H}$ is the *Hypotheses space* in which we choose the function f itself. The real positive number λ is the *regularization parameter* which balances the fidelity of the solution to the training set and its complexity (represented by the norm of f in the Hilbert space $\mathscr{H}$). Low values for λ lead to solutions which behave very well on the training set but which may not be sufficiently accurate on new examples, while on the other hand high values for λ force the solution to be smooth and stable (with respect to variations on the training set) to the detriment of the information contained in the data.

Different machine learning techniques arise from different choices for V and $\mathscr{H}$ ([8, 9]). In this work we point out a family of algorithms which are extremely easy to implement and very fast to provide the solution, especially if the dimensions of the problem are not too large. It can be proved ([10]) that, if we choose the quadratic loss function

$$V(\boldsymbol{x}_i, y_i, f(\boldsymbol{x}_i)) = (y_i - f(\boldsymbol{x}_i))^2, \qquad i = 1, \ldots, n$$

and we pick f in a Reproducing Kernel Hilbert Space $\mathscr{H}_K$ defined by the Mercer kernel $K : X \times X \to \mathbb{R}$ ([11]), then by the Representer Theorem f can be written as

$$f(\boldsymbol{x}) = \sum_{i=1}^{n} c_i K(\boldsymbol{x}, \boldsymbol{x}_i), \qquad x \in X. \tag{1}$$

By straightforward computation it follows that the coefficients $\boldsymbol{c} = (c_1, \ldots, c_n)^T$ are the solution of the linear system

$$(\boldsymbol{K} + n\lambda \boldsymbol{I})\boldsymbol{c} = \boldsymbol{y}, \tag{2}$$

where $\boldsymbol{I}$ is the identity matrix, $\boldsymbol{y} = (y_1, \ldots, y_n)^T$ and $\boldsymbol{K} = \{K_{ij}\}$, $K_{ij} = K(\boldsymbol{x}_i, \boldsymbol{x}_j)$, $i, j = 1, \ldots, n$.

The linear system (2) is the Tikhonov regularized version of the (potentially) ill-conditioned linear system $\boldsymbol{Kc} = \boldsymbol{y}$ ([12]). This approach can be generalized ([13]) by considering other regularization methods already existing in literature and by defining the corresponding learning algorithms to obtain the vector $\boldsymbol{c}$ ([14]). In this paper we consider an iterative algorithm called ν-method ([15]) which collected good results in terms of efficiency and robustness in the classification framework ([16]). The i-th approximation of the coefficients $\boldsymbol{c}$ depends on the two previous iterates and its explicit form is given by

$$\begin{aligned} \boldsymbol{c}^{(i)} &= \boldsymbol{c}^{(i-1)} + u_i \left(\boldsymbol{c}^{(i-1)} - \boldsymbol{c}^{(i-2)} \right) + \frac{\omega_i}{n} \left(\boldsymbol{y} - \boldsymbol{K}\boldsymbol{c}^{(i-1)} \right), \\ & i = 1, \ldots, t, \quad \boldsymbol{c}^{(0)} = \boldsymbol{0}, \end{aligned} \tag{3}$$

where, given $\nu > 0$,

$$u_i = \frac{(i-1)(2i-3)(2i+2\nu-1)}{(i+2\nu-1)(2i+4\nu-1)(2i+2\nu-3)},$$

$$\omega_i = 4\frac{(2i+2\nu-1)(i+\nu-1)}{(i+2\nu-1)(2i+4\nu-1)}, \qquad i = 1, \ldots, t.$$

The role of the regularization parameter here is played by the number of iterations t: on one hand, many iterations lead to the overfitting phenomenon, while on the other hand few iterations give excessively regularized predictors. In this connection, the ν-method provides a significantly faster convergence with respect to one-step iterative methods with fixed steplength; more precisely, it can be proved ([15]) that it needs the square root of the number of iterations required by standard Landweber algorithm to get the regularized solution.

3. THE FMRI EXPERIMENT

3.1 Creation of the dataset

The study was carried out on healthy volunteers who were injected subcutaneously with a dilute ascorbic acid solution (0.04 ml, 20%) into the left thenar eminence. They were instructed to code the sensory intensity of pain throughout the experiments, by moving a computer-controlled visual analogue scale (VAS) using their right (unstimulated)

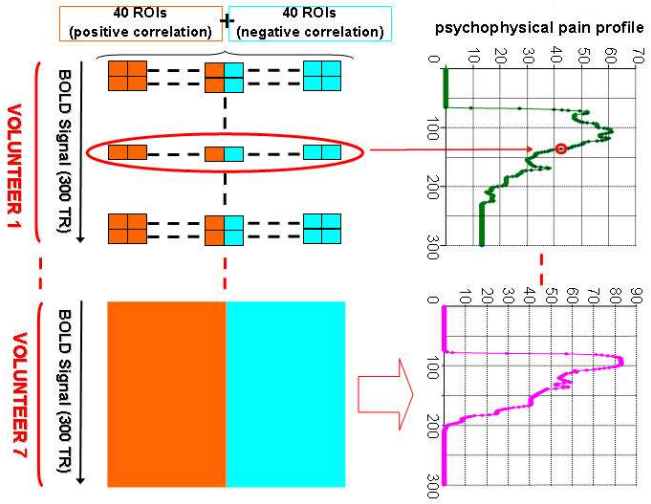

Figure 2: Pictorial representation of the dataset.

hand. Functional images were acquired by a GE 1.5 T scanner, using an EPI BOLD-sensitive sequence (TR= 4s; $3.75 \times 3.75 \times 4$ mm^3, interpolated to $2 \times 2 \times 2$ mm^3). Experiments lasted 20 minutes, during which 300 brain volumes were acquired from 24 contiguous axial planes covering the diencephalon and telencephalon. Based on a priori hypothesis, 20 regions of interest (ROIs) in both hemispheres were identified on anatomical brain images, acquired in the same experimental session. They included the thalamus, basal ganglia, pre- and post-central gyrus and parietal operculum, insular and cingulate cortical areas. After correction of head movements, cluster of voxels, inside the pre-selected ROI, were identified on the functional images whose time course were correlated to the individual psychophysical pain profile ($|r| \geq 0.6$, cluster size = 400 mm^3 - see Figure 1). Subsequently, the clusters signals were averaged together for each ROI according to the sign of their correlation. For each volunteer, the resulting dataset was composed of 80 signals (300 sampled points each), i.e. two signals for every one of the selected 40 ROIs (see Figure 2). We trained the method by using six subjects and predicted the labels of one different subject. The analysis has been carried out on a computer equipped with a 1.66GHz Intel Core Duo T5500 in a Windows XP environment.

3.2 Model construction

We tried several different kernel functions K (e.g., linear, Gaussian, polynomial) and finally we found that a Gaussian kernel

$$K(\boldsymbol{x}_1, \boldsymbol{x}_2) = e^{-\frac{\|\boldsymbol{x}_1 - \boldsymbol{x}_2\|_2^2}{2\sigma^2}}, \qquad \boldsymbol{x}_1, \boldsymbol{x}_2 \in \mathbb{R}^m$$

seems to provide a better accuracy on the reconstructions (although in some cases similar results are achievable even with a linear or polynomial kernel, suitable scaled to assure the convergence of the method - see [17]). Consequently, the parameters that have to be fixed in the training phase are the standard deviation σ of the Gaussian kernel and the number of iterations t performed by the ν-method. As far as concerns the value of ν, we found good results in terms of accuracy and convergence rate by setting $\nu = 1$ (different admissible values for ν vary the number of iterations required but lead essentially to the same solutions).

In our tests the free parameters of the algorithms have been chosen via a "leave-one-volunteer-out" cross validation applied to the training set (see Figure 3). In particular:

- we fixed a grid of possible values $(\sigma_1, \ldots, \sigma_M)$ and $(1, \ldots, t_{\max})$ for the standard deviation of the Gaussian kernel and the number of iterations, respectively;
- for each pair (σ_k, t_j), $k = 1, \ldots, M$, $t_j = 1, \ldots, t_{\max}$, we built the model using five subjects as the training set and tested it on the excluded one. This step is performed six times (exhausting all the possible combinations training set / test set). For a fixed σ_k and for the ℓ-th run of the cross validation ($\ell = 1, \ldots, 6$), we determined the optimal number of iterations $t_{\min}^{(\ell)}(\sigma_k)$ as the one which minimizes the relative Euclidean error $\rho_2 = \|\tilde{\boldsymbol{y}} - \tilde{\boldsymbol{f}}\|_2 / \|\tilde{\boldsymbol{y}}\|_2$, where $\tilde{\boldsymbol{y}}$ and $\tilde{\boldsymbol{f}}$ are the vectors of the real and predicted labels for the subject used as the test set;
- for each $k = 1, \ldots, M$, we defined

$$t_{\text{mean}}(\sigma_k) = \left[(t_{\min}^{(1)}(\sigma_k) + \ldots + t_{\min}^{(6)}(\sigma_k))/6 \right],$$

$$\text{err}_{\text{mean}}(\sigma_k) = (\rho_2^{(1)}(t_{\text{mean}}(\sigma_k)) + \ldots + \rho_2^{(6)}(t_{\text{mean}}(\sigma_k)))/6,$$

where $[\cdot]$ is the floor function;
- we chose as optimal parameters σ_{opt} and t_{opt} the values

$$\sigma_{\text{opt}} = \underset{k=1,\ldots,M}{\text{argmin}}\ \text{err}_{\text{mean}}(\sigma_k),$$

$$t_{\text{opt}} = t_{\text{mean}}(\sigma_{\text{opt}}).$$

Once we built the prediction function f through equations (1) and (3) with the optimal values for σ and t, we applied it to the fMRI data of the testing volunteer to predict its psychophysical pain profile and compared the results with the true ones.

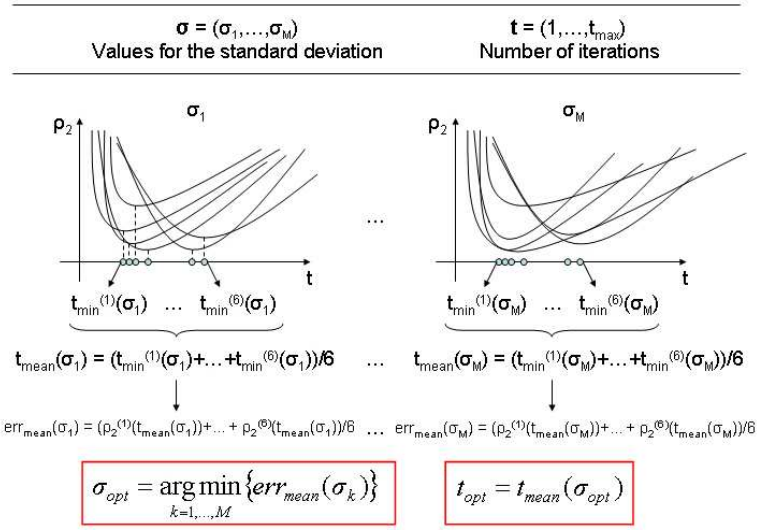

Figure 3: Scheme of the "leave-one-volunteer-out" cross validation for the choice of the optimal values for the standard deviation of the Gaussian kernel and the number of iterations performed by the ν-method.

3.3 Results

In Table 1 the relative reconstruction errors ρ_2 and the Pearson correlation coefficient ρ_P are given when each volunteer has been used as the test set. We chose two different ways to evaluate the accuracy of the results because we found that, in several cases, it is possible to find reconstructions with high values for ρ_P which do not reflect the magnitude of the target. In other cases, especially when the number of non-zero target values is particularly small, it may happen that an almost straight line can provide a very small error combined with an as much small value of ρ_P.

An example of the predicted pain profile, compared to the real target, for one representative volunteer is shown in Figure 4 (on top). For the sake of completeness, the corresponding behaviour on the training set is also reported on the bottom of Figure 4. The very high values of ρ_P obtained in each test suggest that the considered learning algorithm seems well suited to capture the general time course of the psychophysical pain profile, even if an accurate approximation of the real target is not always observed (see ρ_2 values in Table 1). Possible improvements are expected by increasing the size of the training set and with a more specific inclusion of the features, here represented by the selected brain regions.

Table 1: Relative reconstruction errors (ρ_2) and Pearson correlation coefficients (ρ_P) for the ν-method tested on seven volunteers (top rows). The last two rows refer to the performances on the six volunteers used to train the algorithm.

				Test set			
ρ_2	0.27	0.38	0.50	0.48	0.40	0.37	0.48
ρ_P	0.93	0.91	0.95	0.92	0.96	0.93	0.84
	A	B	C	D	E	F	G
ρ_2	0.23	0.18	0.21	0.20	0.25	0.19	0.19
ρ_P	0.96	0.97	0.96	0.97	0.95	0.97	0.97
				Training set			

4. CONCLUSIONS

The aim of the present paper concerns both the machine learning framework from a purely methodological viewpoint and the neuroscience area with the application of the presented method to a fMRI experiment. Regarding the method, we collected some recent results on the relation between machine learning and the theory of linear inverse problems in order to develop a learning algorithm which has the virtue to be extremely simple to understand and to implement on a computer which can provide good reconstructions in a reasonable time. The novelties of the paper consist in the application of this method in a regression problem (while, as far as we know, only applications to classification problems have been deeply investigated in literature).

Regarding the fMRI experiment, the proposed regularization algorithm collected very promising performances in reconstructing the psychophysical pain profiles of the subjects. The adopted model of acute prolonged (tonic) pain bears some similarities with clinically relevant conditions, such as prolonged ongoing activity in nociceptors and spontaneous fluctuations of perceived pain intensity over time. Therefore the approach proposed in this study has the potential to establish grounds for being able to obtain an objective measure of the ongoing level of clinical inflammatory pain.

Finally, the simplicity of schemes like the ν-method makes easy effective implementations providing interesting time saving with respect to state-of-the-art learning approaches. This peculiarity could be very interesting if the presented algorithm is used to quantify the relevance of the single components of the examples in the predicted model through a typical feature selection procedure ([18]). For the considered application, this means to identify those brain areas which role is essential in determining a specific brain state.

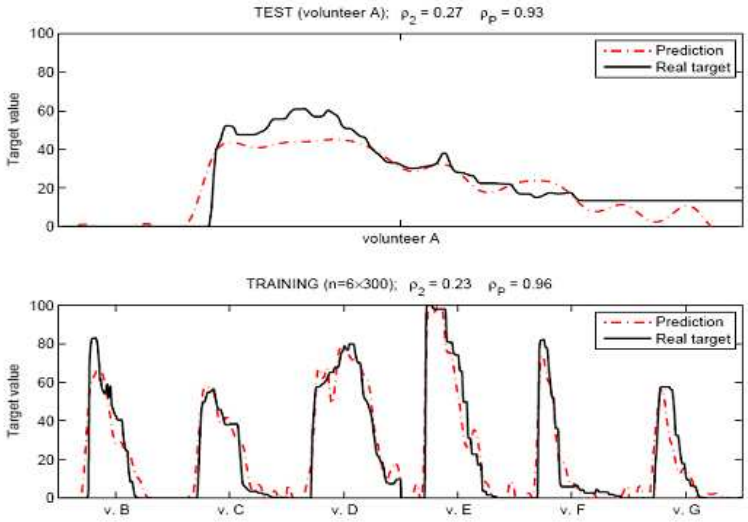

Figure 4: Predictions of the ν-method on volunteer A when volunteers B-G have been used to build the model (top panel). For sake of completeness, we plotted also the predictions on the examples of the training set in order to inspect how much the algorithm has learnt from the data.

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REFERENCES

[1] S. Ogawa, D. W. Tank, R. Menon, J. M. Ellermann, S. G. Kim, H. Merkle, and K. Ugurbil, "Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging," *P. Natl. Acad. Sci. USA*, vol. 89, pp. 5951–5955, Jul. 1992.

[2] K. J. Friston, A. P. Holmes, K. J. Worsley, J.-P. Poline, C. D. Frith, and R. S. J. Frackowiak, "Statistical parametric maps in functional imaging: A general linear approach," *Hum. Brain Mapp.*, vol. 2, pp. 189–210, Nov. 1994.

[3] J. D. Haynes and G. Rees, "Decoding mental states from brain activity in humans," *Nature Rev. Neurosci.*, vol. 7, pp. 523–534, Jul. 2006.

[4] J. Mourao-Miranda, A. L. W. Bokde, C. Born, H. Hampel, M. and Stetter, "Classifying brain states and determining the discriminating activation patterns: Support Vector Machine on functional MRI data," *NeuroImage*, vol. 28, pp. 980–995, Dec. 2005.

[5] T. Mitchell, R. Hutchinson, R. Niculescu, F. Pereira, X. Wang, M. Just, and S. Newman, "Learning to decode cognitive states from brain images," *Mach. Learn.*, vol. 57, pp. 145–175, Oct. 2004.

[6] E. De Vito, L. Rosasco, A. Caponnetto, U. De Giovannini, and F. Odone, "Learning from examples as an inverse problem," *J. Mach. Learn. Res.*, vol. 6, pp. 883–904, May 2005.

[7] C. A. Porro, V. Cettolo, M. P. Francescato, and P. Baraldi, "Temporal and Intensity Coding of Pain in Human Cortex," *J. Neurophysiol.*, vol. 80, pp. 3312–3320, Dec. 1998.

[8] T. Hastie, R. Tibshirani and J. Friedman, *The Elements of Statistical Learning: Data Mining, Inference, and Prediction*. New York: Springer-Verlag, 2001.

[9] V. N. Vapnik, *Statistical Learning Theory*. New York: John Wiley and Sons, 1998.

[10] T. Poggio and S. Smale, "The mathematics of learning: dealing with data," *Notices Amer. Math. Soc.*, vol. 50, pp. 537–544, May 2003.

[11] F. Cucker and S. Smale, "On the mathematical foundations of learning," *Bull. Amer. Math. Soc.*, vol. 39, pp. 1–49, Jan. 2002.

[12] A. N. Tikhonov and V. Y. Arsenin, *Solution of Ill Posed Problems*. Washington D.C.: W. H. Winston, 1977.

[13] F. Bauer, S. Pereverzev, and L. Rosasco, "On regularization algorithms in learning theory," *J. Complex.*, vol. 23, pp. 52–72, Feb. 2007.

[14] M. Prato and L. Zanni, "Inverse problems in Machine Learning: an application to brain activity interpretation," *J. Phys.: Conf. Ser.*, vol. 135, p. 012085, Nov. 2008.

[15] H. W. Engl, M. Hanke, and A. Neubauer, *Regularization of Inverse Problems*. Dordrecht:Kluwer Academic Publishers Group, 1996.

[16] L. Lo Gerfo, L. Rosasco, F. Odone, E. De Vito, and A. Verri, "Spectral algorithms for supervised learning," *Neural Comput.*, vol. 20, pp. 1873–1897, Jul. 2008.

[17] M. Hanke, "Accelerated Landweber iterations for the solution of ill-posed equations," *Numer. Math.*, vol. 60, pp. 341–373, Dec. 1991.

[18] I. Guyon and A. Elisseeff, "An introduction to variable and feature selection," *J. Mach. Learn. Res.*, vol. 3, pp. 1157–1182, Mar. 2003.